Acute Cardiovascular Effects of Magnesium and Their Relationship to Systemic and Myocardial Magnesium Concentrations after Short Infusion in Awake Sheep

D. ZHENG, R. N. UPTON, G. L. LUDBROOK, and A. MARTINEZ
Anaesthesia and Intensive Care, Royal Adelaide Hospital/University of Adelaide, North Terrace, Adelaide, Australia
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ABSTRACT
The temporal relationship between the systemic and myocardial concentrations of magnesium and some of its acute cardiovascular effects were examined after short i.v. infusion administration of magnesium (30 mmol over 2 min) in five awake chronically instrumented sheep. Magnesium decreased mean arterial blood pressure and systemic vascular resistance (SVR) by 23 and 41% from baseline, respectively. These hemodynamic changes were consistent with magnesium producing primary reductions in SVR with partial heart rate (HR)-mediated compensation of blood pressure. Cardiac output and HR increased by 38 and 38% from baseline, respectively. Magnesium had little effect on myocardial contractility, but substantially increased myocardial blood flow (MBF, 77% above baseline) primarily due to direct myocardial vasodilation. The peak arterial and coronary sinus serum magnesium concentrations were 6.94 ± 0.26 (mean ± S.E.M.) and 6.51 ± 0.20 mM, respectively, at 2 min. Both arterial and coronary sinus magnesium concentrations at the end of the study were still more than 3 mM, whereas all the cardiovascular effects were back to baseline. The myocardial kinetics of magnesium was consistent with rapid equilibration of magnesium (half-life 0.4 min) with the extravascular space of the heart. In conclusion, magnesium was shown to have a rapid equilibration between the plasma/serum concentrations of magnesium and its extracellular concentration in the myocardium. However, the primary cardiovascular effect of magnesium (reductions in SVR) preceded its extracellular concentrations, and was a direct function of its arterial concentration. A “threshold” model for changes in SVR was preferred when linked to the arterial magnesium concentration.

Intravenous magnesium has been increasingly used to treat and prevent many acute cardiovascular diseases (Altura and Altura, 1985; Nattel et al., 1991; Hampton et al., 1994; Miller et al., 1995; Fawcett et al., 1999). Functionally, magnesium can be regarded as a cardiovascular drug with calcium antagonistic and antiadrenergic properties (James, 1992). Its cardiovascular effects include direct and indirect dilatation of blood vessels, an antiarrhythmic effect, and possibly myocardial depression. Although it is known that there is a direct relationship between magnesium plasma/serum concentration and cardiovascular effects at near steady state (Friedman et al., 1987; James et al., 1987; Nakagawa et al., 1997), the relationship between the time courses of concentration and effect is poorly understood. Increased knowledge of this temporal relationship may provide a more rational basis for the design of acute intravenous dose regimens of magnesium for the management of cardiovascular symptoms.

There are several issues that need to be resolved before this can be done. First, there is some ambiguity in the literature on the effects of magnesium on some cardiovascular variables such as myocardial contractility and myocardial blood flow, which may be due to differences in magnesium dose and experimental conditions between studies. Second, it is not known to what extent the plasma/serum concentrations of magnesium reflect the concentration of magnesium in important organ systems mediating the cardiovascular effects (e.g., blood vessel walls for vasodilatation, and the myocardium for direct effects on contractility and the ECG). Third, it is unclear whether the cardiovascular effects of magnesium are mediated by its extracellular or intracellular concentration, or a combination of both (Murphy et al., 1991) in these organs.

We have previously examined the relationship between the

ABBREVIATIONS: IVC, inferior vena cava; CO, cardiac output; MAP, mean arterial blood pressure; CVP, central venous pressure; LV dP/dt max, maximum positive rate of change of left ventricular pressure; HR, heart rate; MVO2, myocardial oxygen consumption; MBF or Qm, myocardial blood flow; SVR, systemic vascular resistance; PO2, blood oxygen tension; PCO2, blood carbon dioxide tension; SO2, blood oxygen saturation; MSC, model selection criteria; SV, stroke volume; Cm, arterial magnesium concentration; CS, coronary sinus magnesium concentration; Vm, apparent distribution volume of magnesium in the myocardium.
myocardial pharmacokinetics and dynamic of a number of drugs in sheep (Huang et al., 1993a; Upton et al., 1996, 1999), and in this study applied these methods to intravenous magnesium to address some of these issues. The aims of the study were as follows. 1) To define the time course of some of the cardiovascular effects of magnesium after an intravenous infusion of 30 mmol of magnesium sulfate over 2 min to conscious, instrumented sheep. Myocardial contractility and myocardial blood flow were measured in a closed chested, conscious preparation without concurrent drugs following a high dose of magnesium to deduce the effect of magnesium alone on these cardiovascular variables. 2) To define the time course of the systemic and myocardial concentrations of magnesium, with the latter inferred from the concentration of magnesium in coronary sinus blood leaving the heart. Modeling of myocardial kinetics was used to test the hypothesis that the extracellular magnesium concentration in the heart could be deduced from this coronary sinus concentration (i.e., consistent with venous equilibration of the extracellular space). 3) To examine the temporal relationship between systemic and myocardial concentrations of magnesium and key cardiovascular effects using kinetic-dynamic modeling.

Materials and Methods

General Experimental Preparation

The study was approved by the Animal Ethics Committee of the University of Adelaide. The sheep were prepared in two steps. About 2 weeks before experimentation, sheep (2–3 years of age and approximately 50 kg) were anesthetized with i.v. thiopental (1.5 g) and the trachea intubated with auffed tracheal tube (9 mm i.d.; Sheridan Catheter Corp., Argyle, NY). Anesthesia was maintained with 2% halothane and 100% oxygen and end-expiratory carbon dioxide was monitored using a capnograph (Cardiocap; Instrumentarium Corp, Helsinki, Finland) and kept between 35 and 40 mm Hg.

The right femoral artery and vein were exposed via a groin incision. Using the Seldinger technique (Runciman et al., 1984), a 7-French and a 9-French gauge catheter (Multi-purpose A1 catheter; Cook Australia, Brisbane, Australia) were placed in the abdominal aorta. Through the femoral vein, an 8.5-French introducer catheter (Biosensors International Pty Ltd, Singapore) was placed in the inferior vena cava (IVC). Through the introducer catheter, a 7.5-French mulitilumen thermilization catheter (Swan-Ganz, Biosensors International Pte Ltd) was placed in the pulmonary artery. The position of the Swan-Ganz catheter was confirmed by monitoring the pressure wave pattern with a pressure transducer (model 4-327-1; Bell and Howell Inc., Pasadena, CA) during catheter advancement (Runciman and Ludbrook, 1993).

Two days later, the sheep were anesthetized as described above for probe placement and further catheterization using a modification of the method reported previously (Huang et al., 1992). A left thoracotomy at the 4th intercostal space and a pericardiotomy were performed to expose the left main coronary artery and the pulmonary artery. Doppler flow probes (Titronics Medical Instruments, Iowa City, IA) were placed around the left main stem coronary artery (for measurement of an index of left coronary blood flow) and pulmonary artery (for measurement of cardiac output, CO). The probes were secured around the arteries with cotton tape, which acted as a “cuff” around the arteries and ensured a constant vessel caliber. The apex of the heart was stitched with a 2-0 silk suture, a micro transducer (Codman MicroSensor; Johnson & Johnson Professional, Inc., Raynham, Miami, FL) was placed 3 cm into the left ventricle through a 5-gauge needle via the apex of heart and fixed securely with the suture. The hemiazygous vein, which drains into the coronary sinus of sheep, was ligated outside the pericardium, to ensure the coronary sinus contained pure effluent blood from the myocardium. The leads of the probes and the micro transducer were exteriorized although the chest incision and a subdural tunnel.

The right jugular vein was exposed via a neck incision. A 7-French gauge (B1; Cordis Corporation, Miami, FL) was place into the coronary sinus to sample efferent blood from the myocardium. The position of the catheters was confirmed under direct vision using a fluoroscope with the injection of radio-opaque contrast (Conray 420; May and Baker Ltd, Dagenham, UK) into the coronary sinus. All the surgical procedures were carried out with using sterile technique and all incisions were closed. The sheep were recovered from anesthesia and housed in metabolic crates with free access to food and water. All catheters were flushed at least every 2 days with heparinized (50 IU/ml) 0.9% saline.

Cardiovascular Measurements

During the experiments, the Doppler frequency shifts from both the coronary artery and pulmonary artery Doppler flow probes were recorded at a sampling rate of 1 Hz using a four-channel pulsed Doppler flowmeter (Bioengineering, University of Iowa, 56 M. R.F, Iowa City, IA) and an analog-to-digital card (MetraByte DAS 16-G2; MetraByte Corp., Taunton, Miami, FL) in a personal computer (Microbits 486-based IBM compatible). These were used as indices of myocardial blood flow and cardiac output, respectively. It has been shown that the left coronary artery blood flow velocity was representative of flow in a region corresponding to 77% of the heart (Huang et al., 1993b). The pulmonary artery Doppler flow probes were calibrated in vivo by correlating the Doppler shifts with cardiac output measured intermittently using a thermodilution technique (Huang et al., 1992).

Mean arterial pressure (MAP) and central venous pressure (CVP) were measured using a pressure transducer on an arterial catheter and an IVC catheter, respectively. Left ventricular pressure, MAP, and CVP were recorded using the same data acquisition system. The peak value of the increasing rate of pressure rise of the left ventricle (LV dP/dt max) was calculated and used as an index of myocardial contractility. Heart rate (HR) was also calculated from the pressure wave of the left ventricle.

Myocardial oxygen consumption (MVO2) was calculated as the product of myocardial blood flow (MBF, assuming a baseline flow of 122 ml/min; Huang et al., 1992) and the arteriocoronary sinus oxygen content gradient. Systemic vascular resistance (SVR) was calculated as the difference between MAP and CVP (mm Hg) over CO (l/min) and is reported in resistance units (mm Hg min l-1).

Experimental Design

Studies were conducted in five sheep prepared as described above. On the experimental day, the sheep remained in their metabolic crates with their weight supported by a sling to minimize sheep movement. A study was not commenced until at least 40 min after the placement of the hemodynamic measurement devices, and the hemodynamic measurements had been stable for approximately 10 min. After 5 min of baseline hemodynamic measurements, 30 mmol of magnesium sulfate was infused intravenously via the IVC catheter over 2 min (0.6 mmol/kg). The start of the infusion was designated time zero. Arterial and femoral venous blood samples (5 ml) were taken at 0, 1, 2, 4, 10, and 25 min for serum magnesium assay, and were assayed using an Ektachem 700 analyzer (Kodak GmbH, Stuttgart, Germany). Blood was also sampled from arterial and coronary catheters at 0, 2, and 25 min after commencement of administration of magnesium for blood gas analysis (ABL Radiometer Medical A/S, Copenhagen, Denmark) to determine blood oxygen tension (pO2), pH, blood carbon dioxide tension (pCO2), and blood oxygen saturation (SO2).
Data Analysis

Modeling of Myocardial Kinetics. Hybrid modeling (Upton, 1996; Upton et al., 2000) was used to examine the ability of various kinetic models to describe the observed magnesium concentrations in coronary sinus blood. Models were constructed as a series of differential equations with the Scientist for Windows software package (version 2; Micromath Scientific Software, Salt Lake City, UT), and were fitted to mean data for the five sheep after initial analysis showed little interindividual variation in magnesium concentrations. The measured arterial magnesium concentrations \((C_{\text{art}})\) and blood flow entering the heart were fitted to forcing functions (exponential and polynomial functions, respectively) and these were used as the input functions for the myocardial kinetic models. The measured coronary concentrations \((C_{\text{cs}})\) were used to estimate the parameters of the models by curve fitting. Curve fitting was by a least-squares method based on the maximization of model selection criteria (MSC) of the Scientist program (Upton, 1996; Upton et al., 2000). Three models were examined as outlined below, where \(Q_h\) is myocardial blood flow, and \(V_h\) is the apparent volume of magnesium in the myocardium.

A single flow-limited compartment model:

\[
V_h \frac{dC_{\text{cs}}}{dt} = Q_h \cdot (C_{\text{art}} - C_{\text{cs}})
\]  
(1)

A single flow-limited compartment with first order loss model:

\[
V_h \frac{dC_{\text{cs}}}{dt} = Q_h \cdot (C_{\text{art}} - C_{\text{cs}}) - k_{\text{loss}} \cdot C_{\text{cs}}
\]

where \(k_{\text{loss}}\) governs the rate of the loss and has the units of volume per unit time.

A membrane-limited compartment model. In this model, “PS” is used to represent membrane permeability, and \(C_{\text{deep}}\) is the magnesium concentration in the deep compartment of the myocardium with a volume given by \(V_{\text{deep}}\):

\[
V_h \frac{dC_{\text{cs}}}{dt} = Q_h \cdot (C_{\text{art}} - C_{\text{cs}}) - PS \cdot (C_{\text{deep}} - C_{\text{cs}})
\]

\[
V_{\text{deep}} \frac{dC_{\text{deep}}}{dt} = PS \cdot (C_{\text{cs}} - C_{\text{deep}})
\]

A graphical representation of the three kinetic models is shown in Table 2.

Kinetic-Dynamic Modeling. SVR was considered the primary cardiovascular parameter affected by magnesium. Four dynamic models were examined that related the arterial or coronary sinus magnesium concentrations \((C)\) to this effect:

Linear Model. A simple linear relationship between concentration and effect, defined by the slope and intercept of a line:

\[
SVR = \text{slope} \cdot C + \text{intercept}
\]

Linear Model with Delay. As for the first model, but SVR was related to magnesium concentration in a hypothetical effect compartment whose time course of concentrations was delayed relative to the measured concentration as given by the rate constant \(k_{\text{eff}}\). The rate-constant was constrained during fitting to be between 0 and 100 min \(^{-1}\). \(C_{\text{eff}}\) is the effect compartment concentration:

\[
\frac{dC_{\text{eff}}}{dt} = k_{\text{eff}} \cdot (C - C_{\text{eff}})
\]

\[
SVR = \text{slope} \cdot C_{\text{eff}} + \text{intercept}
\]

Linear Model with a Threshold. This model was the same as the linear model, but SVR was unchanged from baseline \((SVR_{\text{base}})\) below a threshold \((T)\) concentration:

\[
\begin{align*}
\text{If } C < T, & \quad \text{then } SVR = SVR_{\text{base}} \\
\text{If } C > T, & \quad \text{then } SVR = \text{slope} \cdot C + \text{intercept}
\end{align*}
\]

A Tolerance Model. This model was adapted from that used by Ekblom et al. (1993) to describe tolerance to morphine, and was such that the effects of magnesium on SVR could become less with time, even if the magnesium concentrations were held constant. This type of model can empirically account for a variety of mechanisms of tolerance (Mandema and Wada, 1995). Conceptually, the changes in SVR from baseline \((SVR_{\text{base}})\) can be thought of as the net result of a reduction attributed to the effect of magnesium \((SVR_e)\), and an increase due to the development of tolerance \((SVR_t)\):

\[
SVR = SVR_{\text{base}} - SVR_e + SVR_t
\]

The direct effect of magnesium was linearly related to concentration:

\[
SVR_e = \text{slope}_e \cdot C
\]

The tolerance was related to concentrations in a hypothetical tolerance compartment, which could be delayed relative to the measured concentration, as given by the rate constant \(k_{\text{tol}}\):

\[
dC_{\text{tol}}/dt = k_{\text{tol}} \cdot (C - C_{\text{tol}})
\]

\[
SVR_t = \text{slope}_t \cdot C_{\text{tol}}
\]

Statistical Analysis

To compare the effect of magnesium on MAP, SVR, CO, MBF, LV dP/dt\(_{\text{max}}\), HR, pH, pCO\(_2\), pO\(_2\), SO\(_2\), and MVO\(_2\), measurements were expressed as a percentage of baseline, and then the mean and 95% confidence limits were calculated. If the mean and its 95% confidence limits of a measured value lay outside the 95% confidence limits of the baseline data, the value was recorded as being statistically significant. Paired t tests were used to compare the arterial and coronary sinus magnesium concentrations. \(p < 0.05\) was recorded as statistically significant.

Results

Cardiovascular and Other Effects of Magnesium. Magnesium caused minor respiratory depression, as indicated by transient reductions in arterial pO\(_2\) and SO\(_2\), and increases in arterial pCO\(_2\) (Table 1). The increase of arterial pCO\(_2\) at 2 min was 29% above baseline. There were no significant changes in the time course of LV dP/dt\(_{\text{max}}\) (Fig. 1A), indicating that magnesium was not a myocardial depressant in this experimental paradigm.

During and shortly after the infusion of magnesium, there was a substantial increase in MBF from baseline, with a peak increase of 77% at 1 min (Fig. 1B). However, there were no significant changes in MVO\(_2\). The values of MVO\(_2\) at baseline, and 2 and 25 min after the infusion (mean and 95% confidence limits) were 4.4 (3.5–7.7), 3.9 (3.3–4.6), and 3.6 (2.7–4.6) ml/min/100 g, respectively. Increased MBF in the face of unchanged MVO\(_2\) is consistent with the observation that the coronary sinus SO\(_2\) was significantly increased above baseline at 2 min (Table 1). Overall, the increase in MBF caused by magnesium appears to be due to a direct vasodilatory effect on the coronary blood vessels, rather than
secondary to cardiovascular changes that increase myocardial work and therefore MVO₂.

There were significant reductions in MAP and SVR from baseline (Fig. 2, A and B), with peak reductions of 23 and 41% for each, respectively, at 2 min. This was accompanied by an increase in CO (Fig. 3A) and HR (Fig. 3B), with a peak increase of 38% at 2 min for both parameters. Stroke volume (SV) was essentially unchanged (Fig. 3C). This pattern of hemodynamic changes is consistent with magnesium-dependent reductions in SVR, with partial compensation of MAP decreases via reflex increases in heart rate. Increases in preload due to a transient fluid shift from the arterial to venous circuit may also have contributed to the increase in CO, although preload was not measured in the present study.

In subsequent kinetic dynamic analysis, a reduction in SVR was considered to be the primary cardiovascular effect of magnesium, and it was this effect that was related to the measured magnesium concentrations.

**Myocardial Pharmacokinetics of Magnesium.** The observed arterial and coronary sinus blood concentrations of magnesium are shown in Fig. 4. There was a significant difference between arterial and coronary sinus concentration at 1 min after the start of the infusion. There was a general trend for uptake of magnesium into the heart (arterial > coronary sinus concentrations) for approximately 10 min after the start of the infusion.

The goodness of fit of the models of myocardial magnesium kinetics and their parameter values are shown in Table 2.
The flow-limited model was the best fit of the data; the line of best fit to the coronary sinus magnesium concentrations is shown in the inset of Fig. 4. The membrane-limited model collapsed to a flow-limited model, as indicated by very small values of $PS$ and $V_{\text{deep}}$, whereas the flow-limited model with a first order loss returned a low and uncertain value for the $k_{\text{loss}}$.

The good fit of the flow-limited model is consistent with the concept of a distribution volume of magnesium in the heart (approximately 71 ml) that is in equilibrium with coronary sinus blood. This volume can be compared with the true volume of the region of the heart drained by the coronary sinus catheter (233 g in sheep; Huang et al., 1993b), and therefore represents approximately 30% of the total mass of the region of the heart under study. This distribution volume can also be compared with the baseline myocardial blood flow (122 ml/min; Huang et al., 1992); the half-time for equilibration of the volume with serum was therefore 0.40 min.

Pharmacokinetic-Pharmacodynamic Relationships. The parameters' values of the various dynamic models and their MSC values are shown in Table 3. The linear dynamic model produced an acceptable fit of the SVR data when linked to the arterial concentrations (Fig. 5), but was less successful when linked to the coronary sinus concentrations (Table 3). Adding an effect delay to either did not improve the fit, and produced estimates of $k_{\text{eq}}$ that were equal to the upper constraint (100 min$^{-1}$). This value of $k_{\text{eq}}$ produced time course of measured concentration and effect compartment concentration that were essentially identical. Overall, the data suggest that the arterial magnesium concentrations were directly related to the reductions in SVR with no time delay, and that the time course of the coronary sinus concentrations lag behind both the time course of the arterial concentrations and reductions in SVR.

Close inspection of Fig. 5 will show that the greatest discrepancy between the line of best fit for the linear model and the SVR data occurs for the last time point (25 min), although this is also the value of SVR with the widest 95% confidence intervals. The application of threshold and tolerance models to the data were an attempt to account for this discrepancy, which is consistent with SVR returning to near baseline while the magnesium concentrations remained elevated (Figs. 2B and 4). The threshold model was preferred when linked to the arterial concentration, whereas the tolerance model was preferred when linked to the coronary sinus concentrations, but returned an uncertain value for the tolerance rate constant ($k_{\text{tol}}$). This suggests that the threshold dynamic model was suitable for describing the relationship between the arterial magnesium concentration and SVR.

Discussion

Cardiovascular Effects of Magnesium. The pattern of hemodynamic changes observed was consistent with peripheral vasodilatation, hypotension, and a reflex increase in CO, predominantly due to an increase in HR. The use of an awake preparation avoided any anesthetic depression of autonomic reflexes or myocardial function that may complicate the in-
interpretation of some earlier studies (Friedman et al., 1987). The changes observed were similar to those previously reported in studies using lightly anesthetized baboons (James et al., 1987), although decreases in HR were more common in studies where magnesium concentrations reached supratherapeutic concentrations (Nakaigawa et al., 1997).

**Myocardial Contractility.** There was no evidence of myocardial depression, as determined by LV dP/dt\textsubscript{max}, despite magnesium concentrations reaching around 7 mM, although it is possible a small direct myocardial depressant effect may have been countered by a reflex sympathetic response to hypotension. This is consistent with much of the published literature, which generally shows minimal cardiac depression at therapeutic concentrations (in the order of 2–3 times baseline levels). Critelli et al. (1977) reported that bolus administration of magnesium in humans produced only small decreases in indices of myocardial contractility in patients with mild myocardiosclerosis, but more significant decreases in patients with impaired cardiac function (New York Heart Association class III-IV). In lightly anesthetized baboons, magnesium produced minimal myocardial depression, and even at very high magnesium concentrations a decrease in CO seemed to be HR mediated (James et al., 1987). Nakaigawa et al. (1997) reported that magnesium produced dose-dependent decreases in LV dP/dt\textsubscript{max} in anesthetized dogs. This depres-

**Fig. 5.** Kinetic-dynamic relationship for the linear effect model. The solid circles are the observed time course of the arterial magnesium concentration. Data are shown as mean and S.E.M. The open circles are the observed time course of SVR. Data are shown as the mean (symbols) and 95% confidence limits (dashed line). The solid line is the line of best fit of the linear effect model linked to the arterial magnesium concentrations.
sion was, however, minor at blood concentrations similar to those achieved in the current study, but became marked with blood concentrations of around 9 to 14 mg/dl. In vitro, Bass et al. (1958) demonstrated using a modified Langendorff heart preparation that low concentrations of magnesium (0.025–2.5 mg) did not affect myocardial contractility, whereas higher doses (25–250 mg) temporarily depressed contractility. In contrast, Friedman et al. (1987) found magnesium reduced LV dP/dt max by around 30% with magnesium concentrations similar to those in the current study; chloralose anesthesia may have been a contributing factor.

The use of awake animals in the present study meant that some respiratory depression and mild hypercarbia was induced. Although it is possible that hypercarbia influenced the data in the current study, it is known that even very large increases in pCO2 produce minimal or no changes in CO, LV dP/dt max, and HR (Larrieu et al., 1978; Foex and Ryder, 1979; van den Bos et al., 1979), suggesting any influence in the current study was minimal.

### Myocardial Blood Flow

Although an increase in MBF would be expected in the present study, considering the large decrease in SVR, MBF is also influenced by the work performed by the heart. This in turn is influenced (broadly) by SV, MAP, and HR. Following the administration of magnesium in the present study, MAP decreased whereas HR increased. The overall work of the heart therefore appeared unchanged, in agreement with the unchanged MVO2. The increase in MBF in the face of unchanged MVO2 is consistent with the increase in coronary sinus oxygen content. Overall, the data suggest that magnesium produced coronary hyperemia due to direct vasodilatation of coronary blood vessels. This is consistent with the work of Scott et al. (1961) who reported that MBF velocity was almost doubled, and coronary vascular resistance was decreased, after intracoronary infusion of magnesium in the dog heart, and in vitro studies showing, magnesium to have direct coronary vasodilating effects (Bass et al., 1958; Altura and Altura, 1984, 1985). In contrast, Nakaigawa et al. (1997) reported no change in MBF or in CO, but MVO2 and oxygen extraction both decreased.

In the current study, the small decrease in hemoglobin saturation due to magnesium-induced respiratory depression was unlikely to have affected MBF, but it is possible that the concurrent mild hypercarbia may have had a small influence. Hypercarbia has been shown to produce increases in MBF (Foex and Ryder, 1979; van den Bos et al., 1979), and these increases have been shown to exceed increases in MVO2 (Foex and Ryder, 1979; van den Bos et al., 1979). However, these increases have been associated with marked hypercarbia (over 70 mm Hg), and it seems unlikely that the pCO2 of around 45 mm Hg in the current study contributed more than a small degree to the large (77%) increase in MBF velocity. This is supported by the observations from pilot studies using the present experimental preparation where it was found that increasing inspired CO2 from 0 to 10% had a minimal effect on MBF.

### Myocardial Pharmacokinetics of Magnesium

Magnesium ions equilibrate slowly across cell membranes (probably via ion channels). Intracellular concentrations are a function of complex buffering of magnesium ions with ATP and other molecules within the cell (Raftos et al., 1999). The electrochemical gradient across the cell membrane drives the flux of extracellular magnesium into the cell, but the intracellular concentrations of free magnesium are much less than expected by this process. The low intracellular concentration at equilibrium is achieved by relatively slow active transport of magnesium out the cell via a Na⁺-Mg2⁺ antiports (Flatman, 1991).

The kinetic modeling supports the notion that this active transport of magnesium out of the cell is sufficient to constrain the distribution volume of exogenous magnesium to the extracellular space. The distribution volume was found to be 30% of the mass of the region of the heart studied, which includes the blood. The extracellular volume of heart without blood in rat has been reported to be 15 to 18% of the total volume, depending on the markers used (Makos et al., 1998).

In addition to the contribution of blood to the distribution volume, there may be some differences in the binding of magnesium between the serum and interstitial fluid that contributes to the larger volume observed in the present study. Certainly, the data suggest that there is very rapid equilibration of magnesium between serum and the extracellular space, and that the magnesium concentration in venous serum emerging from the heart is representative of its concentration in the extracellular space. In most circumstances where magnesium is administered more slowly than in the present study, it would be expected that the total serum concentrations of magnesium are representative of the total magnesium concentration in the extracellular space.

### Pharmacokinetic-Pharmacodynamic Relationships

Magnesium is known to modify the properties of a number of ion channels in the cell membrane. Although some channels are affected by the intracellular concentration of magnesium, others (including its calcium channel blocking effects) are affected by its extracellular concentration (Murphy et al., 1991; Bara et al., 1993). It would seem likely that the reductions in SVR caused by magnesium are a function of its calcium channel blocking effects relaxing vascular smooth muscle. However, the data suggest that the “global” extracellular concentrations of magnesium, as represented by the effluent concentrations from the heart, do not determine this primary cardiovascular effect of magnesium. The fact that this effect was better related to the arterial concentrations of magnesium suggest that magnesium is acting directly on “proximal” segments of the microvasculature, presumably the arterioles responsible for regulating vascular resistance. Capillary permeability theory dictates that the proximal segments of the exchange microvasculature equilibrate first with the afferent arterial blood, whereas distal segments equilibrate with efferent venous blood (Stec and Atkinson, 1981).

An interesting finding in the study was that both the arterial and coronary sinus magnesium concentrations at the end of the study were more than 3 mM, at which time all the cardiovascular variables had returned to baseline. A threshold effect was tested, as Bolan et al. (1985) demonstrated a lack of hemodynamic effects with blood magnesium concentrations below 4 mM in pregnant sheep. Alternatively, an acute tolerance to the effects of magnesium would explain the same observation. The mechanism of tolerance could take a number of forms, most of which are mathematically equivalent to the tolerance model investigated here. For example, serum magnesium exists in two forms: bound to covalent ligands (i.e., plasma proteins) and free ionized magnesium.
The free magnesium fraction in the whole blood is about 59 to 71% (Brookes and Fry, 1993; Ising et al., 1995; Hafen et al., 1996). Total serum magnesium was measured in the present study, whereas only free ionized magnesium is thought to have biological activity. Tolerance could be accounted for by progressive, slow conversion of free to bound magnesium during the course of the study. In our own laboratory, we have found that the vasodilatory effect of magnesium infused directly into a muscle bed diminishes with time (Zheng et al., 2000).

Implications from the study are first that there is rapid equilibration between the plasma/serum concentrations of magnesium and its extracellular concentration in the myocardium. It can be concluded that monitoring arterial concentrations of magnesium is therefore representative of its extracellular concentrations in the heart. Second, the primary cardiovascular effects of magnesium (reductions in SVR) were initially related to these arterial concentrations. However, important cardiovascular effects may not be directly related to these concentrations after longer time periods (=25 min).

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References


