Mitral Valve Prolapse: Current Views and Challenges (Review)

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Mitral valve prolapse (MVP) is the most common valve abnormality. Many issues relating its diagnosis, epidemiology, prognosis, and genetics have lately been defined more precisely or revised.

The most principal changes in MVP diagnosis are connected with establishing a three-dimensional saddle-like shape of the mitral valve annulus, which made mandatory the assessment of the valve condition from the parasternal longitudinal position during ultrasound examination. Implementation of standard diagnostic criteria based on two-dimensional echocardiography, and making the results of the Framingham Heart Study public made it possible to overcome the contradictions relative to the prevalence of this pathology, which appeared to be lower than it had been considered earlier. Age, gender, and ethnic characteristics of MVP occurrence have been established. Notions not only about the incidence of mitral prolapse development but the severity of its sequelae were subjected to reassessment. If previously MVP was thought to be a disease with serious complications, findings of conducted epidemiological studies gave reasons to consider it as a benign pathology with a low probability of unfavorable consequences. Concurrently, factors of unfavorable prognosis were identified, and mitral regurgitation was recognized to be the main of them.

The results of molecular genetic investigations enriched essentially notion about MVP and improved its diagnosing. At present, this pathology is believed to be a result of multiple genetic disorders caused by identification of several genes linked with the onset of syndromic prolapse, and three loci for nonsyndromic one. Creation of large-scale registers of MVP patients and conduction of genome-wide studies will enable cardiologists to identify new genes related to the emergence of mitral prolapse and provide screening of asymptomatic patients. The leading role in various mechanisms of MVP pathogenesis is played by the impairment of regulation of transforming growth factor beta (TGF-β), understanding of pathogenetic role of which opens new perspectives of conservative treatment of this pathology with the application of antibodies neutralizing TGF-β, and angiotensin II receptor blockers. Such medical approaches may be rather promising at the early stage of undiagnosed MVP phenotypes, and also serve as an alternative to surgical treatment of clinical complications in patients with a verified diagnosis.

Key words: mitral valve prolapse; mitral prolapse diagnosing; MVP epidemiology; prognosis in prolapses; molecular and genetic basics in MVP; mitral regurgitation; transforming growth factor beta.

Mitral valve prolapse (MVP) is the most common valve abnormality, which occurs in 2–3% of population [1–5]. This pathology is thought to be the leading cause of isolated mitral insufficiency demanding surgical intervention [3, 6–8]. Prolapse is known to be primary and secondary. The secondary (syndromic) MVP is the result of monogenic defects of connective tissue such as Marfan, Loeys–Dietz, Ehlers–Danlos syndromes, osteogenesis imperfecta, pseudoxanthoma elasticum, and recently described aneurysms-osteoarthritis syndrome [8–12]. Typical MVP is characterized by myxomatous degeneration of mitral leaflets and their systolic displacement to the left atrium cavity [13, 14].

In recent years, many notions about diagnosis, epidemiology, prognosis, and genetics of MVP have been made more precise or revised, the most important directions of further investigations have been specified.

Diagnosis of mitral valve prolapse

Clinical picture of MVP is very heterogeneous; mitral prolapse can be asymptomatic or have clinical

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manifestations [4, 6, 15, 16]. Physical examination supplemented by two-dimensional echocardiography remains a golden standard of MVP diagnosis [17–19].

A leading mechanism disclosing a diverse MVP semiotics is vegetative dysfunction, though the availability of asymptomatic patients does not permit an unambiguous definition of its pathogenetic role [20, 21]. Nevertheless, the majority of researchers [22–24] consider vegetative changes of homeostasis to be the obligate MVP manifestation. Quite a number of hypotheses have been suggested explaining presence of vegetative dysfunction in MVP, including congenital alterations of perineurium, a systemic defect of biological membranes, perinatal lesion of hypothalamic structures [20, 25, 26], and a version about a pathogenetic role of hypomagnesemia being lately actively discussed [27].

When two-dimensional echocardiography was first implemented into clinical practice, MVP was diagnosed in 5–15% and even in 35% of the examined patients [28, 29]. Such results were mainly connected with erroneous assumption that a mitral valve has a plane configuration. A series of ultrasound examinations [18, 30, 31] allowed the physicians to establish that a mitral valve annulus was saddle-shaped, and made the assessment of the valve condition from the parasternal longitudinal position obligatory [32, 33]. Modern medicine defines MVP as a systolic bulging of one or both mitral valve leaflets by no less than 2 mm beyond the mitral annulus plane with its obligatory long-axis registration [5].

Three-dimensional echocardiography improved essentially understanding of the mechanics of normal and pathologic mitral valves. This method is of value not only in MVP diagnosis but in determining the tactics of its surgical treatment and outcome assessment [18, 34–38].

Prevalence of mitral valve prolapse

Notions about the MVP prevalence remained controversial till the announcement of the results of the community-based Framingham Heart Study [1, 39, 40], and transition to the unified criteria of ultrasound diagnosis [30]. In 47 (1.3%) of 3,491 participants of Framingham study according to the findings of two-dimensional echocardiography performed in compliance with the standard diagnostic criteria there was detected classic MVP (with thickening of mitral leaflets), in 37 (1.1%) nonclassic MVP with an overall prevalence of 2.4% [1]. Turker et al. [41] report much lower values of mitral prolapse prevalence. Besides, they note a fairly even distribution of the pathology among individuals in each decade from 30 to 80 years of age, and identical occurrence rate among men and women. Their findings differ from older studies [42–45] based on echocardiography in M-mode and/or observations of pedigrees that reported that MVP preferentially afflicted women and older individuals.

MVP is a pathology with genetic predisposition, which however does not occur in newborns [21, 46], and is rarely observed in children (0.3%) [47] and young people (0.6%) [48]. These data convincingly characterize MVP as a progressing disease mainly affecting patients of middle years [1].

MVP prevalence does not depend on ethnicity. Incidence of this pathology in the population sample of American Indians (the Strong Heart Study) [2] and Canadians of South-Asian, European and Chinese origin (the SHARE study) [49] are analogous to the data presented in the Framingham study [1, 39, 40], whose participants were mainly white Americans. Similar results were obtained in the investigations based on Russian population [50].

As far as syndromic MVP in congenital disorders of the connective tissue is concerned, the following trends are noted. In Marfan syndrome, the rate of mitral valve involvement is considerable and makes about 75%, while in more severe variants with myxomatous valve alterations it approximates 28% [51]; leaflets of aortic and tricuspid valves are also subjected to the characteristic changes [52]. MVP prevalence in patients with Ehlers–Danlos syndrome is much lower (6%) [9]. A similar trend is noted in Loeys–Dietz syndrome. When 71 patients with mutations of in the *TGFBR2* gene (typical for Loeys–Dietz syndrome) and 243 patients with mutations of in the fibrillin gene (*FBN1*) (typical for Marfan syndrome) were examined, a higher MVP prevalence and mitral regurgitation were found in the last two: 45 and 56% vs. 21 and 35%, respectively [53]. Abnormalities of the mitral valve appeared also frequent among the patients with aneurysms-osteoarthritis syndrome: MVP was found in 45% of cases, mitral regurgitation in 27% [12].

Prognosis in mitral valve prolapse

Previously, MVP was thought to be a pathology with frequent and serious complications (including stroke, atrial fibrillation, heart failure), and a high demand of surgical correction of mitral insufficiency [3, 6–8, 54, 55]. The results of the Framingham study gave grounds to consider MVP as a benign pathology with a low probability of unfavorable sequelae [1]. In the articles published at the turn of the XXI century with the eloquent titles: “Mysteries of mitral valve prolapse”, “Mitral valve prolapse: time for a fresh look”, “Mitral valve prolapse: old beliefs yield to new knowledge”, “Mitral valve prolapse: the merchant of Venice or much ado about nothing”, “When should mitral valve prolapse be considered a real disease?” the authors advocated the idea that serious complications occur in patients with the diagnosis “mitral valve prolapse” as frequent as in the individuals without it [56–60]. In some investigations, in particular, no supporting evidence was found about a close relation of MVP with a cerebral stroke [61, 62], infective endocarditis [63], and other complications [57, 63]. It may be explained by the errors of examination

methods associated with the comparison of clinically manifestant patients with practically healthy volunteers [1, 54, 55]. Reconsideration of diagnostic criteria for mitral prolapse aggravated the difference in the views on the prevalence of complications in this pathology [30]. In the Framingham study, none of the patients with MVP had a registered heart failure; the rate of atrial fibrillation, cerebral stroke, and syncope appeared to be comparable with the similar sequelae in the individuals without prolapse (1.2, 1.2, 3.6% vs. 1.7, 1.5, 3.0%) [1].

Large-scale investigations in Mayo clinic demonstrated clinical heterogenicity of MVP and various prognoses for this pathology [15]. Asymptomatic patients under 50 years of age with a normal left ventricular function have a favorable prognosis even in the presence of heavy mitral regurgitation [15, 64]. Advantages of early surgical correction of the valvular defect compared to a watchful waiting tactics in such patients remain unproved [64–67].

Mitral regurgitation is one of the main risk factors of development of unfavorable cardiovascular events in MVP (congestive heart failure, atrial fibrillation, cerebral disorders, endocarditis) as well as an indication to surgical treatment [1, 54, 55, 68–70]. In the Framingham study, asymptomatic MVP in the period from 3 to 16 years showed itself by the signs of regurgitation in a quarter of patients [71]. According to the data from Mayo clinic, the volume of mitral regurgitation increased by more than 8 ml during 1.5 years of follow-up in 51% of patients with MVP [70]. The two independent factors of the mitral regurgitation volume increase over time were progression of the valve lesion (namely, the appearance of a flail leaflet), and enlargement of a mitral annulus diameter [70]. Atrial fibrillation can also worsen the severity of mitral regurgitation but the intensity of the latter decreases after the restoration of the sinus rhythm [72–74].

In some works [54, 55] thickness of the mitral leaflet more than 5 mm (a sign of myxomatous degeneration) recorded by echocardiography in M-mode was associated with a high risk of endocarditis, mitral regurgitation, and sudden death development. Later and large-scale investigations with the application of two-dimensional echocardiography did not confirm this fact [5]. In the course of a long-term follow-up of 833 patients with asymptomatic MVP the predictors of mortality were presence of mitral regurgitation and left ventricular dysfunction at the time of primary examination, whereas age older than 50, enlargement of the left atrial cavity, and presence of mitral regurgitation were the risk factors for cardiovascular disturbances [68].

Availability of a mitral valve flail leaflet is associated with an ambiguous prognosis [75]. Asymptomatic patients with such leaflet and unaltered left ventricular function receiving medicamentous treatment have a low risk of cardiovascular complications [72, 75]. Indications for surgery on the valves in these patients are progression of atrial fibrillation (4% per year) and heart failure (5.7% per year). Elderly age, clinical symptoms or decrease of ejection fraction by less than 60% at the time of establishing the diagnosis are markers of elevated mortality and speak in favor of performing operations on the heart valves [75, 76].

The Framingham study has demonstrated equal prevalence of MVP in men and women [1], though a community study in Olmsted County (USA) using current echocardiographic criteria showed that this pathology occurs more often in women and at a younger age than in men [15], with complications being revealed less commonly [76]. Investigation in Mayo clinic detected morphofunctional differences of heart structures in men and women with prolapse. In women, prolapse of the anterior or both mitral leaflets occurs more often, more leaflet thickening, less flail registration rate are noted [77]. Besides, they make an essential portion of patients with moderate and severe mitral regurgitation [5]. As a consequence, in a long-term perspective a higher mortality rate but an equivalent survival time after the operation on the valves are noted in women compared to men [77].

Lately, the focus of researchers' attention has shifted from the valvular mechanism to the state of the left ventricular myocardium in the assessment of prognosis in MVP. Impairment of overall hemodynamics in this pathology was shown to occur not only due mitral incompetence but via the defects of structures and functions of extracellular myocardial matrix, which can cause diastolic dysfunction, contractile capability decrease, and development of secondary cardiomyopathy [78–81].

Molecular biology and genetics of mitral valve prolapse

Molecular genetic studies have significantly enriched the notion of MVP and allowed cardiologists to improve its diagnosis [8]. By the present time, participation of several genes and factors of their activation in the process of heart valves formation has been proved. Among them are calcineurin stimulating the family of nuclear factors of activated T cells (NFAT), absence of which leads to the fatal valvular defects [82]; Wnt/β-catenin, determining the development of endothelial cells [83]; fibroblast growth factor FGF4; homeobox gene *Sox4*; modulator of transforming growth factor beta (TGF-β); superfamily of signaling proteins SMAD6 [84, 85], the impaired work of which results in abnormal valve thickening. Defects in genes or signaling molecules may induce myxomatous valvular alterations and promote progressing impairment of their mechanical strength during life [86, 87].

A leading role in various mechanisms of pathogenesis of syndromic and non-syndromic MVP is played by the failure of TGF-β regulation [21, 88]. TGF-β is a protein controlling a number of physiological processes including angiogenesis, proliferation, cellular differentiation and

apoptosis of the majority of cells [85, 89, 90]. This representative of cytokines exerts multidirectional action on the extracellular matrix structure. Stimulation of TGF-β via a canonic SMAD signaling pathway induces profibrotic effect including deposition of collagen and elastin [91], reduction of proteolytic enzyme expression (matrix metalloproteinases (MMP)) [92], and increase of tissue MMP inhibitor activity [93, 94]. Its stimulation via a non-canonical SMAD-independent signaling pathway results in degradation of the extracellular matrix due to the increased proteolysis via MMP-2, 9 and 13 [95], and elevated activation of MMP with the help of plasminogen activators [96].

Some works [85, 97] describe the ability of TGF-β to initiate the development of interstitial cells of a valvular leaflet as a pathological phenotype. The importance of TGF-β signaling pathway in emergence of sporadic MVP cases has been confirmed [98]. In the experiment on the culture of interstitial cells, induced TGF-β production of extracellular matrix is shown to depend on SMAD2/3 and signaling protein p38 and to decelerate by angiotensin II receptor blockers [85, 98]. In the study on the surgical mitral valve specimens in patients with prolapse, it is noted that a stimulating effect of TGF-β is secondary and occurs in response to inhibiting expression of genes regulating the response to the oxidative stress [99]. Activation of TGF-β, in its turn, leads to the inhibition of genes responsible for proteoglycan degradation resulting in excessive accumulation of extracellular matrix [5].

Synthesis of extracellular matrix can be induced both *in vitro* and *in vivo* by mechanical stretching of the valve, which not only provides its normal development but adaptation to pathological conditions as well [86]. The ability of the valve to restore its previous parameters in response to the weakening of the mechanical action is important in the clinical context: annuloplasty by reducing the load on the valves and chord improves a long-term prognosis for patients with MVP [5].

Pathogenesis of chord rupture and generation of flails are explained by the unique properties of the extracellular matrix [72]. The major part of the valvular complex is known to be avascular just like cartilages and ligaments. A local expression of tendon-specific protein, tenomodulin, antiangiogenic properties of which have been recently discovered, is noted in the valvular chords [100]. In the areas of chord rupture tenomodulin is absent, abnormal vascular formations and intensified expression of vascular endothelial growth factor VEGF-A are observed. On the contrary, in normal unaffected chord areas, an elevated concentration of $CD11b^+$, $CD14^+$, and vimentin with enhanced expression of MMP-2 and MMP-13 in combination with tenomodulin inhibition is fixed [100].

Syndromic MVP related to hereditary disorders of the connective tissue manifests itself by the same myxomatous changes as primary prolapse. Marfan syndrome is associated with mutations in the *FBN1* gene located on 15q15-q21 chromosome [85, 90, 101, 102], it may also be caused by mutation in gene TGF-β located on the 3p24.2-p25 chromosome [21, 103]. The role of FBN1 and TGF-β mutation in MVP pathogenesis was confirmed by the experiment on mice with the model of Marfan syndrome [104]. In the prolapsed part of the mice valves with FBN1 deficiency, intensification of TGF-β expression was noted. Application of antibodies neutralizing TGF-β results in the reduction of mitral leaflet thickness and confirms the hypothesis that abnormalities of the mitral valve are linked to the increased level of TGF-β [104]. However, a successful correction of many phenotypic manifestations of the Marfan syndrome on the mice models using TGF-β-neutralizing antibodies is not yet applicable for treating humans [5].

Establishment of interconnection between angiotensin II and TGF-β created premises for experimental treatment of mice with mutation in the *FBN1* gene with losartan, angiotensin II receptor antagonist [105]. It should be noted that in two experimental groups of mutant mice receiving β-adrenoblockers and losartan in the doses equivalent by hemodynamic effect, advantage of the latter in the ability to prevent aortic root widening was shown [105]. In the randomized study COMPARE, losartan decreased the rate of aortic root dilatation in comparison with placebo in adults with Marfan syndrome [106]. Nevertheless, the ability to reduce TGF-β expression is noted in β-adrenoblockers as well [102]. In the researches of Lacro et al. [107, 108], where they compared the effect of losartan and atenolol on aorta dilatation and MVP in children and adolescents with Marfan syndrome, no essential difference between the preparations was found.

Loeys–Dietz syndrome is another disease of the connective tissue associated with the pathology of the mitral valve, which is caused by heterozygous mutations in *TGFBR1* or *TGFBR2* genes encoding subunits of TGF-β receptors [10, 85]. In patients with this pathology, signs of TGF-β activity are observed in the form of elevated accumulation of nuclear phosphorylated SMAD2 and concentration increase of connective tissue growth factor, which is induced by TGF-β [10, 109]. Aneurism-osteoarthritis syndrome (combination of aortic aneurism, tortuous arteries, facial dysmorphias and early onset of osteoarthritis) caused by mutations in the *SMAD3* gene is one more confirmation of the relation of the increased expression of TGF-β and myxomatosis of the mitral valve [12].

A high prevalence of mitral prolapse in Marfan syndrome gives grounds to suggest that primary MVP is linked with mutations in the *FBN1* gene, but nobody could prove yet this hypothesis. Unsuccessful attempts to find definite genetic defects are connected with absence of systematic study of human genome and phenotypic heterogeneity of the pathology [5].

In 1999, the first genetic locus (*MMVP1*) for non-syndromic MVP was mapped on 16p11.2-p12.1 chromosome in the family with the signs of autosomal dominant type of inheritance [110]. In 2003, the second

locus (*MMVP2*) on 11p15.4 chromosome was detected [111]. At last, in 2005, the next locus (*MMVP3*) for autosomal dominant MVP was mapped on 13q31.3-q32 chromosome [112]. Discovery of *MMVP3* confirmed genetic heterogeneity of MVP and allowed the scientists to determine the manifestation spectrum, which should be referred to hereditary pathology rather than to the variants of a norm as it has been thought previously [112].

In recent years, the so-called prodromal (for MVP development) morphology, including abnormal anterior cooptation of the leaflets, has attracted attention of investigators [71, 112]. Patients with such abnormality and minimal systolic leaflet displacement have fully or essentially the same "risk haplotype" as those having MVP, similar morphology is observed also in connection with chromosome 11 [112]. Screening of early MVP forms is necessary as rather often this pathology is clinically manifested in the fifth or sixth decade of life in the form of serious heart events [54, 55, 72, 113]. Timely reduction of hemodynamic load on the mitral valve leaflets in genetically predisposed individuals can prevent progression of MVP and appearance of severe mitral regurgitation [98, 104, 105].

A rare form of myxomatous lesion, X-linked MVP, was first described in 1969 under the name of "myxomatous valvular dystrophy" [114–116]. It is characterized by multiple myxomatous lesions of the valves, though no considerable histopathological differences from heavy forms of autosomal dominant form of MVP are observed.

The case of myxomatous valvular dystrophy combined with hemophilia A in the members of one family [115] allowed researches to collate this variant of MVP with a sex chromosome Xq28; a combination with hemophilia considerably facilitated gene mapping. During the selection of candidate genes, P637Q missense mutation in the filamin A gene was detected in the sick members of the family [21, 115, 116]. The analysis of the mutated filamin gene in other families enabled detection of additional mutations: two new missense mutations (*G288R*, *V711D*) and deletion of bp-segment 1944 [116, 117].

Filamins are large cytoplasmic proteins providing crosslinking of actinic filament into three-dimensional structure and serving as transmitters of cellular signals [118–121]. A group of filaments is presented by A, B, and C variants, the former being responsible for the development of the heart and vessels [118, 122]. Prenatal death and a vast list of cardiovascular developmental defects including abnormal thickening and deformation of valvular leaflets are typical for hemizygous mice with a null allele of filamin A [122, 123]. Defects of other variants of filamin genes (B and C) were not accompanied by cardiovascular defects in the experiment on mutant mice [124, 125]. Pathology of the valves may be realized through the impaired signaling function of filamin A, which coordinates localization and activity of TGF-β receptors-activators of SMAD, especially SMAD2, and can serve as a positive regulator of TGF-β signaling [90, 126, 127]. Mutations in the filamin A may explain the similarity of clinical manifestations of Marfan syndrome and non-syndromic MVP, since both these states are characterized by TGF-β activity increase. In particular, myxomatosis of mitral valvular leaflets found in mice with FBN1 deficiency reflects excessive activation of TGF-β and impairment of filamin A expression regulation [104, 128].

Thus, at present, MVP is assumed to be the result of multiple genetic disorders, which is proved by the identification of several genes related to the occurrence of syndromic mitral prolapse [101, 103], and three loci for non-syndromic prolapse [110–112]. Detection of filamin A mutation in X-linked form of valvular dystrophy [114] confirmed the significance of cytoskeleton not only for structural integrity of the valve but also for the processes in the most important cellular signaling pathways realized, in particular, with participation of TGF-β. Advances in the technology of DNA sequencing may lead to identification of *MMVP1*, *MMVP2,* and *MMVP3* genes in the near future. Creation of large-scale registers of patients with MVP and conduction of genome-wide studies will make it possible to identify new genes related to the occurrence of MVP, and to provide screening of asymptomatic patients for whom the development and progression of mitral regurgitation is a real threat [8, 112, 129]. New perspective ways of MVP management are feasible owing to the results of the operative material investigations *in vitro*, which demonstrated that typical myxomatous alterations can be prevented with the help of pharmacological agents [98, 102, 130]. Understanding the mechanisms of MVP development will allow the scientists to devise new methods of therapy realized via the effect on various cells and signaling pathways including inhibition of excessive TGF-β expression by angiotensin II receptor blockers, manipulations with endothelial cells-precursors, and tissue engineering of heart valves [5, 8, 118]. Such medical approaches are especially perspective at an early stage of undiagnosed MVP phenotypes or as an alternative to surgical treatment of clinical complications in patients with a verified diagnosis.

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