Use of an extracorporeal circuit to evaluate effects of intraluminal distention and decompression on the equine jejunum

Jorge E. Nieto, MVZ; Linda M. Van Hoogmoed, DVM, PhD; Sharon J. Spier, DVM, PhD; Nicholas J. Vatistas,† DVM, PhD; Jack R. Snyder, DVM, PhD; Brenna L. Timmerman, BS

Objective—To use an extracorporeal circuit to evaluate effects of intraluminal distention on the jejunum of healthy horses.

Sample Population—2 jejunal segments from each of 5 horses.

Procedure—Jejunal segments were harvested and maintained in an extracorporeal circuit. One segment was subjected to distention (intraluminal pressure, 25 cm H2O) followed by decompression, and 1 segment was maintained without distention. The influence of distention-decompression on vascular resistance was calculated. Mucosal permeability was evaluated by measuring the clearance of albumin from blood to lumen. After distention and decompression, tissue specimens were collected for histomorphologic evaluation. In addition, the contractile response of the circular smooth muscle layer was determined following incubation with 3 prokinetic agents.

Results—Intestinal vascular resistance increased during intraluminal distention and returned to baseline values after decompression. Albumin clearance rate increased after distention, compared with baseline and control values. Histologic examination of the distended segments revealed grade-1 and -2 lesions of the mucosal villus. Edema and hemorrhage were evident in the submucosa and muscular layers. Mesothelial cell loss, edema, and hemorrhage were also evident in the serosa. Mucosal surface area and villus tip height decreased and submucosal volume increased in the distended tissue. Compared with responses in control specimens, distention decreased the contractile response induced by cisapride, erythromycin, and metoclopramide.

Conclusions and Clinical Relevance—Intraluminal distention of the jejunum followed by decompression increased mucosal permeability and injury and decreased responses to prokinetic agents. Horses with intraluminal intestinal distention may have a decreased response to prokinetic agents. (Am J Vet Res 2002;63:267–275)
Intestinal viability has been maintained for 3.5 hours in this circuit, and we have studied the effects of ischemia-reperfusion on the small intestine and large colon of horses.\textsuperscript{29,30}a

Clearance of radiolabeled albumin from blood to the intestinal lumen has been used as a marker of early mucosal injury.\textsuperscript{29,30}b Injuries leading to an increase in mucosal permeability would result in an increase in clearance rate. Albumin concentrations (in the nanogram range) in blood, urine, peritoneal fluid, and luminal contents have been measured by use of radiolabeled albumin, immunoadsorption assay, immunofluorescence assay, and ELISA.\textsuperscript{36-40}a

However, to overcome the use of radioisotopes, our laboratory has developed a solid-phase sandwich ELISA that uses commercially available reagents for the measurement of low quantities of albumin.\textsuperscript{29}a We have used this ELISA to determine blood-to-lumen albumin clearance rates in intestinal segments maintained in an extracorporeal circuit.\textsuperscript{29,30}a

The objectives of the study reported here were to develop an in vitro model for the study of intestinal distention and decompression in horses and to determine the effects of distention and decompression on vascular resistance, mucosal permeability, histomorphologic abnormalities, and contractile response of smooth muscle to prokinetic agents.

**Materials and Methods**

**Animals**—Five adult horses that were to be euthanatized for reasons other than gastrointestinal tract abnormalities were used in this study. The horses were determined to be free of gastrointestinal tract disorders or systemic disease on the basis of results of physical examination and CBC and by evaluation of the intestine at the time of surgery. Prior to induction of anesthesia for collection of jejunal segments, 5 L of blood was collected from the jugular vein via a 10-gauge catheter into a bag containing 10,000 units of sodium heparin; 5 L of lactated Ringer’s solution (LRS) was administered through a second catheter placed in the opposite jugular vein. All experimental protocols were approved by the Animal Care and Use Committee of the University of California.

**Extracorporeal circuit**—We used an extracorporeal system, which was designed in our laboratory and described in detail elsewhere,\textsuperscript{24,35}a to study the effects of distention and decompression on the small intestine of horses. Because this system consists of 2 identical isolated circuits located side-by-side, 2 jejunal segments could be studied simultaneously. Therefore, control and distended segments from the same horse were evaluated at the same time but completely independent from each other. Briefly, each circuit comprised a water-jacketed primary 2-L glass reservoir connected to a main roller pump of variable speed that delivered the blood harvested from the horse prior to induction of anesthesia to an extracorporeal membrane oxygenator (ECMO) and a gas mixing and metering system. Approximate percentages of gases delivered via the ECMO were as follows: N\textsubscript{2}, 75%; O\textsubscript{2}, 20%; and CO\textsubscript{2}, 5%. Blood in the primary reservoir was continuously mixed by use of a magnetic stirrer. Oxygenated blood was either returned to the primary reservoir or delivered by use of a variable speed peristaltic pump to the cannulated mesenteric artery and vein immediately proximal to the catheter insertion sites. Oral and abdominal vessels were also ligated at the level of intestinal resection to completely isolate the jejunal segment. The arterial end of the intestine was occluded, and 50 ml of oxygenated Krebs-Ringer buffer (KRB) solution containing 1.25 g of glucose\textsuperscript{29}a was added to the lumen of the intestine through the oral incision. The composition of the KRB solution was as follows: NaCl, 110 mM; KCl, 4.6 mM; CaCl\textsubscript{2}, 2.5 mM; NaHCO\textsubscript{3}, 24.8 mM; KH\textsubscript{2}PO\textsubscript{4}, 1.2 mM; MgSO\textsubscript{4}, 1.2 mM; glucose, 5.6 mM; pH 7.3 to 7.4 when equilibrated with 95% O\textsubscript{2} and 5% CO\textsubscript{2}. The oral end of the intestine was then occluded with umbilical tape, and the jejunal segment was cut free and transported in a heated insulated carrier to 1 of the 2 extracorporeal circuits. A second piece of jejunum was collected from each horse, transported, and connected to the other circuit in an identical manner. The horses were euthanatized by IV injection of an overdose of sodium pentobarbital immediately following collection of the intestinal segments.

**Instrumentation of jejunal segments**—Within the extracorporeal circuit system, each isolated jejunal segment was placed in a sealed chamber with a perforated inner layer to allow drainage of fluids, and serosal surfaces were lavaged with warm (37°C) LRS at regular intervals to keep the segment moist. A digital scale was placed beneath each chamber to monitor the weight of each segment. Jejunal segments were maintained at 37°C with heating lamps controlled by use of a thermocoupler probe placed within the lumen. Venous and arterial blood was collected from the cannulated vessels every 30 minutes during the experiment, and concentrations of blood gases, sodium, potassium, calcium, chloride, and glucose were measured, using automated analyzers.\textsuperscript{27} Glucose and bicarbonate were added to the blood in the primary reservoir as needed to maintain concentrations of 7.5 and 24 mmol/L, respectively. Arterial and venous pressures were monitored by use of pressure transducers.\textsuperscript{29} Arterial blood pressure was measured via a 24-gauge catheter placed approximately 5 cm from the ligation in 1 of the collateral arteries. Arterial and venous blood flow rates were measured, using in-line extracorporeal probes\textsuperscript{29}b in the tubing immediately proximal to the arterial and venous catheters. Arterial blood flow rates were regulated to achieve a mean arterial pressure of 75 mm Hg. Prior to entering the artery supplying the jejunal segment, blood passed through a water-jacketed tubing and bubble trap to maintain temperature at 37°C and...
prevent air emboli entering the intestine. In addition, blood was filtered through a pediatric filter to prevent cellular aggregates and fat emboli from reaching the segments.

In the sealed chamber, the tied ends of each jejunal segment were opened, the KRB solution was allowed to drain, and each end was fitted with a 3-cm polyvinyl chloride plug connected to tubing inflow or outflow cannulas (outside diameter, 1 cm). The intestinal lumen was perfused with warm (37°C) LRS delivered through the inflow cannula at a rate of 10 ml/min for 10 minutes. The flow rate was then decreased to 5 ml/min for the rest of the experiment. Luminal perfusate was collected through the outflow cannula at regular intervals, and intraluminal pressure was measured by use of a pressure transducer attached to the outflow cannula by a three-way stopcock.

Time from incision of the linea alba to instrumentation of the jejunal segment in the extracorporeal circuit system was approximately 30 minutes. In addition, segments were supplied with warm heparinized oxygenated blood from collection to placement in the isolated circuit.

Effects of intraluminal distention and decompression—After instrumentation, jejunal segments were allowed to equilibrate for 60 minutes in the extracorporeal system before baseline measurements were obtained. One jejunal segment (control) from each horse was maintained in the system for an additional 120 minutes at an LRS inflow rate of 5 ml/min. The outflow cannula was elevated 1 cm from the level of the intestinal lumen to separate the mucosal surfaces of the control segment and allow exposure of all surfaces to the perfusate. The lumen of the second jejunal segment was distended for 60 minutes by elevating the outflow cannula 25 cm from the level of the intestinal lumen and adjusting the amount of LRS added through the inflow cannula to maintain the intraluminal pressure at 25 cm H2O. Initially, approximately 750 ml of LRS was added to each jejunal segment. Distention was maintained by adding approximately 30 ml of warm LRS during the first 30 minutes and another 8 ml during the final 30 minutes of distention. After distention, segments were allowed to decompress for an additional 60 minutes by lowering the outflow cannula. A 5-cm-long specimen of each control and distended segment was collected after completion of the 120-minute experiment. Specimens were divided into 2; one was placed into oxygenated cold KRB solution for use in the prokinetic experiment. Specimens were processed for histologic evaluation.

Determinations of vascular resistance—Intestinal vascular resistance (R; mm Hg/ml/min/100 g) was calculated at various times throughout the experiment, using the following formula:

$$ R = \frac{P}{[IBF/K]} \times 100 $$

where P is the perfusion pressure, IBF is the intestinal blood flow, and K is the weight of the jejunal segment normalized to 100 g.

Evaluation of mucosal permeability—Mucosal permeability was evaluated by determining the clearance of albumin from blood to the intestinal lumen. Samples of luminal perfusates were collected from control and distended segments at 0 (baseline), 90, and 120 minutes. For the distended segments, 90 and 120 minutes corresponded to 30 and 60 minutes of decompression. Arterial blood samples were collected every 30 minutes. All samples were centrifuged, and supernatant or plasma was collected and stored at −80°C for later determination of albumin concentrations.

Albumin concentrations were determined by use of an ELISA described in detail elsewhere. Briefly, microtiter plates were sensitized by adding 100 µl of sheep anti-horse albumin antibody (8 µg/ml) in PBS solution (PBSS; pH 7.4) to each well. Plates were incubated in the dark for 24 hours at 37°C and washed 3 times with PBSS containing 0.05% Tween 20 (PBSS-T; pH 7.2) in an automated plate washer. Albumin standards were prepared by diluting horse albumin with LRS to a concentration of 0.01 mg/ml. Luminal perfusate and plasma samples were thawed at room temperature (25°C) and diluted 1:100 in LRS. Two hundred microliters of standard or diluted sample was added to duplicate wells of the sensitized microtiter plates, and serial dilutions were made across rows, using PBSS-T. Plates were covered and incubated in the dark for 30 minutes at 37°C. Plates were washed 3 times with PBSS-T, and a solution containing 5 µl of horseradish peroxidase-labeled sheep anti-horse albumin and 100 µl of PBSS-T was added to each well. Plates were incubated in the dark for an additional 30 minutes. After washing plates 3 times in PBSS-T, 100 µl of substrate was added to each well, and plates were incubated for 30 minutes and read immediately by use of an automated ELISA plate reader at 690-nm dual-wave length setting. Albumin concentrations in plasma and luminal perfusates were calculated from the standard curve. Plasma-to-lumen clearance was calculated according to the formula:

$$ Clearance = \frac{(P_x \times pr \times 100)}{(Fp \times X \times wt)} $$

Figure 1—Mean ± SEM vascular resistance in jejunal segments isolated from 5 healthy adult horses and maintained in an extracorporeal circuit for 120 minutes without distention (control) or with 60 minutes of intraluminal distention (intraluminal pressure, 25 cm H2O) followed by 60 minutes of decompression (distention). *Significantly (P < 0.05) different between groups. #Significantly (P < 0.05) different than the baseline value for the same group.

Figure 2—Mean ± SEM blood-to-lumen albumin clearance rate determined for jejunal segments isolated from 5 healthy adult horses and maintained in an extracorporeal circuit for 120 minutes without distention (control) or with 60 minutes of intraluminal distention followed by 60 minutes of decompression (distention). See Figure 1 for key.
where Fp is the amount of albumin (g) in the perfusate, Fpl is the amount of albumin (g) in plasma, pr is the perfusion rate, and wt is the weight of the jejunal segment.

**Histomorphologic examination**—Specimens of jejunal segments were fixed in formalin, embedded in paraffin, sectioned at 4-µm thick, and stained with H&E, using standard methods. Sections were examined by use of bright microscopy, and the mucosa was graded by the first author (JEN), using a described grading system. Using a video camera and frame grabber, images of the mucosa at 4× magnification and the submucosa at 2.5× magnification were interfaced with a computer-based imaging program. Mucosal volume and surface area and submucosal volume were calculated, using a computerized stereology program. Measurements for morphometric analysis were obtained from 10 images created from 2 sections for each specimen. From the mucosal images created, villus height from the muscularis mucosa to the epithelial basement membrane at the villus tip was measured in pixels and expressed in mm, using a computer program.

**Effect of prokinetic agents**—Specimens of each jejunal segment were stored in oxygenated cold KRB solution for 3 hours prior to determining the effects of prokinetic agents on smooth-muscle contractility. Strips measuring 10 X 2 mm were cut parallel to the circular muscle layer from each tissue specimen and suspended in organ baths containing 20 ml of warm (37 C) KRB solution equilibrated with a mixture of 95% O₂ and 5% CO₂. Tension generated was measured by use of force transducers attached to each end of the strips and a polygraph chart recorder. Strips were equilibrated in KRB solution for 90 minutes, and the length of each strip required for optimal force development was determined as described. Strips were then flushed with KRB and allowed to stabilize until spontaneous regular phasic contractile activity was evident. Erythromycin (10⁻⁴ to 10⁻¹ M), cisapride (5 X 10⁻⁸ to 5 X 10⁻⁶ M), or metoclopramide (10⁻⁴ to 10⁻³ M) was added to the organ bath in a cumulative manner every 3 minutes and the isometric force recorded. Cisapride was dissolved in a solution of 0.1% lactic acid and diluted 1:9 with distilled water to make a stock solution of 10⁻³ M; all other prokinetic agents were dissolved in distilled water or KRB solution.

The active contractile force was normalized for cross-sectional area and expressed as grams per centimeter. At the end of each trial, length (cm) and dry weight (g) of each strip was measured. The cross-sectional area was calculated, assuming a tissue density of 1.056 g/cm³, using the following formula:

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\text{Area (cm}^2\) = \frac{\text{mass (g)}}{\text{density [g/cm}^3\)] \times \text{length [cm]}
\]

**Statistical analyses**—Data were expressed as mean ± SEM. Values were compared between and within groups by use of ANOVA followed by the Fisher protected least-significant difference test. Significance was set at P < 0.05.

**Results**

**Intestinal vascular resistance**—Vascular resis-

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Figure 3—Photomicrographs of tissue sections obtained from jejunal segments isolated from a healthy adult horse after maintenance in an extracorporeal circuit for 120 minutes without distention (left) or with 60 minutes of intraluminal distention followed by 60 minutes of decompression (B). A grade-1 mucosal lesion (A) is evident in the section from the segment subjected to distention-decompression. Distention-decompression also resulted in shortening of the villus tips and an increase in the volume of the submucosa. H&E stain.
tance remained stable in the control jejunal segments during the 120-minute trial (Fig 1). In the distended segments, mean (± SEM) baseline intestinal vascular resistance was 2.06 ± 0.29 mm Hg/ml/min/100 g, and vascular resistance significantly increased after 10 and 30 minutes of distention (3.91 ± 0.49 and 3.23 ± 0.39 mm Hg/ml/min/100 g, respectively). During decompression (70, 90, and 120 minutes), vascular resistance returned to baseline values (mean ± SEM for all 3 times, 2.06 ± 0.22 mm Hg/ml/100 g).

Mucosal permeability—Mucosal permeability progressively increased 30 and 60 minutes after cessation of distention, as indicated by a significant increase in the blood-to-lumen clearance rates of albumin determined at these times (Fig 2). In control segments, albumin clearance remained stable (< 0.05 ml/min × 100 g) throughout the experiment.

Histomorphologic examinations—In control jejunal segments, mucosa was assigned a mean score of 0 on a scale of 0 to 5, where 0 indicates no lesions, and 5 indicates severe lesions. Scores for the distended segments ranged from 1 to 2 (Fig 3). Edema and hemorrhage were evident in the submucosal and muscular layers following distention-decompression. Mesothelial cell loss, edema, and severe hemorrhage were also evident in the serosa of these segments. Following distention and decompression, villi were significantly (P < 0.001) shorter (0.7 ± 0.15 mm), compared with control segments (1.1 ± 0.09 mm). In addition, mucosal surface area decreased (53 ± 6% compared to controls), whereas submucosal volume increased (160 ± 21% compared to controls). However, mucosal volume was not significantly affected by distention-decompression.

Effects of prokinetic agents—Compared with control strips, intraluminal distention and decompression induced a reduction in the contractile response to cumulative doses of cisapride, erythromycin, and metoclopramide (Fig 4). For control strips, mean maximum contractile responses (P_max) in response to cisapride, erythromycin, and metoclopramide were 212 ± 13 g/cm², 158 ± 29 g/cm², and 446 ± 98 g/cm², respectively, whereas for distended strips, mean P_max were 74 ± 36 g/cm², 58 ± 33 g/cm², and 201 ± 57 g/cm², respectively.

Discussion
The extracorporeal circuit system developed in our laboratory allowed us to maintain the viability of isolated equine jejunal segments for an extended period in a controlled environment. The stability of the system was evident by the maintenance of mucosal integrity and mucosal permeability in control segments after 3 hours (60-minute equilibration period and 120-minute experimental period) in the isolated circuit. Similar results were recently reported, using the same extracorporeal circuit with a leukocyte-depleted filter added.30 The extracorporeal circuit system provided a stable model for the study of the effects of distention-decompression on the small intestine of horses without the influence of anesthetic agents or host factors. Concentrations of Na⁺, Ca++, K⁺, Cl–, glucose, and bicarbonate, pH, and base deficit of the blood within the isolated system remained stable and within reference limits for the duration of each experiment. Bicarbonate was added to the circuit when concentrations decreased to < 20 mmol/L, because acid-base balance cannot be regulated within an isolated intestinal segment. Glucose was also added to the primary blood reservoir when concentrations were < 8 mmol/L, because tissue consumes glucose during normal cellular metabolism.46 In our system, we are able to control the blood flow to the intestine, and it was adjusted to maintain arterial pressure between 70 and 110 mm Hg.

Intestinal distention created by elevating the intestinal luminal perfusate outflow cannula has been
used to create high intraluminal pressures. We confirmed that this method resulted in the desired pressure by directly measuring intraluminal pressure in the outflow cannula via a 3-way stopcock connected to a pressure transducer. Similar to results of previous studies, we also detected a single increase in intraluminal pressure after distention. This was followed by a decrease in pressure as a result of stress relaxation in the intestinal wall. Similar to results of other studies, only small increases were required in the initial distending volume to maintain a high intraluminal pressure, and the desired pressure was easily controlled and adjusted.

Measurement of albumin clearance has provided consistent results for the evaluation of mucosal integrity. The blood-to-lumen albumin clearance rates determined in our study are similar to those reported for the small intestine of dogs, using an isolated circuit. The use of an ELISA to measure plasma and intestinal perfusate albumin concentrations allowed us to avoid the use of radioactive substances. In addition, interassay variability of the ELISA was low, unlike that of assays that use radioisotopes. Results of these latter assays can vary depending on the time of injection of the radiolabile substance. An ELISA that incorporates the same reagents described in the present report is now commercially available.

Intraluminal pressures of 18 cm H2O and 10 mm Hg in the jejunum of horses and ponies, respectively, result in changes in vascular resistance. Distention of the small intestine to an intraluminal pressure of 18 cm H2O in anesthetized horses induced an increase in vascular resistance to 193% of the baseline values within 60 minutes. Vascular resistance gradually decreased to 79% of the baseline value 2 hours after initiation of distention. In the same study, vascular resistance further decreased to 31% of the baseline value within 5 minutes of decompression (ie, 5 minutes after cessation of distention) and returned to the baseline value within 2 hours. Similar to that study, we observed an increase in vascular resistance immediately after distention; resistance was 189% of the baseline value by 10 minutes after initiation of distention. Vascular resistance stabilized (ie, did not increase further) by 30 and 60 minutes after initiation of distention and remained higher than the baseline value during the entire distention period. However, unlike results of the previous study, vascular resistance during the decompression period was not significantly different from baseline. Differences between results of the present and previous studies may be attributable to differences in degree of distention and between in vitro and in vivo preparations.

Under normal conditions, the mucosal membrane is a relatively impermeable and highly selective barrier, allowing only small quantities of plasma proteins (eg, albumin) to enter the intestinal lumen. Conditions that increase permeability of macromolecules include extracellular volume expansion, irradiation, endotoxemia, hypotension, ischemia, and exposure of the mucosa to histamine, bradykinin, prostaglandins, or acetylsalicylate. Generally, the increased permeability caused by these conditions occurs concomitant to morphologic derangement of the mucosa.

Increases in permeability have been reported following intraluminal distention of the intestine of various species, including horses. Distention to an intraluminal pressure of 30 cm H2O causes multifocal areas of necrosis in the mucosa of rabbits. However, results of a study evaluating equine jejunum revealed that although blood flow is reduced during distention, the effect is more accentuated in the serosa than the mucosa and submucosa. Results from the present study indicate that distention to an intraluminal pressure of 25 cm H2O followed by decompression led to an increase in mucosal permeability as indicated by an increase in the blood-to-lumen albumin clearance rate. The actual mechanism for the increase in albumin clearance, such as ischemia, reperfusion, or effects of mechanical factors, was not determined in this study.

Studies evaluating different degrees of intraluminal distention have been performed in anesthetized horses. We chose an intraluminal pressure of 23 cm H2O because this degree of distention induces intestinal adhesions in foals and morphologic changes in adult horses. To prepare the intestinal wall for mucosal injury, the villous layer contracts, and epithelium from the mucosal crypt migrates to cover denuded portions of the villous layer (epithelial restitution). Detergent-induced epithelial injury and 2 hours of ischemia has resulted in villus contraction of 30 and 40% of the original height, respectively. We detected a decrease in mucosal surface area and villus height in jejunal segments subjected to distention-decompression, compared with control segments. Villus contraction as a response to injury induced by distention-decompression may be responsible for the reduction of surface area and may play a role in epithelial restitution by reducing the size of the injured surface requiring reepithelialization. Results of an in vitro study evaluating the mucosa of the small intestine of guinea pigs revealed that villus shortening after injury is energy dependent and neurally mediated; degree of shortening was less in tissue depleted of ATP and denervated by use of tetrodotoxin. Further, the same investigators observed that injury was routinely accompanied by depletion of vesicles from nerve terminals and was mediated by a network of myofibroblasts. The increase in submucosal volume that we detected in the present study following distention-decompression may reflect severity of edema or fluid accumulation caused by an increase in regional blood flow or an increase in vascular permeability.

Although the grading system for mucosal lesions that we used in the present study was originally described for use in dogs, this system has been used by others to grade mucosal lesions in horses. Severity of mucosal lesions that develop proximal and distal to primary strangulating small-intestinal lesions are most commonly grade 1 and 2 and are more severe than those proximal and distal to simple obstructions. Further, mucosal lesions that develop proximal to the obstruction in horses that survived an episode of small-intestinal obstruction were less severe (grades 1 and 2) than in nonsurvivors (grades 2 to 5). Similar to these previous studies, mucosal lesions that developed in isolated jejunal segments following dis-
tention-decompression in the present study were assigned a grade of 1 or 2. Mucosal damage was not observed in control segments. The lesions that developed in our in vitro model mimicked those that develop clinically. We believe that the lesions in the present study resulted from injury sustained during distention and decompression and were not induced as a result of maintenance in the isolated extracorporeal circuit or the collection procedure. Similar to results of an in vivo study that evaluated the effects of 2 hours of distention (25 cm H2O) followed by 60 minutes of decompression, we found edema in the villus, central lacteal dilatation, hemorrhage within the muscle layers, and edema, hemorrhage, and mesothelial cell loss in the serosa of isolated jejunal segments subjected to 60 minutes of distention and 60 minutes of decompression. In the equine small intestine, ischemic lesions are characterized by the accumulation of fluid in the subepithelial space at the villus tip (Gruenhagen space). This results in pressure at the basal attachment of the epithelial cells. The increased pressure causes a mechanical separation of the epithelial cells from the lamina propria before severe cell damage occurs. With prolongation of the insult, the sloughed epithelial cells migrate down the villus, accompanied by capillary damage and hemorrhage followed by complete degeneration of the villous architecture. Studies in other species have revealed that blood flow in the small intestine and large colon decreases progressively when intraluminal pressure increases. The small intestine is more susceptible to distention-induced hypoperfusion than the large colon, and the decrease in blood flow is greatest in the mucosa. However, an intraluminal pressure of 25 cm H2O in the small intestine of horses decreased the number of perfused vessels in the seromuscular layer to a greater degree than in the mucosal layer. Distention of the equine small intestine to an intraluminal pressure of 18 cm H2O resulted in a reduction in blood flow, oxygen delivery, oxygen consumption, and oxygen extraction during the distention period. In dogs, mucosal permeability increases after blood flow to the small intestine is reduced to such a degree that oxygen consumption is decreased by > 50%. Distention of the intestinal segment induces not only local changes but also affects intestinal circulation and motility. In dogs, mucosal ischemia was not observed until the increase in intraluminal pressure was close to the maximum pressures detected clinically. Although blood flow to the mucosa was not measured in our study, if intraluminal pressure was greater than or equal to mean capillary pressure, this would be expected in the mucosa. Mucosal damage include tissue hypoxia and exposure to superoxide radicals and pancreatic proteases. The low oxygen tension at the villus tip, such as that seen at normal resting perfusion pressures, decreases during hypotension. The vascular pattern of the small-intestinal villus consists of a hairpin vascular arrangement within the villus. This places the artery and vein in close proximity, although blood flows through each in opposite directions. The most likely cause for villus hypoxia in arterial hypotension and shock is an increased activity of this countercurrent exchange mechanism. In our study, histologic evaluation was performed only after decompression. Thus, we were not able to conclude whether lesions were induced during the distention period, the decompression period, or both. Dabareiner et al found progressive morphologic damage following decompression of distended (25 cm H2O) equine small intestine for 2 hours. If mucosal damage was induced during the decompression period in the present study, it may be attributable to the reintroduction of oxygenated blood during this period (ie, reperfusion injury).

Although erythromycin, cisapride, and metoclopramide are some of the more commonly used prokinetic agents for treatment of horses with postoperative ileus, there is still controversy regarding their clinical effectiveness. Results of studies in our laboratory indicate that isolated equine smooth muscle responds in a concentration-dependent manner to erythromycin, cisapride, and metoclopramide. In the present study, we found that the contractile response of the circular smooth muscle layer to erythromycin, cisapride, or metoclopramide was decreased in jejunal segments subjected to intraluminal distention and decompression, compared with control segments. Acute and chronic distention of the ileum of guinea pigs induces an increase in vasoactive intestinal peptide (VIP) synthesis or release at the myenteric plexus. In addition, blood VIP concentration increases in dogs with small bowel obstruction. Nonadrenergic noncholinergic inhibitory neurotransmitters have been detected in the small intestine of healthy horses. On the basis of results of these previous studies, it is possible that intraluminal distention of jejunal segments in the present study resulted in the production of inhibitory neurotransmitters (eg, nitric oxide, VIP, ATP) that may have been responsible for the subsequent reduction in the contractile response of the circular smooth muscle layer to prokinetic agents. Alternatively, other mechanisms such as endotoxin-mediated or ischemic-induced release of inflammatory mediators or injury to the nerve endings or muscle fibers could be involved in the decreased contractile response. Experimentally induced distention of the equine small intestine induces inflammation and edema in the muscle layers, with mitochondrial swelling, vacuolation, and cellular disruption. The lesions that developed in our model of distention are similar to those found proximal and distal to naturally occurring strangulating obstructions. Intraluminal distention may, at least in part, be responsible for the inconsistent response of horses with postoperative ileus following treatment with prokinetic agents.

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