Role of Magnesium in Cardiovascular Diseases

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Abstract: Magnesium, the fourth most abundant cation in the human body, is involved in several essential physiological, biochemical, and cellular processes regulating cardiovascular function. It plays a critical role in modulating vascular smooth muscle tone, endothelial cell function, and myocardial excitability and is thus central to the pathogenesis of several cardiovascular disorders such as hypertension, atherosclerosis, coronary artery disease, congestive heart failure, and cardiac arrhythmias. This review discusses the vasodilatory, anti-inflammatory, anti-ischemic, and antiarrhythmic properties of magnesium and its current role in the prevention and treatment of cardiovascular disorders.

Key Words: magnesium, cardiovascular diseases, hypertension, arrhythmia

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Magnesium (Mg^{2+}) is involved in several essential physiological, biochemical, and cellular processes regulating cardiovascular function. It plays a critical role in modulating vascular smooth muscle tone, endothelial cell function, and myocardial excitability and is thus central to the etiopathology of several cardiovascular disorders, including hypertension, atherosclerosis, coronary artery disease (CAD), congestive heart failure (CHF), and cardiac arrhythmias.[1–4] Hypertension is an important risk factor for endothelial damage/dysfunction, an essential step in the pathogenesis of atherosclerosis, ultimately leading to CAD.[5] CAD, in turn, initiates a sequence of adverse cardiovascular events beginning with myocardial infarction (MI) followed by ischemic cardiomyopathy, heart failure, cardiac arrhythmias, and sudden cardiac death. Because Mg^{2+} is crucial for the normal physiological functioning of vascular smooth muscle cells (VSMCs), endothelial cells, and myocardium, reduced Mg^{2+} levels could represent a common link between these adverse cardiovascular events. Studies have shown that hypomagnesemia is indeed associated with increased cardiovascular morbidity and mortality.[6–9] Therefore, evaluating the potential role of Mg^{2+} in the diagnosis and treatment of cardiovascular disorders becomes imperative.

MAGNESIUM HOMEOSTASIS

Mg^{2+} is widely distributed in plant and animal foods, in beverages, and in over-the-counter dietary supplements and vitamins. In general, foods containing dietary fiber provide Mg^{2+}. For instance, green leafy vegetables, such as spinach, legumes, nuts, seeds, and whole grains are rich sources. Evidence suggests that the typical "American-type" diet is relatively deficient in Mg^{2+} compared with the "Oriental" diet that is richer in Mg^{2+} due to a greater intake of fruits and vegetables.[10]

Mg^{2+} is the second most abundant intracellular cation and the fourth most abundant cation in the body ($Ca^{2+} > K^+ > Na^+ > Mg^{2+}$).[1] Approximately 65% of the total body Mg^{2+} is in bone, approximately 34% in muscle, but 1% in plasma and interstitial fluid.[11] Both intra- and extracellular Mg^{2+} exist in 3 functional states: (1) free or ionized (the physiologically active form), (2) protein bound, and (3) complexed to anions (bicarbonate, phosphate, citrate, and lactate). With regard to extracellular Mg^{2+}, 60% is in the free or ionized form, 33% is protein bound (mostly to albumin), and 7% is complexed to anions.[12] Within cells, Mg^{2+} is compartmentalized in the nuclei, mitochondria, and endo/sarcoplasmic reticulum.[13] Within these compartments, Mg^{2+} binds to chromatin and nucleic acid, matrix adenine phosphonucleotides and intermembrane proteins, and ribonuclear proteins and phospholipids, respectively.[13,14] As a result of this binding, only a small fraction of intracellular Mg^{2+} exists in the free form. The total intracellular Mg^{2+} concentration ranges between 14 and 20 nM, whereas the intracellular free Mg^{2+} concentration is estimated to be about 0.5–0.7 nM.[15,16]

Mg^{2+} is a dynamic ion, the transcellular transport of which involves several efflux and influx systems. Mg^{2+} efflux involves Na^+-dependent (Na^+/Mg^{2+} exchanger) and Na^+-independent (Ca^{2+}/Mg^{2+} exchanger, Mn^{2+}/Mg^{2+} antiporter and Cl^-/Mg^{2+} exchanger) systems.[17–19] The Na^+/Mg^{2+} exchanger is expressed in cardiac, renal, and VSMCs and is regulated by several neurohormones implicated in the pathophysiology of hypertension.[20] Angiotensin II, vasopressin, aldosterone, epinephrine, and norepinephrine have all been shown to enhance Mg^{2+} efflux and decrease intracellular Mg^{2+}.[21–24] Pharmacological and functional studies have shown that Mg^{2+} influx occurs via Mg^{2+}/anion cotransport, counter-transport pathways using the electrochemical gradient of Na^+, and via cation channels. At least 7 transcellular Mg^{2+} channels have been cloned, including the mitochondrial RNA splicing 2 protein, the human solute carrier family 41, members 1 and 2 (SLC41A1, SLC41A2) channels, magnesium transporter 1, ancient conserved domain protein 2, and transient receptor potential melastatin cation channels 6 and 7 (TRPM6, TRPM7). A paracellular Mg^{2+} transporter, paracellin-1, has also been identified.[25–30] Table 1 summarizes the tissue distribution, function, and the disease states associated with dysfunction of each of these transporters involved in Mg^{2+} influx.[30–41]

The above transport processes are intricately involved in the intestinal absorption of Mg^{2+} and renal regulation of Mg^{2+} excretion. Intestinal absorption of Mg^{2+} proceeds in both a passive paracellular manner and an active transcellular manner.[42] Paracellular absorption of Mg^{2+} occurs mainly in the small intestine and is presumably mediated by claudin-16/paracellin-1.[43,44] On the contrary, active transcellular absorption of Mg^{2+} occurs almost exclusively in the colon and may involve Na^+/Mg^{2+} antiport systems and the transcellular transporter TRPM6. Approximately 80% of total plasma Mg^{2+} is filtered at the glomeruli, 15% of which is absorbed proximally, 70% in the thick ascending limb of the loop of Henle, and 15% in the distal convoluted tubule, with the remaining 3% to 5% excreted in the

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TABLE 1. Mg^{2+} Transporters Involved in Mg^{2+} Influx and Disease States Associated With Their Dysfunction[41]

Transporter	Distribution	Function	Associated Diseases
Mrs2p	Inner mitochondrial membrane	Mitochondrial Mg^{2+} influx	—
SLC41A1	Heart, brain, liver, kidney, colon, small intestine	General transporter for divalent cations	Preeclampsia,[31] nephronophthisis,[32] Parkinson disease[33]
SLC41A2	Kidney	General transporter for divalent cations, but not Ca^{2+}	—
MagT1	Distal convoluted tubule cells	Mg^{2+}-specific transporter	X-linked Mg^{2+} deficiency with Epstein-Barr virus infection and neoplasia[34]
ACDP2	Ubiquitous	General transporter for divalent cations, but not Ca^{2+}	Dominant hypomagnesemia[35]
TRPM6	Intestinal epithelial cells, kidney tubules, vascular smooth muscle cells	Renal and gastrointestinal Mg^{2+} absorption	Hypomagnesemia with secondary hypocalcemia[36,37]
TRPM7	Vascular smooth muscle cells, cardiomyocytes, kidney tubules	Cell viability	Cardiac fibrosis,[38] atrial fibrillation,[39] anoxic brain injury[40]
Paracellin-1	Ascending limb of loop of Henle	Paracellular Mg^{2+} and Ca^{2+} reabsorption in the thick ascending limb of loop of Henle	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis[30]

ACDP2 indicates ancient conserved domain protein 2; MagT1, magnesium transporter 1; Mrs2p, mitochondrial RNA splicing 2 protein; TRPM6 and TRPM7, transient receptor potential melastatin cation channels 6 and 7.

Adapted with permission from Sontia et al.[41]

urine. The thick ascending limb is the main site of passive paracellular reabsorption of Mg^{2+}, a process mediated by claudin-16 and -19. The distal convoluted tubule is the site for active transcellular reabsorption of Mg^{2+} mediated via TRPM6. Mutation in TRPM6 is responsible for the rare monogenic disorder hypomagnesemia with secondary hypocalcemia in children who develop seizures and tetany due to extremely low Mg^{2+} levels.

MAGNESIUM DEFICIENCY

The prevalence of hypomagnesemia in hospitalized patients has been estimated to be between 8% and 30%.[45] Studies have shown that intakes of Mg^{2+} are consistently lower than recommended amounts in the United States. Approximately 65% of the American population consumes a diet deficient in Mg^{2+}.[46] Data from the 2005–2006 National Health and Nutrition Examination Survey showed that for all age groups, intake of Mg^{2+} is less than the respective Estimated Average Requirement, with adult men aged ≥71 years and adolescent women most likely to have low intakes. In another study using 2003–2006 National Health and Nutrition Examination Survey data to examine the effect of dietary supplement use on nutrient intake from diet, Bailey et al[47] demonstrated that average intakes of Mg^{2+} from food alone were higher among users of dietary supplements (350 mg for men and 267 mg for women) equal to or slightly exceeding their respective Estimated Average Requirements than among nonusers (268 mg for men and 234 mg for women). Symptomatic Mg^{2+} deficiency due to low dietary intake in otherwise healthy people is uncommon because the kidneys limit urinary excretion of Mg^{2+}. However, patients with certain conditions may be predisposed to or are at a higher risk of developing significant Mg^{2+} deficiency. Table 2 summarizes the common causes of hypomagnesemia due to gastrointestinal or renal losses.

Serum Mg^{2+} concentration is tightly regulated by the kidneys and small intestines, both of which increase their (re)absorption of Mg^{2+} under conditions of Mg^{2+} deprivation. If Mg^{2+} depletion persists, the bone store contributes by exchanging part of its content with extracellular fluid. Because only 1% of total body Mg^{2+} is in the serum, its measurement does not reflect intracellular Mg^{2+} levels. Serum Mg^{2+} can be normal in the presence of intracellular Mg^{2+} depletion, and a low level usually indicates significant Mg^{2+} deficiency.[48] Serum Mg^{2+} concentration is not routinely included in the basic metabolic panel. Therefore, the identification of hypomagnesemia often requires clinical suspicion in patients with risk factors (as mentioned in Table 2) or with clinical manifestations of hypomagnesemia (eg, tremor, ataxia, vertigo, tetany, seizures, cardiac arrhythmias, unexplained hypocalcemia, refractory hypokalemia). In patients diagnosed with hypomagnesemia, the distinction between gastrointestinal and renal losses is easily made from the history, but can also be made by measuring 24-hour urinary Mg^{2+} excretion or fractional excretion of magnesium ($FeMg^{2+}$) on a random urine specimen. A 24-hour urine Mg^{2+} excretion >10 mg or $FeMg^{2+}$ >2% in a patient with hypomagnesemia and normal renal function indicates renal Mg^{2+} wasting.[49]

MAGNESIUM AND VASCULAR SMOOTH MUSCLE CELLS

Clinical and experimental evidence suggests that Mg^{2+} promotes vasodilation, reduces vascular resistance, and improves blood flow in systemic, coronary, cerebral, and renal circulations.[50–54] Both

TABLE 2. Causes of Mg^{2+} Deficiency

Gastrointestinal losses
- Diarrhea (acute or chronic)
- Vomiting
- Malabsorption (Crohn disease, celiac disease, small bowel resection, or bypass)
- Hypomagnesemia with secondary hypocalcemia
- Acute pancreatitis
- Medications (proton pump inhibitors, laxatives)

Renal losses
- Medications (loop/thiazide diuretics, aminoglycosides, amphotericin B, cysplatin, pentamidine, cyclosporine, antiepidermal growth factor receptor antibodies)
- Alcohol use
- Uncontrolled diabetes mellitus
- Primary hyperaldosteronism
- Hypercalcemia (eg, primary hyperparathyrodisim)
- Acquired tubular dysfunction (eg, recovery from acute tubular necrosis, postrenal transplantation)
- Familial renal Mg^{2+} wasting (eg, familial hypomagnesemia with hypercalciuria and nephrocalcinois, hypomagnesemia with secondary hypocalcemia, Bartter syndrome, Gitelman syndrome, isolated dominant hypomagnesemia, isolated recessive hypomagnesemia)

extracellular and intracellular free Mg^{2+} can modulate vascular smooth muscle (VSM) tone. Extracellular Mg^{2+} is considered to be a Ca^{2+} antagonist because it inhibits Ca^{2+} current in excitable cells via several mechanisms (Fig. 1). First, extracellular divalent cations such as Mg^{2+} effectively neutralize the fixed negative charges on the external surface of the cell membrane either by binding or by electrostatic screening. This stabilizes the excitable membranes and raises the excitation threshold for voltage-gated channels. This shift in the current-voltage relationship is responsible for diminished current via the voltage-gated Ca^{2+} channels in response to normal stimuli.[55,56] The screening of surface charges is more marked extracellularly than intracellularly probably due to an asymmetrical distribution of negatively charged sialic acid residues in the cell membrane.[57] Second, some evidence suggests that extracellular Mg^{2+} can decrease Ca^{2+} current by directly binding to the Ca^{2+} channels.[58] Binding of Mg^{2+} may either mechanically block the channel pore or may cause an allosteric modulation of the channel gating, eventually resulting in its closure. Bara and Guiet-Bara[59] have shown that $MgCl_2$ and $MgSO_4$ act at an extracellular site on L-type Ca^{2+} channels to regulate the influx of Ca^{2+} through voltage-gated Ca^{2+} channels in VSMCs and endothelial cells. Serrano et al[60] have shown a similar inhibitory effect of extracellular Mg^{2+} on T-type Ca^{2+} channels. Besides inhibiting Ca^{2+} entry through voltage-gated Ca^{2+} channels, extracellular Mg^{2+} has also been shown to inhibit capacitative Ca^{2+} entry in VSMCs.[61]

Intracellular Mg^{2+} [$(Mg^{2+})_i$] modulates VSM tone via its effects on ion channels and signal transduction pathways, especially those involving Ca^{2+} (Fig. 1). The voltage-dependent L-type Ca^{2+} channels (L_{Ca}) play a critical role in maintaining VSM tone. Changes in $(Mg^{2+})_i$ are known to influence L_{Ca} by affecting its amplitude, its activation/inactivation kinetics, and its modulation by factors such as phosphorylation, ultimately leading to decreased Ca^{2+} entry via these channels.[62] This will be discussed in detail later in this review. Ca^{2+} plays an important role in excitation-contraction coupling in smooth muscle cells. Angiotensin II, vasopressin, endothelin, and epinephrine/norepinephrine exert their vasoconstrictor effect via stimulation of AT_1, V_{1a}, ET_A, and α_1 receptors, respectively, on VSMCs. Activation of these G_q-protein–coupled receptors initiates the phospholipase C, inositol-1,4,5-trisphosphate (IP_3), diacylglycerol, Ca^{2+}, protein kinase C (PKC) signal transduction pathway. Evidence suggests that following receptor-ligand interaction $(Mg^{2+})_i$ is also altered and that it too functions as a second messenger to modulate signal transduction.[23,63] $(Mg^{2+})_i$ regulates G-protein activity, phospholipase C translocation, and PKC activation. Elevated $(Mg^{2+})_i$ stimulates IP_3 breakdown, inhibits IP_3-induced Ca^{2+} release from the sarcoplasmic reticulum, and competes with $(Ca^{2+})_i$ for cytoplasmic and reticular binding sites.[64–66] Lastly, $(Mg^{2+})_i$ activates sarcoplasmic/endoplasmic reticular Ca^{2+} ATPase pump that sequesters $(Ca^{2+})_i$ into the sarcoplasmic reticulum.[1]

Besides the direct effects of Mg^{2+} on VSMCs, Mg^{2+} also modulates endothelial function, which in turn contributes to its vasodilatory actions. Normal endothelium plays a fundamental role in regulating vasomotor tone by synthesizing vasodilatory prostacyclin (PGI_2) and nitric oxide (NO). Mg^{2+} has been shown to increase endothelial release of PGI_2 in cultured human endothelial cells and in healthy human volunteers.[67,68] However, because extracellular Mg^{2+} has also been shown to inhibit both Ca^{2+} influx and intracellular Ca^{2+} release in endothelial cells, it has been speculated that the Mg^{2+}-induced PGI_2 release could be via a Ca^{2+}-independent mechanism.[69] Unlike VSMCs, Ca^{2+} entry in endothelial cells is receptor-mediated and/or capacitative (activated in response to decreased $(Ca^{2+})_i$) rather

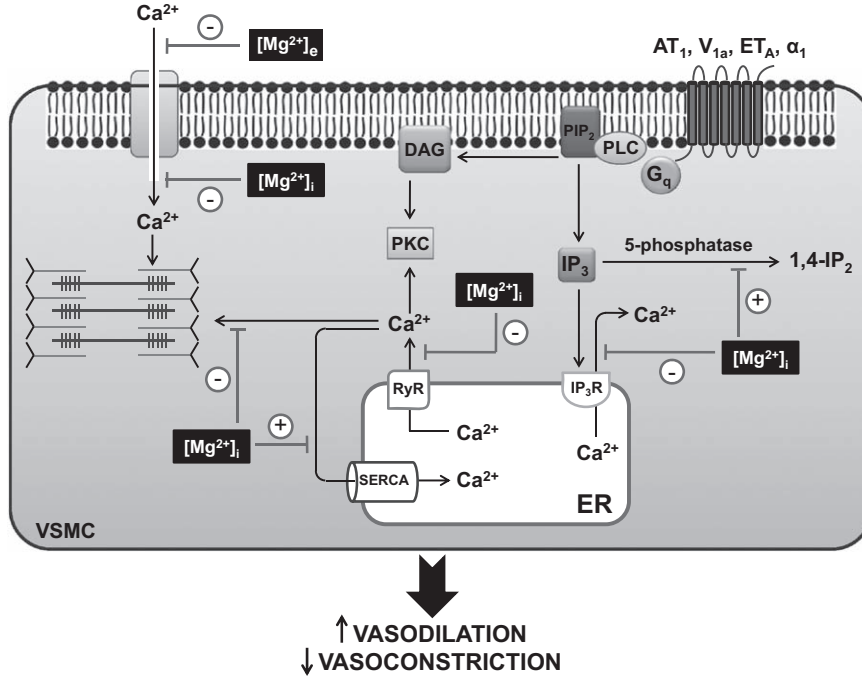

FIGURE 1. Effects of extracellular and intracellular magnesium (Mg^{2+}) on vascular smooth muscle tone via modulation of calcium (Ca^{2+}) entry and intracellular signal transduction pathways. α_1 indicates alpha 1 receptor; AT_1, angiotensin 1 receptor; DAG, diacylglycerol; ER, endoplasmic reticulum; ET_A, endothelin A receptor; IP_3, inositol-1,4,5-trisphosphate; IP_3R, IP_3 receptor; 1,4-IP_2, inositol 1,4-bisphosphate; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C; PLC, phospholipase C; RyR, ryanodine receptor; SERCA, sarcoendoplasmic reticulum Ca^{2+}-ATPase; V_{1a}, vasopressin 1a receptor; VSMC, vascular smooth muscle cell.

than voltage-dependent.[70] Extracellular Ca^{2+} is essential for endothelium-dependent VSM relaxation because elevated $(Ca^{2+})_i$ levels stimulate the synthesis and release of NO via endothelial NO synthase (eNOS) in response to various stimuli. The effects of elevated extracellular Mg^{2+} level on endothelial Ca^{2+} entry and NO synthesis are controversial. Although an elevated level of extracellular Mg^{2+} has been shown to inhibit both receptor-mediated and capacitative Ca^{2+} entry in cultured endothelial cells, it has been shown to enhance NO synthesis, in part, via the upregulation of eNOS.[71,72] In addition, Yang et al[73] have shown that Mg^{2+} stimulates NO release from intact rat aortic rings in a concentration-dependent manner and that the release of NO requires Ca^{2+} and formation of cyclic guanosine monophosphate. Last, Pearson et al[74] have demonstrated that hypomagnesemia selectively impairs the release of NO from canine epicardial coronary artery endothelium, suggesting that Mg^{2+} supplementation can promote vasodilation.

Based on the vascular effects of Mg^{2+}, it is not surprising that low Mg^{2+} levels have been implicated in the pathogenesis of hypertension. Several epidemiological studies have revealed an inverse association between Mg^{2+} consumption and blood pressure. Analysis of 61 dietary variables in 615 elderly participants of the Honolulu Heart Study showed that Mg^{2+} was the variable that had the strongest association with blood pressure.[75] Ascherio et al[76,77] examined the relationship of various nutritional factors with blood pressure levels in 2 prospective studies and found that when adjusted for age, weight, and alcohol consumption, Mg^{2+}, K^+, and fiber were significantly associated with lower risk of hypertension among men but not women who reported a diagnosis of hypertension. However, among both men and women who did not report hypertension during the follow-up period, Mg^{2+}, K^+, and fiber were each inversely associated with systolic and diastolic pressures. Similarly, a prospective study conducted on 28,349 female health professionals participating in the Women's Health Study revealed that Mg^{2+} intake was inversely associated with the risk of developing hypertension, suggesting that Mg^{2+} intake might be beneficial in the primary prevention of hypertension.[9] These data are in support of those from the Dietary Approaches to Stop Hypertension (DASH) clinical trial, which demonstrated that in hypertensive patients, a Mg^{2+}- and K^+-rich diet of fruits, vegetables, and low-fat dairy products lowered blood pressure by 11.4/5.5 mm Hg.[78,79] These epidemiological studies, together with experimental evidence, suggest a strong relationship between Mg^{2+} and blood pressure levels and support a role for hypomagnesemia and/or decreased Mg^{2+} intake in the pathogenesis of hypertension.

While the role of hypomagnesemia and/or decreased Mg^{2+} intake in the pathogenesis of high blood pressure is apparent, the therapeutic role of Mg^{2+} in the treatment of hypertension remains controversial. Loss of arterial compliance is an important feature of essential hypertension. Wu et al[80] demonstrated that Mg^{2+} and K^+ supplementation significantly reduces systolic and diastolic pressures and improves small artery compliance. Recently, it was shown that in emergency department patients with hypertension, intravenous $MgSO_4$ produced reduction in systolic and diastolic pressures similar to other antihypertensive agents.[81] In a double-blind controlled trial, Witteman et al[82] showed that the treatment of middle-aged and elderly women with mild-to-moderate hypertension with oral magnesium aspartate-HCl for 6 months lowered systolic and diastolic blood pressures by 2.7 and 3.4 mm Hg, respectively. Several similar clinical trials have shown a modest reduction in both systolic and diastolic blood pressures in response to oral or intravenous Mg^{2+} treatment in hypertensive patients.[83–85] However, other studies, such as the Trials of Hypertension Prevention, have failed to demonstrate a beneficial effect of Mg^{2+} on lowering blood pressure in adults with hypertension.[86] A meta-analysis of 20 randomized clinical trials testing the effect of Mg^{2+} supplementation on blood pressure revealed that Mg^{2+} supplementation produced a dose-dependent but small overall reduction in blood pressure.[87] While Mg^{2+} supplementation along with other alternative treatments such as vitamin C, coenzyme Q10, and omega-3 fatty acids has been suggested for the management of hypertension in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, evidence for its effectiveness is lacking from well-designed, randomized, controlled trials.[88] Therefore, long-term and better quality double-blind placebo-controlled trials in carefully characterized hypertensive patients are needed to make any definitive recommendations on the therapeutic use of supplemental Mg^{2+} in the management of hypertension.

MAGNESIUM AND THE ENDOTHELIUM

Because endothelial cells are strategically located at the interface of blood and vessel wall, they play an important role not only in controlling VSM tone and blood flow but also in regulating vascular permeability, maintaining a nonthrombogenic environment, and influencing immune and inflammatory reactions. It is well accepted that endothelial dysfunction is central to the pathogenesis of atherosclerosis, thrombosis, hypertension, and diabetes.[89,90] Besides modulating Ca^{2+} entry, NO and PGI_2 production, Mg^{2+} influences several other aspects of endothelial pathophysiology. Low Mg^{2+} levels have been shown to inhibit endothelial proliferation and migration and upregulate the expression of interleukin-1, -6, vascular cell adhesion molecule, and plasminogen activator inhibitor-1, thereby producing a proinflammatory, prothrombotic, and proatherogenic environment.[91,92] Recently, Dong et al[93] showed that $MgSO_4$ enhances the cleavage of the prothrombotic ultra-large von Willebrand factor by *a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13)* and significantly reduces von Willebrand factor–mediated platelet adhesion and aggregation on immobilized collagen, thus preventing the tendency to develop thrombosis. The role of reactive oxygen species and oxidized low-density lipoprotein (OxLDL) in the pathogenesis of atherosclerosis is well-established.[94] Experimental evidence exists, suggesting that Mg^{2+} deficiency potentiates free radical production and oxidative stress in endothelial cells through reduction in plasma antioxidants and increased lipid peroxidation.[95–97] Au-Yeung et al[98] recently showed that magnesium tanshinoate B, a compound purified from a Chinese herb danshen (Salvia miltiorrhiza), significantly inhibits c-Jun N-terminal kinase activation, cytochrome *c* release, and caspase-3 activation induced by Cu-OxVLDL or Cu-OxLDL, resulting in a marked reduction in endothelial cell apoptosis, suggesting that Mg^{2+} could have a potential therapeutic role in the prevention/treatment of atherosclerosis.

Several animal and human experiments also support the role of Mg^{2+} in the pathogenesis and treatment of atherosclerosis and its complications. Sherer et al[99] showed that fortification of drinking water with $MgSO_4$ or $MgCl_2$ attenuates atherogenesis in both male and female LDL receptor–deficient mice fed high-cholesterol diet.[100] In addition, Ravn et al[101] showed that ApoE-deficient mice receiving a low-fat diet and fortification of drinking water with $MgSO_4$ significantly reduced the median plaque area, and cholesterol and triglyceride levels. Recently, in agreement with the above findings, it was demonstrated that rabbits with inadequate dietary intake of Mg^{2+} developed more plaques and had higher total and non-high-density lipoprotein cholesterol and triglyceride levels than controls, suggesting that inadequate intake of Mg^{2+} is an independent risk factor for atherosclerosis.[102] Because postprandial hyperlipidemia has been recognized to be a risk factor for atherosclerosis, Kishimoto et al[103] studied the effect of Mg^{2+} supplementation on postprandial serum lipid levels. Serum and chylomicron triacylglycerol responses after the fat load were found to be reduced and delayed by Mg^{2+} supplementation.

Also, the concentrations of apo-B48, remnant-like particle cholesterol, and nonesterified fatty acids were found to be significantly lower after the fat-with-Mg^{2+} meal compared with the fat-only meal, suggesting that Mg^{2+} supplementation inhibits fat absorption and improves postprandial hyperlipidemia.[103] Lastly, Liao et al[104] examined the relation of serum and dietary Mg^{2+} with cardiovascular disease (CVD) incidence in 13,922 middle-aged adults from 4 US communities in the Atherosclerosis Risk in Communities (ARIC) study. Two hundred twenty-three men and 96 women developed CVD over the 4- to 7-year follow-up period. The relative risk of CAD across quartiles of serum magnesium was found to be 1.00, 0.92, 0.48, and 0.44 among women and 1.00, 1.32, 0.95, and 0.73 among men. The adjusted relative risk of CVD for the highest versus the lowest quartile of dietary magnesium was found to be 0.69 in men [95% confidence interval (CI), 0.45–1.05] and 1.32 in women (95% CI, 0.68–2.55), suggesting that low Mg^{2+} concentration may contribute to the pathogenesis of coronary atherosclerosis. Furthermore, an analysis of the relation between serum Mg^{2+} and the incidence of ischemic stroke among participants of the Atherosclerosis Risk in Communities study revealed that low serum Mg^{2+} levels are associated with increased risk of ischemic stroke, in part, via its effects on hypertension and diabetes.[105]

A recent meta-analysis of prospective cohort studies by Qu et al[106] examined the association between dietary Mg^{2+} intake and serum Mg^{2+} levels and the risk of total CVD events. Analysis of 11 primary studies revealed a nonlinear inverse association between dietary Mg^{2+} intake and total CVD events ($P_{nonlinearity} = 0.024$). The greatest reduction in CVD events was observed for intake between 150 and 400 mg/d. Higher intake was not associated with further reduction in CVD events. A total of 5 studies were included in the dose-response analysis of serum Mg^{2+} concentration to total CVD events. A rise in serum Mg^{2+} concentration of 0.1 mEq/L was linearly associated with a 9% reduction in the risk of total CVD events. However, the authors found a notable lack of data to explain the correlation of dietary Mg^{2+} intake with serum Mg^{2+} concentration. Therefore, given the magnitude of CVD- and Mg^{2+}-deficient diet in the United States, there is an immediate need for several well-designed cohort studies to determine the interrelationship among dietary Mg^{2+} intake, serum (or intracellular) Mg^{2+} concentration, and CVD events.

MAGNESIUM AND THE MYOCARDIUM

Anti-ischemic Effects

The cardioprotective effects of Mg^{2+} are well-established. Several studies have shown that myocardial ischemia followed by reperfusion results in cytoplasmic Ca^{2+} overload.[107,108] Mg^{2+} confers cellular protection during myocardial ischemia by (1) acting as a Ca^{2+} antagonist, thereby reducing Ca^{2+} overload, (2) conserving cellular adenosine triphosphatase (ATP) as the magnesium salt and thereby preserving energy-dependent cellular processes, (3) reducing myocardial oxygen consumption by lowering the heart rate, contractility, systemic afterload, and attenuating catecholamine-induced elevated oxygen demand, and (4) protecting the post-ischemic myocardium from oxidative damage.[109–112] Based on these effects of Mg^{2+}, it is not surprising that Mg^{2+} therapy has been studied extensively in the context of acute MI. The Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) was the first randomized, double-blind, placebo-controlled study demonstrating the efficacy of intravenous magnesium therapy in reducing early mortality in acute MI.[113] Two thousand three hundred sixteen patients with suspected acute MI were randomized to receive either intravenous $MgSO_4$ or placebo. There was a 24% relative reduction in 28-day mortality and a 25% reduction in the incidence of left ventricular failure in the $MgSO_4$ group. The study concluded that intravenous $MgSO_4$ is a simple, safe, and widely applicable treatment for acute MI, and its efficacy in reducing early mortality is comparable with, but independent of, that of thrombolytic or antiplatelet therapy.

However, 2 subsequent mega-trials, ISIS-4 (Fourth International Study of Infarct Survival) and MAGIC (Magnesium in Coronaries), failed to demonstrate a beneficial effect of magnesium therapy in acute MI.[114,115] In the ISIS-4 trial, 58,050 patients with suspected acute MI were randomized to receive oral captopril, oral controlled-release mononitrate, or intravenous $MgSO_4$. The study showed increased 35-day mortality and increased incidence of cardiogenic shock and CHF in the $MgSO_4$ group. No benefit was observed in the treatment group across all major subgroups, whether they were treated early or late and whether they received thrombolysis. The MAGIC trial compared short-term mortality in 6213 patients with ST elevation MI who were randomized to receive either intravenous $MgSO_4$ or placebo. At 30 days, 15.3% patients in the magnesium group and 15.2% in the placebo group had died (odds ratio 1.0; 95% CI, 0.9–1.2, $P = 0.96$). No benefit or harm of magnesium was observed in subgroup analyses. Potential explanations for the conflicting results of these various trials could be differences in time to randomization from symptom onset which might have influenced the attainment of elevated serum Mg^{2+} levels sufficient to prevent myocardial reperfusion injury and the increased use of aspirin, β-blockers, and angiotensin-converting enzyme inhibitors in the ISIS-4 and MAGIC study populations, which might have superseded the potential cardioprotective effects of Mg^{2+}.

A recent meta-analysis of all randomized controlled trials that compared intravenous magnesium with placebo in the presence or absence of thrombolytic therapy in addition to routine treatment in patients with acute MI concluded that (1) magnesium is unlikely to reduce mortality in patients treated early or late and in patients already receiving thrombolytic therapy; (2) magnesium is unlikely to reduce mortality when used at high dose (≥75 mmol); (3) magnesium may reduce the incidence of ventricular fibrillation, ventricular tachycardia, and severe arrhythmia needing treatment, but it may increase the incidence of hypotension, bradycardia, and flushing; and (4) the areas of uncertainty regarding the effect of magnesium on mortality remain the effect of low-dose treatment (<75 mmol) and its efficacy in patients not treated with thrombolytics.[116]

Overall, in light of the current clinical evidence, there is no indication for the routine administration of intravenous magnesium in patients with acute MI. However, owing to the experimentally proven cardioprotective effects of Mg^{2+}, promising results from animal studies, relatively low cost, and ease of administration, together with its generally good tolerability, it could be worthwhile to re-evaluate the potential therapeutic role of Mg^{2+} in acute MI in further clinical trials before this inexpensive therapy is entirely cast aside

Antiarrhythmic Effects

Probably the most widely accepted and practiced use of Mg^{2+} in cardiovascular medicine is for the prevention and/or treatment of cardiac arrhythmias. Mg^{2+} exerts its antiarrhythmic effect via modulation of myocardial excitability. The role of voltage-dependent Na^+, Ca^{2+}, and K^+ channels in the generation of cardiac action potential and the pathogenesis of cardiac arrhythmias is well-established; however, very few studies have evaluated the effect of Mg^{2+} on cardiac voltage-dependent Na^+ channels. Using inside-out patches from guinea pig ventricular myocytes to measure currents through single cardiac Na^+ channels, Mubagwa et al[62] showed that $(Mg^{2+})_i$ had no effect on inward currents but decreased the outward current amplitude in a concentration and voltage-dependent manner.[117] This suggests that $(Mg^{2+})_i$ primarily exerts only an open channel blocking effect, with little or no direct allosteric modulatory action on the voltage-dependent Na^+ channels.

The cardiac membrane stabilizing action of Mg^{2+} is primarily due to its modulation of the voltage-dependent L-type Ca^{2+} channels (L_{Ca}). As mentioned earlier, changes in $(Mg^{2+})_i$ are known to influence L_{Ca} by affecting its amplitude, its activation/inactivation kinetics, and its modulation by factors such as phosphorylation, ultimately leading to decreased Ca^{2+} entry via these channels.[62] L_{Ca} amplitude is decreased by high $(Mg^{2+})_i$ and increased by low $(Mg^{2+})_i$.[118–120] An $(Mg^{2+})_i$-induced decrease in current amplitude involves change in channel gating in the form of shift in voltage-dependent inactivation and/or decreased channel availability. Raising $(Mg^{2+})_i$ has been shown to increase the rate and extent of the decay of Ca^{2+} current, an effect attributed to allosterically induced inactivation.[121] High $(Mg^{2+})_i$ also causes a leftward shift in the steady state voltage-dependent inactivation, probably as a result of screening of internal charges by $(Mg^{2+})_i$.[118]

The effects of Mg^{2+} on L_{Ca} amplitude are modulated by the state of phosphorylation of the L_{Ca}. Phosphorylation via the protein kinase A–dependent pathway enhances the L_{Ca} current amplitude and also enhances the inhibitory action of Mg^{2+}. Conversely, dephosphorylation of the channels by either protein kinase inhibitors or phosphatases decreases the Mg^{2+} effect.[118] The effect of Mg^{2+} is not due to changes in cyclic adenosine monophosphate concentration or channel phosphorylation but appears to be a direct effect of Mg^{2+} on the phosphorylated channel or on channel dephosphorylation.[120] Binding of Mg^{2+} inhibits phosphorylated channels from undergoing the conformational changes that result in more frequent opening. Nonetheless, the ATP-bound form of Mg^{2+} (Mg^{2+}-ATP) is required for protein kinase A– or PKC-mediated L_{Ca} phosphorylation.[122]

$(Mg^{2+})_i$ and guanosine triphosphate (GTP) act synergistically to inhibit L_{Ca}. GTP and other guanine di- or trinucleotides have been shown to inhibit L_{Ca} channels in a G-protein–independent manner.[123] Both Mg^{2+} and GTP can directly bind to L_{Ca}, but because of different charges, Mg^{2+} and GTP^{2-} have independent binding sites, with the binding of one allosterically preventing the binding of the other. Most L_{Ca} bind Mg^{2+} and/or GTP and remain in a nonavailable state under basal conditions. Depletion of $(Mg^{2+})_i$ relieves the Mg^{2+} block because the blocking device in the C-terminal region of α-subunit of L_{Ca} can no longer block the channel when free of Mg^{2+}.[124] However, in the presence of GTP, depletion of $(Mg^{2+})_i$ allows GTP to bind to L_{Ca}, thereby allowing it to exert its inhibitory effect, thus maintaining the channels in a nonavailable state.

Besides voltage-dependent Na^+ and L_{Ca} channels, Mg^{2+} can also influence the inward and delayed rectifier K^+ channels expressed in cardiac cell membrane. The inward rectifier K^+ channels (I_{K1}) are highly expressed in atrial and ventricular contractile cells, and in ventricular conduction cells, but less expressed in nodal cells.[62] I_{K1} current is the primary determinant of resting membrane potential of cardiac cells. It is well-established that the strong inward rectification results from voltage-dependent block by intracellular organic cations called polyamines.[125] Although the polyamines spermine and spermidine are the most potent inducers of inward rectification, $(Mg^{2+})_i$ also plays an important role.[126] Furthermore, this strong voltage-dependent rectification is influenced by extracellular K^+ such that elevated extracellular K^+ levels relieve the polyamine- or Mg^{2+}-induced rectification.[127] The delayed rectifier K^+ (I_K) current, composed of rapidly activating (I_{Kr}) and slowly activating (I_{Ks}) components mediated by 2 different channel proteins, HERG and K_vLQT1, respectively, is critical for the repolarization phase of cardiac action potential.[128,129] Elevated $(Mg^{2+})_i$ in mammalian cardiac myocytes decreases I_K current, whereas decreased $(Mg^{2+})_i$ produces the opposite effect.[130] A small increase in $(Mg^{2+})_i$ in the physiological range from 0.3 to 1.0 mM suppresses the current by 50–60%. Because this effect is observed in both nonstimulated cells and cyclic adenosine monophosphate–treated cells, it has been speculated that these modulatory effects of $(Mg^{2+})_i$ on I_K are independent of channel phosphorylation.[131] Lastly, because voltage-independent modulation of both outward and inward current through I_K occurs, the $(Mg^{2+})_i$ modulation of these channels does not appear to result from the open channel blocking effect observed on the I_{K1} channels. Rather, it has been suggested that the I_K channels express a binding site for $(Mg^{2+})_i$, which may modulate the availability or opening of these channels.[124]

Based on the physiological effects of Mg^{2+} on cardiac ion channels, it is obvious that Mg^{2+} influences cardiac impulse formation and conduction and thereby plays a critical role in the pathogenesis and treatment of cardiac arrhythmias. A recent study of 3530 participants from the Framingham Offspring Study showed that low serum Mg^{2+} is moderately associated with the development of atrial fibrillation (AF) in individuals without CVD.[132] The use of intravenous Mg^{2+} in the prevention and treatment of cardiac arrhythmias has been reviewed recently.[133] Some of the important points together with data from some recent clinical trials will be discussed here. Table 3 summarizes the electrophysiological effects of Mg^{2+} on the supraventricular and ventricular conduction pathways.[134–142]

New-onset AF, atrial flutter (AFL), and other atrial tachyarrhythmias occur in 15–50% of patients after cardiac surgery and are associated with increased risk of CHF and stroke, prolonged hospitalization, and increased costs.[143–145] Based on a meta-analysis of randomized, controlled clinical trials (1979 to 2001), the American College of Chest Physicians (ACCP) recommends the use of β-blockers (Vaughn-Williams Class II antiarrhythmic agents) as the first choice for prophylaxis against postcardiac surgery AF, even in patients receiving long-term therapy with β-blockers prior to surgery.[146] Because only 1 of 14 trials evaluating the potential benefit of $MgCl_2$ or $MgSO_4$ in reducing postcardiac surgery AF showed a statistically significant reduction, the ACCP has recommended against the routine use of magnesium for the prevention of AF/AFL following cardiac surgery.[146] However, the 13 trials that produced inconclusive results had several limitations, including postoperative β-blocker withdrawal in some patients and methodological weaknesses, thus making the overall quality of opposing evidence low. The ACCP does recommend that in patients undergoing cardiac surgery, serum Mg^{2+} levels should be maintained within the normal range, perhaps with empiric supplementation, especially because hypomagnesemia has been shown to exacerbate the proarrhythmogenic effect of hypokalemia, another common occurrence in the patient having undergone cardiac surgery.[147]

Several other meta-analyses have shown that intravenous magnesium is indeed an effective and safe strategy for prophylaxis against postcardiac surgery AF and for acute management of rapid AF.[148–150] Vaughn-Williams Class III antiarrhythmic agents such as sotalol, amiodarone, ibutilide, and dofetilide are considered the second-line drugs for prophylaxis against postcardiac surgery AF/AFL

TABLE 3. Electrophysiological Effects of Mg^{2+} on Supraventricular and Ventricular Conduction Pathways

Supraventricular Conduction Pathway	Ventricular Conduction Pathway
↓ automaticity[134]	Suppresses early and delayed after depolarizations[135,136]
↑ sinus node recovery time[137]	Prolongs His-ventricular conduction[138]
↑ intra-atrial and atrioventricular nodal conduction time[139]	Homogenizes transmural ventricular repolarization[140]
↑ atrial and atrioventricular nodal refractory period[137,139]	
Blocks antegrade and retrograde conduction over an accessory pathway[141,142]	

in patients in whom β-blockers are contraindicated. Cagli et al[151] recently showed that combined prophylactic therapy with intravenous low-dose amiodarone and $MgSO_4$ in the early postoperative period is an effective, simple, well-tolerated, and cost-effective regimen for the prevention of postcardiac surgery AF in high-risk, normomagnesemic patients. Similarly, Sleeswijk et al[152] demonstrated that in critically ill patients with new-onset AF, a magnesium-amiodarone stepup regimen reduces the need for amiodarone and effectively converts new-onset AF into sinus rhythm within 24 hours. Lastly, concurrent use of intravenous Mg^{2+} enhances the ability of intravenous ibutilide and dofetilide to successfully convert AF or AFL to sinus rhythm.[153,154] Thus, intravenous Mg^{2+} is an effective adjuvant therapy for AF/AFL for both rate and rhythm control and can act synergistically with the class III antiarrhythmic agents to prevent their proarrhythmogenic effects and reduce the need for potentially harmful antiarrhythmic drugs such as amiodarone.

The use of Mg^{2+} for the treatment of ventricular arrhythmias associated with long QT syndrome (polymorphic ventricular tachycardia/torsades de pointes) and digoxin toxicity is well established.[155,156] Torsades de pointes is a form of ventricular tachycardia associated with a long QT or QTc and is electrocardiographically characterized by twisting of the peaks of the QRS complexes around the isoelectric line.[157] Long QT syndrome can be congenital (eg, Jervell and Lange-Nielsen syndrome) or acquired, caused by drugs such as class Ia and III antiarrhythmic agents and electrolyte abnormalities, including hypokalemia and hypomagnesemia. Mg^{2+} is therefore the drug of choice for suppressing early after-depolarizations and terminating the arrhythmia and is effective even in patients with normal Mg^{2+} levels.[158,159] Figure 2 summarizes the arrhythmogenesis of torsades de pointes and the mechanism of Mg^{2+} in suppressing EADs and terminating torsades de pointes.[160,161]

Digoxin competes with K^+ for the same external site on Na^+/K^+ ATPase, hence the enhancement of digoxin toxicity by hypokalemia. Mg^{2+}-ATP is essential for the normal functioning of Na^+/K^+ ATPase, which is responsible for the active transport of K^+ intracellularly during cardiac action potential.[162,163] Hypomagnesemia therefore leads to depressed activity of Na^+/K^+ ATPase, cellular K^+ depletion, less negative resting membrane potential, prolongation of the QT interval, and enhanced vulnerability to ventricular arrhythmias and digoxin toxicity.[162–165] Therefore, because Mg^{2+} can act as an indirect antagonist of digoxin at the Na^+/K^+ ATPase pump, intravenous Mg^{2+} is an effective treatment for suppression of cardiac arrhythmias caused by digoxin toxicity.

Mg^{2+} abnormalities are common in patients with CHF. CHF patients with hypomagnesemia have more frequent ventricular premature complexes and episodes of ventricular tachycardia than patients with normal serum Mg^{2+} levels.[166] Supplementation with intravenous Mg^{2+} has been shown to cause a significant decrease in the number of ventricular ectopic beats, couplets, and episodes of nonsustained ventricular tachycardia in patients with New York Heart Association class II–IV heart failure.[167,168] Ventricular arrhythmias are common following coronary artery bypass grafting, and their occurrence coincides with the postoperative decline in serum Mg^{2+} levels. Parikka et al[169] showed that correction of the postoperative decline in serum Mg^{2+} concentration decreases the occurrence of early ventricular premature complexes and complex ventricular arrhythmias in coronary artery bypass surgery patients, and the benefit appears to be the greatest in patients with extensive underlying CAD and prior diuretic therapy. Lastly, data from the Magnesium in Cardiac Arrhythmias (MAGICA) trial showed a significant reduction in ventricular premature beats in patients with frequent ventricular arrhythmias (>720 beats/24 h) following a 50% increase in the minimum daily dietary intake of Mg^{2+} and K^+ for 3 weeks, further emphasizing the beneficial effects of Mg^{2+} in the management of ventricular arrhythmias.[170]

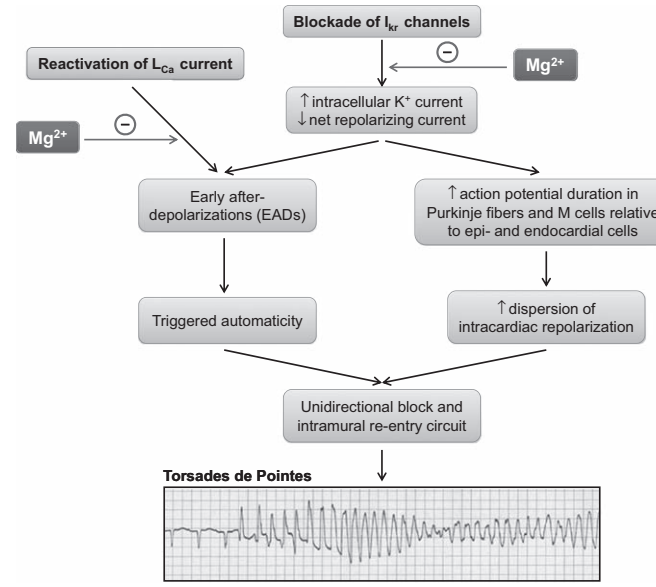

FIGURE 2. Mechanism of action of Mg^{2+} in the treatment of torsades de pointes. Torsades de pointes is thought to result from early depolarizations (EADs) due to blockade of the rapid delayed rectifier K^+ current (I_{Kr}) channel and reactivation of the voltage-dependent L-type Ca^{2+} channels (L_{Ca}) leading to triggered automaticity, unidirectional block, and intramural re-entry circuit. Elevated $(Mg^{2+})_i$ in cardiac myocytes decreases I_{Kr} current. $(Mg^{2+})_i$ also inhibits L_{Ca} by affecting its amplitude, its activation/inactivation kinetics, and its modulation by factors such as phosphorylation. Decreased I_{Kr} current and Ca^{2+} entry via L_{Ca} by Mg^{2+} abolishes EADs and triggered automaticity, thereby terminating the arrhythmia. Adapted with permission from Yap and Camm.[160] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

MAGNESIUM SUPPLEMENTATION

Prior studies suggest that oral Mg^{2+} supplementation is inexpensive, relatively safe, and well tolerated.[171] Pokan et al[172] showed that in 53 male patients with CVD, oral Mg^{2+} therapy (15 mmol twice daily) for 6 months had favorable effects on exercise tolerance and left ventricular ejection fraction during rest and exercise. Similarly, in a study involving 22 symptomatic heart failure patients (New York Heart Association functional class II–III), Fuentes et al[173] demonstrated that oral Mg^{2+} supplementation (800 mg) for 3 months improved small arterial compliance and endothelial function. In a systematic review of 6 studies examining the relationship between Mg^{2+} supplementation and CVD, Mathers and Beckstrand[174] found a modest inverse association between Mg^{2+} supplementation (high Mg^{2+} diet or oral supplementation) and cardiovascular disease risk in men, but not in women. There were no reports of adverse effects from Mg^{2+} supplementation in any of the studies. In patients with normal renal function, hypermagnesemia or Mg^{2+} toxicity is rare. Nonetheless, given the limited data and the recent concerns about the adverse cardiovascular effects of calcium/Vitamin D supplements, it is too premature to advocate for or against routine Mg^{2+} supplementation for primary or secondary prevention of CVD.[175,176] However, increasing Mg^{2+} intake in the diet to maintain high normal serum Mg^{2+} level is critically important and seems more physiologic.

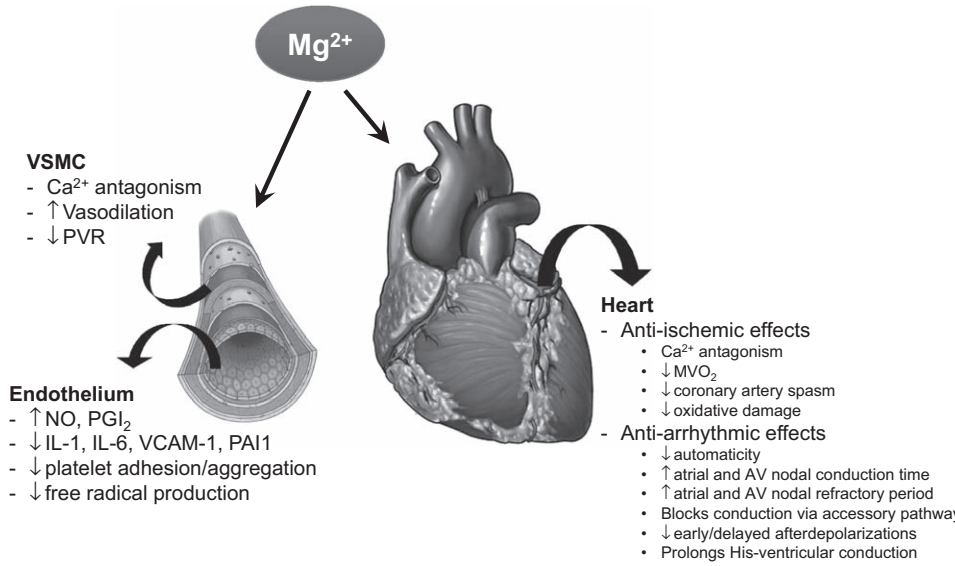

FIGURE 3. Protective effects of magnesium (Mg^{2+}) on vascular smooth muscle cells (VSMC), endothelium and heart. AV indicates atrioventricular; IL-1, interleukin-1; IL-6, interleukin-6; MVO_2, myocardial oxygen consumption; NO, nitric oxide; PAI1, plasminogen activator inhibitor-1; PGI_2, prostacyclin; PVR, peripheral vascular resistance; VCAM-1, vascular cell adhesion molecule-1.

CONCLUSIONS

Mg^{2+} has vasodilatory, anti-inflammatory, anti-ischemic, and antiarrhythmic properties (Fig. 3). It is a critically important nutrient and a potentially useful therapeutic agent in cardiovascular medicine. Several experimental, epidemiological, and clinical studies have established the role of Mg^{2+} in the pathogenesis of cardiovascular disorders. Currently, the use of Mg^{2+} is limited mostly for the prevention and/or treatment of cardiac arrhythmias. We believe that adequate Mg^{2+} intake should be a part of the heart healthy diet. However, there is a compelling need for several well-designed cohort studies to determine the interrelationship among dietary Mg^{2+} intake, serum (or intracellular) Mg^{2+} concentration, and CVD, and to provide concrete evidence on the risks and/or benefits of taking Mg^{2+} supplements. Future basic science research should be focused on gaining a better understanding of the metabolic effects of Mg^{2+} intake in health and disease. Lastly, larger well-designed, randomized controlled trials are needed to widen the therapeutic scope of this inexpensive nutrient.

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