Dose-Related Effects of Magnesium on Myocardial Function in the Neonate

Joseph Caspi, John G. Coles, Lee N. Benson, Stanley L. Herman, Janet Augustine, Gregory J. Wilson

Abstract

The antagonistic effects of magnesium ion as a calcium ion blocker may decrease calcium influx associated with ischemia. However, the effect of magnesium on the presischemic neonatal myocardium has not been investigated previously. The purpose of this study was to investigate the effects of the administration of increasing doses of magnesium on left ventricular performance in the neonate. We assessed left ventricular function (pressure-volume data obtained by the conductance catheter/micromanometer technique) in three groups (n=6 in each) of newborn pigs (3 to 5 days old) differing with respect to magnesium concentrations. End-systolic elastance did not change during infusion in group A (magnesium=8 mmol/L), whereas in groups B (magnesium=8 mmol/L) and C (magnesium=16 mmol/L) it decreased significantly (P<.05) to 67±6% and 44±8% of baseline, respectively. The decrease in end-systolic elastance was associated with a significant reduction in cardiac output (P<.05) and stroke work (P<.05) in group C. After administration of magnesium, end-systolic elastance returned to baseline in group B in contrast to group C (78±3% of baseline value, P<.05). The slope constant of the end-diastolic pressure-volume relation decreased significantly (P<.05) from the preinfusion baseline values of 0.42±0.08 mL/L in group B and 0.46±0.05 mL/L in group C to 0.3±0.04 and 0.26±0.03 mL/L, respectively, versus no change in group A. At the end of the experiment, the slope constant returned to baseline value in group B, whereas in group C it remained significantly lower (P<.05, 78±3% of baseline). We conclude that administration of 8 to 16 mmol/L magnesium affects the systolic function and alters the diastolic properties of the neonatal heart in a dose-response manner. (Hypertension. 1994;23:174-178.)

Key Words: magnesium • ventricular function • swine

Methods

The effects of administration of MgSO4 were studied in newborn pigs aged 3 to 5 days and weighing 1.6 to 2.8 kg. All animals received humane care in accordance with the guidelines of the University of Toronto Animal Care Committee. The animals were anesthetized with intravenous sodium pentobarbital (30 mg/kg) after administration of atropine sulfate (0.1 mg/kg). After endotracheal intubation, ventilation was maintained with a fixed-pressure respirator and inspired mixture of oxygen and room air (FIO2=0.4). A median sternotomy was performed, and the heart was suspended in a pericardial cradle. LV pressure was monitored with a high-fidelity 5F micromanometer-tipped pressure transducer (PC-350, Millar Instruments, Inc, Houston, Tex). A 5F multielectrode conductance catheter (Webster Labs, Baldwin Park, Calif) was inserted through the right carotid artery into the left ventricle with the most distal electrode placed at the apex and the most proximal electrode just cephalad to the aortic valve. Proper position of the conductance catheter was confirmed by palpation and at postmortem.

Left Ventricular Volume Measurement

The conductance catheter was connected to a model Sigma-5 signal-conditioner processor (Leycom, Oegstgeest, the Netherlands) for continuous measurement of absolute LV volume in the neonatal pig as was previously described.

Experimental Protocol

Three experimental groups were studied, differing with respect to the concentration of MgSO4 added to 5% glucose solutions. Solutions with MgSO4 concentrations of 1.2, 8, and 16 mmol/L were given to three groups (n=6 in each). After signal calibration and baseline PV relation measurements, administration of MgSO4 into the external jugular vein was...
The time constant of LV isovolumic relaxation ($\tau$) was computed from LV pressure data and defined as the time required for LV pressure at the time of peak $-(dP/dt)$ to decline to one half of its value at peak $-(dP/dt)$.\textsuperscript{13}

### Statistical Analysis

All data are presented as mean±SEM. A series of repeated hemodynamic variables was subjected to analysis of variance by using the SAS statistical package\textsuperscript{14} to compare changes with baseline measurements. The level of significance was considered at a value of $P<.05$.

### Results

The mean hemodynamic variables obtained before, during, and after administration of MgSO$_4$ for each group are presented in the Table. Baseline values were comparable among the groups. None of the hemodynamic variables changed in group A throughout the course of the experiment. During the infusion of MgSO$_4$, LV end-systolic and end-diastolic pressures reduced significantly in groups B ($P<.05$) and C ($P<.05$). In group C, heart rate, stroke volume, stroke work, and cardiac output decreased significantly during and after administration of MgSO$_4$ compared with baseline ($P<.05$ for all variables).

Fig 1 illustrates representative plots of the linear end-systolic PV relation before and during infusion of MgSO$_4$ from one animal in groups B and C. There was no change in the end-systolic PV relation in group A during and after administration of MgSO$_4$, whereas in groups B and C there was a rightward and downward shift of the end-systolic PV relation, with a significant ($P<.05$) decrease in $E_a$ to 67±6% and 44±8% of baseline (Fig 2). However, after MgSO$_4$ was discontinued, $E_a$ recovered completely in group B, in contrast to group C (78±4% of mean control value within a longer period of time [3 hours]). The decrease in $E_a$ was associated with a significant increase of $V_{\text{st}}$ in groups B and C ($P<.05$) (Fig 3), indicating a greater LV distension.

The exponentially fitted curve of the end-diastolic PV relation demonstrated a rightward and downward shift in groups B and C during infusion of MgSO$_4$. The $k$ constant decreased significantly ($P<.05$) from the preinfusion baseline value of 0.42±0.08 mL$^{-1}$ in group B and 0.46±0.05 mL$^{-1}$ in group C to 0.3±0.04 and 0.26±0.03 mL$^{-1}$, respectively, versus no change in group A. At the end of the experiment, the $k$ constant returned to baseline in group

### Table: Hemodynamic Variables Before, During, and After Administration of MgSO$_4$\textsuperscript{a}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A ([Mg$^{2+}$]=1.2 mmol/L)</th>
<th>Group B ([Mg$^{2+}$]=8 mmol/L)</th>
<th>Group C ([Mg$^{2+}$]=16 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>After</td>
</tr>
<tr>
<td>LVESP, mm Hg</td>
<td>75±4</td>
<td>71±2</td>
<td>70±3</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>9±2</td>
<td>10±1</td>
<td>9±2</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>5±2</td>
<td>4±1</td>
<td>4±2</td>
</tr>
<tr>
<td>Stroke work, erg·10$^9$</td>
<td>200±30</td>
<td>180±10</td>
<td>210±10</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>138±10</td>
<td>140±8</td>
<td>144±8</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>690±60</td>
<td>700±10</td>
<td>720±50</td>
</tr>
</tbody>
</table>

LVESP indicates left ventricular end-systolic pressure; LVEDV, left ventricular end-diastolic volume; and LVEDP, left ventricular end-diastolic pressure. Values are mean±SEM.

\*P<.05.

\textsuperscript{a}The electrocardiogram (ECG) and LV pressure and volume data were recorded on 15½-in magnetic tape (PR 280, Ampex, Redwood City, Calif) and simultaneously displayed on a precalibrated digital X-Y oscilloscope (model 2900, Nicolet Instruments, Madison, Wis). The three signals were digitized by an analog-to-digital converter (Data Translator, DT 2621) at a sample frequency of 333 Hz or every 3 milliseconds through the cardiac cycle. The obtained PV loops were analyzed including one or two steady-state beats and six to eight subsequent cycles in the first 3 seconds after inferior vena caval occlusion. End systole was defined by the points of the ratio of the rate of change of pressure with volume (dP/dt) to the rate of change of volume (V).

\textsuperscript{b}MgSO$_4$ from one animal in groups B and C. There was no change in the end-systolic PV relation in group A during and after administration of MgSO$_4$, whereas in groups B and C there was a rightward and downward shift of the end-systolic PV relation, with a significant ($P<.05$) decrease in $E_a$ to 67±6% and 44±8% of baseline (Fig 2). However, after MgSO$_4$ was discontinued, $E_a$ recovered completely in group B, in contrast to group C (78±4% of mean control value within a longer period of time [3 hours]). The decrease in $E_a$ was associated with a significant increase of $V_{\text{st}}$ in groups B and C ($P<.05$) (Fig 3), indicating a greater LV distension.

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**Fig 1.** Representative plot shows linear end-systolic pressure-volume relation before and during administration of 8 mmol/L (group B, panel A) and 16 mmol/L (group C, panel B) MgSO₄. There was a downward shift of the end-systolic pressure-volume relation during infusion of MgSO₄ in both groups but to a greater extent in group C.

B, whereas in group C it remained significantly (P<.05) lower (78±3% of control value) (Fig 4). Fig 5 illustrates the mean values for LV volume at filling pressures of 2.5, 5, 10, 15, and 20 mm Hg before and during administration of MgSO₄. At each LV diastolic pressure point, the mean end-diastolic volume increased significantly (P<.05) in groups B and C during infusion of MgSO₄.

During infusion of MgSO₄, 𝜏 slowed significantly in groups B (25±1 versus 18±2 milliseconds, P<.05) and C (27±2 versus 16±3 milliseconds, P<.05) compared with baseline; however, it returned to the control value in group B after the infusion of MgSO₄ was discontinued, and it remained significantly slower (P<.05) in group C.

Infusion of 16 mmol/L MgSO₄ resulted in a significant reduction in heart rate (Table). Three animals were excluded from this group because of development of atrioventricular block (n=1) and sinus arrest (n=2).

**Serum Calcium and Magnesium Measurements**

Serum Ca²⁺ level decreased significantly after administration of 16 mmol/L MgSO₄ (from 1.2±0.2 to 0.88±0.06 mmol/L, P<.05). Serum Mg²⁺ concentration increased significantly only in groups B and C (from 0.8±0.1 to 1.8±0.3 mmol/L, P<.05, and from 1±0.2 to 2.6±0.2 mmol/L, P<.05, respectively).

**Fig 2.** Bar graph shows end-systolic elastance during and after infusion of MgSO₄. The difference is expressed as percent change of baseline value. End-systolic elastance decreased significantly (*P<.05) in groups B and C during infusion of MgSO₄ and returned to baseline in group B after infusion of MgSO₄ was discontinued. In contrast, it remained significantly lower in group C at the end of the experiment.

**Fig 3.** Bar graph shows percent change of the chamber constant (k) from baseline value during and after infusion of MgSO₄. There was a significant (*P<.05) reduction of k during infusion of MgSO₄ in groups B and C. After infusion of MgSO₄, k returned to baseline in group B but remained significantly lower in group C.

**Fig 4.** Bar graph shows volume when end-systolic pressure is 100 mm Hg (V100) during and after administration of MgSO₄. V100 decreased significantly (*P<.05) during infusion of MgSO₄ in groups B and C, and after infusion of MgSO₄ was discontinued V100 returned to baseline in group B and remained high in group C.
**Discussion**

This study demonstrates that administration of 8 to 16 mmol/L MgSO₄ significantly affects the systolic function and alters the diastolic properties of the neonatal heart in a dose-response manner. Complete recovery of LV function occurred upon cessation of administration of 8 mmol/L Mg²⁺ but not after administration of 16 mmol/L Mg²⁺. The decrease in myocardial contractility observed after administration of 16 mmol/L Mg²⁺ was associated with a significant reduction in cardiac output and stroke work. These data strongly indicate that Mg²⁺ alters the contractile state of the left ventricle in addition to its effect on the peripheral vascular bed, as previously reported.¹⁵

The total intracellular content of Mg²⁺ is 17 (mmol/L/kg cell water for the rat ventricle; the greater part is bound to enzyme-coenzyme complexes and nucleotides.¹⁵ The ionic activity for Mg²⁺ in the heart muscle was estimated to be less than 1 mg/L close to the extracellular concentration.¹⁶ The factors that regulate Mg²⁺ ionic activity remain obscure, although it has been shown that the mitochondria can accumulate and regulate cytosolic Mg²⁺ by uptake and release of the cation.¹⁷ The exchange between extracellular and intracellular Mg²⁺ is relatively slow. Polimeni and Page¹⁸ described a half-time ($t_{1/2}$) for Mg²⁺ exchange of 180 minutes in the isolated rat heart perfused with an extracellular Mg²⁺ concentration of 0.5 mmol/L at 37°C.

Mg²⁺ has a direct Ca²⁺ antagonistic effect. Studies thus far reported appear to indicate that within the muscle cell Mg²⁺ blocks the influx of Ca²⁺ through the slow channels;¹⁹ inhibits release of Ca²⁺ from sarcoplasmic reticulum in response to a sudden influx of extracellular Ca²⁺, which normally stimulates its release;²⁰ and competes with Ca²⁺ over nonspecific binding sites on troponin C and myosin, thus affecting the ability of Ca²⁺ to develop maximal tension at any given Ca²⁺ concentration.²¹ It also activates the Ca²⁺-ATPase of the sarcoplasmic reticulum, which, by removing Ca²⁺ from the cytosol, decreases diastolic tone.²²

Magnesium sulfate has been used in the management of toxemia of pregnancy, cardiac arrhythmias, and hypertension associated with compromised renal function. It decreases blood pressure by inducing peripheral vasodilatation, an effect comparable with that of Ca²⁺ antagonists.²³ However, the direct effects of Mg²⁺ on cardiac mechanics in the intact animal have not been studied. The use of a conductance catheter to measure LV volume and generate a PV relation provides a precise method to separate the effects of Mg²⁺ on LV function from those on the systemic vasculature.

It is also evident that Mg²⁺ plays a major role in regulating the diastolic properties of the left ventricle. The decrease in the slope constant of the end-diastolic PV relation indicates a greater chamber distensibility. We speculate that this phenomenon is attributable to the competing effect of Mg²⁺ with Ca²⁺ on the binding sites on the actin-myosin crossbridges and the enhanced removal of Ca²⁺ from the cytosol.

The interaction between Mg²⁺, Ca²⁺, and myocardial function has been investigated. Shine and Douglas²⁴ found that the decline in tension development in isolated blood-perfused rat interventricular septa at 28°C after the administration of 0 to 20 mmol/L Mg²⁺ was not dependent on Ca²⁺ level in the perfusate. Similarly, in the present study, despite the maintenance of normal serum ionized Ca²⁺, the change in LV function directly correlated with the increase in Mg²⁺ dose.

Myocardial performance was assessed by using a multielectrode conductance catheter, providing continuous LV volume measurement. The end-systolic and diastolic PV relations, indicative of systolic and diastolic function, respectively, were obtained by reversible load alteration. The validity of this technique for assessment of cardiac contractility has been established previously in adult animals²⁵ and has been adapted for analysis of newborn cardiac function by our group.²⁶ Recently, Applegate et al²⁶ have shown that the conductance catheter accurately measures absolute volumes at steady state but can underestimate the slope and position of the end-systolic PV relation when it is determined by caval occlusion. However, the end-systolic PV relation accurately measures the direction and magnitude of change in LV systolic function. In addition, we have used the volume axis value at P₁₀₀ (V₁₀₀) as a variable describing the position of the slope of the end-systolic PV relation in the normal operating range of the left ventricle, thus avoiding the problems of interpretation of Vₑ in a range in which curvilinearity of the slope may occur.¹⁰

The following important changes in cardiac performance were observed in the present study during the infusion of Mg²⁺: (1) a reduction in systolic function in...
a dose-response manner, (2) a rightward shift in the end-diastolic PV relation caused by decreased chamber stiffness in all groups, (3) slowing of LV isovolumic relaxation, and (4) electrophysiological effects in the high-dose Mg ++ group consisting of sinus bradycardia, decreased atrioventricular conduction, and suppression of sinus node function.

Clinical Implications

The beneficial effects of Mg ++ as a Ca ++ antagonist may be useful in clinical states characterized by increased chamber stiffness such as myocardial ischemia and the presence of high circulating endogenous plasma catecholamines in neonates with congenital heart disease, decreased atrioventricular conduction, and suppression from head trauma.

Acknowledgment

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References

20. Meissner G, Henderson JS. Rapid calcium release from cardiac sarcoplasmic reticulum vesicles is dependent on Ca ++ and is modulated by Mg ++ , adenine nucleotide, and calmodulin. J Biol Chem. 1987;262:3065-3073.
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