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Relation Between Severity of Magnesium Deficiency and Frequency of Anginal Attacks in Men With Variant Angina

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Objectives. **We evaluated whether the severity of magnesium deficiency was correlated with the frequency of attacks of variant angina.**

Background. **Magnesium deficiency may be associated with the development of variant angina. However, the relation between the activity of variant angina and magnesium deficiency remains to be elucidated.**

Methods. **We assessed the body magnesium status of 18 men with variant angina: Group 1 (≥4 attacks/week, n = 7) and Group 2 (<4 attacks/week, n = 11). Concentrations of magnesium were determined in serum, urine, mononuclear cells and erythrocytes, and the 24-h magnesium retention rate was determined.**

Results. **Group 1 showed a higher 24-h magnesium retention rate (mean ± SEM 63.5 ± 7.6% vs. 24.9 ± 2.7%, $p < 0.01$) and a lower intracellular concentration of magnesium in mononuclear cells and erythrocytes than did Group 2 (respectively, 156.3 ± 13.5 vs. 212.1 ± 6.9 fg/cell, $p < 0.01$; and 3.5 ± 0.5 vs. 5.2 ± 0.4 fg/cell, $p < 0.05$), demonstrating the presence of magnesium deficiency in Group 1. The 24-h magnesium retention rate and intracellular concentrations of magnesium in mononuclear cells and erythrocytes correlated well with the frequency of anginal attacks ($r = 0.78$, $p < 0.01$; $r = -0.78$, $p < 0.01$; $r = -0.62$, $p < 0.01$, respectively) for all patients.**

Conclusions. **Data suggest that the magnesium status of men with variant angina is closely related to disease activity.**

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Epidemiologic studies have shown that death from ischemic heart disease is inversely correlated with magnesium intake (1,2). Magnesium deficiency has been described in patients with ischemic heart disease (3,4). The ability of intravenous administration of magnesium to suppress the occurrence of coronary spasm induced by exercise (5) or hyperventilation (6) suggests that magnesium deficiency might be involved in the pathogenesis of coronary spasm. However, whether the severity of magnesium deficiency is related to the severity of variant angina remains to be elucidated.

Because only 1% of total body magnesium is present in the extracellular space (7,8), the serum or plasma concentration of magnesium may not accurately reflect the total body magnesium content. The magnesium concentration of mononuclear blood cells and erythrocytes may be used as an index of recent intracellular or total body magnesium status, or both (9–11). A magnesium loading test has been used to evaluate normomagnesemic magnesium deficiency in several clinical studies (4,12–16). However, the relation among the methods used to evaluate magnesium status has not been investigated. Our objectives were twofold: 1) to examine the magnesium status of patients with variant angina by using the magnesium loading test and intracellular magnesium concentrations of mononuclear cells and erythrocytes to ascertain whether the magnesium retention rate is correlated with the intracellular magnesium concentration; and 2) to investigate whether the severity of magnesium deficiency is correlated with the activity of variant angina.

Methods

Study patients. We studied prospectively 18 Japanese patients with variant angina. All were men aged 45 to 77 years (mean 59.7 ± 2.1) who had experienced spontaneous attacks of angina that occurred at rest between midnight and the early morning in association with verified ST segment elevation in the electrocardiogram (ECG). In all cases, coronary artery spasm, defined as transient occlusion accompanied by chest pain and ST segment elevation >0.2 mV, was documented by coronary arteriography during spontaneous attacks of angina or those induced by acetylcholine (17). Clinical data including age, coronary arteriographic findings after sublingual nitroglycerin and ECG changes during spontaneous attacks are listed in Table 1. On arteriography, no patient had ≥50% fixed lumen diameter narrowing in at least one major coronary artery. None had previous myocardial infarction, heart failure, renal disease, intestinal malabsorption, liver cirrhosis or diabetes mellitus. None had diarrhea, poor diet or mild azotemia that would influence magnesium metabolism either before or during the study. One patient had a chronic excessive alcohol intake >81 g/day. For at least 3 months before the study, no

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Abbreviations and Acronyms
ECG = electrocardiogram
PBS = phosphate buffer solution without magnesium and calcium

patient had received diuretic drugs, digitalis or other agents such as gentamicin or carbenicillin that would affect magnesium metabolism. Twelve of the 18 men had not received calcium antagonists or isosorbide dinitrate before admission to the study, except for transient (<7 days) use. The other six had received calcium antagonists or isosorbide dinitrates, or both, before this study, but care was taken to withhold these drugs for ≥3 days before the study. Sublingual nitroglycerin was given for the relief of an anginal attack. The total number of anginal attacks in the month before the study was determined according to the diary completed daily by each patient. Because magnesium metabolism can be affected by stress (18–20), we used the average number of anginal attacks/week for 1 month as an index of disease activity for that patient.

Patients were classified into two groups according to frequency of anginal attacks. Group 1 (7 men) had anginal attacks ≥4 times a week for 1 month; Group 2 (11 men) had anginal attacks <4 times/week for that period. The incidence of anginal attacks in Group 1 gradually increased during 1 month. Thus, disease activity in these patients increased but could be relieved by administration of sublingual nitroglycerin. Results of 24-h ambulatory ECG (Holter) monitoring during the observation period indicated that both the number of ischemic episodes per day and their total duration was significantly greater in Group 1 than in Group 2 (mean ± SEM 5.9 ± 1.8 vs. 1.1 ± 0.3 times/day, $p < 0.05$; 207.6 ± 12.1 vs. 147.5 ± 7.9 s, $p < 0.01$, respectively), when the ischemic episode was defined as ST segment elevation >0.2 mV from baseline lasting >120 s. However, because we wanted to examine the magnesium status of these patients by using intracellular magnesium concentrations of mononuclear cells and erythrocytes having a certain constant life span (>24 h), we used as the index of disease activity the average number of symptomatic anginal attacks for 1 month, rather than the total number of ischemic episodes or the total duration of these episodes in 1 day as assessed by Holter monitoring. Table 2 shows the clinical profiles of the two groups of patients. There were no significant differences between the groups in age, history of hypertension, diabetes mellitus, alcohol intake, smoking, and blood levels of total cholesterol and high density lipoprotein cholesterol. The number of men who had received calcium antagonists or isosorbide dinitrate, or both, during the observation period did not differ significantly between the two groups. Written informed consent was obtained from each patient before admission to the study.

Magnesium loading test. Patients were allowed to eat a regular diet during the study. Twenty-four-hour urine samples were collected to determine the amount of magnesium excreted per day. After obtaining a baseline 24-h urine collection, patients were given 0.2 mmol/kg of magnesium sulfate in 500 ml of 5% glucose over 4 h by intravenous infusion. This dose was chosen to reduce the effect of the magnesium contained in the regular diet. The magnesium infusion was well tolerated in all patients and did not cause significant changes in blood pressure, heart rate or deep tendon reflexes during and after infusion. Twenty-four-hour urine samples beginning with the infusion were again collected for determination of urinary magnesium. The difference in 24-h urinary magnesium excre-

Table 1. Angiographic and Electrocardiographic Findings in 18 Men

Pt No.	Age (yr)	Coronary Angiographic Findings*	ST Elevation During Angina (ECG lead)
		Group 1 (≥4 attacks of angina/week)	
1	65	Normal	II, III, aVF
2	77	Normal	II, III, aVF
3	60	Normal	II, III, aVF
4	56	LAD (seg 7; 25%)	II, III, aVF
5	49	Normal	V_1–V_4
6	67	Normal	V_1–V_4
7	45	Normal	V_1–V_3
		Group 2 (<4 attacks of angina/week)	
8	63	LAD (seg 6; 50%)	V_1–V_4
9	57	Normal	II, III, aVF
10	65	LCx (seg 13; 25%)	V_3–V_5
11	63	LAD (seg 7; 50%)	II, III, aVF
12	71	LAD (seg 7; 25%)	V_1–V_6
13	60	RCA (seg 2; 50%)	II, III, aVF
14	47	Normal	II, III, aVF
15	60	Normal	V_1–V_4
16	47	Normal	V_1–V_4
17	54	Normal	II, III, aVF
18	69	Normal	II, III, aVF

*After administration of sublingual nitroglycerin. ECG = electrocardiographic; LAD = left anterior descending coronary artery; LCx = left circumflex artery; Pt = patient; RCA = right coronary artery; seg = coronary artery segment number with lumen diameter reduction according to the American Heart Association classification.

Table 2. Clinical Characteristics of the Two Patient Groups

	Group 1 (n = 7)	Group 2 (n = 11)	p Value
Age (yr)	59.9 ± 4.2	59.7 ± 2.4	0.96
Frequency of anginal attacks (per wk)	6.1 ± 0.4	1.6 ± 0.3	<0.01
Alcohol intake (g/day)	28 ± 13	28 ± 6	0.99
Cholesterol (mg/dl)			
Total	172 ± 6	181 ± 8	0.43
High density lipoprotein	50 ± 5	44 ± 5	0.45
Hypertension	1/7	0/11	0.39
Diabetes mellitus	None	None	1.00
Smoking	4/7	6/11	0.65
Medication	2/7	4/11	0.57

Data are expressed as mean value ± SEM or number of patients. Medication refers to continued administration of calcium antagonists or isosorbide dinitrate, or both. Groups are defined in Table 1.

tion before versus after infusion was compared with the total amount of magnesium infused and expressed as a percent of the loaded magnesium retention at 24 h after the infusion. The 24-h magnesium retention rate was calculated according to the formula (4,12–16):

$$\text{24-h Mg retension rate (\%)} = \left[1 - \frac{\text{Postinfusion U-Mg} - \text{Preinfusion U-Mg}}{\text{Total elemental Mg infused}}\right] \times 100,$$

where U-Mg is the 24-h urinary magnesium excretion.

Measurements of serum, urinary and intracellular concentrations of magnesium. Concentrations of serum and urinary magnesium were measured by colorimetric analysis using a spectrophotometer (Chemical Autoanalyzer Hitachi 7250, Japan). Measurements of intracellular concentrations of magnesium in mononuclear cells and erythrocytes were based on the method proposed by Gallacher et al. (21). The collected 10-ml heparinized blood samples were split into 6-ml and 4-ml aliquots. Each aliquot was carefully layered onto 4 ml of Ficoll-Hypaque solution (relative density 1.077 and 1.119) in plastic tubes. They were centrifuged (500 × *g*, 20 min) at room temperature. The plasma and the buffy coats were removed, and the separated mononuclear cells and erythrocyte layers were pooled. The mononuclear cells were washed twice with 6 ml of phosphate buffer solution without magnesium and calcium (PBS), centrifuged at 270 × *g* for 15 min (first wash) and 10 min (second wash). The erythrocytes were washed twice with 6 ml of PBS and centrifuged at 500 × *g* for 10 min. The mononuclear cell pellet was then resuspended. We determined the number of cells present by using a hemocytometer and adjusted the volume within the range of 10^5 to 10^6 cells/ml. The 500-μl volume of mononuclear cell lysate was diluted with 1.5 ml of 720 mmol/liter aqueous lanthanum chloride and centrifuged, and the supernate was collected. The 200-μl volume of packed erythrocytes was resuspended in 1.8 ml of PBS and the number of cells was counted. Erythrocyte lysate as mononuclear cells was diluted and centrifuged, and the supernate was collected. The cells were harvested, washed and counted within 4 h. We analyzed the specimens of erythrocytes and mononuclear cells by the atomic absorption method using Spectrophotometer AA - 855 (Nippon Jarrell Ash Company, Japan). We used a series of five standards with magnesium ion (Mg^{2+}) concentrations ranging from 0.08 to 0.40 mmol/liter to construct a calibration curve to measure mononuclear cell magnesium concentration and a series of standards from 0.42 to 2.4 mmol/liter to measure erythrocyte magnesium concentration. The measurement was done immediately, or after storage at −20°C.

Determination of normal magnesium status. Ten adults who were free of diseases known to be associated with magnesium deficiency served as normal control subjects for serum and urinary magnesium levels, the magnesium loading test and intracellular magnesium concentrations. The normal range of magnesium values was considered to be 0.71 to 1.13 mmol/l in serum, 60 to 120 mg/day in urine, <30% as the magnesium retention rate, 180 to 280 fg/cell in mononuclear cells and 4.5 to 9.5 fg/cell in erythrocytes.

Statistical analysis. Data on magnesium status are expressed as mean value ± SEM. Differences between the clinical characteristics of the two groups categorized by number of anginal attacks were determined by Fisher exact probability test or Mann-Whitney *U* test, or both. Differences in the magnesium status of the two groups were tested by Mann-Whitney *U* test. The Spearman rank correlation test and linear regression fit were used to evaluate correlations of the data. Statistical comparisons were also performed in the patients in each group with the pure form of variant angina unrelated to coronary artery disease. A p value < 0.05 was considered statistically significant.

Results

Correlation between intracellular magnesium concentration and 24-h magnesium retention rate. The 24-h magnesium retention rate was inversely related to the intracellular magnesium concentration in mononuclear blood cells ($r = -0.78$, $p < 0.01$, $n = 18$). An inverse relation was also found between retention rate and level of erythrocyte magnesium ($r = -0.62$, $p < 0.01$) (Fig. 1).

Comparison of magnesium concentrations between Groups 1 and 2. There were no significant differences in the serum concentration of magnesium between Groups 1 and 2 (0.90 ± 0.04 vs. 0.92 ± 0.03 mmol/liter). All values were within the normal range (Fig. 2A). The 24-h magnesium retention rate in Group 1 was well above the normal range and significantly exceeded that of Group 2 (63.5 ± 7.6% vs. 24.9 ± 2.7%, $p <$ 0.01, Fig. 2B). There was a significant difference between the two groups in the intracellular magnesium concentration of mononuclear cells (Group 1 vs. Group 2 156.3 ± 13.5 vs. 212.1 ± 6.9 fg/cell, $p < 0.01$, Fig. 2C). Group 1 also had a lower intracellular magnesium concentration in erythrocytes than that of Group 2 (3.5 ± 0.5 vs. 5.2 ± 0.4 fg/cell, $p < 0.05$, Fig. 2D). Compared with the normal range for magnesium status, a magnesium deficiency was clearly demonstrated in Group 1. Although the urinary excretion of magnesium per day in Group 1 was greater than that in Group 2 (124.5 ± 22.7 vs. 57.4 ± 4.9 mg/day, $p < 0.02$), a magnesium deficiency was also observed in Group 1 (Fig. 2E). Significant differences between the two groups were also demonstrated when comparisons included only the 12 patients with the pure form of variant angina: 24-h magnesium retention rate 67.6 ± 7.5 vs. 23.6 ± 4.0 %, $p < 0.01$; magnesium concentration of mononuclear cells 149.5 ± 13.9 vs. 213.2 ± 9.1 fg/cell, $p < 0.01$ and magnesium concentration of erythrocytes 3.4 ± 0.5 vs. 5.6 ± 0.5 fg/cell, $p <$ 0.03.

Correlation between magnesium status and disease activity of variant angina. There was a significantly positive correlation between the 24-h magnesium retention rate and the average number of anginal attacks/week for 1 month in the 18

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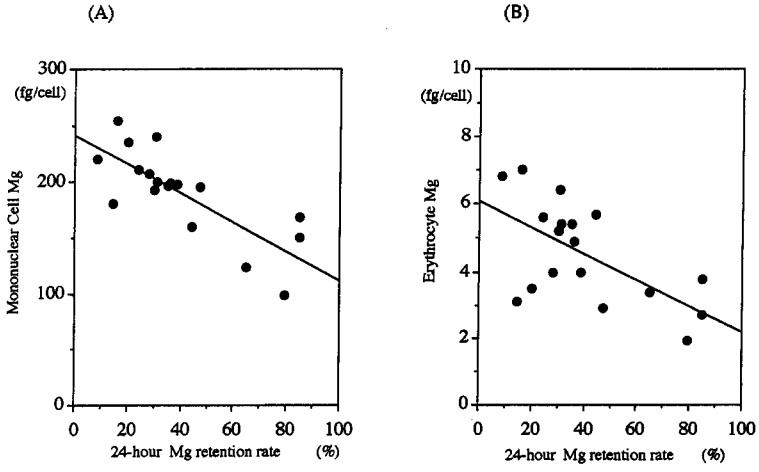
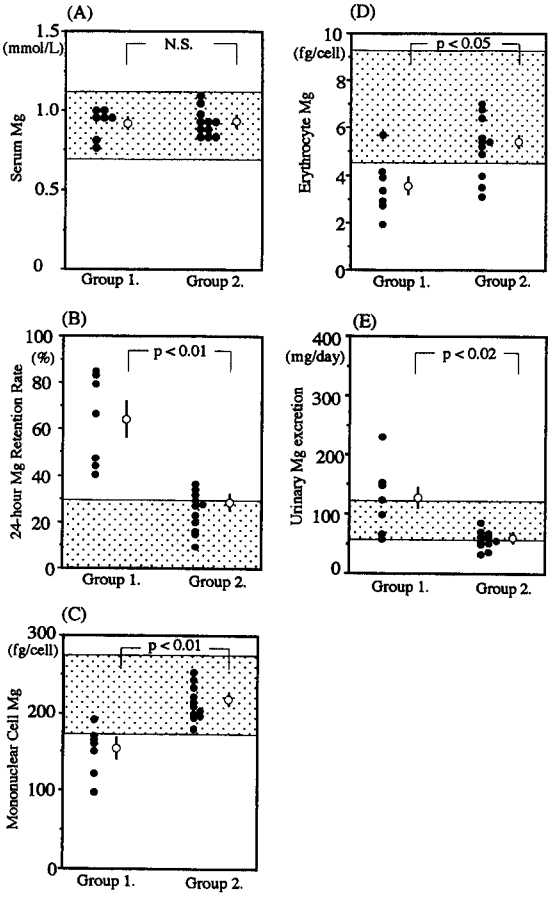


Figure 1. Relation between 24-h magnesium (Mg) retention rate and intracellular magnesium concentrations of mononuclear cells **(A)** and erythrocytes **(B).** The 24-h magnesium retention rate was inversely related to the intracellular magnesium concentration in mononuclear blood cells ($r = -0.78$, $p < 0.01$, $n = 18$). An inverse relation was also found between the retention rate and the level of erythrocyte magnesium ($r = -0.62$, $p < 0.01$, $n = 18$). **Diagonal line** was determined by linear regression.

patients with variant angina ($r = 0.78$, $p < 0.01$, Fig. 3). The intracellular magnesium concentration in the mononuclear blood cells showed a significant inverse relation to the frequency of anginal attacks ($r = -0.78$, $p < 0.01$, Fig. 4A). A weak but statistically significant correlation between the erythrocyte magnesium concentration and the frequency of anginal attacks was also observed ($r = -0.62$, $p < 0.01$, Fig. 4B). Even when analyses included only the 12 patients with pure variant angina, the 24-h magnesium retention rate ($r = 0.77$, $p < 0.01$) and the magnesium concentration of mononuclear cells ($r = -0.73$, $p < 0.02$) each showed a significant relation to the frequency of anginal attacks. The relation between the magnesium concentration of erythrocytes and the frequency of anginal attacks was also statistically significant ($r = -0.75$, $p < 0.01$).

Figure 2. Magnesium (Mg) status in two groups of patients with variant angina. There was no significant difference in serum magnesium concentration **(A).** Magnesium deficiency was obvious in Group 1 by 24-h magnesium retention rate **(B)** and intracellular magnesium concentrations of mononuclear cells **(C)** and erythrocytes **(D).** Urinary magnesium excretion was significantly greater in Group 1 than in Group 2 **(E).** Values are mean ± SEM. **Dotted area** indicates normal range.



Discussion

Methods for evaluating magnesium status. Because only 1% of total body magnesium is present in the extracellular space (7,8), serum magnesium concentration may not accurately reflect total body magnesium. We found no significant difference in serum magnesium concentration between the two groups of patients with variant angina, and values in both groups were within the normal range. However, magnesium status as determined by magnesium loading test and by intracellular magnesium concentration differed between the two groups.

The magnesium loading test is used in evaluating patients with normomagnesemic magnesium deficiency (22,23). Clinical studies have shown a correlation between the magnesium retention rate and the intracellular concentration of magnesium in skeletal muscle (8,23). However, the precise relation among methods for evaluating magnesium status has not been studied in variant angina. The present study demonstrated that the 24-h magnesium retention rate was inversely related to the intracellular concentrations of magnesium in the mononuclear cells and erythrocytes.

Of the three methods for evaluating magnesium status, the intracellular magnesium concentration of the mononuclear cells and the 24-h magnesium retention rate was more closely correlated with disease activity than was the magnesium concentration of erythrocytes. The 24-h magnesium retention rate

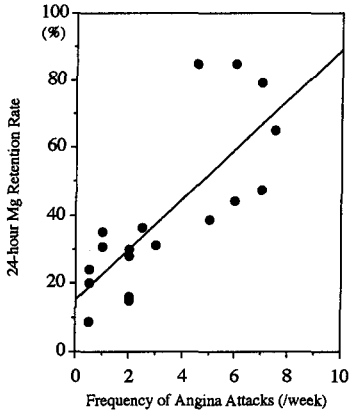


Figure 3. Twenty-four hour magnesium (Mg) retention rate plotted against the frequency of attacks of angina. The 24-h magnesium retention rate was positively correlated with disease activity in patients with variant angina ($r = 0.78$, $p < 0.01$, $n = 18$). **Diagonal line** was determined by linear regression.

and the magnesium concentration of mononuclear cells appeared to be more sensitive than that of the erythrocytes in estimating recent disease activity (frequency of anginal attacks) of the patients with variant angina. This may be because the separated erythrocytes contained various populations of erythrocytes aged up to 120 days. Our findings support those of other investigators (10,11,24). Baron and Ahmed (24) advocated the use of leukocytes in monitoring the intracellular chemical pathway because they are nucleated and metabolically active. Ryan et al. (11) showed the advantages of lymphocytes over erythrocytes and muscle tissue for assessing intracellular magnesium. The magnitude of the loss of magnesium from lymphocytes resembles that of cardiac and skeletal muscle (10,11), which suggests that measurements of the 24-h magnesium retention rate and intracellular magnesium concentration of mononuclear cells are equally useful for estimating the magnesium status of patients with variant angina.

Relation between severity of magnesium deficiency and disease activity of variant angina. What is the clinical significance of magnesium status in patients with variant angina? Using the magnesium loading test, Goto et al. (4) reported that the magnesium deficiency present in patients with variant angina was corrected after the disappearance of the anginal attacks in response to treatment with a calcium antagonist, which suggests that the magnesium deficiency in such patients was secondary to the stress of the attack. We investigated the association between the activity of variant angina and magnesium deficiency and demonstrated the presence of a magnesium deficiency in patients with frequent attacks of angina. The severity of the deficiency was directly related to the frequency of the attacks in both patient groups, suggesting a relation between the magnesium content of smooth muscle cells and magnesium retention rate. Results in the patients with the pure form of variant angina resembled findings in the total study group, which included patients with angina and coronary artery disease. Although a recent clinical study reported that chronic alcohol intake could be a risk factor for coronary artery spasm because of magnesium deficiency (16), we found no significant difference in the mean daily alcohol consumption between Group 1 (28 ± 13 g/day) and Group 2 (28 ± 6 g/day).

The precise mechanism for the development of a deficiency in magnesium in patients with variant angina is unclear. In this study, the daily urinary magnesium excretion was greater in Group 1 than in Group 2, although magnesium deficiency was present in Group 1. Frequent attacks of angina may lead to an increase in urinary magnesium excretion by a change in the renal threshold or in the tubular handling of magnesium, or both, although these have not been proved. Repeated episodes of stress such as chest pain and anxiety greatly increase activity of the sympathetic nervous system. Romani and Scarpa (25) demonstrated that total cellular magnesium content can be altered by adrenergic stimulation. Conditions involving severe pain, surgical stress and prolonged strenuous exercise lead to hypomagnesemia after an increase in serum catecholamines

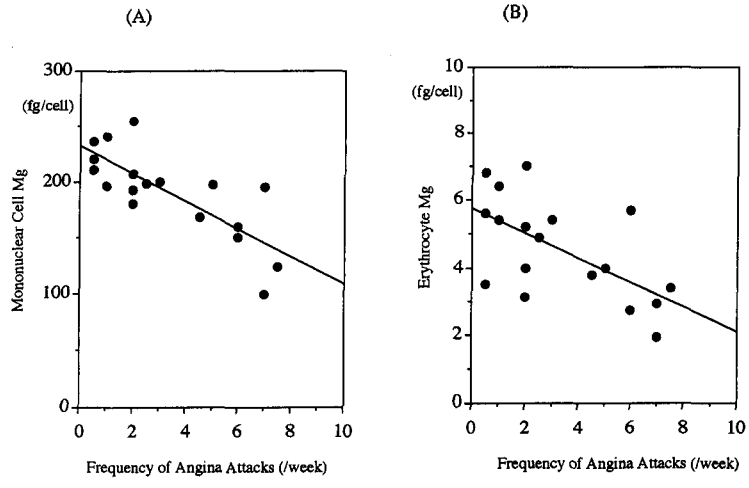


Figure 4. Intracellular magnesium (Mg) concentrations of mononuclear cells (**A**) and erythrocytes (**B**) plotted against the frequency of attacks of angina. The intracellular magnesium concentrations in blood cells in patients with variant angina correlated inversely with their disease activity (**A,** $r = -0.78$, $p < 0.01$, $n = 18$; **B,** $r = -0.62$, $p < 0.01$, $n = 18$). **Diagonal lines** were determined by linear regression.

and lipolysis, suggesting that an increase in serum catecholamines leads to lipolysis with a sharp rise in the serum free fatty acid level and the uptake of magnesium into fatty tissue by chelation (18,19,26,27). In any event, an increase in disease activity appeared to cause a loss of magnesium in patients with variant angina.

Because a major role of magnesium in biologic systems is to modulate the action of the calcium ion in vascular smooth muscle (28–31), a magnesium deficiency may further increase the frequency of anginal attacks. Correction of the magnesium deficiency may lessen the frequency of attacks of variant angina, because we observed an association between the frequency of these attacks and the deficiency of magnesium. Similar to our findings with variant angina, Cox et al. (20) showed that patients with chronic fatigue syndrome had low levels of magnesium in erythrocytes despite a normal serum concentration of magnesium and that magnesium treatment improved the well-being of these patients. Additional studies are needed in patients with variant angina, such as trials of long-term administration of oral magnesium compounds to evaluate their efficacy in reducing the number of attacks.

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