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Relationship of Potassium and Magnesium Concentrations in Serum to Cardiac Arrhythmias

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Low concentrations of potassium and magnesium in serum have been implicated in cardiac arrhythmias; the importance of mild hypokalemia or hypomagnesemia is uncertain. To investigate possible associations among use of diuretics, the concentration of these ions in serum, and the onset of clinically important arrhythmias, we reviewed records of 103 patients admitted to our Coronary Care Unit during three months and found mild to moderate hypokalemia and hypomagnesemia in 18 and 24%, respectively. The significant correlation between the concentrations of magnesium and potassium in serum at admission ($r = 0.27$, $p < 0.007$) remained constant in patients, whether they were receiving diuretics or not. Potassium concentrations were significantly lower ($p < 0.05$) in patients receiving diuretics (3.93 mmol/L) than in those who were not (4.21 mmol/L), but the mean concentrations of magnesium did not differ significantly. Except for myocardial infarction, no single variable or combination of variables was highly predictive of cardiac arrhythmias in these patients. We conclude that there is no strong predictive relationship between mildly decreased concentrations of magnesium or potassium in serum and onset of cardiac arrhythmias.

Additional Keyphrases: *risk factors · hypokalemia · hypomagnesemia · myocardial infarction · hypertension · coronary-care units · diuretics · heart disease · discriminant analysis*

Low concentrations of potassium and magnesium in serum have been implicated in the etiology of cardiac arrhythmias (*1–3*), but the potential role of mild decreases in the concentrations of these ions remains controversial (*4, 5*). Of particular interest has been the question of whether the mild degrees of hypokalemia and hypomagnesemia induced by diuretic therapy constitute a significant risk in patients being treated with these agents for hypertension. Several studies suggest that diuretic-induced hypokalemia is of little consequence clinically and that potassium supplementation is not needed routinely for most such patients (*4–7*). A recent report from the American Multiple Risk Factor Intervention Trial (*8*), however, presented evidence that therapy with thiazide diuretics may have increased the death rate from coronary heart disease (including sudden death) in hypertensive men who had abnormalities in their electrocardiograms taken while resting, possibly by causing arrhythmias.

Because several reports (e.g., *2, 3, 9, 10*) have suggested that the potential for mild hypokalemia and hypomagnesemia to lead to arrhythmias may be greater after myocardial infarction, we studied a series of patients admitted consecutively to the Coronary Care Unit and attempted to identify possible relationships among the use of diuretics, mild hypokalemia and hypomagnesemia, and the occurrence of clinically significant arrhythmias.

Materials and Methods

We gathered our data from the charts for 103 of 113 consecutive patients admitted to our institution's Coronary Care Unit during a three-month period. (Charts for the remaining 10 patients could not be located for study.) For each patient we recorded age and sex; historical evidence of congestive heart failure, hypertension, and diuretic therapy; the serum concentrations of magnesium and potassium at admission; and the final clinical diagnosis as to whether the patient had had a myocardial infarction. To measure concentrations of potassium in serum we used ion-selective electrodes, in either the SMAC (Technicon Corp., Tarrytown, NY 10591) or the Astra-8 (Beckman Instruments, Inc., Brea, CA 92621) analyzers; routine quality-control comparisons of the results obtained for serum with these two instruments did not differ significantly. Magnesium in

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serum was measured by its reaction with methylthymol blue in the *aca* discrete analyzer (Du Pont Co., Wilmington, DE 19898). In our laboratory, the reference interval for potassium is 3.5 to 5.0 mmol/L and for magnesium, 18 to 28 mg/L (0.75 to 1.2 mmol/L).

All patients in the Unit were continuously monitored with electrocardiographs, the tracings being scanned by an automated arrhythmia-monitoring unit (HP78220; Hewlett-Packard, Waltham, MA 02154) and a trained monitor watcher. Tracings were routinely printed out at 4-h intervals and whenever any changes in rhythms were observed.

We subsequently reviewed these printouts, the edited daily trend report, and each patient's chart. A significant ventricular arrhythmia was considered to be present if any of the following occurred: (*a*) sustained ventricular tachycardia or fibrillation that required countershock or medication, whether in the field by paramedics or after arrival in the Coronary Care Unit; (*b*) >30 ventricular premature beats in any hour while the patient was in the Unit; or (*c*) consecutive ventricular premature beats, whether paired or in salvos (≥3). We used only the data acquired during the first 48 h after admission to the Coronary Care Unit or until the time of discharge from it, whichever came first.

Because electrocardiograms and edited daily-trend reports could not be located for 11 of the 103 patients, we excluded data from these patients from consideration in all data analysis of arrhythmias.

For statistical comparisons among groups, we used unpaired *t*-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Logistic discriminant analysis was performed according to the techniques of Anderson (*11*).

Results

At admission, 19 (18%) of the 103 patients had potassium concentrations <3.5 mmol/L. For three, magnesium was not measured at admission; 24 of the remaining 100 had magnesium concentrations <18 mg/L. The prevalence of hypokalemia in patients with concurrent hypomagnesemia (six of 24 patients, or 25%) exceeded that of the overall population admitted to the Coronary Care Unit; so did the prevalence of hypomagnesemia in patients with concurrent hypokalemia (six of 19, or 32%).

The correlation between the 100 paired concentrations of serum magnesium and potassium ($r = 0.27$, $p = 0.006$) was significant, and it apparently was unaffected by therapy with diuretics (for 48 patients receiving diuretics, $r = 0.25$; for the other 52 patients, $r = 0.28$). Statistically significant differences were found between the group of patients treated with diuretics vs the group not treated with diuretics (Table 1) in average patient age, in the frequencies of hypertension and congestive heart failure by history, and in the average concentration of potassium in serum. No differences were found in the frequencies of arrhythmias, in the occurrence of myocardial infarction, or in the mean concentrations of magnesium in serum.

Similarly, we compared the group of patients who experienced significant ventricular arrhythmias during the first two days of hospitalization and the group that did not (Table 1). The only significant difference identified was the more frequent finding of myocardial infarction in the patient group that experienced clinically significant arrhythmias than in the group that had no arrhythmias (Table 1). We found no significant increase in the frequency of arrhythmias in patients with definitely low concentrations of potassium or magnesium in their serum as compared with patients with normal or increased concentrations of these ions (Table 2).

Table 2. Frequency of Arrhythmias in Mild and Severe Hypokalemia and Hypomagnesemia

	Arrhythmias	No arrhythmias
K^+ concn, mmol/L		
≥3.5[a]	43	31
3.0–3.4	10	4
<3.0	3	1
Mg^{2+} concn, mg/L		
≥18[a]	44	27
15–17	9	8
<15	2	1

[a] Lower cutoff value for normal in our laboratory.

To explore the value of simultaneous information in multiple variables for predicting arrhythmias, we used logistic discriminant analysis. Diagnosis of myocardial infarction (yes/no) was the most important variable for the prediction of arrhythmias, and was the only variable for which the discriminant function coefficient differed statistically significantly from zero ($t = 3.08$, $p < 0.005$). Use of this variable alone to predict arrhythmias was accurate in 62% of the cases (Table 3). A history of diuretic use ($t = 0.87$, $p <$

Table 3. Accuracy of Logistic Discriminant Analysis in Predicting Arrhythmias

	Predictive accuracy, % correct[a]			
Variables	Arrhythmia	No arrhythmia	Overall	p
MI[a]	50	81	62	0.007
MI + diuretics	50	81	62	0.007
MI + diuretics + Mg^{2+}	54	72	61	0.03
All variables[b]	61	64	62	0.03

[a] See Table 1 for no. of cases in each category.

[b] The above three variables plus age, sex, history of hypertension, history of congestive heart failure, and concentration of potassium in serum.

MI, myocardial infarction

Table 1. Effect of Treatment with Diuretics, Together with Other Risk Factors, on the Incidence of Arrhythmias in Patients in a Coronary-Care Unit[a]

	Treated with diuretics			Experienced arrhythmias[b]		
Factor	Yes (n = 49)	No (n = 54)	p	Yes (n = 56)	No (n = 36)	p
History of hypertension	34 (69)	21 (39)	0.004[c]	31 (55)	17 (47)	NS
History of congestive heart failure	20 (41)	5 (9)	0.0005[c]	15 (27)	6 (17)	NS
Myocardial infarction	17 (35)	22 (41)	NS	28 (50)	7 (19)	0.007[c]
K^+, mmol/L	3.93 ± 0.65	4.21 ± 0.76	0.05[d]	4.01 ± 0.6	4.05 ± 0.6	NS
Mg^{2+}, mg/L	19.1 ± 3.1	19.4 ± 3.2	NS	19.2 ± 2.9	19.3 ± 3.3	NS

[a] Results given as mean ± SD or as no. of patients affected (and %).

[b] Incomplete data for 11 patients, who were excluded from data analysis of arrhythmias.

[c] Chi-square test with Yates correction for continuity.

[d] Unpaired *t*-test with grouped variance estimate.

NS, not significant.

0.4) and the concentration of magnesium in serum ($t = 0.59$, $p < 0.6$) were the next most valuable prediction variables for arrhythmias, but did not add to the overall predictive accuracy of the discriminant function. Including all variables—age, sex, history of hypertension (yes/no), history of congestive heart failure (yes/no), history of diuretic use (yes/no), concentrations of potassium and magnesium, and diagnosis of myocardial infarction (yes/no)—did not improve the overall accuracy of prediction (Table 3).

Discussion

From these data we found surprisingly few relationships among the use of diuretics, the concentrations of magnesium or potassium in serum, and the onset of cardiac arrhythmias. Of the patients studied, 18 and 24% had mild to moderate hypokalemia and hypomagnesemia, respectively, and in agreement with our previous data (*12*) and the data of Roberts (*13*), the concentrations of potassium and magnesium were significantly correlated ($r = 0.27$, $p = 0.007$). This small but significant correlation was independent of the effects of therapy with diuretics on the concentrations of potassium and magnesium in serum. There was a small but significant difference between the mean concentrations of potassium in patients receiving diuretic therapy as compared with those who were not, but not between the mean concentrations of magnesium in these groups of patients. Despite our findings of a correlation of serum potassium with magnesium and an effect of diuretic use on the mean concentration of potassium in serum, our extensive multivariate analysis of the data showed that only the occurrence of myocardial infarction was of any value in predicting cardiac arrhythmias in these coronary-care patients.

Although several investigators have found low concentrations of potassium and magnesium in serum to be associated with arrhythmias (*1–3, 9, 10*), there has been considerable interest in whether the mild degrees of hypokalemia and hypomagnesemia induced by diuretic therapy would predispose diuretic-treated patients to arrhythmias. Harrington et al. (*5*), criticizing the methods used in earlier studies that found a relationship between potassium or magnesium and arrhythmias, have, with others (*4, 6, 7*), suggested that routine supplementation of diuretic-treated patients with potassium or magnesium may not be necessary for most patients.

Holland et al. (*1*), in a prospective study of the prevalence and type of ventricular ectopic activity in non-digitalis-treated hypokalemic patients, found a greater frequency of complex ventricular ectopic activity with moderate to severe hypokalemia (<3.0 mmol/L) than in mild hypokalemia. In our study, more than 95% of the patients with hypokalemia or hypomagnesemia had what would be considered mild cases—potassium between 3.0 and 3.4 mmol/L or magnesium between 13 and 17 mg/L. Given the known concentration-dependent relationship between serum potassium concentration and electrocardiographic changes (*14*), these data support the view that mild degrees of hypokalemia and hypomagnesemia may not represent as serious a risk for the development of arrhythmias as do moderate to severe decreases in these ions.

Morgan and Young (*15*) found that cases of hypokalemia occurring early during hospitalization resolved spontaneously, whether or not potassium was supplemented. One wonders whether the hypokalemia noted in some patients may be a transient effect of some other underlying event that temporarily shifts potassium within the cells. Several investigators have shown that increases in catecholamine concentrations as great as those seen in myocardial infarction can lower the concentration of potassium in plasma by almost 1 mmol/L (*16, 17*), but that this decrease can be prevented by blockade of beta adrenergic receptors (*18, 19*). Although any relation between hypokalemia and arrhythmias in myocardial infarction has been assumed to be causal, it may be an indirect one, mediated through a common factor such as catecholamine excess (*19*).

Any relationship between clinically important arrhythmias and mild decreases in the serum concentrations of potassium or magnesium, appears from our data to be a weak one. Analysis of the power of the statistical tests used in this study (*20*) showed that our patient population was of sufficient size for us to detect with 85% probability a mean difference in serum potassium concentration of 0.39 mmol/L and a mean difference in serum magnesium concentration of 1.9 mg/L between the patient groups with and without arrhythmias.

We made some compromises in our study design. First, our use only of potassium and magnesium measurements made at the time of the patients' admission to the hospital caused the time relationship between the potassium and magnesium measurements and the onset of clinically important arrhythmias to vary from patient to patient. We used only the admitting concentrations because of our concern that therapeutic manipulations after admission could acutely alter the concentrations of potassium and magnesium in serum so that they would no longer reflect the original balance of these ions. In addition, had data on the concentrations of these ions throughout the patients' hospitalization been collected, the data analysis would have been enormously complicated and required more extensive knowledge of the patients' hospital course than could be gathered from the hospital chart.

A second and related factor that compromised the design of this study was that there was no way to control for the effects of therapy given for hypokalemia or hypomagnesemia. The various physicians involved in the clinical care of these patients exercised different clinical approaches in treating hypokalemia and hypomagnesemia. These differences in treatment may have masked a relationship in the data between arrhythmias and potassium or magnesium.

Although our data suggest that the relationship between cardiac arrhythmias and mild decreases in serum concentrations of potassium and magnesium is either weak or nonexistent, we believe that further investigations with a larger patient population are warranted for the detection of subtler relationships. In addition, because the concentrations of magnesium and potassium in serum may not correlate well with the intracellular concentrations of these ions (*21, 22*), further studies of the relationships between arrhythmias and the intracellular concentrations of magnesium and potassium are needed.

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Values of the U.S. National Reference Serum for Human Antibodies to Native DNA Obtained with Commercial Immunoassays for Anti-DNA in Systemic Lupus Erythematosus

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The Arthritis Foundation and the Centers for Disease Control have recently prepared a "U.S. National Reference Serum" for human antibodies to native DNA. We tested this serum with 13 commercial assays for antibodies to native DNA, to permit comparisons of the values obtained in each test. Titers ranged from 10 to 2560 in *Crithidia luciliae* immunofluorescence assays. The serum produced 794 int. units/mL in the Cordis ELISA assay, 136 Amersham units/mL in a radioimmunoassay, and 88 FIAX units in a fluorometric immunoassay. These results can be used for interlaboratory comparisons of differing methodologies for measuring anti-DNA.

The Arthritis Foundation and the Centers for Disease Control have recently developed a "U.S. National Reference Serum" for human antibodies to native DNA and for fluorescent antinuclear antibody (homogeneous/rim pattern.) This preparation is intended to permit workers to standardize their assays with a single reagent (*1, 2*).

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Many commercial assays for antibodies to native DNA are available for the diagnosis and management of systemic lupus erythematosus (*3*). However, results obtained with these have never been systematically inter-compared with use of a single reference serum.

We therefore tested the U.S. National Reference Serum, using all of the quantitative commercial assays that we knew of. Our values should allow laboratories to evaluate anti-DNA concentrations in their own assays by reference to others.

Materials and Methods

Reference sera. A vial containing a mean of 35.9 mg (dry weight) of the above-mentioned lyophilized U.S. National Reference Serum ANA Human Serum no. 1, cat. no. IS2072, lot 82-007, was obtained from the Arthritis Foundation—Centers for Disease Control Anti-Nuclear Antibody Reference Laboratory, Immunology Branch, CID, Centers for Disease Control, Atlanta, GA 30333 (*1, 2*). The contents of the vial were reconstituted with 0.5 mL of water, aliquoted, and stored at −70 °C for up to four months.

A positive control serum (human), lot 90842, was obtained from Cordis Laboratories, Inc., Miami, FL 33152. The value assigned to this serum (760 int. units/mL) is traceable to the World Health Organization's (WHO) 1st International Reference Preparation of Anti-Nuclear-Factor Serum (Homogeneous), 1970, formerly termed the "Proposed Research Stan-