Joint Hypermobility in Patients with Mitral Valve Prolapse
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Summary
Studies on hypermobility have aroused great interest in the last decades, as they are associated to musculoskeletal disorders, as well as abnormalities in several organic systems, such as the mitral valve prolapse. Therefore, in this study, data on the association between joint hypermobility and the mitral valve prolapse were investigated and reviewed. Studies in the literature have shown that genetic alterations in the collagen composition seem to be the main cause of this association.

Introduction
Association between joint hypermobility and mitral valve prolapse
Joint hypermobility (JH) was first mentioned by Hippocrates as an isolated feature, when he described the Celts’ incapacity to pull a bowstring or throw a dart, due to the slackness of their limbs1. Known as the “enigma of human physiology”, it arouse great interest in the last decades for being associated to musculoskeletal dysfunctions, as well as abnormalities in several organic systems and among them, the mitral valve prolapse (MVP)2.

The MVP is a common cardiovascular disorder, with a strong hereditary component, generally diagnosed in young individuals3 and characterized by the projection of mitral leaflets in the left atrium, often accompanied by mitral regurgitation4, organic deficiency of the papillary muscles and stretching or tearing of chordae tendineae5.

It can present as symptomatic cardiac arrhythmias and present as the asymptomatic form, thus, sudden death can occur in these patients. Therefore, the detection of the characteristics that can identify individuals with a higher probability of presenting MVP can be clinically opportune. It must also be considered that the alteration in collagen that characterizes JH and MVP makes it likely that individuals with MVP also would be more commonly hypermobile6.

This aim of the present study was to update the knowledge on the association between joint hypermobility and mitral valve prolapse in the general population, contributing to the diagnosis and prevention of the cardiovascular alterations.

Mitral valve prolapse
The MVP is a common clinical entity, with a prevalence of 2% to 22%7; according to the Framingham study, 7.6% of the women and 2.5% of the men in the USA have MVP8. The differences in the results of the epidemiological studies are a reflex of the different diagnostic criteria employed and the diversity of the study populations.

Other data related to the prevalence of MVP suggest that it is uncommon before the adolescence, but its prevalence increases after the pubertal growth spurt9. Symptom onset does not take place before the adolescence (approximately 14 years in girls and 15 years in boys) and the adults can be affected at any age. Common symptoms include thoracic pain, fatigue, arrhythmia and low tolerance to exercise; however, most individuals are asymptomatic10.

Araujo and Chaves4 verified the presence of arrhythmias at rest and/or after exercise, behavior of the cardiac parasympathetic component, manual prehension strength or the physical performance itself, evaluated through oxygen consumption at the anaerobic threshold and maximum effort, of which results were similar in women with and without MVP.

In the last decade, new echocardiographic criteria were established, based on the understanding of the 3-D structure of the mitral valve, which defined the prolapse as the dislocation of one or both mitral leaflets for more than 2 mm over the high points of the mitral annulus. The prolapse is subdivided in classic and non-classic, which are based on the thickness of the leaflets: classic > 5 mm and non-classic < 5 mm. Complications such as endocarditis and severe mitral regurgitation can occur in patients with classic prolapse9. Longitudinal studies identified the increase in the leaflet thickness as the main factor of an unsatisfactory prognosis, with high risk of sudden death, bacterial endocarditis, arrhythmias and mitral regurgitation in those individuals with classic prolapse11,11.

The MVP is considered a multifactorial valvular abnormality, as it is caused by histological abnormalities of the valvular tissue, geometric disparities between the left ventricle (LV) and the mitral valve, or several disorders of the conjunctive tissue. The increased thickness and redundancy of the leaflet, known as myxomatous degeneration, are the most common abnormalities in addition to structural alterations of the collagen in all components of the leaflets and the abnormal structure of the chordae tendineae11.

It is known that there is an increase in the glycosaminoglycan content, alterations in types I and III collagen and disarray in the organization of the collagen and elastic fibers12. Moreover, recently, genetic abnormalities in specific loci of chromosomes...
11, 13 and 16 have been related to the etiology of the prolapses\textsuperscript{3,14,11}.

Although the autosomal dominant inheritance has been described for the MVP in conjunctive tissue disorders, as in Marfan syndrome, previous studies have failed in the attempt to establish an association between MVP and collagen genes. These negative results might have been due to the lack of a systematic analysis of the human genome and uncertainty of the phenotypic diagnosis.

A recent research included 43 individuals that lived with three-generation members, with a significant number of individuals presenting MVP and no characteristics of Marfan syndrome. A clinical and echocardiographic assessment was performed, as well as genome analysis, using a program called SLINK. Araujo and Chaves\textsuperscript{6} demonstrated a new autosomal dominant locus in MVP present in the long arm of chromosome 13. These findings confirmed the heterogeneity of the MVP previously found in chromosomes 11 and 16 and in chromosome X\textsuperscript{13}.

Some studies have also reported a high prevalence of MVP in specific populations, similar to Marfan and Ehlers-Danlos syndromes, somehow suggesting biological associations among them\textsuperscript{14,15}.

In addition to the association with JH, individuals with MVP present an increased risk of developing infective endocarditis, due to the turbulent flow caused by the mitral regurgitation and increased thickness of the valvular tissue, as well as increased risk of ischemic and cerebrovascular events, especially in young patients\textsuperscript{13} panic syndrome, anxiety, agoraphobia\textsuperscript{16} and hypothyroidism\textsuperscript{17}.

**Joint hypermobility**

Joint Hypermobility (JH) is defined as the capacity to perform articular movements with a higher range of motion than the normal one\textsuperscript{10,19}. Its prevalence depends on the characteristics of the studied group determined, among others, by age, sex, ethnicity and genetic factors that have an effect on the process of movement evolution. Studies have stated that female individuals have a higher joint mobility than male individuals and that it decreases with age\textsuperscript{20,21}. Approximately 30% of the adult individuals are considered as presenting JH\textsuperscript{22}.

The features of JH that appear in some hereditary diseases such as Marfan syndrome, Osteogenesis Imperfecta, Achard syndrome. Homocystinuria and Hyperlysinemia must be differentiated from those present in the general population\textsuperscript{1}.

All cases present an association with collagen structure alterations, more specifically type III collagen and alterations in the genes involved in the production of fibrillin\textsuperscript{19,22} and, furthermore, with the laxness of ligaments, skin, blood vessels and adjacent muscular tissues\textsuperscript{1-2}.

JH in the general population is a common condition and a genetically determined one\textsuperscript{22}. There is a new consensus that the Benign Joint Hypermobility Syndrome (BJHS) is a multisystemic disorder, of which characteristics coincide with the characteristics of the hereditary disorders of the conjunctive tissue, which include Marfan syndrome, Ehlers-Danlos syndrome and Osteogenesis Imperfecta\textsuperscript{23}. To date, the genetic basis of common hypermobility remains unknown; however, studies of hereditary disorders of the conjunctive tissue provided important discoveries on the underlying mechanisms of JH.

Mutations in the COL3A1 gene were found, codifying type III collagen. Recently, mutations in the non-collagen molecule tenascin-X, a large glycoprotein extracellular matrix, have been identified in a subset of diseases such as Ehlers-Danlos syndrome and Joint Hypermobility Syndrome. Mutations in the collagen type I gene (COL1A1 and COL1A2) also have an important role in the pathogenesis of JH\textsuperscript{19}.

Focusing on diagnosis, Araujo\textsuperscript{24} sought to correlate different linear and adimensional methods of assessment of joint mobility. A total of 30 asymptomatic individuals participated, 16 males and 14 females. The sit-and-reach test, Toe-touch, Brighten-Horan, Rosemloom and Flexitest were used, with the latter being the only method that significantly correlated with the others (p<0.005) and incorporated relevant aspects of each one of them. A better association was observed between the Flex-Index and Brighten-Horan, as they presented a higher degree of similarity. They emphasized that tests developed several decades ago continue to be used routinely, despite their known limitations.

The Flexitest is a passive assessment method of 20 joint movements (Table 1), using a scale of whole numbers between 0 and 4 for each movement (Figures 1 and 2). The ankle, knee, hip, trunk, wrist, elbow and shoulder joints are assessed\textsuperscript{2}, while the method by Brighten-Horan consists in the assessment of joint mobility in the little finger, wrist, elbow, knee and trunk. The angular values and bilateral analyses are obtained with a goniometer, except for the vertebral column and wrist variables\textsuperscript{20,21}.

**Mitrail valve prolapse and joint hypermobility**

Araujo and Chaves\textsuperscript{2} evaluated, using the Flexitest, 125 women with a mean age of 50 years, with 31 of them presenting MVP. They verified that the women with a mitral valve prolapse are approximately 15% more flexible. The Flexitest score was significantly higher in women with MVP in 13 of the 20 joints assessed.

In a similar study, the authors analyzed retrospectively 124 consecutive assessments of adult, non-athlete women carried out in a specialized clinic, of which 34 had a diagnosis of MVP and 90 did not have a diagnosis or clinical evidence of the disease. Body mass index, conventional electrocardiogram, manual prehension with a dynamometer, sit-and-stand test and Flexitest to assess flexibility were verified.

The sit-and-stand test is simple, reliable and fast test to evaluate the dexterity of the actions of sitting and standing from the ground. The interpretation is made for each action, with scores from 0 to 5.

The cineanthropometric variables, notably body weight, flexibility, presence of signs of joint hypermobility and dexterity to sit and stand up from the ground were the ones that better differentiated individuals with from those without MVP, a condition that suggests the inclusion of the analysis
of cineanthropometric variables in the assessment of adult women with suspected or diagnosed MVP.

Yazici et al. investigated the prevalence of the Benign Joint Hypermobility Syndrome (BJHS) in individuals with mitral valve prolapse (MVP) and the correlation between the echocardiographic characteristics of the mitral valve, the elastic properties of the aortic wall and the index of hypermobility of Beighton-Horan. They analyzed 46 patients with prolapse, with a mean age of 26.1 yrs, of which 39 were women and 25 healthy individuals (3 mean and 22 women with a mean age of 25.4 yrs). The presence of BJHS was assessed according to the criteria of Beighton-Horan. The prevalence of BJHS in patients with MVP was significantly higher in the healthy individuals, 45.6% vs. 12% (p< 0.001). The group with MVP+BJHS presented significantly increased thickness of the anterior mitral leaflet (p<0.001). Yazici e cols. concluded that the prevalence of BJHS in individuals with MVP was more frequent than in the general population, considering that the prevalence of BJHS in patients with MVP was 45%.

Martin-Santos et al. sought to evaluate whether the Hypermobility Syndrome was more frequent in patients with panic syndrome, agoraphobia or both and determine if the mitral valve prolapse modified or collaborated in part with the association. A total of 99 patients, who had been recently diagnosed and were not undergoing any treatment for panic syndrome and agoraphobia and 64 patients who had never presented any anxiety disorder participated in the study. The method consisted in a clinical interview, criteria of Beighton-Horan and echocardiogram. The hypermobility syndrome was found in 67.7% of the patients with anxiety disorder, with the latter presenting a 16-fold increased chance of having hypermobility. The MVP was present in 5.4% of the patients with panic disorders and in 17.7% of the control patients.

<table>
<thead>
<tr>
<th>Movement</th>
<th>Description of movement</th>
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<tbody>
<tr>
<td>I</td>
<td>Ankle dorsal flexion</td>
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<tr>
<td>II</td>
<td>Ankle plantar flexion</td>
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<tr>
<td>III</td>
<td>Knee flexion</td>
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<tr>
<td>IV</td>
<td>Knee extension</td>
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<tr>
<td>V</td>
<td>Hip flexion</td>
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<tr>
<td>VI</td>
<td>Hip Extension</td>
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<tr>
<td>VII</td>
<td>Hip adduction</td>
</tr>
<tr>
<td>VIII</td>
<td>Hip abduction</td>
</tr>
<tr>
<td>IX</td>
<td>Trunk flexion</td>
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<tr>
<td>X</td>
<td>Trunk extension</td>
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<tr>
<td>XI</td>
<td>Trunk side flexion</td>
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<tr>
<td>XII</td>
<td>Wrist flexion</td>
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<tr>
<td>XIII</td>
<td>Wrist extension</td>
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<tr>
<td>XIV</td>
<td>Elbow flexion</td>
</tr>
<tr>
<td>XV</td>
<td>Elbow extension</td>
</tr>
<tr>
<td>XVI</td>
<td>Shoulder posterior adduction from 180º of abduction</td>
</tr>
<tr>
<td>XVII</td>
<td>Shoulder posterior adduction or extension</td>
</tr>
<tr>
<td>XVIII</td>
<td>Shoulder posterior extension</td>
</tr>
<tr>
<td>XIX</td>
<td>Shoulder lateral rotation at 90º of shoulder adduction and elbow flexion at 90º</td>
</tr>
<tr>
<td>XX</td>
<td>Shoulder medial rotation at 90º of shoulder abstraction and elbow flexion at 90º</td>
</tr>
</tbody>
</table>

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![Figure 1 - Flexitest: movement number XX (Araujo & Chaves, 2005)](image1)

![Figure 2 - Flexitest: movement number XV (Araujo & Chaves, 2005)](image2)
JH is significantly prevalent in patients with panic disorder, agoraphobia or both and can reflect a predisposition to suffer from anxiety, whereas the MVP has a secondary role in the association between hypermobility and anxiety\(^9,10\), the result of occasional alterations in the scarce collagen of the central nervous tissue\(^9,10\).

Gulpek et al.\(^9\), with the same objective, analyzed 115 individuals divided in 3 groups: Group 1 (n=42), patients with panic disorder with MVP; Group 2 (n=35), patients with panic disorder without MVP; and Group 3 (n=38), control group: individuals with MVP without any psychiatric disorder. The authors used the criteria by Beighton-Horan to assess the hypermobility syndrome and a two-dimensional echocardiogram to detect the MVP. The hypermobility syndrome was identified in 59.5% of the patients with panic disorder and MVP, in 42.9% of the patients without MVP and in 52.6% of the control group. Gulpek et al.\(^9\) no significant association was observed between the panic disorder and the hypermobility syndrome.

Cardiovascular disease with a higher risk of death is common in Marfan syndrome and these individuals present JH. It is a hereditary disease of the conjunctive tissue, of genetic origin, autosomal dominant, with variable expression; it affects mainly the skeletal, ocular and cardiovascular systems. The estimated prevalence is 1/10,000 individuals. The origin of the disease is in the mutation of the fibrillin gene (FBN-1), which is located in chromosome 15. The main cardiovascular alterations are the annuloaortic ectasia and the mitral valve prolapse\(^9,15\). Lopez et al.\(^14\) evaluated 21 children with Marfan syndrome, of which 62% of them were males, aged 9 months to 16 years. At the echocardiographic assessment, 52% of the patients presented valvular prolapse.

**Final considerations**

Joint hypermobility has been the object of several discussions as it affects the common population, predisposing these individuals to several organic alterations, of which the etiology is still debatable. Its characteristic is related to a genetic disorder of the conjunctive tissue that can cause pain and musculoskeletal alterations. The MVP is also a genetic disorder of the conjunctive tissue with possible chromosomal alterations, which affects the mitral valve and is diagnosed in 2.4% of the general population.

The inclusion of tests that measure the joint mobility in the clinical assessment can be relevant, as the identification of JH must lead to the investigation of several alterations that result from this genetic characteristic, including the MVP, thus providing early diagnosis and treatment, considering that the condition many times has an asymptomatic evolution. However, there is a lack of studies that can confirm the association between JH and the evolution and severity of MVP.

The genetic alterations in collagen composition seem to be the main cause of JH and MVP. However, there are no studies that can confirm this association, although they present high prevalence among them. Studies have also associated the MVP, JH and anxiety and panic disorders, which probably present associations caused by collagen alterations, resulting from occasional alterations in the scarce collagen of the central nervous tissue.

Few studies have correlated the mitral valve prolapse and JH using several methods of assessment. Furthermore, the methods used to evaluate joint mobility in several health conditions are considered outdated and limited. There is also need for histopathological studies associated to physical tests to confirm the effectiveness of these tests, associating them to the structural alterations of the joint components.

**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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**Study Association**

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**References**