Alterations in systemic and local colonic hemodynamic variables associated with intravenous infusion of ATP-$MgCl_2$ in healthy anesthetized horses

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Objective—To characterize alterations in systemic and local colonic hemodynamic variables associated with IV infusion of ATP-$MgCl_2$ in healthy anesthetized horses.

Animals—12 adult horses.

Procedure—Six horses were given ATP-$MgCl_2$, IV, beginning at a rate of 0.1 mg of ATP/kg of body weight/min with incremental increases until a rate of 1.0 mg/kg/min was achieved. The remaining 6 horses were given an equivalent volume of saline (0.9% NaCl) solution over the same time period. Colonic and systemic hemodynamic variables and colonic plasma nitric oxide (NO) concentrations were determined before, during, and after infusion.

Results—Infusion of ATP-$MgCl_2$ caused a rate-dependent decrease in systemic and colonic vascular resistance, principally via its vasodilatory effects. A rate of 0.3 mg of ATP/kg/min caused a significant decrease in systemic and colonic arterial pressure and colonic vascular resistance without a significant corresponding decrease in colonic arterial blood flow. Consistent alterations in NO concentrations of plasma obtained from colonic vasculature were not detected, despite profound vasodilatation of the colonic arterial vasculature.

Conclusions and Clinical Relevance—Results revealed that IV infusion of ATP-$MgCl_2$ may be beneficial in maintaining colonic perfusion in horses with ischemia of the gastrointestinal tract, provided a sufficient pressure gradient exists to maintain blood flow. (*Am J Vet Res* 2001;62:1240–1249)

Acute gastrointestinal tract disease (eg, colic) is the leading natural cause of death in adult horses.[1,2]

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Ischemia of the gastrointestinal tract commonly develops secondary to low-flow or no-flow conditions, with volvulus or incarceration of the small intestines[3,4] and volvulus of the large colon[5-7] being common causes. In 1 study,[8] strangulating obstructive lesions were associated with the highest mortality (75%) for all types of colic. Abnormalities of the large colon account for up to half of the horses that die or are euthanatized subsequent to colic.[2-4]

Strangulating volvulus of the ascending colon reportedly results in death or euthanasia of almost 80% of affected horses.[7] The disease is characterized by colonic luminal obstruction and vascular occlusion secondary to the volvulus, thereby resulting in colonic ischemia, mucosal necrosis, and vascular thrombosis.[9] Colonic blood flow remains substantially less than baseline values for at least 4 hours after correction of complete arteriovenous occlusion in horses.[10] The high mortality associated with colonic volvulus may be related to a sustained reduction of blood flow and hypoperfusion (attributable to increased vascular resistance) after surgical correction and continued ischemic injury. Endothelial damage in the colonic vasculature can be seen subsequent to ischemia-reperfusion and may be exacerbated by endotoxins.[11] The sustained decrease in colonic blood flow may be associated with endothelial damage in the colonic circulation, leading to a loss of endothelium-derived vasorelaxants and subsequent vasoconstriction. Many of these horses develop systemic hypotension as a result of hypovolemia and endotoxemia, which contribute to decreased splanchnic blood flow. Additionally, colonic mucosal ATP content decreases 92% during ischemia and recovers to only 44% of control values after reperfusion, thereby limiting substrate availability for cellular metabolic functions.[12] Decreases in blood flow and tissue ATP content during colonic ischemia can lead to disruption of the mucosal barrier and transmural passage of endotoxin into the systemic circulation. If sufficient amounts of endotoxin enter the systemic circulation, death can ensue.

Adenosine triphosphate is principally an endothelium-dependent vasodilator that is rapidly metabolized and has a short duration of action.[13] Vasodilatory effects of ATP are mediated primarily through activation of **purinoreceptors (P_{2Y})** located on endothelial cells.[14] The P_{2Y} are coupled to G-proteins and involve second messenger systems.[15] Activation of inhibitory P_{2Y} results in increased formation of **nitric oxide (NO)**, which increases the concentration of cyclic GMP in smooth

muscle cells.[13] Cyclic GMP is the intracellular messenger involved in smooth muscle relaxation. Endothelial-derived hyperpolarizing factor, and possibly prostacyclin, also are generated, which contributes to the relaxation response.[15] When ATP is degraded by ectonucleotidases into adenosine, an **adenosine purinoreceptor (A_2)** is activated, leading to relaxation of vascular smooth muscle.[16] The A_2 also are coupled to G-proteins.[15] Additionally, magnesium is a potent vasodilator via its important role in regulating arteriolar tone and calcium exchange in vascular smooth muscle.[17]

Administration of **ATP-magnesium chloride (ATP-$MgCl_2$)** in humans results in vasodilatation of peripheral vasculature and increased cardiac output.[18] These findings suggest its potential beneficial use in patients with hypoperfusion (low-flow) or organ ischemia. Use of ATP-$MgCl_2$ following hemorrhagic shock and other adverse circulatory conditions in humans and laboratory animals can improve mitochondrial function and tissue ATP content[19,20]; restore organ function, blood flow, and perfusion[20-23]; improve reticuloendothelial function, survival time, and survival rate[24,25]; and down-regulate synthesis and release of inflammatory cytokines.[26]

Our laboratory group recently investigated hemodynamic and metabolic alterations associated with IV infusion of ATP-$MgCl_2$ in healthy conscious adult horses.[27] Intravenous administration of ATP-$MgCl_2$ caused a rate-dependent increase in cardiac output and decrease in **systemic vascular resistance (SR_L)** without appreciable detrimental effects. On the basis of those results, it was believed that ATP-$MgCl_2$ infusion potentially could increase perfusion of the gastrointestinal tract. Administration of ATP-$MgCl_2$, which has vasodilatory actions, increases cardiac output, and delivers an energy substrate (ATP) and cofactor (magnesium) directly to the tissues, may offer a potential method for treatment of horses with intestinal ischemia, endotoxemia, and shock. Therefore, the purpose of the study reported here was to characterize local colonic and systemic hemodynamic alterations associated with IV infusion of ATP-$MgCl_2$ in clinically normal anesthetized horses. We hypothesized that administration of ATP-$MgCl_2$ would cause a rate-dependent decrease in SR_L and colonic vascular resistance, principally via vasodilatation.

Materials and Methods

Horses—Twelve healthy horses (9 sexually intact females and 3 castrated males) ranging from 3 to 13 years old (median, 7 years) and weighing between 315 and 461 kg (median, 395 kg) were included in the study. All horses were vaccinated against eastern and western encephalitis and had been given tetanus toxoid 3 months prior to the start of the study. Horses were maintained on pasture prior to the study. Food, but not water, was withheld for 12 hours prior to the study to decrease colon contents, which facilitated manipulation of the colon. The study was approved by the Institutional Animal Care and Use Committee of Louisiana State University.

Instrumentation—Horses were sedated by IV administration of xylazine hydrochloride[a] (0.5 mg/kg of body weight) and butorphanol tartrate[b] (0.02 mg/kg). All catheters were placed percutaneously after aseptic preparation of the skin and desensitization accomplished by subcutaneous infiltration of lidocaine solution. A 14-gauge 13.3-cm teflon-coated catheter[c] was inserted into the left jugular vein for administration of anesthetic drugs and isotonic polyionic fluids. A balloon-tipped flow-directed thermodilution catheter,[d] which was used for measurement of cardiac output and **pulmonary artery pressures (PAP)**, was inserted into the right jugular vein and advanced until the distal port was positioned in the main pulmonary artery. Polyethylene tubing[e] (**outside diameter [OD]**, 1.77 mm) was inserted distal to the catheter in the left jugular vein and advanced until the tip was positioned in the right ventricle for infusion of ice-cold polyionic fluids[f] for measurement of cardiac output. Fifty-five milliliters of fluid was infused into the right ventricle during a 4-second period, using a CO_2-driven injector,[g] and cardiac output was derived on the basis of thermodilution.[28] Dead space of the injection catheter was 5 ml. Cardiac output and PAP were recorded, using a cardiac output meter.[h] Thermodilution signal curves were recorded for each cardiac output measurement. Polyethylene tubing[i] (OD, 1.57 mm) was inserted into the right jugular vein proximal to the thermodilution catheter and advanced until the tip was positioned in the right atrium for determination of **mean right atrial pressure (MRAP)**. All catheter positions were confirmed by observation of characteristic pressure wave forms.

General anesthesia was induced by IV administration of guaifenesin[j] (50 mg/kg) and sodium thiopental[k] (4.4 mg/kg). After induction, a loading dose of sodium pentobarbital[l] (7.5 mg/kg) was administered IV, and anesthesia was maintained by continuous-rate infusion of sodium pentobarbital (5 to 15 mg/kg/h). Horses were mechanically ventilated[m] with 100% oxygen at a rate of 6 to 12 breaths/min to a peak inspiratory pressure of approximately 20 cm H_20. Arterial blood gas analyses, PCV, and plasma total protein concentrations were monitored during the study to assess the metabolic and anesthetic status of each horse and to enable investigators to adjust anesthetic management, if necessary. Isotonic polyionic fluids were administered at a rate of 5 to 10 ml/kg/h. Arterial blood pressure was measured, using a 20-gauge 5.1-cm teflon-coated catheter[n] placed in the facial artery. A 14-gauge 5.1-cm teflon-coated catheter[o] was inserted proximally into each of the jugular veins; 1 catheter was used for infusion of the ATP-$MgCl_2$,[p] and the other catheter was used for collection of blood samples.

All horses were positioned in dorsal recumbency and prepared for surgery. Ventral median celiotomy was performed. The ascending colon was exteriorized and positioned on a warm-water heating pad,[q] and instruments were placed (**Fig 1**). Doppler ultrasound flow probes[r] (3 mm) were placed externally around the right ventral and dorsal colonic arteries, and colonic blood flow was measured continuously and recorded. A 20-gauge 5.1-cm teflon-coated catheter was placed in each artery and vein of the ventral and dorsal colon, distal to the flow probes, for determination of ventral and dorsal colonic arterial and venous pressures. A 14-gauge 5.1-cm teflon-coated catheter was placed in a ventral colonic vein, and a 20-gauge 5.1-cm teflon-coated catheter was placed in a ventral colonic artery; each catheter was placed distal to the pressure catheters and used for collection of samples of colonic venous and arterial blood, respectively. A surface laser-Doppler flow probe[s] was positioned on the serosal surface, and a needle probe[t] was positioned in the mucosa of the pelvic flexure of the ascending colon to measure seromuscular and mucosal perfusion, respectively. All blood-flow probes and pressure transducers were interfaced with physiographs,[u] and flow and pressure curves were generated and recorded on chart recorders.[v] A continuous base-apex ECG also was obtained.

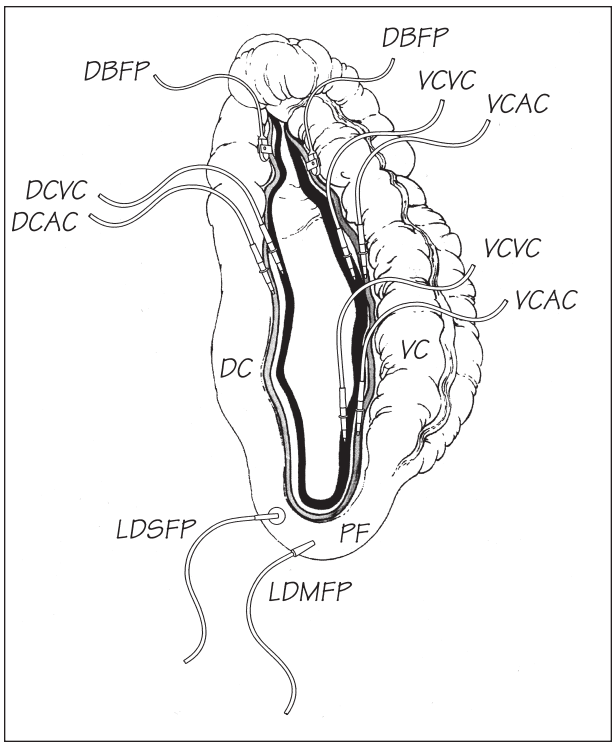

Figure 1—Schematic illustration of instrumentation of the ascending colon of horses to enable measurement of arterial blood flow, arterial and venous blood pressures, and mucosal and serosal perfusion as well as collection of arterial and venous blood samples. DBFP = Doppler blood flow probes. DC = Dorsal colon. DCAC = Dorsal colon arterial catheter. DCVC = Dorsal colon venous catheter. LDSFP = Laser-Doppler serosal flow probe. LDMFP = Laser-Doppler mucosal flow probe. PF = Pelvic flexure. VC = Ventral colon. VCAC = Ventral colon arterial catheter. VCVC = Ventral colon venous catheter. Illustration provided by Michael Broussard.

Experimental design—The formulation of ATP-$MgCl_2$ has been described elsewhere.[29] Twelve horses were randomly assigned to 1 of 2 groups. Group-1 horses served as control horses and received saline (0.9% NaCl) solution. Group-2 horses received an IV infusion of ATP-$MgCl_2$ via an infusion pump,[w] beginning at a rate of 0.1 mg of ATP/kg/min. The infusion rate was increased by increments of 0.1 mg/kg/min at 10-minute intervals until a maximum rate of 1.0 mg/kg/min was achieved. Unless otherwise stated, data were collected before infusion (baseline value; time 0 = start of infusion), at the end of each infusion rate, and 1, 2, 3, 5, 15, 30, 45, and 60 minutes after discontinuation of infusion. Control horses received an equivalent volume of saline solution during the same time frame. Horses were euthanatized at the conclusion of the study by administration of an overdose of sodium pentobarbital (100 mg/kg, IV).

Systemic hemodynamic variables—Systemic hemodynamic variables that were measured included **systolic arterial pressure (SAP)**, **diastolic arterial pressure (DAP)**, **mean arterial pressure (MAP)**, **systolic pulmonary arterial pressure (SPAP)**, **diastolic pulmonary arterial pressure (DPAP)**, **mean pulmonary arterial pressure (MPAP)**, MRAP, and cardiac output. Three measurements were obtained at each time point for each pulmonary and facial artery and for right atrial pressure and were used in the analyses. Five measurements were obtained for cardiac output at each time point, and the 3 middle values were used in analyses. Cardiac index (ie, cardiac output/kg of body weight), SR_L ([MAP – MRAP]/cardiac output), and **pulmonary vascular resistance (PR_L;** MPAP/cardiac output) were calculated. Specific ECG alterations were recorded.

Colonic hemodynamic variables—Colonic hemodynamic variables that were measured included mean **ventral colonic arterial pressure (VCAP)**, **dorsal colonic arterial pressure (DCAP)**, **ventral colonic venous pressure (VCVP)**, **dorsal colonic venous pressure (DCVP)**, **ventral colonic blood flow (VCF)**, **dorsal colonic blood flow (DCF)**, colonic mucosal perfusion, and colonic serosal perfusion. Variables that were calculated included overall mean colonic arterial pressure ([DCAP + VCAP]/2), overall mean colonic venous pressure ([VCAP + VCVP]/2), overall mean colonic arterial blood flow ([VCF + DCF]/2), **ventral colonic vascular resistance (VCR_L;** [VCAP – VCVP]/VCF), **dorsal colonic vascular resistance (DCR_L;** [DCAP – DCVP]/DCF), and overall colonic vascular resistance ([DCR_L + VCR_L]/2).

Measurement of NO—Samples of blood (6 ml) were collected from the ventral colonic artery and ventral colonic vein into tubes containing lithium heparin and processed immediately for analysis of NO concentrations in fresh plasma. Samples were centrifuged at 1,500 × g for 5 minutes, and plasma was harvested and deproteinized by adding 100 µl of trichloroacetic acid (10%) solution to 100 µl of plasma. Samples were vortexed for 30 seconds and then allowed to stand for 15 minutes. Samples then were centrifuged (14,000 × g for 5 minutes), and supernatant was removed for analysis. Aliquots (3 µl) of plasma were added to a purge chamber of vanadium chloride (100 C) in 1N HCl under a nitrogen atmosphere. Nitric oxide (bound or in the form of nitrate) liberated from the samples into the gaseous headspace was conducted to the NO analyzer,[x] where it reacted with ozone to produce a chemiluminescent signal in the range of 6,500 to 8,000 Å. The amount of light generated was proportional to the NO concentration, which was calculated from a standard curve of known nitrate concentrations. Each sample was analyzed in triplicate. Limit of detection for the analysis was 1 pmol (ie, 1 µ*M* NO in 1 µl of plasma).

Statistical analysis—All data were considered continuous and evaluated for normality, using the Shapiro-Wilke statistic. Data were considered to have a normal distribution when there was failure to reject the null hypothesis of normality at $P \leq 0.05$. Data that were not normally distributed were log transformed such that they then had a normal distribution. Data were summarized and reported as mean ± SEM.

Data were analyzed, using the following model:

$$y = \mu + \text{group} + \text{horse(group)} + \text{time} + (\text{group} \bullet \text{time}) + (\text{horse} \bullet \text{time}) + \varepsilon$$

where y is the dependent variable, µ is the overall mean, group is the fixed effect of group (ie, saline or ATP-$MgCl_2$), horse(group) is the random effect of horse nested within group, time is the fixed effect of time of measurement, (group • time) is the fixed effect of group interaction with time, (horse • time) is the random effect of horse interaction with time, and ε is the residual error.

In this model, the effect of horse was considered random and was the error term for the evaluation of group. All other fixed effects were evaluated, using the combined variance of (horse • time) and ε. A 2-sided hypothesis with $P \leq 0.05$ was used to determine significance of fixed-model effects (ie, group, time, and [group • time]). When there were significant model effects, multiple comparisons were made between groups for various time periods and within groups compared with baseline values, using adjusted least-squares means and maintaining an experiment-wise error of 0.05. Thus, when a significant difference was detected among time periods and compared with baseline values, the value used was $P \leq 0.05$. A statistical computer program[y] was used for the analyses.

Table 1—Systemic hemodynamic variables (mean ± SEM) before, during, and after IV infusion of saline (0.9% NaCl) solution to 6 horses

Time	Cardiac index (ml/min/kg)	SAP (mm Hg)	DAP (mm Hg)	MAP (mm Hg)	SPAP (mm Hg)	DPAP (mm Hg)	MPAP (mm Hg)	MRAP (mm Hg)
Before infusion	43.00 ± 2.00	113.67 ± 5.40	94.72 ± 5.86	100.48 ± 5.76	24.40 ± 4.09	11.97 ± 1.15	17.58 ± 2.18	4.49 ± 0.94
During infusion (rate)*								
0.1	42.88 ± 1.83	107.06 ± 5.55	86.06 ± 5.95	93.03 ± 5.78	21.38 ± 2.91	13.15 ± 2.05	16.68 ± 2.37	2.99 ± 1.08†
0.2	41.71 ± 2.13	105.06 ± 4.36	85.50 ± 5.63	92.01 ± 5.16	23.67 ± 3.31	13.17 ± 2.27	18.58 ± 2.50	3.07 ± 1.08†
0.3	43.20 ± 2.44	111.67 ± 4.02	91.50 ± 5.16	98.22 ± 4.74	27.35 ± 2.86	16.20 ± 3.31	21.33 ± 2.60	3.46 ± 1.04
0.4	40.59 ± 1.74	113.83 ± 5.42	92.56 ± 6.09	99.64 ± 5.79	28.17 ± 3.17	16.55 ± 2.45	21.83 ± 2.26	3.38 ± 0.99
0.5	45.19 ± 2.40	105.44 ± 5.14	86.28 ± 5.56	92.68 ± 5.36	26.38 ± 2.86	15.97 ± 1.22	20.63 ± 1.20	3.71 ± 1.02
0.6	43.56 ± 2.52	110.33 ± 6.00	87.72 ± 6.23	95.24 ± 6.14	25.80 ± 3.18	16.77 ± 1.63	20.75 ± 1.79	4.20 ± 0.96
0.7	42.00 ± 1.96	111.72 ± 5.13	88.11 ± 5.50	95.97 ± 5.37	25.63 ± 3.78	13.23 ± 1.32	19.08 ± 1.88	4.01 ± 0.88
0.8	44.71 ± 3.28	115.94 ± 5.02	89.83 ± 5.29	98.53 ± 5.16	28.47 ± 3.69	14.28 ± 2.24	20.93 ± 1.53	3.66 ± 1.10
0.9	44.75 ± 2.43	112.61 ± 5.28	87.89 ± 5.31	96.13 ± 5.27	28.20 ± 4.24	13.00 ± 0.89	19.88 ± 1.55	4.56 ± 0.87
1.0	43.29 ± 3.08	112.44 ± 4.92	86.94 ± 5.31	95.44 ± 5.15	28.10 ± 3.67	13.02 ± 1.47	20.22 ± 0.99	4.61 ± 0.89
After infusion (min)								
1	—	113.50 ± 5.29	89.61 ± 5.23	97.57 ± 5.23	—	—	—	4.80 ± 0.86
2	—	112.61 ± 5.30	88.78 ± 5.55	96.72 ± 5.45	—	—	—	3.90 ± 1.02
3	—	112.67 ± 5.37	87.72 ± 5.50	96.06 ± 5.45	—	—	—	3.77 ± 0.95
5	45.47 ± 2.06	109.78 ± 5.38	86.89 ± 5.41	94.49 ± 5.37	25.83 ± 3.16	13.20 ± 1.46	18.93 ± 1.39	3.87 ± 0.84
15	42.06 ± 1.78	108.61 ± 5.05	86.28 ± 4.99	93.73 ± 4.98	26.57 ± 2.06	16.03 ± 1.89	20.60 ± 1.15	4.24 ± 0.87
30	44.60 ± 2.71	106.61 ± 4.43	81.72 ± 4.45	90.01 ± 4.41	27.73 ± 1.95	17.67 ± 2.06	22.32 ± 1.46	4.59 ± 0.93
45	37.88 ± 2.51	124.42 ± 1.81	100.00 ± 1.55	108.13 ± 1.60	30.33 ± 3.84	15.67 ± 5.24	22.67 ± 2.60	4.53 ± 1.23
60	41.29 ± 5.00	126.83 ± 1.57	104.17 ± 1.18	111.73 ± 1.25	29.58 ± 2.36	15.90 ± 4.15	22.83 ± 2.46	3.42 ± 1.09†

*Horses were given an infusion of saline solution equivalent to the volume that was administered to horses receiving ATP $MgCl_2$. Values represent No. of mg of ATP/kg of body weight/min. Each rate of infusion was maintained for 10 minutes before it was incrementally increased to the next rate, and measurements were obtained at the end of each 10-minute infusion period. †Within a column, value differs significantly ($P \leq 0.05$) from value before infusion value.

SAP = Systolic arterial pressure. DAP = Diastolic arterial pressure. MAP = Mean arterial pressure. SPAP = Systolic pulmonary arterial pressure. DPAP = Diastolic pulmonary arterial pressure. MPAP = Mean pulmonary arterial pressure. MRAP = Mean right atrial pressure. — = Not determined.

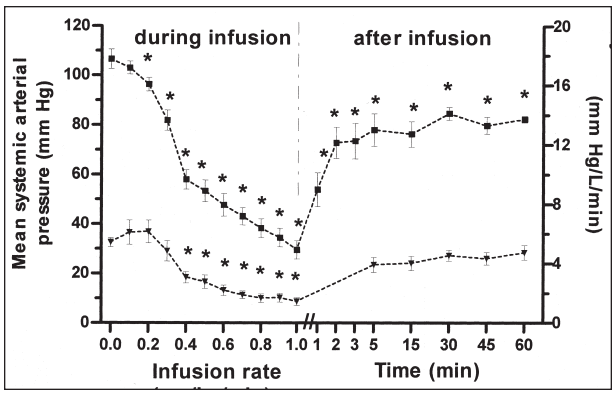

Figure 2—Mean (± SEM) systemic arterial pressure (square) and systemic vascular resistance (triangle) before, during, and after IV infusion of ATP-$MgCl_2$ to 6 horses. Notice the scale on the x-axis represents infusion rate (mg of ATP/kg of body weight/min) during infusion and time (minutes) after infusion. Each rate of infusion was maintained for 10 minutes before it was incrementally increased to the next rate, and measurements were obtained at the end of each 10-minute infusion period. *Value differs significantly ($P < 0.05$) from value obtained before infusion.

Results

Systemic hemodynamic variables—We did not detect significant differences between horses in groups 1 and 2 for any measured or calculated variable before infusion (baseline values). Consistent significant changes over time were not detected for any measured or calculated systemic hemodynamic variable in group-1 horses except for MRAP (**Table 1**). In group-2 horses, significant changes over time were evident for several systemic hemodynamic variables (**Fig 2**; **Table 2**).

Colonic hemodynamic variables—We did not detect significant differences between groups 1 and 2 for any measured or calculated variable before infusion. Significant alterations were not observed for any local colonic hemodynamic variable over time in group-1 horses (**Table 3**). In group-2 horses, significant decreases in hemodynamic variables for the dorsal and ventral colon were detected over time (**Table 4**). Similarly, significant differences were detected over time for overall colonic hemodynamic variables (**Fig 3–5**). Colonic seromuscular perfusion was significantly decreased over time (**Table 5**).

Measurement of NO—Colonic arterial or venous plasma NO concentrations did not differ significantly over time for group-1 horses. However, significant decreases in colonic arterial and venous plasma NO concentrations were observed in group-2 horses 45 and 60 minutes after discontinuation of the ATP-$MgCl_2$ infusion.

ECG abnormalities—Six horses developed cardiac arrhythmias during the study. Arrhythmias were detected in 1 horse in group 1 and 5 horses in group 2. The group-1 horse had atrial premature contractions prior to the start of the infusion, during infusion at rates of 0.2 and 1.0 mg/kg/min, and 3 minutes after completion of the infusion.

Two horses in group 2 developed periods of transient sinus arrest, which were detected in 1 horse before the start of the infusion and 1 horse after the start of the infusion. A third horse had intermittent second-degree atrioventricular block before and after the start of the infusion. A fourth horse had ventricular premature contractions before the start of the infu-

Table 2—Systemic hemodynamic variables (mean ± SEM) before, during, and after IV infusion of ATP-$MgCl_2$ to 6 horses

Time	Cardiac index (ml/min/kg)	SAP (mm Hg)	DAP (mm Hg)	MAP (mm Hg)	SPAP (mm Hg)	DPAP (mm Hg)	MPAP (mm Hg)	MRAP (mm Hg)
Before infusion	46.61 ± 1.38	120.89 ± 4.28	99.44 ± 3.90	106.60 ± 3.90	24.12 ± 3.47	15.80 ± 2.43	19.02 ± 2.73	0.75 ± 1.02
During infusion (rate)*								
0.1	43.50 ± 2.64	117.39 ± 2.88	95.78 ± 2.78	102.99 ± 2.63	39.22 ± 8.54†	27.37 ± 6.62†	33.70 ± 8.10†	0.01 ± 1.03
0.2	39.78 ± 2.25	115.50 ± 3.91	86.78 ± 2.48†	96.34 ± 2.74†	35.48 ± 4.15†	20.33 ± 0.97	28.32 ± 3.00†	0.55 ± 0.88
0.3	41.89 ± 2.30	103.22 ± 5.07†	71.17 ± 3.86†	81.85 ± 4.08†	31.22 ± 2.64	19.15 ± 2.64	25.12 ± 1.94	1.30 ± 0.60
0.4	45.83 ± 2.02	78.61 ± 4.20†	47.61 ± 3.80†	57.94 ± 3.87†	33.83 ± 2.61	20.40 ± 2.77	26.15 ± 1.87	0.94 ± 0.81
0.5	48.28 ± 4.49	72.44 ± 4.81†	43.83 ± 4.24†	53.83 ± 4.35†	25.73 ± 4.93	20.88 ± 1.56	25.95 ± 1.68	0.31 ± 0.93
0.6	52.06 ± 3.61	66.39 ± 5.43†	38.56 ± 4.18†	47.65 ± 4.55†	28.95 ± 2.89	18.40 ± 2.46	24.03 ± 2.56	0.46 ± 0.80
0.7	53.78 ± 4.09	61.22 ± 5.40†	34.06 ± 2.71†	43.12 ± 3.54†	26.38 ± 1.25	17.22 ± 1.57	22.27 ± 1.60	1.56 ± 0.62
0.8	53.06 ± 3.84	53.33 ± 5.74†	30.72 ± 2.90†	38.25 ± 3.80†	23.83 ± 2.12	16.12 ± 2.30	20.30 ± 2.31	0.93 ± 1.01
0.9	44.61 ± 2.32	48.72 ± 5.79†	27.44 ± 2.73†	34.48 ± 3.72†	20.63 ± 1.60	12.50 ± 1.91	17.82 ± 2.10	1.57 ± 0.78
1.0	44.28 ± 2.61	41.56 ± 5.65†	23.56 ± 2.74†	29.56 ± 3.66†	20.95 ± 1.45	13.83 ± 1.49	18.20 ± 1.81	1.33 ± 0.96
After infusion (min)								
1	—	74.94 ± 9.23†	43.39 ± 5.83†	53.91 ± 6.89†	—	—	—	0.26 ± 1.07
2	—	96.00 ± 7.32†	61.28 ± 5.94†	72.86 ± 6.26†	—	—	—	–0.86 ± 0.87†
3	—	96.20 ± 8.26†	62.20 ± 6.95†	73.54 ± 7.24†	—	—	—	–0.92 ± 1.07†
5	49.40 ± 3.01	102.47 ± 7.99†	65.80 ± 6.11†	78.03 ± 6.56†	22.34 ± 1.87	16.72 ± 2.16	19.26 ± 1.73	–1.57 ± 0.95†
15	46.73 ± 1.80	98.93 ± 6.33†	65.00 ± 4.78†	76.31 ± 5.14†	26.20 ± 1.96	17.20 ± 2.54	22.26 ± 1.89	–0.65 ± 0.78
30	46.93 ± 1.30	105.20 ± 3.58†	74.33 ± 2.40†	84.62 ± 2.65†	24.06 ± 0.42	17.46 ± 0.99	21.66 ± 0.80	–1.82 ± 1.00†
45	46.09 ± 1.74	98.67 ± 4.77†	70.50 ± 2.91†	79.88 ± 3.47†	24.33 ± 2.33	14.67 ± 1.45	22.00 ± 2.08	–0.18 ± 0.60
60	43.90 ± 0.97	99.08 ± 1.88†	74.00 ± 1.45†	82.38 ± 1.28†	28.00 ± 4.04	17.33 ± 2.33	22.67 ± 2.60	–1.37 ± 0.89†

See Table 1 for key.

Table 3—Colonic hemodynamic variables (mean ± SEM) before, during, and after IV infusion of saline solution to 6 horses

Time	DCAP (mm Hg)	VCAP (mm Hg)	DCVP (mm Hg)	VCVP (mm Hg)	DCF (ml/min)	VCF (ml/min)	DCR (mmHg/ml/min)	VCR (mm Hg/ml/min)
Before infusion	77.00 ± 6.79	92.67 ± 3.13	9.59 ± 1.32	8.97 ± 1.14	128.83 ± 6.96	434.56 ± 24.66	0.57 ± 0.14	0.20 ± 0.02
During infusion (rate)*								
0.1	69.89 ± 6.58	84.33 ± 4.66	9.72 ± 1.15	8.73 ± 1.15	122.28 ± 7.57	435.78 ± 24.77	0.51 ± 0.11	0.18 ± 0.03
0.2	68.61 ± 7.27	89.00 ± 5.68	9.86 ± 1.23	9.31 ± 1.17	122.11 ± 6.23	419.83 ± 24.09	0.52 ± 0.13	0.20 ± 0.03
0.3	70.94 ± 5.23	87.56 ± 4.40	9.09 ± 1.07	8.18 ± 1.01	124.94 ± 8.00	395.83 ± 24.17	0.52 ± 0.09	0.22 ± 0.03
0.4	75.39 ± 6.53	88.06 ± 3.92	9.49 ± 1.17	8.67 ± 1.13	123.61 ± 6.21	433.17 ± 20.34	0.55 ± 0.11	0.19 ± 0.02
0.5	74.00 ± 6.55	89.50 ± 5.32	9.85 ± 1.21	9.12 ± 1.09	113.28 ± 2.00	416.11 ± 18.23	0.56 ± 0.09	0.20 ± 0.03
0.6	73.22 ± 7.05	88.33 ± 4.42	9.62 ± 1.18	9.11 ± 1.04	114.33 ± 4.10	402.17 ± 12.08	0.54 ± 0.08	0.20 ± 0.02
0.7	71.67 ± 7.21	91.11 ± 3.59	9.81 ± 1.13	9.18 ± 1.13	112.72 ± 3.68	430.33 ± 15.41	0.53 ± 0.09	0.19 ± 0.02
0.8	72.94 ± 6.82	89.06 ± 4.20	10.11 ± 1.11	9.13 ± 1.08	131.67 ± 4.37	463.83 ± 23.35	0.49 ± 0.09	0.18 ± 0.02
0.9	71.61 ± 7.20	90.83 ± 4.41	9.95 ± 1.09	9.28 ± 1.10	150.28 ± 13.92	437.17 ± 23.14	0.44 ± 0.10	0.20 ± 0.03
1.0	70.39 ± 7.18	89.28 ± 4.16	10.32 ± 1.16	9.31 ± 1.14	160.39 ± 14.01	463.22 ± 33.41	0.38 ± 0.08	0.19 ± 0.03
After infusion (min)								
1	75.93 ± 5.70	90.93 ± 5.62	10.67 ± 1.16	9.49 ± 1.06	148.94 ± 15.06	439.67 ± 23.98	0.48 ± 0.06	0.20 ± 0.04
2	76.53 ± 6.18	89.20 ± 5.63	10.52 ± 1.16	9.44 ± 1.18	162.89 ± 15.79	433.83 ± 25.03	0.44 ± 0.05	0.20 ± 0.04
3	70.83 ± 5.78	88.88 ± 4.83	9.86 ± 1.20	9.33 ± 1.14	144.00 ± 12.05	420.56 ± 29.22	0.44 ± 0.06	0.21 ± 0.04
5	66.00 ± 5.95	88.61 ± 4.68	10.01 ± 1.29	9.28 ± 1.20	152.39 ± 13.99	412.94 ± 28.94	0.39 ± 0.06	0.21 ± 0.04
15	66.72 ± 5.01	87.28 ± 4.37	10.17 ± 1.35	9.46 ± 1.25	140.00 ± 11.19	437.61 ± 26.10	0.42 ± 0.06	0.19 ± 0.03
30	70.67 ± 5.32	89.83 ± 4.47	9.94 ± 1.21	9.44 ± 1.12	135.89 ± 11.30	421.00 ± 22.85	0.47 ± 0.07	0.20 ± 0.03
45	85.67 ± 2.66	94.00 ± 1.99	12.29 ± 1.30	12.88 ± 0.51	135.50 ± 3.95	465.58 ± 31.26	0.55 ± 0.06	0.18 ± 0.02
60	82.83 ± 3.57	95.75 ± 2.54	12.35 ± 1.19	11.83 ± 0.85	141.83 ± 6.76	478.75 ± 29.63	0.51 ± 0.07	0.18 ± 0.01

DCAP = Dorsal colon arterial pressure. VCAP = Ventral colon arterial pressure. DCVP = Dorsal colon venous pressure. VCVP = Ventral colon venous pressure. DCF = Dorsal colon blood flow. VCF = Ventral colon blood flow. DCR = Dorsal colon resistance. VCR = Ventral colon resistance.
See Table 1 for key.

sion, during infusion at rates of 0.1 to 0.5 mg/kg/min, and during infustion at ≥ 0.9 mg/kg/min until the end of the study. At 2.75 minutes after discontinuation of the infusion, this horse developed ventricular fibrillation and died. A fifth horse had an undefined atrial arrhythmia before and after start of the infusion.

Discussion

Intravenous infusion of ATP-$MgCl_2$ in clinically normal anesthetized adult horses caused a rate-dependent decrease in SR_L and colonic vascular resistance, principally via its vasodilatory effects. In contrast to studies performed in other species, mild transient pulmonary hypertension developed in the group-2 horses during infusion at rates of 0.1 and 0.2 mg/kg/min. In another study,[27] our group of investigators determined that the maximum rate for safe IV infusion in conscious adult horses was 0.3 mg of ATP/kg/min. Administration of ATP-$MgCl_2$ at a rate of 0.3 mg/kg/min in the study reported here caused a significant decrease in colonic arterial pressure and colonic vascular resistance without a significant decrease in colonic arterial blood flow.

Table 4—Colonic hemodynamic variables (mean ± SEM) before, during, and after IV infusion of ATP-$MgCl_2$ to 6 horses

Time	DCAP (mm Hg)	VCAP (mm Hg)	DCVP (mm Hg)	VCVP (mm Hg)	DCF (ml/min)	VCF (ml/min)	DCR (mm Hg/ml/min)	VCR (mm Hg/ml/min)
Before infusion	88.28 ± 2.64	88.56 ± 2.44	9.38 ± 0.93	10.41 ± 1.12	129.67 ± 12.72	592.00 ± 54.80	0.73 ± 0.15	0.16 ± 0.03
During infusion (rate)*								
0.1	84.67 ± 2.33	85.72 ± 2.06	8.14 ± 0.95	8.91 ± 1.19†	139.28 ± 14.45	571.67 ± 52.29	0.69 ± 0.16	0.16 ± 0.03
0.2	79.33 ± 2.50	79.33 ± 2.70	8.43 ± 1.01	9.20 ± 1.25†	133.56 ± 13.46	514.39 ± 46.27	0.64 ± 0.13	0.16 ± 0.02
0.3	61.61 ± 2.68†	64.83 ± 2.56†	8.22 ± 0.92	8.94 ± 1.06†	135.61 ± 13.42	502.56 ± 70.56	0.43 ± 0.05†	0.14 ± 0.02
0.4	42.78 ± 2.19†	45.22 ± 3.09†	7.87 ± 0.77†	9.00 ± 0.96†	115.67 ± 6.86	460.72 ± 41.70†	0.31 ± 0.03†	0.09 ± 0.01
0.5	40.94 ± 3.93†	42.11 ± 3.69†	8.74 ± 0.72	9.66 ± 0.95	121.33 ± 10.96	431.06 ± 42.24†	0.29 ± 0.04†	0.09 ± 0.02
0.6	36.11 ± 4.36†	36.89 ± 4.23†	9.42 ± 0.84	9.80 ± 1.05	120.06 ± 12.79	418.00 ± 56.14†	0.23 ± 0.04†	0.09 ± 0.02
0.7	35.11 ± 3.72†	36.11 ± 4.49†	8.64 ± 0.81	9.54 ± 0.98	129.72 ± 12.07	411.94 ± 59.14†	0.22 ± 0.04†	0.10 ± 0.03
0.8	29.00 ± 2.98†	29.22 ± 3.09†	7.51 ± 0.76†	8.71 ± 1.03†	105.33 ± 10.43	374.11 ± 46.17†	0.22 ± 0.03†	0.07 ± 0.02†
0.9	23.33 ± 1.45†	26.22 ± 2.64†	7.57 ± 0.80†	8.36 ± 0.95†	93.78 ± 12.16	358.39 ± 46.17†	0.23 ± 0.06†	0.06 ± 0.01†
1.0	20.70 ± 1.45†	22.28 ± 2.59†	6.59 ± 0.77†	7.54 ± 0.91†	90.78 ± 12.77†	316.61 ± 41.54†	0.26 ± 0.10†	0.09 ± 0.04
After infusion (min)								
1	40.78 ± 5.31†	41.72 ± 5.96†	8.36 ± 0.97	9.21 ± 1.09†	133.61 ± 19.65	393.33 ± 34.81†	0.28 ± 0.04†	0.09 ± 0.02
2	57.94 ± 5.87†	61.50 ± 5.80†	7.91 ± 0.85†	8.91 ± 0.98†	118.00 ± 11.23	418.56 ± 39.90†	0.44 ± 0.07†	0.13 ± 0.02
3	63.27 ± 6.90†	62.40 ± 7.07†	8.39 ± 1.15†	8.75 ± 1.33	132.47 ± 16.00	462.73 ± 57.08†	0.45 ± 0.09†	0.12 ± 0.02
5	66.40 ± 5.91†	66.33 ± 6.70†	9.57 ± 1.65	9.65 ± 1.67	142.93 ± 13.39	523.20 ± 55.05	0.42 ± 0.07†	0.12 ± 0.02
15	63.93 ± 4.44†	66.07 ± 4.80†	7.77 ± 1.10†	8.25 ± 1.29†	146.40 ± 14.14	529.73 ± 64.80	0.42 ± 0.07†	0.12 ± 0.02
30	70.27 ± 2.27†	73.60 ± 3.04†	8.36 ± 1.28†	7.81 ± 1.39†	140.00 ± 12.15	512.07 ± 58.23	0.49 ± 0.10	0.15 ± 0.03
45	69.17 ± 2.49†	68.33 ± 3.51†	9.66 ± 0.68	9.50 ± 0.80†	130.83 ± 13.64	496.75 ± 73.68	0.53 ± 0.14	0.14 ± 0.02
60	69.08 ± 1.18†	74.08 ± 3.07†	10.67 ± 1.00	10.13 ± 1.10	120.75 ± 11.97	536.67 ± 76.04	0.55 ± 0.12	0.14 ± 0.02

See Table 1 for key.

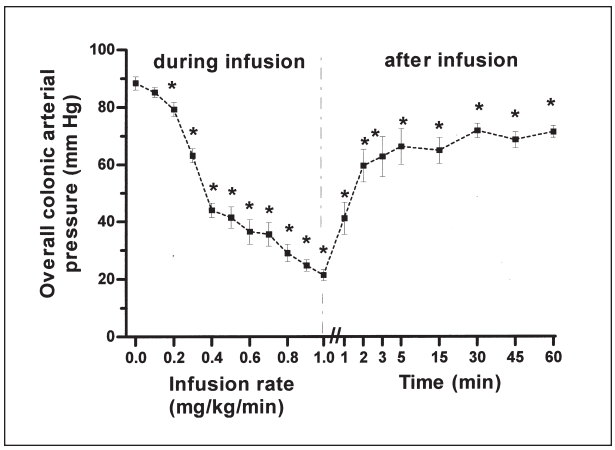

Figure 3—Mean (± SEM) overall colonic arterial pressure before, during, and after infusion of ATP-$MgCl_2$ to 6 horses. *See* Fig 2 for key.

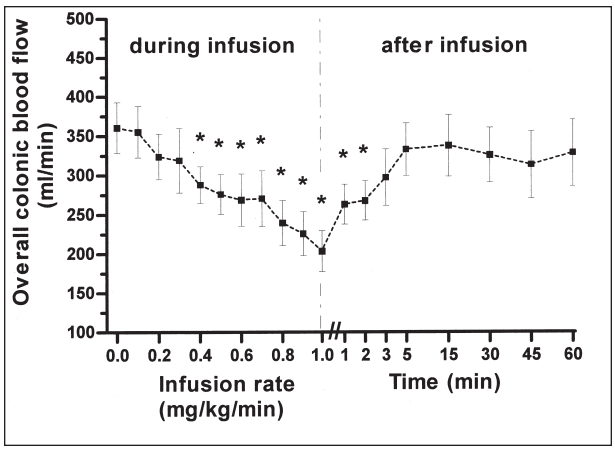

Figure 4—Mean (± SEM) overall colonic arterial blood flow before, during, and after infusion of ATP-$MgCl_2$ to 6 horses. *See* Fig 2 for key.

However, at rates of ≥ 0.4 mg/kg/min, blood flow to colonic vasculature could not be maintained because of an insufficient pressure gradient secondary to a severe decrease in MAP. Below a critical intravascular pressure, blood flow will not be maintained without increasing the pressure gradient. Mean MAP during the infusion at a rate of 0.3 mg/kg/min was 121.9 mm Hg in our previous study[27] and 81.85 mm Hg in the study reported here. The systemic arterial pressure at which the pressure gradient becomes insufficient to maintain blood flow to the splanchnic circulation is not known in horses. In clinical situations, systemic hypotension during anesthetic episodes is generally not treated until MAP reaches ≤ 60 mm Hg. During the infusion at a rate for which a significant alteration in colonic arterial blood flow was observed (0.4 mg/kg/min), mean MAP was 58 mm Hg. Analysis of results of the study reported here suggests that an infusion rate of 0.3 mg of ATP/kg/min may be beneficial to improve tissue perfusion to the ascending colon following an ischemic insult, provided the pressure gradient is maintained. However, the rate of infusion of ATP-$MgCl_2$ may need to be decreased in horses with hypotension secondary to hypovolemia or endotoxemia, which is common with diseases that cause intestinal ischemia.

Systemic and colonic hemodynamic alterations observed in group-2 horses were directly related to administration of ATP-$MgCl_2$. We did not observe significant differences in any measured or calculated variable between the 2 groups before the start of the infusion. Also, there were not consistent significant changes over time in group-1 horses. Therefore, hemodynamic alterations that were observed in group-2 horses were attributed to the effects of ATP-$MgCl_2$ administration and not to differences between groups, effects of anesthesia, or effects of time.

Table 5—Colonic mucosal and seromuscular perfusion (mean ± SEM) before, during, and after IV infusion of saline solution (group 1) or ATP-$MgCl_2$ (group 2)

	Group 1 (n = 6)		Group 2 (n = 6)	
Time	CMP (cpu)	CSP (cpu)	CMP (cpu)	CSP (cpu)
Before infusion	14.65 ± 1.61	17.69 ± 2.38	20.51 ± 2.36	25.03 ± 4.09
During infusion (rate)*				
0.1	13.53 ± 1.26	18.82 ± 2.51	28.41 ± 3.19†	21.36 ± 2.35
0.2	12.06 ± 0.97	18.45 ± 2.00	25.49 ± 3.50	25.30 ± 2.65
0.3	13.01 ± 1.08	16.97 ± 2.14	25.78 ± 2.92	17.72 ± 1.90†
0.4	15.06 ± 1.03	19.56 ± 3.03	24.38 ± 3.25	13.98 ± 0.86†
0.5	12.72 ± 1.16	17.69 ± 3.33	20.36 ± 3.00	16.23 ± 2.57†
0.6	16.79 ± 1.64	18.32 ± 3.08	26.68 ± 5.59	12.24 ± 1.31†
0.7	14.91 ± 1.60	16.25 ± 3.01	22.57 ± 4.86	12.17 ± 1.78†
0.8	16.26 ± 1.37	19.19 ± 3.49	18.01 ± 2.46	10.81 ± 1.59†
0.9	14.69 ± 1.93	20.04 ± 3.60	21.04 ± 4.83	9.68 ± 1.33†
1.0	15.41 ± 1.99	16.73 ± 3.42	18.32 ± 4.08	9.37 ± 1.13†
After infusion (min)				
1	15.17 ± 1.42	17.92 ± 2.69	22.90 ± 4.52	13.74 ± 1.64†
2	16.56 ± 1.65	18.18 ± 3.04	20.62 ± 2.90	16.52 ± 2.49†
3	15.96 ± 2.05	19.57 ± 3.53	24.11 ± 2.28	21.27 ± 3.44
5	16.04 ± 1.28	18.32 ± 3.11	20.74 ± 2.26	15.60 ± 2.44†
15	18.25 ± 1.60	16.45 ± 2.73	19.71 ± 2.14	16.71 ± 1.69†
30	15.24 ± 1.98	17.61 ± 2.64	29.76 ± 5.57†	14.69 ± 1.37†
45	17.82 ± 1.13	21.64 ± 3.38	15.00 ± 1.17	11.35 ± 2.07†
60	16.20 ± 2.19	18.71 ± 2.67	16.55 ± 2.65	12.07 ± 1.50†

CMP = Colonic mucosal perfusion. cpu = Capillary perfusion units. CSP = Colonic seromuscular perfusion. *See* Table 1 for key.

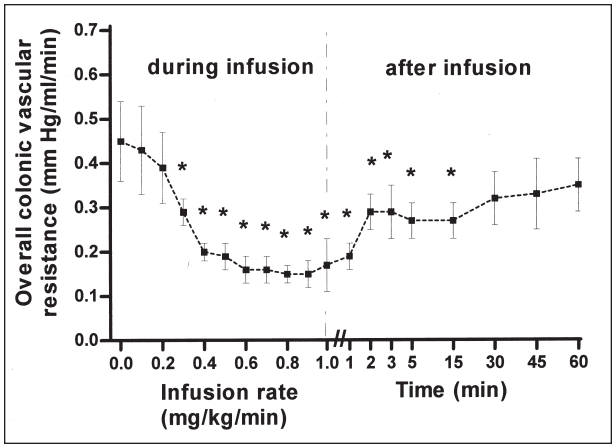

Figure 5— Mean (± SEM) overall colonic vascular resistance before, during, and after infusion of ATP-$MgCl_2$ to 6 horses. *See* Fig 2 for key.

The mechanism by which ATP-$MgCl_2$ induces vasodilatation has been investigated. In lambs, administration of N^{ω}-nitro-L-arginine[30] or methylene blue[31] (an inhibitor or scavenger, respectively, of NO) inhibited vasodilatation, whereas administration of indomethacin (a prostacyclin inhibitor) and theophylline[32] (an adenosine inhibitor) did not. On the basis of those findings, it was concluded that ATP-$MgCl_2$ exerts its vasodilatory effects through endothelial-derived NO rather than prostacyclin, adenosine, or $MgCl_2$.[30,31]

Magnesium reportedly is a potent vasodilatory agent and can potentiate vasodilatation in vivo when combined with ATP.[19] However, we do not believe that magnesium was a major contributor to the vasodilatory response observed in the colonic vasculature in the study reported here. In an in vitro study conducted by our laboratory group, we documented that addition of $MgCl_2$ (10^{-12} to $10^{-4}M$) to equimolar concentrations of ATP did not enhance the relaxation response of equine colonic arterial and venous rings with intact or denuded endothelium that were previously contracted with endothelin-1, compared with ATP alone. Additionally, $MgCl_2$ alone did not cause appreciable relaxation of colonic vascular rings with intact or denuded epithelium that were previously contracted with endothelin-1. On the basis of that information, systemic and colonic vasodilatory responses observed in the study reported here likely were mediated through ATP directly or through an ATP metabolite. However, we do not know whether the in vivo and in vitro vascular responses to magnesium are similar. Whether magnesium contributed to the vasodilatory response observed in the systemic circulation in this study is not known.

Magnitude of the hemodynamic alterations produced by IV administration of ATP-$MgCl_2$ is dependent on rate of administration, site of infusion, species of animal, whether the animals are conscious or anesthetized, and whether the animals are healthy or have signs of systemic disease. In contrast to our study[27] on conscious horses in which we observed significant increases in cardiac output, cardiac index, heart rate, and PAP over time, the group-2 horses in the study reported here did not have a similar pattern. Anesthesia may override the presumed sympathetic stimulation that accompanies ATP-$MgCl_2$ administration. In healthy conscious men, administration at rates of 0.1 to 0.4 mg of ATP/kg/min resulted in significant increases in cardiac output and heart rate without changes in MAP.[18] A study[33] in healthy conscious lambs

receiving ATP-$MgCl_2$ IV at 3 rates of infusion (0.1, 0.5, or 1.0 mg/kg/min) revealed that there was not a change in heart rate and MPAP, but cardiac output increased during the highest rate, and MAP decreased during infusion at rates of 0.5 and 1.0 mg/kg/min. In healthy anesthetized dogs, infusion at rates of 0.6 to 2.5 mg/kg/min increased cardiac output and decreased MAP.[21]

The anesthetized horses in the study reported here and the conscious horses in our other study[27] developed pulmonary hypertension, which is in contrast to a study[30] conducted in resting lambs in which researchers did not document changes in PAP after ATP-$MgCl_2$ administration. The reason for the pulmonary hypertension is not known; however, several possibilities exist. For the action of a vasodilatory agent to be documented, there may have to be tissue vasoconstriction.[14] Results of in vitro studies have indicated that there can be a variation in response to ATP administration in different vascular beds and in vessels under various vascular tensions.[14] In certain blood vessels, ATP can stimulate the smooth muscle directly (via P_{2X}) and cause vasoconstriction.[34] In other vascular beds, ATP stimulates endothelial P_{2Y} and causes vasodilatation.[14] If ATP is metabolized to adenosine, activation of A_2 can lead to vascular relaxation.[16] Under resting tension, ATP induces vasoconstriction in some vascular beds; however, if tension is increased, vasodilatation will result.[14]

Data obtained from the laser-Doppler flow probes located on the serosal and mucosal surfaces of the ascending colon revealed large variation in recorded values. The most likely explanation for this variation is that the intestine is a continually motile organ. A disadvantage of the technique is its high sensitivity to motion-produced disturbances.[35,36] When the laser beam is not directed perpendicular to the tissues, loss of intimate contact of the probe with the tissues results in inaccurate values being recorded.[35,36] Therefore, the method we used here to assess serosal and mucosal blood flow cannot currently be recommended. A superior method to assess distribution of blood flow to various layers of the intestinal tract would be to use radiolabeled or colored microspheres.[37,38]

As previously stated, the mechanism of ATP-induced vasodilatation in other species is through increased production of NO. We did not observe a significant increase in colonic arterial or venous plasma NO concentrations in our group-2 horses despite significant vasodilatation in colonic vasculature. Potential reasons for the apparent lack of increase in NO production during ATP-$MgCl_2$ administration include lack of sensitivity of the assay method, NO release on the basilar rather than apical surface of the cell and subsequent escape into the vascular lumen, another mechanism for ATP-induced vasodilatation in horses, or vasodilatation that results from $MgCl_2$ or breakdown products of ATP. Production of NO is constitutive or inducible.[39] The ATP-induced vasodilatation is through induction of the **constitutive form of NO synthase (cNOS)** in the endothelium.[13] Only picomolar quantities of NO are released via cNOS, making it difficult to detect small changes in concentrations of NO. Reasons for the decrease in NO concentrations observed in the group-2 horses after discontinuation of the infusion are not known but may have been attributable to cessation of stimulation of cNOS.

Short-term homeostatic control of arterial blood pressure is mediated primarily by baroreceptor reflexes.[40,41] Acute decreases (or, conversely, increases) in arterial pressure are detected by arterial baroreceptors and result in reflex increases (or, conversely, decreases) in heart rate.[40,41] In the study reported here, there was failure of the arterial baroreceptor reflex to respond to hypotension induced by administration of ATP-$MgCl_2$. Baroreflex sensitivity is depressed by IV and inhalation administration of anesthetics in numerous species.[42-45] Although IV-administered anesthetic-induced depression of the baroreflex can be less than that for inhalant anethetics,[46,47] there was failure of the baroreflex to correct the profound decrease in systemic arterial pressure in the horses in our study.

Cardiac arrhythmias were observed in 6 of 12 horses in this study. The majority (5/6) of arrhythmias were in horses administered ATP-$MgCl_2$. However, 4 of 5 horses that received ATP-$MgCl_2$ had evidence of cardiac arrhythmias before the start of the infusion. Exact cause of the arrhythmias in the horses is not known, but they may have been associated with administration of preanesthetic and anesthetic agents or use of cardiac catheters. In humans, cardiac catheterization has a reported complication rate of approximately 23%.[48] In our previous study,[27] 3 of 6 conscious horses receiving ATP-$MgCl_2$ had cardiac arrhythmias, all of which were detected before the start of the infusion. In those horses, it was suspected that arrhythmias were associated with the cardiac catheters.

The most common cardiac disturbance detected in the group of anesthetized horses reported here involved slowing of conduction through the heart. Administration of ATP-$MgCl_2$ should be used with caution in horses with pre existing atrioventricular conduction disturbances, because ATP and adenosine are biological compounds with potent depressant activity on the atrioventricular node.[49-51] Because of this effect, ATP has been used to treat supraventricular arrhythmias.[52] Antiarrhythmic effects of ATP are produced by blocking the reentry circuit in the atrioventricular node.[53] Atrioventricular conduction disturbances (first-, second-, and third-degree atrioventricular block) have been observed during continuous IV infusion of ATP.[50] In contrast, ATP can exert an excitatory effect on intraventricular automaticity.[49]

Arrhythmias may be associated with reperfusion of ischemic myocardium, which may be a major progenitor for sudden cardiac death in people.[54] The electrophysiologic basis for arrhythmias associated with reperfusion appears to be heterogenous electrical recovery, but the precise alterations responsible for malignant versus nonmalignant arrhythmias are unknown.[54] Cause of ventricular fibrillation and death in 1 horse in the study reported here is not known, but we speculate that it was attributable to reperfusion phenomenon of the hypoxic myocardium secondary to profound systemic hypotension (MAP of

22.9 mm Hg during infusion at the maximal rate) during the infusion at the higher infusion rates. This horse had evidence of premature ventricular contractions before the start of the infusion, which can be indicative of pre existing myocardial disease or electrolyte imbalances.[55] Electrolyte abnormalities were not detected. Therefore, pre existing myocardial disease that was exacerbated by profound hypotension and secondary hypoxia may have been the cause of ventricular fibrillation in this horse. Because of the potential for atrioventricular conduction disturbances and the increased potential for arrhythmias to develop secondary to systemic hypotension and myocardial ischemia, heart rate and rhythm should be monitored in horses, especially critically ill horses, receiving an IV infusion of ATP-$MgCl_2$.

Administration of ATP-$MgCl_2$ to healthy anesthetized horses caused a rate-dependent decrease in SR_L and colonic vascular resistance. Additional studies are required to determine the efficacy of ATP-$MgCl_2$ for use in the treatment of horses with intestinal ischemia. Reduction in blood flow and decreased mucosal ATP content that persists following correction of experimentally induced ischemia of the ascending colon may be attenuated via IV administration of ATP-$MgCl_2$ by improving blood flow and supplying substrate (ATP) and cofactor (magnesium) to the highly metabolically active mucosal layer.

[a]Rompun, Mobay Corp, Animal Health Division, Shawnee, Kan.
[b]Torbugesic, Fort Dodge Animal Health, Fort Dodge, Iowa.
[c]Angiocath 382269, Becton Dickson Infusion Therapy Systems Inc, Sandy, Utah.
[d]Pentalumen thermodilution catheter 41216–01, Abbott Critical Care Systems, Abbott Laboratories, North Chicago, Ill.
[e]Intramedic polyethylene tubing model PE260, Becton Dickson, Sparks, Md.
[f]Normosol, Abbott Laboratories, North Chicago, Ill.
[g]Injector 500, Columbus Instruments, Columbus, Ohio.
[h]Cardio Max II model 85 thermodilution cardiac output computer, Columbus Instruments, Columbus, Ohio.
[i]Intramedic polyethylene tubing model PE205, Becton Dickson, Sparks, Md.
[j]Guaifenesin 0190–8, Puger Chemical Co Inc, Irvington, NJ.
[k]Pentothal 8912, Abbott Laboratories, North Chicago, Ill.
[l]Sodium pentobarbital injection, The Butler Co, Columbus, Ohio.
[m]Anesthesia Ventilator model NELAC-E, North American Drager, Telford, Pa.
[n]Quick-Cath 2N-11–13, Baxter Healthcare Corp, Deerfield, Ill.
[o]Quik-Cath 2N-11–10, Baxter Healthcare Corp, Deerfield, Ill.
[p]Adenosine 5'-triphosphate disodium salt A3377 and magnesium chloride hexahydrate M2670, Sigma Chemical Co, St Louis, Mo.
[q]K module model K-20, Baxter Healthcare Corp, Pharmaseal Division, Valencia, Calif.
[r]Probe No. 3S1174 model T206, Transonic Systems Inc, Ithaca, NY.
[s]Probe No. HLR1143 model BLF-21D, Transonic Systems Inc, Ithaca, NY.
[t]Probe No. HLN1110 model BLF-21D, Transonic Systems Inc, Ithaca, NY.
[u]Polygraph model 7D, Grass Instruments, Quincy, Mass.
[v]Chart recorder model 25-60, Grass Instruments, Quincy, Mass.
[w]Life Care pump model 4, Abbott Laboratories, North Chicago, Ill.
[x]Model 280 (NOA), Sievers Instruments Inc, Boulder, Colo.
[y]SAS, version 6.12, SAS Institute Inc, Cary, NC.

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