Magnesium Dynamics and Relation to Left Ventricular Function in Acute Myocardial Infarction

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The present study investigated the serial changes in serum magnesium (Mg) and erythrocyte concentration of Mg in patients with acute myocardial infarction (AMI) and the relationship between these changes and left ventricular ejection fraction (LVEF) at 1 month after the onset of infarction. The study group comprised 26 patients with AMI (mean age, 57.9±8.9 years). Serum Mg and erythrocyte Mg were measured on hospital days 1, 2, 4, 7 and 21. The change in erythrocyte Mg during the acute phase was calculated as a ratio: [(erythrocyte Mg at day 2) - (erythrocyte Mg at day 1)] / (erythrocyte Mg at day 1). The change in serum Mg was calculated similarly. The following results were obtained. (1) Serum Mg tended to increase from the onset of myocardial infarction (day 1: 1.8±0.19, day 2: 1.9±0.22, day 4: 2.1±0.23, day 7: 2.25±0.20, day 21: 2.12±0.15 mg/dl). (2) Erythrocyte Mg on day 2 and day 4 showed a significant decrease compared with day 1 (day 1: 2.45±0.40, day 2: 2.0±0.41, day 4: 2.07±0.37, day 7: 2.22±0.33, day 21: 2.34±0.28 mg/dl per 400×10^6 mm^3 cells). (3) A significant positive correlation was observed between the change in serum Mg and LVEF (r=0.55, p<0.05), and a significant negative correlation was observed between the change in erythrocyte Mg and LVEF (r=-0.57, p<0.05). Thus, it was concluded that an extracellular shift in intracellular Mg occurred during the first 2 days after the onset of myocardial infarction. This responsive increase in the extracellular Mg level may be an important factor for maintaining left ventricular function in patients 1 month after the onset of AMI. (Jpn Circ J 2000; 64: 377–381)

Key Words: Acute myocardial infarction; Left ventricular ejection fraction; Magnesium dynamics

There are some reports that hypomagnesemia is closely related to hypertension, ischemic heart diseases, or arrhythmia, but especially to acute myocardial infarction (AMI), ventricular extrasystole, ventricular tachycardia, and ventricular fibrillation. Epidemiologic studies suggest that myocardial hypomagnesemia may predispose to sudden cardiac death. Several studies have shown that the magnesium (Mg) content is decreased in the infarcted portion of the myocardium when compared with non-infarcted segments. In a comparative study of Mg-supplement therapy in the acute phase of AMI, the mortality rate was significantly reduced in the group of patients given intravenous infusion therapy of Mg in the first 24 h. It is therefore likely that Mg is a very important factor in the maintenance of cardiac function and in the prognosis for AMI, but the ISIS-4 study did not reveal evidence of any beneficial effect of Mg. However, the intracellular and extracellular dynamics of Mg after the occurrence of AMI have not been clearly delineated.

The purpose of the present study was to investigate the Mg dynamics using 2 parameters: the serum concentration of Mg as an index of extracellular Mg, and erythrocyte Mg concentration as an index of intracellular Mg. The relation-
Table 1  Clinical Characteristics of Patients

| Age (years) | 57.9±5.8 |
| Height (cm) | 163.2±7.4 |
| Weight (kg) | 60.3±7.7 |
| Peak CK (IU/L) | 3361±1741 |
| LVEF (%) | 47.3±11.7 |

No. of patients with infarct-related artery
- LAD: 1
- LCX: 18
- RCA: 3

No. of patients with significant diameter stenosis (% of coronary artery) (pre PTCA)
- LVD: 19
- 2VD: 4
- 3VD: 2
- LMT: 1

Medication (%)
- Nitrites: 58
- Calcium channel blocker: 31
- β-blocker: 12
- ACE inhibitor: 8
- Diuretics: 8

CK, creatine kinase; LVEF, left ventricular ejection fraction; LMT, left main coronary trunk; LAD, left anterior descending artery; LCX, left circumflex artery; PTCA, percutaneous transluminal coronary angioplasty; VD, vessel disease; ACE, angiotensin converting enzyme.

for 10 min. After removal of plasma and the buffy coat, the erythrocyte sediment was washed 3 times with 0.9% NaCl solution and again centrifuged at 3,000 G at 4°C for 10 min. After removal of the supernatant, 0.9% NaCl solution was added until the total sample volume reached 5 mL, from which two 2-mL samples were taken. One sample was used to count erythrocytes and the other was centrifuged at 3,000 G at 4°C for 10 min. After removal of the supernatant fluid, distilled water was added until the total sample volume reached 2 mL for erythrocyte hemolysis. The erythrocyte Mg concentration was measured by atomic absorption, and the value obtained was corrected for the number of erythrocytes; Mg concentration was expressed per 400 × 10^6 mm^-3 cells. The change in erythrocyte Mg during the acute phase was calculated as a ratio: [(erythrocyte Mg at day 2)–(erythrocyte Mg at day 1)]/[(erythrocyte Mg at day 1)]. The change in serum Mg was calculated similarly.

**Cardiac Catheterization**

Selective coronary angiography was performed in all patients within 12 h of the onset of AMI and again in 16 patients at 1 month after the onset. Of the 10 patients who did not undergo the second cardiac catheterization, 2 were in a state of renal dysfunction, and 8 patients did not

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**Figure 1.** Serial changes in serum magnesium (Mg) concentrations after the onset of acute myocardial infarction (AMI). Serum Mg tended to increase between days 1 and 21, and this increase was significant on days 4, 7, and 21. Data are presented as mean ± SD.

**Figure 2.** Serial changes in erythrocyte magnesium (Mg) concentration after the onset of acute myocardial infarction (AMI). Erythrocyte concentration of Mg revealed a significant decrease from day 1 to day 4. Data are presented as mean ± SD.

*Japanese Circulation Journal  Vol 64, May 2000*
Statistical Analysis

All data are expressed as mean±SD. Analysis of variance was used for comparison of serial changes in serum and erythrocyte Mg concentrations. To determine the relation of changes in Mg concentrations and LVEF, linear regression analysis was performed. A p value of less than 0.05 was considered significant.

Results

Patient Characteristics

Table 1 shows the patient characteristics. Direct PTCA was performed in all patients during the acute phase of AMI (within 12 h of onset). Before the direct PTCA, 19 patients showed single-vessel coronary disease, 4 showed double-vessel disease, 2 showed triple-vessel disease, and 1 showed coronary disease of the left main trunk. Successful recanalization of the infarct-related artery was achieved in all patients. Orally administered drugs included calcium channel blockers (15/26 cases, 58%); β-blockers (8/26, 31%); nitrates (20/26, 77%); angiotensin converting enzyme inhibitors (3/26, 12%); and diuretics (2/26, 8%). Oral medications were given from the second or third day of hospitalization. Intravenous Mg was not administered.

Serial Changes of Serum Mg and Erythrocyte Concentration of Mg

Fig. 1 shows the serial serum Mg concentration changes in all 26 patients after the onset of AMI. The mean serum Mg concentrations on days 1, 2, 4, 7, and 21 were respectively 1.86±0.19, 1.93±0.22, 2.17±0.23, 2.25±0.20, and 2.12±0.15 mg/dl. Serum Mg showed a tendency to increase over the entire 21 day period, and this increase was significant on days 4, 7 and 21 in comparison with the concentration on day 1 (p<0.01).

Fig. 2 shows the serial erythrocyte Mg concentration changes. The mean erythrocyte Mg concentrations on days 1, 2, 4, 7 and 21 were respectively 2.45±0.40, 2.09±0.41, 2.07±0.37, 2.22±0.33, and 2.34±0.28 mg/dl per 400×10^6/mm^3 cells. The erythrocyte Mg concentration on days 2 and 4 was significantly lower than that on day 1 (p<0.01).

Relationship Between the Changes in Serum Mg and Erythrocyte Mg Concentration and LVEF

No correlation was observed between either serum or erythrocyte Mg concentrations on days 1, 2, 4, 7 and 21 and LVEF at 1 month after the onset of AMI. Fig. 3 shows the significant positive correlation between the change in
serum Mg during the first 2 days of hospitalization and LVEF at 1 month after the onset of AMI (r=0.55, p<0.05). Fig 4 shows the significant negative correlation between the change in erythrocyte Mg concentration and LVEF (r=-0.57, p<0.05).

Discussion

Epidemiologic studies have indicated that mortality from ischemic heart disease is inversely correlated with Mg intake. The myocardial Mg content in patients succumbing to sudden death from ischemic heart disease has been reported to be lower than that in patients succumbing to sudden death from other causes. Several clinical reports have suggested the beneficial effects of Mg for AMI. Rasmussen et al. and Schechter et al. showed a decreased mortality rate in AMI patients who received intravenous Mg infusion therapy upon hospital admission. Woods et al. (LIMIT-2 Study) showed that intravenous Mg infusion therapy (8 mmol over 5 min followed by 65 mmol over 24 h) reduced the mortality rate from ischemic heart disease by 21% and the all-cause mortality rate by 16%. In addition, the magnesium treated group had their early left ventricular failure reduced by 25%. However, the detailed mechanisms and pharmacokinetics are not understood. The ISIS-4 study tested intravenous Mg in patients with suspected AMI using a regimen very similar to that in LIMIT-2. Nearly 60,000 patients were randomized to either a 24-h infusion of Mg sulfate (60 mmol total) or placebo. Mortality rates did not differ substantially. However, little is still known about the relationship between serial changes in intracellular and extracellular Mg and left ventricular function after the occurrence of AMI. Only about 1% of total body Mg is in the extracellular space, therefore assessment of the Mg content of muscle, lymphocytes and erythrocytes, and measurement of daily urinary output of Mg have been used as indices of Mg deficiency. Muscle Mg content may well be the best gauge of total body Mg stores, but it is an impractical determination in the usual clinical setting. Reinhart et al reported that mononuclear blood cell Mg concentration, but not serum Mg concentration, correlated weakly with myocardial Mg content in patients undergoing cardiac surgery. Tanabe et al reported that the measurement of erythrocyte Mg concentration is useful to determine how easily vasospasm might occur in patients with vasospastic angina. The present study was undertaken in patients with AMI to investigate the serial changes in serum Mg and erythrocyte Mg concentrations as an index of intracellular Mg and the relation between these changes and LVEF at 4 weeks after the onset of AMI.

Tsutsui et al reported that the erythrocyte Mg concentration decreased significantly during the acute phase of AMI and then normalized gradually by day 28 after hospital admission. We monitored 2 parameters of Mg dynamics after the onset of AMI. The level of serum Mg was the lowest on day 1 and gradually increased until day 4, but the level of erythrocyte Mg was at its maximum on day 1 and at its minimum on day 4. With regard to the mechanism causing serum Mg to be the lowest on day 1, repeated stress induced by the AMI may be a factor. Such stress, by increasing catecholamine secretion, would be expected to liberate free fatty acids into the blood. Altura and Altura suggest that an apparent Mg deficient state might result from 2 major events: (1) the formation of insoluble salts via chelation of Mg with free fatty acids and (2) the excretion of Mg via the kidney because of overproduction of catecholamines. With regard to changes during the first 2 days, serum Mg increased slightly, but the erythrocyte Mg concentration decreased rapidly. Taking the present findings with those of Altura and Altura, the increase in serum Mg and decrease in erythrocyte Mg suggests that the transition from intracellular Mg to extracellular Mg occurs during the first 2 days after the onset of AMI. We considered that free Mg is transported from erythrocyte (intracellular Mg) to serum (extracellular Mg), because Mg administration was not performed during those first 2 days. All subjects were given meals beginning on the second or third day of hospitalization and because intestinal Mg absorption would have increased with the natural dietary Mg supply, the serum Mg may have reached its plateau on the 4th hospital day.

With regard to the relation between Mg dynamics and left ventricular function, we observed a positive correlation between the change in serum Mg and LVEF, and a negative relationship between the change in erythrocyte Mg and LVEF. In other words, patients showing a higher level of serum Mg and a lower erythrocyte Mg level within 2 days of the onset of AMI revealed more favorable LVEF parameters after 4 weeks. Mg is an indispensable ion that produces coronary vasodilation, protects against ischemic injury, protects against catecholamine-induced myocardial necrosis and limits the size of the myocardial infarct. The ability to increase the extracellular Mg level during the acute phase of AMI may be important to maintain left ventricular function through these favorable effects in AMI patients. In the present study, the patients with higher levels of extracellular Mg on the first and second hospital day were still recovering from impaired function after 4 weeks. Conversely, the patients with lower erythrocyte Mg levels during the acute phase showed a higher LVEF after 4 weeks.

Study Limitations

The present study had a small sample size and was unable to supply a detailed fundamental mechanism of either the extracellular shift of Mg or its relation to left ventricular function. Further study is needed to evaluate the relation between the extracellular shift of Mg and mortality in a large sample.

In conclusion, extracellular shift of intracellular Mg occurred during the first 2 days after the onset of AMI. Increasing the extracellular Mg level during the acute phase of AMI could be an important factor for maintenance of left ventricular function.

References


Japanese Circulation Journal Vol 64, May 2000