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Magnesium Inhibits the Hypertensive but Not the Cardiotonic Actions of Low-dose Epinephrine

Richard C. Prielipp, M.D., Gary P. Zaloga, M.D.,† John F. Butterworth IV, M.D.,‡ Paul G. Robertie, M.D.,‡ Louise M. Dudas, R.N.,§ Kimberly W. Black, L.A.T.,§ Roger L. Royster, M.D.†*

Intravenous magnesium supplementation is often used to control cardiac arrhythmias and coronary artery vasospasm resulting from disturbances of magnesium homeostasis after coronary artery bypass surgery. Many such patients also require inotropic drug support of depressed myocardial function. However, increased serum magnesium concentrations directly depress cardiac contractility in animals and may interfere with catecholamine actions. To determine whether small intravenous doses of magnesium sulfate ($MgSO_4$) interfere with the cardiotonic actions of epinephrine, we examined the hemodynamic effects of $MgSO_4$ and epinephrine infusion in 17 cardiac surgical patients on their 1st postoperative day in a prospective, controlled study. In 11 patients, infusion of $MgSO_4$ (7-mg $\cdot$ kg^{-1} bolus followed by 10 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} as a continuous infusion) increased serum magnesium concentrations by 44% (mean ± standard error of the mean [SEM] of 0.8 ± 0.1 to 1.2 ± 0.1 mM; $P < 0.01$) but had no significant effect on heart rate; mean arterial, central venous, or pulmonary arterial occlusion pressures; or cardiac output. Epinephrine infusion (30 ng $\cdot$ kg^{-1} $\cdot$ min^{-1}) significantly increased cardiac index (2.7 ± 0.1 to 3.1 ± 0.2 l $\cdot$ min^{-1} $\cdot$ m^{-2}; $P < 0.05$); this effect was not altered by $MgSO_4$ administration (n = 11). However, $MgSO_4$ significantly blunted epinephrine's hypertensive action and prevented a significant increase in mean arterial pressure during concurrent $MgSO_4$-epinephrine administration. Six placebo control patients were given two sequential infusions of epinephrine separated by a placebo infusion to rule out an effect of time on the hemodynamic response to epinephrine. Mean arterial pressure and cardiac index responses to epinephrine were identical before and after placebo infusion. We conclude that infusion of the small doses of $MgSO_4$ after coronary surgery to treat arrhythmias and vasospasm attenuates the vasoconstrictor actions of epinephrine but has no effect on epinephrine's cardiotonic activity. (Key words: Ions: magnesium. Surgery, cardiac. Sympathetic nervous system, catecholamines: epinephrine.)

MAGNESIUM is an essential cofactor for numerous metabolic and enzymatic pathways.[1] Magnesium also plays a vital role in cardiac excitability and vascular smooth muscle tone.[2-5] Serum magnesium concentrations are frequently decreased in critically ill patients,[6] particularly in those who have suffered myocardial infarction[7] or undergone cardiopulmonary bypass.[8,9] In addition, hypomagnesemia is associated with an increased incidence of cardiac arrhythmias[10] and coronary artery vasospasm.[11,12] As a result of its antiarrhythmic effects, intravenous magnesium supplementation has been recommended for the control of ventricular arrhythmias during myocardial infarction[13-18] and after coronary artery bypass graft operations.[9,19]

Magnesium inhibits the passage of calcium ions through voltage-gated calcium-channels and decreases myocardial and smooth muscle contraction.[12,20-24] In addition, magnesium antagonizes the inotropic actions of cardiotonic steroids, norepinephrine, and calcium.[20] It also depresses the action of α_1-adrenergic agonists on vascular smooth muscle[12,21,25] and inhibits the release of endogenous catecholamines from both nerve terminals and the adrenal gland.[24,25] These effects may predispose the patient to hypotension or cardiac insufficiency.

Given the increasing frequency with which magnesium salts are administered to cardiac surgical patients, coadministration of magnesium and inotropic drugs (*e.g.*, epinephrine) in the early postoperative period after separation from cardiopulmonary bypass is likely. However, the cardiovascular consequences of this combination (*i.e.*, epinephrine–magnesium) have not previously been evaluated in humans. We hypothesized that the administration of magnesium in this setting might lead to cardiovascular depression and might attenuate the cardiovascular actions of epinephrine. Thus, this study was designed to answer two questions: 1) Does acute intravenous magnesium affect hemodynamics in cardiac surgery patients? and 2) Does intravenously administered magnesium attenuate hemodynamic responses to epinephrine infusion?

Materials and Methods

After both approval of our protocol by our institutional review board and informed consent were obtained, 17 adult patients (meeting selection criteria) undergoing coronary artery bypass grafting were studied 24–36 h after surgery. Intraoperative anesthesia used a high-dose opioid (fentanyl 50–75 μg $\cdot$ kg^{-1} intravenously), muscle relaxant technique supplemented with benzodiazepines (intravenous midazolam 0.2–0.3 mg $\cdot$ kg^{-1}). Patients' lungs were ventilated with 100% oxygen to maintain nor-

* Assistant Professor of Anesthesia.
† Associate Professor of Anesthesia–Critical Care and Medicine.
‡ Instructor in Anesthesia.
§ Research Associate in Anesthesia.

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Address reprint requests to Dr. Prielipp: Department of Anesthesia, Bowman Gray School of Medicine, 300 South Hawthorne Road, Winston-Salem, North Carolina 27103.

mocapnia. At the time of study, all patients had undergone tracheal extubation, were receiving supplemental oxygen *via* face mask, and were hemodynamically stable in the intensive care unit. Patients retained the pulmonary and peripheral arterial cannulae that had been inserted preoperatively. No patient had required inotropic, vasoactive, antiarrhythmic, or antihypertensive therapy for at least 2 h before the study. Preoperative selection criteria included good ventricular function (left ventricular ejection fraction > 0.5, measured during cardiac catheterization). No patient had significant renal (creatinine > 2 $mg \cdot dl^{-1}$) or hepatic dysfunction or known disorders of calcium or magnesium metabolism (*e.g.*, hyperparathyroidism). Patients receiving long-acting β-blocker antianginal therapy preoperatively were excluded to avoid potential antagonist interaction with epinephrine during the study. This patient population was chosen for study because it was a hemodynamically stable group of patients who were likely to receive magnesium for its antiarrhythmic effects and who had appropriate monitoring catheters in place. We believed it unethical to study hemodynamically unstable patients with a previously untested drug combination.

Study measurements recorded at each time point included heart rate; mean arterial; central venous, mean pulmonary arterial, and pulmonary arterial occlusion pressures; and thermodilution cardiac output in duplicate. Two milliliters of blood were withdrawn at each time point for serum magnesium determinations. Cardiac index, systemic vascular resistance, and pulmonary vascular resistance were calculated by standard formulas. Systolic and diastolic arterial pressures, systolic and diastolic pulmonary artery pressures, heart rate, and lead II ECG were continuously monitored throughout the study, but were recorded only at the time points described below.

After initial baseline measurements, all patients received epinephrine infusions at 10 and 30 $ng \cdot kg^{-1} \cdot min^{-1}$ for 8 min at each dose. We have previously shown this dose of epinephrine significantly increases cardiac index and is a safe dose to administer to postoperative cardiac surgery patients.[26] After infusion of epinephrine at 30 $ng \cdot kg^{-1} \cdot min^{-1}$ was completed, a 15-min washout period allowed all hemodynamic parameters to return to normal. Then a second baseline was obtained. Next, patients received either intravenous magnesium sulfate ($MgSO_4$, 7 $mg \cdot kg^{-1}$ as a bolus over 5 min followed by 10 $mg \cdot kg^{-1} \cdot h^{-1}$ as a continuous infusion, n = 11) or placebo (infusion of 5% dextrose in water at an identical rate to $MgSO_4$, n = 6) through the side-port adapter of the Swan-Ganz introducer. All infusions were regulated by a volumetric infusion controller (IVAC Corporation, San Diego, CA). This dose of $MgSO_4$ was chosen to produce a 33–50% increase in circulating serum magnesium concentrations and has previously been shown to significantly decrease ventricular ectopy.[13–19] Hemodynamic measurements were obtained 10 and 20 min after the start of $MgSO_4$ or placebo. The 20-min time point corresponds to the time point of the third baseline measurement, which immediately preceded the second epinephrine infusion. Lastly, the experimental epinephrine sequence was repeated, with $MgSO_4$ (or placebo) infused with epinephrine at the same dosages and rates as before (10 and 30 $ng \cdot kg^{-1} \cdot min^{-1}$).

Blood specimens for magnesium determinations (drawn simultaneously with the hemodynamic time points noted above) were collected in chilled glass tubes and within 2 h of collection were centrifuged carefully to avoid red cell contamination. Serum magnesium concentrations were analyzed by the metallochromic dye (Calmagite) colorimetric method[27,28] (Sigma Diagnostics, St. Louis, MO). Concentrations are reported in millimolar units.

Data are presented as means ± standard error of the mean (SEM). Patient demographics were compared by chi-squared analysis. Hemodynamics within each group were analyzed by one-factor repeated measures analysis of variance and Dunnett's comparison test of treatment means with a control. Differences between groups were analyzed by two-factor repeated-measures analysis of variance and Student's *t* test, as appropriate. $P < 0.05$ was considered significant.

Results

Seventeen patients completed the study: 11 were $MgSO_4$ infusion patients and 6 placebo control patients. The 17 patients had a mean age of 63 ± 2 yr and good ventricular function (preoperative ejection fraction 57 ± 2%), were predominantly male (15 of 17), and were revascularized with a median of three coronary bypass grafts (range two to five). Preoperative antianginal drug therapy included β-blockers (10 of 17), calcium-channel blockers (15 of 17), and nitrate therapy (14 of 17).

In the 11 patients who received $MgSO_4$, the $MgSO_4$ bolus significantly increased serum concentrations from baseline, 0.8 ± 0.1 to 1.2 ± 0.1 mM ($P < 0.01$). The $MgSO_4$ infusion effectively maintained increased circulating magnesium concentrations throughout the study (final concentration = 1.2 ± 0.2 mM).

$MgSO_4$ administration did not significantly alter blood pressure or cardiac index (fig. 1). Heart rate, mean pulmonary arterial pressure, and cardiac filling pressure also were not changed by the magnesium bolus or infusion (table 1). No patient expressed subjective symptoms or objections to intravenous $MgSO_4$ administration.

In the 11 patients receiving $MgSO_4$, epinephrine infusion at 30 $ng \cdot kg^{-1} \cdot min^{-1}$ significantly increased cardiac index, by 17% (2.7 ± 0.1 to 3.1 ± 0.2 $l \cdot min^{-1} \cdot m^{-2}$, $P < 0.05$), (fig. 2). After $MgSO_4$ administration, epinephrine at 30 $ng \cdot kg^{-1} \cdot min^{-1}$ again increased cardiac index by an equivalent amount (18%; 2.7 ± 0.1 to 3.2 ± 0.2 $L \cdot min^{-1} \cdot m^{-2}$, $P < 0.05$). There was no significant dif-

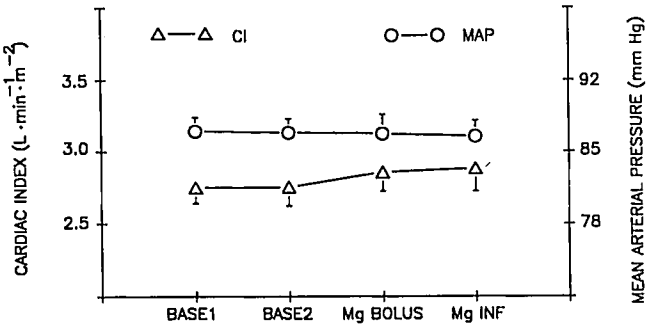

FIG. 1. Comparison of cardiac index and mean arterial pressure in 11 postoperative cardiac surgery patients after administration of intravenous $MgSO_4$. Mg BOLUS denotes 7 $mg \cdot kg^{-1}$ as a bolus over 5 min; Mg INF denotes 10 $mg \cdot kg^{-1} \cdot h^{-1}$ as a continuous intravenous infusion. No significant changes in hemodynamics were found.

ference in epinephrine's effect on cardiac index before or after the $MgSO_4$ infusion. Though this dose of epinephrine did not induce a chronotropic response (heart rate was not changed, table 2), a β_1-adrenergic effect was evident by the significant increase in stroke volume both before and after $MgSO_4$ administration (table 2). Statistical power analysis indicates that our study would detect a difference in cardiac index of 0.5 $l \cdot min^{-1} \cdot m^{-2}$ with 90% power at the 95% significance level.

Epinephrine infusion at 30 $ng \cdot kg^{-1} \cdot min^{-1}$ also significantly increased mean arterial pressure by 9% (84 ± 3 mm Hg to 91 ± 2 mm Hg, $P < 0.01$). After $MgSO_4$ infusion, epinephrine infusion did not significantly increase mean arterial pressure (fig. 3). The difference in mean arterial pressure response to epinephrine before and after $MgSO_4$ administration was statistically significant at the 30 $ng \cdot kg^{-1} \cdot min^{-1}$ infusion rate. Epinephrine infusion alone did not change systemic vascular resistance. Systemic vascular resistance measured during coadministration of $MgSO_4$ and epinephrine 30 $ng \cdot kg^{-1} \cdot min^{-1}$ was significantly less than at the second baseline measurement (table 2), consistent with magnesium's inhibition of epinephrine's hypertensive actions. Concurrent administration of $MgSO_4$ and epinephrine produced no significant changes in mean pulmonary arterial, central venous, or pulmonary arterial occlusion pressure or pulmonary vascular resistance (table 2).

Hemodynamic parameters of the six time-control patients (placebo infusion instead of $MgSO_4$) are summarized in table 3. Cardiac index increased 19% after the first epinephrine infusion and 26% after the second infusion of epinephrine. The increase in cardiac index was statistically indistinguishable between the two infusions. The two infusions of epinephrine were also characterized by similar increases of stroke volume and mean arterial pressure. Cardiac filling pressures (pulmonary arterial occlusion and central venous pressures) and calculated vascular resistances (systemic and pulmonary) were similar during both epinephrine infusions. There was a trend ($P = 0.08$) for heart rate to increase to a greater extent during the second epinephrine exposure.

Discussion

Magnesium has been used for many years to control hypertension and seizures in pregnancy-induced hypertension[29-31] and is increasingly recommended for treatment of cardiac arrhythmias and coronary vasospasm after cardiopulmonary bypass surgery[9,19] and myocardial infarction.[13-18] After cardiac surgery, inotropic support of the failing myocardium is often required simultaneously with antiarrhythmic therapy. Ours is the first study to describe the cardiovascular effects of concurrent administration of epinephrine and magnesium in humans. In this study, the acute administration of antiarrhythmic doses of $MgSO_4$ had no significant effects on hemodynamics in cardiac surgery patients. However, prior ad-

TABLE 1. Comparison of Hemodynamic Parameters of 11 Postoperative Cardiac Surgery Patients before and after Magnesium Administration

Hemodynamic Parameters	Base 1	Base 2	Magnesium Bolus	Magnesium Infusion
HR (beats per min)	86 ± 2	86 ± 3	85 ± 2	84 ± 2
MAP (mmHg)	84 ± 3	84 ± 3	83 ± 4	83 ± 3
MPAP (mmHg)	23 ± 2	24 ± 2	23 ± 2	23 ± 1
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.7 ± 0.1	2.7 ± 0.1	2.8 ± 0.1	2.9 ± 0.2
SV ($ml \cdot beat^{-1}$)	63 ± 4	62 ± 4	65 ± 4	66 ± 4
CVP (mmHg)	13 ± 2	13 ± 2	12 ± 1	13 ± 1
PAOP (mmHg)	13 ± 2	13 ± 2	13 ± 2	12 ± 2
Rs ($dyne \cdot s \cdot cm^{-5}$)	1100 ± 70	1180 ± 70	1060 ± 40	1060 ± 60
Rp ($dyne \cdot s \cdot cm^{-5}$)	150 ± 20	180 ± 30	130 ± 20	140 ± 20
[Mg] ($mM \cdot l^{-1}$)	0.8 ± 0.1	0.8 ± 0.1	1.2 ± 0.1*	1.2 ± 0.1*

Magnesium administration: $MgSO_4$ 7 $mg \cdot kg^{-1}$ as a bolus followed by 10 $mg \cdot kg^{-1} \cdot h^{-1}$ as a continuous infusion.

* $P < 0.01$ compared to base 1 and base 2.

HR = heart rate; MAP = mean systemic arterial pressure; MPAP = mean pulmonary arterial pressure; CI = cardiac index; SV = stroke volume, CVP = central venous pressure; PAOP = pulmonary artery occlusion pressure; Rs = systemic vascular resistance, Rp = pulmonary vascular resistance, [Mg] = serum magnesium concentration. Base 1 is before the first epinephrine infusion; base 2 is following a 15-min washout period after the first epinephrine infusion.

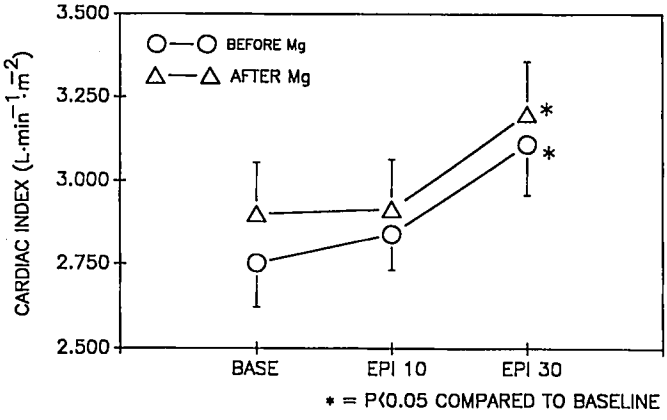

FIG. 2. Comparison of cardiac index in 11 postoperative cardiac surgery patients before and after magnesium administration during concurrent epinephrine infusion at 10 and 30 ng·kg^{-1}·min^{-1}. Cardiac index significantly increased compared to baseline both before and after magnesium administration.

ministration of $MgSO_4$ blunted the hypertensive response to epinephrine administration while preserving epinephrine's cardiotonic properties (increased cardiac index and stroke volume). The blunted hypertensive response seen during $MgSO_4$–epinephrine coadministration appears *not* to be the result of a time effect on the response to epinephrine. The six placebo patients demonstrated identical increases in mean arterial pressure and cardiac index during the two sequential epinephrine infusions. Thus, the altered response to epinephrine we ascribe to $MgSO_4$ coadministration was unlikely to have been induced by adrenergic receptor changes, adrenergic uncoupling, or other reflex changes theoretically possible during repeated exposure to β-agonists.

Our magnesium study patient population (n = 11) limits the statistical power to exclude *any* effect of $MgSO_4$ administration on the hemodynamic variables studied (table 1). Power analyses (of 90%, $\beta = 0.10$) at a 95% level of significance to detect a 10% change in heart rate, mean arterial pressure, and cardiac index would require 19, 17, and 28 patients respectively. Additional subjects would be required to ensure lack of *any* hemodynamic effect of this dose (and rate) of $MgSO_4$ administration to postoperative cardiopulmonary bypass graft patients.

Epinephrine infusion at 30 ng·kg^{-1}·min^{-1} increased cardiac index, stroke volume, and blood pressure (table 2). We have found this dose of epinephrine increases cardiac index 17–30%[26] and increases mean arterial pressure 7–9 mmHg.[26] We believe that these changes reflect epinephrine's cardiotonic and vasopressor activity. Nonetheless, calculated resistance (systemic) did not change during epinephrine infusion (before $MgSO_4$ administration) because the magnitude of increase in both cardiac index and mean arterial pressure was similar. Epinephrine used in this dose range may show primarily a β effect.

TABLE 2. Comparison of Hemodynamic Parameters of 11 Postoperative Cardiac Surgery Patients Following Epinephrine Infusion before and after Magnesium Administration

Hemodynamic Parameters	Before Magnesium Administration			During Magnesium Administration		
	Base 1	Epinephrine 10	Epinephrine 30	Base 2	Epinephrine 10	Epinephrine 30
HR (beats per min)	86 ± 2	84 ± 2	88 ± 3	86 ± 3	86 ± 2	86 ± 3
MAP (mmHg)	84 ± 3	87 ± 3	91 ± 2*	84 ± 3	87 ± 3	86 ± 3†
MPAP (mmHg)	23 ± 2	24 ± 1	25 ± 1	24 ± 2	24 ± 1	25 ± 1
CI (l·min^{-1}·m^{-2})	2.7 ± 0.1	2.8 ± 0.1	3.1 ± 0.2*	2.7 ± 0.1	2.9 ± 0.1	3.2 ± 0.2*‡
SV (ml·beat^{-1})	62 ± 4	65 ± 3	69 ± 4*	62 ± 4	66 ± 4	70 ± 4‡
CVP (mmHg)	13 ± 2	13 ± 2	14 ± 2	13 ± 2	12 ± 1	12 ± 1
PAOP (mmHg)	13 ± 2	13 ± 2	15 ± 2	13 ± 2	13 ± 2	13 ± 2
Rs (dyne·s^{-1}·cm^{-5})	1100 ± 70	1100 ± 60	1080 ± 60	1180 ± 70	1090 ± 60	1000 ± 50*
Rp (dyne·s^{-1}·cm^{-5})	150 ± 20	160 ± 20	140 ± 20	180 ± 30	150 ± 20	150 ± 20
[Mg] (mM)	0.8 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	1.3 ± 0.1*†	1.2 ± 0.2*†
				1.2 ± 0.1†		

Base 1 is before the first epinephrine infusion; base 2 is following a 15-min washout period after the first epinephrine infusion; base 3 is after the magnesium bolus and infusion, and corresponds to magnesium infusion values in table 1. Epinephrine infusions are 10 and 30 ng·kg^{-1}·min^{-1}.

Hemodynamic parameter abbreviations: see Table 1.

* $P < 0.05$ compared to base 2.

† $P < 0.05$ compared to corresponding time period before magnesium.

‡ $P < 0.05$ compared to base 3.

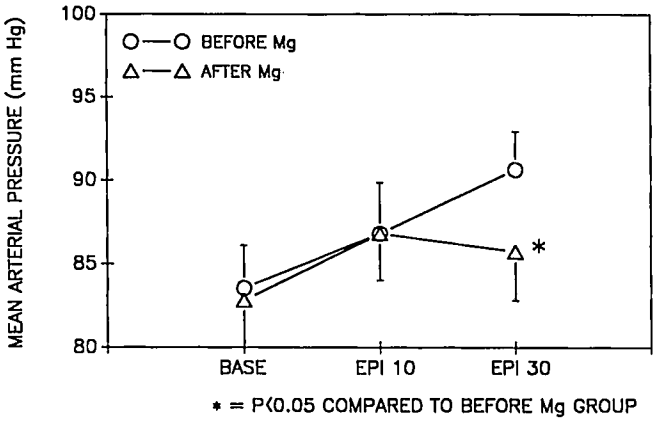

FIG. 3. Comparison of mean arterial pressure in 11 postoperative cardiac surgery patients before and after magnesium administration following concurrent epinephrine infusion at 10 and 30 $ng \cdot kg^{-1} \cdot min^{-1}$. Administration of magnesium significantly blunted the hypertensive response to epinephrine infusion.

Higher doses of epinephrine would likely demonstrate large increases in systemic vascular resistance as epinephrine's vasoconstrictor (α-adrenergic) activity overwhelmed the cardiotonic effects (*i.e.*, the increase in mean arterial pressure would be much larger than the increase in cardiac index). The low-to-moderate dose of epinephrine used in this study may also account for the lack of heart rate changes during epinephrine infusion (table 2). While 10 of 17 patients were receiving preoperative β-blocker therapy, we do not believe that residual β-blockade blunted epinephrine's activity because there was a minimum of 30 h (more than four half-lives of most β-blockers) between the last β-blocker dose and our hemodynamic study.

Abnormally high concentrations of extracellular magnesium (5–20 times higher than those used in this study) directly depress myocardial contractility. Kafiluddi *et al.* found that magnesium elicited a concentration-dependent negative inotropic effect in isolated guinea pig cardiac muscle.[20] Developed tension was inhibited by 50% at a magnesium concentration of 6.4 mM and inhibited the inotropic actions of norepinephrine and calcium in isolated cardiac muscle.[20] Paddle and Haugaard found similar depressant effects in a rat isolated cardiac muscle preparation, with 20 mM magnesium resulting in 85% depression of the contractile response.[32] Restoration of myocardial contractility was achieved, however, after epinephrine infusion ($5\ \mu g \cdot min^{-1}$) to the perfused rat heart. Levin *et al.* also studied the effect of magnesium on the metabolic effects of epinephrine in isolated rat hearts.[33] Although magnesium inhibited the high-energy phosphate degradation that normally follows epinephrine infusion, there was no apparent inhibition of epinephrine stimulation of myocardial contractility in their study, even at magnesium concentrations as high as 20 mM. Thus, high concentrations of magnesium alone manifest negative inotropic effects in the isolated myocardium. However, the cardiotonic actions of epinephrine on myocardial contractility are not inhibited even in the presence of significantly elevated magnesium serum levels.

DiPette *et al.* reported no significant effect of magnesium infusion (serum concentrations of 1.5–2.0 mM) on cardiac index, blood pressure, or heart rate in normotensive rats.[34] Mroczek *et al.* found no effect of magnesium on blood pressure in normotensive human subjects.[35] While James *et al.* reported a dose-dependent reduction in systemic vascular resistance in baboons given $MgSO_4$,[22] arterial blood pressure was minimally affected by serum magnesium concentrations below 5 mM. Kelly *et al.* administered $MgSO_4$ to normotensive and hypertensive subjects.[36] Arterial blood pressure decreased and heart rate increased after large doses of intravenous magnesium (8 g $MgSO_4$ over 1 h, with magnesium concentrations reaching 3.5 mM). We found no significant effects of

TABLE 3. Hemodynamic Parameters of Six Postoperative Cardiac Surgery Patients during Two Sequential Epinephrine Infusions Before and After Placebo Administration

	Before Placebo Administration			After Placebo Administration		
Hemodynamic Parameters	Base 1	Epinephrine 10	Epinephrine 30	Base 3	Epinephrine 10	Epinephrine 30
HR (beats per min)	81 ± 4	80 ± 4	82 ± 3	81 ± 3	81 ± 3	85 ± 2
MAP (mmHg)	83 ± 2	87 ± 1	90 ± 2*	84 ± 2	91 ± 2*	91 ± 2*
MPAP (mmHg)	19 ± 3	20 ± 3	22 ± 3*	20 ± 3	21 ± 3	22 ± 3*
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.7 ± 0.2	2.9 ± 0.2	3.2 ± 0.2*	2.7 ± 0.2	2.9 ± 0.2	3.4 ± 0.2*
SV ($ml \cdot beat^{-1}$)	71 ± 6	76 ± 5	80 ± 3*	71 ± 6	75 ± 5	83 ± 5*
CVP (mmHg)	11 ± 2	11 ± 1	11 ± 1	9 ± 2	9 ± 2	10 ± 2
PAOP (mmHg)	9 ± 2	9 ± 2	9 ± 2	11 ± 1	10 ± 2	11 ± 2
Rs ($dyne \cdot s \cdot cm^{-5}$)	1,080 ± 90	1,070 ± 70	990 ± 60	1,110 ± 100	1,110 ± 90	940 ± 80*
Rp ($dyne \cdot s \cdot cm^{-5}$)	150 ± 30	150 ± 30	170 ± 30	140 ± 30	160 ± 30	140 ± 30

Base 1 is before the first epinephrine infusion; base 3 is immediately before the second epinephrine infusion. Epinephrine infusions are 10 and 30 $ng \cdot kg^{-1} \cdot min^{-1}$.

Hemodynamic parameters abbreviations: see table 1.
* $P < 0.05$ compared to corresponding baseline.

modest $MgSO_4$ doses on arterial pressure, heart rate, or cardiac output in postoperative cardiac surgery patients. Overall, data from numerous studies suggest that moderate doses of magnesium salts, which produce circulating magnesium concentrations of 1.2–1.6 mM, have no detrimental hemodynamic effects.

Alterations in magnesium concentration may directly alter vascular smooth muscle tone.[4] Hypomagnesemia increases vascular smooth muscle tone while hypermagnesemia decreases vascular tone.[4,5] Altura and Altura have attempted to define the underlying mechanism of magnesium-induced vasodilation. They hypothesized that acute changes in extracellular magnesium concentrations alter smooth muscle calcium permeability, binding, and translocation.[5,37] Thus, by reducing calcium entry into smooth muscle, magnesium may attenuate contractility and diminish vascular tone.

Low magnesium concentrations may also potentiate the contractile response of both small and large arteries to vasoconstrictors (*i.e.*, norepinephrine or angiotensin II).[11] Hypermagnesemia, in contrast, directly relaxes vascular smooth muscle,[4,5,33] inhibits the vasoconstrictor effects of norepinephrine,[4] and inhibits catecholamine release after intense sympathetic stimulation.[38] James successfully used repeated doses (2.5 g) of intravenous magnesium to control blood pressure in a patient with pheochromocytoma after α_1- and β_1-adrenergic blockers were found unable to restore adequate cardiovascular control.[39] We found that $MgSO_4$ blunts the vasoconstrictor activity of epinephrine in postoperative patients. Our study confirms the findings of James *et al.*, who infused very high doses of epinephrine ($1\ \mu g \cdot kg^{-1} \cdot min^{-1}$) in baboons, increasing blood pressure by 50% and decreasing cardiac output by 20%.[22,40] Simultaneous magnesium administration ($60\ mg \cdot kg^{-1}$) attenuated the increase in systemic arterial pressure, augmented cardiac output, and abolished epinephrine-induced cardiac arrhythmias. We have previously investigated the interaction of calcium on epinephrine's adrenergic effects in postoperative cardiac surgery patients.[26] Calcium antagonized the action of epinephrine on cardiac β_1-1 receptors (cardiac index) and hepatic β_1-2 receptors (*i.e.*, glucose regulation). Calcium administration alone significantly increased arterial pressure but had no effect on cardiac index. After calcium administration, epinephrine at $30\ ng \cdot kg^{-1} \cdot min^{-1}$ did not increase cardiac index or mean arterial blood pressure.[26] Calcium has previously been shown to attenuate the hypertensive actions of epinephrine in animals.[41,42] In addition, calcium inhibited the constrictor response to norepinephrine in the isolated ear artery of the rabbit[43] and the brachial artery of the dog.[44] Thus, while both magnesium and calcium similarly attenuate the α_1-adrenergic-mediated vasoconstrictor activity of epinephrine, they manifest different effects on epinephrine's β_1-adrenergic-mediated effects (cardiac output). While calcium attenuates epinephrine-induced increases in cardiac output, magnesium does not change epinephrine's effects on cardiac output.

Magnesium plays a critical role in the regulation of cardiac excitability. Hypomagnesemia is common in postoperative and other critically ill patients and predisposes to cardiac arrhythmias.[10–12] Magnesium administration has been shown to reduce the incidence of arrhythmias in patients after myocardial infarction[12–16] and cardiopulmonary bypass.[9,19] We have had good results suppressing arrhythmias with $MgSO_4$ after cardiopulmonary bypass. Magnesium may influence the incidence of arrhythmias by a direct myocardial effect, a direct or indirect effect on cellular potassium and sodium concentrations, antagonism of calcium entry into the cell, prevention of coronary artery vasospasm, antagonism of catecholamine action, and improvement of the myocardial oxygen supply–demand ratio.[21,45,46]

Our study suggests that $MgSO_4$ administration ($7\ mg \cdot kg^{-1}$ as a bolus over 5 min followed by a $10\ mg \cdot kg^{-1} \cdot h^{-1}$ infusion) has no adverse cardiovascular effects in postoperative patients with good baseline ventricular function. Magnesium has previously been shown to significantly decrease ventricular arrhythmias.[18–19] Additional human studies are required to determine whether similar results would be found in patients with depressed preoperative ventricular function or in patients with significant postoperative myocardial dysfunction secondary to reperfusion injury ("stunning") immediately after cardiopulmonary bypass. The $MgSO_4$–epinephrine interaction identified in the current study may be of therapeutic benefit. The combination of epinephrine and magnesium augmented cardiac output while decreasing systemic vascular resistance. The interaction between magnesium and epinephrine may enhance overall myocardial performance while minimizing any increase in myocardial oxygen demand and thereby enhance epinephrine's performance as an inotropic agent.

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