The importance of magnesium status in the pathophysiology of mitral valve prolapse

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Abstract. Idiopathic mitral valve prolapse (IMVP) refers to the systolic displacement of one or both mitral leaflets into the left atrium, with or without mitral regurgitation. It is one of the most common forms of cardiac abnormalities among young people, especially in women. IMVP usually appears to be a benign condition and even capable of recovery. In a minority of cases IMVP may predispose to complications. The data suggest an autosomal dominant inheritance of IMVP that exhibits both sex- and age-dependent penetrance with variable expressivity and genetic heterogeneity. IMVP appear to be one form or aspect of latent tetany due to magnesium deficit (MDLT). The prevalence, latent nature, and symptomatology of these two conditions appear to be strictly similar. Primary magnesium (Mg) deficit may result from Mg deficiency (insufficient Mg intake) and Mg depletion (excessive urinary Mg loss). Constitutional factors (e.g. HLA-B35, type A behavior pattern) should be considered in the aetiology of Mg deficit (MD). MD may cause abnormal fibrosis, abnormalities in collagen synthesis as well as in the myocardium, capable of inducing mitral apparatus dyskinesia. MD is a part of a picture of metabolic abnormalities, alteration of immune and autonomic nervous systems, cardiac arrhythmias and thromboembolic phenomena in IMVP. Laboratory evaluation must involve plasma Mg, erythrocyte Mg, calcemia, calciuria, and daily magnesuria. Normal plasma Mg concentration does not rule out the diagnosis of primary chronic MD. The diagnosis of MD requires the oral Mg load test. Correction of symptomatology by this oral physiological Mg load (5 mg/kg/day) is the best proof that it was due to Mg deficiency. Mg therapy is essential and specific for IMVP. In the majority of cases MD is due to Mg depletion and the oral Mg supplementation must be combined with Mg-sparing diuretics or physiological doses of vitamin D. Partial “Mg analogues” (beta-blockers, verapamil, phenytoin) may prove to be useful in some cases.

Key words: magnesium deficit, magnesium deficiency, magnesium depletion, mitral valve prolapse, latent tetany, arrhythmias, mitral regurgitation, infective endocarditis, embolism

Introduction

Four decades after it was demonstrated that non-ejection systolic clicks and late systolic murmurs have a mitral valve origin and that a specific syndrome is associated with the primary degenerative condition of the mitral valve apparatus, numerous questions concerning the pathophysiology of this condition remain unanswered. Mitral valve prolapse (MVP) occurs when part of one or both leaflets of the mitral valve extend above the plane of the atrioventricular junction during ven-
tricular systole [1]. In most cases, MVP is primary and is due to an inherited abnormality of the mitral valve leaflets and their supporting chordae tendineae. MVP, however, can be caused by several other mechanisms including abnormal left ventricular wall motion in the setting of primary myocardial disease and/or myocardial ischemia, or rupture of chordae tendineae due to infective endocarditis. These and other mechanisms can be considered to be secondary causes of MVP [1-3]. These secondary causes probably form fewer than 5% of all cases [3]. This paper will focus on the idiopathic (primary) form of MVP (IMVP).

The prevalence of IMVP approaches 4-5% in the general adult population, with a higher incidence in women [4-9]. However Theal et al. [10] recently reported that IMVP has a much lower prevalence (2.2%-3.1%) and the prevalence of this cardiac anomaly is similar among different ethnic groups. Nevertheless, it is currently the most commonly diagnosed cardiac valve abnormality in clinical practice, and progressive degeneration of this valve now represents the primary cause of mitral valve dysfunction requiring replacement or repair [11]. The prevalence of IMVP in children and adolescents increases with age [12]. There is a striking decrease in female prevalence from the third decade on, reaching as little as a 1% incidence in women in their ninth decade. No such change in male incidence occurs after adolescence [6, 13].

There is a broad spectrum of severity of valve lesions, ranging from benign forms, through floppy valve to the stage of MVP. Over the past few decades many papers have appeared in the literature discussing various aspects of mitral valve structure and function. The term “bellowing mitral leaflets”, introduced by Carpentier specifies the physiological billowing of the mitral valve leaflet. The term “floppy mitral valve” defines the billowing of the leaflets connected with an increase in mitral valve area, elongation of chordae tendineae and the dilatation of the mitral valve annulus. These changes contribute to regurgitant flow into the left atrium. Intense billowing of the leaflets, together with prolapse of part of, or of one whole leaflet or both leaflets above the plane of the atrioventricular junction, is defined as MVP [14, 15].

Most evidence leads to the belief that MVP is a hereditary disease of connective tissue affecting the mitral valve and the bony and cardiac skeleton. Recently published reports suggest an autosomal dominant inheritance of the trait that exhibits both sex- and age-dependent penetrance with variable expressivity and genetic heterogeneity [16-18]. Loci for MVP, transmitted in an autosomal dominant manner, have been mapped to chromosome 16 (16p11.2-p12.1) [17] and recently to chromosome 11 (11p14.4) [16]. MVP may be associated with inherited disorders of connective tissue, i.e. Marfan’s syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta and pseudoxanthoma elasticum, the common feature of all of which is improper collagen and elastin synthesis.

The aim of this paper is therefore to review the role of magnesium (Mg) deficit in the pathogenesis of the primary form of MVP, its subjective and objective symptomatology, the possible occurrence of complications of IMVP, and the results of Mg treatment of IMVP.

The role of magnesium deficit in the aetiopathogenesis of IMVP

IMVP has been of great interest to clinical investigators for many years due to the controversial views on the etiology and pathogenesis of this condition and the many theories which have been advanced to explain its pathogenesis. These theories can be divided into two main categories. The first postulates myocardial involvement, while the second stresses the abnormality of the valve [19]. The so-called myocardial theory is based primarily on angiographic and hemodynamic findings. Thus, myocardial global or segmental contraction anomalies, abnormal volumetric compliance and left ventricular wall motion could all theoretically produce functional abnormalities of the mitral valve apparatus [20, 21]. Other morphological evidence lends credence to an abnormality of the valve itself as being responsible for prolapse [22].

Durlach & Durlach [23, 24] have hypothesized that latent tetany (LT) due to Mg deficit (MDLT) is a cause of IMVP. In fact the prevalence, latent nature and symptomatology of MDLT and IMVP appear to be closely similar. Nervous hyperexcitability, due to

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**Abbreviations**

IE – infective endocarditis  
IMVP – idiopathic mitral valve prolapse  
LT – latent tetany  
MD – magnesium deficit  
MDLT – latent tetany due to magnesium deficit  
Mg – magnesium  
MR – mitral regurgitation  
MVP – mitral valve prolapse  
TIA – transient ischemic attacks
chronic insufficient Mg intake, results in a non-specific clinical pattern with an associated central and peripheral neuromuscular symptomatology which is strictly similar to that which has been described in latent tetany and IMVP [25]. What is particularly noteworthy is the unique bidirectional association of IMVP and MDLT. Not only is IMVP common in patients with MDLT, but MDLT is almost universal in patients with IMVP. For example, it was shown by Durlach et al. [23], that the features of MDLT are present in the whole IMVP population while, conversely, there is a high incidence (between 25-33%) of IMVP in the group which showed neuromuscular hyperexcitability as a manifestation of Mg deficit (MD).

MDLT is an epidemiological feature still underestimated in many countries and affects at least 15-20% of the population [26]. Many clinical and experimental studies many have confirmed Mg plasma and intracellular deficit in IMVP [23, 24, 27-32]. Primary MD should be split into Mg deficiency and Mg depletion [33-36]. Mg deficiency is due to insufficient Mg intake. Based on long-term balance studies, Durlach et al. [26] and Seelig et al. [37] recommended a daily Mg intake of 6 mg/kg/day. However, this value is frequently not reached in developed countries; the mean Mg daily intake in such populations being only a little over 4 mg/kg/day [26, 38]. Mg depletion, on the other hand is due to deregulation of factors controlling Mg status, such as intestinal Mg hypoabsorption, urinary leakage, reduced Mg bone uptake and mobilization, insulin-resistance, stress, coffee excess and corticosteroid or catecholamine excess [30].

Autonomic dysfunction observed in IMVP may contribute to Mg depletion in this syndrome and exaggerated MD. Significant evaluation of plasma catecholamines and increased catecholamine excretion in patients with IMVP was found in previous studies [29-43]. Inhibition of Mg influx by catecholamines (via a beta-adrenergic receptor) [44, 45] will obviously result in a lower cell content of Mg, and may thus explain the lower than normal intracellular Mg concentration found in patients with IMVP [28, 46]. More recently, autonomic dysfunction in patients with IMVP has been confirmed by heart rate variability analysis (HRV). In recent years the measurement of sinus rhythm R-R intervals, apart from heart rate assessment, has become of greater importance due to its increasing role in variability analysis. At present, it is common knowledge that HRV analysis is a valuable method of functional autonomic system assessment as well as the essential prognostic factor in particular clinical states [47, 48]. In our study of 151 children the autonomic imbalance in patients with IMVP was reflected by significantly lower values of HF, the high frequency component (the parameter reflecting parasympathetic modulation) and significantly higher values of LF, the low frequency component (the parameter reflecting sympathetic modulation) as well as the LF/HF ratio during the night and during daytime compared to a control group of 165 healthy subjects [49]. Moreover, we found a significant positive correlation between serum Mg concentration and the HF value parameter and a significant negative correlation between serum Mg concentration and LF value parameter and the LF/HF ratio in the patients compared to the controls [27].

Support for this concept of excessive urinary Mg loss is provided by the results from studies which showed a strong positive correlation between urinary lactate and Mg excretion in echocardiographically proved IMVP [50]. Epinephrine exerts important metabolic effects on the enzymatic machinery that regulates the production of pyruvate and hence of lactate [51]. Norepinephrine has an intensive vasoconstrictive effect and, through secondary ischemia, may generate hyperlactataemia [27, 51]. Cohen et al. [28] suggest that metabolism in IMVP is associated with increased lactate and Mg excretion which are controlled by independent or indirectly related processes and conclude that stress could possibly be the common denominator of the urinary loss of both Mg and lactate, without these being interrelated. In fact stress is antagonistic to the three main hormonal elements of Mg homeostasis. It substitutes the depleting effect of large, lypolytic doses of catecholamines for the regulatory effects of physiologic doses of epinephrine, reduces the secretion of insulin and increases the excretion of taurine, thus reducing the levels of these two Mg-sparing hormones [26]. Additionally, stress induces urinary elimination of Mg by hypersecretion of corticoids and ADH and thyroid hormones [26]. Conversely, MD creates a state of hypersusceptibility to stress, even in cases of chronic marginal deficit [52, 53]. All these data confirm the suggestion that the MD in IMVP may be also caused by urinary loss and correspond to observations indicating that IMVP complicates LT, especially in the forms with hypermagnesuria [32].

Constitutional factors, e.g. behavioral type A and human leucocyte antigen (HLA) B35 should be considered in the etiology of MD in IMVP [23, 54]. The type A behavior pattern in humans is characterized by time urgency, impatience, extreme competitiveness and hostility when compared to its opposite or type B pattern. When stressed psychologically, type A individuals show a significantly greater increase in
plasma and urinary catecholamines and cortisol than type B individuals, and correspondingly greater changes in heart rate, blood pressure and vascular resistance [55, 56]. Altura [57] first suggested that the type A behavior pattern may be associated with Mg deficiency. Henrotte et al. [58] have studied the effect of a signal detection task on Mg metabolism of 20 type A and 19 type B individuals. Mental stress increased the urinary catecholamine excretion and serum levels of free fatty acids significantly more in type A than in type B patients. Plasma Mg increased and erythrocyte Mg decreased in type A subjects and type A than in type B patients. Plasma Mg increased and erythrocyte Mg decreased in type A subjects and there was no change in these levels for type B subjects.

Two population studies point out a highly significant association between IMVP and HLA-B35 [59, 60]. Moreover, HLA-B35 individuals seem to be more frequently found among stress-sensitive type A behavior subjects [61]. It is important in consider that healthy carriers of HLA-B35 have lower red blood cell Mg levels than noncarriers. Henrotte [62] has shown among 351 unrelated male blood donors, that 57 subjects carrying the HLA-B35 antigen exhibited lower erythrocyte Mg concentration (p<0.001) then the remaining 294 noncarriers. These relationships between MD and HLA-B35 may represent the basis of the concept of genetic control of Mg levels in human erythrocytes. More recently Henrotte et al. [63] have indicated that genetic factors controlling intra- and extracellular Mg levels are composed of at least three components: the major histocompatibility complex (MHC; HLA and H-2) associated genes, non-MHC genes, and tissue factors modulating the respective importance of the two sets of factors. This implies a genetic polymorphism of molecules playing a major role in Mg transport. Moreover, the same group has suggested that among other mouse and rat strains, those having lower blood Mg concentration are also those characterized by a higher humoral immune response and higher sensitivity to stress [61]. Similarly, HLA-B35 individuals exhibit impaired cytotoxicity and higher titers to antibodies after anti-influenza vaccination [64]. MD intervenes in the immunological system in both MDLT and IMVP by promoting immunoglobulin E formation and inducing pseudoallergic manifestations [23, 54]. In the subset of these patients carrying HLA-B35, a link may exist between these constitutional mechanisms of MD and hyperproduction of antibodies which may favor the appearance of infections [23, 65]. The occurrence of a high frequency of Candida albicans infection and hypersensitivity in individuals with MDLT and, conversely, of IMVP in individuals with chronic candidiasis may result from immune dysregulation due to chronic MD [65, 66].

Cardiac muscle may respond to MD with the “signs of tetany” reflected by alteration of collagen and of abnormal myocardial function the same as observed in IMVP [23, 54, 67-71]. These two mechanisms are compatible with the myocardial and valvular theories of MVP. More recent data have indicated that Mg deficiency may trigger a temporal sequence of events involving vasooconstriction, hemodynamic alteration and vascular endothelial injury to produce pro-inflammatory, pro-oxidant, and pro-fibrogenic (through activated cardiac fibroblasts) effects, resulting in initial perivascular myocardial fibrosis which, in turn, would cause myocardial damage and (frequently observed in IMVP hearts [72]) replacement fibrosis [73, 74].

Mg is essential in connective tissue metabolism. It influences the structural elements of extra cellular matrix, both fibrillar – collagens and elastin and non-fibrillar components – proteoglycans and structural glycoproteins. The integrity of the extra cellular matrix requires a balance between synthesis and degradation of these components. The extra cellular matrix degradation is essential for connective tissue remodeling and it is achieved by metalloproteinases [75].

As Mg lithospermate exerts an inhibiting effect on prolyl hydroxylase it can be regarded as antifibrotic. The hydroxy prolyl residues are essential for stabilization of newly synthesized procollagen. And this is the prolyl hydroxylase which is the target for pharmacological modulation in diseases in which collagen is overproduced. The Mg cation associated with the elastin core of elastic fibers plays a protective role in maintaining the extensibility of elastin. On the other hand it has been reported that the Mg deficiency may trigger a temporal sequence of events involving vasooconstriction, hemodynamic alteration and vascular endothelial injury to produce pro-inflammatory, pro-oxidant, and pro-fibrogenic (through activated cardiac fibroblasts) effects, resulting in initial perivascular myocardial fibrosis which, in turn, would cause myocardial damage and (frequently observed in IMVP hearts [72]) replacement fibrosis [73, 74].

Pages et al. [76] reported severe structural alternations in collagens and elastin in the aortic wall in Mg-deficient mice. These changes were related to the expression of matrix metalloproteinases -2 and -9, present in active forms in the Mg-deficient study group and under a form of zymogene in controls. It was suggested that the specific tissue inhibitors of metalloproteinases are inefficient in severe Mg deficiency. The relation of metalloproteinases and Mg remains to be elucidated. However, a specific co-localization of integrins – transmembrane receptors, and metalloproteinases was reported in the extra cellular matrix of cultured chondrocytes and it was suspected that the divalent cation dependent conformational changes of integrins regulate their
MG STATUS IN MITRAL VALVE PROLAPSE

Mitral valve prolapse syndrome (MVPS)

A number of patients with IMVP have symptoms which cannot be explained on the basis of valvular dysfunction alone [2, 8, 78, 79]. We classify these patients as suffering from "mitral valve prolapse syndrome" (MVPS). For many years MVPS has been of great interest to clinical investigators owing to the great variety of symptoms and the controversial views which exist on the pathogenesis of this syndrome. Patients with MVPS may develop symptoms at any age, but the greatest proportion became symptomatic in the second or third decades, with a higher incidence in women [80, 81].

Patients with MVPS complain of many symptoms, the most common of which are atypical chest pain, palpitation, dyspnea, fatigue, dizziness, syncope and anxiety [82-84]. The non-specific pattern of this symptomatology results in patients consulting a wide range of specialists. Many reasons for these symptoms and for the aetiopathogenesis of MVPS have been postulated. A cardiac origin for these symptoms has not been established. Some authors have suggested that symptomatic patients with IMVP, but without significant mitral regurgitation (MR) may manifest a constitutional, neuroendocrine-cardiovascular process resulting from a close, possibly genetic, relationship between IMVP and centrally or peripherally mediated states of autonomic, metabolic or neuroendocrine dysfunction [2, 27, 40, 68, 81, 85, 86]. Autonomic system dysfunction, hyperresponse to adrenergic stimulation, abnormal β-receptor function, catecholamine regulation abnormality, renin-aldosterone regulation abnormality, baroreflex modulation abnormality, or reduced intravascular volume have all been demonstrated in patients with MVPS [2, 15, 27, 40, 85-88]. In some reports the coincidence of migraine and MVP was considered [89, 90].

On the other hand, many of the symptoms associated with IMVP and their prevalence seem to be exactly similar to those in patients with both MVPS and MDLT [23-25, 28, 66]. Durlach et al. [24] suggested as long ago as 1982 that MVPS may be a simple evolutionary form of latent tetany due to Mg deficit. Support for this concept is provided by the results from several studies which showed that the symptoms of IMVP may be alleviated with Mg supplementation [23, 41, 91, 92]. The physiological properties of Mg can be demonstrated by the occurrence of symptoms due to in vivo Mg deficiency followed subsequently by its specific control with supplementation through physiological oral doses of Mg (less than 12 mg/kg/day). Durlach & Durlach [23] reported that after one to three years of Mg treatment, clinical and radiographic examination showed full recovery in 20% of their patients and partial recovery in 40%. Another group documented a significant reduction in weakness, chest pain, dyspnea, palpitation, and anxiety after 5 weeks of Mg supplementation in a double-blind, crossover study of 141 subjects with strongly symptomatic primary IMVP [41]. Correction of clinical symptoms after Mg supplementation at a physiological dose may indicate that these were due to Mg deficiency. More recently Martynov et al. [92]
reported complete or partial reduction of symptoms after 6 months of Mg therapy in more than half of 84 patients with MVPS. It should be pointed out, however, that they used a daily Mg dose of 3000 mg.

Several studies [24, 27, 28, 71, 66, 92] found a deficit of Mg in blood serum and in the lysates of erythrocytes of children and adults with MVPS. MD in patients with MVPS may indicate that the lack of Mg is responsible for at least some of the clinical signs and symptoms of this syndrome. Lichodziejewska et al. [41] found reduced serum Mg levels in 60% of 141 patients with MVPS. A deficit of Mg in blood serum was also reported in 50% of symptomatic children with IMVP [93]. Coghlan & Natello [91] reported low levels of Mg in erythrocytes in 50 of 94 symptomatic patients with IMVP, though the accuracy of the article was disputed [94]. Durlach et al. [24] reported significant differences between the concentrations of Mg in blood serum and in the lysates of red blood cells in patients with MVPS and those in a control group. It should be pointed out, however, that some investigators [29, 46, 9] do not confirm these observations. The observed discrepancies may result from the fact that the Mg content in the blood serum and erythrocytes represents less than 1% of the body’s total Mg store [4, 67]. For that reason variations in the total or ionized erythrocyte and plasma Mg concentration do not necessarily mean that similar changes exist in the Mg pool [95]. It is remarkable that not only does a low serum Mg concentration reflect a significant tissue Mg deficit but also that a moderate tissue MD can exist even when the serum values are normal. Thus, the presence of a normal mean Mg level in blood serum and lysates of red blood cells does not exclude decreased body stores of Mg.

The lymphocytes, representing a homogenous population of nucleated and metabolically active cells, seem to be more suitable for electrolyte studies and better reflect the Mg content in the human body than erythrocytes and the serum level of this cation [88]. Recently Kituński et al. [46] investigated 49 patients with MVPS and 30 healthy individuals, to compare the Mg levels in their blood plasma and lysates of lymphocytes in order to find out if Mg deficit really exists in this syndrome. They found a significantly lower concentration of Mg lysates of the lymphocytes in patients with MVPS than in the control group. Additionally, the distribution of Mg values in patients with MVPS was markedly left-skewed (towards lower values). It should be emphasized that they found no significant differences between the arithmetic means and the median values of Mg concentration in the blood plasma in the two groups. These results strongly suggest a MD in MVPS and indicate the low level of usefulness of determining the concentration of Mg cation in blood plasma if it is for the purpose of discovering lower than normal resources of body Mg in patients with MVPS. Another study [28] also found a significantly lower mean lymphocyte Mg concentration (76 mEq/kg dry weight) than the lower laboratory limit of normal values (78 mEq/kg dry weight).

It should be stressed, however, that a similar array of symptoms may be produced by increased adrenergic activity [2] as shown by the increased plasma catecholamine levels [30, 42] and increased catecholamine excretion [41] in patients with MVPS. Recently, the autonomic dysfunction observed in patients with MVPS has been confirmed by HRV analysis. Kochidakis et al. [85] proved that parasympathetic activity declined and sympathetic activity increased in symptomatic adults with IMVP. Recently similar observations have been reported in children with IMVP by Bobkowski et al. [96]. In a group of 151 children, they found that the autonomic imbalance in symptomatic patients with IMVP was reflected in significantly lower values of high frequency component (HF, the parameter reflecting parasympathetic modulation) and significantly higher values of low frequency component (LF, the parameter reflecting sympathetic modulation) as well as the LF/HF ratio during the night and during daytime, compared to asymptomatic IMVP children and adolescents.

The increased adrenergic activity detected in adults that may lead to increased Mg urinary excretion due to renin-angiotensin-aldosterone system activity, may be an additional predisposing factor to MD in patients with IMVP [41, 42, 85, 87, 97]. Grochowicz et al. [97] proved that an increase in adrenaline urinary excretion is associated with increased Mg urinary excretion in patients with mild to moderate heart failure. Recently, frequency domain HRV analysis revealed a significant relation between the serum Mg concentration and autonomic activity in children with IMVP [27]. In this study there was a positive correlation between the serum Mg values and parasympathetic activity and a negative correlation between the serum Mg values and sympathetic activity. The degree of autonomic modulation imbalance, in the form of increased sympathetic activity as shown by an increased LF/HF ratio, was significantly related to a low serum Mg concentration. The experimental observations of the effects of various types of stress on electrolyte and catecholamine levels are consistent with clinical observations of patients with latent tetany. Excretion of catecholamines was 89% greater (p<0.001), and excretion of vanillylmandelic
acid was 53% greater (p<0.01) in latent tetany patients than in controls. This increase in adrenergic activity correlates with lower serum and erythrocyte Mg concentration [98].

Based on the available data, it is difficult to conclude which is cause and which is effect in the observation between sympathetic activity and serum Mg concentration in patients with MVPS. Increased adrenergic activity leads to Mg depletion but, on the other hand, MD can increase catecholamine secretion and, in consequence, cause increased sympathetic activity. However, in a double-blind, cross-over study in a group of 35 symptomatic patients with MVP, Lichodziejewska et al. [41] found that the mean daily excretion of norepinephrine decreased significantly after 5 weeks of Mg supplementation, compared to a control group who received a placebo. These results suggest that the lessening of symptoms could be due to the antiadrenergic effect of Mg in MVPS. In fact, the ability of Mg to alleviate catecholamine-induced toxic effects has been previously reported in both experimental [99] and clinical [100] settings.

Besides the crucial role of MD in the MVPS, it should be pointed that the aetiopathogenesis of MVPS may be complex, especially in those patients with a multisymptomatic clinical picture of this disorder.

Litman & Friedman [89], during the evaluation of 230 patients with MVPS, discovered a remarkably high incidence of migraine syndrome in these patients. Certain clinical features in both groups suggest a relationship between these two pathological states. Paroxysmal tachycardia, syncope, vertigo and chest pain have been linked to both migraine and MVPS. Moreover, several studies proved the MD in the migraine patients. Thomas et al. [101], in a comparative study in migraine patients and controls, found a significantly greater erythrocyte and serum MD in the migraine group. Similar findings have been noted in a juvenile group [102]. The results have been confirmed by Trauniner et al. [103] who performed an oral Mg load test and noted Mg retention in migraine sufferers, which indicated a systemic Mg deficiency in this group.

Mg deficiency could play a pathophysiological role in migraine expression in several different ways. Mg concentration has an effect on serotonin receptors, nitric oxide synthesis and release, N-methyl-D-aspartate receptors, and a variety of other migraine related receptors and neurotransmitters. Mg, as physiological antagonist of calcium, can exert a beneficial effect in familial hemiplegic migraine, which is supposed to be calcium channelopathy. The Mg antinamigraine effect can result from relaxation of vascular tone or inhibition of platelet hyperaggregability [104]. Mishima et al. [105] suggested that reduced platelet ionized Mg in patients with tension-type headache is related to abnormal platelet function.

Moreover, several studies [104, 106, 107], but not all [108], have proved the efficacy of Mg therapy in migraine treatment and prophylaxis. Mauskop & Altura [106] found that Mg infusion results in a rapid and sustained relief of acute migraine in patients with lowered levels of ionized Mg. Two double-blind studies suggested the efficiency of chronic oral Mg supplementation in migraine headaches [104, 107]. Wang et al. [104] found a significant decrease over time in headache frequency and lower headache severity in children with migraine after oral Mg treatment. Also Peiker et al. [107] noted the reduced attack frequency, duration and intensity, as well as the decrease in number of days with migraine and the drug consumption in adults with migraine, after 12 weeks of high-dose (600 mg per day) oral Mg treatment. However in another double-blind study, Pfaffenrath et al. [108] did not find Mg efficacy in migraine prophylaxis compared to placebo group.

These findings raise the problem of the relationship between migraine and other pathologies, including chronic MD, MDLT and also IMVP.

**Prognosis and complications related to IMVP**

While the data and conventional wisdom presented in the medical literature state that the prognosis of patients with IMVP is benign in the majority of instances, serious complications may and do occur. These include mitral insufficiency, cardiac arrhythmias, infective endocarditis, thromboembolic phenomena and sudden death. In a long-term prospective follow-up of 300 patients with IMVP with an average follow-up of 6 years, 50% of the patients had a stable course, except for supraventricular tachycardia and mild mitral regurgitation [24]. Of the remaining 150 patients, three suffered sudden cardiac death, ventricular fibrillation developed in 2, ventricular tachycardia in 56, and infective endocarditis in 18, while 28 underwent mitral valve repair, 11 suffered cerebrovascular accidents, and 8 suffered from severe mitral regurgitation (MR). Nishimura et al. [109] conducted a prospective study of 237 minimally symptomatic IMVP patients during a mean follow-up period of 6 years. Of this group, 10 patients suffered cerebrovascular accidents, 17 underwent mitral valve replacement and 3 experienced infective endocarditis. Overall mortality
among this group equaled that of the general population, but these patients were selected because they were free of symptoms or their symptoms were minimal. In a retrospective study of 456 patients with IMVP, Marks et al. [110] found that those with thickened and redundant valves had an increased risk of infective endocarditis, mitral regurgitation and mitral valve repair. It appears necessary to define those subgroups of IMVP patients at greater risk of complications more effectively.

Mitral regurgitation
IMVP is probably the most common cause of MR. In certain patients with IMVP, the mitral valve abnormalities progress with time and mild MR may become severe. The development of MR is due to evolution of the degenerative process of the different elements of the mitral valve apparatus and is usually gradual, permitting adaptive compensatory mechanisms. Although progression is slow, it may have an abrupt onset when secondary to ruptured chorda tendineae or infective endocarditis [110-112]. Factors that accelerate the natural course of MR include infective endocarditis, the development of atrial fibrillation, left atrium and left ventricular dysfunction, and chordae tendineae rupture [111]. Interestingly, although IMVP is more prevalent in young women, men over the age 45 years with IMVP have a 2- to 3-fold greater risk of developing a significant progressive MR that ultimately requires surgery. Additionally, aging, posterior leaflet prolapse, thickened mitral valve and holosystolic murmurs were found to be important predisposing factors for severe MR in IMVP [113]. Severe MR is associated with an increased risk of developing clinical symptoms, arrhythmias, infective endocarditis, pulmonary hypertension, congestive heart failure and sudden death [2, 114-117].

Infective endocarditis
Infective endocarditis (IE) is another complication of IMVP. IMVP is reported to be one of the most common causes of IE. Reviews of documented endocarditis cases have consistently shown IMVP to be the underlying defect in nearly one-third of cases. The risk of developing IE is approximately five times greater in patients with IMVP compared to those without this valvular abnormality [118-120].

The pathogenesis of IE complicating IMVP is similar to that for other endomycocardial defects. In IMVP, mechanical stresses, turbulent blood flow, and regurgitant jet streams may injure the endocardial surface, resulting in exposed collagen and the consequential deposition of platelets and fibrin. When a transient bacteraemia occurs, microorganisms may adhere to the thrombus, resulting in microbial colonization [121]. Risk factors for the development of IE in patients with IMVP include MR, valvular redundancy/thickness, male gender, and age>45 years [4, 113, 117, 118, 109]. The current consensus statement from the American Heart Association [122] includes MVP with MR and/or thickened leaflets among the cardiac conditions that warrant endocarditis prophylaxis.

Cardiac arrhythmias
Cardiac arrhythmias, among which serious ventricular arrhythmia is of major importance, affect many individuals with IMVP. Several studies, but not all [123], indicate that the incidence of various types of arrhythmias is greater in IMVP subjects than in the general population [124-127]. A high incidence of arrhythmias has also been reported in children and teenagers with IMVP by many investigators [128-132]. Sudden cardiac death, while rare, is a devastating event that occurs in relatively young individuals with an arrhythmia substrate [121-133]. Ventricular arrhythmia occurs in 48-80% adults with IMVP including ventricular tachyarrhythmia in 5-21% of these patients, but with a lower incidence in children [123, 128, 131, 132, 134]. Repetitive ventricular ectopy or complex ventricular arrhythmias are strong indicators of the electrical instability of the heart in these patients. Multiple aetiologies have been postulated to explain the reported increase in arrhythmias in IMVP. Potential sources of arrhythmia in IMVP exist in the prolapsing valve itself and also in the valve support apparatus, the conduction system, and in the atrial and ventricular myocardium. Mechanical stretch and distortion of the prolapsing mitral valve or its papillary muscle support might initiate arrhythmias. Additionally, mitral insufficiency [116], abnormal innervation of a floppy mitral valve, increased QT dispersion, QT interval prolongation, myocardial fibrosis and autonomic dysfunction may all contribute to ventricular arrhythmias [116, 135]. Electrolyte disturbances have a crucial place among the probable causes of ventricular arrhythmias. However, it should be emphasized that it is very difficult to establish the role of hypomagnesaemia and its possible arrhythmogenic risk in vivo. This depends on various factors. Additionally, the only clinical data available are determinations of total plasma magnesium and the urinary excretion of magnesium. It is well known that neither of these measurements is very
representative of the body’s content in that the plasma quota represents less than 1% of total Mg. While bearing in mind the limitations of this method for identifying a MD, the association between a reduction in serum Mg concentration and the occurrence of ventricular arrhythmias in patients after myocardial infarction, congestive heart failure, long QT syndrome, after cardiac surgery, and in patients with a morphologically normal heart, is well established [136-140]. However, Tsuji et al. [138] did not find any correlation between hypomagnesaemia and the incidence of ventricular premature complexes with a frequency of more than 10 per hour.

More recently, the administration of Mg has proved to be effective in managing arrhythmias, at least in three distinct clinical settings – digitalis toxicity, long QT syndrome, and after myocardial infarction – even in the absence of overt hypomagnesaemia [137, 141, 142]. In a prospective randomized trial, Balkin et al. [143] showed that, following acute myocardial infarction, intravenous Mg was as effective in preventing potentially lethal arrhythmias as propranolol. There are limited data regarding this problem in patients with IMVP. Lower serum Mg and potassium concentrations were observed in children with IMVP and ventricular arrhythmias as compared to those without arrhythmias [93]. Moreover, in the same study, a negative correlation of serum Mg concentration and the degree of ventricular arrhythmias, assessed according to Lown’s scale [144], was revealed.

The mechanism of the antiarrhythmic action of Mg has not yet been fully elucidated, although various hypotheses have been made. The fact that Mg is an important cofactor of the Na-K pump has led to the hypothesis that a lack of Mg may result in reduced Na-K pump activity, resulting in various possible consequences for the voltage-dependent membrane channels and changes in the resting potential and repolarization process in cardiac myocytes [140, 145]. A MD causes disturbances in the transport and diffusion of potassium, sodium and calcium across the membranes, which leads to electrical instability and thereby increases the susceptibility to arrhythmias [116, 141, 142, 145]. Experimental studies show the Mg inhibitory effect on early afterdepolarizations, ectopic triggered automaticity and late afterdepolarizations. Aomine et al. [146] reported the inhibition effect of Mg on aftercontraction in the rat papillary muscle and delayed afterdepolarizations, early afterdepolarizations and triggered activity in Guinea pig myocytes. The Mg solution caused a considerable decrease in the transient inward current amplitude and frequency, as well as inhibiting the calcium transient underlying delayed afterdepolarizations and triggered activity. The authors have suggested that the Mg effect is probably due to combination of a shift of the threshold of various ion channels to less negative potentials, a decrease in calcium (Ca^{2+}) influx via calcium channels, a block of several potassium channels and/or a block of sodium-calcium exchanger [146].

It is also possible that the duration of MD is an important factor in the pathogenesis in the development of arrhythmias. The QT dispersion value reflects the local differences in ventricular repolarization time. Some cardiac diseases influence these differences, causing increased risk of ventricular arrhythmias in the re-entry mechanism. A close relation between QT dispersion, which is an indirect non-invasive measurement of the inhomogeneity of myocardial repolarization, and ventricular tachycardia has been shown in congenital long QT syndrome [147], in hypertrophic cardiomyopathy [145] and following myocardial infarction [148]. Several investigators have shown an increased QT dispersion value in adults and children with IMVP [149-152]. Moreover, increased QT dispersion may play a role in the genesis of cardiac arrhythmias in IMVP, since QT dispersion is a fairly good marker for identifying the high-risk group for ventricular arrhythmias and furthermore, there is a significant relation between QT dispersion and the degree of ventricular arrhythmias in patients with IMVP [149, 152]. A negative correlation between the cellular tissue Mg level and QT interval dispersion and the positive influence of Mg on repolarization homogeneity and a decrease in the QT dispersion value has been found in both clinical and laboratory investigations [139, 153, 154]. The MD observed in patients with IMVP may influence the increase in QT dispersion and, through this mechanism, contribute to the occurrence of ventricular arrhythmias. In the group of 151 IMVP children observed in our Department, a significant negative correlation between the serum Mg concentration and the QT dispersion value was revealed (unpublished data). A relation between QT dispersion and the concentrations of serum sodium, calcium and potassium was not observed in this group. Mg has been proved to have an inhibitory effect on platelet aggregation and fibrination which reduces the probability of coronary embolism, the formation of ischemic necrosis and, in consequence, reduces the probability of arrhythmias [155]. This conclusion appears to be of a considerable significance as a tendency to platelet aggregation was observed in IMVP [156]. Chesler et al. [157] also
suggested that myocardial ischemia due to embolism could be the cause of ventricular arrhythmias in myxomatous mitral valves.

All these findings indicate the wide, potential antiarrhythmic effect of Mg. The efficacy of conventional antiarrhythmic agents is improved by Mg administration. However, in patients with MD, the rhythm disturbances are often resistant to standard antiarrhythmic treatment and unfortunately the risk of a proarrhythmic effect of this therapy increases. The qualification of IMVP patients with no prior Mg supplementation for antiarrhythmic treatment, should therefore be carefully considered due to its only having a therapeutic effect in the majority of these patients, but not all. Nevertheless, it should be realized that protecting the patient from a MD by Mg supplementation is the first and the best strategy to keep the patient free from cardiac arrhythmias.

**Thromboembolic phenomena**

The association of IMVP and stroke was described for the first time by Barnett [158] in 1974 when he reported four patients with stroke and IMVP documented by cardiac angiography. However, the risk of stroke appears to be low [10]. IMVP is identified by echocardiography in 6–40% of individuals with stroke or transient ischemic attacks (TIA), with a higher prevalence in young patients [159-164]. IMVP surface characteristics may predispose to endothelial disruption with platelet aggregation, infective endocarditis, or nonbacterial thrombotic endocarditis, all clinical entities associated with thromboembolic phenomena. Platelet or fibrin thrombi have been identified on the surface of prolapsed mitral valves at autopsy in numerous reports [165-168]. At autopsy, Pomerance & Davies [167] identified gross thrombi on the mitral valve in 35% of the valves of patients with IMVP. In this study, valves without thrombi on the mitral valve in 33% of the valves of autopsy, Pomerance & Davies [167] identified gross lesions frequently had microscopic thrombi. The occurrence of thrombi on the mitral valve leaflets has also been reported in echocardiographic studies of patients with IMVP [169-171]. Emboli from valvular thrombi are the presumed mechanism of stroke or TIA in patients with IMVP. It is essential to realize that several other diseases associated with IMVP, such as atrial fibrillation, atrial septal aneurysm, patent foramen ovale and subacute bacterial endocarditis are potential causes of stroke, independent of IMVP.

Several studies have shown increased platelet aggregation in IMVP [172, 173]. In addition, the lesions of mitral leaflet endothelium observed in IMVP may be conducive to thrombus formation due to activation of platelet aggregation by collagen. However, there are no data concerning the relation between the Mg concentration and platelet aggregatory activity in patients with IMVP, but it is possible that the MD observed in this group may be crucial in this process. MD and its association with platelet hyperreactivity have been well recognized in a variety of diseases, including diabetes mellitus [159] and acute myocardial infarction [115]. The increased platelet aggregability was suggested by Litman & Friedman [89] to be the common pathophysiologic mechanism related to emboli and strokes in migraine.

Mg has been shown to reduce platelet aggregation both in vivo and in vitro. Sheu et al. [155] demonstrated that the pharmacological concentrations of Mg sulphate employed to inhibit platelet aggregation in vitro are reasonably close to those of blood concentrations obtained during a Mg sulfate regimen in vivo. Serebruany et al. [174] found significant increases in ADP-induced and collagen-induced platelet aggregation, and decreased plasma antithrombin-III concentration in female Yorkshire swine after seven weeks on an Mg-deficit diet, when compared to baseline. The study of Gawaz et al. [175] showed a significant prolongation of in vitro bleeding time of 30% and inhibition of fibrinogen-mediated aggregation of washed platelets. In the same study, intravenous administration of Mg2+ to healthy volunteers inhibited both ADP-induced platelet aggregation by 40% and binding of fibrinogen by 30%. In vitro studies have shown reduced platelet release of β-thromboglobulin and thromboxane B2 with increasing Mg concentrations [176-178]. Hwang et al. [176] reported that Mg reduced thrombin-stimulated Ca2+ influx in platelets. The study of Sheu et al. [155] suggests that Mg sulphate inhibits agonist-induced (i.e. collagen) human platelet aggregation. This inhibitory effect may involve the two following mechanisms. First, Mg sulphate may initially induce membrane fluidity changes on the platelet membrane, with a resulting interference of fibrinogen binding to the platelet surface glycoprotein IIb/IIIa complex and activation of phospholipase C, followed by inhibition of phosphoinositide breakdown and thromboxane A2 formation, thereby leading to inhibition of both intracellular Ca2+ mobilization and phosphorylation of protein 47. Second, Mg sulphate triggers the formation of cyclic AMP, which subsequently inhibits phosphoinositide breakdown and protein kinase C activity, finally resulting in inhibition of both the phosphorylation of protein 47 and intracellular Ca2+ mobilization [155]. This is in accordance with the concept that intracellular Ca2+...
release is responsible for the ATP release reaction [179].

Apart from its direct antiplatelet effect, oral Mg therapy has been shown to improve endothelial function significantly in patients with coronary artery disease [180]. An antithrombotic effect can also be derived from nitric oxide and prostacyclin, as Mg has been shown to stimulate the release of these vasodilating and anti-aggregatory substances from the endothelium [181, 182].

The MD observed in IMVP patients may result in increased platelet aggregation and the deterioration of endothelial function and, as a consequence, may contribute to thrombus formation in the areas of damaged mitral valve endothelium. Although there have been no long-term studies concerning the efficiency of supplemental Mg in reducing thromboembolic complication prevalence in IMVP, in the light of the data which are available, oral Mg therapy seems to be highly advisable in the prevention and treatment of thromboembolic complications in these patients. Prophylactic Mg administration should be considered mainly in patients with redundant or thickened mitral valves and in those with other diseases associated with IMVP such as atrial fibrillation, subacute bacterial endocarditis, atrial septal defect and patent foramen ovale, all of which are potential causes of ischemic strokes of cardioembolic etiology. It should be noted, however, that in these patients Mg treatment does not exclude the use of appropriate antiplatelet or anticoagulation therapy where indicated.

**Treatment**

IMVP would usually appear to be a benign condition and is even capable of recovery in a minority of individuals. In some cases IMVP may predispose to complications. It is thus essential to identify adverse prognostic factors such as very marked symptomatology and, in particular, ventricular arrhythmias, evidence of mitral regurgitation, thickened mitral valves, increased QT dispersion and prolongation of the QTc interval, transient ischemic attacks, immunological disorders, a high "excitability index", a family history of sudden death, and a Mg depletion [183]. Patients with IMVP and MR and/or with thickened leaflets require endocarditis prophylaxis in the presence of any circumstances likely to result in bacteraemia [122].

Physiological oral Mg load constitutes the best tool for diagnosis of Mg deficiency and the first step of treatment in IMVP [34, 36]. However the clinician should discriminate between two types of MD in IMVP patients: Mg deficiency due to an insufficient Mg intake and Mg depletion related to dysregulation of Mg status. As the average daily intake of Mg in the population at large is below the recommended dietary amount [26, 37, 38] physiological oral Mg supplementation of 5 mg/kg/day is easy and can be carried out in the diet or with Mg salts [34]. Tolerance of these physiological doses is excellent. Practically, overt renal failure is the only contraindication for such treatment. After long term of Mg treatment, the symptoms, as well as the echocardiographic data may be partially or even totally reversed. In the study of Durlach & Durlach [23] on 42 cases with IMVP, total recovery (clinical and echocardiographic) was observed in 20% of the cases after 3 years of Mg supplementation and partial recovery in 40% of the cases. These findings strongly indicated that the improvement of the echocardiographic changes may depend on very prolonged treatment. On the other hand, the early treatment of MDLT should prevent the development of MVP [183]. It should be emphasized that the maintenance oral treatment of recommended doses of Mg meant to balance Mg deficiency are devoid of any toxicity since their purpose is to restore to normal the insufficiency of the Mg intake [34].

As was pointed out above, MD in IMVP may be due to Mg depletion and is not usually controlled by simple nutritional supplement but requires the administration of Mg. In patients with renal loss of Mg, agents that reduce urinary Mg, either Mg-sparing diuretics i.e. spironolactone (100 to 200 mg/day), amiloride (5 to 10 mg/day), or hygienic life style and tranquilizer prescription may be effective. If these fail, or immediately in cases without urinary Mg leakage, Mg fixing agents (pharmacological doses of vitamin B6 and physiological doses of vitamin D) are indicated [34].

At the beginning of the 1980s, links between Mg and selenium status were reported [184, 185]. Glutathione peroxidase may be lowered either by selenium or MD. Jimenez et al. [186] reported decreased selenium absorption and retention and erythrocyte concentration of selenium in Mg deficient deficit rats. On the other hand, selenium deficiency may contribute to Mg status. Recently, in an experimental study, Sakly et al. [187] showed increased magnesium fractional reabsorption in a group receiving only selenium and in a group receiving selenium in combination with vitamin E, in comparison with the control animals. Evidence exists that in some cases in which MD was not controlled by simple physiological oral supplementation, Mg depletion was cured after two
months of 200 µg/day selenium in addition to the same Mg supplementation [188]. According to Durlach et al. [189], as good prognostic factors to be considered in Mg deficiency are the latency, the moderate onset of clinical signs, the absence of auscultatory symptoms, the absence of valve leaflet redundancy and the absence of mitral regurgitation, normal body weight and no prior estrogen therapy, as well as the MD due to insufficient Mg intake. By contrast, the factors of poor prognosis pointed out, are connected with severe symptomatology, including ventricular arrhythmias, presence of auscultatory symptoms, redundant valves, prolongation of QTc interval, insufficient body weight, thromboembolic complications due to improper platelet aggregation, immunological disorders, genetic factors (carriers of HLA B35), family history of sudden death and MD due to depletion.

Patients with IMVP hardly ever require parenteral Mg treatment. Paroxysmal cardiac arrhythmias (particularly polymorphic and monomorphic ventricular tachycardia) are the main indication for intravenous Mg administration. The effects of parenteral Mg on heart functions include reduced excitability and increased myocardial electrical stability, reduced heart rate and prolonged ventricular diastolic time, and delayed stimulus conduction due to prolongation of atrioventricular conduction [154, 190, 191].

Many diverse compounds are able to palliate some important elements of the symptomatology of both clinical and experimental MDLT, more or less completely. These include beta-blockers (propranolol), calcium antagonists (verapamil), and antiarrhythmic and/or antitetanic agents (phenytoin) [23, 192]. These compounds, which may be considered as “partial Mg analogues”, act either through their pharmacodynamic effects or through physiopathological interventions and may be used in cases of failure of the initial stages of therapy for Mg depletion [94, 192]. Verapamil and phenytoin are rarely used in clinical practice in patients with IMVP because of their limited clinical efficiency (verapamil) and the increased risk of many side-effects during a prolonged course of treatment (phenytoin). Beta-blockers are the most widely used “partial Mg analogues” employed in the treatment of IMVP. These are, however, not free of commonly known side-effects.

**Conclusion**

Mg deficit is one of the most frequent electrolyte abnormalities in current clinical practice. IMVP appears to be a frequent complication of MDLT. While a complete understanding of the role that Mg plays in the etiology, pathophysiology and treatment of IMVP is lacking, it is clear from the growing body of evidence summarized above that MD plays a crucial role in this mitral disorder. The disease occurs in 5% of the general population and is becoming a serious social problem. Early diagnosis (preferably in childhood) and the early introduction of Mg supplementation may alleviate the symptoms associated with IMVP and may protect asymptomatic patients from the onset of symptoms of LT.

**Acknowledgments**

The authors wish to thank Professor Geoffrey Shaw for his critical reading of this manuscript.

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