Epidemiology and Pathophysiology of Mitral Valve Prolapse
New Insights Into Disease Progression, Genetics, and Molecular Basis

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Mitral valve (MV) prolapse (MVP) is a common disorder, afflicting 2% to 3% of the general population. It is characterized by typical fibromyxomatous changes in the mitral leaflet tissue with superior displacement of 1 or both leaflets into the left atrium. With a prevalence of 2% to 3%, MVP is expected to affect ≈7.8 million individuals in the United States and >176 million people worldwide. MVP can be associated with significant mitral regurgitation (MR), bacterial endocarditis, congestive heart failure, and even sudden death.

MVP is a clinical entity that is not fully understood, despite being known for more than a century. A “midsystolic click” was first described in 1887 by Cuffer and Barbillon. In 1963, Barlow and Pocock demonstrated the presence of MR by angiography in patients with the “click-murmur” syndrome. Criley et al subsequently coined the term MVP.

MVP may be familial or sporadic. Despite being the most common cause of isolated MR requiring surgical repair, little is known about the genetic mechanisms underlying the pathogenesis and progression of MVP. Studies on the heritable features of MVP have been limited by the analysis of relatively small pedigrees and by self-referral and selection biases, including a preponderance of data from hospital-based cohorts. Nonetheless, the majority of data favor an autosomal-dominant pattern of inheritance in a large proportion of individuals with MVP. Despite the variability in clinical features, familial MVP might be considered a prevalent mendelian cardiac abnormality in humans. Although filamin A has been identified as causing an X-linked form of MVP, the causative genes for the more common form of autosomal-dominant MVP have yet to be defined. In this review, we summarize our current knowledge of the diagnosis, epidemiology, pathophysiology, and genetics of MVP, with a focus on potential future research directions.

Diagnosis of MVP

Physical examination and 2-dimensional (2D) echocardiography are the diagnostic gold standards for MVP. Various symptoms (including atypical chest pain, exertional dyspnea, palpitations, syncope, and anxiety) and clinical findings (low blood pressure, leaner build, and electrocardiographic repolarization abnormalities) have been associated with MVP, and their constellation has been called the MVP syndrome. Of the numerous reported correlates, only the association with leaner body mass has been reproducibly associated with MVP in the literature. Abnormal autonomic function has been reported as the mechanism explaining symptoms in patients with MVP, but given its absence in asymptomatic MVP patients, it remains unclear whether MVP is directly related to autonomic dysfunction or any reported association is purely incidental. Hypomagnesemia and dysregulation of the renin-angiotensin-aldosterone system have also been demonstrated in MVP syndrome, albeit in small patient samples.

The classic auscultatory finding in MVP is a dynamic, midsystolic to late systolic click frequently associated with a high-pitched, late systolic murmur. A careful physical examination is highly sensitive for making a diagnosis of MVP, but its specificity is limited (with echocardiography used as the gold standard). Redundant leaflets or chordae may produce an audible click without echocardiographic evidence of leaflet prolapse, giving false-positive physical findings. Finally, echocardiographic prolapse may exist without significant auscultatory findings. Patients with physical examination findings that suggest MVP should undergo confirmatory testing with 2D echocardiography.

In the early days of 2D echocardiography, the diagnosis of MVP occurred with a prevalence ranging from 5% to 15% and in as many as 35% of those undergoing imaging. In part, this overdiagnosis was the result of the erroneous assumption that the MV was planar; thus, any sonographic view that showed excursion of the leaflets superior to the mitral annulus was deemed pathological. Pivotal echocardiographic work in the late 1980s redefined normal mitral anatomy. Using 3-dimensional echocardiographic imaging, Levine and colleagues established that the mitral annulus was in fact saddle shaped. Therefore, in the anterior-posterior axis, the mitral annulus is concaved upward, whereas medially to laterally, the annulus is concaved downward. This mitral geometry creates the possibility that, in a sonographic 4-chamber view, the leaflets can appear to “break” the annular plane (creating the appearance of prolapse) when in reality they are normal. Echocardiographic MVP has since been defined as single-leaflet or bileaflet prolapse of at least 2 mm beyond the long-axis annular plane, with or without mitral leaflet thickening (Figure 1A). Prolapse with thickening of the leaflets >5 mm is a diagnosis of severe MVP.
called classic prolapse, whereas prolapse with lesser degrees of leaflet thickening is regarded as nonclassic prolapse.26

Transesophageal echocardiography (TEE) may not adequately visualize the entire MV anatomy. Anatomically, the posterior and anterior leaflets of the MV each may be divided into 3 sections. Carpentier’s widely recognized nomenclature describes 3 posterior leaflet scallops, the lateral (P1), middle (P2), and medial (P3), and 3 anterior segments, the lateral (A1), middle (A2), and medial (A3; Figure 1D).27,28 Most cases of prolapse involve the posterior middle scallop, which is easily identified on long-axis TTE images (Figure 1A). However, the posterior lateral scallop (P1) is not clearly seen on long-axis images but is best visualized in the apical 4-chamber view. As noted above, superior leaflet displacement in a 4-chamber view should not be regarded as diagnostic of prolapse. Thus, TTE can confirm the diagnosis of MVP but may not be able to exclude prolapse of all scallops. Although the Carpentier nomenclature is based on leaflet indentation, in the Duran classification, scallops are grouped on the basis of chordal attachments.29 Specifically, the anterior leaflet is divided into 2 segments (A1 and A2) and the posterior into 4 segments (P1, PM1, P2, and PM2). Segments A1, P1, and PM1 attach to the anterolateral papillary muscle, and segments A2, P2, and PM2 attach to the posteromedial papillary muscle. The modified Carpentier classification30 is a combination of the Carpentier and Duran nomenclatures. Although the Duran and modified Carpentier classifications are anatomically more precise than the classic Carpentier scheme, they are less widely used.

By taking into account several planes of imaging, 2D transesophageal echocardiography (TEE) is more effective in identifying prolapsing MV segments (Figure 1B).28 Three-dimensional TEE has the additional advantage of simulating the surgeon’s view of the MV, with the aortic valve at the 11 o’clock position (Figure 1D), and has become an essential tool in the intraoperative setting.31

Cardiac magnetic resonance (CMR) represents a novel, albeit still not widely used, noninvasive imaging method that identifies MVP with a sensitivity and specificity of 100% with 2D TTE used as the gold standard (Figure 2A).32 In addition, CMR can quantify MR using phase-contrast velocity mapping.33 Because CMR can reliably provide quantitative determination of ventricular volumes and function, it is becoming an important clinical tool for following up patients with MVP-related moderate to severe MR and for surgical decision making.34 Finally, CMR provides novel insight into the biology of the MV and its linked myocardium through improved spatial resolution provided by 3-dimensional acquisition of images with delayed gadolinium enhancement.32 Such enhancement occurs when the kinetics of gadolinium excretion is different in 2 adjacent compartments so that over time 1 compartment enhances more than the other. This has been a powerful tool for delineating infarcted and scarred myocardium, which excrete gadolinium more slowly than viable tissue. The presence of gadolinium enhancement has been shown in both the MV and in papillary muscle tips in patients with MVP but not in normal control subjects (Figure 2B).32 It has been speculated that the papillary muscle is altered in MVP by repetitive traction exerted by the prolapsing leaflets,33 which has been shown experimentally to lower the threshold for arrhythmias.36 Although more frequent complex arrhythmia on 24-hour ambulatory Holter monitor has been demonstrated in MVP patients with scarring of the papillary muscles,32 its clinical significance remains to be established.

Clinical Classification and Prevalence of MVP

MVP can be distinguished into primary or nonsyndromic MVP and secondary or syndromic MVP. In the latter case, MVP occurs in the presence of connective tissue disorders such as Marfan syndrome (MFS), Loeys-Dietz syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, and the recently reported aneurysm-osteoarthritis syndrome.37-42 MVP has also been observed in hypertrophic cardiomyopathy (HCM) and may contribute to the pathophysiology of obstruction typical of this myopathy.43

Figure 1. Prolapse of the intermediate posterior mitral valve scallop (P2) shown in a long-axis view of (A) a 2-dimensional (2D) transthoracic echocardiogram, (B) a 2D transesophageal echocardiogram (TEE) with (C) associated severe, eccentric, anteriorly directed mitral regurgitation, and (D) a 3-dimensional TEE surgical view. AO indicates aorta; LA, left atrium; LV, left ventricle; and RV, right ventricle.

Figure 2. Cardiac magnetic resonance steady state free precession long-axis view of bileaflet mitral valve prolapse (A). Short-axis view with 3-dimensional late-gadolinium enhancement (3D-LGE) showing fibrosis of the papillary muscle tips. Adapted from Han et al32 with permission from the publisher. Copyright © 2008 Elsevier B.V. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
Nonsyndromic MVP

Based on revised echocardiographic diagnostic criteria,²⁶ the prevalence of MVP and its clinical associations were examined in the community-based Framingham Heart Study (FHS).¹ The sample analyzed consisted of 3491 participants in whom routine 2D echocardiograms were available and adequate for the evaluation of the MV. Forty-seven individuals (1.3%) had classic and 37 (1.1%) had nonclassic MVP, yielding an estimated overall prevalence of 2.4%. The prevalence of MVP was distributed fairly evenly among individuals in each decade of age from 30 to 80 years of age. With respect to sex, MVP was equally distributed between men and women. These findings differed from older studies based on M-mode diagnostic criteria or observations of pedigrees¹²,¹³ that reported that MVP preferentially afflicted women and older individuals. Although the genetic predisposition to develop MVP may be present at birth, MVP is not found in newborns,⁴⁴ and its prevalence is low among children (0.3%)⁴⁵ and young adults (0.6%).⁴⁶ These recent studies were based on revised echocardiographic criteria, the prevalence of MVP in blacks was based on older M-mode criteria and nonstandard 2D echocardiographic views.⁴⁸ A systematic review of the published literature did not reveal prior studies that have evaluated the prevalence of MVP in Hispanic samples.

Tricuspid valve prolapse has been observed in up to 40% to 50% of patients with primary or nonsyndromic MVP,⁴⁹ but isolated tricuspid prolapse has rarely been reported.

Syndromic MVP: MFS and Other Connective Tissue Disorders

The prevalence of at least mild MV pathology in MFS has been estimated to be ≈75%, whereas the prevalence of more severe myxomatous MV thickening with prolapse is closer to 25% in these individuals.⁵⁰ The prevalence of MVP in patients with Ehlers-Danlos syndrome using standard echocardiographic criteria appears to be much lower (6%).⁵¹ The prevalence of MV disease also appears to be lower in patients with the Loey-Dietz syndrome (relative to MFS).⁵² One group reported a direct comparison of MVP prevalence in 71 individuals with transforming growth factor-β (TGF-β) receptor 2 (TGFBR2) mutations (characteristic of Loey-Dietz syndrome) with that in 243 people with fibrillin-1 (FBN1) mutations (typical of MFS) and in 50 unaffected family members.⁵³ The investigators observed a substantially higher prevalence of both MVP and MR in the cohort with FBN1 mutations than in the group with TGFBR2 mutations (45% and 56% versus 21% and 35%, respectively). Among affected individuals with the aneurysms-osteooarthrosis syndrome, MV abnormalities were common and ranged from mild to severe: 10 of 22 (45%) had MVP and 6 of 22 (27%) had MR.⁴² The presence of MVP has also been described in osteogenesis imperfecta and pseudoxanthoma elasticum,⁵⁸,⁵² although the true prevalence of the disease is unclear because standard diagnostic criteria were not used in the initial imaging studies performed on these patients.

Hypertrophic cardiomyopathy

The largest study assessing the prevalence of MVP in HCM observed it in 3% (of 528 people with HCM), which might suggest that HCM and MVP are 2 distinct conditions that may coexist in some cases.⁵³ However, the prevalence of other MV abnormalities (leaflet elongation and increased thickness) is much higher in HCM, estimated at 66% in 1 study.⁵⁴ This suggests that MV abnormalities are intrinsic to HCM,⁵⁴ either as a primary trait or as a secondary adaptive response to shear stress in a turbulent outflow tract or paracrine effects arising in the adjacent hypertrophic ventricle (see below).⁵⁵

Prognosis of MVP

A Controversial Past

The prognosis of MVP has varied in the published literature. In the community-based FHS sample, MVP was described as a benign entity with a low occurrence of adverse sequelae.¹ Specifically, none of the individuals with MVP had a history of heart failure, 1 patient (1.2%) had atrial fibrillation, 1 patient (1.2%) had cerebrovascular disease, and 3 patients (3.6%) had syncope. The prevalence of these outcomes in the subjects without prolapse was 0.7%, 1.7%, 1.5%, and 3.0%, respectively. The frequencies of chest pain, dyspnea, and electrocardiographic abnormalities were similar among individuals with and without MVP. Individuals with MVP had a greater degree of MR than those without prolapse, but typically the valvular regurgitation was classified as trace or mild.¹ In prior studies,¹ MVP was portrayed as a disease with frequent and serious complications, including stroke, atrial fibrillation, heart failure, and MR requiring surgery. These discrepancies may be due to selection biases inherent in evaluating symptomatic patients at referral tertiary care centers compared with observations made on healthier asymptomatic volunteers.¹,⁵,⁶ Changes in diagnostic criteria for MVP over time may have further exacerbated these differences in the prevalence of MVP.²⁶ Subsequently, a community-based study from the Mayo Clinic conducted in a primary care setting has underscored the clinical heterogeneity of MVP, including a widely varying prognostic spectrum.⁵⁶ Based on primary (depressed left ventricular ejection fraction, moderate/severe MR) and secondary (age >50 years, mild MR, left atrial enlargement, atrial fibrillation, and flail leaflet) risk factors, different groups of MVP with varying prognoses were identified with regard to cardiovascular morbidity and mortality.⁵⁶ Overall, young (<50 years of age), medically treated patients presenting with normal left ventricular function and no symptoms have excellent survival, even with severe MR.⁵⁶,⁵⁷ The benefit of early surgery (ie, valve repair in asymptomatic patients) versus a watchful wait was suggested in observational studies⁵⁸ but remains controversial.⁵⁷

Impact of MR

The common denominator of the studies evaluating prognosis of MVP is the role of MR at the time of diagnosis in
determining the risk for adverse events (such as congestive heart failure, atrial fibrillation, ischemic neurological event, and endocarditis) and the need for surgery on follow-up.\textsuperscript{1,5–7,50,60} The Mayo Clinic series highlighted that over a follow-up period of 1.5 years, MR volume increased \textgreater 8 mL in 51% of 74 individuals with MVP. In this clinical series, the progression of the valvular lesion (particularly a new flail leaflet) and an increase in the mitral annular diameter were the 2 independent predictors of an increase in the regurgitant volume over time.\textsuperscript{60} Although mitral leaflet thickness \textgreater 5 mm on M-mode echocardiography has been associated with increased risk for sudden death, endocarditis, and MR in patients with classic prolapse in some series,\textsuperscript{5,6} a more recent larger series using 2D echocardiography reported that mitral leaflet thickness was not an independent predictor of mortality and valvular morbidity.\textsuperscript{7}

In this community-based study of 833 individuals diagnosed with asymptomatic MVP and followed up longitudinally in Olmsted County, cardiac mortality was best predicted by the presence of MR and left ventricular dysfunction at the time of diagnosis. Risk factors for cardiac morbidity (defined as the occurrence of heart failure, thromboembolic events, endocarditis, atrial fibrillation, and need for cardiac surgery) included age \textgreater 50 years, left atrial enlargement, MR, the presence of a flail leaflet, and prevalent atrial fibrillation at the time of the baseline echocardiogram.\textsuperscript{7}

### Impact of a Flail Leaflet

The presence of a flail MV leaflet has been associated with a widely varying prognosis.\textsuperscript{65} Survival in medically treated asymptomatic patients with MVP presenting with a flail leaflet and normal left ventricular function is excellent.\textsuperscript{61} Thus, such patients are at relatively low risk of cardiovascular morbidity. The indications for valve surgery in this group include the development of atrial fibrillation (4%/y) and heart failure (5.7%/y). Older age, the presence of symptoms, and a left ventricular ejection fraction \textless 60% at the time of initial diagnosis increase the risk of developing heart failure and atrial fibrillation and are markers of the need for valve surgery and mortality.\textsuperscript{65,66} As for chronic severe MR in general, management decisions for patients with flail leaflet are based largely on the presence or absence of clinical symptoms, the functional state of the left ventricle, and the feasibility of successful MV repair.\textsuperscript{16}

### Sex-Related Differences in Outcomes

As noted, the prevalence of MVP was similar in the 2 sexes in the FHS, a referral-free, community-based sample.\textsuperscript{1} Conversely, in the Olmsted County population, characterized by a mixed spectrum of community-dwelling and referred patients, with the use of similar echocardiographic criteria, women were diagnosed with MVP more often than men and at a younger age.\textsuperscript{59} However, complications (such as the development of a flail leaflet) have been reported more frequently in men.\textsuperscript{65} The Mayo Clinic group also underscored the anatomic and functional differences between the 2 sexes in the context of MVP. Women present with more anterior and bileaflet prolapse, more thickened leaflets, fewer flail leaflets, and less MR compared with men.\textsuperscript{61} These milder clinical features in women have led to the speculation that an interplay may exist between loading conditions on the valve (such as higher blood pressure in men) and the development of complications in MVP. However, women represent a large proportion of patients with moderate or severe MR. In these severe forms, the assessment of left ventricular enlargement in women is challenged by the differences in weight and height between the 2 sexes and the frequent use of an absolute rather than a body size–adjusted left ventricular size measurement. Consequently, for the same degree of MR, women undergo mitral surgery less frequently and later than men. As a consequence, women exhibit excess long-term mortality but equivalent survival after valve surgery compared with men.\textsuperscript{61} Thus, there are important sex-related differences in the morphology, presentation, and prognosis of MVP.

### Pathology and Pathophysiology

#### Myxomatous Valve Degeneration

MVP is characterized by progressive increases in the area and length of the MV tissue and typically progresses with a natural history spanning decades, causing leaflets to thicken anatomically and prolapse superiorly into the left atrium beyond the mitral annulus in systole, leading to MR (Figure 1C). Histologically, the mitral leaflets in MVP are characterized by myxomatous degeneration. A detailed explanation of myxomatous changes requires an understanding of the histology and the development of the normal MV.

#### Normal MV Histology and Alterations in MVP

The extracellular matrix (ECM) constitutes the fibroskeleton of a normal MV. Normal valve tissue is divided into 3 layers: the atrialis on the atrial side; the spongiosa, which is the middle layer; and the fibrosa on the ventricular side (Figure 3).\textsuperscript{64} The atrialis, a dense sheet of elastic fibers, provides elasticity to the valve leaflet. The spongiosa is rich in glycosaminoglycans and proteoglycans within a fine, interweaving, spongy elastin network. It functions to resist compression between the outer layers, gives flexibility to the valve leaflet, and dampens the vibrations resulting from valve closure. The fibrosa, which is the thickest part of the leaflet, is made up primarily of organized collagen fibers that give the valve its tensile strength.\textsuperscript{64}

![Figure 3. Schematic of normal mitral valve histology. ECM indicates extracellular matrix; GAG, glycosaminoglycans; VEC, valvular endothelial cells; and VIC, valvular interstitial cells. Adapted from Bischoff and Aikawa\textsuperscript{66} with permission from the publisher.](image-url)
Valvular leaflets are populated on the surface by endothelial cells (VECs) and by interstitial cells (VICs) within the valve (Figure 3). VICs, which originate from endothelial progenitor cells, are considered the principal initiators of collagen synthesis and degradation in the valve leaflets. Quiescent VICs are noncontractile, α-smooth muscle actin–negative, fibroblast-like cells that can synthesize and degrade matrix enzymes. Enzymes secreted by the VICs include matrix metalloproteinases (MMPs) such as collagenase (MMP-1) and gelatinases (MMP2 and MMP9), as well as tissue inhibitors of MMPs. Quiescent VICs maintain a tight balance between degradation and synthesis of the matrix proteins, thus allowing normal valve leaflet strength and function.

Myxomatous degeneration is characterized by the expansion of the middle spongiosa layer of the valve (resulting from an accumulation of proteoglycans), structural alterations of collagen in all components of the leaflet, and structurally abnormal chordae. Dysregulation of ECM components plays a key role in mediating these changes. In MVP, the VICs acquire properties of activated myofibroblasts characterized by the expression of vimentin and α-smooth muscle actin but not SM1 or SM2 (markers of differentiated smooth muscle cells). Activated myofibroblasts are responsible for increased concentrations of various proteolytic enzymes, including MMPs, which degrade collagen and elastin at a rate exceeding the rate of production seen in quiescent VICs. In addition, cells staining for the pan-hematopoietic marker CD45+ can also be found in myxomatous valve tissue and may represent fibrocytes capable of differentiating into myofibroblasts that can both secrete matrix and degrade collagen and elastin.

The chordae tendineae in myxomatous valves do not appear to have increased cellularity, although they contain increased amounts of glycosaminoglycans. In a study by Grande-Allen et al., myxomatous chordae contained significantly more chondroitin/dermatan 6-sulfate and slightly more hyaluronan than control chordae. In contrast to leaflets, which contained predominantly hyaluronan, the predominant glycosaminoglycan class in chordae was chondroitin/dermatan sulfate. Myxomatous chordae contained more water and less collagen than control chordae. These findings may account for the reduced tensile strength at which the valve leaflets, and especially the chordae, fail in MVP. Chordal rupture is a frequent pathological finding in MVP and may be secondary to mechanical weakening of the chordae, combined with the abnormal hemodynamic stresses arising from the redundancy of the valve leaflets.

Finally, degenerative processes have 2 main histological phenotypes recognized in the surgical literature: diffuse myxomatous degeneration (or Barlow’s disease) and fibroelastic deficiency. Barlow’s disease is characterized by thickened and diffusely redundant myxomatous leaflet tissue with disrupted collagen and elastic layers, leading to prolapse of most of the mitral leaflet segments, severe mitral annular enlargement, and elongated (rarely ruptured) chordae. Patients usually present young or are middle-aged at the time of surgery after a long history of murmur or MR. Fibroelastic deficiency is characterized by decreased connective tissue deficient in collagen, elastin, and proteoglycans; thin, smooth, translucent leaflets without excess tissue and only moderate annulus dilatation; and thin, slightly elongated chordae. Patients frequently present at an older age with chordal rupture and flail leaflet after a shorter (if any) clinical history. Although most of the mitral leaflet is thin, localized myxomatous degeneration and thickening occur within the flail scallop, mainly of the posterior leaflet. Although Barlow’s disease and fibroelastic deficiency are treated with very different surgical approaches, it is unclear whether they represent 2 histopathological features of the same syndrome or 2 genetically distinct entities.

Molecular Biology of Valve Changes in MVP

Some clues to the various signaling pathways involved in abnormal valve biology in MVP can be gleaned from our understanding of normal heart valve development. Early separation of the cardiac tube into distinct chambers is achieved through regional swellings of the ECM, known as cardiac cushions, which form the primordial valves. Reciprocal signaling between the endocardial and myocardial cell layers in the cardiac cushion (mediated in part by members of the TGF-β family) induces a transformation of the endothelial cells (VECs) into interstitial or mesenchymal cells (VICs). This transformation is also known as endothelial to mesenchymal transition. Sox9 is a transcription factor activated when the endothelial cells undergo mesenchymal transformation, and Sox9-deficient mesenchymal cells fail to express ErbB3, an enzyme required for the proliferation of cardiac cushion cells. The mesenchymal cells then migrate into the cardiac cushions and differentiate into the fibrous tissue of the valves.

Several genes have been shown to play pivotal roles in the formation of the heart valves: calcineurin, with the signaling and downstream activation of a family of transcription factors called nuclear factor of activated T cells (the absence of activation of the nuclear factor of activated T cells leads to fatal defects in cardiac valve formation); Wntβ-catenin signaling, which determines the fate of the endothelial cells during valve development; fibroblast growth factor-4 (FGF-4); the homeobox gene Sox4; and the downstream modulator of TGF-β superfamily signaling SMAD6, the disruption of which leads to abnormally thickened, gelatinous valves. Defects in 2 of these genes and their signaling cascades may also conceivably lead to myxomatous change and mechanically weakened valves in adult life. Similar to syndromic MVP (see below), TGF-β upregulation appears to have a pivotal role in various biological pathways in the pathogenesis of primary or nonsyndromic MVP. Specifically, TGF-β is known to activate VICs toward a pathological synthetic phenotype, as shown both in animal models and in human in vitro studies. Geirsson et al. demonstrated TGF-β signaling dysregulation in clinical specimens of sporadic MVP cases undergoing MV repair. TGF-β–induced ECM production in cultured valvular interstitial cells was dependent on SMAD2/3 and p38 signaling and was inhibited by angiotensin II receptor blockers. In another study of human MVP surgical specimens by Hulin et al., upregulation of TGF-β2 was secondary to the reduced expression of metallothioneins, genes involved in the response to oxidative stress. In turn, TGF-β2 upregulation led to downregulation of genes of the ADAMTS family (responsible for degradation of proteoglycans), ultimately causing excessive ECM remodeling. Finally, upregulation of bone morphogenetic protein...
has also been shown to mediate the activation of VICS from healthy quiescent cells to a pathological synthetic phenotype in microarray data of clinical MVP specimens.\textsuperscript{70}

Endothelial to mesenchymal transition can be induced in vitro and is increased in vivo in response to mechanical stretch, suggesting that endothelial to mesenchymal transition not only occurs in normal valve development but also plays a role in adaptation to pathophysiologic conditions.\textsuperscript{68} The ability of valves to remodel and “reset the clock” in response to a reduction in mechanical stretch can be derived from the clinical context: MV repair is typically very durable, suggesting that an annuloplasty ring, by reducing the mechanical load on the valves and chordae, improves long-term valve function.

The mesenchymal differentiation potential of the VECs can be directed toward their transformation into osteogenic and chondrogenic phenotypes, reflecting an ability of these cells to generate VICS that reside in specific regions of the valve.\textsuperscript{66} The multilineage differentiation potential of the VECs, combined with a robust capacity for self-renewal, strongly suggests that at least a subset of the VECs are likely progenitor cells.\textsuperscript{66} Such progenitor cells may be essential for the health and longevity of the valve and may become activated during the disease process. Whether these cells can be harnessed or manipulated to prevent or limit valve disease is an exciting direction for future translational research.

Altered ECM turnover is also crucial in the pathogenesis of ruptured chordae tendineae in MVP. Although the heart is a vascular-rich organ, most of the cardiac valve complex is avascular (similar to cartilage and tendons).\textsuperscript{80} Work by Kimura et al\textsuperscript{8} showed a differential local expression of tenomodulin (a recently isolated antiangiogenic factor) measured in the chordae tendineae. Specifically, tenomodulin is locally absent in the ruptured zones of the chordae, favoring abnormal vessel formation also in combination with enhanced expression of vascular endothelial growth factor-A. Moreover, in contrast to what was observed in normal or nonruptured areas, higher numbers of inflammatory cells positive for CD11b, CD14, and vimentin and with an augmented expression of MMP-2 and -13 were detected in association with the downregulation of tenomodulin.\textsuperscript{85}

**Molecular Biology of Syndromic MVP**

Syndromic MVP associated with connective tissue disorders has been shown to manifest myxomatous changes similar to primary or nonsyndromic MVP.\textsuperscript{83} MFS is associated with mutations in the FBN1 gene (chromosome 15q15-q21).\textsuperscript{83} It can also be caused by inactivating mutations of the TGFBR2 gene, located on chromosome 3p24.2-p25.\textsuperscript{48} A recent study addressed the importance of TGF-\(\beta\) dysregulation in the connective tissue for the development of MVP in MFS. Ng et al.\textsuperscript{45} tested the hypothesis that the FBN1–TGF-\(\beta\) pathway is implicated in the pathogenesis of MVP in a murine model of MFS. Increased TGF-\(\beta\) signaling was observed in the prolapsing valves of FBN1-deficient mice. Treatment with a TGF-\(\beta\)-neutralizing antibody successfully normalized both the length and the thickness of the MV leaflets in these mutant mice, further supporting the hypothesis that the valve abnormalities in this mouse model were caused by increased TGF-\(\beta\) levels.\textsuperscript{85} The responsiveness of the MV length and thickness to excess TGF-\(\beta\) activity has implications for the identification of novel genes that may be implicated in the pathogenesis of MV disease. Furthermore, these findings raise the possibility that myxomatous MV disease could potentially be treated with therapies that reduce TGF-\(\beta\) overexpression. Although treatment with TGF-\(\beta\)-neutralizing antibodies successfully improves many phenotypic manifestations of MFS in murine models, this therapy cannot be readily translated to the treatment of the human form of the disease in the absence of US Food and Drug Administration–approved “humanized” antibodies that block TGF-\(\beta\). Because of the extensive interactions between angiotensin II and TGF-\(\beta\) signaling pathways, mice with a FBN1 mutation were treated with losartan, a selective angiotensin II type 1 receptor antagonist, in an attempt to reduce TGF-\(\beta\) signaling.\textsuperscript{86} Remarkably, the mutant mice treated with losartan had dramatic improvement in their rate of aortic root growth compared with mutant mice treated with \(\beta\)-adrenergic receptor blockers in doses with similar hemodynamic effects.\textsuperscript{80} In the recently published Cozaar in Marfan Patients Reduces Aortic Enlargement (COMPARE) trial,\textsuperscript{87} losartan reduced aortic root dilatation rate compared with placebo in adult humans with MFS. Another trial comparing the effect of losartan and atenolol on aortic dilatation and MVP in children and young adults with MFS is ongoing.\textsuperscript{88,89}

Among other connective tissue disorders commonly associated with MV disease, the Loeys-Dietz syndrome typically involves marked arterial tortuosity and distinct craniofacial abnormalities such as hypertelorism and cleft palate. It is caused by heterozygous mutations in either the TGFBR1 gene or the TGFBR2 gene that encode subunits of the TGF-\(\beta\) receptor.\textsuperscript{90} Immunostaining of diseased tissues from affected individuals with the syndrome shows evidence of increased TGF-\(\beta\) activity such as increased nuclear accumulation of phosphorylated SMAD2 and increased connective tissue growth factor, which is induced by TGF-\(\beta\).\textsuperscript{90} In the aneurysms-osteoarthritis syndrome, characterized by aortic aneurysms, arterial tortuosity, craniofacial features (similar to the Loeys-Dietz), and early-onset osteoarthritis,\textsuperscript{42} inactivating heterozygous mutations in MADH3 encoding SMAD3 (positive regulator of TGF-\(\beta\) signaling) have been identified, once again pointing to the link between TGF-\(\beta\) overexpression and myxomatous MV disease.

**Nonmyxomatous Valve Elongation: HCM and MV Disease**

Elongation and pathological thickening of the MV are commonly seen in HCM, a genetic disorder typically caused by mutations in sarcomere genes and characterized by unexplained thickening of the LV walls and by LV outflow tract obstruction.\textsuperscript{91} For years, it has been recognized that the simple impingement of the MV on the interventricular septum (resulting from high systolic velocities in the vicinity of the leaflets generated by the predominant upper septal hypertrophy) contributes to systolic anterior motion of the MV or SAM (Venturi effect).\textsuperscript{92} Whereas the Venturi effect likely contributes to the propagation and worsening of SAM, it is not adequate to initiate SAM, indicating that complementary mechanisms centered on structural MV abnormalities likely contribute to SAM.\textsuperscript{95} Experimental in vitro studies and computational
models have demonstrated that isolated anterior and internal displacement of the papillary muscles, combined with leaflet elongation (especially of the posterior leaflet), is able to recreate SAM.\textsuperscript{55} The degree of SAM is related to leaflet length, even in the absence of septal hypertrophy. Typically, basal and midanterior MV leaflet elongation causes SAM with prolapse, whereas distal anterior leaflet elongation creates SAM with a mobile flap. Leaflet elongation without papillary muscle displacement creates prolapse.\textsuperscript{55} Several mechanisms may contribute to MV disease in HCM, including the primary sarcomeric gene mutation, the response to shear stress in a turbulent outflow tract, and concomitant but unrelated familial MV disease.\textsuperscript{55} Paracrine factors such as periostin have also been implicated in the pathogenesis of MV disease in HCM.\textsuperscript{90} Periostin is a TGF-β–inducible secreted protein originally identified in mouse osteoblasts.\textsuperscript{91} In the heart, periostin is expressed physiologically in embryonic cardiac valves, whereas it is re-expressed abundantly in the adult left ventricle after pressure overload or myocardial infarction.\textsuperscript{91} Markedly elevated levels of periostin are indeed secreted by nonmyocyte elements in the left ventricular walls and expressed in HCM mice.\textsuperscript{90} Periostin promotes VIC proliferation, differentiation, and matrix production, therefore potentially driving leaflet elongation in HCM.\textsuperscript{12,55,90}

### Genetics of Nonsyndromic MVP

A familial basis for MVP has long been recognized, with an autosomal-dominant mode of inheritance, a variable penetrance influenced by age and sex, and a marked heterogeneity of clinical presentation even among the affected members within a family.\textsuperscript{12,13,92}

Because MVP is found in many but certainly not all patients with MFS, it was suggested that primary MVP may be due to a mutation of FBN1. However, studies have failed to link nonsyndromic familial MVP with variants in fibrillar or other collagen genes.\textsuperscript{93,94} Negative genetic linkage results may have been related to a lack of systematic examination of the entire human genome and to phenotypic ambiguity. More recently, our understanding of the 3-dimensional shape of the MV has improved the specificity of MVP diagnosis and in turn the yield of genetic studies.\textsuperscript{76} On the basis of this newer MVP phenotype, 3 loci for autosomal-dominant, nonsyndromic MVP have been identified on chromosomes 16, 11, and 13.\textsuperscript{95–97} Although filamin-A has been identified as causing an X-linked form of MVP,\textsuperscript{14} the genes for the more common form of autosomal-dominant MVP have yet to be defined (Table 1).

In 1999, the first genetic locus for MVP was mapped to chromosome 16p11.2-p12.1 (MMVP1) in a family with the trait segregating in an autosomal-dominant fashion.\textsuperscript{95} Genetic linkage studies yielded maximum multipoint LOD scores of 5.4 and 5.6. This was confirmed by haplotype analysis demonstrating that a chromosomal region of \( \approx \) 5 cM containing the locus (a genetic distance equivalent to 5 million DNA base pairs) was present in all affected individuals.\textsuperscript{95} In 2003, Freed et al\textsuperscript{96} identified a second locus for MVP (MMVP2) at chromosome 11p15.4. The risk haplotype comprised a 4.3-cM region on this chromosome. In 2005, a new locus for autosomal-dominant MVP was mapped to chromosome 13q31.3-q32 with a multipoint LOD score of 3.17 (MMVP3).\textsuperscript{97} Haplotype analysis showed that a portion of the chromosome containing the locus was present in all affected members of the family. The discovery of MMVP3 not only confirmed the genetic heterogeneity of MVP but also provided important clinical lessons. Specifically, phenotyping of the chromosome 13 pedigree revealed a spectrum of expression that included valve morphologies previously considered to be normal variants but now for the first time were recognized as having the same genetic substrate in the familial context.\textsuperscript{97} Prodromal morphologies shared 2 salient features with fully diagnostic MVP: an anteriorly displaced coaptation point and posterior leaflet asymmetry (Figure 4). The term prodromal used in the initial literature may not be ideal outside the familial context because its prognostic significance is unclear at this time. Therefore, these morphologies are better defined as abnormal anterior coaptation (AAC) to underline their similarity with fully diagnostic MVP. Individuals with minimal systolic displacement shared the posterior leaflet asymmetry with individuals with full-blown MVP, but their coaptation point was posterior (as in normal individuals). Individuals with AAC and minimal systolic displacement shared either the complete or a major

<table>
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<tr>
<th>Table 1. Summary of Linkage Studies of Nonsyndromic MVP</th>
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<tr>
<td><strong>Probands, n</strong></td>
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<tr>
<td><strong>Pedigrees, n</strong></td>
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<tr>
<td><strong>Total subjects in pedigrees with echocardiography+DNA, n</strong></td>
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<tr>
<td><strong>Affected individuals, n</strong></td>
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<tr>
<td><strong>Ethnicity</strong></td>
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<tr>
<td>Ashkenazi Jewish (pedigree 1), western France (pedigrees 2,4), eastern France (pedigree 3)</td>
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<tr>
<td><strong>LOD score</strong></td>
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<td><strong>Chromosome</strong></td>
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<td><strong>Gene map locus</strong></td>
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\( \text{MMVP} \) indicates myxomatous mitral valve prolapse; \( \text{MVP} \), mitral valve prolapse; \( \text{N/A} \), non applicable; and \( \text{XMVD} \), X-linked myxomatous valvular dystrophy. Adapted from Grau et al.\textsuperscript{5} Copyright © 2007 John Wiley & Sons, Inc. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
portion of the at-risk haplotype with fully diagnostic MVP. This same AAC morphology was also observed in the family linked to chromosome 11.97 Quantitatively, the height of coaptation relative to the annulus or left ventricular diameter (Figure 4) correlated well with the ratio of posterior to anterior leaflet length ($r = 0.83–0.85$) in the members of the family with a genetic linkage signal on chromosome 11. Thus, the spectrum of valvular abnormalities (AAC or minimal systolic displacement) may represent, in the familial context, early disease expression in gene carriers, a stage of progression, or the result of disease-modifying factors.

Recognizing early forms of MVP may be important because the condition often manifests clinically in the fifth or sixth decade of life as a severe cardiac event.5,6 It is conceivable that earlier targeted intervention to reduce hemodynamic stresses on the MV leaflets in genetically susceptible individuals (as shown in a murine model of MFS with aortic dilatation and in surgical specimens of nonsyndromic MVP)77,85,86 may potentially prevent the progression of MVP and severe MR requiring surgery, although this premise remains to be tested.

A rare form of myxoid heart disease, X-linked myxomatous valvular dystrophy, was first described >3 decades ago.14,98 It is characterized by multivalvular myxomatous degeneration, although the histopathological features of the MV do not differ significantly from the severe form of autosomal-dominant MVP. In 1 large family, X-linked myxomatous valvular dystrophy cosegregated with hemophilia A.98 This relatively large familial study that included >92 individuals over 4 generations, with a full penetrance for men (men were either clearly affected or not), was the first investigation that mapped this rare clinical dystrophy to a sex chromosome, Xq28. Thus, the genetic linkage analysis, facilitated by the X-linked mode of inheritance and by the linkage with a mild form of hemophilia A in this pedigree, permitted rapid mapping of this X-linked myxomatous valvular dystrophy gene, with a highly informative LOD score of 6.57 (Table 1). Coupling genealogical surveys of the larger family with linkage analyses, Kyndt et al14 refined the previously mapped locus on chromosome Xq28 to a 2.5-Mb region. Screening of candidate genes revealed a P637Q missense mutation in the filamin-A gene in the affected members of the larger family.14 Mutational analyses of the filamin-A gene in the other families identified 3 additional filamin-A gene mutations: 2 more missense mutations (G288R, V711D) and a 1944–base pair in-frame deletion.14 Both male and female carriers were affected, but the affected female carriers had a less severe phenotype.

Filamins are large cytoplasmic proteins that play an important role in cross-linking cortical actin filaments into a dynamic 3-dimensional structure and thereby transmit extracellular signals through their interactions with the integrin receptors.99 These proteins not only serve a structural role in cytoskeletal organization but also appear to serve as hubs or docking platforms for second messengers important in signal transduction. The filamin group of proteins contains 3 members: A, B, and C. Filamin-A and filamin-B are reported as ubiquitously expressed in tissues, whereas filamin-C expression is restricted to the cardiac and the skeletal muscle.99 The filamins are present as homodimeric or heterodimeric Y-shaped proteins with each chain consisting of an actin-binding domain at the amino terminus. The core of the protein consists of 24 highly homologous immunoglobulin-like repeats followed by a carboxyl integrin binding domain.99 Gene knockout studies have indicated the importance of these proteins in diverse developmental processes, and filamin-A appears to be the major family member responsible for cardiac and vascular development.100 Hemizygous mice for the filamin-A-null allele show embryonic lethality and a wide range of cardiovascular malformations, including incomplete

Figure 4. Two-dimensional parasternal long-axis images of posteriorly coapting leaflets (anterior leaflet [AL]; posterior leaflet [PL]) in a normal individual (A) vs increased coaptation height and an elongated posterior leaflet in a patient with abnormal anterior coapta- tion (AAC) features (B) and in a patient with bileaflet mitral valve prolapse (MVP) into the left atrium (LA; C). Schematics (D) showing the projections of anterior (A) and posterior (P) leaflets onto the mitral annular diameter (D). C indicates the coaptation height relative to the annulus and is calculated as $P/D$ or $C/LVID$, where LVID is left ventricular internal diameter. AO indicates aorta; LV, left ventricle; and RV, right ventricle.
septation of the outflow tract that leads to a common arterial trunc and double outlet, abnormally thickened and malformed outflow tract valves, atrial and ventricular septal defects, type B interruption of the aortic arch, abnormal endothelial organi-

zation in blood vessels, abnormal vascular permeability, and
thickening of the MV. Compensation of the other filamin
genes does not seem to occur, nor have cardiovascular defects
been described in mouse mutants for either the filamin-B or
the filamin-C gene. Filamin-A appears as a functional
hub in many signaling pathways that may contribute to the
development of valvular disease. Filamin-A coordinates local-
ization and activation of TGF-β receptor–activated SMADs,
particularly SMAD2, to act as a positive regulator of TGF-
β signaling. One potential mechanism underlying cardiac
valvular dystrophy could involve increased TGF-β signaling
secondary to perturbed filamin-A–SMAD interactions with
consequent dysregulation of endothelial-to mesenchymal
transition. Filamin-A mutations may provide a link between
MFS and nonsyndromic MVP, conditions that are character-
ized by increased TGF-β signaling. Specifically, myxomatous
MVs found in fibrillin-1–deficient mice (which model MFS)
display excessive TGF-β activation and upregulated expres-
sion of filamin-A.

Remaining Questions

MVP Pathophysiology and Genetics

In this review, we present a unifying theory for the pathogen-
esis of MVP based on our knowledge of the biology of valves
and the dynamic interplay of differentiating cells and growth
factors. However, a full understanding of the molecular basis
of MVP requires 2 additional steps (Table 2): identification
of the genetic variants responsible for nonsyndromic autosomal-
dominant MVP, including the role of both susceptibility and
modifier genes, and functional studies with animal models to
corroborate the clinical relevance of identified mutations.

MVP appears to be the result of multiple genetic pathways,
as illustrated by the identification of several genes in syndromic
MVP and 3 loci for nonsyndromic MVP. The identification
of filamin-A mutations in an X-linked form of valvular dystrophy
highlights the importance of the cytoskeleton not only in providing structural integrity but also in critical cellular
signaling pathways, specifically the TGF-β pathway. Advances
in DNA sequencing technologies may lead to the identifica-
tion of the MMVP1, MMVP2, and MMVP3 genes in the near
future. Large-scale collections of MVP patients and genome-
wide association studies will allow identification of additional
MVP genes and will finally elucidate the pathways leading to
the occurrence of MVP. Identification of the genes involved
in the development of MVP is important because the disease
typically manifests later in life, and earlier intervention in sus-
ceptible individuals may potentially prevent progression to a
clinically severe stage, a premise that remains to be tested.
In vitro studies of surgical specimens have shown for the first time
that the myxomatous changes characteristic of MVP are phar-
macologically preventable, which offers great hope for the
development of therapies based on future genetic discoveries.

Mouse models have proved to be essential for demon-
strating the importance of filamin-A mutations in cardiac
valve development. Further opportunities for understanding
human MV disease may derive from a study of the King
Charles Spaniel, a species in which MVP naturally occurs
with a frequency of 1% to 5%, similar to that in humans. In
addition, the zebrafish has recently been identified as an ideal
model for genetic knockdown experiments and understanding
of valve development. Although zebrafish display differences in atrioventricular canal and valve morphology com-
pared with other model organisms (such as mice and chicken),
they share the same molecular and cellular mechanisms for
valve development with humans. Thus, several signaling
pathways implicated in MVP also contribute to atrioven-
tricular canal formation in zebrafish (eg, the TGF-β pathway).

Identification of the mutations responsible for autosomal-
dominant MVP and their corrobororation through functional
studies will provide a potential screening tool to help clinici-

ans identify asymptomatic patients who may progress to
significant MR, perhaps among the individuals with diagno-
sis MVP without MR or among AAC individuals who do not
have genetic determinants of MVP and related biochemical
pathways. MVP epidemiology

Better characterize the natural history of nondiagnostic MVP morphologies
Identify genetic and environmental risk factors responsible for accelerated
MVP progression
Examine whether specific risk factors act differently at different stages of
MVP progression
Evaluate the duration of the different stages of MVP progression
Assess whether response to future nonsurgical therapies (losaratan?) varies
on the basis of different MVP stages (nondiagnostic MVP morphologies vs
full-blown MVP)

MVP indicates mitral valve prolapse.

Table 2. Summary of Future Research Directions

<table>
<thead>
<tr>
<th>MVP pathophysiology and genetics</th>
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| Identify the genetic variants responsible for nonsyndromic autosomal-domi-
| Develop functional studies with animal models to corroborate the clinical
| Develop new nonsurgical therapies based on a better understanding of
| Identify genetic and environmental risk factors responsible for accelerated
| Examine whether specific risk factors act differently at different stages of
| Evaluate the duration of the different stages of MVP progression
| Assess whether response to future nonsurgical therapies (losaratan?) varies
|

MVP indicates mitral valve prolapse.
Progression of MVP

Although the natural history of MVP has been studied since the 1980s, these investigations have focused on individuals with fully diagnostic MVP and its clinical outcomes, including cardiac death, heart failure, endocarditis, or severe MR requiring surgery. The natural history of early echocardiographic stages of MVP leading to diagnostic MV leaflet displacement and to subsequent clinical outcomes has yet to be described in both tertiary care and community-based studies (Table 2). In the familial context, previously nondiagnostic morphologies that share features of excessive leaflet motion with fully diagnostic MVP have been shown to represent mild or early stages of phenotypic expression in gene carriers. The existence of early MVP morphologies in the general population would raise the possibility of echocardiographic screening and provide an opportunity for potential intervention at an early phase of disease. As suggested in Figure 5, the progression of MVP may occur in stages over a lifetime, beginning with a genetic substrate, leading to mild, nondiagnostic valve morphologies, developing into full expression of the MVP phenotype, and culminating in severe MR requiring valve surgery. The duration of the individual stages of the disease can range from months to years, the shorter progression duration being a consequence of the development of a flail mitral leaflet. Various risk factors, including genetic modifiers, environmental factors (smoking, diet, body mass index, hypertension), and nonmodifiable characteristics such as race or sex, may influence the progression from one stage of MVP to the other and the duration of the different stages.

Several questions about the epidemiology of MVP remain unanswered (Table 2). Specifically, it is unknown whether early, nondiagnostic MVP morphologies progress within or outside the familial context; whether some risk factors more than others contribute to progression and at which stages; and whether the response to future nonsurgical therapies varies as MVP progresses from early disease to significant MR. Further longitudinal studies with a focus on specific clinical, demographic, and ethnic subgroups are needed to answer these important questions.

Conclusions

MVP is a common clinical phenotype and remains the most common valvular pathology requiring surgery. Multiple loci for autosomal-dominant nonsyndromic MVP and a gene responsible for a rare X-linked form of MVP have been discovered. Studies in a mouse MFS model and in clinical specimens of excised myxomatous MVs have underlined the role of excessive TGF-β signaling in the development of degenerative MV disease and the potential of angiotensin I receptor blockade in limiting MVP progression. These discoveries overall have exponentially accelerated our understanding of MVP. However, many questions remain unanswered in relation to both MVP pathophysiology and epidemiology, and future studies are needed to address these important issues.

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Disclosures

None.

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