Published in final edited form as:
Can J Cardiol. 2014 September ; 30(9): 971–981. doi:10.1016/j.cjca.2014.06.022.

Basic Mechanisms of Mitral Regurgitation

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Abstract

Any structural or functional impairment of the mitral valve (MV) apparatus that exhausts MV tissue redundancy available for leaflet coaptation will result in mitral regurgitation (MR). The mechanism responsible for MV malcoaptation and MR can be dysfunction or structural change of the left ventricle, the papillary muscles, the chordae tendineae, the mitral annulus and the MV leaflets. The rationale for MV treatment depends on the MR mechanism and therefore it is essential to identify and understand normal and abnormal MV and MV apparatus function.

Keywords

mitral regurgitation; mitral valve; mitral annulus; papillary muscles; chordae tendineae

Introduction

Normal mitral valve (MV) function is dependent on the integrity of the MV apparatus and the harmonious interplay of its main components - the mitral annulus (MA), the MV leaflets, the chordae tendineae, and the LV wall with its attached papillary muscles (PMs) (Figure 1 A, B). This spatially and temporally finely tuned system maintains the MV leaflets within the LV preventing prolapse, and maintains them beneath LV outflow tract (LVOT) flow and taut, preventing systolic anterior motion (SAM). Adequate MV leaflet closure and

Correspondence to: Robert A. Levine.

Financial Disclosure: The authors have nothing to disclose.

All authors have participated in the work and have reviewed and agree with the content of the article.

coaptation depend on the balance of systolic leaflet tethering vs LV closing forces and leaflet size [1]. Tethering forces are dependent on and transmitted via the LV wall - PM - chordae system, and closing forces reflect the pressure generated by the contracting LV [2–4] (Figure 1A). MV dysfunction is relatively uncommon in patients younger than 65 years [5], but structural and / or functional impairment of any MV apparatus components can unsettle the tethering force - closing force balance and result in mitral regurgitation (MR) [2–4].

Mitral Valve Apparatus

The MV has anterior and posterior leaflets and variable commissural scallops. The leaflet bases circumferentially insert into the mitral annulus, and the ventricular leaflet body and edges are connected to the PMs and LV wall via chordae (Figure 1B, C). The leaflet cross sectional structure is trilaminar and each layer's extracellular matrix (ECM) has unique characteristics and biomechanical properties important to the normal function of the MV. On the atrial side, the atrialis layer is rich in subendothelial elastic proteins that buffer leaflet stretch during systole. The atrialis is covered by endotheliumin continuum with the LA. Towards the leaflet core, the spongiosa layer contains hydrophilic proteins that act as cushion-like coaptation zone shock absorbers and therefore promote a tight MV seal. Facing the ventricular side, the fibrosa / ventricularis layer is characterized by a sub-endothelial collagen fiber network aligned to transmit and spread the LV closure / chordal force optimally towards the mitral annulus. Valve interstitial cells can be found in all layers and have an important role in maintaining leaflet homeostasis. Mostly quiescent in the normal adult leaflets, these interstitial cells can become activated in response to mechanical stress or injury to promote ECM remodeling [6]. The anterior leaflet is larger (4–7 vs 2–3 cm^2), longer (18–24 vs 11–14 mm) and usually thicker than the posterior leaflet and is trapezoid / dome-shaped [7–12]. It shares a rigid fibrous tissue continuity with the noncoronary cusp of the aortic valve (Figure 1 B, C). The posterior leaflet is crescentic-shaped with short radial length [12] and a long circumferential base that is attached to the posterior MA (Figure 1 B, C). The MA is a non-planar saddle shaped tissue structure that interconnects the LA, the LV and the mitral leaflets [13, 14] (Figure 1 B, C; Figure 2 A). The MA is innervated and supplies blood vessels and nerve fibers to the attached leaflet bases [15, 16]. The anterior portion of the MA is continuous with the rigid aortic annulus and is the elevated (most atrial) "horn" of the saddle shape [13, 17] (Figure 2 A). The posterior MA includes the low points of the saddle (most ventricular), close to the lateral and medial commissures and the posterior saddle horn (Figure 2 A). The average MA area in healthy subjects is ~10 cm^2 [10, 18–21]. The flexible posterior MA allows for systolic apical bending along a commissural axis [17, 22]. This mechanism, in combination with the planar kidney-bean and horizontal saddle-shape configuration allows the MA to sphincter-like shrink in area by ~ 20 – 42% from diastole to systole [19–21, 23, 24], which reduces leaflet tissue stress and is important to maintain coaptation (Figure 2 B, C) [25–30]. The chordae tendineae originate from the PM heads and are fibrous strings composed of an interfacing, tightly linked collagen and elastin network. They insert fan5 like into the anterior, posterior and commissural leaflets and dampen the PM - leaflet force transmission (Figure 1 B) [31, 32]. Chordae can be distinguished by leaflet location insertion as primary and secondary. Primary (marginal)

chordae attach to the leaflet free edges, are thinner and have limited extensibility due to higher collagen fibril density and reduced crimping [33]. These characteristics ensure a stable systolic coaptation location. Secondary (basal) chordae insert into the central anterior and posterior leaflet bodies [34] are thicker and have more tightly crimped collagen that makes them more extensible [33]. The PMs are labeled by their projected relationship to the mitral commissures as lateral and medial [11] (Figure 1 B, C). Their bodies originate from the apical 1/3 of the LV and protrude finger-like into the cavity [35] (Figure 1 A, B; Figure 3). In the majority of cases the lateral PM has a single head and dual blood supply from the left circumflex and left anterior descending coronary arteries. The medial PM has commonly 2 heads and is either supplied by the right or circumflex coronary artery based on dominance [8, 11, 36]. PM contraction maintains the spatial relationship between the MA and the PM heads during systole and prevents leaflet prolapse [37–39].

Mitral Regurgitation Mechanism

MR develops if the MV leaflets do not sufficiently cover the MA orifice throughout LV systole, and is commonly classified as primary MR - indicating leaflet pathology - or secondary MR in the setting of LV myocardial pathology. MR can also be functionally classified based on MV leaflet pliability and motion (Carpentier Classification) [40, 41]. To facilitate medical communication, MV leaflet malcoaptation and MR jet origin are commonly indicated by anterior (A) or posterior (P) leaflet and lateral (A1 / P1), central (A2 / P2) or medial scallop location (A3 / A3) [31] (Figure 1 C).

It is important to understand that significant MR regardless of etiology can prompt independent and ongoing LV and MV apparatus remodeling and start a vicious circle whereby reactive remodeling contributes to MR [4, 10, 42]. An example is MA dilatation and dysfunction, which is rarely a primary cause for MR, but much more commonly a consequence of other MV or LV diseases. Significant MR is uncommon if the MV leaflet - MA area ratio is larger than ~1.5 – 2 [8, 10], but this ratio is in jeopardy once the MA dilates and loses its saddle shape and sphincter function [10, 19, 21, 24, 43]. MA remodeling additionally increases leaflet stress [25–30, 44]. MA flattening has also been described in myxomatous MV disease, associated with more severe MR and chordal rupture, potentially related to increased out-of-plane stresses [30, 45, 46]. MA remodeling has also been recently reported in patients with atrial fibrillation and MR, termed atrial functional MR [47, 48].

Primary Mitral Regurgitation

1) Chordal Rupture / Papillary Muscle Rupture

Elongation or rupture of marginal chordae due to degenerative tissue abnormalities, iatrogen, or endocarditis almost always lead to significant MR due to leaflet edge eversion (=flail leaflet; Figure 3 A) [49]. Secondary chordae rarely rupture, and due to their leaflet body insertion, are not critical to maintain coaptation. To the contrary, cutting secondary chordae is a strategy to potentially treat secondary MR when chordal tethering restricts coaptation (please see below). Due to its single coronary artery supply, the medial PM is at higher risk to necrose and rupture in myocardial ischemia and infarction.

Treatment strategies—Chordal or PM rupture almost always results in flail leaflets and acute severe MR, with intermediate MR degrees with isolated rupture of structurally less important chords or an individual PM tip rather than a full head. Acute severe MR is a medical catastrophe that in the majority of patients leads to flash pulmonary edema and cardiogenic shock. The underlying etiology determines the mortality, which is up to 55% in patients presenting with acute MI [50]. Nonischemic chordal rupture in the setting of degenerative MV disease or endocarditis has a lower mortality rate, and the clinical presentation may be less dramatic if there was antecent MR and the LV and LA have adapted to MR hemodynamics. Since the underlying problem of acute severe MR is mechanical, surgical MV repair or replacement are the only sustainable treatment options. Pre- and afterload-reducing medical and interventional therapies (e.g. percutaneous LV assist device, Intra-aortic balloon pump) can be used as a bridge to potential surgical MV leaflet coaptation restoration. Transcatheter MV repair with a MitraClip (Abbott Laboratories, Abbott Park, Illinois) may become an alternative to openheart surgery if leaflet anatomy and underlying MR etiology are suitable and the risks for open-heart surgery prohibitive [51].

2) Mitral Valve Prolapse

Mitral valve prolapse (MVP) is defined as anterior, posterior or bileaflet MV billowing toward the left atrium by more than 2mm above the anterior and posterior MA horns during LV systole, and affects about 2.5% of the general population [52, 53]. MV coaptation geometry is altered due to a combination of leaflet and chordal extensibility, redundancy and elongation, potentially combined with MA flattening and enlargement [30, 45, 46]; whether superior PM displacement or traction is cause or effect of prolapse is unclear [54, 55]. MR severity depends on the degree of leaflet malcoaptation; it can range from trace to severe and increases over time [56]. MVP is usually a manifestation of degenerative MV disease, and as such resulting MR is often termed degenerative MR (DMR). MVP is characterized by mainly two leaflet pathologies that have been described in the literature, although it is not known whether they are discrete etiologies or parts of a continuum: In the first, termed “Barlow’s disease”, the billowing leaflets are diffusely thickened, redundant and discolored. Bi-leaflet prolapse is common and patients tend to need MV intervention by age 50. Barlow leaflets are characterized by an altered trilaminar architecture, abnormal accumulation of myxomatous ECM, disordered collagen and elastin fibers and activated interstitial cells that express excessive levels of catabolic enzymes [57]. The other reported MVP phenotype is called “Fibroelastic deficiency” (FED) [12], in which the MV is in general thin to lucid except in flail leaflet portions, which may be due to secondary changes triggered by turbulent MR flow [58]. Patients with FED commonly present with ruptured chords and a variably flail posterior leaflet in their 6^{th} decade. FED leaflets are deficient in collagen, elastin and proteoglycans. MVP is associated with connective tissue syndromes, in particular collagen mutations (e.g. Ehlers-Danlos, Osteogenesis imperfecta) and Marfan syndrome, in which current knowledge suggests that abnormal fibrillin-1 leads to overexpression of transforming growth factor beta (TGF-β), an important regulator of MV leaflet ECM formation and remodeling [59, 60]. Similar valve abnormalities can be seen in patients with mutation of TGF-β receptors (Loeys-Dietz syndrome) [61]. Nonsyndromic MVP can be sporadic or familial, and appears to be transmitted via various genetic pathways and

penetrance. Family MVP studies have suggested an autosomal dominant transmission and identified specific chromosomes [62–64]. Studies of X-linked forms of myxomatous valve disorders have revealed FLNA gene mutations [65, 66] that result in impaired filamin A, a protein vital to normal actin cytoskeleton structure and function that protects cells from mechanical stress [67].

Treatment strategies—Hemodynamically significant DMR is commonly considered to be at least moderate to severe, and lesser MR - unless in patients in need for open-heart surgery for other reasons – is usually clinically monitored and followed. Significant DMR is a mechanical problem of leaflet malcoaptation, and unless as a bridge to surgery or in inoperable patients, medical therapy has a rather limited role with poor long-term outcome (up to 8% yearly mortality; up to 10% yearly morbidity; up to 90% chance of need for surgery / death over 10 years) [68–70]. Surgical or transcatheter MV interventions on the other hand aim to restore effective MV leaflet coaptation by reducing leaflet redundancy, MA dimensions, and if needed, implanting artificial neo-chordae to restrain leaflet excursion. Suitable leaflet characteristics may allow leaflet free edge approximation at the MR site (edge-to-edge technique) by a stich (Alfieri stitch) [71] or a clip (MitraClip) [51]. Repair techniques aim to restore leaflet function while preserving the native valve and mechanical or tissue MV replacement is rarely needed in patients with MVP and a skilled surgeon [40]. Improving the natural history of chronic degenerative significant MR hinges on intervening at a time point that maximizes patient survival and minimizes disease and intervention morbidity. The evidence base supporting such an optimal intervention time-point in chronic significant DMR is unfortunately, however, imperfect due to a lack of randomized and prospective studies. Currently, the AHA / ACC Valvular Heart Disease guidelines recommend that patients with symptomatic severe DMR (with a LV ejection fraction (LVEF) > 30%) as well as asymptomatic patients who have an LVEF ≤ 60% or an LV end-systolic LV chamber dilatated ≥40mm should have MV surgery with emphasis on MV repair of either the anterior or posterior leaflet when possible and durable as opposed to MV replacement (Class I Level B) [72]. This approach has been criticized for intervening too late, as patients with significant symptoms and LV dysfunction have worse postoperative outcome in terms of mortality and durability of MV repair [73]. Class IIa Level B MV surgery recommendations are for asymptomatic patients with severe DMR with 1) new onset of atrial fibrillation or 2) resting pulmonary hypertension >50 mmHg as long as there is a high likelihood of a successful and durable MV repair. An important and Class IIa Level B recommendation is to consider MV surgery in asymptomatic patients with severe DMR with preserved LV function and dimensions 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 [72]. This approach is supported by the progressive and dire natural history of chronic severe DMR when treated medically and decreased postoperative survival once significant symptoms or LV dysfunction develop [70, 73]. The long-term success of this strategy that ultimately restores life expectancy to normal is, however, absolutely dependent on a predictable, successful and durable MV repair [74, 75]; it is also worthwhile to point out that mainly patients over the age of 50 seem to benefit [75]. A recent guideline addition was the consideration of transcatheter MV repair in

severely symptomatic patients with chronic severe DMR but prohibitive surgical risks and a reasonable life expectancy (the only FDA approved approach is the MitraClip) [72].

Besides surgical techniques, the routine intra-op MV surgical use of transesophageal echocardiography (TEE) has contributed significantly to predicting, guiding and assessing successful MV repair: TEE imaging can determine MV annuloplasty ring size by measuring the anterior leaflet length and required neo-chord lengths, which is especially helpful in less invasive MV repair [76]. TEE can predict post MV repair development of systolic anterior motion (SAM, see below) based on LV cavity size <45mm in end-diastole, aorto-mitral angle <120 degrees, MV leaflet coaptation-septum distance <25 mm, posterior leaflet height >15 mm and basal septal diameter ≥ 15 mm [77, 78]. Transcatheter MV repair with a MitraClip would be close to impossible without TEE guidance.

3) Leaflet Perforation

Anterior or posterior MV leaflet perforation can be the result of trauma, but is most commonly due to localized tissue destruction from endocarditis. Besides primary MV endocarditis, AV endocarditis can directly extend towards the anterior MV leaflet via the anatomically shared fibrous trigone (Figure 1C) or be transmitted via the AV regurgitation blood jet.

Treatment strategies—Depending on the size and location of the MV leaflet perforation, potential endocarditis extent, and overall clinical presentation, such tissue defects can be closed with a pericardial patch.

Secondary Mitral Regurgitation

Functional or ischemic MR is the result of systolic leaflet restriction and tethering to displaced PMs in the setting of a distorted, remodeled LV (Figure 3 B). LV remodeling can be global, with LV dilatation and increased sphericity [3, 79–82], or localized, affecting mainly the PM - bearing LV walls [83]. LV remodeling that leads to outward apical / posterior / posterolateral PM displacement (Figure 3 B) [83–88] will increase the systolic PM heads - MA distance [89–92], which restricts MV leaflet closure motion and increases tethering forces. Leaflet coaptation is impaired and MR results [93]. In secondary MR, the MV leaflets are classically considered normal and to be innocent bystanders. Recent investigations, however, show significant MV leaflet tissue changes and adaptation [4, 10, 94–98]. Indeed, active leaflet growth and enlargement can occur in reaction to mechanical stretch, sometimes matching even severe LV dilatation to prevent secondary MR [4, 10, 42, 98, 99]. Reactivation of embryonic growth processes such as endothelial-to-mesenchymal transformation and mild TGF-β expression in response to mechanical stretch have been shown in-vitro [100] and in-vivo in tethered leaflets [42]. Insufficient leaflet growth in the setting of heart failure is however frequent and secondary MR remains common. Preliminary data recently showed that excessive leaflet thickening can occur after myocardial infarction and is associated with subsequent MR [101], which is in accordance with previous work suggesting the presence of adverse fibrotic leaflet changes in secondary MR. These changes include abnormal matrix composition, increased collagen concentration and turnover and activation of valvular interstitial cells leading to stiffer valves, potentially

impairing coaptation and contributing to MR [96, 97, 102]. These observations are currently challenging leaflet “normality” in secondary MR.

Treatment strategies

The aim of significant secondary MR therapy is to reduce apical and mitral annular leaflet tethering to restore MV leaflet tissue redundancy for effective MV coaptation. Every effort should be made to improve LV function by optimally treating coronary artery disease (medically / revascularization) [103–105], and cardiomyopathy and heart failure medically, if indicated by cardiac resynchronization therapy [106, 107] and potentially by gene / cell therapy [108–111]. Acknowledging the limited evidence, the current AHA / ACC Valvular Heart Disease guidelines recommend that MV surgery is reasonable in patients with chronic severe secondary MR who are undergoing coronary artery bypass grafting or aortic valve replacement (Class IIa Level C); MV surgery may be considered for severely symptomatic patients with chronic severe secondary MR (Class IIa Level B); MV repair may be considered for patients with chronic moderate secondary MR who are undergoing other cardiac surgery (Class IIa Level C) [72]. Surgical techniques besides current mitral annulus area reduction and / or MV repair / replacement [112] may target PM repositioning by addressing the LV shape [113–115], isolated PM approximation [116], chordal cutting [117–120] and MV leaflet edge-to-edge approximation technique [71]. Therapy strategies that deal with the MV annulus alone but not apical leaflet tethering are often limited and result in recurrent MR [112, 121–124]; leaflet tethering can additionally be reduced, for example by cutting selected secondary chordae without deleterious effects on LV function [118–120, 125]. Transcatheter MV repair in symptomatic, at least moderate to severe secondary MR patients is currently studied in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) Trial. Although therapeutic strategies promoting compensatory MV leaflet growth with minimal fibrosis would be of interest, factors underlying valve tissue adaptation and remodeling are still poorly understood at this time.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is morphologically characterized by significant LV hypertrophy in the absence of chronically elevated afterload or infiltrative diseases (e.g. cardiac amyloidosis) (Figure 3 C double-arrow) [126]. In HCM, total PM muscle mass is doubled and the number of heads increased [127]. The PMs are anteriorly displaced (Figure 3 C arrow) and the heads closer to each other [128, 129], which increases MV leaflet slack and positions the leaflets closer towards the LVOT. Larger and elongated MV leaflets additionally contribute to leaflet slack [9, 130]. This PM – MV constellation favors a MV coaptation location more anteriorly and closer to the LVOT, which predisposes the anterior leaflet to being pushed into the LVOT by blood-flow drag forces (=systolic anterior motion (SAM)) [129, 131–135]. Subsequent LVOT narrowing increases the blood flow velocity above the leaflet and propagates SAM through airplane-like lift forces [136, 137]. MR will develop once anterior leaflet displacement interferes with MV leaflet coaptation (Figure 3 C red lines) [138]. Frequent MV and PM anomalies predispose to SAM [139]. Mechanisms leading to leaflet growth in HCM are still poorly understood; paracrine effects coming from

the abnormal myocardium, or mechanically induced growth secondary to turbulent or increased shear flow have been suggested; direct effects of gene defects / mutation on sarcomeric proteins are less likely as they do not appear to be expressed in the bulk of leaflet tissue [140].

Treatment Strategies

Since PM position is a major culprit, surgical or interventional septal reduction therapy does not always eliminate SAM [141, 142]. Additional effective repair strategies can include partial LV wall detachment of atypical anteriorly displaced PM insertions and trimming PM muscle mass [143], along with leaflet redundancy reduction, such as by an Alfieri stitch [144] or MitraClip [145].

Rheumatic Heart Disease

Rheumatic heart disease (RHD) can develop when T- & B- cell guided autoimmune response triggered by an untreated streptococcus pharyngitis mistargets heart tissue (molecular mimicry) [146]. Streptococcal carbohydrate-directed antibodies recognize cardiac myosin and also target heart valve endothelium via the protein laminin. This prompts a local inflammatory response and exposure of collagen with development of autoantibodies against exposed collagen. Endothelial expression of vascular cell adhesion molecule-1 (VCAM-1) drives further immune cell leaflet infiltration. The accumulating cocktail of inflammatory cells and cytokines promotes a vicious cycle of valvular interstitial cell activation, fibrotic leaflet remodeling and interstitial neovascularization [146]. Significant MR is the predominant valvular pathology during the initial phase of rheumatic fever and carditis. The MR mechanism is anterior leaflet prolapse due chordal elongation and MA annular dilatation [147, 148]. In the initial disease phase the MV leaflets appear normal, which is in stark contrast to advanced rheumatic heart disease, in which leaflet fibrosis, thickening and commissural fusion predominate. These MV changes restrict systolic and diastolic leaflet mobility and result in mitral stenosis (MS) and / or MR [148].

Treatment Strategies

Acute rheumatic MR treatment is similar to MVP patients and MV repair the goal whenever possible. Treatment of later rheumatic heart disease stages and combined MS and MR oftentimes requires MV replacement [149].

Future Directions

Cardiovascular imaging advancements in MR quantification and LV function and structure assessment will be critical to refine the optimal time point of therapeutic MV intervention, which will no doubt further develop towards less invasive and transcatheter MV repair options. Ongoing genetic studies will lead to improved understanding of the mechanisms underlying and promoting primary MV disease. Such knowledge could allow to identify patients at risk without yet established MV disease and may open a therapeutic time window to medically prevent or limit degenerative / myxomatous leaflet remodeling. Mechanistic studies in secondary MV disease will likewise explore associated leaflet changes on a cellular and tissue level to identify therapies that maintain and promote leaflet function and

thereby reduce adverse outcomes. Significant MR related to LV dysfunction might also conceivably be rescued and its development limited by future directed cell / gene therapies targeting the myocardium.

Summary

Normal anatomy and function of the LV, papillary muscles, chordae, mitral annulus and leaflets ensures effective leaflet coaptation and prevents leaflet tethering, prolapse and LVOT obstruction. Any temporal and spatial impairment of leaflet coaptation that exhausts leaflet redundancy may result in mitral regurgitation. Apical – annular leaflet tethering with restricted leaflet motion is characteristic for functional / ischemic MR; excessive leaflet and chordal motion and extensibility are characteristic for MVP (posterior leaflet), flail leaflets and rheumatic MR (anterior leaflet); SAM and elongated MV leaflets are typical for MR in HCM [77, 150]. A comprehensive understanding of MR and its mechanisms is essential for correct diagnosis and explains the rationale for optimal treatment [40].

Acknowledgments

Financial support:

This work is supported in part by grant 07CVD04 of the Leducq Foundation, Paris, France, for the Leducq Transatlantic MITRAL Network, and by National Institutes of Health grants K24 HL67434, R01 HL72265, and HL109506.

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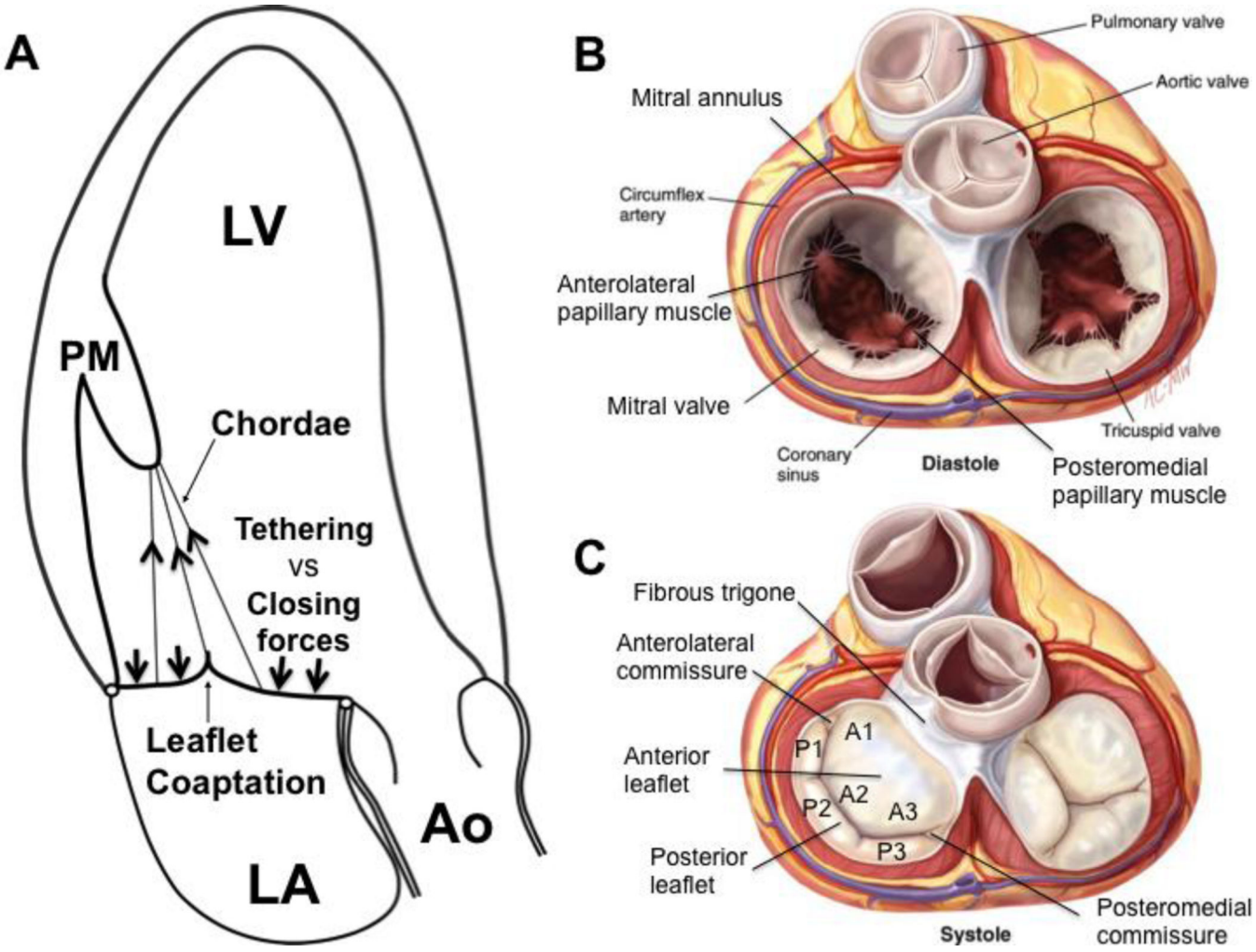

Figure 1.

A. Schematic apical long-axis view of the heart in systole (apex on top). There is normal function and spatial relationship of the left ventricular myocardium, the papillary muscles (PM), chordae, leaflets and mitral annulus. The tethering force - closing force relationship is balanced, both leaflets normally configured and concave toward the LV, and leaflet tissue coaptation sufficient preventing mitral regurgitation. **B. Surgical view of the open mitral valve in diastole. C. Surgical view of the closed mitral valve is systole.** (Ao, aorta; LA, left atrium; LV, left ventricle; PM, papillary muscle; Panel A adapted from Dal-Bianco et al. Anatomy of the mitral valve apparatus: role of 2D and 3D echocardiography. Cardiology Clinics. 2013 Elsevier; Panels B and C are adapted from Carpentier A et al. Carpentier's Reconstructive Valve Surgery. From Valve Analysis to Valve Reconstruction. 2010 Saunders Elsevier).

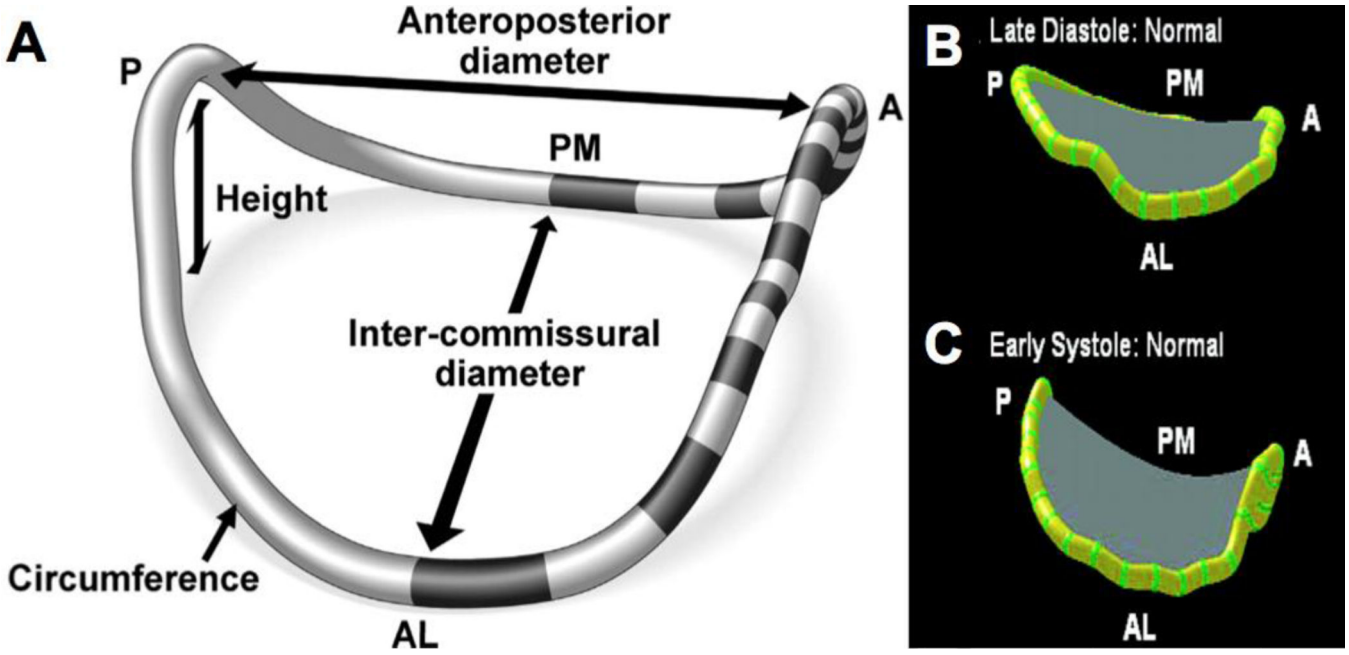

Figure 2.

A. Normal 3–dimensional mitral annulus shape: This schematic shows the complex saddle horn shape of the mitral annulus (MA). The anterior and posterior MA horns are most atrial. The commissures are close to the most ventricular nadirs of the MA. **B and C. Dynamic normal mitral annulus function.** (B) Profile view of a normal MA in late diastole while maximally expanded. (C). MA sphincter-like contraction in systole promotes it's saddle shape, which minimizes leaflet stresses and reduces the MA opening area in need to be covered by the leaflets. Normal dynamic MA function therefore allows brisk LV filling in diastole and promotes optimal MV closure and coaptation in systole. (A, anterior; P, posterior; AL, anterolateral; PM, posteromedial; Adapted from Grewal et al. Mitral Annular Dynamics in Myxomatous Valve Disease, Circulation 2010, Wolters Kluwer Health).

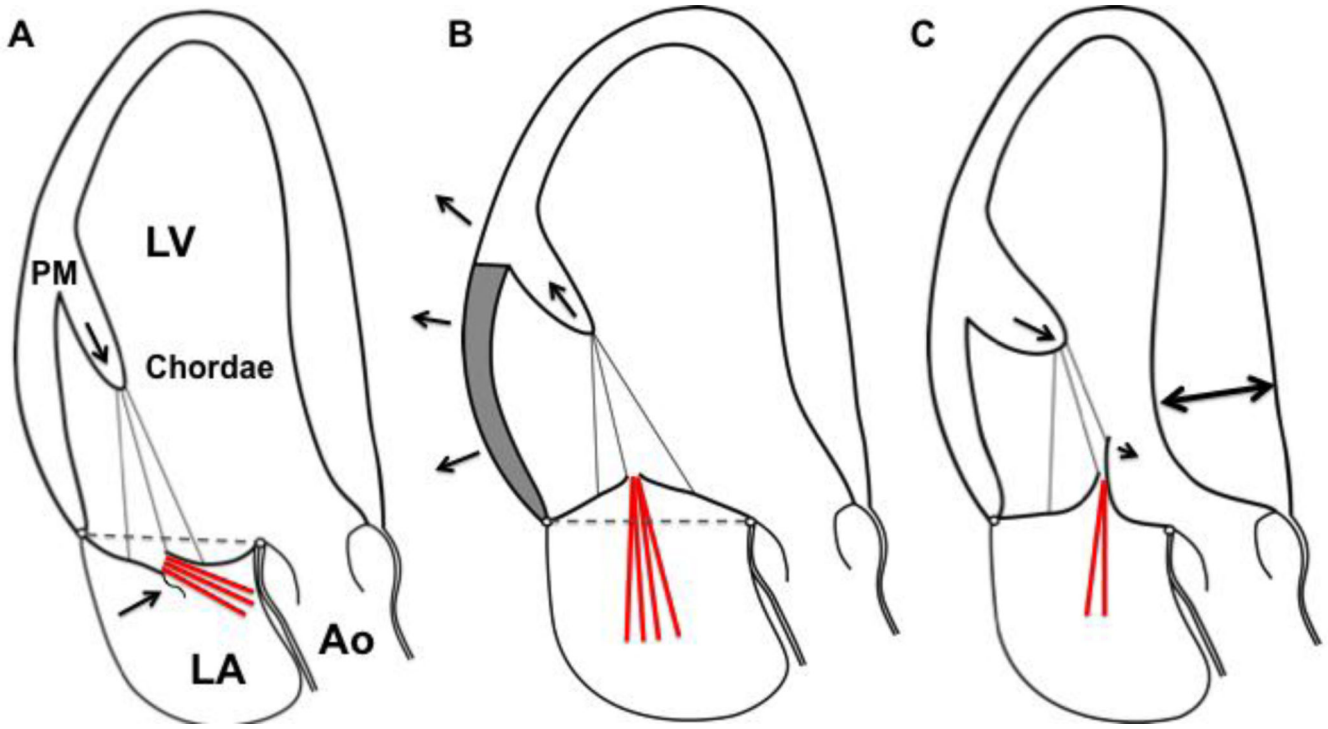

Figure 3.

A. Mitral valve prolapse with a flail posterior leaflet: The schematic shows bileaflet mitral valve prolapse with anterior directed mitral regurgitation (red lines) due to a flail posterior leaflet (arrow: ruptured chord) and loss of leaflet coaptation. Mitral valve prolapse with intact chordae is otherwise characterized by 1) leaflet coaptation that is displaced into the left atrium superior to the annular plane (dashed line), 2) superior displacement of the papillary muscle tip and 3) excessive leaflet and chordal tissue and mobility. **B. Functional / ischemic mitral regurgitation:** The papillary muscle is displaced posteriorly, laterally and, to the extent allowed by the chords, apically (arrow) due to left ventricular local dilatation & remodeling (arrows) caused by ischemic / myocardial infarction (shaded area). The LV wall-PM displacement tethers the mitral leaflets apically and limits coaptation. If there is not enough leaflet tissue available for coaptation to compensate for leaflet tenting (area apical to the dashed line) mitral regurgitation will develop (red lines). **C. Hypertrophic cardiomyopathy:** The geometry of the left ventricle and papillary muscles is altered by myocardial hypertrophy (double arrow). The papillary muscles are enlarged and displaced anteriorly (arrow) and closer to each other (not shown). This decreases intercommissural leaflet tension and moves the coaptation point and distal leaflets closer into the left ventricular outflow tract and at risk of being displaced into the LV outflow tract by blood-flow drag. If anterior leaflet displacement is severe enough and posterior leaflet apposition restricted, mitral regurgitation will occur (red lines). (Ao, aorta; LA, left atrium; LV, left ventricle; PM, papillary muscle; Adapted from Dal-Bianco et al. Anatomy of the mitral valve apparatus: role of 2D and 3D echocardiography. Cardiology Clinics. 2013 Elsevier;).