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Effects of Magnesium Chloride on Cardiovascular Hemodynamics in the Neurally Intact Dog

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ABSTRACT

To assess the cardiovascular actions of magnesium in neurally intact animals, magnesium chloride (1–4 mM/min) administered i.v., producing a peak arterial magnesium level between 4.7 and 7.2 mg/dl, was given to α-chloralose-anesthetized, open-chest dogs. Magnesium lowered heart rate by 36 ± 11 beats/min ($P < .05$), cardiac output by 0.7 ± 0.2 liters/min ($P < .05$), left ventricular (LV) peak *dP/dt* by 410 ± 96 mm Hg/sec ($P < .05$) and aortic and pulmonary artery pressures, but it did not change LV end-diastolic pressure, systemic resistance or pulmonary resistance. Coronary blood flow also decreased by 39 ± 11% ($P < .05$), myocardial oxygen consumption by 88 ± 22% ($P < .05$) and myocardial oxygen extraction by 53 ± 16% ($P < .05$). When heart rate was held constant, magnesium still decreased LV systolic pressure, LV peak *dP/dt* and coronary blood flow. The increase in serum magnesium was accompanied by an increase in serum calcium (by 1.4 ± 0.2 mg/dl; $P < .05$) and a fall in serum potassium (by 0.21 ± 0.1 mEq/l), but not by a change in serum sodium, myocardial electrolyte arteriovenous differences or arterial pH. Thus, at blood concentrations that are observed in humans after therapeutic dosages of magnesium, a depression of cardiac performance is observed in the anesthetized dog. Although magnesium produces a fall in coronary blood flow, this appears to be due at least in part to a decrease in myocardial oxygen requirements because myocardial oxygen extraction also decreases. Rapid changes in serum electrolytes accompany these hemodynamic effects.

Magnesium salts have vasodilating actions (Altura, 1982; Altura and Altura, 1985). Because magnesium also influences myocardial contraction (Shine, 1979) and neural transmission (Stanbury, 1948), its cardiovascular actions in intact animals may vary with experimental conditions. Although hypotension is generally observed after magnesium administration (Hoff *et al.*, 1939; Kelly *et al.*, 1960; Maxwell *et al.*, 1965; Mroczek *et al.*, 1977; Engbaek, 1952; Scott *et al.*, 1961), the effects of this cation on cardiac output (Maxwell *et al.*, 1965; Mroczek *et al.*, 1977; Engbaek, 1952) and coronary blood flow (Maxwell *et al.*, 1965; Scott *et al.*, 1961; Bass *et al.*, 1958) are less clear. Accordingly, to clarify the cardiovascular effects of magnesium, hemodynamic measurements were made in dogs during an i.v. infusion of magnesium chloride. To examine the effects of different concentrations, two rates of infusion were used. Because magnesium may slow heart rate, experiments with rate held constant were also performed. The changes in hemodynamics and coronary blood flow and myocardial energetics were related to concomitant arterial and coronary sinus electrolytes.

Methods

Preparation. Mongrel dogs weighing 20 to 35 kg were anesthetized with α-chloralose (100 mg/kg i.v.). A midline thoracotomy was performed, and the heart was suspended in a cradle. Body temperature was maintained by heating pads and monitored by intravascular thermistors. pH and arterial oxygen saturation were measured throughout the experiment and steady-state conditions controlled by adjustments in respiratory rate and periodic lung expansion.

Measurements. Fluid-filled catheters were positioned in the aorta and pulmonary artery, and a Millar catheter-tipped micromanometer was positioned in the left ventricle through an apical cannula and calibrated *in vivo* with a fluid-filled catheter system. Pressures were examined from fluid-filled catheters with a P23dB strain gauge, with zero reference taken as the midchest. A Swan Ganz thermodilution catheter (American Edwards Laboratory) was positioned in the pulmonary artery for recording pressures and measuring cardiac output (Brathwaite and Bradley, 1968). Cardiac output was taken as the mean of the computed values (American Edwards Laboratory, Santa Ana, CA) obtained in triplicate after bolus injections of ice-cold saline in the right atrium. The coefficient of variation for this method has an average value of 2%. Electrodes were attached to the right atrium and right ventricle for atrial pacing and recording local electrograms. Through an incision in the right atrial appendage, a special catheter with distal thermistors (Wilton Webster Laboratories, Altadena, CA) was positioned and firmly secured in the coronary sinus at the obtuse margin of the left ventricle, which was used to measure coronary sinus blood flow by the Ganz method (Ganz *et al.*, 1971) and to aspirate blood. In this position, a bolus of ice-cold saline in the right atrium produced no change in temperature of the coronary sinus thermistors,

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ABBREVIATION: LV, left ventricular.

demonstrating that these thermistors were not influenced by atrial reflux (Mathey *et al.*, 1978). Vascular resistances were calculated as mean arterial pressure divided by blood flow and were expressed as millimeters of mercury per unit of flow. Concurrent arterial and coronary sinus blood samples were assayed for sodium, potassium, chloride, magnesium, calcium and phosphate. Sodium, potassium and chloride were measured by flame photometry, magnesium and calcium by sensitive colorimetric methods (Dito, 1976; Gindler and Heth, 1971) and phosphate by the ammonium molybdate method (Tietz, 1976).

Protocol. After a 15-min control period in which steady-state hemodynamics were demonstrated, $MgCl_2$ was administered i.v.; 1 mM/min was given for 10 min, followed by 4 mM/min for 10 min. If marked changes in hemodynamics were produced by the low infusion, the higher dosage was not given. Hemodynamic measurements were begun at 5 min of each infusion; blood samples were obtained just before and after each infusion.

In five dogs, measurements were made with atrial rate fixed at 10 to 20 beats above the control spontaneous rate. $MgCl_2$ (1 mM/min) was then administered for 10 min.

Statistical analysis. Data were analyzed by the Student's *t* test for paired data, using Dunnett's table (Dunnett, 1964). Data are expressed as the means ± S.E.M. $P < .05$ was considered statistically significant.

Results

The magnesium chloride infusion increased arterial magnesium concentration from an average control value of 1.1 ± 0.6 mg/dl to a peak concentration of 5.8 ± 0.4 mg/dl, which produced marked hemodynamic, coronary blood flow and electrolyte changes. The hemodynamic findings are shown in table 1. Heart rate decreased by 36 ± 11 beats/min ($P < .05$), and atrioventricular conduction time lengthened by 18 ± 5.6 msec ($P < .05$). LV, aortic and pulmonary artery pressures decreased, but LV end-diastolic pressure did not change. LV peak *dP/dt* also decreased by 410 ± 86 mm Hg/sec ($P < .05$) and cardiac output by 0.7 ± 0.2 liters/min ($P < .05$). However, pulmonary and systemic resistances did not change.

Coronary blood flow and myocardial energetics at peak magnesium concentrations are shown in Table 2. Coronary blood flow decreased by 39 ± 14% ($P < .05$), but myocardial oxygen consumption decreased by 88 ± 22% ($P < .05$), resulting in a 53 ± 16% ($P < .05$) reduction in myocardial oxygen extraction. Coronary resistance did not change (from 0.9 ± 0.1 to 0.9 ± 0.2 mm Hg/l/min).

TABLE 1

Hemodynamic findings at peak magnesium concentration

Values are mean ± S.E.M.; $n = 10$ dogs. HR, heart rate; AVCT, atrioventricular conduction time; LVSP, LV systolic pressure; LVEDP, LV end-diastolic pressure; Aod, aortic diastolic pressure; Aom, aortic mean pressure; PAs, pulmonary artery systolic pressure; PAd, pulmonary artery diastolic pressure; PAm, pulmonary artery mean pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; Ao, aorta; PA, pulmonary artery.

	Control	$MgCl_2$
HR (beats/min)	149 ± 10	113 ± 9*
AVCT (msec)	107 ± 7	125 ± 7*
LVSP (mm Hg)	133 ± 6	106 ± 4*
LVEDP (mm Hg)	12.7 ± 1	12.3 ± 1
Aod (mm Hg)	102 ± 7	75 ± 5*
Aom (mm Hg)	115 ± 6	85 ± 5*
PAs (mm Hg)	34 ± 3	29 ± 2*
PAd (mm Hg)	16.7 ± 1	15.7 ± 1*
PAm (mm Hg)	23 ± 1	20 ± 1*
LV peak *dP/dt* (mm Hg/sec)	1391 ± 84	982 ± 114*
CO (liters/min)	2.9 ± 0.3	2.2 ± 0.3*
SVR (mm Hg/l/min)	41 ± 4	41 ± 4
PVR (mm Hg/l/min)	3.3 ± 0.6	3.5 ± 0.9
pH	7.36 ± 0.02	7.36 ± 0.02
Ao oxyhemoglobin saturation (%)	92 ± 1	90 ± 2
PA oxyhemoglobin saturation (%)	69 ± 2	72 ± 2

*$P < .05$.

TABLE 2

Coronary flow and energetics at peak magnesium concentration

Values are mean ± S.E.M.; $n = 10$ dogs. CBF = coronary sinus blood flow; MVO_2, myocardial oxygen consumption; CS, coronary sinus; AO-CS, myocardial oxygen extraction.

	Control	$MgCl_2$
CBF (ml/min)	142 ± 15	108 ± 13*
MVO_2 (ml/min)	7.3 ± 1.2	4.1 ± 0.6*
CS oxyhemoglobin saturation (%)	53 ± 2	62 ± 2*
AO-CS oxyhemoglobin saturation (%)	37 ± 3	26 ± 3*

*$P < .05$.

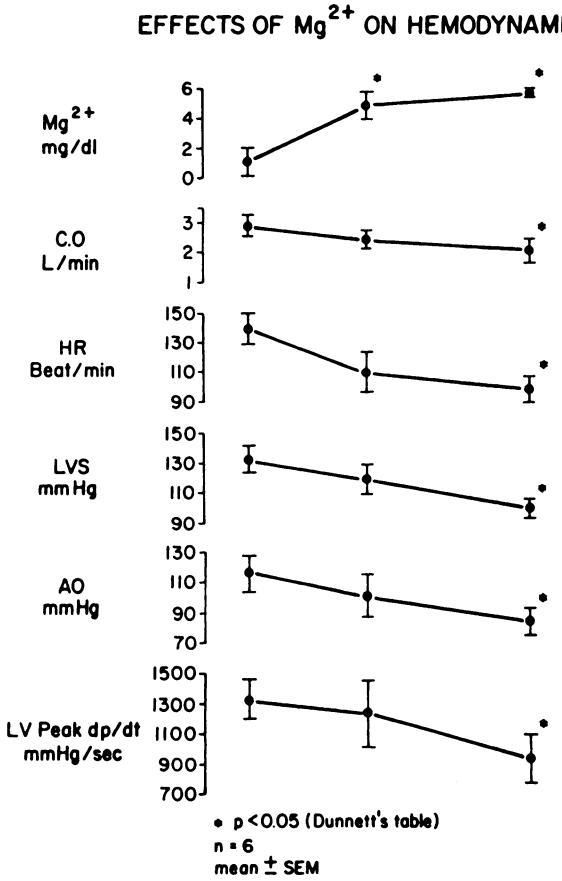

Fig. 1. The hemodynamic findings produced by $MgCl_2$ infusion. Statistically significant changes were evident at the higher Mg concentration. CO, cardiac output; HR, heart rate; LVS, LV systolic pressure; AO, mean aortic pressure.

Figures 1 and 2 display the hemodynamic and coronary blood flow findings at two arterial magnesium concentrations. Although at a concentration of 4.9 ± 0.9 mg/dl there was a tendency toward a lower heart rate, LV systolic pressure, cardiac output and LV peak *dP/dt*, only at a concentration of 5.8 ± 0.6 mg/dl was a significant reduction of these variables observed. Even though a reduction in coronary blood flow was also observed only at the higher arterial magnesium concentration, the decrements in both myocardial oxygen consumption and myocardial oxygen extraction were already evident at the lower values.

In five dogs, atrial rate was held constant at 160 ± 11 beats/min. At an average arterial magnesium concentration of 4.9 ± 0.8 mg/dl, LV systolic pressure decreased by 28 ± 9 mm Hg (P

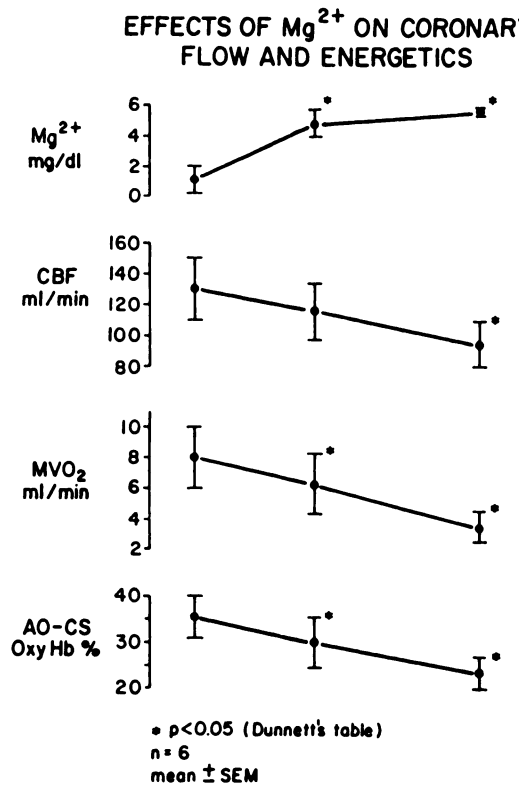

Fig. 2. The coronary flow findings produced by $MgCl_2$ infusion. Changes of myocardial oxygen consumption (MVO_2) and myocardial oxygen extraction (AO-CS Oxy Hb) were evident before those of coronary blood flow (CBF).

TABLE 3

Effects of magnesium on hemodynamics with heart rate controlled

Values are mean ± S.E.M.; n = 5 dogs. HR, heart rate; LVSP, LV systolic pressure; LVEDP, LV end-diastolic pressure; Aom, aortic mean pressure; CO, cardiac output.

	Control	$MgCl_2$
HR (beats/min)	160 ± 11	160 ± 11
LVSP (mm Hg)	134 ± 11	106 ± 5*
LVEDP (mm Hg)	14 ± 1	13 ± 1
Aom (mm Hg)	114 ± 12	88 ± 8
LV peak *dP/dt* (mm Hg/sec)	1559 ± 118	1031 ± 166*
CO (liters/min)	3.0 ± 0.5	2.4 ± 0.5

*P < .05.

TABLE 4

Effects of magnesium on hemodynamics with heart rate controlled

Values are mean ± S.E.M.; n = 5. CBF, coronary sinus blood flow; MVO_2, myocardial oxygen consumption; CS, coronary sinus; AO-CS, myocardial oxygen extraction.

	Control	$MgCl_2$
CBF (ml/min)	150 ± 19	108 ± 22*
MVO_2 (ml/min)	10.8 ± 3.3	6.5 ± 1.3
CS oxyhemoglobin saturation (%)	56 ± 6	61 ± 6
AO-CS oxyhemoglobin saturation (%)	39 ± 4	33 ± 5

*P < .05.

< .05), and LV peak *dP/dt* by 527 ± 196 mm Hg/sec (P < .05) (table 3). Coronary blood flow also decreased by 30 ± 9% (P < .05) (table 4). Although the changes in myocardial oxygen consumption and myocardial oxygen extraction paralleled those observed in spontaneously beating hearts, these changes did not reach statistical significance (Table 4).

The effects of magnesium on blood electrolytes are displayed in figure 3. The elevation of arterial magnesium by 4.7 ± 0.3

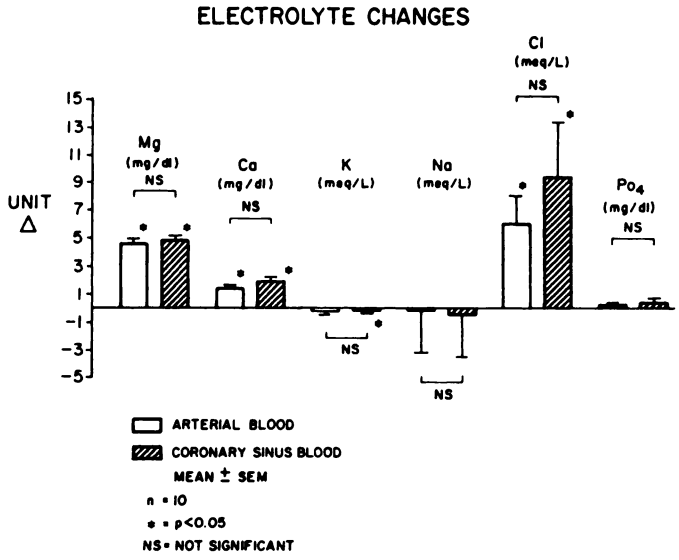

Fig. 3. Summary of blood electrolyte changes occurring after $MgCl_2$ infusion. A statistically significant increment of Mg, Ca and Cl and a decrease of K occurred, but no differences between the arterial and coronary sinus blood concentrations of these electrolytes were found.

mg/dl (P < .05) was accompanied by an elevation in arterial calcium of 1.4 ± 0.2 mg/dl (P < .05) and in arterial chloride of 6.1 ± 1.9 mEq/l (P < .05), but by a fall in arterial potassium of 0.2 ± 0.1 mEq/l. Arterial sodium and phosphate concentrations did not change. Also, there were no differences between arterial and coronary sinus electrolyte values either before or after the magnesium infusion.

Discussion

The present study demonstrates that magnesium has marked effects on cardiac performance in intact dogs at blood levels that are reached in humans after therapeutic administration of magnesium salts. Despite the vasodilating actions of magnesium that have been found in isolated canine and rat blood vessels (Altura, 1982; Altura and Altura, 1985), in our experiments a fall in aortic and pulmonary pressures was observed that could not be explained by changes in vascular resistances. Although slowing of heart rate was also observed, this too would not explain entirely the changes in cardiac performance because changes in cardiac function occurred after magnesium administration even with rate held constant. Also, before a change in cardiac function was evident, myocardial oxygen consumption had fallen significantly. These cardiovascular effects were accompanied by immediate and pronounced changes in blood electrolytes. As blood magnesium increased, blood calcium also increased, but blood potassium decreased. However, an effect on myocardial electrolytes, which might be reflected by a difference between aortic and coronary sinus concentrations, was not observed.

Magnesium slowed heart rate and atrioventricular conduction. These effects have been shown not to be blocked by atropine (Dellen and Miller, 1939). Although the sympatholytic actions of magnesium (Stanbury, 1948) might contribute to this response, the effects are consistent with the direct actions of magnesium that have been observed on the sinoatrial (Hof *et al.*, 1983) and atrioventricular nodes (Nishimura *et al.*, 1985). In humans, magnesium has been shown to delay atrioventricular conduction, but bradycardic effects have not been reported

(DiCarlo *et al.*, 1986). Electrophysiologic studies in humans have demonstrated, however, that magnesium prolongs sinoatrial recovery time (DiCarlo *et al.*, 1986), a property related to sinoatrial bradycardias. Moreover, lower basal rates were present in human studies than were observed in experimental animal investigations, a condition that would mitigate the effects of bradycardic influences. Species differences, however, may account for these differences.

As observed previously (Hoff *et al.*, 1939; Kelly *et al.*, 1960; Maxwell *et al.*, 1965; Mroczek *et al.*, 1977; Altura and Altura, 1984), we have found that magnesium lowers arterial blood pressures. However, despite the vasodilating actions of this cation in isolated blood vessels and the microvasculature of several regions (Altura, 1982; Altura and Altura, 1985), magnesium did not change vascular resistances. Moreover, the decrease of cardiac output that accounted for the fall in arterial pressures occurred even with heart rate held constant and was observed without a change in LV end-diastolic pressure and, inferentially, without a change in LV end-diastolic dimensions. This suggests that a direct or neurohumorally mediated depression of myocardial contractility had ensued. Magnesium has, in fact, been shown to have myocardial depressant actions in both isolated and intact animal preparations (Shine, 1979). Thus, in the intact dog, the reflex responses to such myocardial depression may overcome the direct vasodilating actions of magnesium on the arterial and arteriolar circulation.

Previous studies on canine coronary strips (Altura and Altura, 1984) and others in the perfused canine heart (Scott *et al.*, 1961, Bass *et al.*, 1958) have demonstrated that magnesium has direct coronary vasodilating effects. Despite such actions, in the neurally intact dog, magnesium administration did not change coronary resistance. Coronary blood flow, in fact, decreased, an effect that was related to a fall in myocardial metabolic requirements resulting from the slowing of rate and lowering of systemic blood pressure. However, the coronary blood flow response to magnesium did not strictly follow *pari passu* with the changes in myocardial oxygen demand because myocardial oxygen extraction also decreased. An attenuating effect of magnesium on coronary vascular tone was therefore suggested, albeit not reflected by a change in coronary vascular resistance.

The fall in myocardial consumption appeared to precede the decline in the hemodynamic determinants of myocardial oxygen demand measured. However, because instantaneous and simultaneous changes were not recorded and LV dimensions were not measured, myocardial oxygen supply-demand relations could not be precisely defined. Also, although hemodynamic changes were not different from control at the low concentrations, when a fall in myocardial oxygen consumption was already evident, the changes were directionally the same as those observed at the high concentrations. Accordingly, the additive effects of the changes in myocardial oxygen demand may have been sufficient to account for the reduction in myocardial oxygen consumption. However, coronary blood flow also did not change at the low magnesium concentrations. The fall in myocardial oxygen consumption reflected only the decrease in myocardial oxygen extraction. Perhaps, therefore, the changes in myocardial oxygen consumption were in part the result of the effects of magnesium on the myocyte. Magnesium has, in fact, been shown to affect myocardial cellular energetics (Sunamori *et al.*, 1980). Recently, moreover, in the isolated perfused working rat heart, using reflectance spectrophotometry, magnesium administration (11.5 mg/dl) has been found to increase oxymyoglobin and to lower reduced cytochrome oxidase (Reiner *et al.*, 1987).

Although both blood magnesium and calcium increased, the absolute and relative concentrations of magnesium increased substantially more than those of calcium, producing a higher magnesium/calcium ratio. The change in this relation may be more influential in determining the hemodynamic effects of magnesium than absolute concentration of magnesium by itself (Maxwell *et al.*, 1965). Also, in this study, total cation concentrations were measured. Because ionized magnesium is the active form, the relations found with total magnesium may not have precisely reflected these associations. However, a previous study with experimental conditions similar to ours has demonstrated that the changes of unbound magnesium parallel those of total magnesium (Maxwell *et al.*, 1965). Moreover, despite the lack of any detectable coronary arteriovenous electrolyte differences after the magnesium infusion, myocardial electrolyte changes probably occurred. The magnitude of the extracardiac electrolyte changes and the insensitivity of the methods for detecting micromolar changes probably obviated the identification of such findings.

Thus, magnesium has been shown to slow heart rate, delay atrioventricular conduction, lower arterial and pulmonary pressures and reduce myocardial oxygen requirements. These findings—and others that have demonstrated that magnesium has myocardial protective actions (Sunamori *et al.*, 1980; Reiner *et al.*, 1987) and that a magnesium deficiency produces myocardial infarction enhancement (Chang *et al.*, 1985)—support the recent interest in this cation as a myocardial anti-ischemic agent.

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