Clinical Symptoms of Mitral Valve Prolapse Are Related to Hypomagnesemia and Attenuated by Magnesium Supplementation

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Mitral valve prolapse syndrome (MVP) is a frequent disorder characterized by a number of complaints which lessen the quality of life. The pathogenesis of MVP symptoms has not been fully elucidated. Hyperadrenergic activity and magnesium deficiency have been suggested. This study was designed to verify the concept that heavily symptomatic MVP is accompanied by hypomagnesemia and to elucidate whether magnesium supplementation alleviates the symptoms and influences adrenergic activity. We assessed serum magnesium in 141 subjects with heavily symptomatic primary MVP and in 40 healthy controls. Decreased serum magnesium was found in 60% of patients and in 5% of controls ($p < 0.0001$). Patients with low serum magnesium were subjected to magnesium or placebo supplementation in a double-blind, crossover fashion. Typical symptoms of MVP ($n = 13$), intensity of anxiety, and daily excretion of catecholamines were determined. After 5 weeks, the mean number of symptoms per patient decreased from 10.4 ± 2.1 to 5.6 ± 2.5 ($p < 0.0001$), and a significant reduction in weakness, chest pain, dyspnea, palpitations, and anxiety was observed. Increased noradrenaline excretion before and after magnesium was seen in 63% and 17% of patients, respectively ($p < 0.01$). Mean daily excretion of noradrenaline and adrenaline was significantly diminished after magnesium. It is concluded that many patients with heavily symptomatic MVP have low serum magnesium, and supplementation of this ion leads to improvement in most symptoms along with a decrease in catecholamine excretion. *©1997 by Excerpta Medica, Inc.*

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The pathogenesis of symptoms of mitral valve prolapse (MVP) has not been fully elucidated. Some investigators[1–3] have found magnesium deficiency to have a causal relation to the clinical picture of MVP, although the effect of magnesium supplementation has not been definitely established (only 2 uncontrolled studies have addressed this issue[4,5]). Other workers[6–8] point to enhanced adrenergic activity as a possible cause of symptoms. The present study was designed to confirm or refute the concept that heavily symptomatic MVP is accompanied by hypomagnesemia. If so, the clinical picture of MVP may be improved by magnesium supplementation, and this was the aim of the study. We also investigated the influence of magnesium supplementation on catecholamine excretion.

METHODS

Patient population: The study group consisted of 141 subjects (124 women and 17 men, aged 16 to 57 years, mean ± SD 31 ± 9) with heavily symptomatic MVP who were free of other diseases. They were enrolled in the study from January 1989 to October 1995. During that period, 529 previously nontreated persons had been referred to the outpatient unit of our cardiology department because of suspected MVP. The diagnosis was confirmed by echocardiography in 217 patients. Thirty-two patients with concomitant diseases and 44 with mild symptoms were excluded. The remaining 141 persons formed the study group. The baseline characteristics of the study population are listed in Table I.

Control group: The incidence of hypomagnesemia in the sample of healthy persons living in the same district as patients with MVP was established. The control group consisted of 40 unselected persons (30 women and 10 men, aged 19 to 49 years, mean ± SD 33 ± 7). They proved to be healthy based on routine examination, chest x-ray, electrocardiogram, echocardiography, and routine laboratory tests.

Methods: The echocardiogram was recorded using a 3.5-MHz transducer ultrasonograph (Acuson 128 XP/10, Acuson Corporation, Mountain View, California, or Ultramark 8, Advanced Technology Laboratories, Bothell, Massachusetts) (M-mode, 2-dimensional view and spectral Doppler flow). MVP was diagnosed in accordance with the criteria of Levine et al.[9] They include mitral leaflet displacement above the annular hinge points in the apical 4-chamber view, and in 1 of the long-axis views of the left ventricle. Analysis of the echocardiograms was performed by 2 independent observers unaware of the study protocol.

Heavily symptomatic MVP was arbitrarily defined. Patients who had at least 7 of 13 symptoms

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TABLE I Characteristics of Patients (n = 141) With Heavily Symptomatic Mitral Valve Prolapse

Characteristics	Number (%)	Incidence of Clinical Symptoms*	Number (%)
Men	17 (12)	Chest pain	137 (97)
Women	124 (88)	Palpitations	135 (95)
Auscultation		Anxiety	129 (92)
Click	62 (44)	Hyperemotional	129 (92)
Murmur	12 (9)	Dyspnea	127 (90)
Both	64 (45)	Headache	127 (90)
None	3 (2)	Weakness	123 (87)
Heart rate (beats/min)	82 ± 8.7	Numbness	123 (87)
(mean ± SD)		Fainting	113 (80)
Blood pressure (mm Hg)		Dizziness	107 (76)
(mean ± SD)		Low vital energy	105 (75)
Systolic	111 ± 12	Musculoskeletal pains	95 (67)
Diastolic	71 ± 10	Cramps	88 (62)

*Number of symptoms per patient: 10.9 ± 1.7 (mean ± SD).

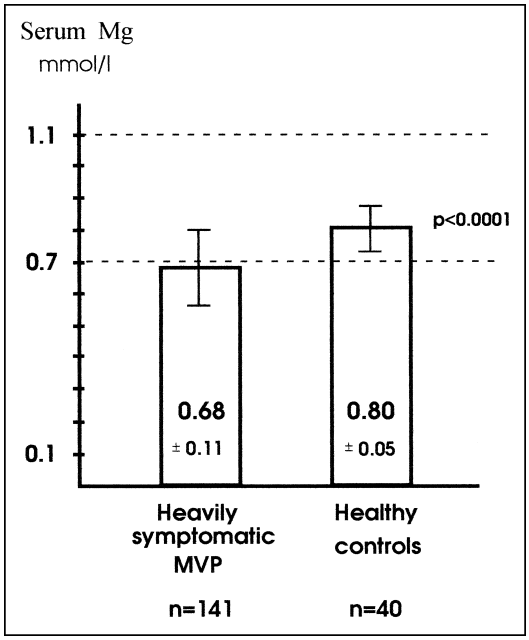

FIGURE 1. Serum magnesium (Mg) (mean ± SD) in patients with mitral valve prolapse (MVP) and healthy controls. *Broken lines* indicate normal range.

most frequently observed in those with MVP[1,3,6,10] were considered as ''heavily symptomatic'' (Table I). The presence of these symptoms was established according to the questionnaire by an independent investigator unaware of the study protocol.

The intensity of anxiety was evaluated according to Spielberger's ''TPI'' psychological questionnaire.[11] The level of anxiety was defined as low, moderate, or high. The questionnaires were analyzed by an independent investigator unaware of the protocol of the study.

Adrenaline and noradrenaline excretion in daily urine was assessed by the spectrofluorometric method.[12] Upper normal values in our laboratory are 7.5 μg/24 hours for adrenaline, 37 μg/24 hours for noradrenaline.

Serum magnesium was determined by atomic absorption spectrophotometry.[13] Normal levels range from 0.7 to 1.1 mmol/L according to the guidelines of the Commission of Experts of the Society for Magnesium.[14]

The protocol was approved by the ethical committee of the Postgraduate Medical School in Warsaw.

Study design: Serum magnesium was determined on 3 consecutive days in 141 patients in the study group and in 40 healthy controls. Those with serum magnesium <0.7 mmol/L in at least 1 sample were considered to have hypomagnesemia. The lowest value in each patient was taken for further calculations. Patients with hypomagnesemia were subjected to magnesium supplementation.

Magnesium supplementation was carried out in a double-blind, placebo-controlled, crossover fashion. Eligibile patients were randomized to receive oral magnesium carbonate ($MgCO_3$) or matching placebo (saccharum lactis) of identical appearance administered for 5 weeks. Before commencement of the study and after each phase of the treatment, the symptoms of MVP, the level of anxiety, serum magnesium, and excretion of adrenaline and noradrenaline were determined.

$MgCO_3$, 0.6 g/capsule (i.e., 7 mmol of elementary magnesium) was given in the following way: first week, 21 mmol/day; and second to fifth week, 14 mmol/day in accordance with the guidelines of the Commission of Experts of the Society for Magnesium.

Statistical analysis: Parametric data were expressed as mean ± SD and analyzed by the Smirnov-Koumogorov test if they had a normal distribution. The number of symptoms was compared by U Mann-Whitney test. Serum magnesium, adrenaline, and noradrenaline concentrations were compared using the paired and unpaired Student's *t* test. Comparisons between nonparametric data were evaluated by the chi-square test with the Yates' correction when appropriate. A p value <0.05 was considered statistically significant for all tests.

RESULTS

Serum magnesium and the incidence of hypomagnesemia: Serum magnesium in patients with heavily symptomatic MVP and in controls was 0.68 ± 0.11 mmol/L and 0.80 ± 0.05 mmol/L, respectively ($p < 0.0001$) (Figure 1).

Of 141 heavily symptomatic patients, 84 (60%) had decreased serum magnesium in at least 1 blood sample compared with 2 of 40 controls (5%), $p < 0.0001$. These 84 patients were given magnesium supplementation.

Magnesium supplementation: Of 84 patients, 14 withdrew in the initial phase of the study because of

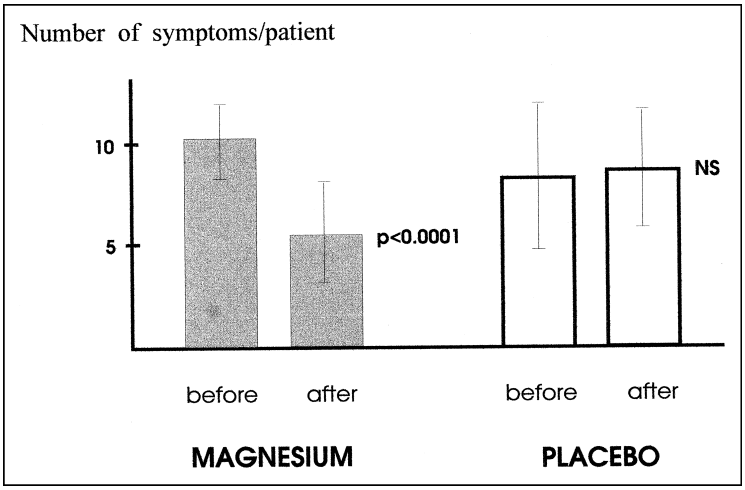

FIGURE 2. Number of symptoms (mean ±SD) in patients with mitral valve prolapse and hypomagnesemia before and after administration of magnesium or placebo.

TABLE II Percentage of Patients (n = 70) Who Experienced Individual Symptoms Before and After Administration of Magnesium or Placebo

	Magnesium (%)			Placebo (%)	
Symptoms	Before	After	p Value	Before	After
Faintness	64	6	0.0001	47	36
Weakness	87	39	0.005	66	64
Chest pain	96	47	0.01	71	86
Dyspnea	84	39	0.01	61	70
Low vital energy	74	34	0.01	57	33
Anxiety	84	47	0.05	69	77
Palpitations	93	51	0.05	76	83
Cramps	56	27	0.05	53	44
Hyperemotional	97	67	NS	77	87
Dizziness	79	50	NS	70	64
Numbness	86	51	NS	79	80
Headache	86	64	NS	76	74
Musculoskeletal pains	59	37	NS	54	56

poor cooperation. Thus, the study was completed by 70 patients (64 women and 6 men, aged 16 to 47 years, mean ± SD 31 ± 8).

CLINICAL SYMPTOMS: The number of symptoms per patient before magnesium administration was 10.4 ± 2.1, decreasing after 5 weeks of magnesium supplementation to 5.6 ± 2.5 ($p < 0.0001$) (Figure 2). Administration of placebo did not bring about detectable changes (8.5 ± 3.7 vs 8.9 ± 2.9; p = NS). The effect of magnesium supplementation on individual symptoms experienced by patients is shown in Table II.

PSYCHOLOGICAL TEST: Of 59 patients who completed the psychological questionnaire, 32 (54%) displayed a high level of anxiety, detected only in 9 (15%) after magnesium supplementation ($p < 0.002$). Anxiety was moderate in 25 (42%) persons before and in 35 (59%) after magnesium treatment (p = NS). A low level of anxiety was found initially in 2 (3%), and after magnesium supplementation in 15 (25%) ($p < 0.005$) (Figure 3). Placebo administration did not influence the level of anxiety.

CATECHOLAMINES: The levels of these hormones were assessed in daily urine in 35 patients. Augmented noradrenaline excretion was found at baseline in 22 patients (63%), compared with 6 (17%) after magnesium supplementation ($p < 0.01$). In the placebo group, a reverse trend was observed. The mean daily excretion of noradrenaline decreased significantly after magnesium administration, as opposed to placebo (Figure 4). The number of patients with augmented excretion of adrenaline did not change in the course of magnesium supplementation. However, the mean daily excretion of adrenaline was 12.2 ± 5.1 μg before and 8.95 ± 4.1 μg after administration of magnesium ($p < 0.005$). Placebo did not exert a significant effect (Figure 5).

MAGNESIUM: After each phase of the controlled trial, the serum magnesium level was measured. As expected, serum magnesium concentration increased after oral administration of $MgCO_3$ from 0.63 ± 0.11 mmol/L to 0.73 ± 0.08 mmol/L ($p < 0.0001$). This effect was not observed after placebo; respective values were 0.67 ± 0.1 mmol/L and 0.65 ± 0.09 mmol/L (p = NS).

DISCUSSION

This study revealed a high incidence of hypomagnesemia in patients with heavily symptomatic MVP. Serum magnesium does not accurately represent intracellular magnesium, because it may change from day to day, and it depends on many factors.[15] However, there is no doubt that when serum magnesium is low, intracellular magnesium is unquestionably low.[16,17] Although the deficit of magnesium in MVP has previously been suspected, little research was done on the subject. Early studies[18–21] have essential limitations, such as imprecise echocardiographic diagnostic criteria of MVP and an unreliable method of magnesium determination. In a recent study, Coghlan and Natello[22] reported low magnesium in erythrocytes in 59 of 94 patients with MVP. To our knowledge, our investigation based on 141 patients with primary MVP is the largest in among published reports. The results obtained strongly support the hypothesis of a causal relation of symptoms of MVP and magnesium deficit.

The reason for the magnesium deficit in MVP is unclear. It is unlikely that it is due to low magnesium content in drinking water, because only few healthy controls living in the same area had hypomagnesemia. This phenomenon may well be due to increased sympathetic activity,[7,8] which stimulates the renin-angiotensin-aldosterone system with subsequent urine magnesium loss, previously observed in MVP.[18] Lipolysis, induced by increased sympathetic activity, may lead to magnesium depletion because of binding of these ions to adipocytes.[23] In most of our patients, catechol-

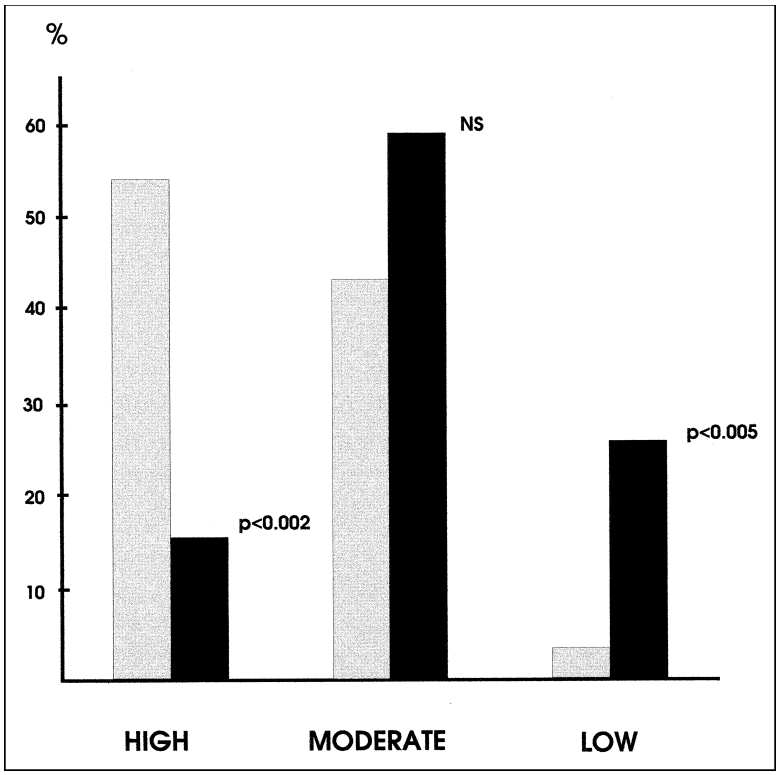

FIGURE 3. Percentage of patients with mitral valve prolapse and hypomagnesemia (n = 59) who had high, moderate, and low intensity of anxiety before and after administration of magnesium or placebo.

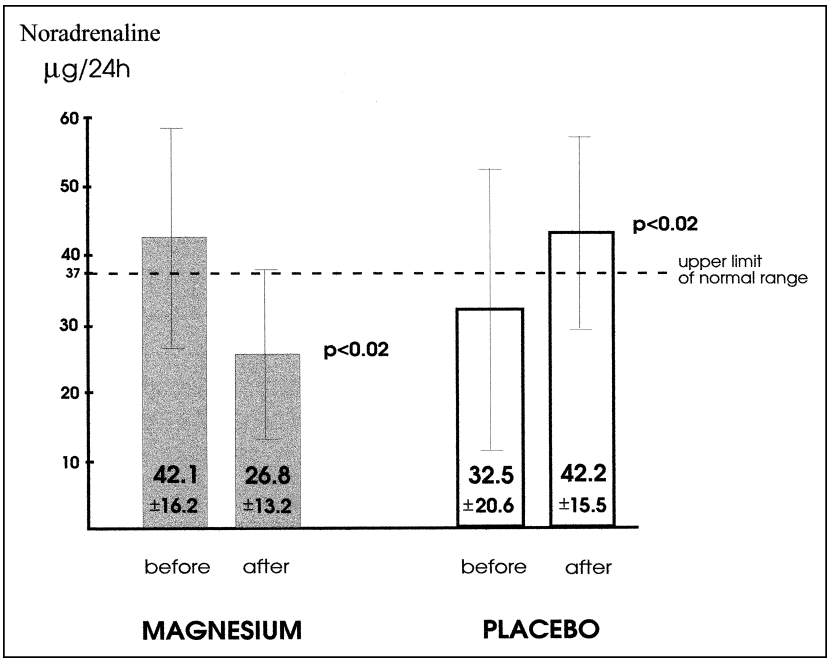

FIGURE 4. Daily excretion of noradrenaline (mean ± SD) in patients with mitral valve prolapse and hypomagnesemia (n = 35) before and after administration of magnesium or placebo.

amine excretion was increased, indicating an increased adrenergic drive.

Dürlach and Dürlach[1] hypothesized that magnesium deficiency even may be the cause of MVP. Cardiac muscle (like skeletal striated muscle) may respond to magnesium deficit with the ''signs of tetany'' reflected by the left ventricular dyssynergy and propensity to the prolapse of the mitral valve leaflets. Magnesium deficiency may also lead to alteration of collagen synthesis and subsequent degeneration of mitral valve leaflets. These 2 plausible mechanisms are compatible with the myocardial and valvular theories of MVP.[10]

Magnesium deficiency may produce a variety of cardiac, neurologic, psychosomatic, and neuromuscular symptoms[1,15,24]; the causal relation between the clinical picture of MVP and magnesium deficit has long been suspected[1–3,10,21,22] but not documented. It should be stressed, however, that a similar array of symptoms may be produced by increased adrenergic activity[6] also described in cases of MVP.[7,8]

The hypothesis that magnesium deficit is at least in part responsible for the clinical picture of MVP encouraged supplementation of this ion. Simoes-Fernandes et al[4] and Kłoś et al[5] in small, uncontrolled studies obtained encouraging results. This prompted us to initiate the present trial, providing evidence that magnesium supplementation improves several symptoms of MVP and supporting the hypothesis of a cause-and-effect relation between magnesium deficit and symptoms of MVP. Anxiety is a common and troublesome symptom in MVP[25]; tranquilizers are sometimes used and psychotherapy suggested.[10] The present study revealed that magnesium supplementation is effective in decreasing the level of anxiety.

The mechanism whereby clinical symptoms of MVP are relieved by magnesium remains obscure. The lessening of symptoms could be due to the antiadrenergic effect of magnesium, because we found a significant decrease in catecholamine excretion during the course of magnesium administration. This observation seems to be the first in a published report on the subject. Symptomatic patients with MVP are currently treated with β blockers,[10] although the effectiveness of this approach has not been documented. The ability of magnesium to alleviate catecholamine-induced toxic effects was previously

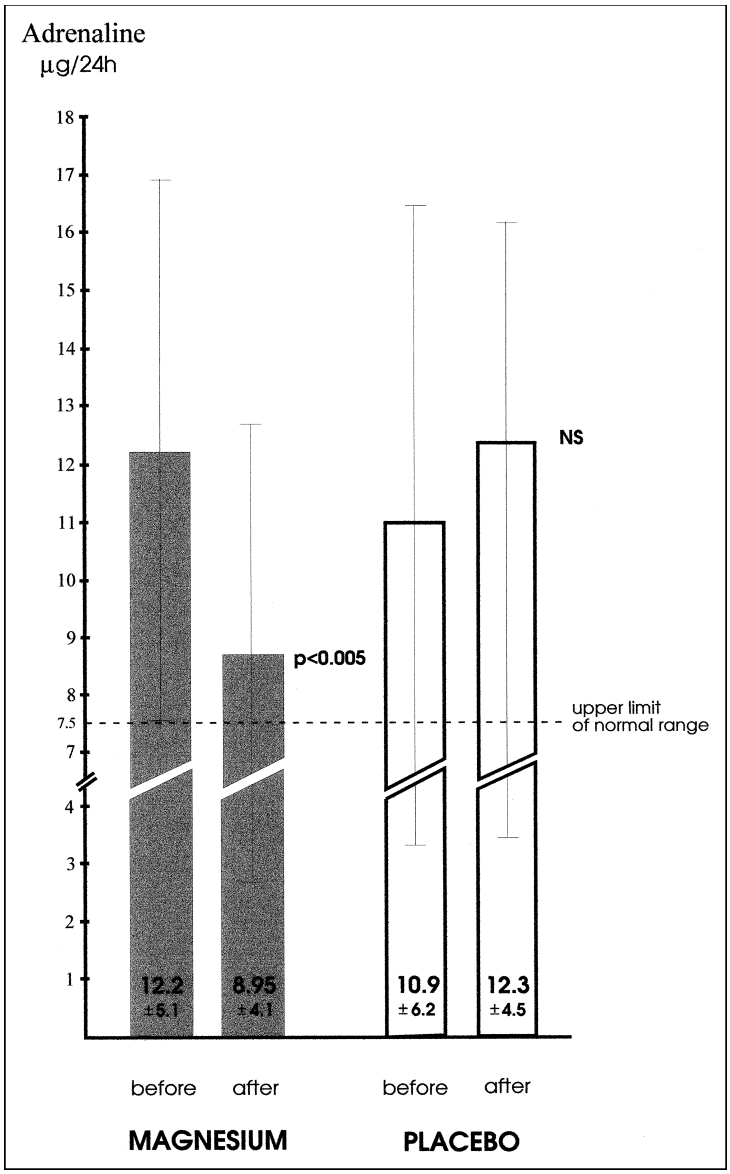

FIGURE 5. Daily excretion of adrenaline (mean ± SD) in patients with mitral valve prolapse and hypomagnesemia (n = 35) before and after administration of magnesium or placebo.

reported in an experimental[26,27] and clinical[28] setting, but not in patients with MVP.

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1. Dürlach J, Dürlach V. Idiopathic mitral valve prolapse and magnesium. State of the art. *Mag Bull* 1986;8:156–169.
2. Dürlach J, Lutfalla G, Poenaru S, Reba A, Henrotte JG, Fabiani F, de Vernejoul F. Latent tetany and mitral valve prolapse due to chronic primary magnesium deficit. In: Halpern MJ, Dürlach J, eds. Magnesium Deficiency. First European Congress on Magnesium, Lisbon 1983. Basel: Karger, 1985:102–112.
3. Galland LD, Baker SM, McLellan RK. Magnesium deficiency in the pathogenesis of mitral valve prolapse. *Magnesium* 1986;5:165–174.
4. Simoes-Fernandes J, Pereira T, Carvalho J, Fransca A, Andrade R, Noqueira-Pereira J, Rodrigues JC, Laires MJ, Halpern MJ. Therapeutic effects of a magnesium salt in patients suffering from mitral valve prolapse and latent tetany. *Magnesium* 1985;4:283–290.
5. Kłoś J, Lichodziejewska B, Budaj A, Grudzka K. The results of treatment of magnesium-calcium metabolic disorders in mitral valve prolapse syndrome (in Polish). *Pol Tyg Lek* 1988;43:1330–1333.
6. Boudoulas H, Kolibash AJ, Baker P, King BD, Wooley CF. Mitral valve prolapse and the mitral valve prolapse syndrome: a diagnostic classification and pathogenesis of symptoms. *Am Heart J* 1989;118:796–818.
7. Boudoulas H, Reynolds JC, Mazzaferri E, Wooley CF. Metabolic studies in mitral valve prolapse syndrome. A neuroendocrine-cardiovascular process. *Circulation* 1980;61:1200–1205.
8. Pasternac A, Tubau JF, Puddu PE, Krol RB, de Champlain J. Increased plasma catecholamine levels in patients with symptomatic mitral valve prolapse. *Am J Med* 1982;73:783–789.
9. Levine RA, Triulzi MO, Harrigan P, Weyman AE. The relationship of mitral annular shape to the diagnosis of mitral valve prolapse. *Circulation* 1987;75:756–767.
10. Jeresaty RM. Mitral valve prolapse. An update. *JAMA* 1985;254:793–795.
11. Spielberger CD. Preliminary Test Manual for the State-Trait Anxiety Inventory. Consulting Psychologists. Palo Alto, CA: 1973.
12. von Studnitz W. Fluorometrische Bestimmung von Adrenalin und Noradrenalin in Urin. In: Breuer H, Hamel D, Krüskemper HL, eds. Methoden der Hormonbestimmung. Stuttgart: Georg Thieme Verlag, 1975:150–154.
13. Boos N, Paschen K, Strobel B. Vergleich zwischen Xylidylblau—Methode und AAS. *Mag Bull* 1985;7:163–169.
14. Classen HG, Achilles W, Bachem MG, Conradt A, Fehlinger R, Gossmann HH, Günther T, Münzenberg KJ, Paschen K, Schreiber G, Schroll A, Spätling L, Wischnik A, Zümkley H. Magnesium: indications concerning diagnosis and treatment in man. Reccommendations of a Commission of Experts of the Geselschaft für Magnesiumforschung e.V. Symposium held in Münich on 29–30 November 1985. *Mag Bull* 1986;8:117–135.
15. Reinhart RA. Magnesium metabolism. A review with special reference to the relationship between intracellular content and serum levels. *Arch Intern Med* 1988;148:2415–2420.
16. Whang R. Routine serum magnesium determination—a continuing unrecognized need. *Magnesium* 1987;6:1–4.
17. Elin RJ. Overview of problems in assessment of magnesium salts. In: Altura BM, Dürlach J, Seelig MS, eds. Magnesium in Cellular Processes and Medicine. Basel: Karger, 1987:67–76.
18. Cohen L, Bitterman H, Grenadier E, Laor A, Lahat N, Palant A. Idiopathic magnesium deficiency in mitral valve prolapse. *Am J Cardiol* 1986;57:486 –487.
19. Frances Y, Collet F, Luccioni R. Long term follow up of mitral valve prolapse and latent tetany. Preliminary data. *Magnesium* 1986;5:175–181.
20. Gerard R, Luccioni J, Gatau-Pelanchon G, Duport G, Julien G, Bouteau JM, Chabrillat Y, Duport MY. Prolapsus valvulaire mitral et spasmophilia chez l'adulte. *Arch Mal Coeur* 1979;72:715–720.
21. Kłoś J, Lichodziejewska B, Grudzka K, Budaj A, Śliwińska J, Ceremużyński L. Magnesium-calcium metabolic disorders in the mitral valve prolapse syndrome (in Polish). *Pol Tyg Lek* 1988;43:1326–1329.
22. Coghlan HC, Natello G. Erythrocyte magnesium in symptomatic patients with primary mitral valve prolapse: relationship to symptoms, mitral leaflet thickness, joint hypermobility and autonomic regulation. *Magnesium Trace Elem* 1992;10:205–214.
23. Vormann J, Forster R, Günther T, Ebel H. Lipolysis-induced magnesium uptake into fat cells. *Mag Bull* 1983;5:39–41.
24. Seelig MS. Magnesium Deficiency in the Pathogenesis of Disease. New York: Plenum Press, 1980.
25. Carney RM, Freedland KE, Ludbrook PA, Saunders RD, Jaffe AS. Major depression, panic disorder and mitral valve prolapse in patients, who complaints of chest pain. *Am J Med* 1990;89:757–760.
26. Herbaczynska-Cedro K, Gajkowska B. Effect of magnesium on myocardial damage induced by epinephrine. Ultrastructural and cytochemical study. *Cardiosci* 1992;3:197–203.
27. Zdanowicz MM, Barletta MA. Protective role of magnesium in catecholamine-induced arrhythmia and toxicity in vitro. *Mag Res* 1991;4:153–162.
28. Caspi J, Coles JG, Benson LN, Herman SL, Diaz RJ, Augustine J, Brezina A, Kolin A, Wilson GJ. The protective effect of magnesium on acute catecholamine cardiotoxicity in the neonate. *J Thorac Cardiovasc Surg* 1993;105:525–531.