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Interactions of Magnesium and Potassium in the Pathogenesis of Cardiovascular Disease

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Abstract. The interactions of Mg and K in cardiovascular disease are diverse and complex. However, Mg deficiency and loss from the heart and arteries, caused e.g. by dietary deficiency or imbalance, or by diseases and their treatment, can contribute to cardiovascular damage, and to functional abnormalities. Although Mg deficiency interferes with K retention, it is seldom measured in routine clinical practice, and the need to correct low Mg levels, in order to replete K, is rarely considered.

The heart, with its high metabolic activity, is particularly vulnerable to Mg deficiency or loss because of the importance of Mg in mitochondrial structure and enzymatic function. The need for Mg to activate Na/K ATPase has long been known. Mg has also been shown to be structurally part of the enzyme in cardiac mitochondria. Additionally, Na/K exchange occurs in association with phosphorylation and dephosphorylation, reactions that are also Mg-dependent. The demonstration that Mg modulates K^+/proton (H^+) exchange, and that cation selectivity in Na^+ and K^+ exchange for H^+ is highly dependent on the concentration of Mg^{++}, provides new insights into how Mg protects against K loss.

The loss of myocardial K that results from Mg deficiency contributes to electrophysiologic changes, as can the Ca shifts of Mg loss. A high Ca/Mg ratio also predisposes to arterial spasms, and increases catecholamine release. Thus the arrhythmogenic potential of Mg deficiency can be related to imbalances between Mg and K or between Mg and Ca, or both. Electrical or K-induced catecholamine release is increased by a low Mg/Ca ratio, as are increased fatty acids and lipids and intravascular hypercoagulability. K or Ca loading of the patient with undiagnosed Mg inadequacy is not only often unsuccessful, but it may carry inherent risks. It can intensify the Mg depletion, the arterial contractility, and ECG abnormality. In the patient receiving digitalis, Mg deficiency can increase drug toxicity. In the case of myocardial infarction, Mg deficiency can increase the risk of malignant ventricular arrhythmias and sudden cardiac death.

In the absence of alcoholism or gastrointestinal disease, the use of loop diuretic therapy for congestive heart failure, especially in elderly patients, is the most common cause of Mg depletion. A high concurrence of hypomagnesemia with hypokalemia, from whatever cause, has been documented. However, systemic Mg deficiency can exist despite normal Mg serum levels. Methodological difficulties hamper direct detection of cellular Mg deficiency, but patients can be indirectly evaluated by use of Mg-loading tests, which may be of combined diagnostic and therapeutic value. The percentage retention of the load, coupled with clinical response – (1) correction of neuromuscular symptoms of fatigue, somnolence, cramps and pain, and (2) amelioration of hypertension, hypokalemia and arrhythmias – serves to confirm the clinical significance and severity of the Mg deficiency.

Ongoing studies with Mg loading of patients deemed at risk for Mg deficiency, despite normal serum Mg, are revealing retention of sufficient Mg to suggest a high frequency of Mg deficiency in patients with prior or concurrent hypokalemia. Some gave evidence of dietary Mg inadequacy, some had disease- or therapy-induced Mg loss. Dramatic has been the Mg responsiveness of hitherto refractory ventricular ectopy of patients with normomagnesemia.

Introduction

Mg and K have many complex independent and interdependent actions in the pathogenesis of disease [73–75, 77, 78] which can complicate its management. Mg has a central role in membrane structure and in the enzymatic regulation of intracellular concentration of both K and Ca [1, 94]. Low levels of Mg, whether caused by dietary deficiency or imbalance, stress or diseases and their treatment, play important roles in cardiovascular damage and in the ability of the body to maintain K homeostasis [73, 77, 78, 96–99]. Mg deficiency has been implicated in atherosclerosis, increased arterial tone and hypertension, and direct myocardial damage [65], conditions all of which often necessitate the prescription of diuretics with their attendant risk of further Mg and K losses. Furthermore, Mg depletion in this not uncommon clinical setting can result in lowered cellular content of K and the failure to repair the K deficit in spite of even copious K supplementation. Combined K and Mg deficiency can then facilitate the development of digoxin toxicity in patients with congestive heart failure or exert an independent cumulative arrhythmic effect which is most critical in the case of myocardial infarction (MI), increasing the risk of sudden death [65]. In addition to the review of background data, evidence is presented in this paper of the improved management of patients with arrhythmias and hypokalemia following the addition of Mg to their therapeutic regimens.

Mg Dependence of K Retention

Both cellular and extracellular Mg is important in K homeostasis. Intracellular Mg deficiency has a crucial role in the preservation of intracellular K in view of its effect on cellular energy metabolism, membrane permeability and numerous enzymatic reactions [1, 94]. The Mg atom is necessary for energy transfer and for K retention. The ion pump concept first explained the importance of Mg

for Na/K adenosine triphosphatase (ATPase) in the active transport of Na^+ and K^+ [23]. Catalysis of the Na^+/K^+ exchange was then shown to occur in association with cyclic phosphorylation and dephosphorylation [17], Mg-dependent reactions as well [1, 94]. Cation selectivity in Na^+ and K^+ exchange for H^+ (protons) has been found to be highly dependent on the concentration of Mg^{++} [19]. Depletion of mitochondrial Mg activates K^+ efflux [18, 84]. The observation that Mg modulates K^+/H^+ exchange provides new insight into how Mg protects against K loss [37]. Respiring mitochondria accumulate H^+ in exchange for K^+ which move out during physiological mitochondrial swelling. Mg acts as a 'carrier-brake', binding reversibly to a K^+/H^+ exchanger or carrier and decreasing the K^+ efflux [37]. Removal of Mg stimulates K^+/H^+ exchange and increases K^+ efflux; addition of Mg restores K^+ retention. It is not surprising, thus, that Mg deficiency causes loss of volume control with loss of K and retention of Na and water, such as has been seen in acutely Mg-deprived rats [10]. It is conceivable that this disruption of ionic and volume control is contributory to clinical diuretic-refractory hypokalemia and edema, which can be associated with Mg deficiency. Extracellular Mg depletion enhances the efflux from the cells also on a physical, nonenergy-dependent basis [85, 100].

K depletion may prove impossible to correct without Mg replacement. Clinical studies have shown that in doubly deficient patients, not only is skeletal muscle K not repleted without Mg administration [26, 67, 70, 96, 100], but ventricular ectopy is not corrected either [26, 32, 38]. Thus, compounding clinical K deficiency is the Mg loss caused by diuretics, the kaliuresis of which is always treated, and the secondary aldosteronism of congestive heart failure, cirrhosis and nephrosis which also causes Mg loss [45, 59]. It is important to keep in mind that K depletion and repletion are critically dependent on the restoration of Mg.

Mg and K Deficiency in Cardiovascular Disease

Dietary Deficiency

Deficiencies of Mg and K, whether from inadequate dietary intake, failure of absorption or inadequate renal conservation, might play a pathogenic role in a number of disease states in which the use of diuretic therapy worsens both deficiencies [73]. For example, either or both deficiencies in the diet increase the vulnerability of experimental animals to cardiomyopathic agents [53, 73, 75, 78]. As shown in laboratory and farm animals, direct myocardial damage from Mg deficiency is manifested first by mitochondrial swelling, distortion of the cristae and vacuolization, and then by mononuclear infiltrates, edema, focal necrosis, calcification and fibrosis [42, 53, 56, 60]. Mg deficiency increases the propensity to atherosclerosis of animals fed high fat diets [43, 63, 73, 93]. Epidemiologic data suggest a heightened risk of cardiovascular disease and sudden death in areas where the soil is deficient in Mg [52] and the local water supply is soft [3, 13, 15, 52, 58]. Intravascular thrombosis can also be enhanced through diminution of the modulation by Mg of the Ca-mediated steps in coagulation and through the decrease of the stabilizing effects of Mg on platelet membranes and increased platelet aggregation [24]. Peripheral vascular resistance can also be increased in Mg deficiency as a result of the increased arterial tone and spasm which have been demon-

strated in vitro to be associated with a low Mg/Ca ratio and which are inhibited by increasing Mg concentrations [2, 92].

Stress, Stress Hormones, Magnesium and Potassium

It appears plausible that, in an essentially normal subject, nutritional imbalances that increase magnesium requirements can create problems under a variety of conditions of stress, whether metabolic, psychological or physical [74]. The deleterious effects of stress-induced catecholamine and corticosteroid secretion on the mobilization of tissue Mg are frequently compounded by the administration of diuretics that waste K and Mg, but retain Ca, and which secondarily induce mineralocorticoid secretion that intensifies K and Mg losses [45, 59]. High-dose K supplementation in patients deficient also in Mg may cause further outpouring of catecholamines, as indicated by in vitro evidence that high K and low Mg concentrations in suspending fluids increase catecholamine release from adrenergic granules [4, 5, 9, 20].

On the other hand, β_2-catecholamines have been shown to cause hypokalemia [7] which is reversed by β-blockers [11]. β-Catecholamines have also been shown to interfere with Mg entry across cell membranes, possibly through an intermediate channel [29].

Myocardial Magnesium Loss Secondary to Stress

In experimental catecholamine-induced myocardial necrosis, the first change observed is lowering of myocardial Mg which precedes the drop in K and the rise in Ca, and the microfocal necrosis produced by minimally toxic doses [53, 65]. Perhaps the β-catecholamines cause Mg loss by interfering with its uptake through the 'intermediate channel', as has been shown in vitro in lymphoma cells [29]. This, in combination with catecholamine enhancement of Ca entry through the slow channel, can intensify the cardiac lesions caused by Mg deficiency.

Since catecholamines are released in response to stress, since the heart synthesizes, stores and releases norepinephrine [8, 64], and since low Mg^{++}/Ca^{++} ratios increase catecholamine release by adrenergic granules [4, 5, 9, 20], suboptimal Mg levels might well contribute to stress-related cardiac disorders. In Mg-deficient animals, stress of isolation, cold or noise increases Mg loss from the heart and increases the extent of myocardial necrosis, collagen deposition, and calcification [41, 44, 49].

Stress, either physical or psychological, may further aggravate Mg deficiency, perhaps in part due to the effects of catecholamines on lipolysis [66]. Substantial surges of catecholamines have been reported in patients with MI [51, 62]. Catecholamine-mediated lipolysis might be augmented by stress-induced glucocorticoid secretion with resultant elevation in free fatty acid levels and removal of Mg from the available pool, as has been shown in experimental acute alcohol withdrawal [35] and in MI [34]. This has been suggested to contribute to cardiac arrhythmia of MI [32, 34, 38]. The mechanism might be intramyocardial binding and thus inactivation of Mg by free fatty acids, and associated interference with energy metabolism and membrane function.

Electrophysiologic Alterations in Magnesium Deficiency

Interrelations with Potassium and Calcium. The loss of K which results from myocardial Mg loss contributes to the electrophysiological changes of Mg deficiency [72,

73]. Severe acute Mg loss unaccompanied by generalized K depletion (in young dogs) has caused shortening of the atrioventricular conduction time (P-Q interval) and of the intraventricular time (QRS), with some prolongation of the electrical systole (Q-T interval) and T-wave abnormalities [90, 95]. Subacute Mg deficiency, sufficient to cause predominantly intracellular K deficiency, has resulted in ECG changes (peaking of T-waves) comparable to those of hyperkalemia [80]. Following long-term deficiency and/or with serum Mg values less than 0.8 mEq/l, and more profound K deficiency, ST-segment depression, occasionally T-wave inversion, ventricular beats, bigeminy and prolongation of the QRS complex are seen. Ca shifts, varying with the degree of Mg deficiency, also influence the ECG [72, 73]. When hypomagnesemia causes parathyroid hyperplasia and/or excess secretion, the ECG reflects the hypercalcemia. When chronic hypomagnesemia causes target organ refractoriness to parathyroid hormone, or impairs its release, the ECG reflects the hypocalcemia.

The clinical expression of combined Mg-K deficiency includes cardiac arrhythmia. Hypokalemia per se renders the resting membrane more electronegative and the associated decrease in K conductance increases the duration of repolarization, thereby enhancing the development of re-entry rhythms [31, 35]. Differential effects on the conducting tissue may result in increased spontaneous diastolic depolarization (phase 4), manifesting as increased automaticity and emergence of ectopic foci. K depletion is known to increase the incidence of arrhythmias, particularly ventricular arrhythmias, predominantly in patients with acute MI [22, 25, 27, 47, 86]. The incidence of ventricular tachycardia rises steeply with the severity of the hypokalemia [86].

Intensification of Magnesium Deficiency by Excess Potassium. K repletion in patients with myocardial infarction can be life-saving, in that the therapeutic response to conventional antiarrhythmics is weakened in the presence of hypokalemia [16, 26]. However, failure to consider the possibility of Mg deficiency in the patient with hypokalemia and to administer copious K supplements may not only be ineffective, but might intensify the underlying Mg deficiency. First observed in grazing animals on K-rich, Mg-poor forage [46, 89], K loading was shown to worsen manifestations of experimentally induced Mg in rats [14, 21]. The clinical relevance of the finding that high K^+/Mg^{++} and Ca^{++}/Mg^{++} ratios in media suspending adrenergic granules from nerve endings and adrenal medulla increase catecholamine secretion has yet to be demonstrated. An occasional case report described the development of clear signs of Mg deficiency when hypokalemia was treated with high-dosage K [33, 36], which indicates the potential clinical risk of K repletion without simultaneous repair of the concurrent Mg deficiency.

Association with Diuretics, Digitalis and Alcohol. More than 40% of the patients with acute MI had been users of diuretics [86]. Since concurrent Mg deficiency has been reported in more than 40% of patients having been treated with diuretics [99], and since low intracellular Mg is common in patients with diuretic-induced hypokalemia [82], the possibility of its depletion should be considered when K treatment of hypokalemia is to be instituted, and especially when K therapy fails to suppress ventricular ectopy [26]. Digoxin, like Mg deficiency, causes inhibition of Na-K ATPase, and, with myocardial digoxin uptake being enhanced by Mg [39], the intensification of K loss by the drug, with

resultant increase of its toxicity, is obvious. In addition, K depletion gives rise to a 50% reduction in tubular secretion of digoxin [88], thus adding further to the likelihood of development of adverse reactions. The frequency of digoxin toxicity despite nontoxic serum levels [87], even with serum Mg and K concentrations within normal limits, suggests that intracellular deficiencies of one or both cations, coupled with Ca excess, might become a critical factor: reduction in body K of 5–10% results in a 60% reduction of the digoxin dosage required to induce toxicity [57]; Mg deficiency also reduces the toxic dose of digoxin [79]. In clinical practice, it is noteworthy that hypomagnesemia has been reported to occur more frequently than hypokalemia in association with digoxin toxicity [69]. Without the physiological antagonism between Mg and Ca, the surges in intracellular Ca are of special consequence in the genesis of the Ca-dependent highly arrhythmogenic oscillatory after-potentials. These oscillatory after-potentials are of special importance in digoxin-related arrhythmias [31, 91]. Among the independent antiarrhythmic effects of Mg described in this context are the decreased periodicity of the sinoatrial node, slowing of atrioventricular conduction, and retardation of intra-atrial and intraventricular conduction with extension of the absolute refractory period. The frequent prescription of digoxin in conjunction with diuretics clearly paves the way for digoxin-related arrhythmias because of the increased vulnerability to this side effect in patients with K or Mg deficiencies and Ca retention.

Even moderate alcohol ingestion by normal nonalcoholic subjects causes magnesiuresis [50]. The intrinsic arrhythmic potential of its consumption in excess, which has been termed the 'holiday heart syndrome' [30, 40], might well be contributed to by alcohol-induced Mg deficiency.

Myocardial Infarction. Especially in the situation of acute MI, which itself has a propensity to inducing refractory arrhythmias and sudden death, the arrhythmogenicity of Mg deficiency, alone or in combination with K deficiency, is of special importance. Refractory arrhythmias of Mg deficiency, even in noninfarcted patients, have been reported [12, 55, 71], and indeed Mg has been advocated for routine use in refractory ventricular arrhythmias even in the absence of hypomagnesemia [48, 83].

Hypertension. In addition to the potential pathogenic role of Mg in hypertension [2], its deficiency can increase the requirements for antihypertensive medications. Mg supplementation, even in the absence of overt hypomagnesemia and evidence of deficiency, indicated by increased serum Mg after its supplementation, has an improved response to antihypertensive medication [28].

Congestive Heart Failure. Prolonged poor dietary intake or severe gastrointestinal dysfunction in elderly patients with congestive heart failure requiring large doses of loop diuretics is commonly leading to significant hypomagnesemia [81]. In contrast to an early study [54] which indicated that overt hypomagnesemia was uncommon in congestive heart failure patients, a more recent study of an older patient population suggests a much higher frequency of hypomagnesemia [81]. Dietary Mg deficiency is probably a significant contributory factor in the older age group [76]. Most of the patients in the recent study as well as in ongoing investigations were ill enough to require hospitalization and were screened selectively on the basis of neuromuscular symptomatology, hypokalemia and arrhythmias, especially refractory atrial

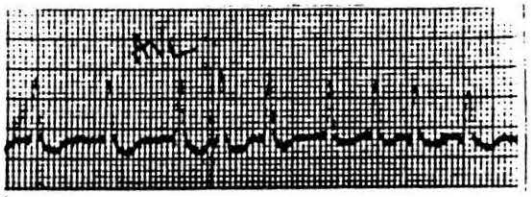

Fig. 1. Uncontrolled atrial fibrillation associated with cardiogenic shock in a 66-year-old woman, 7 days after MI. Serum Mg^{++} 1.6 mg/dl; serum K^{+} 3.2 mEq/l. Nontoxic digoxin levels.

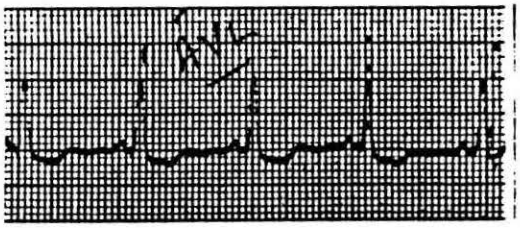

Fig. 2. Reversion to sinus rhythm within 2 h of intramuscular magnesium sulfate, correction of hypotension and hypokalemia with decreasing diuretic requirements.

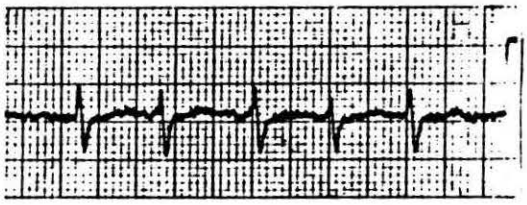

Fig. 3. 70-year-old male with uncontrolled atrial fibrillation with therapeutic levels of digoxin. Serum Mg^{++} 0.5 mg/dl; serum K^{+} 3.1 mEq/l.

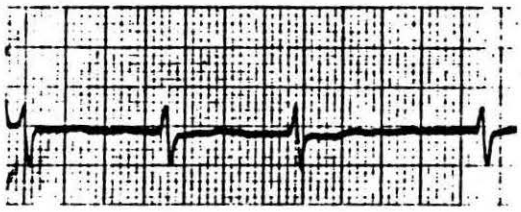

Fig. 4. Control of atrial fibrillation following intramuscular magnesium sulfate.

fibrillation (fig. 1–4). In less selected series of patients, Mg deficiency was documented on the basis of low Mg levels in skeletal muscle [26] or lymphocytes [68]. Mg repletion of deficient patients has not only resulted in the control of refractory arrhythmias and hypokalemia, but has also decreased diuretic requirements and improved the heart failure status. This latter response might be partially due to afterload reduction secondary to reduction of vasoconstriction and to improved myocardial contractility with increased stroke volume or both, as has been observed in the recent and in the current study.

Ongoing Study of Clinically Significant Intracellular Magnesium Deficiency

Patients at risk of Mg deficiency, including those using diuretics, those with poor dietary intake, poorly controlled diabetes mellitus or a history of alcohol abuse, but with serum Mg levels within normal limits, are being tested for Mg deficiency by intravenous loading with magnesium sulfate. In addition to determining the percentage retention of the load [73], the therapeutic response is being monitored in order to find out whether there is an amelioration in presenting symptomatology of muscle weakness and/or cramps, fatigue and somnolence, hy-

Table I. Reduction in ventricular ectopy despite normal serum Mg^{++}

Patient	Age years	Sex	Serum Mg^{++} mg/dl	Retention %	Premature ventricular contractions/24 h		Reduction %
					pre	post	
D.R.	63	F	2.1	53	8,121	53	99
R.C.	61	M	2.0	42	5,128	995	81
M.W.	65	M	2.0	52	14,000	559	96
W.S.	68	M	2.2	95	10,215	42	99

8 g of magnesium sulfate were infused in 500 ml of dextrose over 24 h.

pokalemia and ventricular ectopy. Preliminary results confirm the frequent intracellular Mg depletion in patients with prior or current diuretic-associated hypokalemia [82], and the presence of Mg deficiency on the basis of diet alone [73, 74, 83]. Most important is the dramatic reduction in hitherto poorly controlled ventricular ectopy based on serial Holter monitoring (table I). In addition, several patients have had significant reduction in ventricular ectopy on oscilloscope monitoring and/or serial ECG and rhythm strips (fig. 5, 6). Mg deficiency should thus be considered in patients with diuretic-associated hypokalemia and ventricular ectopy, regardless of the serum value.

Magnesium Deficiency and Advancing Age

Increasing age has been associated with declining myocardial Mg levels in rats [6, 61]. Significantly, the greatest decrease was in septal Mg [6], possibly a factor in the increased risk of dysrhythmia with advancing age, and contributing to the decreased tolerance of stress seen in the aged subject. Mg deficiency thus constitutes a high risk in the elderly, especially in view of other dietary imbalances, some of which increase Mg requirements, and the use of drugs that interfere with the utilization of Mg and cause its loss like the diuretics [76], and a vulnerable ischemic myocardium.

Conclusions

The declining Mg content of the Western diet [74], coupled with the frequent ingestion of alcohol and the use of diuretics expose many cardiovascular patients to the risk of Mg deficiency. Self-induced and iatrogenic factors, such as alcohol abuse and use of Mg-wasting drugs, impair the renal capacity to conserve Mg that might otherwise maintain adequate levels in the face of borderline dietary deficiency. It is unfortunate that Mg, which plays such a pivotal role in the regulation of cellular bioenergetics and in K and Ca homeostasis, and has a life-saving potential in the management of cardiovascular emergencies, receives scant attention from the practicing physician. It is hoped that the ever-expanding fund of knowledge from experimental studies and clinical experience will hasten the day when Mg assumes its belated rightful role in routine clinical practice.

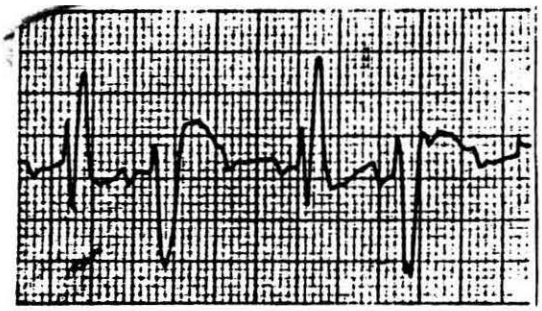

Fig. 5. 71-year-old female with chronic mild congestive heart failure; recent forced saline diuresis for hypercalcemia of myeloma. Atrial fibrillation, bigeminy, on digoxin with nontoxic serum levels. Serum Mg^{++} 2.4 mg/dl; serum K^{+} 3.4 mEq/l.

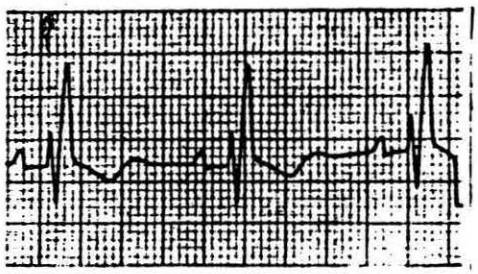

Fig. 6. Reversion to sinus rhythm, cessation of bigeminy and marked reduction in frequency of premature ventricular contractions following Mg^{++} infusion.

Les interactions du magnésium et du potassium dans la pathogenèse des affections cardiovasculaires

Les interactions de Mg et de K dans les affections cardiovasculaires sont diverses et complexes. Le déficit de Mg et sa perte à partir du cœur et des artères (provoqués, par exemple, par un déficit ou un déséquilibre alimentaire, ou par des affections et leurs traitements) peuvent contribuer à une lésion cardiovasculaire, et à des anomalies fonctionelles. Bien que le déficit magnésique interfère avec le rétention du K, il est rarement mesuré en pratique clinique courante, et la nécessité de corriger les taux abaissés du Mg, afin de permettre la réplétion en K, est rarement prise en considération.

Le cœur, avec son activité métabolique élevée, est particulièrement vulnérable au déficit ou à la perte de Mg, par suite de l'importance du Mg dans la structure mitochondriale ou les fonctions enzymatiques. La nécessité de Mg pour activer la Na/K ATPase est connue depuis longtemps. Il a été montré aussi que le Mg entre dans la structure de l'enzyme des mitochondries du cœur. De plus, l'échange Na/K se produit en association avec la phosphorylation et la déphosphorylation, réactions qui sont aussi Mg-dépendantes. Il a été démontré que le Mg module l'échange K^{+}/proton (H^{+}), et que cette sélectivité cationique dans l'échange de Na^{+} et de K^{+} avec H^{+} est hautement dépendante de la concentration de Mg^{++}, ce qui apporte de nouveaux aperçus sur la façon dont le Mg protège contre la perte de K.

La perte de K du myocarde qui résulte du déficit magnésique contribue aux modifications électrophysiologiques, aussi bien que le remplacement par le Ca des pertes de Mg. Un rapport élevé Ca/Mg prédispose aussi à des spasmes artériels, et accroît la libération des catécholamines. Ainsi le potentiel arythmogène du déficit magnésique peut être en relation avec les déséquilibres entre Mg et K ou entre Mg et Ca, ou avec les deux types. La libération de catécholamines induite électriquement ou par K est accrue par un rapport Mg/Ca faible; de même, les acides gras et les lipides et la coagulation intravasculaire sont accrus. La charge par le K ou le Ca de patients avec une insuffisance magnésique non diagnostiquée est non seulement souvent sans résultat, mais elle peut entraîner des risques par elle-même. Elle peut renforcer la déplétion magnésique, la contractilité des artères, et l'anomalie de l'ECG. Chez les patients recevant des digitaliques le déficit magnésique peut accroître la toxicité de ces médicaments. Dans le cas d'un infarctus du myocarde, le déficit magnésique peut accroître le risque d'arythmies ventriculaires et de mort cardiaque subite.

En l'absence d'alcoolisme ou d'affections gastro-intestinales, l'emploi d'une thérapeutique par des diurétiques actifs sur l'anse de Henle, spécialement chez les patients âgés, est la cause la plus fréquente de la déplétion magnésique. Une concomitance fréquente de l'hypomagnésémie avec l'hypokaliémie, quelle qu'en soit la cause, a été mise en évidence. Cependant

un déficit magnésique systémique peut exister malgré des taux sériques normaux de Mg. Des difficultés méthodologiques empêchent la détection directe du déficit magnésique cellulaire, mais son évaluation peut être pratiquée indirectement chez les patients en employant des tests de charge magnésique, qui peuvent présenter un intérêt diagnostique et thérapeutique associé. La rétention en pourcentages de la charge, associée à la réponse clinique 1) correction des symptômes neuromusculaires de fatigue, de somnolence, de crampes et de douleurs; 2) évolution dans un sens favorable de l'hypertension, de l'hypokaliémie et des arythmies, permet de confirmer la signification clinique et la gravité du déficit magnésique.

Des études en cours avec charge magnésique de patients considérés comme présentant un risque de déficit magnésique, malgré un Mg sérique normal, révèlent une rétention de Mg suffisante pour suggérer une fréquence élevée de déficit magnésique chez des patients avec hypokaliémie préalable ou concomitante. Certains des patients ont manifesté un apport alimentaire inadéquat de Mg, d'autres ont présenté une perte de Mg induite par un état pathologique ou par des diurétiques. La faculté de réponse au Mg d'une ectopie ventriculaire, jusque là réfractaire chez des patients avec une normomagnésémie, a été spectaculaire.

Wechselwirkungen von Mg und K in der Pathogenese kardiovaskulärer Krankheiten

Die Wechselwirkungen von Mg und K bei kardiovaskulären Krankheiten sind verschiedenartig und von komplexer Natur. Mg-Mangel und -Verluste im Herzen und in den Arterien, ob sie nun verursacht wurden durch Mangel oder Ungleichgewicht in der Ernährung oder durch Krankheiten und deren Behandlung, können zur Entstehung kardiovaskulärer Schäden und funktioneller Störungen beitragen. Obwohl Mg-Mangel mit der K-Retention interferiert, wird er in der klinischen Routine selten gemessen, und die Notwendigkeit, niedrige Mg-Konzentrationen zu korrigieren, um K wieder aufzufüllen, wird selten in Betracht gezogen. Das Herz mit seiner hohen metabolischen Aktivität ist für Mg-Mangel und -Verluste wegen der Bedeutung des Mg für die Struktur der Mitochondrien und der enzymatischen Funktionen besonders empfindlich. Der Bedarf an Mg zur Aktivierung der Na-K-ATPase ist seit langem bekannt. Es wurde auch gezeigt, dass Mg ein struktureller Bestandteil des Enzyms in den Mitochondrien des Herzens ist. Zusätzlich tritt ein Na-K-Austausch im Zusammenhang mit Phosphorilierungs- und Dephosphorilierungsvorgängen auf, Reaktionen, die ebenfalls von Mg abhängig sind. Der Nachweis, dass Mg den K/Proton-Austausch moduliert und dass diese Kationenselektivität im Austausch von Na und K für Protonen in hohem Masse abhängig von der Mg-Konzentration ist, liefert neue Einsichten, wie Mg vor K-Verlusten schützt. Der Verlust von myokardialem K, der eine Folge des Mg-Mangels ist, trägt zu physiologischen Veränderungen bei, ebenso wie dies durch Ca-Verschiebungen infolge von Mg-Verlusten der Fall sein kann. Ein hoher Ca-Mg-Quotient prädisponiert in gleicher Weise zu arteriellen Spasmen und erhöht die Katecholaminfreisetzung. Infolgedessen kann das arrhythmogene Potential des Mg-Mangels zu Ungleichgewichten zwischen Mg und K oder zwischen Mg und Ca oder beidem in Beziehung gesetzt werden. Elektrische oder K-induzierte Katecholaminfreisetzung wird durch einen niedrigen Mg-Ca-Quotienten verstärkt, ebenso wie dies bei erhöhten Fettsäuren und Lipiden sowie intravaskulärer Hyperkoagulationsfähigkeit der Fall ist. K- oder Ca-Gabe bei Patienten mit nicht festgestelltem Mg-Mangel ist nicht nur oft nicht erfolgreich, dies kann auch zugehörige Risiken in sich bergen. Mg-Depletion kann die arterielle Kontraktilität und die EKG-Abnormalitäten verstärken. Bei Patienten mit Digitalis kann Mg-Mangel die Arzneimitteltoxizität erhöhen. Bei Herzinfarkt kann Mg-Mangel das Risiko maligner ventrikulärer Arrhythmien und des plötzlichen Herztodes erhöhen. Liegen Alkoholismus oder gastrointestinale Krankheiten nicht vor, ist die Anwendung von Schleifendiuretika zur Behandlung der Herzinsuffizienz besonders bei älteren Patienten der häufigste Grund für eine Mg-Verarmung. Häufig wurde ein gleichzeitiges Vorhandensein von Hypomagnesiämie und Hypokaliämie, welcher Ursache auch immer, dokumentiert. Jedoch kann ein systemischer Mg-Mangel trotz normaler Mg-Serum-Konzentrationen existieren. Methodische Schwierigkeiten hindern die direkte Bestimmung des zellulären Mg-Defizits, aber Patienten können indirekt durch Anwendung von Mg-Aufsättigungstests erkannt werden, die sowohl von diagnostischem als auch von therapeutischem Wert sein können. Die prozentuale Retention der verabreichten Menge zusammen mit dem klinischen Ansprechen: 1. Korrektur der neuromuskulären Symptome bei Ermüdung, Somnolenz, Krämpfen und

Schmerzen sowie 2. Verbesserung der Hypertonie, Hypokaliämie und Arrhythmien dienen dazu, die klinische Bedeutung und den Schweregrad des Mg-Mangels zu bestimmen. Angelaufene Studien mit Mg-Aufsättigung bei Patienten, die ein Risiko für einen Mg-Mangel trotz normaler Serum-Mg-Konzentrationen zu haben scheinen, zeigen eine ausreichende Retention von Mg, was auf eine Häufung von Mg-Mangel bei Patienten mit früherer oder begleitender Hypokaliämie hinweist. In einigen Fällen wurde eine unzureichende Zufuhr mit der Nahrung aufgezeigt, andere hatten durch Krankheit oder Therapie induzierte Mg-Verluste. Dramatisch war das Ansprechen auf Mg bei Patienten mit Normomagnesiämie und bisher therapierefraktären ventrikulären Ektopien.

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