Magnesium and Cardiovascular Disease

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IN 1935, Zwillinger reported that administration of magnesium (Mg2+) restored sinus rhythm in patients with digitalis-induced tachyarrhythmias. Since that time, Mg2+ has been used for prophylaxis or therapy in a variety of cardiovascular disorders: myocardial ischemia and infarction, coronary spasm, ventricular and supraventricular arrhythmias, digoxin toxicity, pre-eclampsia–eclampsia, cerebral vasospasm, and stroke. Chronic Mg2+ deficiency and acute hypomagnesemia are associated with increased cardiovascular morbidity and mortality. Therapeutic effects, however, have been reported after pharmacologic administration, even in the absence of known Mg2+ deficiency or hypomagnesemia. Because many of the abnormalities for which Mg2+ therapy has been advocated are common among patients undergoing anesthesia and surgery, the anesthesiologist should be familiar with the rational use of this cation. Accordingly, this article addresses (1) the physiology and pharmacology of Mg2+ relevant to patients with cardiovascular disease; (2) evidence supporting the use of Mg2+ in a variety of disease states; and (3) current applications of Mg2+ therapy.

Magnesium Homeostasis

Mg2+ metabolism and its derangements have been reviewed recently. Mg2+ is the second most abundant cation in the body, the second most abundant intracellular cation after potassium (K+), and a critical cofactor in >300 enzymatic reactions involving energy metabolism and protein and nucleic acid synthesis. Total body stores of Mg2+ average 1,000 mmol for a 70-kg individual, with >50% in bone, nearly 50% in soft tissues, and <1% in blood. In contrast to the tight hormonal control of concentrations of calcium (Ca2+) in blood, the kidney is the primary regulator of Mg2+ balance. Although there is some hormonal influence on the renal handling of Mg2+ (primarily by parathyroid hormone, calcitonin, and antidiuretic hormone), changes in dietary intake of Mg2+ or concentrations of Mg2+ in blood do not evoke hormone secretion. Mg2+ (intra- and extracellular) exists in three states: (1) free, ionized fraction (the physiologically active form); (2) complexed to anions (citrate, phosphate, bicarbonate); and (3) protein bound. In extracellular fluid, free Mg2+ composes 61% of total Mg2+, 6% is complexed, and 33% is protein bound. In this article, the symbol Mg2+ designates total Mg2+ cation unless otherwise modified (e.g., ionized Mg2+ or complexed Mg2+).

Assessment of Magnesium Status

The diagnosis of Mg2+ deficiency (defined as a reduction in total content of Mg2+ in the body) is difficult to establish because (1) it may be asymptomatic; (2) concentration of total Mg2+ in serum may be normal despite depletion in tissue; and (3) measurement of concentrations in tissue is not readily available and may be specific for the tissue sampled. Nonetheless, studies reporting Mg2+ assays on a variety of tissues suggest that many patients with cardiovascular disease exhibit depletion of Mg2+ compared with healthy individuals. For example, Haigney et al. found that concentrations of Mg2+ in buccal mucosal cells were reduced in patients with coronary artery disease compared with healthy volunteers, despite normal concentrations in serum, and concentrations of Mg2+ in buccal cells correlated well with atrial concentrations of Mg2+.
The diagnosis of Mg\(^{2+}\) depletion also has been based on the percent of Mg\(^{2+}\) retained after an intravenous infusion of Mg\(^{2+}\).\(^{37,38}\) The Mg\(^{2+}\) retention test requires a baseline 24-h urine collection, after which Mg\(^{2+}\) (0.2 mEq/kg lean body weight) is infused for 4 h and urine is again collected for 24 h. Mg\(^{2+}\)-replete individuals should excrete at least 60% of the administered load.\(^{27}\) Although the retention test is considered highly sensitive for depletion of Mg\(^{2+}\), it has not been possible to correlate the percent retention with the degree of total body Mg\(^{2+}\) deficiency.\(^{37}\) The test has been used to screen critically ill patients\(^{39}\) and patients with diseases in which deficiency of Mg\(^{2+}\) has been implicated as contributory (e.g., variant angina).\(^{30–32}\) Goto et al.\(^{35}\) found that patients with vasospastic angina had normal concentrations of total Mg\(^{2+}\) in serum, but they excreted only 40 ± 5% of the Mg\(^{2+}\) load, whereas healthy individuals excreted 64 ± 3% (P < 0.001).

In clinical practice, laboratory assessment of Mg\(^{2+}\) status usually begins with measurement of concentration of total Mg\(^{2+}\) in serum. Serum rather than plasma is used because the anticoagulants (e.g., citrate, ethylene-diaminetetraacetic acid) for plasma affect the assay procedure.\(^{32}\) This test, however, has several limitations in the assessment of Mg\(^{2+}\) status, despite its ready availability. First, hypomagnesemia (defined as concentration of Mg\(^{2+}\) in serum less than the normal range; table 1) is often not present in patients with chronic depletion of Mg\(^{2+}\) because of very slow equilibration of Mg\(^{2+}\) among tissue compartments and because the compartment being sampled, namely blood, contains a small fraction of total Mg\(^{2+}\).\(^{17}\) Second, concentration of total Mg\(^{2+}\) in serum may not reflect concentration of ionized Mg\(^{2+}\) in serum.\(^{31,34–36}\) These findings may explain at least part of the beneficial effect of administration of Mg\(^{2+}\) in some patients who appear to be normomagnesemic.

Although the Mg\(^{2+}\)-selective electrode has been commercially available for several years,\(^{37,38}\) it is not widely used because the clinical utility of ionized Mg\(^{2+}\) measurement has not been established. Some authors have recommended measuring ultrafilterable Mg\(^{2+}\) (the combination of complexed and ionized Mg\(^{2+}\)) to approximate ionized Mg\(^{2+}\),\(^{59–61}\) but this method also is not widely used.

**Depletion of Mg\(^{2+}\) and Hypomagnesemia**

**Sequelae.** There is substantial evidence that chronic depletion of Mg\(^{2+}\) and acute hypomagnesemia are associated with increased cardiovascular morbidity and mortality.\(^{11–15,20,55,42–49}\) Animal studies have shown that chronic depletion of Mg\(^{2+}\) exacerbates hypertriglyceridemia, hypercholesterolemia, and decreased high-density lipoprotein concentrations.\(^{43,44}\) Dogs fed a Mg\(^{2+}\)-free diet and subjected to coronary artery occlusion develop myocardial infarcts twice as large as dogs that are fed a normal diet.\(^{45}\) Similarly, chronically Mg\(^{2+}\)-depleted swine have prolonged postschismic myocardial dysfunction (stunning) compared with Mg\(^{2+}\)-replete control animals.\(^{46}\) Human epidemiologic studies indicate that chronic depletion of Mg\(^{2+}\) is associated with ventricular arrhythmias\(^{12}\) and increased atherosclerotic vascular disease and associated cardiovascular mortality.\(^{11,13,14}\) Myocardial depletion of Mg\(^{2+}\) is associated with an increased incidence of arrhythmias after cardiac surgery.\(^{20}\) Finally, recent results suggest that early and progressive ionized hypomagnesemia during pregnancy is associated with the development of preclampsia at term.\(^{47}\)

Acute hypomagnesemia in isolated hearts subjected to ischemia worsens postschismic function and arrhythmias.\(^{48}\) In contrast, Madias et al.\(^{39}\) found that, in patients with acute myocardial infarction (AMI), low concentrations of Mg\(^{2+}\) in serum on admission were not associated with arrhythmias or increased hospital mortality. However, ionized and tissue concentrations of Mg\(^{2+}\) were not measured, and patients who were hypomagnesemic in the emergency department were more likely to be treated with MgSO\(_4\) (P < 0.001).\(^{49}\) Landmark and Urdal\(^{15}\) reported that large decreases in concentrations of total Mg\(^{2+}\) in serum during AMI were associated with higher peak concentrations of creatine kinase. Finally, hyperventilation-induced acute ionized hypomagnesemia is associated with variant anginal episodes despite normal concentrations of total Mg\(^{2+}\).\(^{35}\)

**Mechanisms.** Although many patients with chronic heart disease are Mg\(^{2+}\)-depleted,\(^{21}\) a variety of superimposed stressors cause additional decreases in concentra-
Concentrations of Mg\(^{2+}\) in serum by redistribution (table 2). Patients presenting with AMI, for example, have a precipitous decrease in concentrations of Mg\(^{2+}\) in serum, with the lowest concentrations seen 12-20 h after hospital admission.\(^{50}\) The postulated mechanism involves catecholamine-induced lipolysis and generation of free fatty acids, which then chelate free Mg\(^{2+}\) to form insoluble salts that are sequestered intracellularly.\(^{51,52}\) Catecholamines increase uptake of Mg\(^{2+}\) by adipose cells.\(^{53,54}\) Other high-stress states, such as major burns, sepsis, trauma, alcohol withdrawal, hypothermia, or cardiac surgery, also may be accompanied by catecholamine-induced hypomagnesemia.\(^{50,53,56}\)

Concentrations of total Mg\(^{2+}\) in serum decrease significantly during cardiopulmonary bypass (CPB), and these concentrations persist into the post-CPB period, during which they are associated with increased morbidity.\(^{57,58}\) Recent reports indicate that concentrations of ionized Mg\(^{2+}\) also decrease during and after CPB.\(^{34,59}\) Several factors have been implicated in CPB-related hypomagnesemia. First, measurable preoperative hypomagnesemia is common in patients undergoing cardiac surgery.\(^{39,58,60,61}\) Second, there may be additional decreases in concentrations of Mg\(^{2+}\) in serum after induction of anesthesia but before CPB, probably as a result of hemodilution with Mg\(^{2+}\)-free fluids.\(^{39,58}\) Increasing concentrations of catecholamines also may have contributed to the decrease. Third, during CPB, further decreases in concentrations of Mg\(^{2+}\) in serum are caused by additional hemodilution, binding to albumin in the pump prime, and redistribution secondary to catecholamine-induced increases in concentrations of free fatty acid.\(^{39,62}\) Although urinary excretion of Mg\(^{2+}\) may increase slightly during CPB, it is probably not a major factor in CPB-related Mg\(^{2+}\) flux unless exogenous Mg\(^{2+}\) is administered.\(^{63,64}\)

Intraoperative administration of Mg\(^{2+}\)-containing cardioplegia solutions\(^{65}\) (or the equivalent intravenous bolus dose of Mg\(^{2+}\)) prevents the decrease in concentrations of total Mg\(^{2+}\) seen during and after CPB, but concentrations of ionized Mg\(^{2+}\) may still be decreased.\(^{54}\)

### Mg\(^{2+}\) and the Cardiovascular System

**Intracellular Mg\(^{2+}\).** Although the important pharmacologic actions of Mg\(^{2+}\) are primarily extracellular, free cytosolic Mg\(^{2+}\) (Mg\(_{cyt}\)) modulates the intracellular milieu through its influence on ion channels and transport mechanisms.\(^{65,70}\) Although this area has been reviewed,\(^{71-74}\) two general points are important. First, Mg\(^{2+}\) modulates Ca\(^{2+}\) flux in pathophysiologic and physiologic states.\(^{71-73}\) Increasing concentrations of Mg\(^{2+}\) during early ischemia or hypoxia\(^{67,75}\) have beneficial effects on L-type Ca\(^{2+}\) channels during stress\(^{69,71,74}\); i.e., Ca\(^{2+}\) influx is inhibited.\(^{68}\) Second, depletion of Mg\(^{2+}\), as occurs after prolonged ischemia and reperfusion,\(^{76}\) contributes to progressive Ca\(^{2+}\) overload and subsequent cell damage (discussed subsequently).\(^{75}\) In addition, loss of Mg\(^{2+}\) may promote cytosolic Ca\(^{2+}\) overload from intracellular sources: Elevated concentrations of Mg\(^{2+}\) inhibit efflux of Ca\(^{2+}\) from sarcoplasmic reticulum.\(^{77,78}\)

**Extracellular Mg\(^{2+}\).** For nearly two decades, extracellular Mg\(^{2+}\) (and several other divalent cations) has been considered to be a Ca\(^{2+}\) antagonist because it inhibits Ca\(^{2+}\) current in excitable cells. This has several clinical implications because (1) virtually all excitable cells have voltage-gated Ca\(^{2+}\) channels\(^{79}\); (2) in general, these channels transduce electrical signals (that is, membrane depolarization) into various cellular actions (e.g., muscle contraction, neurotransmitter release) via modulation of Ca\(^{2+}\) flux\(^{80}\); (3) Ca\(^{2+}\) current supports excitation in the sinoatrial and atrioventricular nodes

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Table 2. Common Causes of Hypomagnesemia

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Diminished intake</td>
</tr>
<tr>
<td>Alcoholism</td>
</tr>
<tr>
<td>Liquid-protein diet</td>
</tr>
<tr>
<td>Gastrointestinal losses</td>
</tr>
<tr>
<td>Laxatives</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
</tr>
<tr>
<td>Renal losses</td>
</tr>
<tr>
<td>Diuretic phase of acute tubular necrosis</td>
</tr>
<tr>
<td>Post renal transplant</td>
</tr>
<tr>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Amphotericin</td>
</tr>
<tr>
<td>Digitalis</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hyperaldosteronism</td>
</tr>
<tr>
<td>Redistribution</td>
</tr>
<tr>
<td>High catecholamine levels</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Major trauma, burns</td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td>Massive blood transfusion</td>
</tr>
</tbody>
</table>

Modified from Arsenian.\(^{2}\)
and conduction through the atrioventricular node\textsuperscript{81}, and (4) voltage-sensitive Ca\textsuperscript{2+} channels also play important roles in arrhythmogenesis.\textsuperscript{82}

Two mechanisms are believed to be involved in inhibition of Ca\textsuperscript{2+} current by extracellular Mg\textsuperscript{2+}: (1) effects mediated by cationic screening of fixed negative external surface charges\textsuperscript{83}-\textsuperscript{85}; and (2) competition with permeant ions (Ca\textsuperscript{2+}) for a site within the channel itself.\textsuperscript{86} Elevated extracellular divalent cation concentrations stabilize excitable membranes and raise the excitation threshold in voltage-dependent channels.\textsuperscript{87,88} The net result for a given voltage-sensitive channel is a shift of the current–voltage relationship so that current is diminished in response to a standard stimulus.\textsuperscript{87,89} Divalent cations such as Mg\textsuperscript{2+} effectively neutralize fixed negative charges on the outside of the cell membrane either by binding or, more likely, by electrostatic screening.\textsuperscript{85,90} The result is a change in the effective local transmembrane potential sensed by the voltage-sensitive Ca\textsuperscript{2+} channel.\textsuperscript{91} This offset in the transmembrane potential across the channel, sensed by the voltage sensor, alters any voltage-dependent processes such as gating (\textit{i.e.}, channel activation and inactivation).\textsuperscript{85} In addition to alterations of transmembrane potential in the vicinity of the channel, it is also possible that divalent cation screening of fixed negative charges on the channel entrance itself effectively decreases the local permeant cation (Ca\textsuperscript{2+}) concentration, thereby reducing current flow.\textsuperscript{85,92} Mg\textsuperscript{2+} affects both L-type and T-type Ca\textsuperscript{2+} channels.\textsuperscript{93,94}

Although early studies showed that, during some experimental conditions (\textit{i.e.}, use of Ba\textsuperscript{2+} as charge carrier in the presence of Bay KB644, a Ca\textsuperscript{2+} channel opener\textsuperscript{95}), Mg\textsuperscript{2+} has relatively weak direct channel blocking activity,\textsuperscript{86} evidence to date indicates that elevated extracellular concentrations of Mg\textsuperscript{2+} effectively decrease Ca\textsuperscript{2+} current by altering the membrane surface potential in the vicinity of the Ca\textsuperscript{2+} channel, rather than by lodging in the channel pore itself.\textsuperscript{95}

\section*{Magnesium and the Myocardium}

\textbf{Mg\textsuperscript{2+} and Ischemic–Reperfusion Injury.} Studies in the 1970s showed that myocardial ischemia followed by reperfusion results in cytoplasmic Ca\textsuperscript{2+} overload.\textsuperscript{76,96-99} There is now general agreement that during and after periods of ischemia, transmembrane Ca\textsuperscript{2+} influx occurs by several routes.\textsuperscript{97,100-112} and that cytoprotective agents, including Mg\textsuperscript{2+}, attenuate the increase in intracellular Ca\textsuperscript{2+} via multiple mechanisms.\textsuperscript{102,103,113-122}

\textbf{Antischemic Effects.} In animals, administration of Mg\textsuperscript{2+} before permanent coronary artery occlusion is highly effective in limiting the size of myocardial infarcts.\textsuperscript{123} Clinical management of AMI, however, involves reperfusion therapy as early as possible after the onset of ischemia. Recent attention has shifted toward identifying agents that may be administered before or concurrently with reperfusion therapy, with particular emphasis on drugs that reduce myocardial injury caused by reperfusion.\textsuperscript{124} There is experimental evidence that Mg\textsuperscript{2+} is cardioprotective.\textsuperscript{125-127} Recent models designed to simulate the clinical setting in which Mg\textsuperscript{2+} is administered during the interval beginning shortly after coronary occlusion and extending through initial reperfusion have shown significant reductions in the size of myocardial infarcts\textsuperscript{125,126} and in the severity of regional myocardial stunning.\textsuperscript{127} Numerous cardioprotective effects have been attributed to Mg\textsuperscript{2+} (table 3).\textsuperscript{119,127-144}

\textbf{Mg\textsuperscript{2+} Cardioplegia.} Effects of cardioplegia on reperfusion injury have been reviewed recently.\textsuperscript{145-149} A brief period of ischemia causes reversible cell injury, defined by the finding that reperfusion prevents infarction and allows eventual recovery of normal cellular structure, function, and metabolism.\textsuperscript{146} Complete recovery, however, is not immediate; profound metabolic and functional abnormalities may persist for hours or days after as few as 5–15 min of coronary occlusion.\textsuperscript{147} These abnormalities are manifestations of reperfusion injury and include (1) postischemic contractile dysfunction (stunning); (2) reperfusion arrhythmias (see arrhythmogenic effects); and (3) damaged microvasculature preventing continued reperfusion (no reflow).\textsuperscript{148}

Stunning occurs in many clinical settings, particularly interventional (and spontaneous) thrombolysis in acute coronary syndromes\textsuperscript{149} and in the post-CBP period.\textsuperscript{149} Studies using isolated perfused hearts subjected to periods of global ischemia and reperfusion have shown that Mg\textsuperscript{2+} cardioplegia significantly reduces myocardial stunning and cytosolic Ca\textsuperscript{2+} overload\textsuperscript{115,116,150-155} when given concurrently with or before reperfusion.\textsuperscript{126}

Ischemic–reperfusion injury of the microvasculature results in progressive diminution of perfusion to previously ischemic tissues despite restoration of flow in the conduit arteries supplying these tissues, \textit{i.e.}, the no-reflow phenomenon.\textsuperscript{148} The no-reflow phenomenon is a significant clinical problem. It occurs in 2% of coronary interventions (\textit{e.g.}, balloon angioplasty, directional ather-
Table 3. Cardioprotective Effects of Mg²⁺

<table>
<thead>
<tr>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct cellular protective effects, i.e., reduced Ca²⁺ influx during ischemia</td>
<td></td>
</tr>
<tr>
<td>Prevention and relief of coronary spasm</td>
<td>128-131</td>
</tr>
<tr>
<td>Reduction of MVCA (and increased myocardial oxygen supply) by slowing the heart rate during AMI</td>
<td>132-133</td>
</tr>
<tr>
<td>Further reduction of MVCA secondary to direct depression of contractility, reduced systemic afterload, and attenuation of catecholamine-induced elevated oxygen demand</td>
<td>134,135,136</td>
</tr>
<tr>
<td>Additional systemic anticatecholamine effects, including suppression of noxious stimulation-induced NE release and associated hemodynamic effects, as well as suppression of catecholamine release in pathologic hyperadrenergic states</td>
<td>138,139</td>
</tr>
<tr>
<td>Inhibition of platelet adhesion, aggregation, and thromboxane release</td>
<td>140-144</td>
</tr>
</tbody>
</table>

MVCA = myocardial oxygen consumption; AMI = acute myocardial infarction.

cotomy, stent placement) and in 23-27% of patients receiving thrombolytic therapy during AMI. No reflow is associated with a higher incidence of early and prolonged congestive heart failure (CHF) compared with the absence of no reflow. The primary insult in no reflow is probably reperfusion-induced (and oxygen free radical-mediated) injury to endothelium. Circumstantial evidence suggests that Mg²⁺ reduces endothelial injury. First, deficiency of Mg²⁺ potentiates oxygen free radical-induced postischemic injury in working isolated rat hearts. Second, agents that attenuate the initial ischemic injury, namely Ca²⁺ antagonists administered before reperfusion, also reduce the severity of no reflow and preserve endothelial function. Finally, experimental areas of no reflow are decreased, and vascular endothelial and smooth muscle function are preserved after administration of Mg²⁺ cardioplegia (16 mm) cardioplegia.

Antiarrhythmic Effects

Mechanisms. Despite improved understanding, pharmacologic control of cardiac arrhythmias is still largely empiric because there are few criteria to differentiate underlying mechanisms. Moreover, many antiarrhythmic agents (including Mg²⁺) have multiple effects on the key components of arrhythmogenesis (and their interactions), namely substrate, trigger, and modulating factors. The nature and severity of the substrate derangement itself can affect the specificity of antiarrhythmic drug activity. For example, in experimental models of ventricular tachycardia involving different arrhythmogenic mechanisms (e.g., ischemic, digitalis toxic, catecholamine induced), Mg²⁺ possesses class IV (Ca²⁺ channel inhibition) and weak class I (Na⁺ channel inhibition) antiarrhythmic activities. Several specific and related antiarrhythmic mechanisms involving Mg²⁺ have been inferred after nearly seven decades of clinical and experimental observations (table 4).

Electrophysiologic Effects. Administration of MgSO₄ during electrophysiologic evaluation of patients has demonstrated two effects of Mg²⁺ relevant to the treatment of supraventricular tachyarrhythmias: (1) prolongation of atioventricular nodal conduction time (anterograde and retrograde) and refractory period, and (2) suppression of conduction in accessory pathways with and without atioventricular node-like properties, although conflicting results have been reported. Prolongation of atioventricular nodal conduction by Mg²⁺ is most likely attributable to inhibition of Ca²⁺ current, the primary mode of impulse conduction through the atioventricular node, but also may result from Mg²⁺-induced attenuation of sympathetic activity at the atioventricular node.

Other antiarrhythmic effects of Mg²⁺ have been reported, although the underlying mechanisms have not been defined: (1) restoration of sinus rhythm in critically ill medical and surgical patients with supraventricular tachycardias; (2) suppression of intractable ventricular tachyarrhythmias; (3) control of ventricular rate in new-onset atrial fibrillation (AF); prophylaxis of AF after coronary artery bypass grafting; (5) slowing of digoxin-facilitated ventricular rate during AF in Wolff-Parkinson-White syndrome; (6) abolition of preexcitation (Δ wave) in patients with Wolff-Parkinson-White syndrome during normal sinus rhythm; (7) suppression of multifocal atrial tachycardia; (8) suppression of digoxin-induced ectopic tachyarrhythmias; (9) prevention of bupivacaine-induced arrhythmias, and (10) treatment of amitriptyline-induced ventricular fibrillation.
Table 4. Postulated Antiarrhythmic Mechanisms for Mg²⁺

- Decreases cellular ischemia-reperfusion injury
- Prevents early ischemia-induced prolongation of action potential duration¹⁷⁸
- Suppresses early afterdepolarizations¹⁷¹-¹⁷³ and associated torsade de pointes¹⁷⁴-¹⁷⁷
- Suppresses delayed afterdepolarizations in the setting of digitalis-, catecholamine-, or ischemia-reperfusion-induced Ca²⁺ overload¹⁷⁹,¹⁸²-¹⁸⁵
- Suppresses NE release in the ischemic-reperfused myocardium¹⁷⁶
- Prevents secondary intracellular Ca²⁺ overload caused by ischemia-induced accumulation of arrhythmogenic phospholipid metabolites¹³⁴
- Similar to extracellular Ca²⁺, Mg²⁺ attenuates hyperkalemia-induced myocyte depolarization and prolonged QRS duration¹⁷⁵
- Attenuates digitalis-induced myocyte K⁺ loss¹⁷⁶
- Attenuates reperfusion-induced myocyte Na⁺ overload and K⁺ loss¹³³
- Attenuates ischemia-induced myocyte depolarization¹⁷⁹

Hemodynamic Effects

**Intact Individuals.** Circulatory effects of rapid administration of Mg²⁺ in awake individuals are minimal even in the presence of hypertension or moderately severe ventricular dysfunction. In several studies, Mg²⁺ was administered as a bolus dose with or without continuous infusion, sufficient in some cases to achieve a threefold increase in concentrations of Mg²⁺ in serum (table 5).¹⁴¹,¹⁸⁰,¹⁹⁷-²⁰³ The most common finding was a small decrease in blood pressure accompanied by a decrease in systemic vascular resistance and an increase in cardiac output and stroke volume. These results suggest that negative inotropic effects of moderately elevated concentrations of Mg²⁺ are effectively counterbalanced by Mg²⁺-induced afterload reduction.

The few studies that have involved administration of Mg²⁺ in anesthetized individuals (not during CPB) either have not reported hemodynamic effects,⁶⁰ or have involved infusion of Mg²⁺ for control of pathologic hypodynamic states associated with pheochromocytoma²⁰⁴,²⁰⁵ or severe tetanus.¹³⁸,¹³⁹ Because volatile anesthetic agents depress intracellular Ca²⁺ flux,²³⁶ however, it is likely that the circulatory effects of high concentrations of Mg²⁺ in serum are potentiated by these agents, particularly in patients with ventricular dysfunction. Recent experimental evidence suggests, however, that a 10-fold increase in concentrations of Mg²⁺ in blood during sevoflurane - N₂O or sevoflurane - fentanyl anesthesia results in minimal cardiovascular depression.²⁰⁷,²⁰⁸

**Regional Circulations.** Mg²⁺ vasodilates by inhibiting Ca²⁺ influx at the vascular smooth muscle membrane²⁰⁹-²¹¹ and possibly by interfering with release of Ca²⁺ from intracellular sites.²¹² Mg²⁺ increases renal blood flow in healthy individuals,¹⁴¹,²¹³ increases uterine blood flow in pregnant patients,²¹⁴ and dilates isolated human (pregnant) uterine artery segments.²¹⁵ Experimental and clinical observations indicate that Mg²⁺ dilates coronary arteries, particularly when coronary vasoreactivity is pathologic. Mg²⁺ dilates preconstricted segments of human (fresh cadaver) coronary arteries,¹²⁸ decreases coronary vascular resistance (and increases coronary blood flow) moderately in healthy individuals,²⁰⁰ provides rapid relief of vasospastic angina,¹²⁹,¹³² and prevents inducible episodes of vasospastic angina.¹²⁹-¹³¹,¹⁹⁷ In addition, coronary artery spasm occurs in eclampsia,²¹⁶ and it is likely (albeit unproven) that one of the myriad beneficial effects of Mg²⁺ in this potentially lethal condition is cardioprotection.¹²⁹

The cerebral circulation also responds to changes in concentrations of Mg²⁺. Withdrawal of Mg²⁺ rapidly increases the tension in canine middle and basilar cerebral arteries.²¹⁷ In contrast, sudden increases in Mg²⁺ cause rapid and concentration-dependent relaxation of basal tension in all cerebral arteries tested.²¹⁸ Mg²⁺ relaxes preconstricted (by serotonin, prostaglandins, or Ca²⁺) cerebral arteries.²¹⁸-²²⁰ and arteries subjected to delayed spasm secondary to subarachnoid hemorrhage.²²¹ Mg²⁺ also produces dose-dependent relaxation of cerebral arterioles (17 - 30 µ in diameter).²¹⁸ Cerebral arteriolar dilation, with the accompanying increased cerebral blood flow, is one of the salutary effects of administration of Mg²⁺ in severe eclampsia²²² and may account, at least in part, for the anticonvulsant effect of Mg²⁺ in this setting.⁸ Diffuse and intense cerebral vasospasm associated with preeclampsia-eclampsia has been documented angiographically.²²³-²²⁵ Another potential anticonvulsant effect of Mg²⁺ in preeclampsia, in addition to its vascular (antiischemic) actions, is attenuation of ischemia-induced neuronal Ca²⁺ influx via...
Table 5. Hemodynamic Effects of Magnesium Administration in Awake Subjects

<table>
<thead>
<tr>
<th>Authors (no. of subjects, n)</th>
<th>Cardiovascular Disease?</th>
<th>Dosing Regimen (iv)</th>
<th>Heart Rate</th>
<th>Blood Pressure</th>
<th>Cardiac Output</th>
<th>Systemic Vascular Resistance</th>
<th>Stroke Volume</th>
<th>Average Peak Serum Mg²⁺ Level (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kulick et al.1901 (n = 8)</td>
<td>No</td>
<td>MgSO₄, Load: 0.04 g/kg Infusion: 0.025 g·kg⁻¹·h⁻¹</td>
<td>No change</td>
<td>No change</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
<td>2.24</td>
</tr>
<tr>
<td>Mroczek et al.201 (n = 10)</td>
<td>HTN: 6 subjects</td>
<td>MgSO₄, 4 g over 10 min</td>
<td>Variable</td>
<td>HTN: MAP: 10% increased by 34% (HTN: MAP: 10% decreased by 34%)</td>
<td>Increased by 23% (1793 → 1419)</td>
<td>2.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigonti et al.200 (n = 9)</td>
<td>Mild HTN: 4 subjects</td>
<td>MgSO₄, 4 g over 10 min</td>
<td>Increased (81 → 93 bpm)</td>
<td>MAP: no change</td>
<td>Normals: 1 by 21% (149 → 1419)</td>
<td>NS</td>
<td>2.57</td>
<td></td>
</tr>
<tr>
<td>Priempp et al.199 (n = 11)</td>
<td>24 h post-CABG; stable; normal LV function</td>
<td>MgSO₄, Load: 7 mg/kg Infusion: 10 mg·kg⁻¹·h⁻¹</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>1.2</td>
</tr>
<tr>
<td>Crnelli et al.196 (n = 18)</td>
<td>All subjects had cardiomyopathy, ranging from moderate to severe</td>
<td>MgSO₄, two regimens, at least 3 days apart, 1) 50-50 mg·kg⁻¹·h⁻¹ 2) 2.5 g bolus</td>
<td>Infusion: no change in HR Infusion: no change in HR</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>2.49</td>
</tr>
<tr>
<td>Nadler et al.147 (n = 10)</td>
<td>No</td>
<td>MgSO₄, 200 mg/h × 3 h</td>
<td>No change</td>
<td>↓ systolic BP (119 → 109 mmHg)</td>
<td>↓ diastolic BP (74 → 64 mmHg)</td>
<td>2.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miyagi et al.197 (n = 27)</td>
<td>Variant angina</td>
<td>MgSO₄, 0.07 g/kg over 20 min</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>2.47</td>
</tr>
<tr>
<td>Rasmussen et al.202</td>
<td>No</td>
<td>MgCl₂, 2.5 g over 30 min</td>
<td>No change</td>
<td>Small↑ transient, MAP: 7% transient (30 min)</td>
<td>↑ by 12.5% transient (30 min)</td>
<td>2.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotton et al.200 (n = 5)</td>
<td>Severe pregnancy-induced HTN; all had BP = 160/110</td>
<td>MgO₂, 2 g</td>
<td>No change</td>
<td>Small↑ transient, NS (30 min)</td>
<td>Small↑ transient, NS (30 min)</td>
<td>2.37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HTN = hypertension; LVEF = left ventricular ejection fraction; LV = left ventricular; CABG = coronary artery bypass grafting; NM = not measured; NS = not statistically significant; BP = blood pressure; MAP = mean arterial pressure; STI = systolic time intervals; ↓ = decreased; ↑ = increased.
MAGNESIUM AND CARDIOVASCULAR DISEASE

channels associated with the excitatory N-methyl-D-aspartate subtype of glutamate receptor. 226-228

Endothelial Effects. Normal endothelium modulates the state of contraction of the underlying vascular smooth muscle. 229-232 Endothelial dysfunction is implicated in several disease processes, including atherosclerosis, 233 pathologic coronary vasoreactivity with and without significant coronary stenoses, 234 and preeclampsia 235 Normal endothelium synthesizes the vasodilators prostacyclin and nitric oxide (NO). 236-238 Infusion of Mg\textsuperscript{2+} increases endothelial release of prostacyclin, not only by cultured human endothelial cells 239 but also in healthy nonpregnant volunteers 240 and preeclamptic patients. 241 These results suggest that vascular actions of Mg\textsuperscript{2+} in healthy individuals and preeclamptic patients are mediated, at least in part, by release of prostacyclin. Further, in preeclampsia, Mg\textsuperscript{2+}-induced release of prostacyclin antagonizes pathologic platelet adhesion, aggregation, and resulting microvascular occlusion secondary to endothelial dysfunction in this disorder. 242-245

Similar to the reciprocal or mutual antagonistic relationship between Ca\textsuperscript{2+} and Mg\textsuperscript{2+} at the level of the vascular smooth muscle cell membrane, 212,213,218 there appears to be a reciprocal interaction at the level of the vascular endothelial cell membrane (see subsequent section). Extracellular Ca\textsuperscript{2+} is essential for endothelium-dependent vascular smooth muscle relaxation 241; an increase in endothelial cell intracellular Ca\textsuperscript{2+} accompanies basal production or release of NO and the release of NO in response to a wide variety of endothelium-dependent dilators. 242 Entry of Ca\textsuperscript{2+} in endothelial cells, however, is not voltage-gated; i.e., these cells are nonexcitable. 243 Rather, Ca\textsuperscript{2+} entry is capacitative: It is activated by depletion of intracellular Ca\textsuperscript{2+} stores. 244 Although the effect of Mg\textsuperscript{2+} on capacitative entry of Ca\textsuperscript{2+} in endothelial cells has not been addressed specifically, elevated extracellular Mg\textsuperscript{2+} has been shown to inhibit capacitative Ca\textsuperscript{2+} entry in other cells. 245

Experimental studies have shown that (1) removal of extracellular Mg\textsuperscript{2+} causes a potent, endothelium-dependent vasodilatory response 246-249. (2) In contrast, removal of Mg\textsuperscript{2+} in arteries with disrupted endothelium leads to vasoconstriction; and (3) both responses are reversible with readdition of Mg\textsuperscript{2+}. 246-248 When concentrations of Mg\textsuperscript{2+} or Ca\textsuperscript{2+} are increased to higher than the physiologic range (>1.2 and >1.5 mm, respectively), the direct endothelium-independent effects dominate. When the concentration of Ca\textsuperscript{2+} is >1.5 mm

in the presence of a normal concentration of Mg\textsuperscript{2+}, endothelium-intact rings contract; when the concentration of Mg\textsuperscript{2+} is >1.2 mm, endothelium-intact rings relax. 248 Because Ca\textsuperscript{2+} is obligatory for smooth muscle contraction and basal NO formation or release, and because Mg\textsuperscript{2+} opposes the action of Ca\textsuperscript{2+} at both sites, these studies suggest that the responsiveness of vascular smooth muscle to changes in concentrations of Mg\textsuperscript{2+} and Ca\textsuperscript{2+} reflects the sum of responses at the endothelial and smooth muscle cells. 248 Studies of the effects of Mg\textsuperscript{2+} on agonist-induced, NO-mediated relaxation of arteries have produced contradictory results. 250-253

The clinical significance of these results is not clear for two reasons. First, these studies used different types of isolated blood vessels from a variety of species. Second, and more important, most of these studies used extracellular concentrations of Mg\textsuperscript{2+} outside the physiologic range (e.g., Mg\textsuperscript{2+}-free perfusate). In one study, however, human pial arteries were used to show that even slight changes in extracellular concentration of Mg\textsuperscript{2+} within the physiologic range (i.e., 1.2 mm to 0.8 mm) resulted in relaxation of endothelium-intact arteries and constriction of endothelium-disrupted arteries. 249

These results suggest that normal endothelium protects against the vasospastic effect of low extracellular concentrations of Mg\textsuperscript{2+}. 249

Clinical Applications

Acute Myocardial Infarction

In 1991, Teo et al. 254 reported a metaanalysis of seven small randomized, placebo-controlled trials of Mg\textsuperscript{2+} in AMI conducted during the previous decade. They found a reduction in mortality from AMI of 55% and a significant reduction in serious arrhythmias with Mg\textsuperscript{2+}. A second metaanalysis of eight trials, which included the studies analyzed by Teo et al., yielded similar results. 255 Two additional randomized trials found that Mg\textsuperscript{2+}-treated patient groups had significantly lower in-hospital 256 and 30-day mortality. 257

Recently, however, two large randomized trials of Mg\textsuperscript{2+} in AMI yielded conflicting results. It is worthwhile to comment on these trials because significant methodologic differences may account for the disparate findings. Woods et al. 258 studied 2,316 patients in the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), which showed that doubling the concentration of Mg\textsuperscript{2+} in serum in the acute phase of AMI im-

Anesthesiology, V 89, No 1, Jul 1998
proved outcome significantly. Mortality at 28 days, the primary trial end point, was reduced by 24% in the Mg$^{2+}$ group compared with the placebo group (7.8% mortality vs. 10.3% respectively; two-tailed $P = 0.04$). LIMIT-2 was a single-center, double-blinded trial, and the median interval from onset of symptoms to administration of the study drug was 3 h. Other treatments for AMI were given as clinically indicated; therefore, some patients received a thrombolytic agent, aspirin, or both immediately after receiving the study drug. Analysis of these subgroups and others, including those receiving previous β-adrenergic blocker, diuretic, nitrate, or Ca$^{2+}$ antagonist, showed that Mg$^{2+}$ improved survival significantly in all subgroups. Reduction in mortality was accompanied by a 25% reduction in the incidence of left ventricular failure (two-tailed $P = 0.009$), but there was no evidence of antiarrhythmic action of Mg$^{2+}$. Favorable outcome was attributed to direct myocardial protective effects of Mg$^{2+}$, as evidenced by (1) a reduced incidence of pump failure, despite transient Mg$^{2+}$-induced afterload reduction, and (2) a lack of antiarrhythmic effect. Additional support for cardioprotection by Mg$^{2+}$ in AMI was provided by a report of long-term outcome in the LIMIT-2 study patients. Because left ventricular function after AMI is the strongest predictor of subsequent survival, Woods et al. analyzed mortality for an average of 2.7 yr (range, 1.0-5.5 yr) after initial randomization in LIMIT-2. Mortality from ischemic heart disease during follow-up was reduced by 21% in the Mg$^{2+}$ group ($P = 0.01$). The authors postulated that Mg$^{2+}$ provided cardioprotection in accordance with its effects in experimental models of ischemia-reperfusion injury.

A subsequent trial, the fourth International Study of Infarct Survival (ISIS-4), has shown no apparent benefit from administration of Mg$^{2+}$ during AMI. Although >58,000 patients were enrolled in ISIS-4 and the LIMIT-2 study dose of Mg$^{2+}$ was used, a number of important methodologic differences compared with LIMIT-2 may account for the apparent lack of benefit from Mg$^{2+}$ in ISIS-4. The ISIS-4 study, which also was designed to evaluate the effects of thrombolytic therapy, captopril, and oral nitrates, involved (1) a median of 8 h between onset of symptoms and administration of Mg$^{2+}$; (2) administration of thrombolytic drug and completion of lysis before randomization to Mg$^{2+}$; and (3) a median of 12 h between onset of symptoms and administration of Mg$^{2+}$ in the 30% of patients not given thrombolytic agents. The difference in timing of administration of Mg$^{2+}$ is probably the critical factor accounting for the conflicting results in these trials. Recent animal studies undertaken specifically to address this conflict clearly demonstrate that Mg$^{2+}$ is effective in AMI only if given before reperfusion occurs or during the first 15 min of reperfusion. Another multicenter trial is being conducted because of the controversy generated by ISIS-4. The Magnesium in Coronaries (MAGIC) trial will randomize high-risk patients presenting within 6 h of AMI to immediate Mg$^{2+}$, thrombolytic therapy, both, or neither.

A recent single-center trial showed that Mg$^{2+}$ reduces mortality in high-risk AMI patients. Shechter et al. conducted a prospective, randomized, double-blind, placebo-controlled trial involving 215 high-risk patients admitted for AMI and deemed unsuitable for thrombolytic therapy. Patients receiving Mg$^{2+}$ (MgSO$_4$, 6 g over 3 h, followed by 16 g over 45 h) had significantly lower in-hospital mortality than control patients (4% vs. 17%, respectively; $P < 0.01$). In addition, left ventricular ejection fraction 3 days and 1-2 months after admission was significantly higher in patients receiving Mg$^{2+}$. The authors concluded that Mg$^{2+}$ reduced overall mortality to levels seen with thrombolytic therapy and reduced mortality in elderly patients (>70 yr-old) to levels lower than those seen with thrombolytic agents. They also concluded that Mg$^{2+}$ is a valuable first-line treatment because only 15-22% of patients with AMI (and even fewer elderly patients) in the United States receive thrombolytic therapy.

**Perioperative Use**

**Intraoperative Myocardial Protection.** Although substantial experimental evidence supports the use of Mg$^{2+}$ in cardioplegia solutions, few clinical studies have been reported. Shakernia et al. found that patients undergoing coronary artery bypass grafting who received Mg$^{2+}$-containing cardioplegia had higher concentrations of Mg$^{2+}$ in serum, fewer ischemic changes in their electrocardiograms, and fewer ventricular arrhythmias postoperatively. Despite this evidence, however, a recent survey of current clinical practice indicates that only 30% of cardioplegia formulations include Mg$^{2+}$.

**Postoperative Arrhythmias.** Atrial tachyarrhythmias (ATs) are common after cardiothoracic surgery and are associated with increased morbidity, prolonged hospital stay, and increased cost. Nearly all clinical trials of Mg$^{2+}$ for prophylaxis of postoperative arrhyth-
MAGNESIUM AND CARDIOVASCULAR DISEASE

...ria have shown beneficial effects.\cite{189,190,270-274} In most trials, supplementation with Mg$^{2+}$ was effective in suppressing ATs.\cite{189,190,272-274} In the other trials, however, no effect on ATs was seen, but Mg$^{2+}$ suppressed ventricular arrhythmias.\cite{39,65,270,271} Differences in timing of administration of Mg$^{2+}$ and in duration of monitoring for postoperative arrhythmias could account for the conflicting results. Specifically, trials showing suppression only of ventricular arrhythmias involved administration of a single dose of Mg$^{2+}$ at approximately the time of CPB with or without additional doses for up to 24 h.\cite{39,65,270,271} In contrast, trials showing suppression by Mg$^{2+}$ of ATs used continuous postoperative infusions of Mg$^{2+}$ for up to 120 h.\cite{109,190,272-274} Further, continuous monitoring of arrhythmias on electrocardiogram was conducted for >24 h postoperatively only in the trials showing suppression of ATs by Mg$^{2+}$.\cite{189,190,272-274} These methodologic differences are important because more than half of ATs occur after the second postoperative day.\cite{205} In one study,\cite{275} supplementation with Mg$^{2+}$ affected neither ATs nor ventricular arrhythmias. Despite randomization, however, patients receiving MgSO$_4$ were older (P = 0.032) and were more likely to have had a history of AF than control patients (P = 0.061).\cite{275} Advanced age and previous AF are important risk factors for postoperative AF.\cite{269,276,277}

Other beneficial effects of Mg$^{2+}$ noted in these trials include decreased incidence of postoperative hypertension, decreased concentrations of myocardial creatine kinase, decreased incidence of elevation of the ST segment, and increased cardiac output.\cite{39,270,271} Additional potential benefits of perioperative administration of Mg$^{2+}$ include improved left ventricular diastolic function,\cite{278} reduced postoperative pain, and reduced requirement for analgesic agents.\cite{279}

Adverse Effects

The effects of hypermagnesemia have been reviewed.\cite{280} Interactions between Mg$^{2+}$ and neuromuscular blocking agents are well known,\cite{281} and potential interactions with volatile anesthetic agents have been noted. Few adverse effects have been reported with perioperative administration of Mg$^{2+}$. Only one study has suggested the possibility of adverse effects of intraoperative use of Mg$^{2+}$. Hecker et al.\cite{60} administered Mg$^{2+}$ before or during CPB (before aortic unclamping) to 48 patients undergoing coronary artery bypass graft surgery; another 24 control patients received no Mg$^{2+}$ (unblinded and apparently unrandomized). The authors found that concentrations of total Mg$^{2+}$ higher than the midnormal range were associated with a requirement for more direct current shocks during cardio defibrillation, but their analysis appears flawed. They initially found no statistically significant differences among groups for the number or energy of direct current shocks needed or for development of ventricular fibrillation after initial spontaneous electrical activity. When they subsequently divided the treatment groups into "low" and "high" total Mg$^{2+}$ subgroups (0.94 mmol/l was arbitrarily chosen to allow statistical analysis at higher and lower concentrations of Mg$^{2+}$), however, they found that concentrations >0.94 mmol/l (normal range, 0.75 - 1.16 mmol/l) were associated with a requirement for more direct current shocks (4 ± 2 vs. 2 ± 1; mean ± SD; P = 0.05). Further, despite statistically significant differences among groups for CPB perfusate temperature and for ventricular myocardial thickness, the authors concluded that adverse cardiac effects may occur when concentrations of total Mg$^{2+}$ exceed the midnormal range.\cite{282} This study contradicts an earlier report by Scheinman et al.\cite{57} in which Mg$^{2+}$ added to the pump prime (1 mmol final concentration) resulted in the need for fewer direct current shocks compared with patients receiving Mg$^{2+}$-free prime (concentration of Mg$^{2+}$ was 0.68 mmol/l during CPB). Further, Scheinman et al. noted that three patients receiving Mg$^{2+}$-free prime had ventricular fibrillation that was refractory to direct current cardioversion until Mg$^{2+}$ was administered intravenously. Similarly, Mg$^{2+}$ was found to be beneficial by Wistbacka et al.,\cite{272} who reported that patients undergoing coronary artery bypass grafting given 4 g MgSO$_4$ (peak concentration of Mg$^{2+}$ of 1.6 mmol/l) before and during CPB had more frequent spontaneous conversion to normal sinus rhythm after aortic unclamping (P = 0.016) compared with patients receiving MgSO$_4$ postoperatively only. There have been no reports of difficulty with defibrillation, increased requirement for inotropes or artificial pacing, or increased use of intraaortic balloon counterpulsation in any perioperative therapeutic trial of Mg$^{2+}$.

Other reported adverse effects of Mg$^{2+}$ include increased bleeding time,\cite{282-289} and the potential for increased fetal mortality during maternal hemorrhage.\cite{285} A recent trial of MgSO$_4$ in pre eclampsia, however, did not show any statistically significant differences in change in hematocrit, incidence of postpartum hemorrhage, or neonatal outcome.\cite{286} Further, a recent study of very low birthweight children found no increased...
mortality or adverse neurologic outcomes associated with prenatal exposure to MgSO₄.²⁸⁷ There have been no reports of adverse effects of Mg²⁺ on coagulation in the setting of cardiothoracic surgery, although this possibility has not been studied specifically.

Recommendations

Suspected Acute Myocardial Infarction. Despite the results of LIMIT-²⁵⁸ and Scheckter et al.,²⁶⁴ the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines²⁸⁸ does not advocate routine use of Mg²⁺ in AMI. Rather, pending the outcome of the MAGIC trial,²⁶³ ACC/AHA recommends the use of Mg²⁺ for early correction of documented Mg²⁺ deficits (i.e., total hypomagnesemia), especially in patients receiving diuretic agents before AMI; treatment of torsade de pointes (polymorphic ventricular tachycardia); and AMI in high-risk patients, such as the elderly or those for whom thrombolytic therapy is contraindicated. If use of Mg²⁺ is considered during AMI, it should be given as early as possible unless complete heart block or severe renal failure is present. Although the optimal dose has not been established, the following MgSO₄ regimen has been suggested: 2 g given intravenously over 5-15 min followed by 18 g over 24 h.²⁸⁹

Cardiothoracic Surgery. Evidence is sufficient (and adverse effects sufficiently few) to warrant administration of MgSO₄ in patients receiving Mg²⁺-free cardioplegia during CPB: 4 g MgSO₄ given over 20 min just before CPB.³⁴ When Mg²⁺ cardioplegia (16 mm MgSO₄, or 4 g/l) is used intermittently, but without a dose immediately before aortic unclamping, then a single bolus dose of MgSO₄ (2 g) just before removal of the aortic cross-clamp should be considered. Postoperatively, supplementation with Mg²⁺ should be continued despite normal concentrations of total Mg²⁺ in serum because ionized⁴ or ultrafilterable³⁵ hypomagnesemia may occur. MgSO₄ should be given at a dose of 12 g for 24 h, followed by 3 g each day for 3 days (unless renal insufficiency is present; serum creatinine > 2 mg/dl).²⁷⁴ Concentrations of total Mg²⁺ in serum should be measured daily.

Refractory Arrhythmias. In addition to well-established uses for Mg²⁺ in the treatment of torsade de pointes and digoxin-toxic arrhythmias, evidence suggests that a trial of MgSO₄ may be useful to manage AF with rapid ventricular rate, supraventricular tachycardia and ventricular arrhythmias during AMI, refractory ventricular tachycardia or ventricular fibrillation, and multifocal atrial tachycardia (table 3).

Summary

Mg²⁺ is a critically important nutrient and a useful therapeutic agent. Depletion of Mg²⁺ and hypomagnesemia are relatively common, are difficult to diagnose, and have been implicated in several cardiovascular disorders. In pharmacologic doses, Mg²⁺ is a useful anti-ischemic and antiarrhythmic agent. Perioperative use of Mg²⁺ is increasing,²⁸⁹ particularly in the setting of cardiovascular surgery, and Mg²⁺ continues to be a mainstay in obstetric management of pre-eclampsia, at least in North America. Additional experimental and outcome studies will continue to define the clinical scope of therapy with Mg²⁺.

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References

12. Tsuji H, Venditti F, Evans J, Larson M, Levy D: The associations of levels of serum potassium and magnesium with ventricular prema-
MAGNESIUM AND CARDIOVASCULAR DISEASE

42. Abraham A, Rosenman D, Zion M: Lymphocyte potassium and magnesium concentrations as prognostic factor after myocardial infarction. Cardiology 1988; 75:194-9
50. Fink E, Brick J, Shane S: Alterations of long chain free fatty

Anesthesiology, V 89, No 1, Jul 1998


70. Yamaoka K, Seyama I. Modulation of Ca²⁺ channels by intracellular Mg²⁺ ions and GTP in frog ventricular myocytes. Pfuiigers Arch 1996; 432:433-8.


77. Meissner G, Henderson J. Rapid calcium release from cardiac sarcoplasmic reticulum vesicles is dependent on Ca²⁺ and is modulated by Mg²⁺, adenosine nucleotide, and calmodulin. J Biol Chem 1987; 262:3065-73.

78. Xu L, Mann G, Meissner G. Regulation of cardiac Ca²⁺ release channel (ryanodine receptor) by Ca²⁺, Mg²⁺, and adenosine nucleotides under normal and simulated ischemic conditions. Circ Res 1996; 79:1100-9.


86. Lansman J, Hess P, Tsim R. Blockade of current through single calcium channels by Cd²⁺, Mg²⁺, and Ca²⁺. J Gen Physiol 1986; 88:321-47.


90. Dörrschmidt-Käfer M. The action of Ca²⁺, Mg²⁺, and H⁺ on the...
contraction threshold of frog skeletal muscle. Pflugers Arch 1976; 362:33-41
94. Sanguinetti M, Kass R: Regulation of cardiac calcium channel current and contractile activity by the dihydropyridine Bay K8644 is voltage dependent. J Mol Cell Cardiol 1984; 16:667–70
104. Smart S, LoCurto A, el Schultz J, Sagar K, Warltier D: Intracoronary amiloride prevents contractile dysfunction of postischemic ‘stunned’ myocardium: Role of hemodynamic alterations and inhibition of Na⁺/H⁺ exchange and L-type Ca²⁺ channels. J Am Coll Cardiol 1995; 26:1365–73

126. Christensen C, Rieder M, Silverstein E, Gencheff N. Magnesium sulfate reduces myocardial infarct size when administered before but not after coronary reperfusion in a canine model. Circulation 1995; 92:2617–21


133. Leor J, Klener R. An experimental model examining the role of magnesium in the therapy of acute myocardial infarction. Am J Cardiol 1995; 75:1292–3


162. Bolli R, Triana J, Jeroudi M. Prolonged impairment of coro-

Anesthesiology, V 89, No 1, Jul 1998
MAGNESIUM AND CARDIOVASCULAR DISEASE

Anesthesiology, V 89, No 1, Jul 1998


196. Knudsen K, Abrahamsen J: Magnesium sulfate in the treat-


234. Meredith I, Yeung A, Weidinger F, Anderson T, Uehata A, Ryan T, Selwyn A, Ganz P. Role of impaired endothelium-dependent...


