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Hypothesis

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Autonomic dysregulation as a novel underlying cause of mitral valve prolapse: A hypothesis

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Summary

Mitral valve prolapse is a common valvular abnormality that is caused by myxomatous degeneration, characterized macroscopically by leaflet thickening and redundancy accompanied with histologically marked proliferation of the spongiosa and mucopolysaccharide acid replacement of leaflet collagen in the prolapse leaflets. Nevertheless, the discrepant natural history and various concomitant syndromes cannot be explained completely by the current genetic autosomal dominant inheritance theory. In addition, autonomic dysregulation has been commonly reported in mitral valve prolapse, but has never been indicated as a major underlying cause. This article attempts to interpret the occurrence of primary pathology and progression in mitral valve prolapse on a common basis of improper autonomic tone. The imbalanced background of autonomic nervous firing leads to disharmonized synthetic/catabolism balance in the extracellular matrix, disrupted transition in the interstitial cellular component and invalided anti-inflammatory pathway in the endothelium, which trigger and accelerate the progression of this condition. Such a hypothesis not only unifies the seemingly disparate syndromes and valvular disorder, but also has implications for future biopharmaceutical and mechanical treatment.

key words: **mitral valve prolapse • autonomic dysregulation • etiology**

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Background

Mitral valve prolapse (MVP) has been described as the most common valvular abnormality contributing to mitral regurgitation [1], accompanied by late systolic murmur and associated with 1 or both of the redundant, floppy mitral leaflets in the left atrium. With the steadily decreasing rate of rheumatic heart valve disease, mitral valve prolapse has become the leading cause of mitral valve surgery for isolated mitral insufficiency in industrialized countries [2]. Several clinical studies have reported prevalence rates ranging from 5% to 15% and even as high as 35% [3–7] among specific populations. The controversies have not ceased in spite of the introduction of echocardiography and the established guidelines for diagnosis of MVP. Nowadays, based on echocardiography, large sample database and more realistic representation, the prevalence of mitral valve prolapse was found to be less than 1% in a cohort of healthy teenage students, young athletes and patients undergoing echocardiography for clinical reasons [8–10]. While the negative events associated with congestive heart failure, progressive mitral insufficiency, bacterial endocarditis, thromboembolism and even sudden death may emerge at the endpoint in the course of aging and occur far more frequently in patients with MVP compared to controls, which have been determined. However, the natural course of mitral valve prolapse is markedly heterogeneous, varying from benign with a normal lifespan to malignant manifestation with significant morbidity and mortality caused by the progressive valvular regurgitation. Hence, management of this potentially malignant entity should consider the underlying etiology and perform close follow-up to allow for early identification of the subjects requiring medical or surgical intervention. However, the underlying causative pathogenesis is incompletely understood. A view that mitral valve prolapse has a well-recognized concerning with heritable genetic connective tissue disorders [11–13], is the most popular and feasible mechanism among the several putative hypotheses. A familial basis for this circumstance has long been established with an autosomal dominant mode of inheritance [14]; nevertheless, the variable penetrance is probably influenced by age, sex and autonomic nervous state, manifesting a marked heterogeneity of clinical presentation even between affected members of the same family. Hence, we wondered whether there is any environmental factor that has a triggering role in the development of mitral valve prolapse.

The Hypotheses

Patients with mitral valve prolapse were found to be associated with the coexistence of symptoms that cannot be explained on the basis of valvular regurgitation alone. Various accompanying symptoms including palpitations, orthostatic rhythm disturbances, atypical chest pain, exertional dyspnea and neuropsychiatric symptoms [15,16] have been referred to as "mitral valve prolapse syndrome". Abnormal autonomic regulation has been reported to be responsible for symptomatic subjects with a complex of presenting symptoms such as elevated circulating concentrations of catecholamines and enhanced β receptor affinity, suggesting the existence of a hyperadrenergic state, diminished vagal tone and other autonomic malfunctions [17]. Moreover, decreased heart rate variability (HRV), indicating an imbalance in the cardiac autonomic responsiveness, had been well documented in symptomatic patients [18]. This autonomic imbalance parameter contributes to disease progression, is an indicator of disease pathogenesis, and is a better predictor of poor prognosis than other hemodynamic measures in heart-related diseases [19]. In addition, female sex was found to be a notable predominance by the Framingham Study, especially among young women [20] who were prone to dysautonomias. Mitral valve prolapse is absent from echocardiographs in newborns [21], and an autosomal dominant mode did not express, even in members of the same family, suggesting that clinical presentation of patients with MVP might exhibit complex interactions with environmental factors. Hence, it is hypothesized that autonomic dysregulation may be a key determinant in the origin and progression of mitral valve prolapse. Such a hypothesis not only accounts for the seemingly disparate syndromes and valvular disorder, but also has future implications for biopharmaceutical and mechanical treatment.

Evaluation of Hypothesis

Heart valves and neuroregulation

The function of heart valves is far more complicated than acting as mere passive flaps that open and close like a door, as the valves have a dense innervation and a large subpopulation of nerves. According to studies identifying their specific transmitters and neurons of origin, some of the inherent nerves can be divided into afferent fibers, such as calcitonin gene-related peptide (CGRP), and efferent fibers, including norepinephrine (NE) and neuropeptide Y (NPY) [22]. Studies in various species have demonstrated a clear characteristic pattern of density and distribution innervating in both leaflets, suggesting an additional physical function [23]. Furthermore, 4 main types of cells found in valves – endocardial cells, myocardial cells, smooth muscle cells, and cardiac valvular interstitial cells (VICs) – have been demonstrated to be coupled by functional gap junctions with nerve endings [24]. *In vitro,* cultured valvular interstitial cells were reported to present contractility in response to adrenaline [25]. Kawano et al. [26] indicated that contractile cells in the basements of the mitral and tricuspid valves were associated with valvular active movements, independent of the cardiac cycle movement. Therefore, based on the profuse subpopulations of motor and sensory nerves, we consider a novel hypothesis that the valve is involved in processing sensory information and is manipulated by the motor fibers. An experimental model for mitral insufficiency reported that peculiar lesions of mitral valves developed in 50% to 80% of rabbits after vagus manipulations [27]. In clinical practice, patients with mitral or aortic regurgitation can to a certain extent respond to administration of adrenergic receptor blockers [28,29]. From the above experimental and clinical observations, the correlation between heart valves and neuroregulation appears possible. In regard to aortic valve calcification, recent evidence [30] demonstrated that human aortic valve leaflets expressed β-adrenoreceptors (β-ARs), and that valves affected with calcific disease exhibited enhanced β-ARs, which play a crucial role in regulating aortic valve interstitial cells differentiating toward an osteoblast-like cell phenotype. That is a novel role of the sympatho-adrenergic system in regulating valve calcification. In addition, several years ago research strongly supported a causal relationship between the

occurrence of drug-induced "restrictive" valvular heart disease and treatment with dopamine receptor agonist. 5-hydroxytryptamine (5-HT), a well-known neurotransmitter, was found to induce fibrotic changes in valve leaflets, causing thickening, retraction, and stiffening of valves [31]. It was found that the valvular interstitial cells exhibited active proliferation along with increasing synthesis of collagen when incubated with 5-HT. In conclusion, neuroregulation plays a pivotal role in biological and mechanical properties, fibrosis, calcification and the cellular phenotype transition of heart valves.

Mitral Valve Prolapse and the Autonomic Nervous System

Initially, the gene mutation with autosomal dominant inheritance was assumed to be responsible for the origin of mitral valve prolapse [11–14], while the cases can be sporadic and cluster in a familial fashion. Even in an affected family, only half of first-degree relatives were found to be involved with MVP [32]. The natural course of the disease manifests a marked heterogeneity of clinical presentation, even between affected members of the same family, varying from benign with a normal lifespan to malignant manifestation with significant morbidity and mortality. Screening previous clinical studies, we found body habitus was associated with MVP, which was independently linked with low body mass index even in a large size of samples [33,34]. In investigating the potential causes, autonomic function is a possible clue that has attracted a great deal of research attention, particular in females, besides the significantly smaller thoracic cage index. The well-recognized relationship between autonomic nervous system function and body habitus has been thoroughly addressed in some cardiovascular diseases such as coronary heart disease [35], in which the decreased functioning of the parasympathetic nervous system could play an important role. Hence, we have hypothesized that the underlying mechanism of autonomic nervous system function in patients with coronary heart disease also applied to mitral valve prolapse patients. In addition, available surveys reported an incidence of 6% in adult women and as high as 38% among teenage girls [36], who account for two-thirds of subjects. From a series of observational trials, cardiac arrhythmia was frequently detected in patients with mitral valve prolapse, with complex ventricular arrhythmias increasing as mitral regurgitation progresses [37,38]. Additionally, various accompanying symptoms, including palpitations, orthostatic rhythm disturbances, atypical chest pain, exertional dyspnea and neuropsychiatric symptoms, cannot be explained based on valvular regurgitation alone [15,16]. Improper autonomic regulation, which can interpret these phenomena to a certain extent, is considered the underlying pathogenesis. An experimental model of mitral insufficiency reported that peculiar lesions of mitral valves developed in 50% to 80% of rabbits after vagus manipulations [27]. Consistent with this, Bell and Acton [39] reported that 45.1% of patients with diabetes had autonomic neuropathy complications, and also had mitral valve prolapse. In clinical practice, patients with mitral regurgitation can to a certain extent respond to the administration of adrenergic receptor blockers [25]. This considerable body of evidence suggests that imbalanced autonomic tone may play a key role in the occurrence and progression of mitral valve prolapse.

Autonomic Nervous System and Cellular Biological Activity

Autonomic nerves, a pivotal constituent in the global nervous system, play a more significant role in the collaboration of vital organs than merely innervating the voluntary muscles. The organic activity modulation is achieved by norepinephrine (NE) and acetylcholine (ACH) secretion of the autonomic ending responding to the specific receptors. With regard to the extracellular matrix, norepinephrine could activate hepatic stellate cells (HSC) transiting from a quiescent phenotype to a proliferative, fibrogenic, myofibroblastic phenotype, which could be responsible for the progressive accumulation of collagen [40]. The noradrenergic system plays a critical role in triggering this chemical plasticity associated with structural plasticity. From several species and organic systems, the positive cell number and gelatinolytic activity of MMP2 and MMP9 displayed markedly higher levels after NE treatment [41,42]. In contrast, the vagal fiber demonstrates an antagonistic function. Laboratory work has demonstrated that chronic electrical stimulation of the vagal nerve ameliorated left ventricular remodeling after myocardial infarction in rats, the underlying mechanism of which was identified as the increasing TIMP-1 levels and reduced endogenous active MMP-9 protein after stimulation of the efferent vagal nerve in rabbits [43]. Regarding proliferation and apoptosis, Chida [44] found that hepatic sympathetic denervation exaggerated programmed apoptosis in the liver and accelerated the mortality of experimental mice, while NE addition completely inhibited this deterioration, which was associated with antiapoptotic protein levels of FLIP, Bcl-xL, and Bcl-2. Finally, endothelial cells, playing a critical role in host immune responses during inflammation and infection, also are involved with the autonomic system, in the cholinergic anti-inflammatory pathway, which is a physiological mechanism that modulates host inflammatory responses via cholinergic mediators like ACH, or by electrical stimulation of the vagus nerve against endothelial cell activation and leukocyte recruitment [45]. Returning to consideration of the mitral valve, immunohistochemical analysis demonstrated expressions of β2-ARs, β1-ARs, and β3-ARs in valves [30]. Furthermore, the main types of cells in valves are demonstrated to be coupled by functional gap junctions with microscopic nerve endings, which may not be impotent [20]. Along with improper autonomic tone, in the majority of cases of mitral valve prolapse with myxomatous degeneration, the most common and clinically import are prolapsed leaflets, characterized macroscopically by leaflet thickening and redundancy accompanied with histologically marked proliferation of the spongiosa and mucopolysaccharide acid replacement of leaflet collagen. Thus, the morbid valves are expected to be greatly affected by the autonomic nerve as regards both gross properties and molecular biology.

Implications of this Hypothesis

Converging evidence from many areas supports a unifying hypothesis to link together the disparate accompanying syndromes and discrepant clinical manifestations along a common axis, implicating the role of improper autonomic tone as a triggering event in the causation of mitral valve prolapse and a propelling factor in the course of exacerbation. Hence, the susceptibility to mitral valve prolapse could

become a recognizable factor that can be assessed with non-invasive electrophysiological studies or a behavioral questionnaire of para- and sympathetic activity. Although some high-risk factors have been suggested by multiple studies, indicating that leaflet thickening greater than 5 mm and mitral regurgitation during exercise, but not at rest, were associated with a 12-fold higher risk of complications [46], these index seemed be late for prophylaxis since doing little to prevent the endpoint: surgery intervention. If there is any family history of mitral prolapse the dysautonomia preceding the molecular change in the valve should be corrected, avoiding subsequent morbidity. On the other hand, it should be emphasized that it is of great clinical importance to avoid the over-diagnosis of MVP, which is largely due to overestimating the non-specific subjective dysautonomia symptoms (e.g., anxiety, chest pain, palpitations). Echocardiograms have become sensitive enough that it is possible to detect trace regurgitation in healthy people, and MVP has become a convenient diagnosis, thus objective electrophysiological studies of para- and sympathetic activity are essential. In addition, experimental research in animals and *in vitro*, where responses to the autonomic nerve can be assessed in models of imbalanced tone, are recommended to test this hypothesis. Furthermore, well-controlled prospective trials should be conducted to confirm the role of the autonomic system in the pathogenesis and development of MVP. Finally, novel diagnostic and therapeutic strategies may emerge as previously unrecognized pathway links reveal new targets for intervention along these emerging biologic circuits.

Conclusions

Dysautonomia leading to improper modulation of cellular synthetic metabolism in mitral valves can describe the gross property as well as histological changes taking place in the pathogenesis of mitral valve prolapse. We propose that autonomic dysfunction has a facilitatory role in the pathogenesis of mitral prolapse. In a manner similar to other organic systems, autonomic imbalance of mitral valves gives rise to a circumstance of hypersensitivity or of susceptibility to remolding in the extracellular matrix and phenotype transiting in cellular components.

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