Intracellular Magnesium Deficiency in Acute Myocardial Infarction

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SUMMARY

It has been hypothesized that intracellular magnesium deficiency is a pathogenetic factor in acute myocardial infarction. This study examined the time course of changes in the erythrocyte magnesium concentration and the correlation between the erythrocyte magnesium concentration and the severity of acute myocardial infarction in 49 consecutive patients with transmural acute myocardial infarction. The data were compared with results from 20 control patients without ischemic heart disease. The erythrocyte magnesium concentration (mg/dl) decreased significantly during the acute phase of the infarction (4.86 ± 0.09 on day 1, 4.89 ± 0.10 on day 2 and 4.86 ± 0.10 on day 3 versus 5.26 ± 0.19 for controls, all $P < 0.05$) and then normalized gradually to 5.25 ± 0.10 on day 28. The serum magnesium concentration (mg/dl) also decreased significantly during the acute phase of the infarction (1.93 ± 0.04 on day 1 and 2.11 ± 0.03 on day 2 versus 2.26 ± 0.08 for controls, all $P < 0.05$), before recovering to 2.28 ± 0.06 on day 28. There were significant correlations between the erythrocyte magnesium concentration on day 1 and maximal values of serum cardiac enzymes ($r = -0.30$ for creatine kinase, $r = -0.34$ for glutamic oxaloacetic transaminase and $r = -0.57$ for lactate dehydrogenase, all $P < 0.05$). Moreover, the erythrocyte magnesium concentration was significantly lower in patients with (4.32 ± 0.08 mg/dl, $n=13$) than in those without (5.06 ± 0.09 mg/dl, $n=36$, $P < 0.0001$) serious arrhythmias. These data indicate that intracellular magnesium deficiency is involved in the acute phase of myocardial infarction. (Jpn Heart J 34: 391-401, 1993.)

Key Words:

Arrhythmia Ischemic heart disease Myocardial necrosis Sudden death

PREVIOUS epidemiological studies have shown significant correlations between low magnesium content in the drinking water and a high preva-

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lence of cardiovascular disease,¹⁾ and between low magnesium consumption and a high mortality rate from ischemic heart disease.²⁾ Thus, it has been suggested that magnesium deficiency plays an important role in the pathogenesis of ischemic heart disease.

Previous studies have reported that the serum magnesium concentration decreases during the acute phase of myocardial infarction^{3,4)} and that intravenous magnesium therapy dramatically improves the survival of patients with acute myocardial infarction.⁵⁾ However, the issue of whether the intracellular magnesium concentration, which is more relevant to cell function than its serum level, decreases during the acute phase of myocardial infarction is controversial.⁵⁻¹⁰⁾ Since the erythrocyte magnesium concentration is a useful index of intracellular magnesium levels, it provides a simple means of examining this issue.¹¹⁻¹⁵⁾

Therefore, this study has examined the erythrocyte magnesium concentration to elucidate the involvement of intracellular magnesium deficiency in acute myocardial infarction.

METHODS

Patients and study protocol

The subjects in this study were 49 consecutive patients with transmural acute myocardial infarction. The mean age of the patients was 70 years (range 44 to 88 years); 30 were men and 19 were women. The diagnosis of transmural acute myocardial infarction was made by a history of typical chest pain, the appearance of characteristic electrocardiographic (ECG) changes including the emergence of abnormal Q waves and an elevation of serum cardiac enzymes.

After admission, all patients were treated in the coronary care unit for 3-7 days by oxygen inhalation, intravenous nitroglycerin, heparin and calcium channel blockers. When necessary, intravenous catecholamines were administered. Continuous ECG monitoring was performed for at least two weeks. Thirty patients underwent percutaneous transluminal coronary recanalization (PTCR) using urokinase (n=29) or tissue plasminogen activator (n=1) within six hours after the onset of the infarction. The remaining 19 patients did not receive thrombolysis therapy, due either to the prolonged time period after the onset of the infarction (>6 hours) or contraindications for the therapy. A successful recanalization was achieved in 27 of the 30 patients. No patient had received intravenous thrombolysis or catecholamine therapy prior to admission. Intravenous magnesium therapy was not administered.

Measurements of erythrocyte and serum magnesium concentrations were performed on days 1, 2, 3, 7, 14 and 28. Forty patients were followed until day 28, while the remaining 9 patients were dropped due to re-infarction (n=1),

emergent cardiac surgery (n=3), cardiac death (n=2) and death from other causes [cerebral hemorrhage (n=1), acute renal failure associated with disseminated intravascular coagulation syndrome (n=1) and respiratory failure (n=1)]. In one patient, the serum magnesium concentration was not measured on day 2; this patient was excluded for the analysis of the time course of serum magnesium concentration. The measurements were also performed in 20 age- and gender-matched control patients without ischemic heart disease (mean age 69 years; 9 men and 11 women). Measurements of serum cardiac enzymes [creatinine kinase (CK), glutamic oxaloacetic transaminase (GOT) and lactate dehydrogenase (LDH)] were performed every 6 hours after admission for at least 2 days in order to obtain peak values of those enzymes. All patients gave informed consent and the institutional committee on human research of our hospital approved the study protocol.

Measurements

The erythrocyte magnesium concentration was measured by atomic absorption spectrophotometry. After the erythrocytes were washed and hemolyzed,¹¹⁾ the measurements were made in triplicate and the mean value was used. If there was a difference greater than 0.3 mg/dl between minimum and maximum values, the measurement was repeated. The range of the measurement by this method is 0.06–10.00 mg/dl and the coefficient of variation of the method is 1.59%. The serum magnesium concentration was measured by the xylydyl blue method. Serum levels of CK, GOT and LDH were measured with an SMAC autoanalyzer (Technicon Instruments Corporation, New York, U.S.A.). All blood sampling on day 1 was carried out immediately after admission before starting any intensive interventions. The mean latency between the onset of acute myocardial infarction and admission was 3.8 ± 0.6 hours. After day 2, blood sampling was carried out in the morning (7:00–8:00 AM) before breakfast.

Data analysis

Results are expressed as mean $\pm$ SEM. Statistical analysis of the data was performed by unpaired t-test, chi-square test and regression analysis (least-squares linear estimation). When more than two means were compared, analysis of variance was used. If a significant F value was found, Duncan's test for multiple comparisons was used to identify differences among groups. Values were considered to be statistically different when P was less than 0.05.

RESULTS

Time course of erythrocyte and serum magnesium concentrations in acute myocardial infarction

The erythrocyte magnesium concentration was significantly lower in patients with acute myocardial infarction on day 1 than in control patients (Fig. 1). These low values persisted until day 3. After day 7, the erythrocyte magnesium concentration in acute myocardial infarction patients had returned to control values (Fig. 1).

The serum magnesium concentration was also significantly lower in patients with acute myocardial infarction than in control patients on day 1 (Fig. 2). However, the value recovered rapidly after day 2, reaching the control level on day 3 (Fig. 2).

Factors that may influence magnesium level

There was no significant difference in either the erythrocyte or the serum magnesium concentration between patients as a function of hypertension, diabetes mellitus, renal dysfunction or alcoholism (Table I). We also confirmed that medication with diuretics or digitalis did not significantly affect the erythrocyte or the serum magnesium concentrations (Table I). Among the 49 patients with acute myocardial infarction, 19 were given magnesium oxide (1.0–2.0 g/day,

Fig. 1. Time course of changes in the erythrocyte magnesium concentration (Erythrocyte Mg) in patients with acute myocardial infarction (AMI). Data shown as mean $\pm$ SEM. *= P <0.05 vs control group; †= P <0.05 vs day 1 to day 3.

Fig. 2. Time course of changes in the serum magnesium concentration (Serum Mg) in patients with acute myocardial infarction (AMI). Data shown as mean $\pm$ SEM. * = $P < 0.05$ vs control group; + = $P < 0.01$ vs day 1.

p.o.) to maintain bowel movements. The magnesium oxide administration affected only the time course of serum magnesium concentration from day 3 to day 14; the erythrocyte magnesium concentration was unaffected (Table II).

Table I. Erythrocyte and Serum Magnesium Concentrations in Patients with Acute Myocardial Infarction

		Day 1			Day 28		
		n	E-Mg	S-Mg	n	E-Mg	S-Mg
Hypertension	(+)	18	4.98 $\pm$ 0.13	1.98 $\pm$ 0.07	15	5.35 $\pm$ 0.20	2.39 $\pm$ 0.14
	(-)	31	4.81 $\pm$ 0.11	1.90 $\pm$ 0.06	25	5.22 $\pm$ 0.12	2.20 $\pm$ 0.06
Diabetes mellitus	(+)	9	4.97 $\pm$ 0.21	2.02 $\pm$ 0.15	8	5.38 $\pm$ 0.28	2.44 $\pm$ 0.28
	(-)	40	4.85 $\pm$ 0.09	1.91 $\pm$ 0.04	32	5.24 $\pm$ 0.11	2.23 $\pm$ 0.05
Renal dysfunction	(+)	7	4.90 $\pm$ 0.26	1.87 $\pm$ 0.19	4	5.48 $\pm$ 0.51	2.73 $\pm$ 0.39
	(-)	42	4.87 $\pm$ 0.09	1.94 $\pm$ 0.04	36	5.24 $\pm$ 0.11	2.22 $\pm$ 0.06
Alcoholism	(+)	1	4.90	1.60	1	5.90	1.90
	(-)	48	4.87 $\pm$ 0.08	1.94 $\pm$ 0.04	39	5.25 $\pm$ 0.10	2.28 $\pm$ 0.06
Use of Diuretics	(+)	—	—	—	7	5.14 $\pm$ 0.17	2.16 $\pm$ 0.07
	(-)	—	—	—	33	5.29 $\pm$ 0.12	2.30 $\pm$ 0.08
Use of Digitalis	(+)	—	—	—	7	5.34 $\pm$ 0.18	2.40 $\pm$ 0.28
	(-)	—	—	—	33	5.25 $\pm$ 0.12	2.25 $\pm$ 0.06

Data shown as mean $\pm$ SEM (mg/dl). (+)=present; (-)=absent; E-Mg=erythrocyte magnesium concentration; n=number of patients; S-Mg=serum magnesium concentration.

Table II. Erythrocyte and Serum Magnesium Concentrations in Patients as a Function of Magnesium Oxide Administration

	E-Mg		S-Mg	
	(+) MgO (n=19)	(-) MgO (n=21)	(+) MgO (n=18)	(-) MgO (n=21)
Day 1	4.82±0.14	4.90±0.13	1.95±0.06	1.91±0.04
Day 2	4.86±0.16	4.91±0.14	2.10±0.06	2.12±0.04
Day 3	4.79±0.14	4.90±0.15	2.36±0.07*	2.19±0.05
Day 7	4.97±0.17	5.24±0.15	2.44±0.06*	2.15±0.06
Day 14	5.10±0.16	5.20±0.16	2.39±0.08*	2.19±0.06
Day 28	5.34±0.18	5.16±0.11	2.33±0.09	2.23±0.09

Data shown as mean±SEM (mg/dl). E-Mg=erythrocyte magnesium concentration; MgO=magnesium oxide; (+) and (-) MgO=patients with and without magnesium oxide administration; S-Mg=serum magnesium concentration; *= $P<0.05$ vs patients without MgO.

Fig. 3. Correlations between erythrocyte magnesium concentration (Erythrocyte Mg) on day 1 and maximum CK values (Panel A) for all patients and (Panel B) for patients without successful pharmacological or mechanical recanalization.

Erythrocyte magnesium concentration on day 1 and cardiac enzymes

There was a significant correlation between the erythrocyte magnesium concentration on day 1 and the maximum CK value (Fig. 3). A significant correlation was observed for all patients (Fig. 3A) and for patients in whom successful pharmacological or mechanical recanalization was not achieved (Fig. 3B). There was also a significant correlation between the erythrocyte magnesium concentration on day 1 and both the maximum GOT value ($r = -0.34$, $P < 0.05$ for all patients, $r = -0.57$, $P < 0.01$ for the patients without successful pharmacological or mechanical recanalization) and the maximum LDH value ($r = -0.32$, $P < 0.05$ for all patients, $r = -0.61$, $P < 0.005$ for the patients without successful pharmacological or mechanical recanalization).

Fig. 4. A comparison of the erythrocyte magnesium concentration (Erythrocyte Mg) on day 1 for patients with and without serious arrhythmias. Data shown as mean $\pm$ SEM.

Erythrocyte magnesium concentration on day 1 and serious arrhythmias

Serious arrhythmias were defined as ventricular tachycardia (n=11), the R on T phenomenon (n=1) and ventricular fibrillation (n=1) within 24 hours after the onset of acute myocardial infarction. The arrhythmias which occurred during PTCR or percutaneous transluminal coronary angioplasty (PTCA) were excluded. The erythrocyte magnesium concentration on day 1 was significantly lower in patients with serious arrhythmias (Fig. 4). There was no significant difference between patients with and without serious arrhythmias in the serum potassium level on day 1 (3.9 ± 0.1 vs 4.0 ± 0.1 mEq/L), the prevalence of patients with cardiogenic shock (3/13 vs 4/36) or a successful outcome of recanalization (9/13 vs 21/36).

DISCUSSION

The present study has three main findings. First, the erythrocyte magnesium level decreased significantly during the acute phase of myocardial infarction, then normalized gradually. Secondly, there was a significant correlation between the erythrocyte magnesium level on day 1 and peak values of serum

cardiac enzymes. Finally, a low erythrocyte magnesium level was associated with the occurrence of serious arrhythmias during the acute phase of myocardial infarction.

Since magnesium is the second richest cation in the cell next to potassium,¹⁶⁾ the intracellular magnesium level is useful to evaluate the systemic magnesium balance. In the present study, the erythrocyte magnesium concentration was used as an index of intracellular magnesium, because it is easier to obtain than other blood cells or tissues.¹¹⁾⁻¹⁵⁾ In many studies, the erythrocyte magnesium concentration has been used as an index of intracellular magnesium level.^{6)-10),12)}

The intracellular and serum magnesium level can be affected by factors such as hypertension, diabetes mellitus, renal dysfunction and alcoholism.^{17),18)} However, there was no significant difference in either the erythrocyte or serum magnesium concentrations between patients with these disorders and controls. We also confirmed that medication with diuretics or digitalis^{17),18)} did not significantly affect the erythrocyte or the serum magnesium concentrations. Congestive heart failure and cardiogenic shock also influence both the erythrocyte and the serum magnesium concentrations.^{6),18)} However, the magnesium levels were uncorrelated with either Killip classes or Forrester subsets on day 1 (data not shown). No patients in the present study had endocrine or gastrointestinal disorders, which may influence the magnesium levels.^{17),18)} Serum magnesium level may be influenced by serum protein level because about 30 % of serum magnesium is bound to serum protein (mainly albumin).¹⁶⁾ However, there was no difference in serum albumin level between patients with acute myocardial infarction on day 1 (4.2 ± 0.5 g/dl) and control patients (4.3 ± 0.4 g/dl); all these values were within the normal range (3.6 ± 5.2 g/dl). Finally, the magnesium oxide administration affected only the time course of changes in the serum magnesium concentration from day 3 to day 14, without affecting the erythrocyte magnesium concentration.

Our data showed that the erythrocyte and serum magnesium levels decreased significantly during the acute phase of myocardial infarction and that they normalized gradually. These findings support previous reports that serum magnesium levels are consistently depressed during the acute phase of myocardial infarction.^{3),4)} However, the issue of changes in erythrocyte magnesium levels during acute myocardial infarction has been controversial: it decreased in one study,⁶⁾ was unchanged in others⁷⁾⁻⁹⁾ (in fatal patients and non-fatal male patients in reference 9) and increased in two studies^{9),10)} (in non-fatal female patients in reference 9). However, even in the study which reported a low erythrocyte magnesium level in acute phase of the infarction,⁶⁾ there was no difference in the magnesium level between on day 1 and the day of discharge. In the studies which reported an unchanged or increased level of erythrocyte magnesium, several

factors may have contributed to findings as follows; for example, the magnesium concentration was measured only at one time point (day 1 through day 5),⁷⁾ the control group included patients with accidents or operations⁸⁾ which can affect the erythrocyte magnesium level¹⁹⁾ and only a small number of patients was included (n=4 on day 1 in reference 10). Finally, patient profiles were not shown in the remaining study.⁹⁾ By contrast, the present study included a sufficient number of patients who were completely followed from day 1 to day 28.

The correlative results in this study cannot distinguish whether an intracellular magnesium deficiency is a cause or a result of acute myocardial infarction. Increased catecholamines in acute myocardial infarction may induce lipolysis and increase the level of free fatty acids, which then chelate magnesium into an insoluble magnesium salt.^{4),20),21)} However, an animal experiment has demonstrated that exogenous catecholamines have no effect on the erythrocyte magnesium level.²²⁾ Furthermore the effects of endogenous and exogenous catecholamines on serum magnesium levels in humans are controversial.²³⁾ On the other hand, two lines of evidence suggest that intracellular magnesium deficiency could be a primary cause of acute myocardial infarction. First, there is a significant correlation between magnesium deficiency and the severity of coronary atherosclerosis.²⁴⁾ Secondly, magnesium deficiency can induce coronary artery spasm.^{25),26)} In fact, the erythrocyte magnesium level is decreased in the active phase of variant angina.²⁷⁾

The serum magnesium level recovered prior to the erythrocyte magnesium level, indicating that normalization of circulating magnesium levels preceded the normalization of intracellular magnesium levels. This observation may reflect the slow magnesium equilibrium in erythrocytes.¹⁰⁾ It is unclear, though, why the intracellular magnesium level normalized gradually during the course of acute myocardial infarction. This observation could be due to effects of medication or a result of washout of magnesium from infarcted myocardium like other cardiac enzymes.⁹⁾ However, the time course of the magnesium level can not be explained by the latter possibility alone because, unlike other cardiac enzymes, serum and erythrocyte magnesium levels did not decrease in the late phase of the infarction. Finally, it has been reported that magnesium deficiency in patients with variant angina is corrected after treatment with calcium channel blockers.²⁶⁾ Because all patients were treated by calcium channel blockers after the onset of acute myocardial infarction, the recovery may reflect effects of calcium channel blockade.

There was a significant correlation between the erythrocyte magnesium level on day 1 and maximum values of CK, GOT and LDH. The maximum CK level is correlated with the infarct size and is influenced significantly by recanalization and by CK release from other tissues.²⁸⁾ In the present study,

however, there was a significant correlation between the erythrocyte magnesium concentration on day 1 and maximum CK value even in patients without successful pharmacological or mechanical recanalization. This finding suggests that intracellular magnesium deficiency may be involved in myocardial necrosis. In animal experiments, magnesium deficiency caused an acceleration of myocardial necrosis after coronary ligation²⁹⁾ or catecholamine injection.³⁰⁾

There was also a highly significant correlation between the erythrocyte magnesium level on day 1 and the occurrence of serious arrhythmias. Previous studies have confirmed a significant correlation between serum magnesium levels and the occurrence of serious arrhythmias.^{4),5)} Only one study has examined but failed to confirm this relationship.⁶⁾ However, the efficacy of intravenous magnesium therapy in controlling arrhythmias and mortality in acute myocardial infarction⁵⁾ is consistent with a role of low intracellular magnesium levels in arrhythmogenesis. Thus, it may be important to examine intracellular magnesium levels in order to establish strategies for the initial treatment of acute myocardial infarction.

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