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Intracellular Magnesium Predicts Functional Capacity in Patients with Coronary Artery Disease

Key Words
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Abstract
To determine whether increased intracellular levels of magnesium ($[Mg]_i$) are associated with enhanced functional capacity, we performed symptom-limited exercise treadmill testing on 42 stable coronary artery disease (CAD) patients (37 men, 5 women, mean age 68 ± 9 years). $[Mg]_i$ was found to be an independent and significant predictor of exercise duration ($R = 0.31$, $p = 0.02$) in a multivariate stepwise regression model. Patients with > normal $[Mg]_i$ of 1.23 μg/mg protein ($n = 13$) had a significantly greater mean functional capacity, measured in higher achieved metabolic equivalents (10.6 ± 2.5 vs. 8.9 ± 2.3, $p < 0.05$) and exercise duration (9.4 ± 2.3 vs. 7.9 ± 2.2 min, $p < 0.05$) compared to patients with $[Mg]_i \leq$ the normal ($n = 29$). Thus, functional capacity is greater in stable CAD patients with higher $[Mg]_i$, suggesting that magnesium may play a role in CAD pathophysiology, possibly via ventricular unloading.

Magnesium ions are essential for the maintenance of functional and structural integrity of the myocardium. Magnesium is an important intracellular cation and an obligatory cofactor in many enzymes in the human body [1]. Numerous metabolic pathways, especially those involved in energy production and muscle contraction, are magnesium dependent [2]. Hypomagnesemia is common in patients with coronary artery disease (CAD) [3], in part, due to diuretic therapy [4]. Syndrome X (insulin resistance, hypertension, dyslipidemia), which is present in approximately half of CAD patients, is also associated with hypomagnesemia [5, 6]. Magnesium is considered to be the nature's physiologic calcium blocker [7]. It has coronary [8] and systemic [9] vasodilator effects, with mild reduction in systolic blood pressure [10], and may act as an afterload reducer, and thus unload the left ventricle [2, 9].

We hypothesized that higher intracellular levels of magnesium ($[Mg]_i$) would enhance functional capacity in patients with stable CAD via left-ventricular unloading. We conducted a prospective study to determine whether increased $[Mg]_i$ was associated with enhanced functional capacity measured by metabolic equivalents and exercise duration in CAD patients.

Methods

Study Design and Population

The study was performed in consecutive patients who were recruited from a supervised cardiac exercise and rehabilitation program at Cedars-Sinai Medical Center for an oral magnesium intervention study. The following results represent pilot data from the baseline phase (before intervention). Inclusion criteria included men

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Table 1. Baseline characteristics of the study population

CAD risk factors	Patients		Concomitant medication	Patients	
	n	%		n	%
Diabetes mellitus	2	6	β-Blocking agents	15	42
Hypertension	21	58	Calcium antagonists	14	39
Current smokers	0	0	Hypoglycemic agents	2	6
Hypercholesterolemia	27	75	Lasix	5	14
			Digoxin	4	11
			Aspirin	36	100
			Long-acting nitrates	4	11
			ACE inhibitors	12	33
			Lipid-lowering agents	27	75

ACE = Angiotensin-converting enzyme.

and women aged >20 years, with CAD documented by prior myocardial infarction, coronary artery bypass grafting, coronary angiography or angioplasty. Exclusion criteria included unstable angina, congestive heart failure > NYHA class IV, chronic diarrhea, renal failure (serum creatinine >3 mg/dl), acute myocardial infarction within the preceding 3 months, hyper/hypothyroidism, insulin-dependent diabetes mellitus, peripheral vascular disease, history of drug or alcohol abuse, chronic liver disease, or refusal to sign the informed consent. The study was approved by the institutional review board, and all participants gave written informed consent.

Study Protocol

After signing the informed consent, the patients underwent a physical examination, blood tests for measurement of $[Mg]_i$, lipids, blood cell count, electrolytes, and fibrinogen levels and treadmill exercise test.

Treadmill Exercise Test

After an overnight fast, a maximum symptom-limited exercise treadmill test (Bruce protocol [11]) was performed on all patients. The following parameters were recorded: blood pressure and heart rate at each exercise stage, and at peak exercise, time to onset of angina and 1-mm ST-segment depression, ST-segment depression at peak exercise, maximal ST-segment depression, presence of cardiac arrhythmias, metabolic equivalents achieved, double-product [heart rate (beats/minute) × systolic blood pressure (mm Hg)] and total exercise duration. Myocardial ischemia was defined as the presence of episodes showing ≥0.1 mV horizontal or downsloping ST-segment depression 80 ms after the J-point.

Intracellular Magnesium Concentration

Mononuclear cells were isolated from the whole blood by a modification of the method of Elin and Johnson [12]. Heparinized blood, 10 ml at room temperature, was mixed with an equal volume of buffered saline and glucose solution (BSG) at pH 7.4, containing NaCl 8.1 g/l (0.14 *M*), Na_2HPO_4, 1.22 g/l, and Na $H_2PO_4 \cdot H_2O$, 0.194 g/l. Twenty milliliters of Ficoll-paque (Pharmacia Fine Chemicals) were then layered below the blood and BSG using a clean pipette and were then centrifuged at 400 *g* for 35 min. The mononuclear cell layer was collected from the Ficoll-plasma interface, washed with 10 ml BSG and centrifuged at 600 *g* for 10 min. The supernatant was then discarded and the pellet was washed in another 10 ml BSG and centrifuged at 2,000 *g* for 10 min. The pellet was then brought up in 2 ml distilled water and frozen until time of assay. Prior to assay, the cells were thawed and then lysed by sonication. The $[Mg]_i$ in isolated mononuclear cells was measured by atomic absorption spectrophotometry (normal value: 1.23 ± 0.02 μg/ml protein) [13]. Intra-assay variability for $[Mg]_i$ 5.1 ± 7.2% and interassay variability was 7 ± 5%.

Lipids, Blood Cell Count and Electrolytes

Fasting blood samples were taken for hemoglobin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, triglycerides, glucose, serum magnesium, apolipoprotein A-I and B, and fibrinogen levels, using standardized autoanalyzer techniques.

Statistical Analysis

Group data are expressed as means ± SD. Comparison of biochemical measurements was performed using the unpaired Student's t test. Associations between normally distributed variables were determined using Pearson correlation coefficient analysis. The Wilcoxon signed-rank test and Spearman correlation coefficients were used to analyze data that were not normally distributed. Logarithmic transformations were used to normalize data for regression analysis. Predictors of functional capacity were determined using log linear regression and multiple stepwise regression analysis. A p value <0.05 was considered significant.

Results

The study population included 42 coronary patients (37 men and 5 women), with a mean age of 68 ± 9 years (range: 48–83; table 1). All patients had stable CAD as evidenced by a previous myocardial infarction (n = 23), coronary artery bypass grafting (n = 26), or coronary angioplasty (n = 23); 25 patients had multiple diagnoses.

Table 2. Correlation of exercise duration

Variable	R	p
Correlation analysis		
Age	−0.51	0.0006
$[Mg]_i$	0.31	0.02
Rest SBP	−0.39	0.01
ST-segment depression	−0.32	0.04
Regression analysis[a]		
Age		0.01
BMI		0.02
$[Mg]_i$		0.02
SBP at peak exercise		0.02

R = Spearman rank correlation coefficient; SBP = systolic blood pressure; BMI = body mass index.

[a] Overall model: $R^2 = 0.43$, $p = 0.009$.

Table 3. Exercise test results

Variable	$[Mg]_i$	
	≤ 1.23 μg/mg protein	> 1.23 μg/mg protein
Patients, n (%)	29 (100)	13 (100)
Exercise angina, n (%)	2 (7)	1 (80)
ST-segment depression, n (%)	5 (17)	2 (15)
Target HR achieved, n (%)	26 (90)	11 (88)
HR at peak exercise, beats/min	136 ± 21	135 ± 23
Rest SBP, mm Hg	150 ± 25	146 ± 24
Rest DBP, mm Hg	68 ± 13	72 ± 13
SBP at peak exercise, mm Hg	191 ± 34	170 ± 21
DBP at peak exercise, mm Hg	71 ± 17	75 ± 17
Double product	25,742 ± 5,905	22,922 ± 4,531

Values are means ± SD; HR = Heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; double product = [HR] × [SBP] at peak exercise; all p = NS.

All patients received aspirin and two thirds used lipid-lowering agents.

Correlation and regression analyses are presented in table 2. Univariate regression analysis demonstrated that five variables predicted exercise duration (table 2), including age, $[Mg]_i$, resting systolic blood pressure and ST-segment depression on exercise test. $[Mg]_i$ remained an independent and significant predictor of exercise duration ($p = 0.02$) following adjustment for the other major predictors of age, body mass index, and systolic blood pressure at maximal exercise in a multivariate stepwise regression model.

We then divided patients into two groups: below or equal to (n = 29), and above (n = 13) the normal $[Mg]_i$ of 1.23 μg/mg protein. The two groups were similar with respect to male gender, age, body mass index, and clinical features. The two groups were also similar with regard to the presence of chronic angina, hypertension, diabetes mellitus and hypercholesterolemia. Frequency of exsmoking was similar and no patients were current smokers. The two groups were similar with regard to the use of cardiac medications, including diuretics.

Serum and $[Mg]_i$

There was no difference in the mean serum magnesium level between the two groups (2.13 ± 0.14 vs. 2.02 ± 0.21 mg/dl, $p = 0.10$), although the mean $[Mg]_i$ was significantly higher in the group above compared with the group below or equal to the normal $[Mg]_i$ (1.51 ± 0.28 vs. 1.03 ± 0.10 μg/mg protein, $p = 0.0001$).

Exercise Test Results

There were no significant group differences in exercise-induced ischemia measured by angina or ST-segment depression at peak exercise (table 3). The percent target heart rate achieved between the two groups was the same. There were also no significant differences in the hemodynamic parameters of rest and exercise heart rate, blood pressure and double product between the two groups (table 3). Patients with $[Mg]_i$ higher than the normal $[Mg]_i$ had a significantly greater mean functional capacity, measured in higher achieved metabolic equivalents (10.6 ± 2.5 vs. 8.9 ± 2.3, $p < 0.05$) and exercise duration (9.4 ± 2.3 vs. 7.9 ± 2.2 min, $p < 0.05$) compared to patients with $[Mg]_i$ below or equal to normal (fig. 1).

We next explored mechanisms of this increased functional capacity. Among patients with exercise-induced ischemia, there was no significant correlation between magnitude of ST-segment depression or hemodynamic ischemic threshold and $[Mg]_i$. There were also no significant differences in the magnitude of ST-segment depression or hemodynamic ischemic threshold according to $[Mg]_i$ above or below or equal to the normal. These negative findings are limited by our relatively few patients (n = 7) with exercise-induced ischemia. We next plotted ventricular work load, expressed as double product, accord-

ing to exercise duration (fig. 2). Despite similar resting baseline hemodynamics, patients with $[Mg]_i$ above normal demonstrated lower double products at the late exercise stages, resulting in a longer time to peak work load conditions (fig. 2). Only patients with $[Mg]_i$ above normal were able to exercise beyond stage 4 of the exercise protocol.

Discussion

Our study demonstrates that functional capacity (expressed in metabolic equivalents and exercise duration) is greater in stable CAD patients with higher $[Mg]_i$. This benefit appears to be confirmed via a lowering of the double product via reduced blood pressure at peak exercise, or ventricular unloading. This finding is consistent with previous work suggesting that magnesium is nature's physiologic calcium blocker [2, 7]. It reduces the release of calcium from and into the sarcoplasmic reticulum, and reduces systemic and pulmonary vascular resistance, with a concomitant decrease in blood pressure and a slight increase in cardiac index [2, 9, 10]. Elevation in extracellular magnesium levels reduces arteriolar tone and tension in a wide variety of arteries [2] and potentiates the dilatory action of some endogenous (adenosine, potassium and some prostaglandins) and exogenous (isoproterenol and nitroprusside) vasodilators [2]. As a result, magnesium mildly reduces systolic blood pressure [10], and may provide afterload reduction [2, 9]. Although not comparable to our patient population, Kugiyama et al. [14] demonstrated that exercise-induced angina is suppressed by intravenous magnesium in patients with variant angina, probably the result of improvement in coronary artery spasm, suggesting that the vasodilating effect is related to a variety of pathophysiologic conditions.

In our current study we did not demonstrate any significant difference in the hemodynamic parameters at rest or during exercise between CAD patients with $[Mg]_i$ below or above normal. We also did not observe any differences in exercise-related ischemic parameters (neither clinical symptoms nor ST-segment depression) related to the $[Mg]_i$ levels. These negative findings might be explained

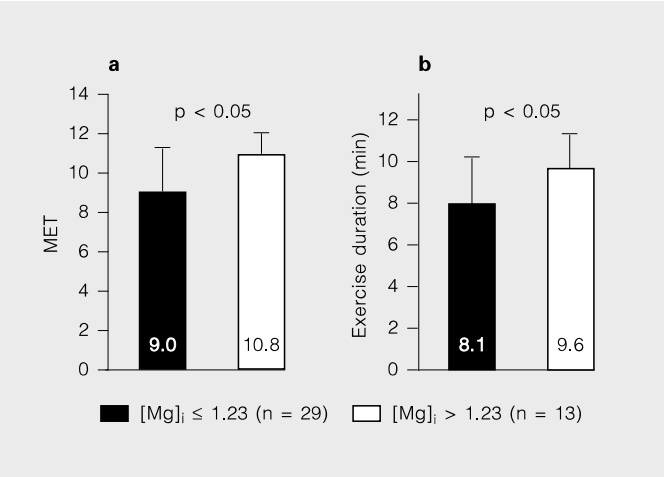

Fig. 1. Bar graphs showing functional capacity, expressed in metabolic equivalents (MET, **a**) and exercise duration (**b**), by the two groups. Data are expressed as means ± SD.

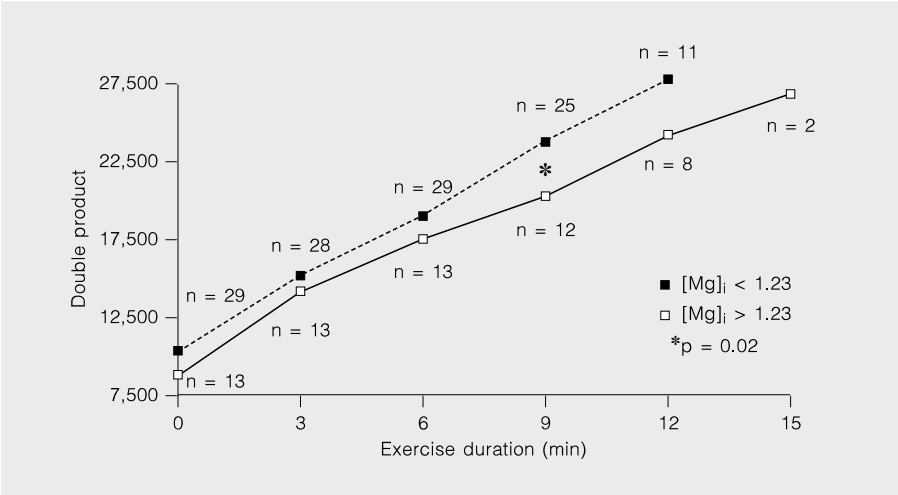

Fig. 2. Ventricular work load, expressed in double product [heart rate (beats/min) × systolic blood pressure (mm Hg)] and exercise duration.

by the relatively small number of patients with exercise-induced ischemia and the relatively stable clinical condition of their hypertension and CAD.

Elderly patients, especially with CAD and heart failure, are known to have low total body magnesium levels. The mechanisms responsible for hypomagnesemia among CAD patients are likely multifactorial. Evidence suggests that the occidental 'American diet' is likely to be deficient, and that the oritental diet is rich in magnesium [15]. While 37% of patients with congestive heart failure who receive diuretic therapy with the loop and thiazide diuretics have hypomagnesemia [3], only 5 patients (14%) in the current study were on loop diuretics. It has been observed that CAD patients absorb more magnesium than those without the disease during magnesium loading testing, which suggests excessive loss and a relative magnesium-deficient state [16]. Consistent with this observation, 66% of our patients had a baseline $[Mg]_i < 1.23$ μg/mg protein, reflecting a magnesium-deficient state despite above normal serum magnesium levels. Syndrome X (insulin resistance, hypertension and dyslipidemia), which is present in approximately half of all CAD patients, is also associated with hypomagnesemia [5, 6]. Rosolova et al. [6] recently demonstrated that low plasma magnesium concentration in nondiabetic subjects was associated with relative insulin resistance, glucose intolerance and hypertension, suggesting that magnesium may contribute to both islet β-cell response and insulin action in non-insulin-dependent diabetic subjects [5].

Study Limitations

We studied a relatively small number of low-risk patients with stable CAD, all receiving aspirin, with near-optimal lipid values and participating in a supervised cardiac exercise program. It is possible that potential beneficial effects related to $[Mg]_i$ were less likely to be evident in our study due to this low-risk population. Further studies with larger numbers of patients who are at higher risk are indicated. Given these pilot study results, an exogenous magnesium treatment trial with the functional capacity as the outcome is also indicated.

Conclusion

In conclusion, our study demonstrates that functional capacity (expressed in metabolic equivalents and exercise duration) is higher in stable CAD patients with higher $[Mg]_i$, suggesting that magnesium plays a role in CAD pathophysiology, possibly via ventricular unloading.

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