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Prognostic Importance of the Serum Magnesium Concentration in Patients With Congestive Heart Failure

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Magnesium abnormalities are common in patients with congestive heart failure but the clinical and prognostic significance of an abnormal serum magnesium concentration in this disorder has not been investigated. Therefore, the relation between serum magnesium concentration and the clinical characteristics and long-term outcome of 199 patients with chronic heart failure was evaluated. The serum magnesium concentration was <1.6 mEq/liter in 38 patients (19%), within the normal range in 134 patients (67%) and >2.1 mEq/liter in 27 patients (14%).

Patients with hypomagnesemia had more frequent ventricular premature complexes and episodes of ventricular tachycardia than did patients with a normal serum magnesium concentration ($p < 0.05$). Even though the two groups were similar with respect to severity of heart failure and neurohormonal variables, patients with a low serum magnesium concentration had a significantly worse prognosis during long-term follow-up (45% versus 71% 1 year survival, $p < 0.05$). Patients with hypermagnesemia had more severe symptoms, greater neurohormonal activation and worse renal function than did patients with a normal serum magnesium concentration but tended to have fewer ventricular arrhythmias. Hypermagnesemic patients had a worse prognosis than did those with a normal magnesium concentration (37% versus 71% 1 year survival, $p < 0.05$).

***In conclusion,* the measurement of serum magnesium concentration provides important clinical and prognostic information in patients with chronic heart failure.**

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Patients with congestive heart failure characteristically manifest a variety of electrolyte abnormalities that are related to both the pathophysiology and the treatment of the disorder. These patients may have hypokalemia (1,2) (secondary to activation of the renin-angiotensin system or the use of diuretic drugs) or hyperkalemia (2,3) (secondary to the development of renal insufficiency or the use of angiotensin-converting enzyme inhibitors). Patients with heart failure may also exhibit hyponatremia, which may be related to the enhanced release of both angiotensin and vasopressin and can be exacerbated by diuretic therapy (4). Such altered concentrations of potassium and sodium have important clinical and prognostic significance. Hypokalemia and hyperkalemia may increase the risk of sudden death by their effects on cardiac excitability and conduction (2,5) and hyponatremia has been associated with an increased risk of death from progressive heart failure (4), bradyarrhythmias and electromechanical dissociation (6).

Many of the factors that interact to alter the concentration of sodium and potassium in patients with heart failure may also disturb magnesium homeostasis in this disorder. Digoxin, diuretics and activation of the renin-angiotensin system may increase the renal excretion of magnesium and lead to hypomagnesemia (7), whereas poor renal function may impair the excretion of this cation and lead to hypermagnesemia (8). Despite the prevalence of these factors, the clinical significance of hypomagnesemia and hypermagnesemia in heart failure has not been evaluated; even the prevalence of an abnormal serum magnesium concentration in this disorder remains controversial (9–11). To address

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these questions, we investigated both the prevalence and clinical importance of an abnormal serum magnesium concentration in a large group of patients with chronic heart failure.

Methods

Study patients. Our study group consisted of 199 patients with chronic congestive heart failure referred for treatment with vasodilator or inotropic drugs. There were 144 men and 55 women aged 28 to 90 years (mean 64). The cause of heart failure was ischemic heart disease in 102 patients, dilated cardiomyopathy in 88 and primary mitral or aortic valvular insufficiency, or both, in 9 patients. The left ventricular ejection fraction by radionuclide ventriculography ranged from 2% to 39% (mean 19%). Thirty-seven patients were in New York Heart Association functional class II, 77 patients were in class III and 85 patients were in class IV but all were clinically stable at the time of evaluation. All patients were receiving constant doses of digoxin and diuretics and none had received any vasodilator or antiarrhythmic medications within 5 days.

Patient characterization. After an indwelling intravenous line was inserted, patients were permitted to rest for 30 min in a quiet room. After this equilibration period, blood was collected for the following measurements: 1) serum magnesium, potassium, sodium, creatinine and blood urea nitrogen (199 patients); 2) plasma norepinephrine by radioenzymatic assay (114 patients); and 3) plasma renin activity (146 patients), aldosterone (99 patients) and arginine vasopressin (89 patients) by radioimmunoassay.

Twenty-four hour ambulatory electrocardiographic (ECG) recordings were obtained in 106 patients within 7 days of these hormonal and electrolyte measurements and were scanned for the presence of ventricular premature complexes and ventricular tachycardia. Ventricular tachycardia was defined as three or more consecutive ventricular complexes at a rate of at least 100 beats/min.

Data analysis. Patients were divided into three groups based on their serum magnesium concentration (low, normal or high); a normal serum magnesium level was defined as a concentration between 1.6 and 2.1 mEq/liter, range of values obtained in 90% of control subjects. Qualitative and quantitative differences among the three subgroups were tested for significance with use of the chi-square statistic and analysis of variance, respectively.

Long-term survival was assessed from the day of magnesium determination to the day of death or to June 1, 1988. Death was classified as sudden if unexpected circulatory collapse occurred in a clinically stable patient (12); this assessment was made without knowledge of the patient's serum magnesium concentration. Patients were considered lost to follow-up if the long-term clinical outcome was unknown (eight patients, survival censored after date of last visit) or if cardiac transplantation occurred (one patient, survival censored after date of transplantation). Cumulative survival curves for the three magnesium groups were constructed by Kaplan-Meier survivorship methods (13) and the differences between the survival curves were tested for significance by both Mantel-Cox log rank and Wilcoxon-Breslow methods (14,15).

Results

The serum magnesium concentration in the 199 patients ranged from 1.0 to 3.6 mEq/liter (mean 1.8 ± 0.3 mEq/liter). The magnesium concentration was >2.1 mEq/liter in 27 patients (14%), within the normal range in 134 patients (67%) and <1.6 mEq/liter in 38 patients (19%).

Hypomagnesemia. The 38 patients with a serum magnesium concentration <1.6 mEq/liter were similar to those with a normal concentration with respect to age, gender, cause of heart failure, functional class and neurohormonal variables (Table 1). Hypomagnesemic patients, however, had more frequent ventricular premature complexes and episodes of ventricular tachycardia and had a higher serum creatinine concentration than did patients with a normal magnesium level (Fig. 1). These factors may explain why patients with a low serum magnesium concentration had a significantly worse survival rate than did patients with a normal level (1 and 2 year survival of 45% and 42% compared with 71% and 61%, respectively, $p < 0.05$) (Fig. 2).

Hypermagnesemia. In contrast to the clinical similarity of the low and normal magnesium groups, the 27 patients with a serum magnesium concentration >2.1 mEq/liter demonstrated clinical and biochemical evidence of more severe heart failure than the normal magnesium group (Table 1). Despite similar values for left ventricular ejection fraction, patients with a high magnesium concentration were older and had more severe symptoms, higher circulating levels of neurohormones and worse renal function than did patients with a normal serum magnesium. Despite their more advanced heart failure, patients with a high magnesium concentration tended to have a reduced (rather than increased) frequency of premature ventricular complexes and episodes of ventricular tachycardia compared with that in patients who had a normal magnesium concentration (Fig. 1). Nevertheless, patients in the high magnesium group had a significantly worse prognosis than did those in the normal magnesium group (1 and 2 year survival of 37% and 30% compared with 71% and 61%, respectively, $p < 0.05$) (Fig. 2).

Cause of death. Of the 93 cardiac deaths in this study, 25 were classified as sudden and unexpected, including 37% of the deaths that occurred in patients with a low serum magnesium concentration, 29% of the deaths in patients with a normal concentration and 17% of the deaths in patients with a high concentration.

Table 1. Characteristics of 199 Patients With Chronic Heart Failure Grouped According to Serum Magnesium Levels

	<1.6 mEq/liter	1.6–2.1 mEq/liter	>2.1 mEq/liter
Age (yr)	62 ± 2	63 ± 1	71 ± 2*
Gender			
Men	26	98	20
Women	12	36	7
Etiology			
Ischemic	18	67	17
Primary	18	62	8
Valvular	2	5	2
NYHA functional class			
II	3	34	0
III	18	52	7
IV	17	48	20*
Ejection fraction (%)	19 ± 2	19 ± 1	19 ± 2
Serum potassium (mEq/liter)	3.8 ± 0.2	4.2 ± 0.1	3.7 ± 0.3
Serum creatinine (mg/dl)	2.1 ± 0.3*	1.6 ± 0.1	2.5 ± 0.2*
Serum blood urea nitrogen (mg/dl)	41 ± 6	33 ± 2	67 ± 7*
Plasma renin activity (ng/ml per h)	5.6 ± 1.3	5.0 ± 1.0	11.0 ± 2.8*
Plasma aldosterone (ng/dl)	20 ± 6	30 ± 6	46 ± 16
Plasma norepinephrine (pg/ml)	706 ± 151	653 ± 96	966 ± 166
Plasma arginine vasopressin (pg/ml)	4 ± 1	5 ± 1	13 ± 3*
Furosemide dose (mg/day)	95 ± 11	82 ± 6	103 ± 11

*Statistical significance ($p < 0.05$) as compared with values in the patients with a normal serum magnesium concentration. Group data are mean values ± SEM. NYHA = New York Heart Association.

Discussion

This study is the first report to demonstrate the clinical significance of an abnormal serum magnesium concentration in patients with chronic heart failure. Compared with patients whose values fell within the normal range, patients with hypo- and hypermagnesemia had a significantly worse prognosis that appeared to be related to specific ECG and metabolic abnormalities. Previous investigations of the potential role of magnesium in heart failure simply defined the prevalence of an abnormal magnesium value; they did not attempt to show that an abnormality was associated with particular clinical characteristics or future events. In the absence of such information, it was possible that the finding of a serum magnesium concentration outside the normal range had only statistical, not biologic, significance. This

Figure 1. Frequency of ventricular premature complexes and episodes of ventricular tachycardia in 199 patients with a serum magnesium (Mg) concentration <1.6 (n = 38), 1.6 to 2.1 (n = 134) and >2.1 mEq/liter (n = 27). An asterisk indicates a statistically significant difference ($p < 0.05$) as compared with values in patients with a normal serum magnesium concentration.

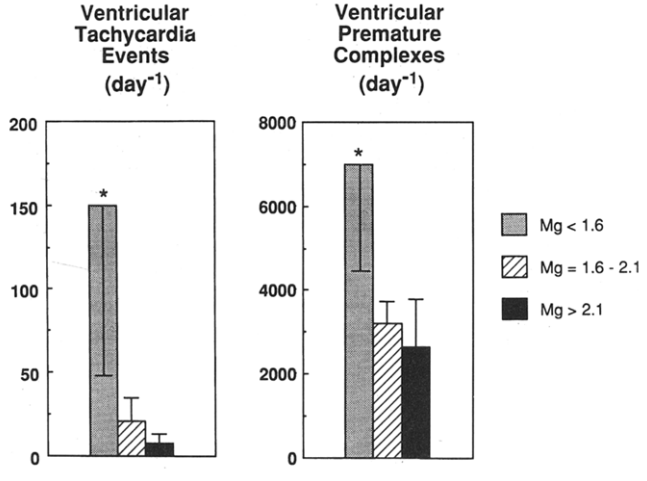
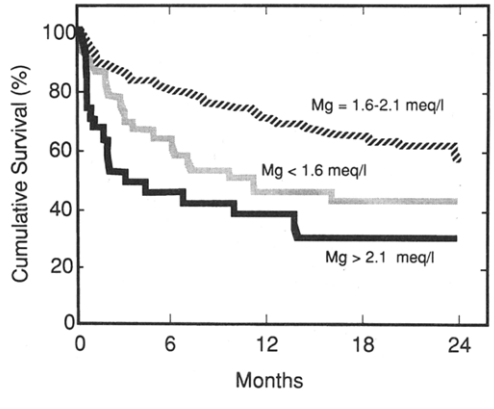


Figure 2. Actuarial survival rate of patients with a serum magnesium (Mg) concentration <1.6 (n = 38), 1.6 to 2.1 (n = 134) and >2.1 mEq/liter (n = 27). Patients with a normal magnesium concentration had a more favorable prognosis than that of patients with a low or high serum level (both $p < 0.05$).



study indicates that abnormalities of the serum magnesium concentration are not merely laboratory curiosities but have important clinical implications.

Patients with hypomagnesemia. Previous investigators have reported a prevalence of hypomagnesemia varying from 7% of patients admitted to a coronary care unit with acute heart failure (11) to 37% of diuretic-treated patients with chronic cardiac decompensation (10). The present study confirms the high prevalence of hypomagnesemia in patients with heart failure (nearly 20%) but fails to elucidate the mechanisms responsible for this electrolyte abnormality. Although treatment with digitalis and diuretics and high circulating levels of aldosterone and vasopressin can increase the urinary excretion of magnesium (7), these factors did not differ between the low and normal magnesium groups.

Our data strongly support the conclusion that, regardless of its cause, the low serum magnesium concentration noted in many patients with chronic heart failure has clinical significance; patients with hypomagnesemia had a worse prognosis than did patients with a normal concentration. This finding has two possible explanations. First, the low magnesium concentration may be simply a marker of more advanced disease; hypomagnesemic patients could have been more severely ill than patients with a normal concentration. However, the two groups did not differ with respect to any of the hemodynamic or neurohormonal variables that we measured. Second, the low magnesium concentration may have had direct pathogenetic significance. Magnesium depletion can impair cardiac performance either by reducing cardiac contractility (16) or by causing peripheral vasoconstriction (17). However, hypomagnesemic patients in our study did not show evidence of worse ventricular function. Instead, their poor prognosis appeared to be related to their more frequent and complex ventricular arrhythmias because these patients had a higher prevalence of sudden death than did the other two magnesium groups. Previous studies support the concept that magnesium depletion may increase the frequency of ventricular arrhythmias. A low magnesium concentration enhances the development of arrhythmias in the laboratory (18) and clinical setting (19) and the administration of magnesium suppresses electrophysiologic abnormalities in dogs (20) and in patients (21,22). These actions of magnesium may be related to its function as a critical cofactor in the cellular activities that regulate intracellular electrolyte concentrations (23).

Patients with hypermagnesemia. This study is the first to identify the presence of an elevated serum magnesium concentration in a substantial number of patients with chronic heart failure; nearly one of seven patients had a serum magnesium level >2.1 mEq/liter. The most common cause of hypermagnesemia in general medicine is chronic renal insufficiency (8) presumably because the kidneys provide the most important route of excretion for magnesium. Impaired renal clearance of magnesium may therefore explain the high magnesium concentrations observed in our patients with chronic heart failure; patients with a high serum concentration of magnesium had worse renal function than did patients with a normal serum concentration. The renal insufficiency in these patients is probably related to their more advanced age and severity of heart failure, both of which decrease glomerular filtration (24).

As in the case of hypomagnesemia, the high serum magnesium concentration seen in some patients with chronic heart failure was associated with a poor long-term prognosis. However, this unfavorable outlook did not appear to be a direct effect of the electrolyte abnormality but may have been related to the high prevalence of several adverse prognostic factors in these patients. Patients with a high serum magnesium concentration were older, had more severe symptoms of heart failure, had worse renal function and had higher levels of plasma renin activity than did patients with a normal serum magnesium concentration. All of these factors have been shown to adversely modify the long-term outcome of patients with chronic heart failure (25–27). Only two variables reflecting the severity of heart failure—left ventricular ejection fraction and ventricular arrhythmias—were not worse in hypermagnesemic patients than in the normal magnesium group. The similarity of values for ejection fraction is not unexpected because the left ventricular ejection fraction loses its prognostic significance in patients with advanced heart failure as neurohormonal (rather than hemodynamic) factors emerge as the primary determinants of mortality (28). On the other hand, we would have expected patients with more advanced disease to have more frequent ventricular arrhythmias (29) but our patients with hypermagnesemia were least likely to have complex arrhythmias and experience sudden death. These observations suggest that high levels of magnesium may be associated with clinically important antiarrhythmic effects.

Limitations. The present study needs to be interpreted cautiously. Although our findings demonstrate the clinical importance of serum magnesium measurements in patients with chronic heart failure, serum levels of magnesium relate poorly to the levels of magnesium measured in skeletal muscle, myocardium, lymphocytes or erythrocytes. Tissue magnesium depletion is common even in patients with a normal serum magnesium concentration and, conversely, hypomagnesemia may coexist with normal tissue levels of the cation (30,31). However, the clinical relevance of tissue levels of magnesium is not known. It is possible that serum levels may be as important (if not more important) as tissue levels in determining the arrhythmogenic potential of magnesium depletion; rapid changes in serum magnesium level produce significant electrophysiologic effects (32). Future investigations are needed to determine whether cellular or serum levels of magnesium are the more important determinant of the cation's electrophysiologic actions.

Conclusions. The findings of the present study indicate that patients with chronic heart failure frequently have clinically important abnormalities of the serum magnesium concentration. Patients with hypomagnesemia have a poor prognosis that is probably related to a high prevalence of ventricular arrhythmias and an increased risk of sudden death. In contrast, hypermagnesemic patients have a poor prognosis that is related to the severity of disease, poor end organ function and neurohormonal activation. Further work is needed to determine whether efforts to change the serum magnesium concentration can modify the prognosis of these severely ill patients.

References

1. Dargie HJ, Cleland JGF, Leckie BJ, Inglis CG, East BW, Ford I. Relation of arrhythmias and electrolyte abnormalities to survival in patients with severe chronic heart failure. Circulation 1987;75(suppl IV):IV-98–107.
2. Packer M, Lee WH. Provocation of hyper- and hypokalemic sudden death during treatment with and withdrawal of converting-enzyme inhibition in severe chronic congestive heart failure. Am J Cardiol 1986;57: 347–8.
3. Lawson DH, O'Connor PC, Jick H. Drug attributed alterations in potassium handling in congestive cardiac failure. Eur J Clin Pharmacol 1982;23:21–5.
4. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. Circulation 1986;73:257–67.
5. Holland OB, Nixon JD, Kuhnert L. Diuretic induced ventricular ectopic activity. Am J Med 1981;70:762–8.
6. Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. Circulation 1989;80:1675–80.
7. Gottlieb SS. Importance of magnesium in congestive heart failure. Am J Cardiol 1989;63:39G–42G.
8. Popovtzer MM, Massry SG, Coburn JW, Kleeman CR. The interrelationship between sodium, calcium, and magnesium excretion in advanced renal failure. J Lab Clin Med 1969;73:763–71.
9. Whang R, Oei T, Wantanabe A. Frequency of hypomagnesemia in hospitalized patients receiving digitalis. Arch Intern Med 1985;145:655–6.
10. Wester PO, Dyckner T. Intracellular electrolytes in cardiac failure. Acta Med Scand 1986;707(suppl):33–6.
11. Kafka H, Langevin L, Armstrong PW. Serum magnesium and potassium in acute myocardial infarction. Arch Intern Med 1987;147:465–9.
12. Packer M. Sudden unexpected death in patients with congestive heart failure: a second frontier. Circulation 1985;72:681–5.
13. Kaplan EL, Meier PL. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
14. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163–70.
15. Breslow NE. Covariance analysis of censored survival data. Biometrics 1979;30:89–99.
16. Polimeni PI, Page E. Magnesium in heart muscle. Circ Res 1973;33:367–74.
17. Dagirmanjian R, Goldman H. Magnesium deficiency and distribution of blood in the rat. Am J Physiol 1970;218:1464–7.
18. Ghani MF, Rabah M. Effect of magnesium chloride on electrical stability of the heart. Am Heart J 1977;94:600–2.
19. Flink EB. Hypomagnesemia in patients receiving digitalis. Arch Intern Med 1985;145:625–6.
20. Bailie DS, Inoue H, Kaseda S, Ben-David J, Zipes DP. Magnesium suppression of early afterdepolarizations and ventricular tachyarrhythmias induced by cesium in dogs. Circulation 1988;77:1395–1402.
21. Iseri LT, Freed J, Bures AR. Magnesium deficiency and cardiac disorders. Am J Med 1975;58:837–46.
22. Ramee SR, White CJ, Svinarich JT, Watson TD, Fox RF. Torsade de pointes and magnesium deficiency. Am Heart J 1985;109:164–7.
23. White RE, Hartzell HC. Magnesium ions in cardiac function: regulator of ion channels and second messengers. Biochem Pharmacol 1989;38:859–67.
24. Cody RJ, Ljungman S, Covit AB, et al. Regulation of glomerular filtration rate in chronic congestive heart failure patients. Kidney Int 1988;34: 361–7.
25. Kukin ML, Packer M, Gottlieb SS, et al. Age is an independent prognostic factor in determining long-term outcome in patients with congestive heart failure (abstr). J Am Coll Cardiol 1988;11(suppl A):160A.
26. Packer M, Lee WH, Kessler PD, Gottlieb SS, Bernstein JL, Kukin ML. Role of neurohormonal mechanisms in determining survival in patients with severe chronic heart failure. Circulation 1987;75(suppl IV):IV-80–92.
27. Massie BM, Conway M. Survival of patients with congestive heart failure: past, present, and future prospects. Circulation 1987;75(suppl IV):IV-11–9.
28. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819–23.
29. Wilson JR, Schwartz JS, St. John Sutton M, et al. Prognosis in severe heart failure: relation to hemodynamic measurements and ventricular ectopic activity. J Am Coll Cardiol 1983;2:403–10.
30. Reinhart RA. Magnesium metabolism: a review with special reference to the relationship between intracellular content and serum levels. Arch Intern Med 1988;148:2415–20.
31. Ralston MA, Murnane MR, Kelley RE, Altschuld RA, Unverferth DV, Leier CV. Magnesium content of serum, circulating mononuclear cells, skeletal muscle, and myocardium in congestive heart failure. Circulation 1989;80:573–80.
32. DiCarlo LA Jr, Morady F, de Buitleir M, Krol RB, Schurig L, Annesley TM. Effects of magnesium sulfate on cardiac conduction and refractoriness in humans. J Am Coll Cardiol 1986;7:1356–62.