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Reiview Article,

"Surgical Treatment of Degenerative Mitral Valve Disease-Causing Mitral Regurgitation: State Of The Art"

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Abstract:
Degenerative Mitral Valve Disease (DMVD) is common in developed countries that frequently causes mitral regurgitation (MR). The natural history of DMVD is not well demonstrated. Therefore, timely and suitable interventions are the determinant of post-intervention clinical outcomes, life quality, and life expectancy of patients. The severity of MR can be precisely assessed by doppler-echocardiographic imaging. However, no medical management has been proven to be effective in averting the volume overload related sequel of asymptomatic degenerative MR. Therefore, mitral valve surgery (MVS) is the gold standard treatment strategy for DMVD. Notwithstanding, MVS is the only sorts of treatment strategy which provides long term natural and complication-free clinical outcome to otherwise healthy DMVD patients. However, mitral valve (MV) repair provides better clinical outcomes compared to MV replacement, along with the significant reduction of postoperative mortality rate about 70%. Currently, MVS is carried out using minimally invasive techniques or robotic-assisted techniques. Nonetheless, MVS using percutaneous techniques is evolving in the treatment for DMVD patients. This state-of-the-art-review is aimed to delineate the recent knowledge of DMVD, which includes the natural history of the disease, diagnostic modalities, recent treatment strategies, and clinical follow-up results.

Keywords: Degenerative Mitral Valve Disease, Barlow's Disease, Mitral Valve Prolapse, Mitral Regurgitation, Mitral Valve Surgery.

Introduction:

DMVD first characterized by a South African cardiologist J. B. Barlow in 1965 [1]. He reported an assemblage of conditions, which include mitral annular dilatation, chordal elongation, or rupture, that leads to mitral valve prolapse (MVP), and the aftereffect of this MVP is MR. In the beginning, this MR due to MVP causes trivial MV dysfunction, but in long-standing cases when MV degeneration progressed, thereafter MR due to MVP is proven to the vital cause of cardiovascular morbidity and mortality [2]. Therefore, MVS usually required in patients with severe MR to restore normal life. Nowadays, MV repair is well recognized and effective treatment strategy that is performed in all diagnosed patients with MR due to DMVD. After the evaluation of several studies, it is demonstrated that the MV repair rate is around 50% in developed countries [3-5].

The term DMVD incorporates a spectrum of conditions, in which myxomatous infiltrative changes or dysplastic changes in mitral leaflet tissue causing elongation or rupture of the MV chordae, that lead to MVP and/or mitral annular dilatation; these ultimately lead to MR [6]. However, DMVD is a common disease that affects around 2% of the general population [7]. The primary etiology for DMVD includes Barlow's disease, fibroelastic deficiency, and Marfan syndrome.

With the advent of modern medical science, several new surgical approaches evolved, including minimally invasive techniques and trans-catheter-based techniques for MVS. Nowadays, the imaging techniques evolved so precisely; thus, the high-resolution 3D image of the diseased part of the

body is readily available for surgeons. Therefore, surgeons can operate the most suitable surgery for a particular individual. Moreover, the multidisciplinary implementation approach further alleviates the postoperative complication rate. This study focuses on pathophysiology and classification, assessment and diagnosis, recent surgical approaches, and clinical follow-up results of DMVD.

Pathophysiology and Classification:

For understanding the MV anatomy and pathophysiology of MR, it is prudent to know different anatomical structures related to MV. It also helps to plan surgical treatment strategy and has an impact on long-term clinical outcomes after treatment.

Leaflet: the saddle-shaped MV consists of two leaflets (Figure 1). The semi-circular shaped mitral anterior leaflet is attached across the 2/5 length of the mitral annular circumference. There is no indentation of the anterior mitral leaflet and usually continuous; thus, only a small portion of the leaflet can be safely resected during MV repair. The motion of the anterior leaflet also delineates a meaningful boundary between the outflow (during systole) and the inflow (during diastole) tracts of the left ventricle [6]. The anterior mitral is a little bit higher than the posterior mitral leaflet, whereas the surface area of both leaflets is almost equal. The quadrangular shaped mitral posterior leaflet is attached to about 3/5 of the mitral annular circumference. It is divided into three individual scallops defined as P1 (anterior or lateral scallop), P2 (middle scallop), and P3 (posterior or medial scallop) by two well-defined indentations; whereas A1 (anterior segment), A2 (middle segment), and A3 (posterior segment) are three corresponding segments of the anterior mitral leaflet are [8]. This specific segmental anatomy is crucial for diagnosis and surgical treatment.

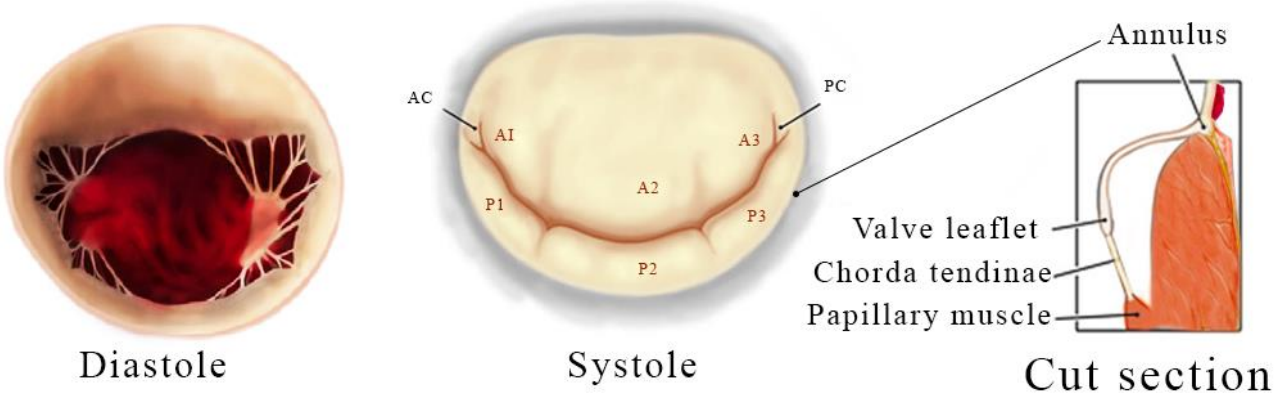

Figure1: Segmental anatomy of the mitral valve and the sub-valvular structures. The mitral valve is divided into eight segments. AC-anterolateral commissure; PC-posteromedial commissure; segments of posterior leaflet (P1, P2, P3); segments of anterior leaflet (A1, A2, A3); primary (marginal) chordae are attached to the free margin of the leaflet. Modified from Ref. [9]

Commissure: It is a particular area where both leaflets conjugate and inserts into the mitral annulus. Occasionally, a well-defined bur small leaflet segments may present at commissure that can be easily located using the axis of corresponding papillary muscles or the commissural chordae. Mitral annulus is separated from commissure by some millimeters of valvular tissue, and it is a crucial area for the surgeon because if commissurotomy extends up to annulus during performing commissurotomy, it can augment new iatrogenic MR.

The zone of coaptation: MV consists of two zones on the left atrial surface, body or peripheral smooth zone and coaptation zone or rough central zone. However, the coaptation surface of the valve represents the rough zone. From an atrial view (Fig. 1), the gently curved coaptation line can be seen between the two leaflets. This coaptation zone is much vital for pre and post-operative MV competency.

Mitral annulus: Being an atrioventricular valve,

the MV annulus comprises the anatomical junction between the left ventricle and the left atrium; thus, it provides an insertion site for the leaflet tissue. The mitral annulus is segmentally divided into two portions, anterior more developed portion, and the posterior less developed portion. The anterior portion is attached to the fibrous trigone, which is divided into the right and left part. In the past, it was thought that this portion of the annulus could not increase in circumference because of its relation with trigones, but modern 3D imaging techniques and several autopsy studies have proven that this area dilates in pathologic conditions which trigger MR [10, 11]. However, the posterior mitral annulus is not attached to any fibrous structures because the fibrous skeleton in this region is discontinuous, hence this portion is prone to increase its circumference in case of MR associated with the left ventricle and/or left atrial dilation. Therefore, the reduction of the annular dimension is a crucial part of MV reconstructive surgery. The MV is saddle-shaped; thus, it helps leaflet coaptation during systole and diastole, but this could be affected when mitral annular calcification and dilatation occurred. Notwithstanding, the mitral annulus is encircled by several significant structures such as an aortic valve, coronary sinus, and circumflex coronary artery, which must be esteemed during MVS.

Chordae tendinae: Primarily, the end-systolic position of the anterior and posterior leaflets is maintained by chordae tendinae. Chordae tendinae originates from the papillary muscles. However, they categorized based on their site of insertion between the free margin and the base of leaflets (Fig. 1). Primary chordae (marginal) are inserted on the free margin of the leaflets, and secondary chordae (intermediate) are inserted on the ventricular surface of the leaflets. The primary chordae prevents prolapse of the leaflet margin, whereas secondary chordae release increased valvular tissue tension. Some authors demonstrated that secondary chordae preserve ventricular shape and function [12, 13]. Tertiary chordae (basal) connect the mitral annulus with the leaflet base to the papillary muscle that is confined to the posterior leaflet. Preserving this "connection" of leaflets and annulus by chordae to the ventricle is exceptionally crucial; this significantly improves the postoperative clinical outcome [14].

Papillary muscles and the left ventricle: MV is connected to the left ventricle via chordae tendinae and papillary muscle; thus, MV opens and closes during ventricular diastole and systole. In the left ventricle, there are two papillary (anterolateral and posteromedial) muscles that originate from the area between the middle and apex of the left ventricular, whereas each papillary muscle sends chordae to both leaflets. The posteromedial papillary muscle is more prone to injury from coronary artery disease due to its single arterial blood supply. Papillary muscle can be calcified that may cause restrict chordae and leaflet motion in the severe case of DMVD. An axiom "mitral regurgitation begets mitral regurgitation" may be developed when left ventricular and annular dilatation developed due to papillary muscle displacement.

The spectrum of Degenerative Mitral Valve Disease:

(Carpentier pathophysiological trad)

DMVD occurs due to a spectrum of lesions, that includes simple to multiple chordae rupture, single or multiple segment prolapses of the leaflet and annular dilatation. However, it is challenging to describe deep insight into the MV dysfunction causing MR following DMVD and clinical outcome of MV repair due to unavailability of globally recognized terminology for defining MR; several authors describe this by different terms such as "MV billowing," "MV prolapse," "mitral flail leaflet," "myxomatous MV disease," "floppy MV," "Barlow's disease" and "fibroelastic degeneration of MV" [15]. Carpentier described this situation as "the Babel Syndrome" of confusion.

In 1983, a French physician Carpentier had reported a "pathophysiological triad" to clarify all of these confusions, which include leaflet dysfunction, MV lesion, and etiology (Table 1) [8]. Initially, Carpentier categorized leaflet dysfunction into three types: Type I-normal leaflet motion, Type II-increased leaflet motion, and Type III-restricted leaflet motion (Figure 2) [8,16]. Later Type III leaflet dysfunction further subdivided into two types. Type IIIa-demonstrated as restricted leaflet motion (opening) during diastole and systole, whereas Type IIIb-demonstrated as restricted leaflet motion (closing) during systole [17]. Besides, Carpentier described a functional classification by combining leaflet dysfunction classification with segmental mitral valve anatomy (Figure 2), to provide a well explained systemic nomenclature of MV study that would be central to any authentic understanding of MV repair. However, most commonly type II leaflet

dysfunction is found in the general population. Notv
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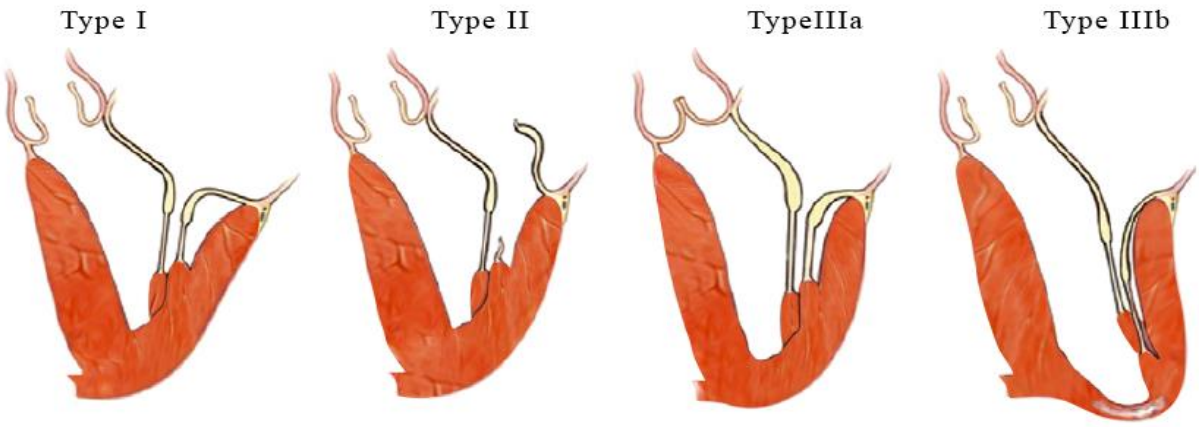


Figure2: Carpentier's functional classification. Type I, normal leaflet motion; Type II, increased leaflet motion (leaflet prolapse); Type IIIa, restricted leaflet motion (opening) during diastole and systole; Type IIIb, restricted leaflet motion (closing) predominantly during systole. Modified from Ref. [9].

Table1: Carpentier's Pathophysiological triad with the anatomical lesion of the mitral valve and recommended mitral valve repair techniques.

Leaflet dysfunction	Anatomical Lesion of mitral valve	Etiology	Recommended mitral valve repair techniques
Type I Normal leaflet motion	Leaflet perforation	Endocarditis	Pericardial patch repair
	Annular Dilatation	Dilated CM Ischemic CM	Annuloplasty
Type II Leaflet prolapse	Chordal rupture Chordal elongation PM elongation	Barlow's Disease FED	Gortex neo-chordae Chordal transfer Triangular resection Quadrangular resection Resection and sliding plasty Commissural suture
	PM rupture	Ischemic CM	
Type IIIa Restricted leaflet opening	Commissural fusion Leaflet thickening Leaflet calcification	Rheumatic Heart Disease (RHD)	Commissurotomy
	Chordal fusion	Rheumatic Heart Disease (RHD)	Chordal fenestration
Type IIIb Restricted leaflet closing	PM displacement Chordal thickening Chordal shortening LV dilatation	Dilated CM Ischemic CM	Chordal division Chordal shortening Annuloplasty

CM = Cardiomyopathy; PM = Papillary muscle; FED = Fibroelastic Deficiency; LV = Left Ventricle. Modified from Ref. [9].

Barlow's disease:

It is characterized by myxoid infiltration of the valve, which results from a myxomatous appearance of the valve along with excessive thickening of leaflet tissue (floppy leaflets) and enlargement valve size (Figure 3) [17-19]. The exact etiology is unknown, but a genetic factor or familial history can be a precipitator [20]. Diffuse

chordal elongation is more common than rupture, whereas chordal thickening is more common than chordal thinning. However, sub-valvular fibrosis and calcification of the papillary muscles with annular dilatation and calcification can be found. The pathological hallmark is myxoid infiltration, which destroys all 3-layer of leaflet structure with collagen structure alteration that identified on histological examination [21]. Typically, the mitral ring size of ≥36 mm corresponds to the anterior leaflet surface area [22]. Generally, the posterior leaflet is displaced toward the left atrial free wall, which far from the ventricular hinge point, producing a cul-de-sac together the posterior portion of the mitral annulus that can cause mitral annular fissures and calcification [23].

Fibroelastic deficiency:

It is characterized by fibrillin (connective tissue) deficiency that usually produces a rupture of one or more elongated and thinned chordae, leads to holosystolic MR. Impaired production of connective tissue, collagen, elastin, and proteoglycan leads to continuous thinning of leaflet but 3-layer architecture preserved. Generally, the middle scallop of the posterior leaflet more prone to rupture. The etiology of this disease is unknown but may be connected with the aging process. In some patients, the prolapsing segment can be affected by secondary myxomatous changes that cause accumulation of mucopolysaccharide in the valve mucosa, but this change is strictly confined to the prolapsed segment. The affected patients are usually asymptomatic until unless chordae rupture. Most of the surgical candidate patients are aged >60 years during referral time with a relatively short disease history. The more differentiating characteristics between Barlow's disease and fibroelastic deficiency are tabulated hereinbelow (Table 2).

Table2: Differentiating characteristics between two main entities of Degenerative Mitral Valve Disease (DMVD).

Differentiating Characteristics	Barlow's Disease (Myxomatous degeneration)	Fibroelastic Deficiency
Pathophysiology	Myxoid infiltration of MV	Impaired production of connective tissue, collagen, and elastin
The usual age of onset	Comparative younger 40-60 years	Comparatively older >60 years
Etiology	Unknown and/or Related to familial	Unknown and/or Related to the aging process
Time required for The onset of MV disease	Long duration (years to decades)	Short duration (months)
Familial History	Occasionally	No
Association with MS	Occasionally	No
Abnormal Heart sound	Midsystolic click, Late systolic murmur	Holosystolic murmur (short history)
On echocardiography	Thick/bulky leaflets, prolapsed/billowing leaflets, Multi segmental prolapsed.	Thin leaflets, Single segmental prolapse, Chordae rupture.
Surgical Treatment	MV repair more critical	MV repair less critical
Intraoperative findings	Excess thickened, long leaflet, Chordal thinning or thickening, Chordal elongation or rupture, Chordal fibrosis or calcification, Papillary muscle calcification, Annular dilation or calcification, Atrialization of MV leaflets.	Thin leaflets, Chordal thinning, Chordal elongation, Chordal rupture, Excess thickening of the prolapsed segment (occasionally)

MV = Mitral Valve; MS = Marfan Syndrome.

Other Degenerative Diseases:

DMVD can be associated with any other connective tissue disease such as Marfan's syndrome, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, and osteogenesis imperfecta. Genetic diseases like Turner's syndrome may produce Barlow type MV pathology. However, Marfan's syndrome causes similar pathological changes like Barlow's disease; thus, surgical repair approaches and clinical outcomes are comparable to Barlow's disease. Therefore, some authors suggest that Barlow's disease is a *forme fruste* of Marfan's (Figure 3) [24]. Categorization of DMVD by echocardiography is not possible always, because occasionally patients may present with features of both (Barlow's and fibroelastic deficiency) disease [21]. However, some DMVD remain uncategorized due to extremely complex features.

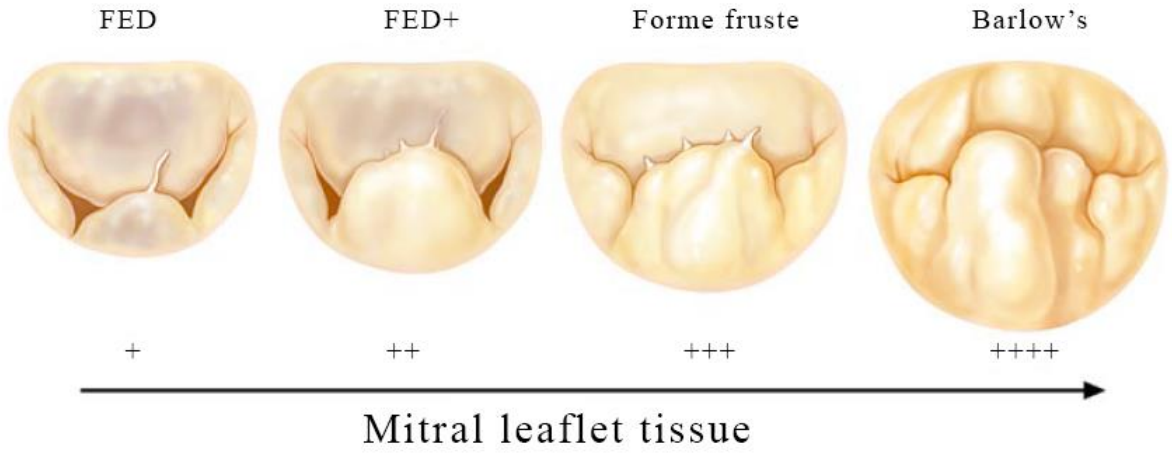


Figure3: Spectrum of degenerative mitral valve disease (DMVD) ranging from fibroelastic deficiency (FED) to Barlow's disease. In FED connective tissue synthesis is deficient that causes thin leaflet with thin chordae. In long-standing cases, that thin chordae usually got ruptured, and myxomatous changes occurred in the prolapsed segment. In forme fruste, more than one leaflet segment involves that affected by myxomatous changes but not involves large valve leaflet area; this differs forme fruste from Barlow's disease. Barlow's disease is the hallmarks of DMVD that involves diffuse myxomatous changes, excessive redundant valve tissue, overall large valve size with thick, elongated, and usually ruptured chordae. Modified from ref. [22].

Assessment and Diagnosis:

Usually, most of MR patients remain asymptomatic for long periods. However, an experienced physician can diagnose MR only by history and physical examination alone [25]. Generally, MR patients present with fatigue decreased exercise capacity, dyspnea, and palpitations, or supraventricular arrhythmias. However, physical signs of severe MR may be found, such as systolic thrill, displaced apical impulse, high-pitched holosystolic murmur radiating from the apex to the axilla, S3, early diastolic rumble, and atrial fibrillation. On chest radiography, left-atrial or ventricular enlargement with cardiomegaly usually found. The electrocardiogram can be normal, or provide some evidence of atrial fibrillation or left atrial enlargement. The presence of features of cor pulmonale or pulmonary hypertension or embolic events may influence directly to the decision of whether or when referring to surgery. However, these features and findings are crucial but not precisely specific enough to decide for surgery.

Echocardiography with Doppler imaging is the recommended modalities for precise evaluation of MV pathology. Transesophageal or Transthoracic echocardiography, both imaging modalities, provides precise anatomical and functional information of MV that is the key for judicious assessment of operability of MV [26,27]. However, transesophageal echocardiography produces a better informative image than transthoracic echocardiography, but its ability to identify more information such as ruptured

chordae, seldom alter treatment plan [26,27]. The vital information that provides by echocardiography is categorized in Table 3. Usually, MR severity is graded as a rank order variable of 1+ trace, 2+ mild, 3+ moderate, and 4+ severe.

An MRI scan useful in the measurement of regurgitation jets, detection of ventricular scars (assessment of the viability of myocardium after ischemic events), and in the measurement of ventricular volumes, but still its diagnostic value remains unevaluated. Hormonal study (Atrial and B-type natriuretic peptide) has little role in the diagnosis of MR. Cardiac catheterization is not used routinely in clinical purposes but seldom performed for academic study for obtaining precise information about hemodynamics.

Table 3: Echocardiographic grading of mitral regurgitation (MR) severity.

Variables	Mild MR	Moderate MR	Severe MR
Angiographic grade	**1+**	**2+**	**3+/4+**
Qualitative variables			
Specific signs	Small central jet <4 cm. or <10% of LA, vena contracta width <0.3 cm, no or minimum flow convergence	MR more than mild, without any criteria for severe MR	Vena contracta width ≥0.7 cm with large central MR jet (area >40% of LA) or with a wall-impinging jet of any size; large flow convergence; systolic reversal in pulmonary veins; prominent flail leaflet or ruptured papillary muscle
Supportive signs	Systolic dominant flow in pulmonary veins; A-wave dominant mitral inflow; low-density doppler MR signal; normal LV size	MR more than mild, but no criteria for severe MR	Dense, triangular doppler MR signal; E-wave dominant mitral inflow (>1.2 m/s); enlarged LV and LA, (particularly with normal LV function)
Quantitative variables			
RVol (ml. per beat)	<30	30-44 45-59	≥60
RF	<30%	30-39% 40-49%	≥50%
ERO area (mm^2)	<20	20-29 30-39	≥40

ERO = Effective Regurgitant Orifice area; LA = Left Atrium; LV = Left Ventricle; MR = Mitral Regurgitation; RF = Regurgitant Fraction; RVol = Regurgitant Volume. Modified from ref. [28].

Natural History of the Disease:

It takes around 15 years from diagnosis of MV prolapse to the onset of clinical symptoms and signs, but left ventricular dysfunction may occur earlier [29]. However, the natural history of organic MR is poorly demonstrated due to lack of severity assessment studies, but some authors reported that a five-year survival rate 30 to 95%, while others reported that long-term survival rate varies widely [29]. In most cases, post-operative death occurs due to heart failure and ventricular arrhythmias. However, mortality is higher in those patients who had left ventricular dysfunction pre-operatively, and this may cause post-operative sudden cardiac death [30].

Timing of Surgery:

In MR patients, medical management is done for the prevention of further progression of the disease. Endocarditis is a catastrophic infectious

event that can cause severe complications and sudden progression of MR. Usually, diuretics offer a temporary reduction of the disease symptoms, but such improvement should not provide reassurance to the physicians. Therefore, a suitable and effective surgical technique for chronic severe MR is often provoked by the onset of symptoms, deterioration of left ventricular function, the onset of atrial fibrillation, severe pulmonary hypertension, or moderate to severe left atrial/ventricular enlargement [31]. Some authors have been suggesting earlier surgical intervention concepts for the past few years. However, controversy remains to continue whether asymptomatic patients with severe MR and standard LV function should undergo elective surgical repair or not [3,32,33]. Recent studies are showing promising outcomes for those patients who underwent early surgical intervention. Besides, some other studies reported that long term survival rate following surgical repair is compromised in patients who had New York Heart Association Class III or IV symptoms [34].

Indication for Surgery:

Several factors determining the indication of surgery for MR cause by DMVD, such as clinical symptoms, left ventricular ejection fraction, pulmonary hypertension, left ventricular end-systolic dimension, and atrial fibrillation [35]. However, after the evaluation of several guidelines provided by world-leading cardiac societies, the summarized indications of surgery are tabulated below (Table 4).

Table 4: Indication of mitral valve surgery

Indication of mitral valve surgery.	
Class I	Acute severe symptomatic MR, chronic severe DMR, and LVEF >30%
	Asymptomatic patients with chronic severe DMR and LV dysfunction (LVEF 30%–60% and/or LVESD ≥40 mm)
	MVR is preferred over replacement for patients with chronic severe DMR limited to the posterior leaflet
	MVR is recommended over replacement for patients with chronic severe DMR involving the anterior leaflet or both leaflets when a successful and durable repair can be accomplished
	Concomitant MV repair or replacement is indicated in patients with chronic severe DMR undergoing cardiac surgery for other indications
Class II	MVR is reasonable in asymptomatic patients with chronic severe DMR with preserved LV function (LVEF >60% and LVESD <40 mm) in whom the likelihood of a successful and durable repair without residual MR is >95% with an expected mortality rate of <1% when performed at a Heart Valve Center of Excellence. Also, severe MS if PAP >60mmHg.
	MVR is reasonable for asymptomatic patients with chronic severe DMR and preserved LV function in whom there is a high likelihood of a successful and durable repair with (1) new onset of AF or (2) resting pulmonary hypertension (systolic PAP >50 mmHg)
	Concomitant MVR is reasonable in patients with chronic moderate DMR undergoing cardiac surgery for other indications.
	MV surgery may be considered in symptomatic patients with chronic severe primary MR and LVEF ≤30%
	Transcatheter MVR may be considered for severely symptomatic patients (NYHA class III/IV) with chronic severe primary MR who have a reasonable life expectancy but a prohibitive surgical risk because of severe comorbidities
Class III	Chronic severe MR due to severe LV dysfunction despite optimum medical therapy + biventricular pacing.
	MVR should not be performed for treatment of isolated severe primary MR limited to less than one half of the posterior leaflet unless MVR has been attempted and was unsuccessful

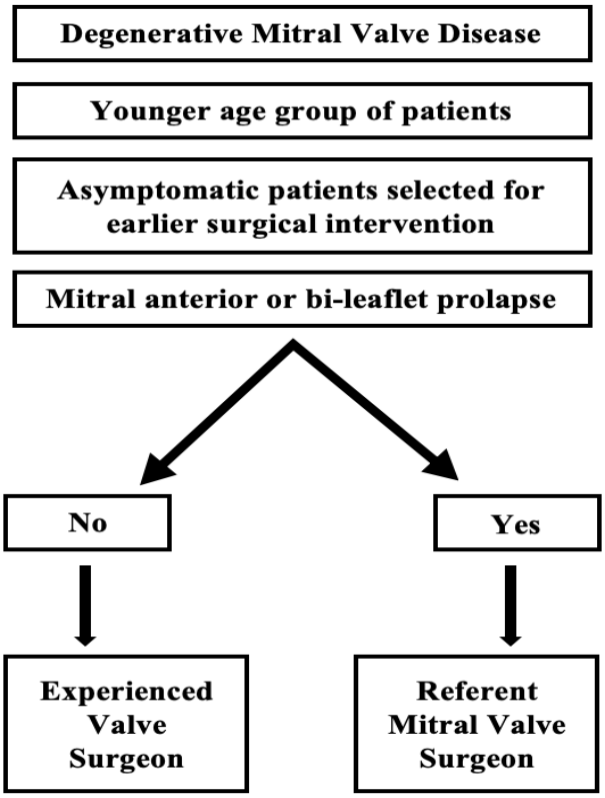
MR = Mitral regurgitation; DMR = Degenerative mitral regurgitation; LV = Left ventricle; LVEF = Left ventricular ejection fraction; LVESD = Left ventricular end systolic dimension; MVR = Mitral valve repair; MV = Mitral valve; MS = Mitral stenosis; PAP = Pulmonary artery pressure; AF = Atrial fibrillation; NYHA = New York Heart Association. Modified form ref. [35,36].

Who should operate?

It is now globally recognized that the DMVD patients who underwent MV repair will have a better long-term clinical outcome with fewer complications as compared to MV replacement [37]. The sub-optimal outcome of MV replacement is due to morbidity associated with the prosthesis, higher re-intervention rates, and life-long

anticoagulation intake. Regrettably, still in developed countries, MV replacement remains frequent (around 50%) for DMVD [4]. However, many recent studies report that the MV replacement rate in the highest of 90% in highly developed hospitals [5]. Nowadays, it is strictly recommended for referring selected patients to those cardiac surgeons who experienced in performing MV repair [35]. Besides, DMVD patients are usually younger, so that they are likely to get the best benefit from MV repair. Therefore, they should get referred to an MV "referent surgeon" [38]. The precise identification of MVP (anterior, posterior, or bi-leaflet) is also crucial because it significantly reduces the rate of MV replacement [38]. By considering all this information, a recommendation is formulated for DMVD patients (Table 5).

Table 5: Targeted surgeon referral recommendation for degenerative mitral valve disease patients. Modified from ref. [22].



Surgical Techniques for DMVD:

Significant improvement was noticed over the last 45 years in the history of MVS since Carpentier demonstrated the "Golden Rules" into three basic tenets: preserve leaflet mobility, restore a large coaptation surface, and remodel the annulus [39]. Still, those tenets remain key to successful MV repair because these tenets allow MV reconstruction in almost all patients with MR caused by DMVD. However, meticulous systemic evaluation of MV and the exact mechanism of MR by intraoperative transesophageal echocardiography; thereafter MV repair by the implementation of standard approach is mandatory. Notwithstanding, saline testing just after valve repair and post-cardiopulmonary bypass transesophageal echocardiography for checking any remaining regurgitation is crucial for successful completion of MV repair surgery.

Current Surgical Access Strategies:

Traditionally, MVS is performed through a 15-20cm skin incision with full median sternotomy. Nowadays, other minimal invasive techniques such as right lateral minithoracotomy with or without video assistance and partial sternotomy with small skin incision (8-10cm) are successfully practiced in many advanced centers [5,40]. These minimally invasive approaches provide cosmetic satisfaction of patients, early recovery, and need less blood transfusion. Recently, the utterly endoscopic MV repair technique (with or without robotic assistance) successfully performed in some advanced centers, and that has significantly

improved in the last few years [41]. In 2002, the Federal Drug Administration approved the Da Vinci intra-cardiac surgical System in the United States, and currently, it is the only robotic surgical system approved for MVS. Because of its higher costs, long learning curve, and undocumented clinical advantage, the adoption rate of the robotic system is tardy. Despite these difficulties, some advance centers of developed countries adopted this in their MV repair armamentarium.

Usually, cardiopulmonary bypass is achieved by direct aortic and bi-caval cannulation for full sternotomy; but for minimally invasive techniques, peripheral cannulation (femoral artery and vein) are used. The MV exposure is obtained by a trans-atrial septal incision (through the right atrium, when concomitant tricuspid valve intervention is needed), a direct left atriotomy through Waterstone's or Sondergaard's groove, an incision at the roof of the left atrium (superior approach) or no atriotomy (transaortic and transventricular). However, intraoperative assessment and MV analysis are carried out by transesophageal echocardiography.

Mitral Valve Repair:

Carpentier first describes the MV repair procedure, till now that procedure followed globally by surgeons. Over time, several new concepts added with that procedure, such as edge-to-edge repair technique, repair by artificial neochordae. Nowadays, around 90% of DMVD can be surgically amenable by these procedures. However, the basic aim of MV repair is obtaining 5-8 mm long good leaflets coaptation line. Therefore, detection of exact MV pathology by echocardiography is crucial.

In contemporary MV repair practice, two important tenets emerged. Carpentier's procedure includes resection of pathologic or redundant tissue with meticulous repair to restore 'normal valve anatomy,' and it remains the most practiced globally due to better long-term results. However, another comparatively new tenets "respect rather than resect tissue" get popularity, which includes the repair MV using polytetrafluoroethylene (PTFE) neochordae. The early clinical outcomes of this procedure are promising and need no or subtle tissue resection with PTFE loops; that is why it is now the most practiced procedure in many centers today.

The Posterior leaflet prolapse: The posterior (P2) is the most prolapsed segment that causes MR frequently. Therefore, triangular resection (Figure 4: A) is recommended for small segment prolapse of flail and quadrangular resection (Figure 4: B) is recommended for relatively large segment prolapse, followed by annular plication of the base of the resected segment and posterior leaflet for approximation is used (Figure 4: C and D). If there is the danger of postoperative systolic anterior motion (SAM) of the anterior leaflet by excessive leaflet tissue, then sliding and folding valvoplasty is recommended. However, for diseased chordae (rupture, thickening or shortening), chordal replacement ("respect rather than resect" approach) with a polytetrafluoroethylene (PTFE) suture is a popular procedure. Nowadays, different sizer/technique available that can detect the exact size of the PTFE neochordae loop. Recently, premeasured modified artificial chordae introduced and widely accepted for "respect rather than resect" approach, especially for MV repair through a minithoracotomy.

The Anterior leaflet prolapse: Mitral anterior leaflet prolapse reconstruction is more complicated than a posterior leaflet. However, some procedures evolved to correct this anterior leaflet prolapse. *The chordal transfer* involves resection a secondary chord from its insertion, thereafter reattached to the anterior leaflet margin with 5/0 prolene suture. *Chordal transposition* involves the transfer of a native chordae from the posterior leaflet to the anterior leaflet for repairing a leaflet prolapsed segment if that occurs due to chordal rupture or elongation. *Papillary muscle repositioning* involves separating the anterior head of the papillary muscle from the other heads with putting a stitch in the fibrous segment of the anterior head and tying it to the fibrous segment of the posterior head. *Implantation of artificial chordae* is now a widely used technique for the correction of anterior leaflet prolapse. Sometimes, an edge-to-edge (double or triple orifice) technique is needed for the correction of anterior leaflet or bi-leaflet prolapse in DMVD patients [42].

In DMVD patient's calcification of the annulus, leaflets, chordae, papillary muscles can befall [43]. Therefore, for the restoration of normal mobility of leaflets, debridement of calcification is recommended. Calcification can be diffuse; it is prudent to respect that part and pledged suture from the ventricular side. Occasionally, an 'en bloc' resection of the calcium bar in the annulus is

needed for decoupling the atrioventricular groove [43].

Annuloplasty is typically recommended for all cases regardless of which technique applied for valve or chord repair. This procedure includes a prosthetic band or ring that restores the typical saddle-shaped circumference of the MV (Figure 4: E and H) [39,44]. Most of the surgeons measure the anterior leaflet with sizer to calculate the annular prosthesis size. Several kinds of the mitral annular prosthesis (rigid, semi-rigid, flexible, complete ring, partial posterior band) are currently available. However, a significant predictor of MV repair failure is unable to perform annuloplasty, and that frequently causes recurrent MR.

Mitral Valve replacement:

Nowadays, MV replacement for DMVD is not primarily recommended since the precise evolution of MV repair approaches. The long-term clinical outcome of MV repair is way better than MV replacement in many ways, such as better post-operative ventricular function, avoidance of anticoagulation, lesser risk of endocarditis, free from a foreign body (prosthesis) related hazard. Lee and colleagues demonstrated a 12% survival advantage at six years of MV repair over MV replacement, but the significant benefit was the reduction of heart-failure related mortality [45]. However, in end-stage and long-standing cases of DMVD that is usually seen in geriatric patients, MV replacement generally recommended. These cases are found sporadically and categorized as Class I indication for surgery. Currently, a valve with the chordae sparring approach (without resection of papillary-valve-annular continuity) is recommended during MV replacement [14]. If the calcified segment detected, it is necessary to resect that part rest part should incorporate with prosthesis annulus by sutures.

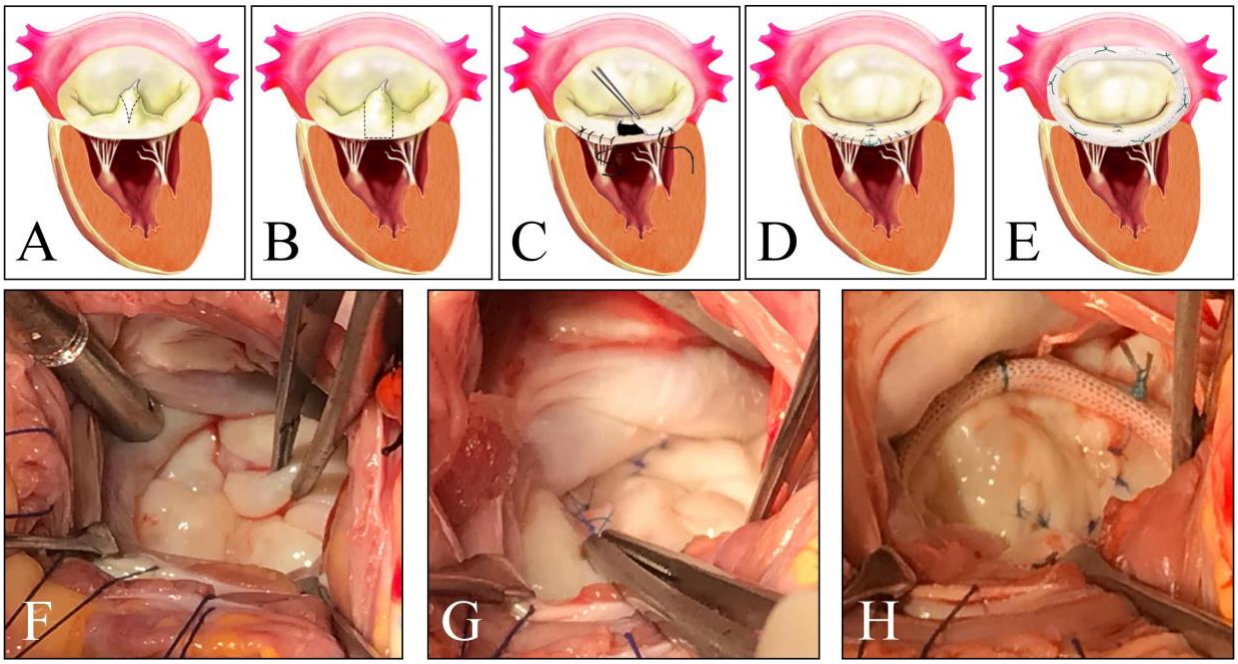


Figure4: Mitral valve repair. Panel A-E: illustrative image (A) Triangular resection of P2 (posterior middle scallop) prolapse. (B) Quadrangular resection of P2 (posterior middle scallop) prolapse. (C) Reconstructed leaflet after leaflet resection. (D) Completed repair after resection. (E) Ring annuloplasty; Panel F-H: intraoperative image (F) Thickened and excessive leaflet tissue. (G) After completion of resection and reconstruction. (H) Completed mitral valve repair after ring annuloplasty.

Clinical outcome following mitral valve Surgery:

MV repair is the better treatment option when compared to MV replacement in DMVD patients. It provides better long-term survival with low morbidity and very low perioperative mortality (<1%). The 15-year freedom from re-operation is 95% in the case of MV repair [46]. However, the

leading causes of death after MVS are heart failure, stroke, arrhythmia, and endocarditis. If the surgery can be performed before the onset of symptoms and LV dysfunction (ejection fraction ≥60%), the outcome is comparable to the healthy population. The postoperative outcome is being compromised if surgery performed when ejection fraction <60%. The post-operative mild residual MR is the significant predictor of procedure failure. After the evaluation of some influential studies of long-term follow-up of MVS, the summary of the results is tabulated in table 6 [5,46-49]. Many authors' long-term outcomes measured based on the freedom from reoperation, but it is not always accurate. However, MR due to posterior leaflet prolapse provides better long-term outcomes than MR due to anterior or bi-leaflet prolapse after surgery [46-49]. Surgical referral for MV repair due to atrial fibrillation is controversial, but if present while performing surgery, it prudent to perform Maze procedure using radiofrequency or cryotherapy for correction of atrial fibrillation. However, the number of MV repair cases is increasing globally because of the advent of surgical expertise, along with medical technology. Despite that, some conditions such as extensive valve prolapse, annular calcification, prolapse with hypoplasia of the opposite leaflet, and extreme fibroelastic deficiency need to correct using surgical replacement; in the long-run, it provides better clinical outcome with low operative mortality and morbidity.

Table6. Outcomes of mitral valve repair.

Variables Study year/ patients' number	**Mean Age (years)**	**Mean follow-up (years)**	**30-days mortality**	**Freedom From CI MR≥3**	**Freedom from CI REDO**	**Overall survival**
Braumberger E 2001/162 [46]	56±10	17 (1-29)	1.9%	-	PL-96.9% AL-86.2% BL-82.6% at 20 years	48% at 20 years
Seeburger J 2008/1339 [5]	60±12.7	2.34±2	2.4%	-	96.3% at 5 years	82.6% at 5 years
Di Bardino DJ 2010/1042 [47]	60±13	-	0.6%	-	82% at 20 years	62% at 20 years
David TE 2013/606 [48]	56±13.3	10±4.5	0.8%	67.5 ±4.2% at 18 years	90.2 ±2.4% at 18 years	66.8 ±3.3% at 18 years
Suri RM 2016/1218 [49]	64±13	11.5 (9.2-13.6)	-	13.3 ±1.2% at 15 years	6.9 ±1% at 15 years	-

CI = Cumulative incidence; MR = Mitral regurgitation; AL = Anterior Leaflet; PL = Posterior leaflet; BL = Both leaflets.

Prospects

At present days, due to the higher prevalence of non-communicable life-threating diseases such as coronary artery disease, diabetes, kidney disease, etc., a large number of advance aged MR patients are surgically inoperable as they have comorbidities; thus, considered as a high-risk surgical group [50]. Recently, some authors reported percutaneous transcatheter transseptal MV repair by MitraClip (edge-to-edge) and MV replacement [51,52]. However, the clinical benefit of this technique is suboptimal, and long-term clinical benefit is not well documented. Additionally, this technique is associated with a higher rate of repeat intervention compare to surgical MV repair [51].

Very recently, some other authors reported trans-apical off-pump MV repair with expanded PTEE (ePTFE) chordal implantation for the treatment of leaflet prolapse in DMVD [53,54]. This technique is performed through the cardiac apex with a small anterolateral left thoracotomy (4^{th} or 5^{th} intercostal space). At present, Neochordae DS1000 and Harpoon system, these two devices available for this technique [53,54]. The early post-intervention outcome of this technique is promising. However, a long-term follow-up study is mandatory before the comprehensive implementation of this "micro-invasive" beating heart technique. Nonetheless, careful selection of eligible patients for these techniques is the main challenge and crucial for

successful clinical outcomes.

Conclusion:

MV repair in DMVD remains an under practiced procedure globally. However, precise early diagnosis in younger aged asymptomatic patients would be crucial for them to get early referred to the MV experienced surgeon. Admittedly, these will significantly improve the postoperative clinical outcome. Besides, the minimal invasive MV repair techniques still need more evolution to fit for very severe MR patients with serious comorbidities, who are currently recognized as surgically unfit. Nonetheless, post-operative long-term follow-up study is pivotal.

Declarations:

Competing interests

The authors declare that none of them have competing interests concerning the authorship, research, and/or publication of this article.

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