Magnesium Content of Serum, Circulating Mononuclear Cells, Skeletal Muscle, and Myocardium in Congestive Heart Failure

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Deranged magnesium concentrations in serum and cardiovascular structures have been implicated in the pathophysiology of hypertension, ischemic heart disease, arrhythmias, and sudden death. This study was conducted to determine the status and interrelation of serum and tissue concentrations of magnesium in patients with congestive heart failure, a clinical setting purportedly predisposed to the development of depleted levels of this cation. Magnesium concentrations of serum, circulating mononuclear cells, skeletal muscle, and myocardium were measured in 23 patients with heart failure on standard therapy. Two patients were hypomagnesemic (<1.6 meq/l). Poor or no correlations were found between serum and tissue magnesium concentrations and among the magnesium concentrations of the three tissues studied. Strong direct correlations were, however, noted between magnesium and potassium concentrations of the tissues examined. The prevalence of hypomagnesemia in this typical ambulatory heart failure population is relatively low (9%) and serum, circulating mononuclear cell, skeletal muscle, and myocardial magnesium concentrations correlate poorly with each other. Serum, circulating mononuclear cell, and skeletal muscle magnesium concentrations are thus of little predictive value in assessing the status of myocardial magnesium in humans with heart failure. (Circulation 1989;80:573–580)

Magnesium, a biologically essential cation, has recently received considerable attention in clinical medicine, especially with regard to its depletion in cardiovascular pathophysiology. Decreased magnesium stores have been implicated in the development and complications of atherosclerosis, myocardial infarction, hypertension, and dysrhythmias.1,2 Severe magnesium deficiency in animals has been shown to cause direct myocardial damage.3

Patients with congestive heart failure would seem to be a group adversely susceptible to altered magnesium metabolism because these patients often have underlying myocardial damage and dysrhythmias and are receiving diuretics chronically. Diuretic therapy increases urinary magnesium losses and may cause depletion of total body and regional magnesium stores when administered on a long-term basis.3–8

This study was performed to determine the status and interrelation of serum and tissue (myocardial, skeletal muscle, and circulating mononuclear cells) concentrations of magnesium in a representative population of ambulatory heart failure patients and, because of their mechanistic interaction at the cellular level, to relate these magnesium data to concomitantly determined serum and tissue potassium concentrations in the same patients.

Methods

Patient Population

Twenty-three patients (17 men and six women; mean age, 45 years; range, 24–74 years) with symptoms of heart failure ranging from mild (New York Heart Association [NYHA] functional Class II) to severe (functional Class IV) were studied. Each had clinical and echocardiographic signs of left ventricular systolic dysfunction. All patients underwent diagnostic cardiac catheterization and angiography within 3 months before the study. Because myocardial fibrosis and ischemia pose major variables in myocardial magnesium determinations, patients with
occlusive and/or symptomatic (angina) coronary artery disease were excluded. Because intrinsic renal dysfunction may alter serum and total body magnesium stores, patients with evidence of chronic renal failure (serum creatinine > 2.5 mg/dl) were also excluded.

Except for antiarrhythmic agents, all drugs were discontinued a minimum of 12 hours before study. Thirteen patients were chronically receiving diuretics orally: 10 patients were taking furosemide from 20 mg once daily to 80 mg twice daily; one patient, spironolactone 25 mg four times daily; one patient, combination amiloride 5 mg and hydrochlorothiazide 50 mg once daily; and one patient, furosemide 80 mg twice daily, spironolactone 25 mg twice daily, and metolazone 2.5 mg every other day. Eight patients were taking a potassium preparation orally (8–30 meq/day). Twelve patients were taking digoxin orally at 0.125–0.25 mg daily, and six patients were taking captopril 6.25–25 mg three times daily.

**Procedures and Measurements**

The experimental protocol was approved by the Human Subjects Review Committee of The Ohio State University. All subjects gave written informed consent.

The study was performed in a postabsorptive state. Sampling of blood, myocardium, and skeletal muscle was completed for each patient within a 1-hour time period between 8:00 AM and 10:00 AM.

Peripheral venous blood was obtained from each subject. The whole blood was placed in a glass tube and centrifuged at 1,200g for 5 minutes. The magnesium and potassium concentrations in the serum were determined by atomic absorption spectrophotometry (Model Spectr AA-20, Varian, Palo Alto, California) with a protein-free dialysate of serum. The serum dialysis technique used, reported from our institution,9 provides a dialysate containing all nonbound magnesium and potassium and extracts for measurement virtually all (>95%) protein-bound magnesium and potassium as well.

Mononuclear cells were separated from peripheral venous blood, counted, and lysed by the method described by Elin and Hosseini.10 The lysed cells were mixed with 2 ml 0.6N perchloric acid containing 5.86 g/l lanthanum oxide, and the suspension was centrifuged at 15,000g for 1 minute. The supernatant was collected, and the procedure was repeated for a total of three washes, resulting in 6 ml supernatant. The supernatant was analyzed for magnesium and potassium concentrations by atomic absorption spectrophotometry. The remaining pellet was analyzed for protein content by the Lowry method.11 The results are expressed both as nanomoles of magnesium or potassium per milligram of protein and as femtograms per cell.

Skeletal muscle biopsies were performed in 20 of the 23 patients. The biopsies were taken from the left Vastus Lateralis muscle (15 cm above the knee) using the method described by Bergstrom.12 Fat and obvious fibrous material were carefully dissected from the sample (required in two samples). The muscle tissue was then frozen at −20°C until analyzed. At the time of magnesium and potassium analysis, the tissue was weighed (average weight of sample was 5.6 mg) and placed in 0.2 ml 0.6N perchloric acid containing 5.86 g/l lanthanum oxide. The sample was then mechanically homogenized and centrifuged at 15,000g for 1 minute. The supernatant was collected, more lanthanum perchlorate was added to the pellet, and the process of homogenization repeated for a total of three extractions per biopsy sample. Pooled supernatants were further diluted with lanthanum perchlorate to bring the total volume to 2.5 ml. The supernatant was then analyzed for magnesium and potassium content by atomic absorption spectrophotometry, and the pellet was analyzed for protein content.11 The results are expressed as nanomoles of magnesium or potassium per milligram of protein.

Endomyocardial biopsies of the right ventricular septum were obtained in 21 of the 23 patients by a previously described technique.13 The biopsies were analyzed for magnesium, potassium, and protein content by the methods described above for skeletal muscle and expressed as nanomoles of magnesium or potassium per milligram of protein.

Perchloric acid was obtained from Fisher Scientific (Fairlawn, New Jersey) and the lanthanum oxide was purchased from Alfa Inorganics (Beverly, Massachusetts). Standard solutions of magnesium and potassium used to calibrate the atomic absorption spectrophotometer were from Alfa Products (Danvers, Massachusetts). All water used for solutions in this experiment was double-distilled and double-deionized.

**Statistics**

A Hewlett-Packard Model 85 computer and curve-fitting analysis program were used for data reduction and to determine the interrelations of serum, skeletal muscle, myocardial, and mononuclear cell magnesium and potassium.

**Results**

The results of this study are presented as individual data (Table 1) and as analyzed by correlation regression formulae (Tables 2 and 3 and Figures 1–3).

Serum magnesium concentrations did not significantly correlate with myocardial, skeletal muscle, and circulating mononuclear cell magnesium concentrations (Figure 1 and Table 2). Two (patients 12 and 18) of the 23 (9%) patients with heart failure had low serum magnesium concentrations; for both, the concentrations were 1.4 meq/l (normal range, 1.6–2.0 meq/l; n=30) (Table 1). These two patients had myocardial magnesium concentrations residing well above the group mean.

Figure 2 depicts the relation between skeletal muscle and myocardial magnesium concentrations. If all data points are included, the correlation coef-
TABLE 1. Individual Magnesium and Potassium Concentrations

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The correlation between circulating mononuclear cell and myocardial magnesium concentrations is presented in Figure 2. Again, if all data points are included, the correlation coefficient is 0.40 (p<0.10). If the two most oulying data points are excluded, the correlation coefficient becomes 0.52 (p<0.05). Among the various combinations of serum, skeletal muscle, myocardial, and mononuclear cell potassium concentrations, the only correaltive trend occurred between serum and myocardium (Table 3). With all data points included, the correlation coefficient is 0.33 and not statistically significant. When the two most oulying points are excluded the correlation becomes 0.48 at p<0.05.

Strong direct correlations were observed between the intracellular concentrations of magnesium and potassium in each of the tissues examined (Figure 3). The correlation coefficient is 0.83 for skeletal muscle, 0.91 for myocardium, and 0.86 for circulating mononuclear cells (all p<0.001).

Additional Clinical and Laboratory Data

Ten patients were chronically receiving furosemide as the sole diuretic, and one patient was taking furosemide in combination with spironolactone and metolazone. Both patients (patients 12 and 18) with low serum magnesium levels (<1.6 meq/l) were on long-term furosemide; the remaining nine patients on furosemide had normal serum magnesium levels. Only two (patients 7 and 18) of five patients (patients 6–8, 13, and 18) with mononuclear cell magnesium levels of less than 200 nmol/mg protein were taking furosemide. The two patients (3 and 7) with the lowest skeletal muscle magnesium concentrations were receiving furosemide chronically. Two patients had myocardial magnesium levels below 50 nmol/mg protein; one (23) never received diuretic therapy and the other (11) was taking furosemide, metolazone, and spironolactone over a 4-month period before this study. There were no statistically significant differences in serum and tissue magnesium...
concentrations between patients receiving and those not receiving chronic diuretic therapy; their respective mean (±SD) values for serum magnesium were 1.71±0.20 and 1.71±0.09 meq/l; circulating mononuclear cell magnesium, 300±140 and 257±76 nmol/mg protein; skeletal muscle magnesium, 72±24 and 81±15 nmol/mg protein; and myocardial magnesium, 69±15 and 66±15 nmol/mg protein. In addition, there were no statistically significant differences between serum and tissue potassium concentrations between patients on long-term diuretic therapy and those not taking diuretics. It is important to note, however, that all of the 11 patients taking furosemide chronically were also taking a potassium supplement, a potassium-sparing diuretic, and/or a converting enzyme inhibitor.

The patients in this study were part of a study examining various determinants of severe ventricular dysrhythmias in heart failure. Each patient was monitored for a minimum of 24 hours (ambulatory Holter or coronary care unit) within 1 week of this study. While none of the patients had experienced a sudden death event before or during the study, nine (patients 1–3, 6, 7, 10, 15, 16, and 22) of the 23 patients had documented periodic sustained (>20 seconds in duration) ventricular tachycardia. The remaining 14 patients had an occasional premature atrial or ventricular beat. With respect to individual data, each of the nine patients with ventricular tachycardia had normal serum magnesium levels, two had mononuclear cell levels of less than 200 nmol/mg protein, two had skeletal muscle magnesium concentrations of less than 50 nmol/mg protein, and four had myocardial magnesium levels below the group mean, but none had less than 50 nmol/mg protein. Except for a statistically significant reduction in the skeletal muscle potassium concentration for the ventricular tachycardia group, there were no statistically significant differences in mean serum magnesium or potassium, mononuclear magnesium or potassium, myocardial magnesium or potassium, or skeletal muscle magnesium concentrations between patients with, compared to those without, serious ventricular arrhythmias.

A biopsy sample for histologic analysis was included in all myocardial biopsy procedures. Generally, the myocardial histopathology of this population consisted of mild-to-moderate myocyte hypertrophy and mild fibrosis. Because of the possible association of magnesium deficiency and myocardial pathologic changes noted in an animal model of severe magnesium depletion,3 the myocardial biopsies of the two patients (patients 11 and 23) with the lowest myocardial magnesium levels were reexamined; neither manifested unique or more severe histopathology compared with the biopsies of the remaining patients.

**Discussion**

Several studies have focused on the role of magnesium in cardiovascular pathophysiology and disease. Severe and prolonged magnesium depletion results in direct myocardial damage in animal models.3 Epidemiologic studies have suggested there may be an association between low magnesium intake and the development of ischemic heart disease.2,14 Magnesium deficiency has also been implicated in sudden death,15 notably in patients with congestive heart failure.16 The development of arrhythmias secondary to hypomagnesemia has been frequently discussed.3,15–18 Modulation of vascular tone and the development of systemic hypertension are other areas in which magnesium is suspected of having a role.14,19

Because of the cardiovascular manifestations, some potentially lethal, purported to occur with magnesium depletion, the authors believed it was important to compare in patients with cardiovascular disease the magnesium concentrations of readily accessible tissues (serum, circulating mononuclear cells, and skeletal muscle) with myocardial magnesium concentrations. It was hypothesized that in
patients with congestive heart failure, a population perhaps predisposed to magnesium depletion, the magnesium concentration in one of the more easily accessible tissues would correlate well with that of myocardium and thus serve as an indicator of the status of myocardial magnesium concentrations.

This study has shown in a reasonable clinical spectrum of patients with dilated cardiomyopathy and congestive heart failure that the prevalence of hypomagnesemia is relatively low (9%) and is not necessarily associated with depressed myocardial levels; serum magnesium levels do not correlate well with the magnesium content of skeletal muscle, myocardium, and circulating mononuclear cells; serum potassium levels do not correlate well with the potassium content of skeletal muscle or mononuclear cells; a weak (at best) correlation exists for circulating mononuclear cell and skeletal muscle magnesium compared with myocardial magnesium concentrations and for serum potassium compared with myocardial potassium concentrations with considerable interpatient variability; and tissue concentrations of magnesium correlate strongly with those of potassium in skeletal muscle, myocardium, and circulating mononuclear cells.

The mean serum magnesium levels in these patients with congestive heart failure (1.7 meq/l or 0.85 mmol/l) corresponds to previously reported values for normal healthy subjects,4,5,20 However, normal serum magnesium levels can exist in the presence of low tissue levels.1,5,20,21 Our values for mean magnesium concentrations in skeletal muscle and myocardium (76.7 and 67.2 nmol/mg protein, respectively) are somewhat difficult to compare with those of other published studies. First, the authors are not aware of any studies, using comparable analytical methods, of myocardial magnesium concentrations in living humans. In the case of skeletal muscle, others have generally used millimoles of magnesium per 100 grams of fat free dry solids20,21 or millimoles of magnesium per gram wet weight tissue22 as units of tissue concentration. From previous work in our laboratory, the fat free dry weight to Lowry protein ratio is 1.8 for both myocardium and skeletal muscle. This conversion yields in this heart failure population a mean magnesium level of 4.26 mmol/100 g fat-free dry solids for the skeletal muscle, which is in agreement with published values for normal human subjects,20,22 and 3.73 mmol/100 g fat free dry solids for myocardium.

Lim and Jacob2 noted that patients with heart failure treated chronically with diuretics had depressed levels of skeletal muscle magnesium (58.3±5.5 meq/kg fat-free solid) compared with a control group (70.8±5.7, p<0.01). In a report by Dyckner and Wester,8 65% of patients with heart failure chronically treated with diuretics had lower levels of skeletal muscle magnesium than those of nondiuretic-treated patients. The degree of depression in skeletal muscle magnesium was generally related to the duration of diuretic therapy. While
FIGURE 3. Plots relating magnesium and potassium concentrations for serum (best-fit formula is $y=1.45e^{0.038x}$, $r=0.15$, $p=NS$), circulating mononuclear cells ($y=0.08x+47.9$, $r=0.86$, $p<0.001$), skeletal muscle ($y=57.5\ln x-292$, $r=0.83$, $p<0.001$), and myocardium ($y=0.092x^{0.909}$, $r=0.91$, $p<0.001$).

The mean skeletal muscle magnesium concentration of our population was not lower than that reported for normal subjects and the magnesium levels were not lower for those treated with diuretics compared to those without diuretic therapy, the two patients with the lowest skeletal muscle magnesium concentrations were chronically receiving furosemide. Differences in patient populations and duration of diuretic therapy could account for some of the disparities between studies.

The mean magnesium concentration of circulating mononuclear cells was found to be 278±111 nmol/mg protein or 86.2±23.9 fg/cell. Elin and Hosseini, using the same analytic methods in normal subjects, found a mean magnesium concentration of 70.7±14.1 fg/cell, comparable with that of the present study (86.2±23.9 fg/cell). However, Sjogren et al noted a mean magnesium concentration of 70–74 nmol/mg protein in normal subjects, and Kulick and colleagues, also in normal human subjects, reported a mean magnesium concentration of 1.18 μg/mg protein or 48.5 nmol/mg protein. Ryzen and colleagues found depressed magnesium levels in the circulating mononuclear cells of severely ill patients, patients who were considerably more compromised than those reported in the current study. Ryan et al noted a drop in lymphocyte magnesium in patients with heart failure receiving long-term diuretic therapy and reversed this fall in magnesium with the potassium-sparing diuretic, amiloride. The differences in mononuclear cell magnesium values and findings of the various studies are related to differences in extraction and analytic techniques and patient populations. Nevertheless, it appears that the mean circulating mononuclear cell magnesium concentration in most ambulatory patients with heart failure is essentially the same (or higher) than the values previously reported in normal subjects, irrespective of the extraction or analytic methods used.

No statistically significant correlations were found between the magnesium concentration of serum and that of skeletal muscle, myocardium, or mononuclear cells (Figure 1 and Table 2). This lack of correlation was also noted in normal subjects by others. Only 1% of total body magnesium is contained in the serum. It is likely that serum magnesium is regulated very closely through ready bidirectional movement with vast body stores to maintain a “normal” serum magnesium level. This is supported by the fact that the normal serum magnesium range is relatively narrow (1.6–2.0 meq/l) and by magnesium balance studies in animals.

A weak correlation was noted between skeletal muscle and myocardial magnesium concentrations (Figure 2); this suggests that while a trend may be present, the correlation is not strong enough to use skeletal muscle concentrations of magnesium to reliably predict myocardial concentrations. Differences in magnesium kinetics and exchanges between these two muscles may account for some of the lack of correlation.

Circulating mononuclear cell magnesium levels also correlated weakly with myocardial magnesium
concentration (Figure 2); again, the relation was not strong enough to allow circulating mononuclear cell magnesium to predict myocardial levels.

Despite the apparent (albeit weak) correlation between circulating mononuclear cell and myocardial magnesium, no correlation whatsoever was found between mononuclear cell and skeletal muscle magnesium concentrations. Sjogren and colleagues\textsuperscript{20} found a correlation of 0.63 between mononuclear cell and skeletal muscle magnesium concentrations in 20 healthy subjects. Dyckner and Wester\textsuperscript{21} demonstrated a correlation of 0.74 in normal subjects that subsequently dropped to no correlation (0.22) when patients with congestive heart failure were added to the analysis. It appears that the magnesium content of mononuclear cells correlates moderately well with that of skeletal muscle in healthy subjects but not in patients with congestive heart failure. The explanation for this disparity is uncertain. The condition of heart failure and the drugs used to treat it could influence various tissues differently. Dyckner and Wester\textsuperscript{21} have suggested that either the mononuclear cell membrane may be more fragile in congestive heart failure, there may be a disturbance of ionic transport across the mononuclear cell membrane, or the lifespan of the mononuclear cell is shortened in congestive heart failure.

After the exclusion of two outliers, serum potassium correlated weakly ($r=0.48$, $p<0.05$) and certainly not at a predictive level with myocardial potassium (Table 3). No other correlations were noted between the potassium levels of the various tissues sampled. In particular, no correlation was seen between circulating mononuclear cell and skeletal muscle potassium content. Once again, and probably for the same reasons mentioned for magnesium, Dyckner and Wester\textsuperscript{21} demonstrated a moderate correlation between these two tissues in normal subjects, but the correlation disappeared when patients with congestive heart failure were included. Magnesium concentrations correlated strongly with potassium in skeletal muscle, myocardium, and circulating mononuclear cells (Figure 3). This close, direct relation has been noted by other investigators for skeletal muscle\textsuperscript{4,20} but not quite to the degree noted in this study. Although not addressed by this study, we postulate that this close correlation is due, in large part, to the close metabolic interaction and relation of these two cations. In severe magnesium deficiency states, cellular and total body loss of potassium is probably related to a varying combination of defective membrane transport (depressed activity of magnesium-dependent sodium-potassium ATPase), increased permeability of the cell membrane, and enhanced systemic catecholamine release with elevated circulating levels.\textsuperscript{3,24,27} The mechanistic explanation for the close relation of magnesium and potassium at normal-to-high tissue concentrations is less well defined.

**Additional Issues, Concerns, and Limitations of This Study**

This study has several limitations. The data presented represent only a limited spectrum of the magnesium status of human subjects. Normal subjects were not studied; adding normal subjects to the study population pool would have likely strengthened the correlations. On the other hand, magnesium disturbances occur in disease states and, therefore, an entity such as heart failure is an appropriate population to target for study. In addition, none of the patients had extremely low or high values; inclusion of such would have widened the data range to strengthen the correlations. Again, the patients selected represent the mild-to-severe spectrum of clinical congestive heart failure rather than a spectrum of laboratory-derived (serum or tissue) magnesium concentrations. Thus, a more relevant and pragmatically guided study evolved. It must be noted, however, that patients with terminal heart failure requiring parenterally administered agents (e.g., dopamine, dobutamine, and nitroprusside) were not included in the study population because of innumerable variables and ethical considerations (specifically, investigational myocardial and skeletal muscle biopsies) in this extremely ill subgroup.

Only 23 patients were studied. It is possible that the findings and conclusions may be different for a much larger population; this is particularly true for the marginal correlations, which could be strengthened by a larger study group.

Excessive fat or fibrous tissue could cause an inappropriately low magnesium or potassium concentration for myocardium or skeletal muscle and weaken the correlation of the concentrations of these cations in muscle compared with serum or mononuclear cells. Myocardial biopsies have little fat content and visually apparent fat and fibrous tissue were meticulously dissected from the skeletal muscle biopsy (two instances) or the biopsy was repeated. While differences in the microscopic content of fat cannot be excluded as a variable, it is unlikely that variations in fat and fibrous content explain the poor or lack of correlations noted. In addition, all tissue magnesium and potassium content data were standardized for tissue protein content, further minimizing the influence of fat on the data.

The magnesium and potassium concentration data obtained and reported in this study do not provide information on free compared with bound cation of cells or tissue or the concentrations of these elements in various cell compartments. It is possible that the serum or tissue magnesium concentrations (or the concentrations in certain cellular compartments of these tissues) correlate well with the concentrations within one or more specific compartments of the myocardial cell. Intracellular to extracellular magnesium (or potassium) ratios may be more relevant to the pathophysiology of heart fail-
ure than the absolute tissue levels. This is particularly true for membrane mechanisms and activity, which relate directly to intracellular electrolyte and ion concentrations, conduction, arrhythmogenicity, and other functions. In addition, serum and tissue magnesium (and potassium) kinetics were not examined in this study. It is quite possible that cellular and subcellular disturbances in magnesium movement, uptake, and metabolism are important in the pathophysiology of heart failure despite “normal” tissue concentrations. Differences in tissue magnesium (and potassium) kinetics (e.g., myocardium compared with skeletal muscle) may explain some of the poor interregion correlations. Considerably more investigation will be required to address these important questions.

References

KEY WORDS • potassium • heart failure, congestive • metabolism • myocardial • magnesium • muscle, skeletal • cells
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