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EFFECTS OF DISTENTION AND NEOSTIGMINE ON JEJUNAL VASCULAR RESISTANCE, OXYGEN UPTAKE, AND INTRALUMINAL PRESSURE CHANGES IN PONIES

By

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ABSTRACT

EFFECTS OF DISTENSION AND NEOSTIGMINE ON JEJUNAL VASCULAR RESISTANCE, OXYGEN UPTAKE, AND INTRALUMINAL PRESSURE CHANGES IN PONIES

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Postoperative ileus is associated with intestinal hypomotility and distension; neostigmine methylsulphate is the drug most commonly employed clinically in the treatment of ileus in the horse. The influence of distension (high baseline intraluminal pressure) and neostigmine methylsulphate on intestinal vascular resistance, oxygen uptake, and intraluminal pressure changes (rhythmic contractions) was studied in terminal jejunal segments, which were perfused at a constant blood flow, in 16 anesthetized ponies. When baseline intraluminal pressure was increased from 0 to 10 mm Hg, the intestinal vascular resistance and amplitude of rhythmic contractions were increased. Neostigmine induced cyclic increases in amplitude of rythmic contractions whether intraluminal pressure was 0 or 10 mm Hg. Neostigmine also increased intestinal oxygen uptake at intraluminal pressures of 0 mm Hg but not at 10 mm Hg, and vascular resistance was not altered at either intraluminal pressure. The results indicate that intestinal hemodynamics are adversely affected

by distension. Further, neostigmine did not adversely effect intestinal hemodynamics while increasing rhythmic contractions, suggesting that neostigmine may be useful in the treatment of ileus in equids.

This thesis is dedicated to the memory of my father Alan Guyatt Parks for imparting his love of scholarly pursuits and to my mother Caroline Jean Parks for extolling the virtue of common sense.

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INTRODUCTION

The incidence of ileus after surgery in the horse with colic is high; in one survey, 43.9% of postoperative deaths were attributed to this complication.[1] Ileus is associated with intestinal distension[2] and high intraluminal pressures,[3] which further inhibit intestinal motility via the intestino-intestinal reflex.[4] High intraluminal pressures have been shown to reduce intestinal blood flow in dogs[5,6] and have been implicated as a contributing factor to mucosal injury in rabbits.[7] Additionally, small intestinal intraluminal pressures measured during colic surgery are considerably higher in horses that die than in those that survive.[3] Cholinesterase inhibitors have been advocated for the treatment of postoperative ileus in horses.[8,9] Neostigmine methylsulphate is the most commonly used drug of this group.[9] However, experimentally, neostigmine delays gastric emptying and prolongs the small intestinal migrating myoelectric complex in ponies.[10,11] The purpose of the study reported here was to evaluate the effects of distension (higher than normal intraluminal baseline pressure) and neostigmine on intestinal vascular resistance, oxygen uptake, and intraluminal pressure changes (rhythmic contractions) in the jejunum of ponies.

LITERATURE REVIEW

Colic is a major cause of economic loss to the equine industry. The term colic means abdominal pain but is commonly used to collectively describe the multitude of conditions that cause abdominal pain. This pain, usually associated with the gastrointestinal tract, originates from tension on the mesentery, intestinal ischemia and intestinal distension.[12,13] Diseases causing colic have been grouped by pathogenesis: simple obstruction, strangulating obstruction, non-strangulating infarction, and inflammatory disease.[14]

Common causes of small intestinal simple obstruction include ileal impaction, ascarid impaction, and adhesions associated with either previous surgery or abdominal abscesses.[14,15] Strangulating obstruction of the small intestine commonly occurs following volvulus, incarceration through a mesenteric rent, a hernia, or by pedunculated tumors.[14,15] Non strangulating ischemia of the small intestine is uncommon but is probably associated with parasitic larval migration through the intestinal vasculature.[14,15] Proximal duodenitis/jejunitis, an inflammatory condition of the small intestine is associated with functional obstruction of the small intestine.[16] These

conditions cause either a mechanical or functional intestinal obstruction that inhibits aboral movement of ingesta, fluid, and gas within the small intestine. Accumulation of ingested fluid, gas and ingesta, salivary and alimentary secretions and gas from bacterial fermentation proximal to the obstruction distends the intestine.[17] The intestine proximal to the obstruction initially responds with periods of vigorous activity interspersed among quiescent periods, while intestinal motility distal to the obstruction is diminished or unaffected.[18-20] Later, motility is decreased throughout the gastrointestinal tract.[17] As the intraluminal pressure increases, net absorption of the accumulated fluid changes to net secretion of water exacerbating the distension.[21] Concurrently, decreased fluid intake, insensible fluid loss and sequestration of fluid within the intestine make the horse hypovolemic. Progression of the disease may cause either gastric rupture or cardiovascular failure or both.[15,17]

Strangulating obstructions may cause mesenteric vascular occlusion of either veins or both veins and arteries in addition to the changes seen with simple intestinal obstruction.[17] Venous obstruction without attending arterial occlusion initially results in the intestine becoming edematous, whereas accompanying arterial occlusion will arrest mesenteric blood flow with resulting ischemia.[22] Initially epithelial cells from the villus tip

loosen from the basement membrane and later slough.[23] Prolonged ischemia leads to complete mucosal necrosis. Reperfusion of the damaged intestine can exacerbate the mucosal injury, further damaging the mucosal barrier.[24] Damage to the mucosa allows rapid luminal to vascular transport, and transperitoneal absorption of bacterial toxins which may result in endotoxemia and shock.[15,17]

The clinical signs of horses with small intestinal obstruction include pain, abdominal distension, gastrointestinal reflux, and distended stomach and small intestine.[15] The time course of events is dependent on the site and nature of the obstruction; proximal obstructions are more acute than distal, and strangulating obstructions more acute than simple.[15] The patient's systemic parameters reflect pain or compromized cardiovascular function or both. The variables most likely to predict the prognosis ranked in descending order of accuracy are: systolic blood pressure, blood lactate concentration, oral mucous membrane capillary refill time, diastolic pressure and arterial pulse amplitude.[25] These variables are those that best assess the integrity of cardiovascular function.[25] Even though the surgical treatment of small intestinal obstructions has become routine, survival is still limited by accessiblitiy of the obstruction, amount of bowel involved, severity of the intestinal lesions and the cardiovascular function of the animal. Postoperative complications, including

persistent endotoxemia, peritonitis, adhesions, laminitis and ileus, add to the morbidity and mortality rate.[9]

Distension and hypomotility are two of the hallmarks of ileus and form the subject of the present study. The following sections of the literature review discuss the physiologic regulation of intestinal motility and blood flow, and the pathophysiologic findings in postoperative ileus and intestinal distension.

Intestinal motility

The complex control and integration of intestinal motility is regulated by neural, humoral and myogenic responses. The principle patterns of motility seen in intermittent feeders, i.e. carnivores and omnivores are postprandial segmental contractions and peristaltic contractions with temporally interposed interdigestive complexes called the migrating myoelectric complex.[26,27] Horses feed almost continuously and the predominant motility pattern is the migrating myoelectric complex.[11,28]

The segmental contractions and peristaltic activity observed are caused by the regulated contraction of intestinal smooth muscle. The intestinal muscle coat is made of two layers, an inner circular layer and an outer longitudinal layer.[29] The smooth muscle cells within each layer act as a syncytium, but there is no direct communication between the muscle cells of the respective layers.[30] The smooth muscle cells of the longitudinal

muscle layer generate an intrinsic myogenic rhythmic depolarization called the slow wave, basic electric rhythm or electrical control activity.[30,31] The slow wave is propogated by the smooth muscle syncytium in an aboral direction, and is electrically connected to the circular muscle layer.[32] The frequency of the slow wave is greatest in the duodenum and lowest in the ileum.[30] Slow waves do not initiate smooth muscle contractions.

Smooth muscle contraction occurs in response to action or spike potentials.[30] The stimulus for action potential formation is depolarization of the cell membrane, mostly caused by the release of acetylcholine by postganglionic neurons, but there are also noncholinergic stimulatory neurons.[33,34] Hyperpolarization of the cell membrane, probably mediated by purine nucleotide transmitters, inhibits action potential formation.[30] Therefore action potential formation is more likely to occur when the cell membrane is already less polarized, i.e. at the peak of the slow wave. Action potentials in smooth muscle are not an 'all or none' phenomenon as they are in skeletal muscle.[30] The force of smooth muscle contraction is related to the number, frequency and magnitude of action potentials.[30,32] Slow waves therefore act as a pacemaker by directing the direction and rhythm of intestinal smooth muscle action potential activity.

Neural regulation of intestinal smooth muscle activity occurs at three levels, 1) the enteric nervous system which

includes the myenteric and submucosal plexuses, 2) the prevertebral ganglia and 3) the parasympathetic and sympathetic divisions of the autonomic nervous system and higher centers.[35] Ten percent of the nerve cells in the submucosal and myenteric plexuses are afferent and efferent neurons to and from the mucosa, muscularis and serosa, the rest are integrative neurons.[12] In the absence of external influences, the enteric nervous system provides the basic neural circuitry that governs the different patterns of intestinal activity seen in the intact animal.[36]

The parasympathetic and sympathetic nervous systems provide extrinsic control of intestinal motility. Parasympathetic preganglionic neurons reach the enteric plexuses through the vagus nerve and are of 2 types, those that terminate on excitatory cholinergic neurons and those that terminate on inhibitory, nonadrenergic, noncholinergic neurons.[37] The postganglionic neurons are cholinergic and terminate at the neuromuscular junction where they are excitatory; they form the final common pathway for short and long enteric reflexes.[34] In most species, vagal stimulation causes excitation.[37]

Sympathetic preganglionic neurons leave the spinal cord through the ventral roots, and reach the prevertebral ganglia via the splanchnic nerves.[37] In the prevertebral ganglia the preganglionic neurons synapse with the postganglionic neurons. The postganglionic neurons are adrenergic and inhibitory, most terminate on cholinergic

neurons in the enteric plexuses and the rest end in the smooth muscle.[37] Sympathetic inhibitory activity is modulated by visceral and somatic input, and by higher central influences such as stress.[12] The long enteric reflexes are inhibitory and sympathetically mediated at three levels, within the mural plexuses, through the prevertebral ganglia, and via the spinal cord.[12] The best understood of these reflexes is the intestino-intestinal reflex. This reflex causes inhibition of motility throughout the intestinal tract in response to a regional stimulus such as distension or surgical manipulation.[37] In summary, the sympathetic nervous system normally exerts a tonic inhibitory influence on intestinal motility but can suppress motility further when subject to other influences.

Humoral factors may affect gastrointestinal motility via the systemic circulation, paracrine action or through a neural pathway.[38] Inhibitory influences on the stomach and small intestine are exerted by glucagon, serotonin, gastrin and cholecystokinin, while somostatin and motilin increase motility.[38] The search for the role of gastrointestinal hormones in the regulation of itestinal motility patterns has been inconclusive.[27] Peak plasma motilin concentrations have been shown to coordinate with the cyclic activity of the migrating myoelectric complex in the dog, but in humans this correlation is not as convincing because some complexes are not accompanied by increases in motilin concentration.[27]

Therefore, the exact role of gastrointestinal hormones in regulating the various patterns of motility is uncertain.

Intestinal Blood Flow

The small intestinal blood supply comes from the cranial mesenteric artery which divides into anastomosing arcuate vessels within the mesentery.[39,40] The vasa recti branch from the arcuate vessels, enter the serosa, and arborize into several branches. Some branches form the subserosal trunks and course towards the antimesenteric border. Other branches pierce the muscular layers to form the submucosal plexus. The blood supply to the muscular layers is derived from the serosal and submucosal vascular plexuses. From the submucosal plexus, arteries traverse towards the mucosa and some arborize around the crypts while others reach the villi.[39] The microvascular structure within the villus is complex and variable between species, however, most patterns have a principle villus arteriole that extends to the tip of the villus with or without prior branching.[41] The arteriole arborizes into a dense capillary latticework directly beneath the mucosa. One or two venules drain the villus and merge with the submucosal vessels. The efferent vasculature parallels the arterial supply, eventually to exit the mesentery via the portal vein.[41] The presence of specialized arteriovenous anastomoses within the subserosal plexus is controversial,[41,42] but microvascular casting studies at elevated intraluminal pressures

identified vascular junctions highly suggestive of arteriovenous anastomoses.[43]

Blood flow to the gastrointestinal tract has been measured under resting conditions in several species and ranges from 30-70 ml/100 g in humans, cats and rabbits; higher flows, up to 150 ml/min/100g, occur in the rat and dog.[39] The majority of the intestinal blood flow, approximately 60-90% is directed to the submucosa and mucosa, presumably reflecting the higher metabolic demands of these tissues.[39] Within the submucosa/mucosa 5-37%, 24-37% and 21-27% is delivered to the submucosa, villi and crypts respectively.[39] Both pharmacologic and physiologic interventions may alter total blood flow and the mural distribution of blood flow to the intestine.

Intestinal blood flow is regulated through intrinsic factors, extrinsic neural input and vasoactive agents.[39,44] Moment to moment control of the intestinal circulation is performed mainly by local regulatory mechanisms which function independently of neural control. Of the intrinsic mechanisms proposed to control the intestinal circulation, the myogenic and metabolic factors are the most important. The metabolic theory dictates that the local blood flow is regulated so that delivered nutrients meet local metabolic demand.[39,44,45] If oxygen delivery does not equal demand there is a local accumlation of metabolites, many of which have been shown to possess local vasodilatatory properties, for example H^+, K^+, adenosine and adenosine nucleotides.[39]

In this way reduced oxygen availability is compensated by vasodilation, causing an increase in blood flow in order to restore the balance between oxygen delivery and demand. The myogenic theory of local blood flow control postulates that the vascular resistance is directly proportional to arteriolar transmural pressure due to the effect of stretch on vascular smooth muscle activity.[39,44,46] In other words, in response to an increase in arterial pressure, which would increase blood flow if the vessel diameter remained constant, the myogenic response causes a decrease in lumen diameter, an increase in vascular resistance and subsequently a modulation of blood flow. From a homeostatic point of view, the myogenic mechanism maintains capillary pressure and transcapillary fluid exchange constant, while the metabolic mechanism ensures that oxygen delivery matches the tissue requirements.[39]

Autoregulation is the intrinsic phenomenom that maintains organ blood flow constant despite fluctuations in arterial pressure.[44] Intestinal autoregulation is weak compared to other organs and is dependant on the physiologic state of the intestine, the fasted state and distension both reduce autoregulatory capacity.[47,48] In the small intestine blood flow is maintained over an arterial pressure range of 40 - 125 mm Hg.[47] Intestinal oxygen uptake, the amount of oxygen removed from the blood per unit time and weight of tissue, is also maintained constant at blood flows greater than 30 ml/min/100g and arterial pressures greater than 30

mm Hg.[39,49] As blood flow decreases oxygen extraction, the amount of oxygen removed per unit of blood, increases to keep oxygen uptake constant.

Extrinsic regulation of intestinal blood flow is both neural and humoral. The intestinal vasculature is richly supplied with sympathetic neurons but is devoid of parasympathetic neural input.[39] Stimulation of the splanchnic nerves initially causes intestinal vasoconstriction, but continued stimulation causes partial or complete restoration of blood flow, a phenomenon known as autoregulatory escape.[39] Following restoration of blood flow a transient active hyperemia can occur. Stimulation of the vagus causes little or no alteration in intestinal blood flow.[39] Neural control on intestinal blood flow, therefore, is modulated by variation in sympathetic tone.

Vasoactive agents including catecholamines, serotonin, vasoactive peptides and gastrointestinal peptides, may increase or decrease intestinal blood flow.[39,50] The intestinal effects of those agents which have a systemic action must be interpreted in the light of these actions, i.e. drugs that cause a decrease in systemic blood pressure may reduce intestinal blood flow despite a decrease in intestinal vasculature resistance. Naturally occuring catecholamines, norepinephrine and epinephrine, cause vasoconstriction of the splanchnic vasculature.[39] This is related to the effects of these agents on alpha and beta receptors and the numerical predominance of the different

receptors. Acetylcholine decreases intestinal vascular resistance, however, it also decreases systemic blood pressure and increases intestinal smooth muscle activity thereby potentially compressing the mural vasculature.[51-53]

The interrelationship between intestinal motility and blood flow have been extensively studied and reviewed.[5,54-56] Mild rhythmic contractions may increase intestinal blood flow related to an increase in metabolic demand.[5] When this occurs, the increase in blood flow is confined to the muscularis.[57] Local vascular compression may overcome the vasodilator response. Studies concerning the effect of altered blood flow on intestinal motility show no change with increases in blood flow and variable changes with ischemia.[56] Generally, severe ischemia causes an initial phase of hypermotility followed by hypomotility for the duration of the ischemia.[56]

Postoperative ileus

The original meaning of the word ileus is abdominal pain due to intestinal obstruction but has come to be synonymous with intestinal obstruction.[58] It may be subcategorized into mechanical ileus caused by a physical obstruction, and functional ileus caused by a functional intestinal obstruction and by common usage has often come to imply the latter. There are many causes of functional ileus, of which intestinal postoperative ileus is only one, but most are thought to have a common pathogenesis.[2,59]

In 1890 Pal noted the absence of intestinal mechanical activity after opening an animals abdomen.[2] In 1899 Bayliss and Starling showed that the inhibition of intestinal motility induced by opening an animals abdomen could be abolished by splanchnicectomy, thereby implicating the sympathetic nervous system in the pathogenesis of postoperative ileus.[60] This is supported by other studies in which spinal cord ablation, spinal anesthesia and chemical sympathectomy all alleviate the inhibition of intestinal motility secondary to ileus inducing stimuli.[2,59,61] Vagotomy, on the other hand, does not alter the course of ileus.[2]

Electromechanical studies of postoperative ileus show that the basic electrical rhythm is unaltered but the spiking activity associated with the migrating myoelectrical complex is disrupted or absent.[28] Mechanical activity is depressed in association with the decreased electrical activity[28] but the intestinal musculature is not paralysed and is still responsive to electrical and chemical stimuli.[2] It is thought, therefore, that functional ileus is caused by sympathetic hyperactivity and parasympathetic hypoactivity.[28]

From our current understanding of the innervation of the gastrointestinal tract and the pathogenesis of ileus, several potential avenues of treatment for postoperative ileus are apparent, increase cholinergic activity, decrease

ganglionic inhibition by sympathetic innervation, and decrease dopaminergic inhibition.

Increased cholinergic activity within the intramural plexuses and at the neuromuscular junction can be achieved by increasing the release of acetylcholine by the nerve terminals, delaying the degradation of acetylcholine at the receptor site with anticholinesterases and direct stimulation of the muscarinic and nicotinic receptors with pharmacologic agonists. The latter two options have received the most attention. Experimentally, neostigmine, an anticholinesterase, has been shown to restore gastric emptying and colonic transit, and improve small intestinal transport in rats with ileus, however, clinically the results of treatment with anticholinesterases has been dissapointing.[61,62] Bethanacol and carbacol, direct cholinergic agonists, both partially restored small intestinal transit in postoperative ileus.[61,63] Cisapride, which enhances release of acetylcholine from nerve terminals, has been recently shown to enhance small intestinal motility in phase III of the migrating myoelectric complex and decreases the duration of postoperative ileus in human clinical patients.[64]

Adrenergic antagonists have been used both experimentally and clinically to alleviate postoperative ileus. Both alpha and beta receptors have been shown to be important in the pathogenesis of postoperative ileus, however, as with anticholinesterases, the results achieved

with antagonists have been mixed.[65,66] Synergism between adrenergic antagonists and anticholinesterases in restoring intestinal motility has been demonstrated clinically.[67] Guanethidine and bethanidine inhibit norepinephrine release by adrenergic nerve terminals.[68] Guanethidine increased gastric emptying and colonic transit in postoperative ileus in rats but did not increase small intestinal transit.[61] No response was seen with bethanidine in a human clinical double blind study.[69]

Metoclopramide has several mechanisms of action which include an antidopaminergic and a direct cholinergic effect.[71-73] Metoclopramide increases small intestinal contractile activity during phase three but does not increase the duration of the migrating myoelectric complex in the normal dog.[73] In a model of postoperative ileus, metoclopramide reversed inhibition of phase three of the migrating myoelectric complex at the antrum and pylorus of the stomach and partially reversed the inhibition at the duodenum and jejunum.[74] Clinical trials in human patients have not shown a consistent decrease in the duration of postoperative ileus.[62,74,75]

Small intestinal motility patterns in fasted horses resemble those seen in the dog.[11,28] Motility changes seen following adrenergic agonists, direct parasympathomimetics and metoclopramide are comparable to those seen in other species.[72,77] Studies on gastric and small intestinal electromechanical activity in horses with postoperative

ileus show prolonged periods without gastric action potentials, disruption of the normal migrating myoelectric complex, and uncoupling of the normal synchrony between gastric and jejunal cycles of activity.[28] Return of the latter is thought to be the most significant event in the resolution of postoperative ileus.[28] Although neostigmine decreases gastric emptying and prolongs the migrating myoelectric complex in normal horses,[10,11] suggesting that in normal horses neostigmine may decrease intestinal motility,[10,11] it has been shown to hasten the return of normal motility after a an experimental strangulating obstruction.[78] In another study of postoperative ileus, propranolol, yohimbine, yohimbine plus bethanacol, and metoclopramide all caused an earlier return of motility compared to controls, however, metoclopramide was the most effective in restoring the synchrony of gastric and jejunal cyclic activity.[28] Domperidone, a peripheral dopamine antagonist, decreases the duration of experimentally induced postoperative ileus, thus confirming the importance of dompamine inhibition in the pathogenesis of postoperative ileus.[79] In the same study cisapride also decreased the duration of postoperative ileus.[79] More recently, working on a different approach to the problem, Coatney has shown that motilin, an intestinal polypeptide, increases postoperative intestinal motility.[80] Various therapies have been outlined and several have shown promise in experimentally induced equine postoperative ileus but

controlled trials are needed to determine their clinical applicability.

Intestinal Distension

Surgeons have long been peturbed by intestinal distension because the prognosis in patients with intestinal obstruction was worse in those patients with extensive small intestinal distension.[81-83] These changes were thought to be the result of distension induced ischemia and gangrene.[82,83] Basal intraluminal pressures in resting bowel have been determined in man, cat and dog to be 2-4 mm Hg.[43,84,85] After simple obstruction, sustained basal intraluminal pressure increases to 5-10 mm Hg in the cat and dog.[84-86] In ponies intraluminal pressures in resting intestine and in intestine after 12 hours simple obstruction are 8-20 and 8-24 mm Hg respectively.[20] Intraluminal pressures ranged from 4.5 - 21 cm of water in horses with naturally occuring intestinal obstruction.[3] There is little evidence, however, to confirm that distension, at intraluminal pressures observed in clinical patients, causes morphologic changes in the intestine.[85] One study reported villus necrosis in rabbit small intestine associated with distension to 30 cm water,[7] but distension at 18 cm water for 4 hours failed to show any changes other than interstitial edema in the horse.[87]

The first attempts to quantify the effect of distension on blood flow were made by timed collection of venous return

from isolated segments of intestine and showed decreased venous outflow with increased intraluminal pressure.[81-83] Previous qualitative experiments had examined distended intestine microscopically by direct or transmural illumination. There is now a general agreement that an increase in intraluminal pressure decreases small intestinal blood flow when the intraluminal pressure is greater than 20 mm Hg.[88-91] Above this threshold stepwise increases in intraluminal pressure cause further reductions in blood flow until a minimum plateau is reached.[88,90] Because pressure equals the product of flow and resistance, the decrease in blood flow with distension indicates an increase in vascular resistance. Vascular resistance also increased in distended intestine perfused at a constant blood flow.[92] In intestine perfused at constant arterial pressure, blood flow may return to near control with time at lower distension pressures.[48] This has been attributed to stress relaxation; encasing the bowel in plaster of Paris to prevent stress relaxation after distension of the intestine by a constant volume, prevented the return of blood flow to control levels.[93] Following release of intestinal distension there is an overshoot in blood flow before returning to control flows.[48] This may be attributed to a reactive hyperemia.

Investigations into the distribution of blood flow within the intestinal wall during distension show that the increase in blood flow sometimes seen at 20 mm Hg intraluminal pressure is confined to the muscularis.[57] At

higher intraluminal pressures injection studies have shown there a relative reduction in blood flow to the mucosa and muscularis compared with the serosa and submucosa, but microsphere studies indicate a greater decrease in blood flow to the mucosa than to the muscularis.[90,91,94] At these higher distending pressures it is thought that arteriovenous fistulae allow diversion of blood away from the capillary beds. The evidence for the existence of arteriovenous fistulae is fourfold. Firstly, regardless of the distension pressure there is always a residual mural blood flow suggesting that some blood manages to bypass the collapsed capillary beds.[90] Secondly, at distension pressures of at least 30 mm Hg arteriovenous oxygen differences decrease indicating that blood is bypassing the capillary beds.[90,95,96] Thirdly, a decrease in capillary filtration coefficient occurs exceeding that which would be expected to accompany the decrease in blood flow observed.[88] Lastly, arteriovenous fistulae have been shown in casts of the intestinal vasculature made when the intestine was distended.[43]

Oxygen uptake either increases[97] or is unaffected by intestinal distension pressures of 20 mm Hg.[43,89,92] When the intraluminal pressure is elevated more that 20 mm Hg oxygen uptake decreases. This decrease in oxygen uptake occurs partly because oxygen availability is decreased with decreased blood flow, but also because oxygen extraction

decreases, thought to be caused by arteriovenous shunting.[90,95,96]

Artificial distension, produced by rapid increases in intraluminal pressure, does not resemble the dilation of intestine found after prolonged obstruction for 2 reasons; artificial distension causes an increase in rhythmic contractions while prolonged obstruction decreases intestinal motility,[57,89] and obstructed small intestine is much more compliant.[98] Therefore several studies have compared the hemodynamics of obstructed intestine to both resting intestine and artificially distended intestine. An initial study showed that feline intestine obstructed for 72 hours and then decompressed has similar hemodynamics and oxygen consumption to non-obstructed intestine.[99] Other studies have shown that blood flow to obstructed intestine may actually increase.[100,101] Therefore it is unlikely that distension <u>per se</u> compromizes intestinal viablility.

The combined effects of distension and obstruction have been examined, again in feline intestine after 72 hours of obstruction. The obstructed intestine was decompressed and then artificially distended by 20 mm Hg increments in intraluminal pressure, the controls were non-obstructed intestine subject to the same distension protocol. At 20 mm Hg, the capillary filtration coefficient and oxygen consumption were decreased.[102] The capillary filtration coefficient is a measure of hydraulic conductance which is proportional to capillary permeability and the surface area

of perfused capillaries. In this experiment a decrease in the capillary filtration coefficient represents compression of the microvascular beds because it is unlikely that capillary permeability decreases. To evaluate these findings, these investigators compared artificial distension at 20 mm Hg in intestine after uninterrupted obstruction to controls in which the obstruction was decompressed. Artificial distension caused the capillary coefficient to decrease in both groups but to a much greater extent in the uninterrupted distension group.[98] It would seem then, that obstruction predisposes the intestine to the effects of repeated distension and ischemia. This effect is partially reduce by intestinal decompression.

In summary, artificial distension deleteriously effects intestinal hemodynamics and oxygen consumption. But at intraluminal pressures that are present in naturally occuring disease, the balance of evidence suggests that distension does not compromize intestinal viability. Natural and experimental obstruction in the horse causes higher intestinal intraluminal pressures compared to other species, however, the effect of distension on the equine intestinal vasculature has not been examined. Ileus is the result of an imbalance between the sympathetic and parasympathetic stimulus to the intestine. Therapies, of which neostigmine has received the most clinical attention in the horse, aimed at decreasing sympathetic stimulation or

increasing parasympathetic stimulation have been tried with mixed results.

The present study was designed to investigate the following hypotheses. Firstly, distension adversely effects equine intestinal hemodynamics and oxyxgen consumption. Secondly, neostigmine increases motility in both non-distended and distended equine intestine.

MATERIALS AND METHODS

Sixteen healthy adult ponies (118 to 219 kg) were vaccinated against equine influenza, encephalomyelitis, and tetanus, treated with an anthelminthic (pyrantel pamoate,[a] 6mg/kg of body weight, PO), and fed a diet of mixed hay and oats for 1 month before entering the study. Results of physical examination verified that each pony was healthy before being studied. Food, but not water, was withheld for 12 hours before each experiment.

All experiments were performed under general anesthesia and were terminal. Preanesthetic medication was not used. A 14-gauge, 13-cm catheter was inserted into the left jugular vein. Anesthesia was induced with a bolus of thiamylal sodium administered IV to effect (6.6 mg/kg of body weight); following endotracheal intubation, anesthesia was maintained with 2% halothane and oxygen in a semi-closed anesthetic system. Manual ventilation with a rebreathing bag and hourly blood gas analyses were used to ensure normal arterial blood pH, $PaCO_2$, and hemoglobin saturation with oxygen. Lactated Ringers solution was given through the jugular catheter at 11 ml/kg of body weight/h.

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a Strongid paste, Pfizer Inc, New York, NY.

The ponies were positioned in dorsal recumbency. The facial artery was cannulated with PE-240 tubing,[b] which was connected to a pressure transducer.[c] Through a midline celiotomy, a 12 to 15 cm segment of terminal jejunum, approximately 1 m from the ileocecal valve, was exteriorized.

An extracorporeal circuit was established between the femoral artery and the single perfusing artery of the jejunum (Figure 1). Heparin sodium (500 U/kg of body weight) was administered IV (jugular vein) hourly 3 times. The femoral artery was cannulated with PE 320 tubing and the perfusion artery of the jejunum with a 14 gauge needle. The intestine was perfused with arterial blood by a pulsatile pump[d] interposed inbetween the femoral and jejunal arteries. The perfusing artery pressure was measured via a 20 gauge needle connected to the perfusion tubing between the pump and the perfusing artery attached to a pressure transducer (Figure 2). The single vein draining the segment was cannulated with a 14 gauge catheter attached to PE 320 tubing and the venous outflow directed into a reservoir. Blood was returned to the pony from the reservoir by a second pump[e] through the jugular catheter. The ends of the

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b Intramedic polyethylene tubing, Clay Adams Inc, Parsippany, NJ.

c Model P-23 Db, Statham Instruments Inc, Cleveland, Ohio.

d Model T8SH, Sigmamotor Inc, Middleport, NY.

e Model 7535-00, Masterflex, Cole-Palmer Instrument Co, Chicago, Illinois.

Figure 1. Extracorporeal circuit. Femoral arterial blood was used to perfuse the intestinal segment with a peristaltic pump, venous blood from the intestinal vein was drained into a reservoir. Blood from the reservoir was returned to the pony via the jugular vein using a non-peristaltic pump. Portions of arterial and venous blood were diverted from the main extracorporeal circuit and pumped through the arteriovenous oxygen content analyzer with a second non-peristaltic pump. Solid lines signify arterial blood, long dashes signify venous blood and short dashes signify mixed arteriovenous blood.

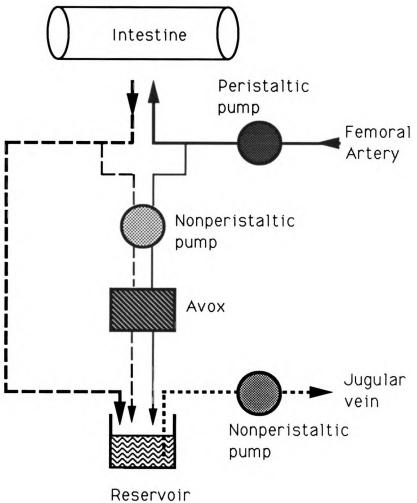

Figure 1. Extracorporeal Circuit

Figure 2. Isolated segment preparation. The segment was perfused by a single artery and vein. Arterial perfusion pressure was determined by means of a 20 gauge needle inserted into the perfusion tubing close to the segment and connected to a blood pressure transducer. A latex balloon was inserted into the lumen of the segment and tied at each end. After saline infusion into the balloon, intraluminal pressure changes were recorded by means of a pressure transducer connected to the balloon by a 3-way stopcock.

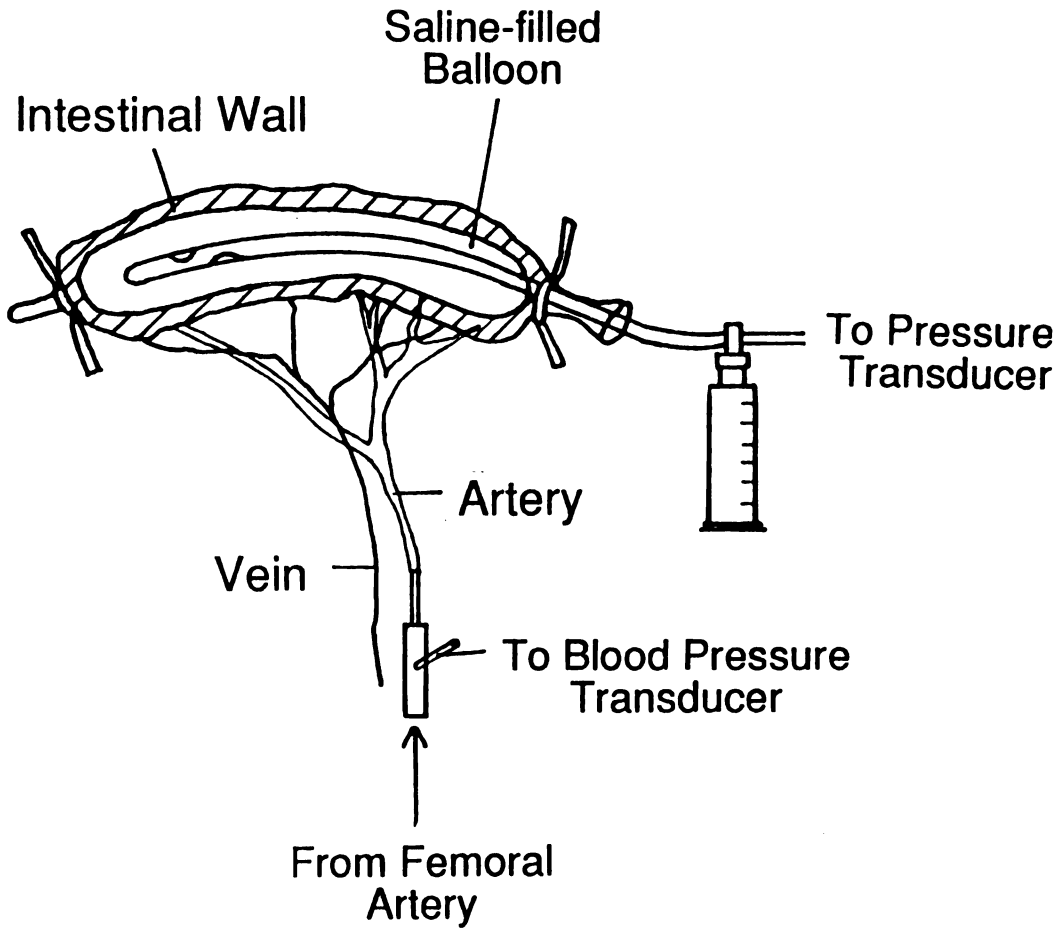

Figure 2. Isolated Intestinal Segment Preparation

segment were ligated and severed from adjacent bowel to exclude collateral blood flow. Blood flow, was adjusted to keep perfusion pressure equal to systemic arterial pressure during isolation of the intestinal segment and then maintained constant for the duration of the study. At the end of the experiment, the intestinal blood flow was measured with a graduated cylinder and stopwatch, and the segment weighed. Vascular resistance (R) was calculated by dividing perfusion pressure (P) by IBF and the weight of the segment (K), using the following equation:

$$R\ (\text{mm Hg/ml/min/100 g}) = \frac{P}{(IBF / K) \times 100}$$

A portion of both arterial and venous blood was diverted from the afferent and efferent arcs of the extracorporeal circuit to a spectrophotometric arteriovenous oxygen content analyzer (AVOX).[f,104] Arteriovenous oxygen difference (AVO_2) was determined continuously by perfusing the diverted blood through separate cuvettes within the arteriovenous oxygen content analyser with a nonperistaltic pump[g] at 14 ml/min. The AVOX was balanced at the beginning of the experiment by simultaneoulsy perfusing both cuvettes with arterial blood and and balancing was repeated every 20 minutes throughout the experiment. Oxygen uptake (VO_2) was calculated as the

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f Avox Systems Inc, San Antonio, Texas.

g Minipuls 2, Gilson, Middleton, Wisconsin.

product of the AVO_2 and the IBF divided by the segment weight (K), using the following equation:

$$VO_2 \text{ (ml/min/100 g)} = \frac{IBF \times AVO_2 \times 100}{K}$$

A thin-walled rubber balloon connected to a latex tube was placed into the lumen of the intestinal segment and the balloon was tied in place to the each end of the segment. The latex tube was connected to a pressure transducer by a 3-way stopcock. The intestinal segment was covered with a plastic sheet to keep it moist and kept at 37° C by suspending a heat lamp above it. Five to 10 ml of warm physiologic saline (37° C) was introduced into the balloon through the stopcock until the baseline intraluminal pressure (BILP) was 0 mm Hg in groups 1 and 3 and the segments allowed to recover from surgery for 45 minutes.

A single increase in intraluminal pressure caused by increasing intraluminal volume is followed by a steady decrease in intraluminal pressure, as a result of stress relaxation in the bowel wall.[104] Repeated small increases in distending volume are required to maintain a given intraluminal pressure.[88] To avoid repeated additions of saline solution to the balloon during the 1 hour measurement period (which would falsely alter intraluminal pressure changes of rhythmic contractions) yet maintain a stable BILP of 10 mm Hg during distension, we raised and maintained BILP between 12.5 and 15 mm Hg for 30 minutes by incremental increases in balloon volume in groups 2 and 3. The balloon

volume was then decreased until BILP was 10 mm Hg, which is within the range of intraluminal pressures found in equine small intestinal obstruction. Then the segment was allowed to recover from manipulation for an additional 15 minutes. Rhythmic contractions were defined as regular oscillations in intraluminal pressure and were analyzed by measuring the frequency, amplitude, and baseline of the pressure recording. For the purposes of this study, resting intestine is defined as intestine with a BILP of 0 mm Hg, while distended intestine is defined as intestine with a BILP of 10 mm Hg.

Experimental Design

The 16 ponies were allotted to 4 groups. In group 1 (n=3), baseline intraluminal pressure was set at 0 mm Hg and control measurements were taken. In group 2 (n=3) BILP was set at 10 mm Hg to study the effects of distension. The influence of neostigmine on resting intestine (BILP = 0 mm Hg) was determined in group 3 (n=5). The effect of neostigmine on distended intestine (BILP = 10 mm Hg) was studied in group 4 (n=5). Measurements were started 45 minutes after surgical manipulation was complete in groups 1 and 2 (t=0) and 45 minutes after the initiation of distension in groups 3 and 4 (t=0) and continued for 1 hour (t=60). Neostigmine[h] was administered as a bolus into the jugular vein at 0.022 mg/kg of body weight at t=15 minutes.

h Stiglyn 1 = 500, Pitman-Moore Inc, Washington Crossing, NJ

Mean systemic arterial pressure, segment artery perfusion pressure, arteriovenous oxygen difference and intraluminal pressure were recorded continuously for 60 minutes using a 4 channel physiograph[i] and a direct writing oscilloscope. Control group data (groups 1 and 2) were analysed every 15 minutes. Neostigmine induced cyclic fluctuations in amplitude of rhythmic contractions, with periods of increased rhythmic contractions, defined as active periods, alternating with periods of normal rhythmic contractions, defined as quiescent periods. Therefore, in neostigmine treated groups data were recorded 5 minutes before neostigmine administration for baseline and at each subsequent active and quiescent period.

To determine the effects of distension, data from groups 1 and 3, and groups 2 and 4 were combined to form single groups of 8 and variables were compared 10 minutes after the study period began (t = 10) (before neostigmine was administered in groups 3 and 4), using the Students' t test.

The effect of neostigmine on intestinal vascular resistance, oxygen uptake and intraluminal pressure changes, were analyzed, using a single factor repeated measures analysis of variance. Differences between the control and treatment means were evaluated, using the Student-Newman-Keuls procedure. Significance level for all tests was set at $P \leq 0.05$.

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i Model SP2000, Gould Inc, Cleveland, Ohio.

RESULTS

Mean systemic pressure remained unchanged throughout the experimental period in all groups. Mean blood flows for groups 1 through 4 were 63, 71, 58, and 66 ml/100g respectively.

Intestinal distension resulted in a significant increase in the amplitude of rhythmic contractions and in intestinal vascular resistance (Table 1). However, the frequency and baseline values of rhythmic contractions were unchanged.

Control groups were stable throughout the experiment except: in group 1 a decrease in frequency of rhythmic contractions occured by 60 minutes and in group 2 vascular resistance had decreased from baseline by 30 minutes (Appendix, Tables 2 and 3).

Neostigmine induced cyclic changes in intestinal intraluminal pressure changes, with active periods alternating with quiescent periods (Figures 3 and 4). Active periods were defined by an increase in amplitude of rhythmic contractions. During quiescent periods, amplitude of rhythmic contractions was not different from pretreatment values. No difference was seen in the number of cycles between resting (group 3) and distended intestine (group 4)

Table 1. Effects of Distension. To determine the effects of distension, data from resting controls and resting neostigmine treated ponies (groups 1 and 3), and distended controls and distended neostigmine treated ponies (groups 2 and 4) were combined to form 2 groups of 8 and variables were compared 10 minutes after the study period began. Data is shown as mean $\pm$ SEM. Data followed by similar superscripts are significantly different at $P < 0.05$. RC = Rhythmic contractions.

Table 1. Effects of distension.

Variable	Resting	Distended
Vascular Resistance ± SEM (mm of Hg/ml/min/100 g)	0.88 ± 0.05[a]	1.41 ± 0.08[a]
Oxygen uptake ± SEM (ml/min/100 g)	0.87 ± 0.11	1.03 ± 0.18
Frequency of RC ± SEM (/min)	7.3 ± 1.09	7.78 ± 0.4
Amplitude of RC ± SEM (mm of Hg)	1.25 ± 0.23[b]	4.16 ± 0.53[b]

Figure 3. Motility changes with neostigmine treatment in pony 8 (group 3). Neostigmine (0.022 mg/kg intravenously) induced cyclic fluctuations in intestinal intraluminal pressure changes, with periods of increased activity (active periods = A) alternating with periods of normal activity (quiescent periods = Q). In pony 8 the increase in amplitude of rhythmic contractions was not accompanied by an increase in intraluminal baseline pressure.

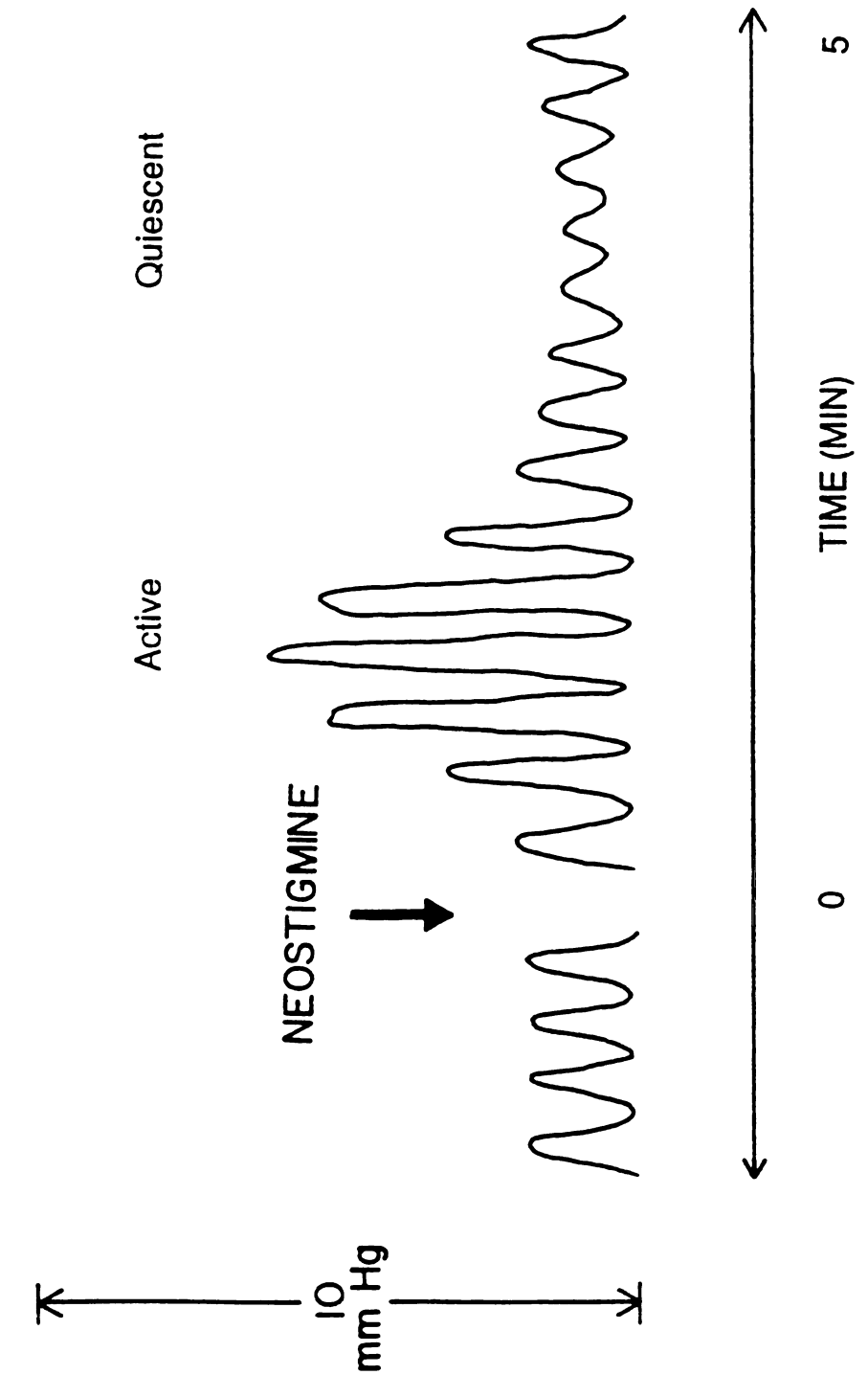

Figure 3. Motility changes with neostigmine treatment in pony 8 (group 3)

Table 2. Group 1. Resting Controls. In resting control ponies the baseline intraluminal pressure was 0 mm Hg. All variables were monitored for 1 hour, the data were recorded every 15 minutes and reported as mean $\pm$ SEM. Data followed by asterisks are significantly different from baseline values at $P < 0.05$. RC = Rhythmic contractions.

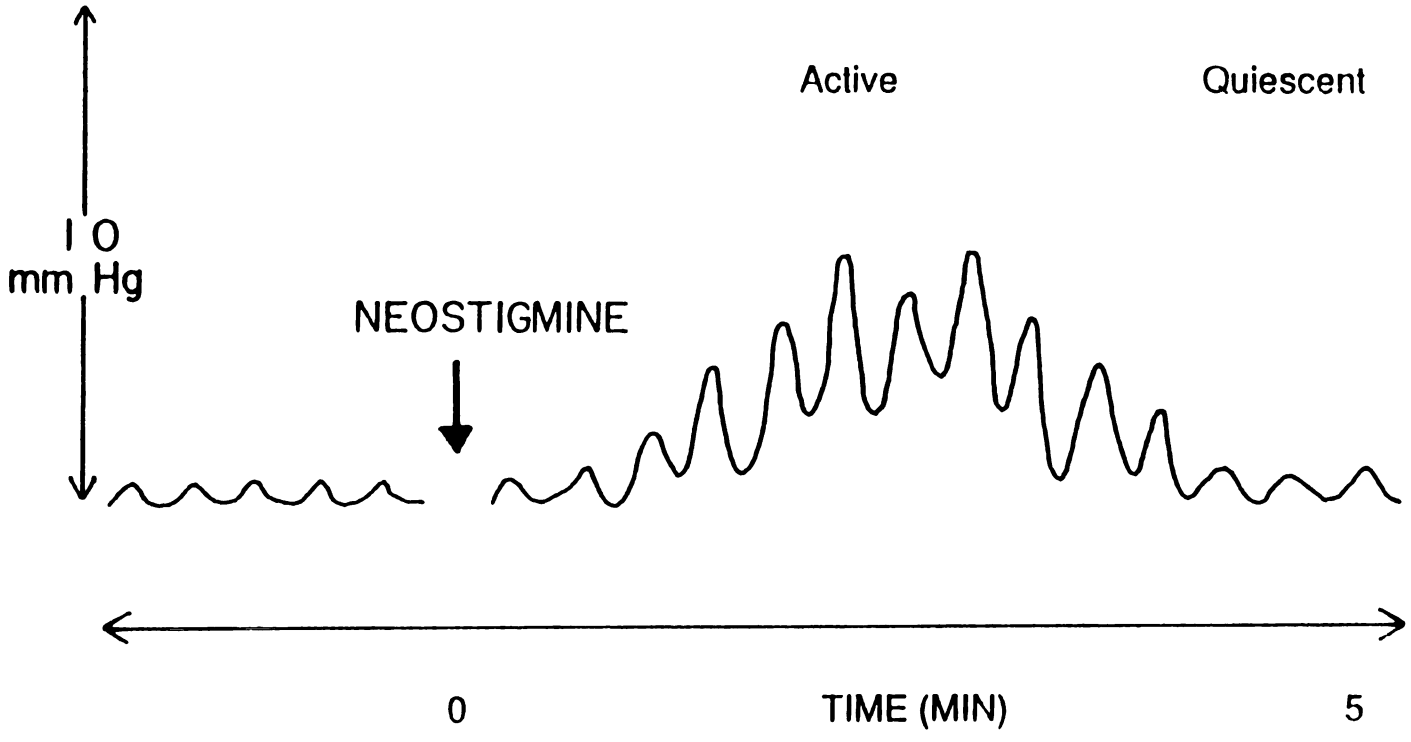

Figure 4. Motility changes with neostigmine treatment in pony 9 (group 3)

(5.4 ± 0.6 and 5.6 ± 0.51, respectively), with a range of 4 to 7 cycles in both groups. The mean periodicity of cycles was 5.7 minutes in group 3 and 4.7 minutes in group 4. Because the cyclic fluctuations in rhythmic contractions showed no temporal consistency between ponies, data were analysed during both active and quiescent periods for 4 cycles in each pony.

In resting intestine (group 3; Appendix, Table 4), vascular resistance (0.96 ± 0.06 mm Hg/ml/min/100g) and frequency of rhythmic contractions (9.05 ± 1.78 /min) did not change after neostigmine administration. However, neostigmine caused an increase in oxygen uptake during all 4 active and quiescent periods analysed (figure 5), amplitude of rhythmic contractions was increased during active periods (figure 6) and baseline values of rhythmic contractions were increased during quiescent periods (figure 7). Vascular resistance (1.47 ± 0.12 mm Hg/ml/min/100g), oxygen uptake (0.91 ± 0.57 ml of O_2/min/100g), frequency of rhythmic contractions (7.48 ± 0.56 /min), and baseline values of rhythmic contractions (10.15 ± 0.23 mm Hg) were not significantly altered by neostigmine administration in distended intestine (group 4; Appendix, Table 5). However, the amplitude of rhythmic contractions during the first active period was significantly increased by neostigmine (figure 8).

Figure 5. Effect of neostigmine on oxygen uptake in resting intestine. Neostigmine (0.022 mg/kg intravenously) induced cyclic fluctuations in intestinal intraluminal pressure changes, with periods of increased activity (active periods = A) alternating with periods of normal activity (quiescent periods = Q). Therefore data were recorded 5 minutes before neostigmine administration for baseline and at each subsequent active and quiescent period. Values are reported as the mean $\pm$ standard error of the mean. Asterisks indicate values significantly different from baseline at $P < 0.05$.

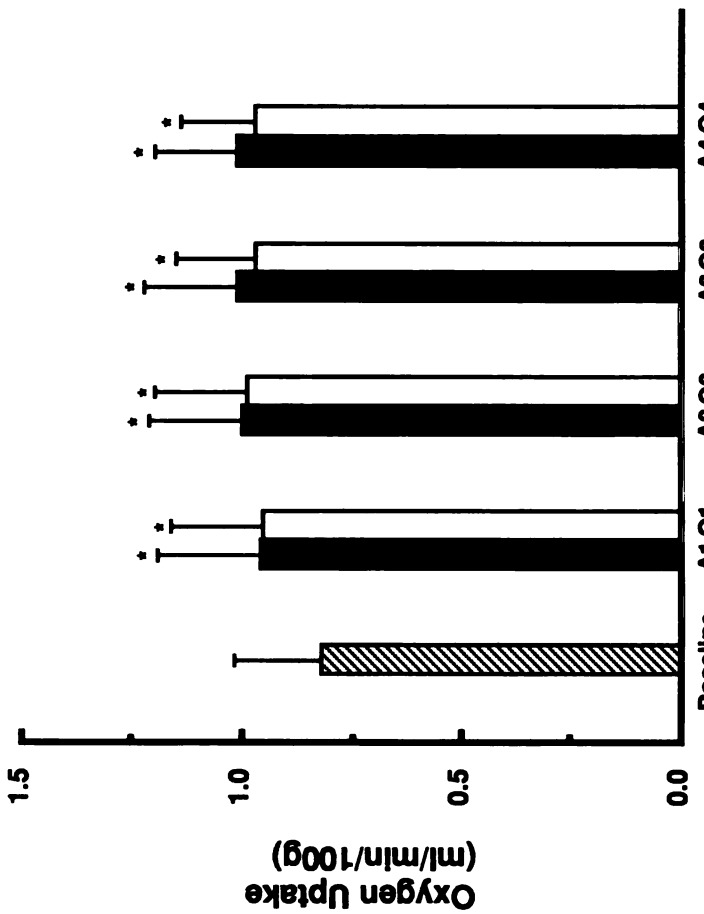

Figure 5. Effect of neostigmine on oxygen uptake in resting intestine.

Figure 6. Effect of neostigmine on amplitude of rhythmic contractions in resting intestine. Neostigmine (0.022 mg/kg intravenously) induced cyclic fluctuations in intestinal intraluminal pressure changes, with periods of increased activity (active periods = A) alternating with periods of normal activity (quiescent periods = Q). Therefore data were recorded 5 minutes before neostigmine administration for baseline and at each subsequent active and quiescent period. Values are reported as the mean $\pm$ standard error of the mean. Asterisks indicate values significantly different from baseline at $P < 0.05$.

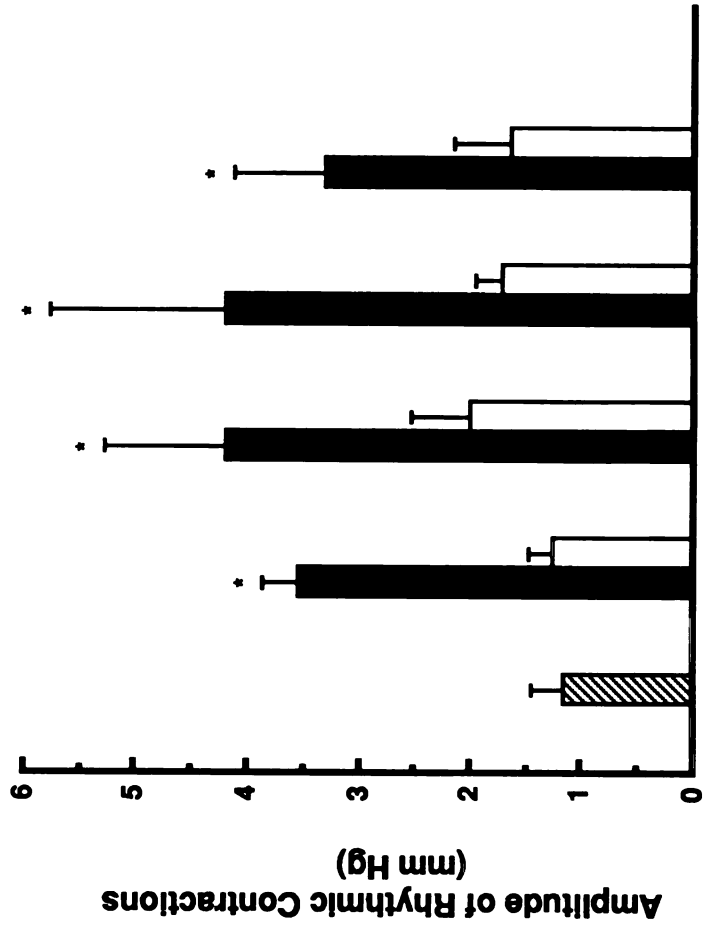

Figure 6. Effect of neostigmine on amplitude of rhythmic contractions in resting intestine

Figure 7. Effect of neostigmine on baseline intraluminal pressure in resting intestine. Neostigmine (0.022 mg/kg intravenously) induced cyclic fluctuations in intestinal intraluminal pressure changes, with periods of increased activity (active periods = A) alternating with periods of normal activity (quiescent periods = Q). Therefore data were recorded 5 minutes before neostigmine administration for baseline and at each subsequent active and quiescent period. Values are reported as the mean $\pm$ standard error of the mean. Asterisks indicate values significantly different from baseline at $P < 0.05$.

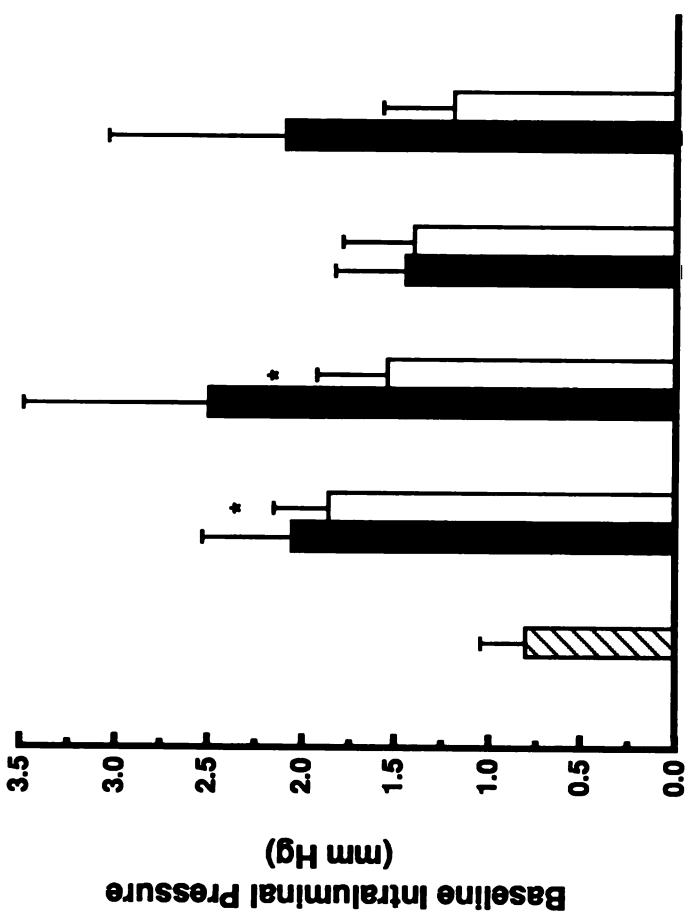

Figure 7. Effect of neostigmine on baseline intraluminal pressure in resting intestine

Figure 8. Effect of neostigmine on amplitude of rhythmic contractions in distended intestine. Neostigmine (0.022 mg/kg intravenously) induced cyclic fluctuations in intestinal intraluminal pressure changes, with periods of increased activity (active periods = A) alternating with periods of normal activity (quiescent periods = Q). Therefore data were recorded 5 minutes before neostigmine administration for baseline and at each subsequent active and quiescent period. Values are reported as the mean $\pm$ standard error of the mean. Asterisks indicate values significantly different from baseline at $P < 0.05$.

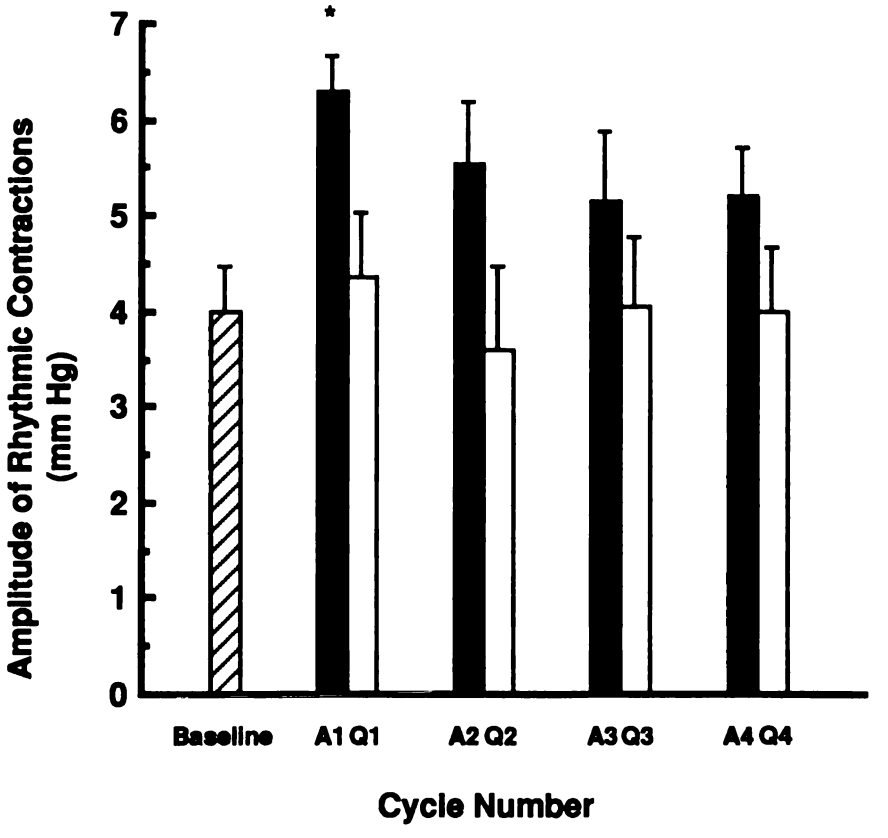

Figure 8. Effect of neostigmine on amplitude of rhythmic contractions in distended intestine

DISCUSSION

Maintaining intestinal distension at an intraluminal baseline pressure of 12.5 - 15 mm Hg for 30 minutes by adding increments of saline to the balloon, followed by reduction of baseline intraluminal pressure to 10 mm Hg, resulted in a stable baseline intraluminal pressure for the entire measurement period, without adding further increments of saline to the balloon, in groups 2 and 4. This procedure also eliminated changes in distensibility that occur as the bowel relaxes,[102] which is associated with a decreased capillary filtration coefficient and blood flow when the intestine is distended.[98,102]

Groups 1 and 2 show that the preparation was remarkably stable. A significant decrease in frequency of rhythmic contractions was seen in group 1 by 60 minutes, the same trend was seen in the other three groups but was not significant. Slow wave frequency is remarkably resistant to change after various stimuli, however it does slowly decrease with decreases in body temperature[32] and this is the most likely explanation for this finding. The decrease in vascular resistance that occured in group 3 is probably related to further slight stress relaxation and was not seen in group 4, either because group 4 parameters were not

measured for so long or because the effects of neostigmine obscured the stress relaxation.

Intestinal distension caused increases in amplitude of rhythmic contractions (Table 1), as previously reported in dogs.[57] Vascular resistance was higher in distended intestine than in resting intestine, but oxygen consumption did not differ (Table 1). This suggests that although equine intestinal hemodynamics are adversely affected by distension, intestinal viability is not compromised because oxygen uptake did not change. Studies in other species indicate that, at intraluminal pressures of 20 mm Hg, intestinal blood flow may either be increased,[57] or unaffected;[43,88,94,100] but at higher intraluminal pressures, blood flow is decreased.[43,90,91,94,100] Microsphere studies have indicated that redistribution of blood flow within the bowel wall develops with increases in intraluminal pressure, the mucosal/submucosal blood flow decreases while the muscularis/serosal blood flow may actually increase because of active hyperemia.[57,94] The reduction in mucosal/submucosal blood flow is attributed to mechanical compression of vessels. The difference in vascular resistance between distended and resting intestine at 10 mm Hg intraluminal pressure suggests that equine intestinal vascular resistance may be more easily increased by distension than that of other species. However, because no accompanying decrease in oxygen uptake developed, it is unlikely that intestinal viability is compromised when BILP

is 10 mm Hg. The absence of histologic lesions after prolonged artificial distension in another study in horses supports this suggestion.[80]

At an intraluminal pressure of 20 mm Hg, oxygen uptake is reported to increase[96] or remain unchanged,[43,88] but at higher distending pressures a stepwise reduction in oxygen uptake occurs that is caused by a reduction in blood flow due to increased vascular resistance,[88] and decreased oxygen extraction through opening of arteriovenous shunts.[43] Therefore it is not supprising that no decrease in oxygen uptake was seen at 10 mm Hg in ponies. However, as ileal oxygen consumption in the dog shows a direct relationship to motility,[105] it is more supprising that no increase in oxygen uptake was seen with the increase in motility provoked by distension. This may be because of the wide individual variation between animals and that each animal did not act as its own control for the determination of variables altered by distension. Alternatively, an increase in oxygen uptake by the muscularis may be offset by a decrease in mucosal oxygen consumption.

Neostigmine did not alter vascular resistance in either group 3 or 4, which suggests that neostigmine is unlikely to compromise intestinal viability in the horse with colic, but redistribution of blood flow cannot be excluded. In contrast, physostigmine increases vascular resistance,[57] probably related to the large increase in baseline intraluminal pressure observed.

Oxygen uptake increased after neostigmine administration in both active and quiescent periods in group 3. This is most likely related to increased smooth muscle activity. There is no apparent explanation why oxygen uptake did not increase after neostigmine administration in distended intestine.

Neostigmine induces a cyclic increase in motility in resting and distended intestine. Amplitude of rhythmic contractions was increased during active periods. Baseline values of rhythmic contractions were increased during quiescent periods in resting but not distended intestine. Neostigmine prolongs the half-life of acetylcholine at the synapse, thereby amplifying the action of cholinergic synapses on receptor tissues.[106] Thus, the persistence of acetylcholine at the motor end plate of intestinal smooth muscle would increase the tension in the bowel wall. The cyclic fluctuation in amplitude of rhythmic contractions may be caused by amplification of cyclic fluctuation in motility that was already present but not apparent before neostigmine administration. Cyclic fluctuations in the intestinal slow wave would cause similar fluctuations in the number and size of action potentials generated in response to constant acetylcholine release, with corresponding variation in smooth muscle tone. Cyclic fluctuations in amplitude of slow wave depolarization (spindling) occur in the cat and rabbit, but have not been investigated in the horse.[107] They are localized, and of shorter periodicity than seen in

our study, but they may form the basis of this phenonenom; however, further study is needed to substantiate this hypothesis. Alternatively, a cylic release of acetylcholine at the motor end plate may either be caused or exaggerated secondary to ganglionic effects of neostigmine.

In healthy conscious ponies, neostigmine is reported to delay gastric emptying and prolong the migrating myoelectric complex;[10,11] these findings are taken to indicate a decrease in motility. However, in our study neostigmine increased segmental motility and it caused an earlier return of migrating myoelectric complexes in postoperative ileus in another.[78] Bethanacol, a direct cholinergic agonist, is reported to reduce the duration of postoperative ileus when used in combination with yohimbine.[28] More recently cisapride, which augments acetylcholine release, has also been shown to be effctive in reducing the postoperaive inhibition of intestinal motility.[79] Although neostigmine may deleteriosly effect the patterns of motility in normal intestine, this experiment shows that neostigmine increases segmental contractions. In ileus, the intestinal musculature is still responsive to pharmacologic stimuli,[2] therefore, the stimulation of segmental contractions with neostigmine may initiate a return to normal myoelectrical activity.

Baseline intraluminal pressure (P) is related to the bowel wall tension (T) by the equation:

$$P = T/r$$

where r is the radius.[103] The tension in the bowel wall that develops secondary to neostigmine administration is dependent on the smooth muscle fiber length and the thickness of the bowel wall.[103] Because the radius, the smooth muscle fiber length, and bowel wall thickness are unknown, direct comparisons between the effects of neostigmine on baseline intraluminal pressure and amplitude of rhythmic contractions between groups 3 and 4 cannot be made. The larger intestinal segment radius in group 4 could explain why an increase in baseline intraluminal pressure was seen in group 3 and not group 4.

These results indicate that, although intestinal hemodynamics are adversely effected by distension at 10 mm Hg baseline intraluminal pressure, this is unlikely to compromise intestinal viability in normotensive animals because oxygen uptake remains unchanged. Further, neostigmine did not adversely effect intestinal hemodynamics while increasing rhythmic contractions, suggesting that neostigmine may be useful in the treatment of ileus in equids.

CONCLUSIONS

1) Distension of equine small intestine to 10 mm Hg increased intestinal vascular resistance but oxygen consumption was not changed. This indicates that distension to 10 mm Hg adversely affects intestinal hemodynamics but is unlikely to compromise intestinal viability.

2) Neostigmine induced cyclic increases in rhythmic contractions in both resting and distended intestine but did not adversely affect intestinal hemodynamics suggesting that neostigmine may be useful in the treatment of equine ileus.

APPENDIX

Table 2. Group 1. Resting Controls. In resting control ponies the baseline intraluminal pressure was 0 mm Hg. All variables were monitored for 1 hour, the data were recorded every 15 minutes and reported as mean $\pm$ SEM. Data followed by asterisks are significantly different from baseline values at $P < 0.05$. RC = Rhythmic contractions.

Table 2. Group 1, Resting Controls

Variable	0 Min	15 min	30 min	45 min	60 min
Systemic Pressure mm Hg	65.8 ±3.6	64.2 ±3.0	61.8 ±4.3	65.0 ±7.6	63.5 ±5.9
Vascular Resistance mm Hg/ml/min/100g	0.8 ±0.06	0.76 ±0.05	0.74 ±0.04	0.72 ±0.03	0.74 ±0.04
Oxygen Consumption ml/min/100g	0.96 ±0.07	0.95 ±.04	0.94 ±0.04	0.92 ±0.03	0.90 ±0.10
Frequency of RC S^{-1}	8.07 ±0.35	8.33 ±0.43	8.20 ±0.36	7.90 ±0.46	7.47* ±0.30
Amplitude of RC mm Hg	2.42 ±0.92	2.00 ±1.00	2.00 ±1.00	1.83 ±1.09	1.83 ±1.09
Baseline of RC mm Hg	0.33 ±0.17	0.67 ±0.33	0.67 ±0.33	0.67 ±0.33	0.67 ±0.33

Table 3. Group 2. Distended Controls. In the distended control ponies the baseline intraluminal pressure was 10 mm Hg. All variables were monitored for 1 hour, the data were recorded every 15 minutes and reported as mean $\pm$ SEM. Data followed by asterisks are significantly different from baseline values at $P < 0.05$. RC = rhythmic contractions

Table 3. Group 2, Distended Controls

Variable	0 Min	15 min	30 min	45 min	60 min
Systemic Pressure mm Hg	82.5 ±6.6	82.5 ±6.3	75.8 ±5.8	76.7 ±13.6	77.5 ±13.8
Vascular Resistance mm Hg/ml/min/100g	1.33 ±0.10	1.29 ±0.09	1.22* ±0.08	1.22* ±0.08	1.20* ±0.09
Oxygen Consumption ml/min/100g	1.22 ±0.25	1.25 ±0.26	1.22 ±0.22	1.21 ±0.26	1.17 ±0.25
Frequency of RC S^{-1}	8.27 ±0.59	8.27 ±0.68	8.37 ±0.73	8.27 ±0.77	8.10 ±0.85
Amplitude of RC mm Hg	7.75 ±1.77	7.42 ±1.80	7.33 ±1.83	7.25 ±1.63	7.17 ±1.42
Baseline of RC mm Hg	10.08 ±0.30	9.92 ±0.51	9.58 ±0.79	9.50 ±0.87	9.42 +1.08

Table 4. Group 3. Effects of neostigmine on resting intestine. Neostigmine (0.022 mg/kg intravenously) induced cyclic fluctuations in intestinal intraluminal pressure changes, with periods of increased activity (active periods = A) alternating with periods of normal activity (quiescent periods = Q). Therefore data were recorded 5 minutes before neostigmine administration for baseline and at each subsequent active and quiescent period. All data is shown as mean $\pm$ SEM. Data followed by asterisks are significantly different baseline values at $P < 0.05$. RC = Rhythmic contractions.

Table 4. Group 3, Effects of neostigmine on resting intestine.

Variable	Baseline	A1	A2	A3	A4	Q1	Q2	Q3	Q4
Systemic Pressure mm Hg	75.5 ±2.3	79.5 ±3.4	73.0 ±9.6	68.0 ±7.3	69.5 ±5.8	78.5 ±6.7	72.5 ±8.0	70.0 ±6.0	65.0 ±4.2
Vascular Resistance mm Hg/ml/min/100g	0.96 ±0.06	1.05 ±0.06	1.12 ±0.06	1.14 ±0.10	1.07 ±0.09	1.03 ±0.06	1.06 ±0.06	1.04 ±0.08	1.03 ±0.08
Oxygen Consumption ml/min/100g	0.82 ±0.20	0.96* ±0.23	1.00* ±0.21	1.01* ±0.21	1.01* ±0.19	0.95* ±0.21	0.99* ±0.21	0.97* ±0.18	0.97* ±0.17
Frequency of RC S-1	9.05 ±1.78	9.54 ±1.38	10.12 ±1.68	9.44 ±1.40	9.02 ±1.33	9.98 ±0.97	10.26 ±1.67	9.06 ±1.23	9.30 ±1.49
Amplitude of RC mm Hg	1.15 ±0.30	3.55* ±0.31	4.20* ±1.07	4.20* ±1.55	3.30* ±0.82	1.25 ±0.21	2.00 ±0.53	1.70 ±0.25	1.65 ±0.50
Baseline of RC mm Hg	0.80 ±0.24	2.05 ±0.48	2.50 ±0.98	1.45 ±0.38	2.10 ±0.94	1.85* ±0.30	1.55* ±0.38	1.40 ±0.39	1.20 ±0.38

Table 5 Group 4. Effects of neostigmine on distended intestine. Neostigmine (0.022 mg/kg intravenously) induced cyclic fluctuations in intestinal intraluminal pressure changes, with periods of increased activity (active periods = A) alternating with periods of normal activity (quiescent periods = Q). Therefore data were recorded 5 minutes before neostigmine administration for baseline and at each subsequent active and quiescent period. All data is shown as mean $\pm$ SEM. Data followed by asterisks are significantly different form baseline values at $P < 0.05$.

Table 5. Group 4, Effects of neostigmine on distended intestine.

Variable	Baseline	A1	A2	A3	A4	Q1	Q2	Q3	Q4
Systemic Pressure mm Hg	81.0 ±9.1	90.1 ±7.8	85.5 ±6.0	79.0 ±4.6	81.0 ±3.5	85.5 ±7.1	85.0 ±5.2	79.5 ±4.4	81.5 ±4.3
Vascular Resistance mm Hg/ml/min/100g	1.47 ±0.12	4.53 ±0.09	1.50 ±0.11	1.48 ±0.11	1.50 ±0.09	1.50 ±0.11	1.50 ±0.11	1.50 ±0.09	1.52 ±0.08
Oxygen Consumption ml/min/100g	0.91 ±0.26	0.89 ±0.22	0.85 ±0.20	0.92 ±0.20	0.89 ±0.19	0.87 ±0.21	0.88 ±0.19	0.85 ±0.20	0.86 ±0.20
Frequency of RC S-1	7.48 ±0.56	7.6 ±0.56	7.84 ±0.54	7.80 ±0.52	7.72 ±0.57	7.90 ±0.57	8.00 ±0.46	7.98 ±0.51	8.82 ±0.50
Amplitude of RC mm Hg	4.00 ±0.47	6.30* ±0.36	5.55 ±0.63	5.15 ±0.72	5.2 ±0.50	4.35 ±0.69	3.60 ±0.86	4.05 ±0.66	4.00 ±0.67
Baseline of RC mm Hg	10.15 ±0.23	10.05 ±0.36	10.60 ±0.76	10.25 ±0.40	10.2 ±0.37	11.05 ±1.10	10.95 ±0.82	10.35 ±0.46	10.20 ±0.48

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