Magnesium Profile in Vasospastic Angina

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Zusammenfassung

Bei 12 Patienten mit vasospastischer Angina und 38 Patienten mit koronarer Herzkrankheit wurden die Magnesiumkonzentrationen im Serum bestimmt. In der Patientengruppe mit vasospastischer Angina wurden zusätzlich die Daten von Magnesium, Epinephrin und Nor-epinephrin, während und 10 Minuten nach szintigraphisch dokumentierten passageren myokardialen Perfusionsveränderungen unter Kälteprovokation bestimmt. Die Ergebnisse zeigen einen signifikanten Unterschied der Basiswerte von Magnesium bei Patienten mit Vasospasmus im Vergleich zu den Patienten mit koronarer Herzkrankheit ($p < 0.0001$). Die Nor-epinephrin Konzentration bei der Gruppe mit Vasospasmus stiegen während des Kälteprovokationstests signifikant an ($p < 0.005$) und normalisierten sich wieder in der Erholungsphase. Das Magnesiumprofil während der Kälteprovokation zeigte bei Patienten mit leicht vermindertem Basiswert eine Abnahme, bei Patienten mit stark verringertem Basiswert einen Anstieg, wobei eine Katecholamininduzierte intrazelluläre Magnesiumdepletion und damit eine Steigerung der konstriktorischen Effekte während des Vasospasmus vermutet wird.

Summary

Magnesium concentrations at baseline were measured in serum of 12 patients suffering from vasospastic angina and 38 consecutive patients with obstructive coronary artery disease. Furthermore, magnesium, epinephrine and norepinephrine levels were determined prior, during, and ten minutes after scintigraphically documented transient cold-induced myocardial perfusion abnormalities in the patient group with vasospasm. The results indicate a significant difference of baseline magnesium concentration in patients with spasm compared to subjects with coronary artery disease ($p < 0.0001$). Similarily in all patients with coronary arterial spasm norepinephrine levels increased significantly ($p < 0.005$) during cold pressor test and normalized after recovery. Magnesium profile during cold provocation revealed a trend to decrease in patients with slight reduction of baseline magnesium, whereas subjects with deminished baseline magnesium showed an increase, suggesting catecholamine related intracellular magnesium depletion and potentiation of constrictory effects during vasospasm.

Résumé

Nous avons mesuré la concentration du magnésium dans le sérum de 12 patients avec angor vasospastique et de 38 patients avec cardiopathie coronaire avans d'effectuer un test par provocation de froid. Chez les 12 patients d'angor vasospastiqne nous avons mesuré en outre la concentration du magnésium, de l'épinéphrine et de nor-épinéphrine pendant et 10 minutes après de déterminer le changement de perfusion myocardiaque passager documenté par scintigraphie sousle test par provocation de froid. Les résultats montrent une différence signifiquante de concentration de magnésium entre les deux groupes ($p < 0.0001$).

Dans le groupe avec angor vasospastique la concentration du norépinéphrine augmentait significativement ($p < 0,005$) pendant le test par provocation de froid pour se normaliser après 10 minutes.

Les patients du groupe d'angor vasospastique qui avaient ayant le test par provocation de froid une concentration de magnésium légérement réduite seulement par rapport au groupe avec cardiopathie coronaire montraient une réduction de magnésium dans le sérum pendent le test, tandis le reste de ce méme groupe ayant une concentration de magnésium fortement réduite ayant le test montrainent une augmentation.

Nous croyons que l'épinéphrine provoque une déplétion de magnésium intracellulre accompagnée d'une augmentation des effects vasoconstrictoire pendant le vasospasme.

Introduction

Small changes in free external or cytoplasmatic magnesium can exert significant effects on cardiac and/or vascular smooth muscle contractility by altering membrane and intracellular organelle binding and transport of calcium [2, 24]. Recent investigations have suggested a causal relationship between serum magnesium concentrations, tone and reactivity of blood vessels, and the etiology of vascular diseases, like sudden cardiac death [8, 16], malignant arrhythmias and acute myocardial infarction [1, 7, 14, 20], idiopathic dilated cardiomyopathy [22] and certain forms of hypertension [12, 21], respectively. Further in-vitro studies indicated that hypermagnesemia induces vasodilatation and attenuation of reactivity to contractile neurohumoral substances, whereas hypomagnesemia can produce vasospasm and potentiation of contractility [3–5, 19, 29]. Clinically, the prompt termination of spontaneous anginal attacks as well as cold-pressor-stimulus-in-

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duced vasoconstriction by magnesium-sulfate has been reported [9, 10]. However, it has not been demonstrated if either an increased response to adrenergic stimulus in the course of 'stable'hypomagnesemia, or a possible alteration of extracellular magnesium following catecholamine-induced iutracellular magnesium depletion during provocation may play an important role in initiation of arterial spasm in patients with vascular hyperreactivity.

In the present study we measured magnesium concentrations in patients with coronary artery spasm compared with subjects suffering from obstructive coronary artery disease. Furthermore, serum magnesium, epinephrine and norepinephrine concentrations were determined during transient, cold-induced myocardial perfusion abnormalities in the patientgroup with vasospastic angina.

Patients and methods

Twelve patients with vasospastic angina (7 female, 5 male; age: 36–67 years, mean age [± SD]: 46 ± 6 years) entered the study. Patients underwent full history and physical examination. The diagnosis 'vasospatic angina'based on the presence of four criteria:

1. typical history of chest pain at rest with
2. ischemic electrocardiographic changes during attack (ST-segment elevation or depression ≥ 2mV),
3. negative bicycle stress test, and
4. angiographically normal or not significant diseased coronary arteries (luminal narrowing less than 50 % in angiogram). Primary valve disease, cardiomyopathy, myocardial hypertrophy, hypertension, diabetes mellitus or a connective tissue disease had been excluded. All patients denied smoking habits. No patient was receiving digitalis or diuretic therapy.

Vascular hyperreactivity in further circulation areas like migraine and/or *Raynaud*'s phenomenon were judged by a standardized questionnaire [18] and peripheral cold pressor test [25].

Venous blood was withdrawn for routine blood chemistries (including sodium, potassium und calcium) and estimation of serum magnesium concentrations using an 'Automatic clinical analysator', E.T. du Pont de Nemours (reference range in our laboratory: 0.77–0.99 mmol/l). All measurements were done concurrently in time. Baseline magnesium concentrations of patients with vasospastic angina were compared with the magnesium levels of 38 consecutive patients with angiographically documented coronary artery disease (luminal narrowing more than 75 % in at least one vessel), with (n = 18) or without (n = 20) previous myocardial infarction and stable effort angina at time of examination (7 female, 31 male; age: 38–75 years, mean age: 56 ± 9 years).

Ten patients with vasospactic angina underwent cold pressor test with blood sampling for serum magnesium, epinephrine and norepinephrine (reference range for epinephrine 6.4 ± 2.6ng %, norepinephrine: 30.5 ± 14.1ng %; radioenzymatic assay kit, Amersham). Measurements were performed between 9 and 10 a.m. after 24 hours without any medication and a resting period of 30 minutes in supine position at baseline, after 5 minutes hand immersion into 12° C cold water, and following 10 minutes recovery. To examine, whether cold provocation as performed in our protocol leads to alterations of myocardial perfusion, 2 mCi thallium-201 were applicated after cold exposure [26, 27]. Scintigraphy was performed in 3 projections according to standard techniques with redistribution scan after 3 hours; a segmental judgement approach was used based on a 5 segment per view score [23]. Statistic analysis included student test and *Wilcoxon* test.

Results

Serum magnesium values were dimished significantly in 9 of 10 patients with vasospastic angina, compared with subjects suffering from sclerotic coronary artery disease (mean: 0.66 ± 0.13 mmol/l vs 0.81 ± 0.1mmol/l, $p < 0.0001$); no difference was observed between patients with and without history of myocardial infarction (p = ns) (Fig. 1). Sodium, potassium and calcium were in the normal range in all patients and did not differ in both groups.

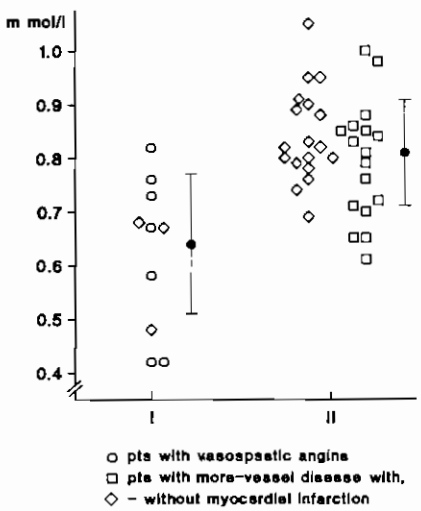

Fig. 1: Magnesium concentrations at baseline in patients with coronary artery spasm (I) and more-vessel disease (II): $p<0.0001$

Raynaud's phenomenon and migraine were present in 3 of 10 and 2 of 10 patients with coronary artery spasm, respectively; two subjects (magnesium concentrations 0.42 mmol/l and 0.48 mmol/l) revealed hyperreactivity in both vascular regions simultaneously.

During cold pressor test systemic arterial pressure increased 10.5 ± 4.5 mmHg significantly ($p < 0.005$) and normalized after 5 minutes recovery (25); heart rate remained unchanged. Electrocardiogram revealed a slight ST-depression in 2 patients who also complained from angina. Thalium-201 imaging dis-closed transient myocardial perfusion defects after cold provocation in all patients.

Norepinephrine increased from 30.4 ± 10 ng % at baseline to 43.5 ± 5.3 ng % after cold water hand immersion ($p < 0.001$) and normalized following 10 minutes redistribution (p = ns, compared with baseline); epinephrine did not alter significantly. No change of magnesium concentrations were observed following cold provocation as a mean (0.62 ± 0.11 mmol/l vs 0.62 ± 0.96mmol/l and 0.58 ± 1.11mmol/l, respectively; p = ns) (Fig. 2). However, in four patients with magnesium concentrations less than 0.67 mmol/l a trend to increase could be shown while patients with higher levels tended to decrease during cold (none of these patients complained from angina during one month before entering into the study). The subjects with ST-depression and angina during cold revealed magnesium levels of 0.42 mmol/l; both had a history of malignant arrhythmias (ventricular fibrillation, intermittent total av-block) and the highest frequency of recurring anginal attacks in spite of therapy with calcium channel blokkers during the preceeding months.

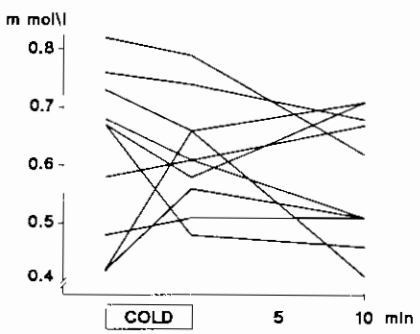

Fig. 2: Magnesium profile of patients with coronary artery spasm during cold pressor test and redistribution

Discussion

Our results indicate a significant decrease of extracellular magnesium in patients with vasospastic angina. Magnesium concentrations of patients with obstructive coronary artery disease and stable effort angina were normal at time of examination, no difference could be demonstrated in subjects with or without history of myocardial infarction.

Previous preponderant in-vitro studies have noted that the greater the deficit in extracellular magnesium concentration, the greater the degree of contraction or constriction and the greater the potentiation of constrictor agents [3, 6, 29]. Our clinical data further indicate that the greater the deficit in serum magnesium, the greater the frequency of ischemic events. One patient with vasospastic angina and normal extracellular magnesium and patients with magnesium concentrations at the upper limit were symptom-free during the preceeding months. In contrast, two patients with magnesium concentrations diminished to 0.42 mmol/l complained from angina at rest twice and three times a week in history as well as during cold pressor test. Furthermore, patients with extreme deficit of extracellular magnesium (in our small population less than 0.66 mmol/l) revealed also ischemic attacks in at least one further circulation area, whereas none of the patient group with coronary artery disease have had digital and/or cerebral ischemic events. This fact could refer to hypomagnesemia as a possible common pathomechanism of coronary artery vasospasm, *Raynaud*'s phenomenon and migraine, representing manifestations of a postulated generalized vasospastic disorder [18, 25].

High incidences of malignant arrhythmias in patients with hypomagnesemia as well as beneficial effects of magnesium-sulfate in the treatment of arrhythmias have been reported [1, 13, 15, 20]. Some authors claim that magnesium mitigates excessive sympathetic activity and improves the equilibrium of the cardiac conduction system, thus acting as an anti-arrhythmic agent. Both of our patients presenting ventricular fibrillation or total av-block in history had magnesium concentrations of 0.42 mmol/l at the time of examination. However, there is no proof of a causal relation, because magnesium was not determined during arrhythmias.

A possible limitation of our study may be due to the lack of a matched control group. Our controls were consecutive patients with angiographically documented obstructive coronary artery disease and, as a mean ten years older than the patients with vasospasm. In part, however, differences of magnesium values may be also related to differences in age and sex. However, this limitation cannot explain the extent and high significance of differences between the two groups in our study.

A positive thallium scan with transient reduction of tracer uptake after cold pressor test strongly suggests coronary artery spasm [28]. The lack of subjective complaints and/or electrocardiographic changes after cold pressor test in our patients is in accordance to previous studies who stated, that perfusion defects in thallium 201 imaging with peripheral cold provocation might occur without ST-changes and angina pectoris [11, 16]. Myocardial perfusion abnormalities of our patients were accompanied by a significant increase of norepinephrine. This increase was similar in all patients with vasospasm. Although mean magnesium concentration of all patients with coronary arterial vasospasm was unaltered during cold provocation, magnesium profile depended on the degree of deficit of extracellular magnesium. The greater the reduction of baseline magnesium, the greater the increase of serum magnesium after stimulation. This strongly suggests further depletion of intracellular magnesium in the course of cold water hand immersion and a clinically relevant potentiation of constrictory effects, leading to instability of vascular smooth muscle cells and high frequency of anginal attacks in these patients. In conclusion, the present data indicate that hypomagnesemia may play an important pathophysiological mechanism in individuals with vasospastic angina.

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