CARDIOVASCULAR CHANGES ASSOCIATED WITH INTRAVENOUS ADMINISTRATION OF *E. COLI* ENDOTOXIN IN CONSCIOUS PONIES

by

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LITERATURE REVIEW

Endotoxins are large macromolecular aggregates of lipopolysaccharides and proteins derived from the cell wall of gram-negative bacteria.[1] They have been suspected as causative agents of equine disease for a number of years. In 1963, Rooney et al[2] produced a syndrome in horses identical to "Colitis X" by intravenous injection of Escherichia coli endotoxin. Since that time, numerous investigators have studied the effects of lethal or sublethal doses of endotoxin administered to horses and ponies.[3-23] A number of hematologic, metabolic, and hemodynamic responses to endotoxin, as well as responses to various therapeutic agents, have been characterized.

In 1968, Nelson et al[24] surgically created acute colonic infarction in horses. Findings observed in this model suggested that the resultant hematologic and hemodynamic changes might be due to either endotoxin or the direct presence of coliform bacteria. Subsequently, small intestinal strangulation and its sequelae have been studied experimentally by Datt and Usenik,[25] McClure,[4,23,26] White et al,[27] and Moore et al.[8] The latter group demonstrated the presence of endotoxin in the systemic circulation following restoration of mesenteric blood flow. McClure[4,23] reported detection of endotoxin in the peritoneal fluid and peripheral blood following experimentally induced small intestinal volvulus. Endotoxemia has also been implicated by Moore et al[28] and Sprouse and Garner[29] as a factor in the pathogenesis of equine laminitis.

In 1965, Carroll et al[11] reported on one trial in which a lethal dose of endotoxin was injected intraperitoneally in a horse and various hematologic parameters were monitored. In 1970, Burrows[5] administered

lethal doses of endotoxin to anesthetized ponies by slow intravenous infusion. He found their hemodynamic response to be similar to that reported for the cat, rabbit, and sheep, in that transient pulmonary hypertension occurred along with a marked decrease in aortic blood pressure and marked increase in central venous and right ventricular pressure. The increase in pulmonary arterial pressure occurred slightly earlier than the increase in central venous pressure and decrease in systemic arterial pressure. Burrows and Cannon[6] repeated the work using a rapid intravenous injection of endotoxin and found the initial five minutes after endotoxin administration to be the critical period. The hemodynamic response was divided into two phases. Initially, a sharp decrease in mean arterial pressure occurred. One to two minutes later, mean arterial blood pressure returned to levels equal to or exceeding control values, while the central venous pressure returned more slowly toward control levels. During the second phase, the mean arterial blood pressure decreased again to reach a minimal level at 1½ to 2 hours. In 1971, Burrows[7] repeated the latter study in conscious ponies and found the hemodynamics to be similar to those observed in the anesthetized ponies. In 1975, Burrows[12] reported hematologic alterations of endotoxemia in horses. In 1977, Beadle and Huber[3] reported blood chemistry and blood gas changes for a four hour period following endotoxin administration, finding a decrease in blood pH, elevated lactate and pyruvate, and an increase in arterial-venous blood oxygen differences. In 1979, Burrows[13] compared intravenous and intraperitoneal routes of administration of endotoxin and noted increases in blood lactate values, which peaked at four to six hours. Moore,[14,18,30] using a lower (sublethal) endotoxin dose, found an early increase in systemic and pulmonary

arterial pressure, and a slight decrease in cardiac output. He also reported on blood lactate and arterial blood gases during sublethal endotoxemia.[31]

Blood lactic acid concentration has been studied for its value as a prognostic aid in cases of endotoxemia associated with colic and intestinal strangulation. In 1975, Donawick et al[32] reported on the use of blood lactate as a predictor of survivability and of the indication for surgery in horses with an abdominal crisis. Others have also reported a similar correlation.[13,33] A relationship between plasma lactate levels and laminitis has been noted.[28,34]

Several review articles have been written on endotoxemia in general[1,4] and in the horse.[35-37] In 1981, progress in the study of endotoxemia in the horse was reported at the First Equine Endotoxin/Laminitis Symposium.[15-23,25,28,30,38-44]

The use of the small grade pony as a suitable laboratory model for research in cardiopulmonary physiology was described by Garner et al[45] in 1971 and subsequently characterized further as a model in sublethal endotoxin studies.[14,18,30] Alterations in cardiopulmonary parameters,[14,18,20] arterial blood gas values and serum lactate values,[20,30,31] following sublethal intravenous administration of endotoxin have been reported; the responses in the pony model have been compared to those in horses and found to be similar,[14,19] suggesting that the pony is a valid and useful model for the horse in this area of research.

It has been theorized that the early phase of the response to sublethal intravenous doses of endotoxin reflects pulmonary hypertension, possibly due to severe vasoconstriction and/or vascular occlusion.[18,33]

Increased pulmonary artery pressure has been observed in other species, including the dog,[46] pig,[47] and calf.[48] The present study was undertaken to further define the cardiopulmonary hemodynamics and to characterize the response of the right ventricle to administration of sublethal doses of endotoxin in ponies.

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SUMMARY

Six resting conscious ponies were given sublethal (10 ug/kg) doses of Escherichia coli endotoxin by rapid intravenous bolus and certain blood chemistry, hemodynamic and physical parameters were measured for a two-hour period. The severity of the response to endotoxin was of variable intensity in these ponies but was characterized, in general, by restlessness, depression, pyrexia, and lactic acidemia. Hemodynamically, heart rate, mean and systolic carotid arterial pressure, right ventricular (RV) systolic blood pressure, mean pulmonary arterial velocity, and RV dP/dt_{max} were significantly elevated by five minutes. Heart rate and RV dP/dt_{max} remained elevated throughout the observation period. Attempts were made to correlate the findings in this study with those of other studies using similar sublethal doses of E. coli endotoxin.

INTRODUCTION

Endotoxins, the lipopolysaccharide components of the outer cell walls of gram-negative bacteria, have been the subject of extensive research. Endotoxins have been implicated as contributing to the pathophysiologic process in equine colic[1] and laminitis.[2] Intravenous injection of sublethal doses of endotoxin produces profound effects on cardiopulmonary hemodynamics in the dog,[3] calf,[4] pig,[5] and horse.[6,7] Recently, Moore[8] characterized a model for the study of sublethal doses of endotoxin in the pony. He has also compared the responses of ponies and horses to endotoxin and concluded that they respond similarly to a sublethal intravenous bolus of endotoxin, validating the grade pony as a useful model for the horse for this area of research.[9] The purpose of this study was to further characterize the cardiopulmonary response of the grade pony to a sublethal dose (10 micrograms per kg) of Escherichia coli endotoxin with specific emphasis on right ventricular dynamics.

MATERIALS AND METHODS

Six grade (Shetland type) ponies of mixed age and sex weighing 129-192 kg (158 kg ± 2.4 kg SE) were used in this study. Prior to the endotoxin trial, the ponies were dewormed twice, first with mebendazole[a] paste, followed six weeks later by administration of pyrantel pamoate[b] and trichlorfon[c] by nasogastric tube, and immunized against tetanus,[d] eastern and western equine encephalomyelitis,[d] equine influenza[e] and rhinopneumonitis.[f] They were maintained on free choice prairie hay and pasture.

The left common carotid artery was elevated to a subcutaneous location using a modification of the method described by Tavernor.[10] A minimum of four weeks was allowed for healing of the surgical site prior to endotoxin administration.

On the day of the endotoxin trial, under local anesthesia, catheters were placed in the elevated portion of the left common carotid artery and in the proximal portion of the right jugular vein. Distal to the jugular catheter, the right jugular vein was cannulated using a 7 French USCI percutaneous catheter introducer set.[g] All catheters were capped, heparinized and sutured to the skin.

Three to four hours later, the catheterized ponies were placed in the stocks. A temperature probe[h] was placed in the rectum. Measurement of systemic blood pressure and collection of arterial blood samples were accomplished by use of the carotid arterial catheter. A 7 French Millar "Mikro-Tip" pressure-velocity transducer[i] was passed through the USCI catheter introducer into the right jugular vein. The Millar transducer used has a velocity sensor about 7 cm proximal from the tip and

and a pressure sensor about 7 cm proximal from the velocity sensor. The Millar transducer was placed so that the velocity sensor was located in the main pulmonary artery and the pressure sensor in the right ventricle.

The following parameters were measured: rectal temperature, carotid artery pressure, heart rate, right ventricular pressure, pulmonary artery velocity, and right ventricular dP/dt. Arterial blood samples were taken and analyzed for pH, P_{CO_2}, P_{O_2}, and lactic acid.

Pre-exposure baseline samples were taken after the pony was settled quietly in the stocks. Ten micrograms per kg of Escherichia coli 055:B5 endotoxin[j] were administered as an intravenous bolus.

Rectal temperature was recorded and arterial blood samples were taken at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-exposure. The carotid arterial pressure, heart rate, right ventricular pressure, pulmonary artery velocity and dP/dt were measured continuously for the two-hour period.

The pulmonary arterial velocity was measured by a square-wave electromagnetic flow meter[k] and recorded on a Beckman multi-channel recorder.[l] The right ventricular (RV) pressure and dP/dt, carotid arterial pressure, and heart rate were all recorded on the Beckman multi-channel recorder.

RV dP/dt was determined with a Beckman type 9879 dP/dt coupler.[m] Heart rate was determined from RV pressure with a Beckman type 9857B cardiotachometer.[n] Arterial pH, P_{CO_2}, and P_{O_2} were determined using a pH/blood gas analyzer,[o] and corrected to body temperature. Heparinized samples were analyzed immediately after collection. Arterial lactic

acid was determined by an enzymatic assay.[p]

Statistical analysis was done using a Hewlett-Packard computer[q] and printer,[r] using a two-way analysis of variance program with results reported as mean ($\bar{X}$) and standard error of the mean (SEM).

RESULTS

CLINICAL OBSERVATIONS

During the first ten to fifteen minutes following endotoxin administration five of the six ponies appeared anxious and exhibited restlessness and rapid shallow respiration. Several of the ponies were intermittently restless throughout the two-hour observation period. Overall, the ponies defecated more frequently than would normally be expected although the feces were formed or semi-formed. Between thirty minutes and two hours following endotoxin administration, two of the ponies (numbers 2 and 5) showed abdominal discomfort evidenced by raising a rear leg, cramping, and attempting to lay down in the restraint stocks. Pony number 5 became markedly cyanotic and collapsed in the stocks near the end of the two-hour observation period and refused to rise. At the end of the observation period, therapeutic measures (flunixin meglumine and lactated Ringer's solution intravenously) were required to enable her to return to her stall. All but one of the ponies was noted to be depressed and reluctant to walk when returned to the stall area at the end of the two-hour observation period. One pony, number 3, showed little, if any overt clinical response to endotoxin administration.

BODY TEMPERATURE, BLOOD GAS TENSIONS, AND PLASMA LACTATE

Mean values (± 1 SEM) are presented in Table 1. Body temperature increased linearly to a peak value of 38.7°C at 105 minutes post-endotoxin. Arterial plasma lactate values increased from a control level of 18.2 mg/dl to a peak value of 29.7 mg/dl at the 120 minute sample (Figure 1). Arterial pH initially increased to 7.48 (control

7.45) at five minutes and then declined to a plateau of 7.42 at thirty minutes post-endotoxin, remaining there for the rest of the observation period (Figure 1). Arterial P_{O_2} and P_{CO_2} did not change significantly.

HEMODYNAMIC VALUES

Mean hymodynamic values (± 1 SEM) are presented in Table 2. Heart rate increased significantly from a control of 51 beats/min to 80 beats/min by five minutes after endotoxin administration. Heart rate remained significantly elevated throughout the 120 minute observation period with the exception of the thirty and 45 minute values (Figure 2). Mean and systolic carotid artery pressure increased significantly at five minutes but were not significantly different from the control values during the remainder of the observation period (Figure 3). Right ventricular systolic pressure was nearly twice the control value (82 mm Hg vs. 44 mm Hg) at five minutes post-endotoxin and thereafter declined steadily to 35 mm Hg at 105 minutes. RV end-diastolic pressure slowly declined from 12 mm Hg to a low of 5 mm Hg (Figure 3). Mean pulmonary artery velocity values increased significantly at five minutes post-endotoxin but were not significantly different from the control value thereafter; peak pulmonary artery velocity decreased at ten minutes but was not statistically significant at any time (Figure 4). Pulmonary artery velocity measurements were not valid in ponies 3 and 6, so peak and mean pulmonary artery velocity are based on data from four ponies.

RV dP/dt_{max} increased dramatically to 1000 mm Hg/sec at five minutes, more than doubling the control value of 483 mm Hg/sec. The overall pattern of dP/dt_{max} was diphasic with a second peak at 75 minutes

post-endotoxin. The dP/dt_{max} was elevated from the control value throughout the test period (Figure 2). A similar pattern was observed in RV dp/dt_{min}, which peaked at five minutes at 1074 mm Hg/sec (control value 533 mm Hg/sec) with a second peak at 75 minutes (996 mm Hg/sec).

Table 1

Temperature, Lactic Acid, and Blood Gas Measurements after Intravenous Endotoxin (10 ug/kg) Administration (Mean ± SEM)

Time (min)	0	5	10	15	30	45	60	75	90	105	120
Body temp. (°C)	37.8 ±.2	37.9 ±.2	37.9 ±.2	38.0 ±.2	38.1 ±.2	38.2* ±.2	38.2* ±.2	38.3* ±.2	38.5* ±.2	38.7* ±.2	38.6* ±.3
Arterial lactic Acid (mg/dl)	18.2 ±5.8	21.2 ±5.1	21.6 ±5.0	21.5 ±4.7	21.1 ±4.5	20.6 ±4.2	20.2 ±4.1	19.8 ±3.7	21.8 ±3.0	22.3 ±3.3	29.7* ±7.8
Arterial P_{CO_2} (mm Hg)	36.9 ±1.3	34.6 ±2.0	35.9 ±1.8	37.7 ±1.3	39.9 ±1.6	37.6 ±1.9	38.0 ±2.0	38.5 ±2.0	37.9 ±2.5	37.8 ±2.2	36.4 ±1.8
Arterial P_{O_2} (mm Hg)	95.1 ±3.1	85.6 ±8.2	91.5 ±6.2	91.1 ±4.3	88.1 ±3.1	95.6 ±2.6	97.9 ±2.2	98.1 ±1.9	95.3 ±2.1	95.1 ±3.1	99.4 ±3.7
Arterial pH	7.45 ±0.02	7.48* ±0.02	7.46 ±0.01	7.44 ±0.01	7.42* ±0.01	7.43 ±0.01	7.42* ±0.01	7.42* ±0.01	7.42* ±0.01	7.42* ±0.02	7.43 ±0.02

*= significant at 0.05 level

Table 2

Hemodynamic Effects of Intravenous Endotoxin Administration (10 ug/kg) (Mean ± SEM)

Time (min)	0	5	10	15	30	45	60	75	90	105	120
Heart Rate (beats/min)	51 ±5	80* ±7	74* ±9	75* ±9	59 ±8	65 ±8	75* ±9	82* ±8	81* ±8	76* ±7	77* ±7
Mean Carotid Arterial Pressure (mm Hg)	111 ±7	140* ±13	116 ±7	115 ±7	110 ±6	111 ±6	109 ±7	105 ±6	97 ±10	98 ±11	101 ±12
Systolic Carotid Arterial Pressure (mm Hg)	137 ±8	185* ±23	146 ±5	139 ±6	138 ±5	138 ±8	138 ±9	128 ±8	123 ±12	119 ±14	121 ±14
Mean Pulmonary Arterial Velocity (cm/sec)	15 ±2	24* ±7	21 ±8	21 ±8	17 ±6	19 ±5	21 ±5	19 ±6	16 ±3	16 ±3	16 ±3
Peak Pulmonary Arterial Velocity (cm/sec)	64 ±14	66 ±11	51 ±14	54 ±12	59 ±12	56 ±11	61 ±11	56 ±4	54 ±7	51 ±6	51 ±6
Right Ventricular Pressure - Systolic (mm Hg)	44 ±5	82* ±12	67* ±8	68* ±10	56 ±6	49 ±5	44 ±4	40 ±3	37 ±3	35 ±3	36 ±3
Right Ventricular Pressure - Diastolic (mm Hg)	12 ±3	13 ±4	13 ±5	12 ±3	10 ±2	9 ±2	8 ±2	6* ±2	6* ±2	5* ±1	5* ±1
dP/dt_{max} (mm Hg/sec)	483 ±65	1000* ±196	721* ±56	721* ±67	550 ±52	613* ±68	654* ±70	679* ±90	625* ±66	588 ±41	583 ±66
dP/dt_{min} (mm Hg/sec)	533 ±77	1074* ±215	842 ±116	896* ±159	792 ±116	696 ±70	771 ±96	996* ±254	738 ±145	746 ±142	663 ±72

* = significant at 0.05 level

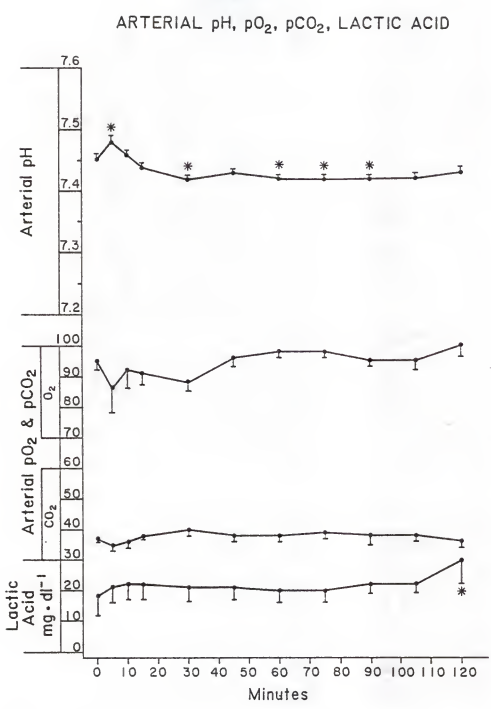


Figure 1. Arterial pH, P_{O_2}, P_{CO_2}, and Lactic Acid Values. (* = $P \leq 0.05$)

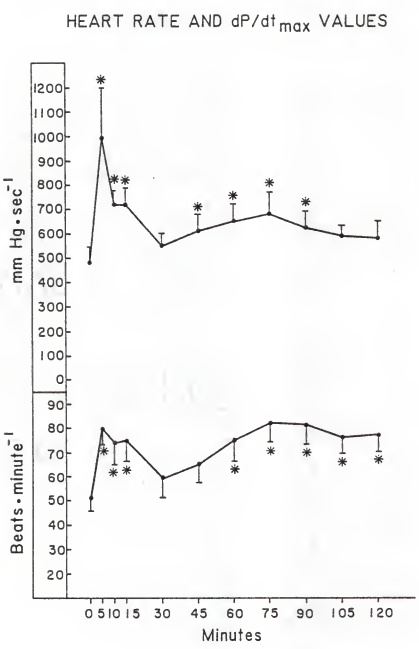
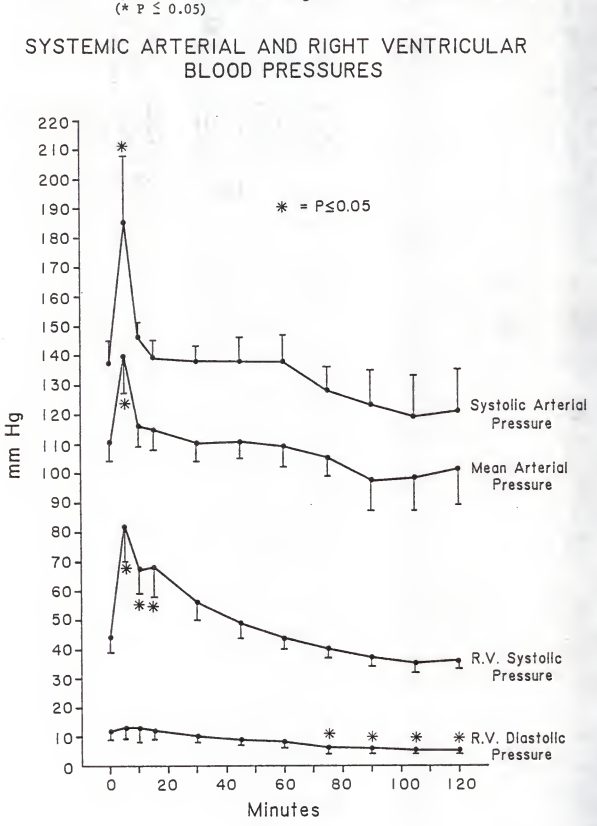


Figure 2. Heart Rate and dP/dt_{max} values. (* = $P \leq 0.05$)

Figure 3. Systemic Arterial and Right Ventricular Blood Pressure. (* $P \leq 0.05$)



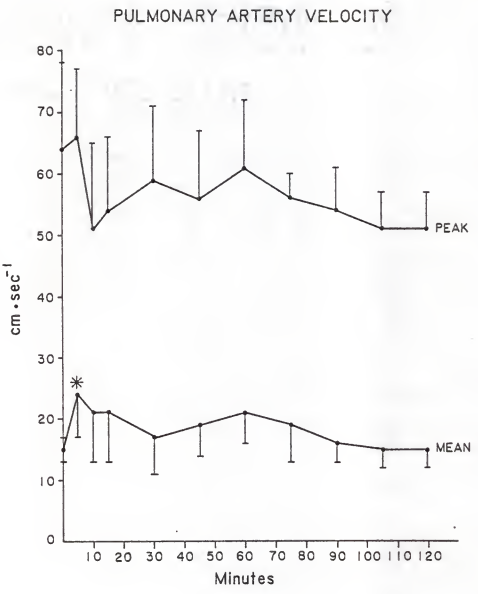


Figure 4. Pulmonary Artery Velocity. (* = $P \leq 0.05$)

DISCUSSION

The control data in the present study were comparable to previously reported normal values for conscious ponies.[6,11-14]

Administration of endotoxin resulted in clinical signs similar to those noted by Moore[6-8,15] who used the same dose of endotoxin. However, considerable variation was seen in overt clinical signs in our ponies. One pony showed no clinical signs; a slight (0.3°C) rise in temperature was the only noticeable change. This is consistent with the observations of Burrows,[16] who noted that some ponies react severely to a minimal dose of endotoxin; he also encountered one pony that responded minimally even to large doses of endotoxin.

Body temperature increased in all ponies, as has been previously reported.[7,17-21] Pyrexia is thought to be due to at least two mechanisms: direct effect on the thermoregulatory center in the brain and release of endogenous pyrogens from phagocytic cells.[22]

Plasma lactate concentration increased less rapidly in this investigation than in previously reported studies[9,23] which used the same dose of endotoxin. However, there was a wide variation in normal values in these ponies; control values ranged from 7.3 mg/dl to 45.4 mg/dl, reducing the significance of this parameter during the early measurement period. The pony with the control value of 45.4 mg/dl was consistently intractable and vigorously resisted the usual restraint procedures for catheter placement. Muscular exertion resulting in release of lactic acid prior to the start of the observation period may have obscured the effects of endotoxin on lactic acid in this pony, since lactate declined to 34.6 mg/dl at 120 minutes. Mean lactate values remained in the range

previously reported as being consistent with survival,[24-26] although one pony reached a level of 57.8 mg/dl at 120 minutes, which is in a transitional zone according to a previous report.[19]

Arterial pH values were consistent with a previous report.[15] An increase at five minutes post-endotoxin injection correlates with the onset of tachypnea and may reflect respiratory alkalosis. A slight non-significant decrease in P_{CO_2} was seen concurrently. Following the initial increase, arterial pH dropped, reaching its lowest value at 90 minutes. Previously, this drop in arterial pH has been attributed to lactic acidosis.[15] However, in the present study, the decline in pH preceded any significant increase in blood lactate concentration. Also, the pH decline was not accompanied by an elevated P_{CO_2}, ruling out respiratory acidosis as a cause. The accumulation of other organic acids or a loss of bicarbonate into the intestinal lumen could result in a lowered arterial pH. Bicarbonate levels were not measured in this study, but a significant decrease has been reported.[15]

Arterial oxygen tension did not change significantly, nor were any significant changes seen in the P_{CO_2} levels, although a slight decrease was observed in both at five minutes post-injection. In the sublethal endotoxin model described previously,[15] a more marked initial drop occurred in both values, suggesting pulmonary ventilation-perfusion mismatch (intrapulmonary shunting or alveolar-capillary perfusion impairment).

Heart rate increase was similar to that previously reported.[9] Peak pulmonary artery velocity was not significantly changed while the mean velocity was significantly elevated at five minutes. Normal data for this value has not been reported for the horse. In man, when aortic

measurements are taken near the upper border of the sinuses of Valsalva, blood velocity can be related to blood flow per unit of time, or cardiac output, because changes in aortic internal diameter in this area are minimal (less than 5%). Therefore, the diameter can be assumed to be constant without resulting in large errors occurring in extrapolation of data.[27] While the pulmonary artery is significantly thinner and more distensible than the aorta,[28] Nichols et al[29] found the average cross-sectional area change to be only ± 6% in man. The main pulmonary artery was examined in the ponies in this study at necropsy, but it was not possible to accurately determine the in vivo internal diameter by this method, due to the elasticity and distensibility of the artery. In our opinion, pulmonary artery velocity can best be related to cardiac output if the diameter of the pulmonary artery is measured simultaneously in vivo. No studies on the correlation of pulmonary arterial velocity with cardiac output in the horse have been reported.

Systolic and mean systemic (carotid) arterial pressure were significantly elevated at five minutes but unremarkable thereafter. This is consistent with Moore's findings in his sublethal endotoxin model.[8] He also reported a marked increase in pulmonary arterial pressure,[7,8] which was not measured in this study. RV systolic pressure was sharply elevated at five minutes and then declined steadily over the two-hour observation period while end-diastolic pressure was declined. The cause of these initial elevations is not proven but might be related to catecholamine release.

The most striking hemodynamic change was the increase in dP/dt_{max} which more than doubled at five minutes and then showed a biphasic

pattern, remaining elevated for most of the observation period. Peak dP/dt (dP/dt_{max}) is considered to be a reflection of myocardial contractility, elasticity, and ventricular configuration.[30] If end-diastolic volume is constant, dP/dt_{max} is related to changes in myocardial contractile strength. Left ventricular (LV) dP/dt_{max} has been measured more frequently in the horse[12,30-32] than RV dP/dt.[12,21,33] In general, LV dP/dt_{max} is reported to be consistently reached prior to onset of aortic valve opening[34,35] although this concept is challenged.[36] Regardless, Brown and Holmes[31] found LV dP/dt_{max} to be always an isovolumic occurrence in a group of eight horses. However, they did not find this to be consistently true of RV dP/dt_{max}. Therefore, the validity of RV dP/dt_{max} as an index of contractility has been questioned,[36] although Schmidt and Hoppe,[37] and Hoppe et al[38] found it to be reflective of induced changes in contractility. Hoppe et al[38] have recommended the use of RV dP/dt_{max} for evaluation of relative changes in the inotropic state.

Maximum dP/dt is influenced by hemodynamic changes. Elevation of ventricular end-diastolic pressure (preload), increase in heart rate, and increase in mean aortic pressure (afterload) all resulted in increased LV dP/dt_{max} in dogs.[34] Infusion of a positive inotropic agent (norepinephrine) also increased dP/dt_{max} in these dogs. It is logical to assume that the same parameters would apply to the right ventricle.

In this study, heart rate increased; right ventricular end-diastolic pressure declined. Although pulmonary artery pressure was not measured, Moore[6-9] has shown it to be markedly elevated following an identical dosage of endotoxin in ponies. Assuming a similar increase in pulmonary

artery pressure occurred in our ponies, the increase in RV dP/dt_{max} could have been influenced by that change, by the increased heart rate, by increased right myocardial contractile power as a result of catecholamine release, or the additive effect of more than one of these factors. While it is not possible to determine from this investigation which of the above possibilities, if any, played a predominant role in the marked dP/dt_{max} increase, one can make some speculations, based on the data known.

If one relates findings in the left ventricle to that of the right, the change in heart rate in these ponies would not be expected to be the exclusive cause of such a large increase in dP/dt_{max}, when compared to findings in dogs,[34] although both parameters show a biphasic pattern. When using intravenous boluses of endotoxin at a lethal dosage, Burrows[39] found central venous pressure to be increased dramatically very early. Central venous pressure has not been measured in the sublethal model, but RV end-diastolic pressure was measured in our model. There was little change in RV end-diastolic pressure during the course of the study; it increased slightly at 5-10 minutes post-endotoxin and then gradually decreased by 8 mm Hg over the 120 minute observation period. Central venous pressure fell by thirty minutes in Burrow's investigation[39] and was near or below control levels until after 120 minutes. Therefore, preload probably plays a very minor role in the early rise in dP/dt_{max}, and little, if any, role in the continued elevation.

While catecholamine release is known to occur in endotoxemia,[40-42] its importance in the elevation of RV dP/dt_{max} is not known. Some of the early hemodynamic effects seen in sublethal endotoxemia (increases in heart rate, systemic arterial pressure, and RV dp/dt_{max}) could

logically be at least partly attributed to catecholamine release. Interestingly, during the period of time prior to administration of endotoxin, while the ponies were becoming adjusted to the restraint stocks and laboratory equipment, the hemodynamic changes seen with sudden excitement mirrored those seen in the initial period following endotoxin administration, except for a shorter duration following an excitatory stimulus. Documentation of the part catecholamine release plays in equine endotoxemia, possibly by the use of adrenergic blockade prior to endotoxin administration, appears to be an area that warrants further study.

The dramatic increase in RV dP/dt_{max} did not result in increased pulmonary artery velocity. Moore[6] calculated pulmonary vascular resistance and found it markedly increased during the first fifteen minutes following intravenous administration of sublethal amounts of endotoxin and right ventricular work to be significantly increased during the same period; however, cardiac output was not significantly altered, which is consistent with the mean pulmonary artery velocity measurements in our study. Since most parameters in these ponies correlated closely with Moore's[8] sublethal endotoxemia model, one can speculate that similar hemodynamic events to those he described occurred in the ponies in this investigation. The fact that RV dP/dt_{max} and right ventricular work were increased while pulmonary velocity and cardiac output are not suggests an increase in pulmonary vascular resistance. This study, then, supports the conclusion[7,8,43] that increased pulmonary vascular resistance and right ventricular contractility are significant events in sublethal equine endotoxemia.

FOOTNOTES

[a]"Telmin" paste formula, Pitman-Moore, Inc., Washington Crossing, NJ

[b]"Strongid-T", Pfizer, Inc., New York, NY

[c]"Combot", Bayvet, Shawnee, KS

[d]"Encevac-T", Bayvet, Shawnee, KS

[e]"Equine Influenza Vaccine", Burroughs-Wellcome Co., Kansas City, MO

[f]"Pneumabort-K", Fort Dodge Laboratories, Fort Dodge, IA

[g]USCI Cardiology and Radiology Division, C.R. Bard, Inc., Billerica, MO

[h]YSI Tele-Thermometer, Yellow Springs Instrument Co., Yellow Springs, OH

[i]Model VPC-673B, Millar Instruments, Inc., Houston, TX

[j]No. L-2880 Lipopolysaccharide from E. coli Serotype 055:B5, Sigma Chemical Co., St. Louis, MO

[k]Model 501D, Carolina Medical Electronics, King, NC

[l]Series 9800 "Dynograph", Beckman Instruments, Inc., Shiller Park, IL

[m]Beckman Instruments, Inc., Shiller Park, IL

[n]Beckman Instruments, Inc., Shiller Park, IL

[o]Model 213-10 pH/Blood Gas Analyzer, Instrumentation Laboratory, Lexington, MA

[p]Lactic Acid Procedure No. 826-UV, Sigma Chemical Co., St. Louis, MO

[q]Model 9845-T Desk Top Computer, Hewlett-Packard, Fort Collins, CO

[r]Model 2631B Printer, Hewlett-Packard, Fort Collins, CO

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APPENDIX I

ADDITIONAL METHODOLOGY

SURGICAL PREPARATION:

Each pony was preanesthetized with 1.1 mg/kg xylazine[a] intravenously, followed by anesthetic induction using 5% glyceryl guaiacolate[b] solution intravenously to effect, followed by a bolus of thiamylal sodium[c] at the rate of 6.6 mg/kg. The ponies were positioned in right lateral recumbency, incubated and maintained in surgical anesthesia with a halothane[d]-oxygen mixture.

The left jugular furrow was clipped, shaved, and surgically scrubbed, using povidone-iodine[e] and isopropyl alcohol.

The left common carotid artery was elevated into a subcutaneous location using a modification of the method described by Tavernor,[1] as follows: an elliptical skin incision was made on the left lateral aspect of the neck, exposing the jugular furrow. The common carotid artery was located by dissection between the jugular vein and the brachiocephalicus muscle, followed by separation of the omohyoideus muscle fibers. The carotid sheath was incised and the artery dissected free from the vagus nerve and sympathetic trunk for 10 cm and elevated. The edges of the brachiocephalicus and cutaneous colli muscles were

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[a] "Rompun", Bayvet, Shawnee, KS

[b] "Guifenesin", Lee Laboratories, Inc., Petersburg, VA

[c] "Bio-Tal", Bioceutics Laboratories, Inc., St. Joseph, MO

[d] Halothane, U.S.P., Halocarbon Laboratories, Inc., Hackensack, NJ

[e] "Betadine Surgical Scrub", Purdue Frederick Co., Norwalk, CT

approximated with simple interrupted sutures of size 0 polyglactin synthetic absorbable suture material,[f] assuring maintenance of the common carotid artery in its subcutaneous location. The subcutaneous layer of the incision was closed with a simple continuous suture pattern of size 00 synthetic absorbable polyglactin[f] and the skin was closed with non-absorbable monofilament[g] simple interrupted sutures.

Sutures were removed fourteen days after surgery. A minimum of four weeks was allowed for healing of the surgical site prior to endotoxin administration.

CATHETERIZATION:

Three to four hours prior to endotoxin administration, the ponies were sedated with 1.1 mg/kg xylazine and the right jugular furrow and the area over the left carotid elevation were clipped and surgically scrubbed with povidone-iodine and isopropyl alcohol.

One ml of 2% lidocaine hydrochloride[h] was infiltrated over the right jugular furrow midway along its length and a small stab incision was made through the skin using a #15 scalpel blade. A fourteen gauge three inch needle, threaded approximately two inches into the right jugular vein, was used as a guide for placement of a seven French USCI venous percutaneous catheter introducer set[i] in the following manner: the flexible wire portion of the introducer set was threaded

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[f]"Vicryl", Ethicon, Inc., Somerville, NJ

[g]"Vetafil", Look, Inc., Boston, MA

[h]Elkins-Sinn, Inc., Cherry Hill, NJ

[i]USCI Cardiology and Radiology Division, C. R. Bard, Inc., Billerica, MA

through the fourteen gauge needle into the jugular vein. The fourteen gauge needle was then removed, leaving approximately 12.5 cm of the wire in the vein. The remaining two pieces of the introducer set were threaded onto the wire and into the jugular vein. The wire and the inner guide of the introducer set were removed, leaving the seven French outer cannula in the jugular vein. The cannula was then sealed with an injection cap,[j] heparinized, and sutured to the neck using a butterfly of one-half inch adhesive tape around the cannula hub.

An additional two inch indwelling catheter,[k] for endotoxin infusion, was placed in the right jugular vein by percutaneous puncture about 7.5 cm proximal to the introducer cannula. This catheter was also capped, heparinized and sutured in place as described for the introducer cannula.

The elevated carotid artery was located by palpation over the cranial portion of the left jugular furrow. One ml of lidocaine hydrochloride was infiltrated over the middle of the most palpable section of the common carotid artery, and a fourteen gauge two inch indwelling catheter[k] was seated by percutaneous puncture. This catheter was capped, heparinized, and sutured to the skin as described above.

EXPERIMENTAL PROCEDURES:

Following recovery from sedation, the catheterized ponies were placed in the stocks. A temperature probe[l] was placed in the rectum and taped to the base of the tail. Polyethylene tubing filled with heparinized

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[j] Becton Dickinson, Rutherford, NJ

[k] "Sovereign" large animal indwelling catheter, Sherwood Medical, St. Louis, MO

[l] "YSI Tele-Thermometer," Yellow Springs Instrument Co., Yellow Springs, OH

physiological saline solution was attached to the carotid catheter for measurement of systemic blood pressure and for obtaining arterial blood samples. A seven French Millar "Mikro-Tip" pressure-velocity transducer[m] was passed through the USCI catheter introducer into the right jugular vein. The Millar transducer used has a velocity sensor about seven cm proximal from the tip and a pressure sensor about seven cm proximal from the velocity sensor. The transducer catheter was advanced into the right ventricle, then into the main pulmonary artery until both the velocity and pressure sensors were in the main pulmonary artery. This was determined by the change in the pressure wave form and the diastolic pressure baseline. Then the Millar catheter was pulled slowly cranially until the pressure sensor first recorded a waveform consistent with placement in the right ventricle. At this point, the velocity sensor was known to be in the main pulmonary artery.

The following parameters were measured: rectal temperature, carotid artery pressure, right ventricular pressure and pulmonary artery velocity. Right ventricular dP/dt was determined with a Beckman type 9879 dP/dt coupler.[n] Heart rate was determined from the right ventricular pressure with a Beckman type 9857B cardiotachometer.[o] Arterial blood samples were taken and analyzed for pH, P_{CO_2}, P_{O_2}, and lactic acid.

Pre-exposure baseline samples were taken after the pony was settled quietly in the stocks. Ten micrograms/kg of Escherichia coli 055:B5 endotoxin[p] were given as an intravenous bolus.

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[m]Model VPC-673B, Millar Instruments, Inc., Houston, TX

[n]Beckman Instruments, Inc., Shiller Park, IL

[o]Beckman Instruments, Inc., Shiller Park, IL

Rectal temperature was recorded and arterial blood samples were taken prior to endotoxin administration and at 5, 10, 15, 30, 45, 60, 75, 90, 105, and 120 minutes post-endotoxin. The carotid arterial pressure, heart rate, right ventricular pressure, pulmonary artery velocity, and dP/dt were measured continuously for the two hour period.

The pulmonary arterial velocity was measured by a square-wave electromagnetic flow meter[q] and recorded on a Beckman multi-channel recorder.[r] The right ventricular pressure and dP/dt, carotid arterial pressure, and heart rate were all recorded on the Beckman multi-channel recorder. Arterial pH, P_{CO_2}, and P_{O_2} were determined using a pH/blood gas analyzer,[s] and corrected to body temperature. Heparinized samples were analyzed immediately after collection.

Arterial lactic acid was determined by an enzymatic assay based upon the following chemical reaction:

$$\text{Pyruvic acid} + \text{NADH}^* \rightleftharpoons \text{Lactic acid} + \text{NAD}^{**}$$

The above reaction is catalyzed by the enzyme lactic dehydrogenase (LDH).

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[p]No. L-2880 Lipopolysaccharide from E. coli Serotype No. 055:B5, Sigma Chemical Co., St. Louis, MO

[q]Model 501D, Carolina Medical Electronics, Inc., King, NC

[r]Series 9800 "Dynograph," Beckman Instruments, Inc., Shiller Park, IL

[s]Model 213-10 pH/Blood Gas Analyzer, Instrumentation Laboratory, Lexington, MA

[t]Lactic Acid Procedure No. 826-UV, Sigma Chemical Co., St. Louis, MO

*Reduced nicotinamide adenine dinucleotide

**Nicotinamide adenine dinucleotide

To measure lactic acid, the reaction is carried out from right to left by providing excess NAD. The pyruvic acid formed is trapped with hydrazine to force the reaction to go to completion.

The generation of NADH is measured spectrophotometrically at 340 nm. The absorbance at 340 nm increases when NADH is formed, and measurement of this increase is indicative of the amount of lactic acid present in the original sample.

At each sampling interval, a 2 ml aliquot of arterial blood was drawn and immediately placed in a chilled tube containing 4 ml of 8% perchloric acid. The tube was shaken vigorously for thirty seconds and then placed in an ice bath for five minutes, to assure complete protein precipitation. The mixture was then centrifuged for ten minutes and the protein-free supernatant drawn off. The supernatant fluid was stored under refrigeration at 3°C until all samples from one trial were obtained.

An 0.2 ml aliquot of the supernatant fluid was added to 2.8 ml of a solution containing NAD and LDH. The solution was mixed by gentle shaking and incubated for thirty minutes at 37°C. A control blank (0.2 ml of 8% perchloric acid plus 2.8 ml of NAD and LDH solution) was always prepared with each batch. The control tube served as a reference for the test samples. The absorbance of the test samples at 340 nm was recorded using a Bausch and Lomb spectrophotometer.[u] Since it is a wide-bandwidth spectrophotometer, values were determined from a calibration curve, calculated from standard dilutions of lactic acid.

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[u]"Spectronic 20," Bausch and Lomb, Rochester, NY

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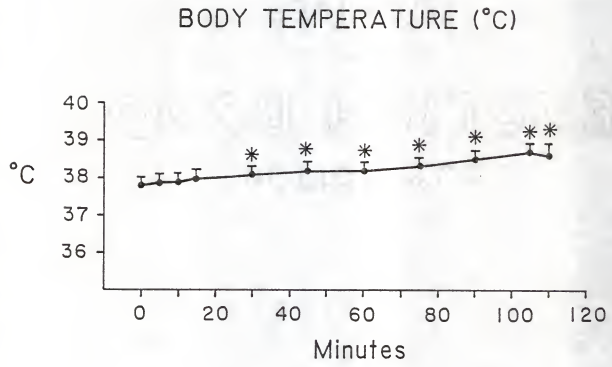
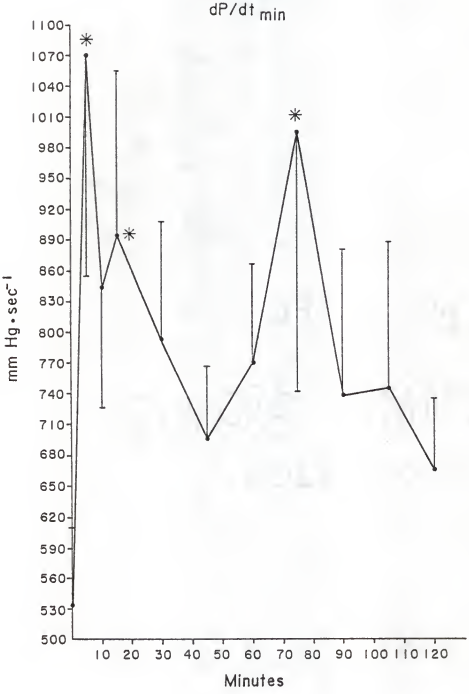
APPENDIX II

Additional Figures



Appendix Figure 1. Body Temperature (* = $P \leq 0.05$)



Appendix Figure 2. dP/dt_{min} (* = $P \leq 0.05$)

APPENDIX III

Additional Tables

Table 1 (Appendix)

Body temperature °C

Pony No.	0	5	10	15	30	45	60	75	90	105	120
1	38.2	38.2	38.2	38.2	38.2	38.2	38.3	38.4	38.4	38.4	38.5
2	38.0	38.0	38.1	38.1	38.5	38.6	38.9	39.0	39.2	39.4	39.5
3	38.3	38.3	38.2	38.2	38.3	38.3	38.4	38.4	38.4	38.6	38.6
4	37.3	37.3	37.3	37.4	37.5	37.6	37.6	37.6	---*	---*	---*
5	37.4	37.4	37.4	37.4	37.5	37.6	37.6	37.6	37.9	38.2	37.6
6	37.7	38.4	38.4	38.4	38.5	38.6	38.6	38.6	38.6	38.7	39.9
$\bar{X}$	37.8	37.9	37.9	38.0	38.1	38.2^{+}	38.2^{+}	38.3^{+}	38.5^{+}	38.7^{+}	38.6^{+}
SEM	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3

* = unable to get sample due to fire in building

$^{+}$ = $P \leq 0.05$

Table 2 (Appendix)

Arterial Blood pH

Pony No.	0	5	10	15	30	45	60	75	90	105	120
1	7.377	7.411	7.415	7.410	7.407	7.406	7.398	7.400	7.412	7.413	7.405
2	7.442	7.499	7.490	7.484	7.444	7.467	7.448	7.431	7.428	7.469	7.480
3	7.453	7.424	7.431	7.402	7.392	7.423	7.402	7.384	7.370	7.367	7.374
4	7.459	7.510	7.458	7.431	7.396	7.423	7.430	7.434	----*	----*	----*
5	7.488	7.489	4.780	7.439	7.424	7.418	7.416	7.418	7.412	7.417	7.424
6	7.490	7.522	7.485	7.471	7.462	7.456	7.455	7.464	7.460	7.459	7.461
$\bar{X}$	7.452	7.476^{+}	7.460	7.440	7.421^{+}	7.432	7.425^{+}	7.422^{+}	7.416^{+}	7.425^{+}	7.429
SEM	.017	.019	.013	.013	.011	.010	.010	.011	.015	.018	.019

*= unable to get sample due to fire in building

+= $P \leq 0.05$

Table 3 (Appendix)

Arterial Blood P_{CO_2} (mm Hg)

Pony No.	0	5	10	15	30	45	60	75	90	105	120
1	40.6	41.3	40.2	39.3	41.0	38.7	39.3	37.3	35.9	34.2	34.5
2	39.8	31.8	35.5	36.0	40.7	38.2	41.1	41.4	42.9	39.9	39.7
3	35.1	40.3	40.9	41.9	43.6	42.2	43.9	44.0	42.9	45.0	41.5
4	38.3	31.3	37.2	39.7	41.8	37.0	36.5	37.9	---*	---*	---*
5	35.1	32.5	30.4	34.1	39.9	40.8	37.9	40.1	38.1	37.2	33.8
6	32.7	30.3	31.0	35.1	32.6	28.7	29.4	29.9	29.5	32.8	32.4
$\bar{X}$	36.9	34.6	35.9	37.7	39.9	37.6	38.0	38.5	37.9	37.8	36.3
SEM	1.3	2.0	1.8	1.2	1.6	1.9	2.0	2.0	2.5	2.2	1.8

*= unable to get sample due to fire in building

Table 4 (Appendix)

Arterial Blood P_{O_2} (mm Hg)

Pony No.	0	5	10	15	30	45	60	75	90	105	120
1	97.4	99.0	103.8	98.0	88.3	98.2	91.2	98.6	100.6	102.2	103.2
2	96.3	74.3	72.1	72.5	85.7	96.6	96.5	97.7	99.7	99.7	104.8
3	105.1	99.7	96.1	94.2	94.8	97.1	98.1	97.8	94.0	97.1	101.7
4	102.3	49.6	72.0	86.2	96.5	104.3	107.7	105.7	---*	---*	----*
5	97.8	98.9	101.2	93.2	74.9	86.3	97.0	91.4	91.2	92.0	102.5
6	71.9	92.0	103.5	102.7	88.1	90.8	98.1	97.2	90.9	84.7	84.9
$\bar{X}$	95.1	85.6	91.5	91.1	88.1	95.6	97.9	98.1	95.3	95.1	99.4
SEM	3.1	8.2	6.2	4.3	3.1	2.6	2.2	1.9	2.1	3.1	3.7

*= unable to get sample due to fire in building

Table 5 (Appendix)

Arterial Lactic Acid (mm/100 ml)

Pony No.											
1	45.4	45.0	43.9	41.4	41.3	38.7	38.5	37.0	33.7	34.3	34.6
2	11.6	12.5	11.8	10.6	13.9	14.2	15.5	16.7	17.9	19.9	57.8
3	16.2	18.8	18.2	18.6	18.9	18.7	19.1	18.0	17.7	14.4	14.2
4	8.1	12.8	11.0	12.4	11.2	10.3	9.5	9.8	---*	---*	---*
5	20.8	23.9	26.7	27.7	24.9	25.3	22.4	19.6	20.6	22.3	22.5
6	7.3	14.3	18.2	18.4	16.6	16.6	16.2	17.8	19.2	20.6	19.4
$\bar{X}$	18.2	21.2	21.6	21.5	20.1	20.6	20.2	19.8	21.8	22.3	29.7^{+}
SEM	5.8	5.1	5.0	4.7	4.5	4.1	4.1	3.7	3.0	3.3	7.8

*= unable to get sample due to fire in building

$^{+}$= $P \leq 0.05$

Table 6 (Appendix)

Heart Rate (beats per minute)

Pony No.	0	5	10	15	30	45	60	75	90	105	120
1	50	70	70	60	50	50	60	80	90	80	80
2	60	100	110	110	90	80	100	100	100	100	100
3	65	65	65	65	60	60	65	70	60	60	65
4	40	100	50	45	35	45	45	50	50	60	60
5	35	85	90	90	45	60	85	90	90	90	90
6	35	60	60	80	75	95	95	100	95	65	65
$\bar{X}$	51	80*	74*	75*	59	65	75*	82*	81*	76*	77*
SEM	5	7	9	9	8	8	9	8	8	7	7

* = $P \leq 0.05$

Table 7 (Appendix)

Systolic Carotid Arterial Pressure (mm Hg)

Pony No.											
1	147	150	140	140	135	125	120	110	85	75	85
2	125	170	160	160	150	160	170	160	150	150	145
3	125	125	130	125	145	155	150	130	145	140	135
4	125	190	140	125	115	125	125	125	125	115	115
5	125	288	145	130	135	115	110	110	90	85	80
6	175	185	160	155	150	150	150	140	140	150	165
$\bar{X}$	137	185*	146	139	138	138	138	128	123	119	121
SEM	8	23	5	6	5	8	9	9	12	14	14

*= $P \leq 0.05$

Table 8 (Appendix)

Mean Carotid Arterial Pressure (mm Hg)

Pony No.	0	5	10	15	30	45	60	75	90	105	120
1	130	110	100	110	100	95	90	85	65	60	70
2	105	135	140	140	127	130	133	125	120	125	122
3	105	110	100	100	115	115	120	115	110	115	115
4	90	147	113	100	85	100	100	100	92	85	85
5	100	198	115	110	115	100	95	90	75	75	75
6	135	140	130	130	116	125	115	115	120	125	140
$\bar{X}$	111	140*	116	115	110	111	109	105	97	98	101
SEM	7	13	7	7	6	6	7	6	10	11	12

* = $P \leq 0.05$

Table 9 (Appendix)

Right Ventricular Systolic Pressure (mm Hg)

Pony No.	0	5	10	15	30	45	60	75	90	105	120
1	50	106	65	95	68	63	48	45	38	35	32
2	35	100	100	100	75	62	58	48	42	40	35
3	42	37	40	40	45	45	48	45	40	38	38
4	38	112	75	65	38	37	37	37	37	37	37
5	33	58	58	55	58	37	30	27	23	23	23
6	63	77	65	53	50	50	43	40	40	40	45
$\bar{X}$	44	82*	67*	68*	56	49	44	40	37	35	36
SEM	5	12	8	10	6	5	4	3	3	3	3

* = $P \leq 0.05$

Table 10 (Appendix)

Right Ventricular Diastolic Pressure (mm Hg)

Pony No.	0	5	10	15	30	45	60	75	90	105	120
1	25	31	33	23	18	15	10	10	8	8	8
2	10	12	12	15	10	8	8	5	5	3	3
3	12	12	12	12	12	10	12	10	8	8	7
4	15	12	15	15	12	12	12	10	10	8	8
5	8	8	3	2	2	2	2	0	0	0	0
6	2	2	2	2	5	5	2	2	3	5	5
$\bar{X}$	12	13	13	12	10	9	8	6*	6*	5*	5*
SEM	3	4	5	3	2	2	2	2	2	1	1

* = $P \leq 0.05$

Table 11 (Appendix)

RV dP/dt_{max} (mm Hg · sec^{-1})

Pony No.	0	5	10	15	30	45	60	75	90	105	120
1	350	1000	625	625	500	500	600	600	550	550	450
2	400	750	850	900	500	500	600	625	625	625	625
3	750	700	750	750	750	875	875	1000	875	750	875
4	350	1950	500	450	400	450	450	450	500	600	600
5	450	700	750	750	500	600	550	500	450	450	450
6	600	900	850	850	650	750	850	900	750	550	500
$\bar{X}$	483	1000*	721*	721*	550	613*	654*	679*	625*	588	583
SEM	65	196	56	67	52	68	70	90	66	41	66

* = $P \leq 0.05$

Table 12 (Appendix)

RV dP/dt_{min} (mm Hg · sec^{-1})

Pony No.	0	5	10	15	30	45	60	75	90	105	120
1	600	1875	1250	1500	1250	875	850	1000	600	550	500
2	300	950	950	1000	750	600	1000	2125	1375	1375	875
3	550	550	650	625	500	750	875	1000	750	750	750
4	400	1500	750	900	550	500	500	450	450	400	400
5	850	1000	1000	1000	1000	900	950	1000	850	850	750
6	500	550	450	350	700	550	450	400	400	550	700
$\bar{X}$	533	1071*	842	896*	792	696	771	996*	738	746	663
SEM	77	215	116	159	116	70	96	254	145	142	72

*= $P \leq 0.05$

Table 13 (Appendix)

Peak Pulmonary Artery Velocity (cm · sec^{-1})

Pony No.	0	5	10	15	30	45	60	75	90	105	120
1	30	60	55	60	50	45	55	60	50	50	50
2	Not available										
3	100	90	90	85	90	85	85	65	75	60	60
4	60	75	30	40	60	60	70	55	50	60	60
5	65	40	30	30	35	35	35	45	40	35	40
6	Not available										
$\bar{X}$	64	66	51	54	59	56	61	56	54	51	51
SEM	14	11	14	12	12	11	11	4	7	6	6

Table 14 (Appendix)

Mean Pulmonary Artery Velocity ($cm \cdot sec^{-1}$)

Pony No.	0	5	10	15	30	45	60	75	90	105	120
1	20	45	45	45	35	35	35	35	25	25	25
2	15	20	15	15	10	15	15	15	15	15	10
3	Not available										
4	12	15	12	12	12	15	15	10	--*	--*	--*
5	12	15	12	12	10	12	20	15	15	15	15
6	Not available										
$\bar{X}$	15	24+	21	21	17	19	21	19	16	16	16
SEM	2	7	8	8	6	5	5	6	3	3	3

*= Fire in building - unable to get mean

+= $P \leq 0.05$

CARDIOVASCULAR CHANGES ASSOCIATED WITH INTRAVENOUS ADMINISTRATION OF *E. COLI* ENDOTOXIN IN CONSCIOUS PONIES

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AN ABSTRACT OF A MASTER'S THESIS

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ABSTRACT

Six resting conscious grade ponies were given sublethal (10 ug/kg) doses of Escherichia coli endotoxin by rapid intravenous bolus and certain blood chemistry, hemodynamic and physical parameters were measured for a two-hour period. The following parameters were measured: rectal temperature, carotid artery pressure, heart rate, right ventricular pressure, pulmonary artery velocity, and right ventricular dP/dt. Arterial blood samples were taken and analyzed for pH, P_{CO_2}, P_{O_2}, and lactic acid.

Surgical elevation of the left common carotid artery one month prior to the study allowed percutaneous catheterization for obtaining carotid artery pressure and arterial blood samples. Heart rate, right ventricular pressure, pulmonary artery velocity, and right ventricular dP/dt were obtained by means of a Millar "Mikro-Tip" pressure-velocity transducer that was introduced into the right ventricle and pulmonary artery via the right jugular vein.

Rectal temperature increased linearly to a peak value of 38.7°C. Arterial plasma lactate values increased to a peak value of 29.7 mg/dl at 120 minutes. Arterial pH declined from 7.45 to 7.42 at thirty minutes and remained stable thereafter. Arterial P_{O_2} and P_{CO_2} did not vary significantly.

Heart rate increased significantly by five minutes and remained elevated throughout the measurement period. Right ventricular (RV) systolic pressure nearly doubled in the first five minutes and then declined steadily. RV end-diastolic pressure declined significantly. Mean and systolic carotid artery pressures were elevated at five minutes

post-endotoxin but were not significantly different from control values thereafter. Mean pulmonary artery velocity was increased at five minutes post-endotoxin but was not significant after that; peak pulmonary artery velocity did not change significantly. RV dP/dt_{max} more than doubled in the first five minutes and the overall pattern was diphasic with a second peak at 75 minutes.

This study supported the conclusion that pulmonary vascular resistance and right ventricular contractility are significant events in sublethal equine endotoxemia.