

- cation of abnormal aromatic compounds in the urine of a child with Reye like syndrome. *Biomed Mass Spectrom* 11:127-131
26. Chalmers RA, Lawson AM 1982 *Organic Acids in Man*. Chapman and Hall, New York
 27. Bieber LL, Lewin LM 1981 Measurement of carnitine and O-acylcarnitines. *Methods in Enzymology* 72:282-286
 28. Engel AG, Rebouche CJ 1984 Carnitine metabolism and inborn errors. *J Inher Metab Dis* 7(suppl 1):38-43
 29. Roe CR, Millington DS, Maltby DA, Bohan TB, Hoppel CL 1984 L-Carnitine enhances excretion of propionyl-coA as propionylcarnitine in propionic acidemia. *J Clin Invest* 73:1785-1788
 30. Roe CR, Hoppel CL, Stacey TE, Chalmers RA, Tracey RM, Millington DS 1983 Metabolic response to carnitine in methylmalonic aciduria: an effective strategy for elimination of propionyl groups. *Arch Dis Child* 58:916-920
 31. Roe CR, Millington DS, Maltby DA, Kahler SG, Bohan TP 1984 L-Carnitine therapy in isovaleric acidemia. *J Clin Invest* 74:2290-2295.
 32. Mamunes D, DeVries CH, Miller CD, David RB 1974 Fatty acid quantitation in Reye syndrome. In: Pollack JD (ed) *Reye Syndrome*. Grune and Stratton, New York, pp 245-254
 33. Trauner DA, Adams H 1981 Intracranial pressure elevations during octanoate infusion in rabbits: An experimental model of Reye syndrome. *Pediatr Res* 15:1097-1099
 34. Ogburn PL, Sharp H, Lloyd-Still JD, Johnson SB, Holman RT 1982 Abnormal polyunsaturated fatty acid patterns of serum lipids in Reye syndrome. *Proc Natl Acad Sci USA* 79:908-911
 35. Kim CS, Dorgan DR, Roe CR 1984 L-Carnitine: therapeutic strategy for metabolic encephalopathy. *Brain Res* (in press)

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Effects of Hypoxemia on Gastrointestinal Blood Flow and Gastric Emptying in the Newborn Piglet

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ABSTRACT. The effects of severe hypoxemia on gastrointestinal (GI) blood flow and gastric emptying were studied in nine 2- to 4-day-old piglets which were mechanically ventilated while receiving nitrous oxide anesthesia. Each animal was studied during a control period of oxygenation (PaO_2 91 ± 8 torr), 35 min of hypoxemia (PaO_2 29 ± 1 torr), and a recovery period (PaO_2 90 ± 5 torr) (mean \pm SEM). During each study period, the animal received a 10% dextrose test meal with phenol red marker (22 ml/kg), gastric residual volumes were determined at 10-min intervals over 30-min study periods using a dye dilution double sampling technique, and GI blood flow (radio-nuclide-labeled microspheres), O_2 delivery, O_2 extraction, and O_2 consumption were measured at the end of the 30-min period. Hypoxemia resulted in decreased blood flow to the following GI organs: stomach, jejunal and ileal mucosa-submucosa, and colon decreased 62, 31, and 35%, respectively ($p < 0.05$). Jejunal and ileal muscularis blood flow remained unchanged. Oxygen delivery and consumption by GI tract decreased 79 and 58%, respectively; whereas oxygen extraction of GI tract increased 115%. Values returned toward baseline levels during the recovery period. The hypoxemic gastric emptying pattern showed significantly greater gastric residuals at 20 min compared to the 10-min value ($p < 0.05$). This pattern was different than that observed during control and recovery periods. We conclude that severe hypoxemia results in decreased GI blood flow, tissue oxygenation, and an altered gastric emptying pattern. These observations may have clinical significance for feeding infants following an hypoxemic episode. (*Pediatr Res* 19: 466-471, 1985)

Abbreviations

CaO_2 , arterial oxygen content
 CpvO_2 , portal venous oxygen content
 DO_2GI , oxygen delivery to gastrointestinal tract
 NO_2 , nitrous oxide
 O_2ExGI , oxygen extraction of the GI tract
 OG , orogastric
 $\dot{\text{V}}\text{O}_2\text{GI}$, oxygen consumption by GI tract
 GI , gastrointestinal

Hypoxemia places the neonate at risk for developing GI complications. Among those suggested by clinical studies are necrotizing enterocolitis as a result of perinatal asphyxia and decreased GI blood flow (1), and decreased gastric emptying resulting from respiratory distress syndrome and congenital cyanotic heart disease (2, 3).

The effect of hypoxemia on GI blood flow appears to vary depending on the degree of hypoxemia and perhaps the age of the subject. Moderate hypoxemia causes intestinal hyperemia in adult animals as a means of maintaining constant O_2 delivery and consumption to the GI tract (4, 5). Severe hypoxemia in fetal and newborn ruminant animals results, instead, in significant increases in O_2 extraction as an attempt to maintain GI O_2 consumption (6, 7). The compensatory response utilized by hypoxemic, nonruminant newborn animals to maintain adequate GI tissue oxygenation has not been previously defined.

Hypoxemia and ischemia alter the viability of GI motor function (8). Previous studies in adult animals show an association between GI blood flow and motility (9-13). These studies suggest that changes in blood flow may produce alterations in motility and vice versa. Such an association would be important to verify in the newborn since altered gastrointestinal motility may ac-

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count for many of the clinical features of feeding intolerance in hypoxemic and formerly hypoxemic infants.

This study examined the effects of hypoxemia on GI blood flow and oxygen transport in the newborn piglet, as well as the effect on one aspect of GI motility—the gastric emptying pattern.

MATERIALS AND METHODS

Animal preparation. Nine 2- to 4-day-old piglets with a mean weight of 1.11 kg (range 0.85–1.45 kg) were studied. Animals were obtained from a local breeder 24 h prior to the study and received *ad libitum* feedings by mouth of 10% dextrose in order to reduce milk curd residual and facilitate gastric emptying studies. On the morning of the study, animals were weighed, restrained supine, and maintained normothermic on an infant radiant warmer. They received nitrous oxide (40%) and local (1% lidocaine) anesthesia for surgical placement of catheters which included: 1) a left ventricular catheter (via left common carotid artery) for microsphere injections, 2) a portal venous catheter (via common umbilical vein) for venous oxygen content, 3) a distal aorta catheter (via femoral artery) for arterial oxygen content, arterial blood gas samples, and reference blood sample withdrawal during microsphere injections, 4) a femoral artery catheter for continuous heart rate and blood pressure monitoring, and 5) a femoral or jugular venous catheter for blood replacement. In preliminary studies, gastric emptying was initially attempted in awake, unanesthetized newborn piglets. Because of excitability during manipulative procedures (OG tube placement) and difficulty in interpreting gastric emptying patterns, animals were tracheotomized and mechanically ventilated with a volume ventilator (Harvard Apparatus, Millis, MA, Rodent Respirator, model 681) at a stroke volume of 10 ml/kg with a rate of approximately 40/min to maintain the PaCO₂ 27–49 torr. Animals remained under NO₂ anesthesia throughout the remainder of the study. An 8-French polyethylene feeding catheter was passed orally into the stomach, measured, and secured with the tip approximately 2.5 cm. below the xyphoid process. This catheter placement resulted in an intragastric position above the pyloric antrum on all autopsy examinations. The stomach contents were aspirated through the OG tube and the stomach was washed with approximately 100 ml H₂O to ensure that it was empty of food and bile. The animal was allowed a 60-min equilibration period prior to beginning the study.

Experimental protocol. Each animal was studied during control, hypoxemic, and recovery periods. Under control conditions, gastric emptying was determined at 10-min intervals over a 30-min sampling period. An arterial blood gas and arterial and portal venous samples were drawn for oxygen content determinations, and an injection of radionuclide-labeled microspheres was given to determine GI blood flow. At 85 min following this determination, the animal was rendered hypoxemic with a mixture of 10% O₂, 5% CO₂, balanced N₂ added through a Y-connector to the ventilator. Arterial blood gases were obtained at 5-min intervals for 15 min until the PaO₂ was stable at approximately 30 torr. The animal remained hypoxemic, was given a test meal, and had gastric emptying pattern, blood gases, oxygen contents, and GI blood flow determined in the same manner as in the control period. At the end of this study period, the ventilator gas mixture was returned to prehypoxemic levels. The animal was allowed to recover for 70 min, when the above determinations were repeated. Hematocrits were followed on arterial blood samples using a microcapillary technique. Plasma glucose values were determined using a glucose analyzer (YSI model 23A, Fisher Scientific Co., Yellow Springs, OH). Arterial blood gas measurements were made using a Corning 175 Blood Gas Analyzer (Corning Scientific, Medford, MA). Oxygen contents were determined in duplicate using a Lex-O₂-Con (Lexington Instruments, Waltham, MA). At the conclusion of the study the animal was given a lethal injection of sodium thiamylal.

Blood flow and oxygen transport determinations. Blood flow determinations were made using the radionuclide-labeled microsphere technique (14–16). Microspheres, 15 ± 5 μ in diameter, were labeled with one of six radionuclides: ⁴⁶Sc, ⁵¹Cr, ⁵⁷Co, ⁹⁵Nb, ¹⁰³Ru, and ¹¹³Sn (New England Nuclear Inc., Boston, MA). Approximately 6 × 10⁵ microspheres, suspended in a 10% Dextran solution with 0.01% Tween 80 were continuously agitated and injected into the left ventricular catheter for 30 s, the catheter was flushed with 2.0 ml of 0.9% NaCl, and a reference blood sample was withdrawn from the femoral artery catheter at a rate of 1.03 ml/min beginning 10 s before microsphere injection and lasting for 120 s. Heart rate and blood pressure were monitored throughout the study using a Hewlett-Packard transducer and polygraph recorder (7754 A series, Lexington, MA), and remained stable throughout each period of microsphere injection and blood withdrawal. The animal was transfused with an equal volume of young donor pig blood of similar hematocrit, following each microsphere sample, in order to maintain the hematocrit at control values.

At autopsy, catheter placement was verified. The stomach, small intestine, and colon were removed, washed gently in normal saline, weighed, and fixed in 10% formaldehyde for a minimum of 48 h. The small intestine was divided into proximal (jejunum) and distal (ileum) sections and further separated into submucosa-mucosa and muscularis-serosa segments using a blunt dissection technique (15, 17). Previous studies have shown that microspheres 15 ± 5 μ do not accurately distinguish submucosal and mucosal flow because of series arrangement of these circulations. By fractionating the intramural flow into the parallel circulations of mucosa-submucosa and muscularis-serosa, this problem, as well as migration of previously lodged spheres, is overcome since migration would occur only within series circulations (15, 18). Tissue samples were packed to approximately 1 cm in height in plastic counting vials. Blood and tissue specimens were counted in a well-type gamma scintillation spectrometer (Packard Auto-gamma Scintillation Spectrometer, Packard Instruments, Downers Grove, IL). All samples were corrected for isotope decay and spillover counts using a Digital Pdp-11/34 computer (Digital Equipment, Maynard, MA). In all cases, more than 400 microspheres were present in the tissue and reference blood samples to ensure accuracy of blood flow determinations to within 5–10% (16).

GI tissue blood flow was determined by the following equation: GI tissue blood flow = cpm GI tissue/cpm reference × rate of reference blood withdrawal.

Total GI blood flow and regional blood flows were determined by summation of the appropriate tissue samples. DO₂, VO₂, and VO₂/DO₂ were calculated using the following formulas derived from the Fick principle:

$$DO_2 = \dot{Q} \times CaO_2$$

$$\dot{V}O_2 = \dot{Q} \times (CaO_2 - CpvO_2)$$

$$\dot{V}O_2/DO_2 = (CaO_2 - CpvO_2)/CaO_2$$

where \dot{Q} is blood flow, CaO₂ is arterial oxygen content, and CpvO₂ is portal venous oxygen content. The validity of CpvO₂ to represent GI venous samples has been confirmed previously (7, 17). Blood flow was expressed as ml · min⁻¹ · 100 g⁻¹ and DO₂ and VO₂ were expressed as ml O₂ · min⁻¹ · 100 g⁻¹.

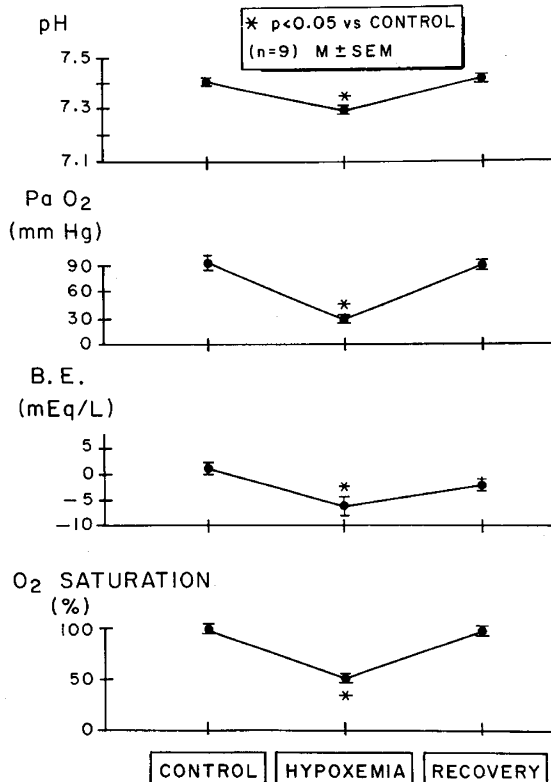
Gastric emptying determination. Gastric emptying was determined at 10-min intervals for a total of 30 min using a phenol red dye dilution double sampling technique (19, 20). Approximately 60 min prior to the gastric emptying determinations, the stomach was aspirated of all contents, washed until the aspirate was clear and free of milk curds, then completely emptied. At the time of each study, the animal was given 22 ml/kg test meal by OG tube. The test meal consisted of 10% dextrose in water with 60 mg/liter phenol red (Sigma Chemical Co., St. Louis,

MO) adjusted to pH 7.0 using 1.0 N NaOH. The feeding was administered at room temperature (~25°C) and allowed to drip in by gravity for 2 min (range 1–3 min). At 10 min after completion of the feeding, 2.5 ml of gastric content were removed, 5 ml of stock solution (phenol red 250 mg/liter H₂O) were added through the OG tube and mixed (45 sec in 5-ml aliquots), and a second 2.5-ml sample of gastric contents was removed (2.5 ml was the minimum volume needed to assay samples in duplicate). This resulted in no net change in volume due to sampling. For the study done at 20 min following feeding, 2.5 ml of stock solution were added, and at 30 min 1.0 ml of stock solution was added. The volume of the added stock solution was reduced during the 20- and 30-min periods to take into account the smaller gastric volumes during these study periods (20). This resulted in a small loss of volume due to sampling, which should not have interfered with the gastric emptying pattern (21).

Gastric samples were centrifuged to remove mucous and debris, then diluted 1:24 with 0.02 M trisodium orthophosphate buffer (Sigma Chemical Co.). The absorbance of this mixture was determined in duplicate using a Gilford 240 spectrophotometer at 560 m μ , and the concentration of samples was determined from a standard curve. By determining the concentration of gastric residuals before and after the addition of a known volume and concentration of stock solution, gastric residual volume at the end of each 10-min test interval could be calculated from the following equation:

$$V_t = \frac{V_2 (C_2 - C_3)}{C_3 - C_1} + V_1$$

V_t = gastric residual volume at each time period; C₁ = phenol red concentration of initial gastric residual; V₂ = volume of added stock solution; C₂ = phenol red concentration of added stock solution; C₃ = phenol red concentration of final gastric



Pa CO₂ Baseline (38 ± 2 mm Hg) Unchanged

Fig. 1. Arterial blood gas values during control, hypoxemic, and recovery periods.

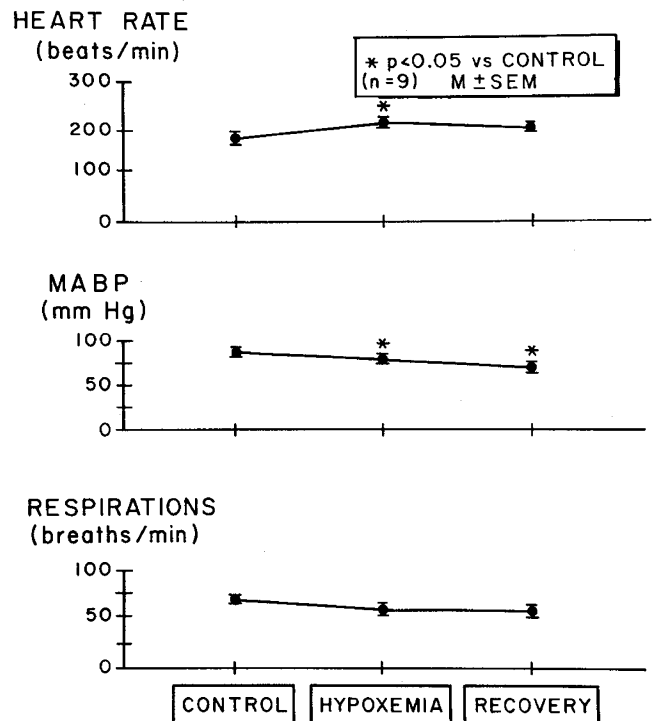


Fig. 2. Heart rate, mean arterial blood pressure, and respiratory rate during the three study periods.

residual; V₁ = volume removed for sampling initial gastric residual. Because all volumes added and removed for sampling purposes were precisely measured, the small net loss of volume was added to the calculated gastric residual volume where appropriate.

Simulated *in vitro* gastric emptying studies were performed to test the validity of our technique. At each time period we determined the measured percentage total volume of test meal, the estimated percentage total volume of test meal, and the measured *versus* experimentally estimated volume (error percentage total volume). In conditions simulating the 10-min sampling period, the mean error estimation was 5.5 ± 2.7%, 20-min mean error estimation was 10.6 ± 2.4%, and 30-min mean error estimation was 10.8 ± 4.4% (mean ± SEM).

DATA ANALYSIS

Data analysis was performed using a blocked one-way analysis of variance for repetitive measures to detect statistical significance. If a significant difference was found ($p < 0.05$), the Dunnett's multiple range T test was used to compare the means. Values were expressed as mean ± SEM.

RESULTS

The arterial blood gas values during the three study periods are shown in Figure 1. During hypoxemia, pH, PaO₂, base excess, and oxygen saturation were significantly reduced compared to control and recovery values ($p < 0.05$). The animals were mechanically ventilated with stable PaCO₂, and the acidosis occurred on a metabolic basis. These variables corrected spontaneously to baseline during the recovery period. As shown in Figure 2, heart rate and mean arterial blood pressure changed significantly from baseline values during hypoxemia. Heart rate increased by 21% over baseline values during hypoxemia, and returned toward baseline during recovery. Although mean arterial blood pressure decreased significantly from baseline during the hypoxemic and recovery periods ($p < 0.05$), at no time did the blood pressure fall into the hypotensive range (study range

56–96 mm Hg). The respiratory rates did not increase with hypoxemia because animals were mechanically ventilated at 61 ± 6 breaths/min. During the control period, serum glucose values were 92 ± 10 mg/dl and hematocrits were $31 \pm 2\%$, and these values did not change significantly during the three study periods.

Figure 3 depicts total GI blood flow changes, arterial oxygen contents, and arterial-venous oxygen content differences across the GI tract during the three study periods. Total GI blood flow decreased significantly by 34% during hypoxemia ($p < 0.05$). CaO_2 in our animals during the hypoxemic period ranged from 2.8–6.3 ml/dl with a mean of 4.4 ± 0.5 ml/dl. Because of similar decreases in arterial and portal venous oxygen contents, the arteriovenous difference remained essentially unchanged. The reduction in GI blood flow resulted from significant reductions in regional blood flow to the stomach, small intestinal mucosa, and colon (Fig 4). Stomach blood flow decreased 62% during hypoxemia as compared to baseline and recovery values ($p < 0.05$). Total small intestine blood flow decreased significantly ($p < 0.05$), with jejunal and ileal mucosa flow decreased by 30 and 33% (210 ± 34 to 148 ± 35 and 147 ± 19 to 99 ± 23 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$), respectively. Jejunal mucosa flow was lower during recovery than during the baseline period. Muscularis blood flow remained unchanged except for the jejunum which showed an increase in flow by 59% above baseline during the recovery period (44 ± 4 to 70 ± 11 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$). Colon blood flow decreased by 35% during the hypoxemic period and returned toward baseline during the recovery period.

Figure 5 illustrates changes in DO_2GI , O_2ExGI , and $\dot{\text{V}}\text{O}_2\text{GI}$ resulting from hypoxemia. DO_2GI decreased 79%, O_2ExGI increased 115% in order to compensate for decreased tissue oxygenation; nevertheless oxygen consumption was reduced by 58% ($p < 0.05$). DO_2GI and O_2ExGI returned toward baseline during the recovery period; however, $\dot{\text{V}}\text{O}_2\text{GI}$ remained lower than baseline values.

The gastric residual volumes, expressed as ml/kg body weight of the nine piglets, are shown in Figure 6. The gastric residual

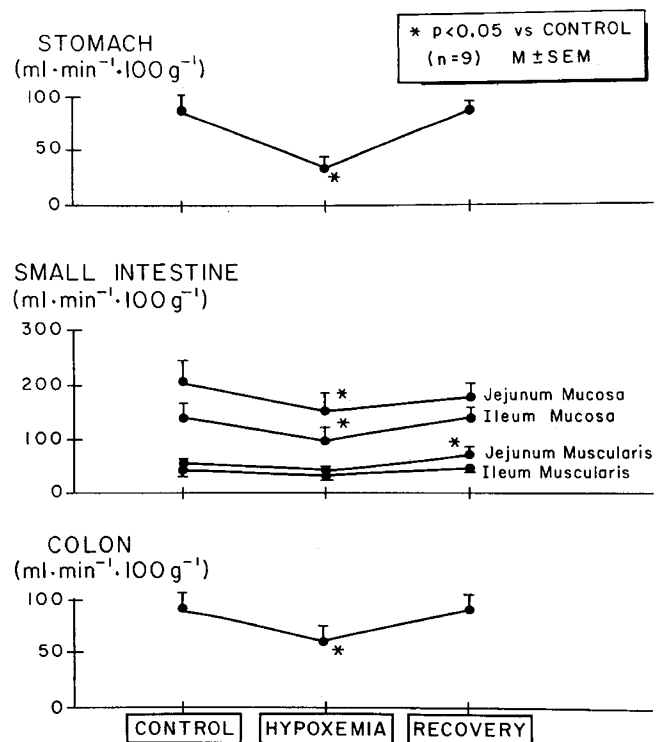


Fig. 4. Regional GI blood flow during control, hypoxemic, and recovery periods.

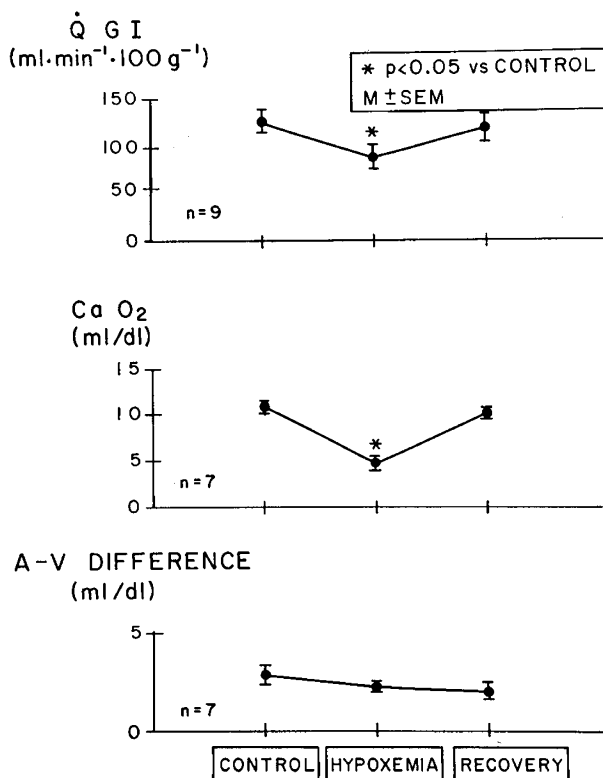


Fig. 3. Total gastrointestinal blood flow, arterial oxygen content, and arterial-venous oxygen difference during the three study periods.

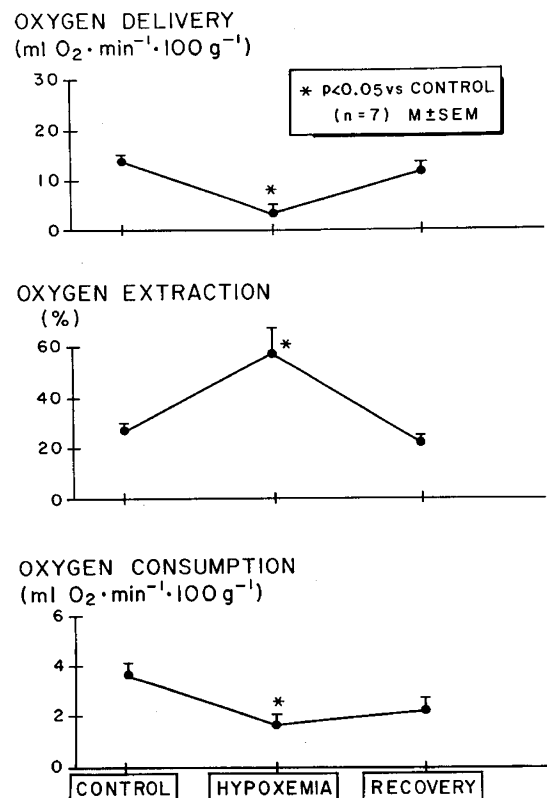


Fig. 5. DO_2GI , O_2ExGI , and $\dot{\text{V}}\text{O}_2\text{GI}$ during the three study periods.

volumes (mean \pm SEM) during the control period at 10, 20, and 30 min were 22.9 ± 3.1 , 24.7 ± 2.5 , and 19.8 ± 2.6 , respectively. During hypoxemia, the 20-min residual was significantly higher ($p < 0.05$) than the 10-min residual (30.8 ± 6.1 versus 21.3 ± 2.8 , respectively). Recovery values at 10, 20, and 30 min were

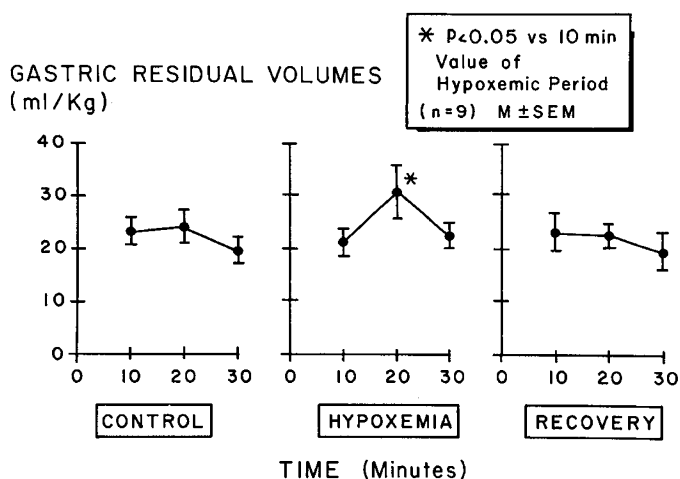


Fig. 6. Gastric emptying patterns during control, hypoxemic, and recovery periods.

not significantly different from control. When comparisons were made at 10, 20, and 30 min among the three study periods, no significant differences were found.

DISCUSSION

Our piglets were studied under nitrous oxide anesthesia in order to facilitate the gastric emptying studies. NO_2 has no effect in newborn piglets on arterial pH, PaO_2 , PaCO_2 , heart rate, mean arterial blood pressure, respiratory rate, or hematocrit; however, it may result in significant increases in total peripheral resistance and decreases in cardiac output when compared to control values (22). Since our animals received constant amounts of NO_2 throughout the study and hypoxemic values returned to baseline during the recovery period, anesthesia probably did not contribute to differences observed during the three study periods.

The effects of severe hypoxemia (PaO_2 29 ± 1 torr) on the newborn piglet were studied. These levels were chosen to be similar to other newborn studies (6) and to reflect levels that infants might acutely experience during asphyxia, respiratory distress, or severe apnea. The metabolic acidosis resulting from anaerobic metabolism at this low level of oxygenation was unavoidable; however the degree and severity of hypoxemia was not sufficient to cause permanent damage, as evidenced by the return of most study variables toward baseline during the recovery period. The vasodilatory effects of hypercapnea (5) were controlled by providing ventilatory support at a level sufficient to maintain PaCO_2 within the normal range.

The baseline heart rates of our study animals were comparable to those recorded by others (17, 23). Our respiratory rates were higher than those seen in awake, unanesthetized animals; however baseline blood gas variables were comparable. Baseline mean arterial blood pressure values in our restrained anesthetized animals were higher than control values in awake, unanesthetized piglets (17, 23) but similar to those in restrained animals (24, 25). The decrease in blood pressure toward normal values during the study may have resulted from adaptation to the study environment. Because mean arterial blood pressures remained within normal limits in all animals, the decreases noted would, in all likelihood, not have resulted in decreased perfusion pressures.

Our baseline values of 30-min postprandial GI blood flow, oxygen delivery, extraction, and consumption were similar to previously reported studies in awake, unanesthetized piglets (17), except for slightly lower stomach blood flows which may have reflected differences in the type of feeding. Studies in adult dogs have shown that moderate hypoxemia results in marked increases in intestinal blood flow to maintain O_2 delivery and consumption (4). We have shown that severe hypoxemia in the newborn piglet

causes significant decreases in stomach, small intestinal mucosa, and colon blood flow, as well as decreases in oxygen delivery and consumption. These results are consistent with those seen in the ovine fetus (7). These changes most likely reflect the compensatory routing of cardiac output to high priority organs (brain and heart) in the presence of hypoxemia, at the expense of low priority organs such as the GI tract (26, 27). We could not calculate oxygen consumption of the stomach directly because of lack of gastric venous oxygen content data, but it is likely that gastric tissue oxygenation was reduced similarly to the total GI tract.

Most of the parameters that we measured returned to baseline values during the recovery period. Oxygen consumption increased, but remained below baseline values (2.2 ± 0.4 versus 3.6 ± 0.5 $\text{ml O}_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$). Edelstone reported similar results in fetal lambs with $\text{CaO}_2 \leq 4.4$ ml/dl (7). In four of seven of our animals, we noted a failure to meet oxidative demands when O_2 delivery decreased below a critical level ($<20\%$ of baseline values) or O_2 extraction did not sufficiently increase (to $\geq 63\%$ above baseline values).

The composition of a meal affects gastric emptying and intestinal hyperemia (28–31). The 10% dextrose test meal minimized such variables as fat, amino acid content, and physical composition, yet provided sufficient caloric content (32–34) to slow gastric emptying enough to allow us to detect differences among study periods. This test meal has an osmolality of ~ 615 mOsmol/kg . Hyperosmolar feedings lead to greater stimulation of endogenous secretions, intraluminal water diffusion (35), and mucosal damage (36). However, osmolalities ≤ 448 mOsmol/kg have not been associated with significant changes in gastric emptying (37), and ≤ 1000 mOsmol/kg have not been associated with intestinal hyperemia (38). Changes produced with a dextrose meal may not be reflective of the response to a milk feeding (17, 39), since unanesthetized hypoxemic piglets given a milk feeding demonstrate a greater ability to maintain GI O_2 consumption (40).

Motor, neural, and hormonal factors interact to regulate gastric emptying. Ischemia may alter the mechanical and electrical activity of the GI tract (8), resulting in decreased motility and the increased gastric residuals we observed at 20 min; however with such a mechanism we would expect residuals to remain unchanged or be increased at 30 min. Sympathetic nervous discharge in response to hypoxemia suppresses gut activity (41), and neural factors may act directly or in conjunction with motor influences. GI hormonal response to hypoxemia remains to be explored; perhaps hypoxemia alters the duodenal receptor responses regulating gastric emptying.

Increased saliva and gastric secretions could account for the greater than expected dilution of phenol red in those instances of increased gastric residuals at 20 min (five of nine animals). However, we would expect secretory response to be impaired in view of sympathetic stimulation and the significantly decreased stomach blood flow (9). Another more likely explanation for increased residuals relates to increased gastric emptying resistance or duodenal reflux. Ischemia leads to a pattern of sustained tonic intestinal contractions with active hyperemia in the intestinal muscularis (11). The absence of jejunal and ileal muscularis ischemia during hypoxemia and presence of jejunal muscularis hyperemia during recovery suggest intestinal motility may be increased, at least transiently, during hypoxemia. Bean and Sidky (42) observed that hypoxemia-induced tone and motility depression was preceded by a brief stimulation. Such transient increases in tone could account for duodenogastric reflux and the increased gastric residual volumes observed at the 20-min period during hypoxemia.

We have demonstrated that severe hypoxemia in the newborn piglet leads to reduced GI tract blood flow in the stomach, small intestinal mucosa-submucosa, and colon following a 10% dextrose meal. Blood flow to the mucosa-submucosa is more significantly reduced than flow to the muscularis as a result of preferential arteriolar shunting of blood away from the mucosa-sub-

mucosa, with sparing of flow to the muscularis layer (27). This may reflect less intrinsic protection of the mucosa-submucosa against the damaging effects of ischemia. In cases of reduced blood flow and O₂ delivery, the fetal and newborn intestinal tract is capable of increasing O₂ExGI in order to maintain stable oxygen consumption (6, 7). It appears that at critically low levels of O₂, this compensatory mechanism is impaired or insufficient and VO₂GI is reduced.

Concomitant with these hypoxemic-induced blood flow and oxygen transport changes an altered gastric emptying pattern is noted. The increased gastric residual volumes that we noted at the 20-min period of hypoxemia were probably produced by transient increases in intestinal tonicity with resultant increased gastric emptying resistance or duodenogastric reflux. The transient nature of this phenomenon would suggest that increased intestinal tone or motility was not responsible for the decreased blood flow we observed during hypoxemia.

These observations may have clinical significance for feeding infants following a hypoxemic episode. GI blood flow reduction appears to resolve rapidly following transient hypoxemia; however recovery is less in the jejunal mucosa. Oxygen consumption is impaired at critically low levels of oxygen despite the ability to increase oxygen extraction, and appears to be one of the last variables to recover following a hypoxemic insult. Altered gastric emptying patterns during hypoxemia may or may not be related to blood flow changes and, after limited periods of hypoxemia, appear transient in nature.

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REFERENCES

- Kliegman RM, Hack M, Jones P, Fanaroff AA 1982 Epidemiologic study of necrotizing enterocolitis among low-birth-weight infants. *J Pediatr* 100:440-444
- Yu VYH 1975 Effect of body position on gastric emptying in the neonate. *Arch Dis Child* 50:500-504
- Cavell B 1981 Gastric emptying in infants with congenital heart disease. *Acta Paediatr Scand* 70:517-520
- Shepherd AP 1978 Intestinal O₂ consumption and ⁸⁶Rb extraction during arterial hypoxia. *Am J Physiol* 234:E248-E251
- Svanvik J, Tyllstrom J, Wallentin I 1968 The effects of hypercapnia and hypoxia on distribution of capillary blood flow in the denervated intestinal vascular bed. *Acta Physiol Scand* 74:543-551
- Nowicki PT, Hansen NB, Oh W, Stonestreet B 1984 Gastrointestinal blood flow and oxygen consumption in the newborn lamb: effect of chronic anemia and acute hypoxia. *Pediatr Res* 18:420-425
- Edelstone DI, Holzman IR 1982 Fetal intestinal oxygen consumption at various levels of oxygenation. *Am J Physiol* 242:H50-H54
- Kowalewski K, Zajac S, Kolodej A 1976 Effect of ischemic anoxia on electrical and mechanical activity of the totally isolated porcine stomach. *Eur Surg Res* 8:12-25
- Bynum TE, Jacobson ED 1971 Blood flow and gastrointestinal function. *Gastroenterology* 60:325-335
- Chou CC 1982 Relationship between intestinal blood flow and motility. *Ann Rev Physiol* 44:29-42
- Chou CC, Grassmick B 1978 Motility and blood flow distribution within the wall of the gastrointestinal tract. *Am J Physiol* 235:H34-H39
- Jacobson ED, Brobmann GF, Brecher GA 1970 Intestinal motor activity and blood flow. *Gastroenterology* 58:575-579
- Walus KM, Jacobson ED 1981 Relation between small intestinal motility and circulation. *Am J Physiol* 241:G1-G15
- Archibald LH, Moody FG, Simons M 1975 Measurement of gastric blood flow with radioactive microspheres. *J Appl Physiol* 6:1051-1056
- Bond JH, Levitt MD 1979 Use of microspheres to measure small intestinal villus blood flow in the dog. *Am J Physiol* 236:E577-E583
- Heymann MA, Payne BD, Hoffman JIE, Rudolph AM 1977 Blood flow measurements with radionuclide-labeled particles. *Prog Cardiovasc Dis* 20:55-79
- Nowicki PT, Stonestreet BS, Hansen NB, Yao AC, Oh W 1983 Gastrointestinal blood flow and oxygen consumption in awake newborn piglets: effect of feeding. *Am J Physiol* 245:G697-G702
- Maxwell L, Shepherd A, Riedel G, Morris M 1981 Effect of microsphere size on apparent intramural distribution of intestinal blood flow. *Am J Physiol* 241:H408-H414
- Cavell B 1979 Gastric emptying in preterm infants. *Acta Paediatr Scand* 68:725-730
- George JD 1968 New clinical method for measuring the rate of gastric emptying: the double sampling test meal. *Gut* 9:237-242
- Cooke AR 1975 Control of gastric emptying and motility. *Gastroenterology* 68:804-816
- Bailie MD, Alward CT, Sawyer DC, Hook JB 1979 Effect of anesthesia on cardiovascular and renal function in the newborn piglet. *J Pharm Exp Ther* 208:298-302
- DeRoth L, Downie HG 1978 Basic cardiovascular parameters in the underweight neonatal swine. *Biol Neonate* 34:155-160
- Laptook A, Stonestreet BS, Oh W 1982 The effects of different rates of plasmanate infusions upon brain blood flow after asphyxia and hypotension in newborn piglets. *J Pediatr* 100:791-796
- Stephens DB, Rader RD 1983 Effects of vibration, noise and restraint on heart rate, blood pressure and renal blood flow in the pig. *J R Soc Med* 76:841-847
- Stonestreet BS, Laptook A, Schanler R, Oh W 1982 Hemodynamic responses to asphyxia in spontaneously breathing newborn term and premature lambs. *Early Hum Dev* 7:81-97
- Touloukian RJ, Posch JN, Spencer R 1972 The pathogenesis of ischemic gastroenterocolitis of the neonate: selective gut mucosal ischemia in asphyxiated neonatal piglets. *J Pediatr Surg* 7:194-205
- Hunt JN, Knox MT 1968 A relation between the chain length of fatty acids and the slowing of gastric emptying. *J Physiol* 194:327-336.
- Cooke AR, Moulang J 1972 Control of gastric emptying by amino acids. *Gastroenterology* 62:528-532
- Kelly KA 1980 Gastric emptying of liquids and solids: role of proximal and distal stomach. *Am J Physiol* 239:G71-G76
- Siregar H, Chou CC 1982 Relative contribution of fat, protein, carbohydrate, and ethanol to intestinal hyperemia. *Am J Physiol* 242:G27-G31
- McHugh PR, Moran TH, Wirth JB 1982 Postpyloric regulation of gastric emptying in rhesus monkeys. *Am J Physiol* 243:R408-R415
- Siegel M, Lebenthal E, Krantz B 1984 Effect of caloric density on gastric emptying in premature infants. *J Pediatr* 104:118-122
- Husband J, Husband P Aug 23 1969 Gastric emptying of water and glucose solutions in the newborn. *Lancet* 409-411
- Hinder RA, Kelly KA 1977 Canine gastric emptying of solids and liquids. *Am J Physiol* 233:E335-E340
- Johnson L, Lundquist PG, Nordstrom H, Nylander G 1978 Experimental studies on fluid pathophysiology in small intestinal obstruction in the rat. *Scand J Gastroenterol* 13:373-384
- Siegel M, Lebenthal E, Topper W, Krantz B, Li PK 1982 Gastric emptying in premature of isocaloric feedings with differing osmolalities. *Pediatr Res* 16:141-147
- Kvietys PR, Pittman RP, Chou CC 1976 Contribution of luminal concentration of nutrients and osmolality to postprandial intestinal hyperemia in dogs. *Proc Soc Exp Biol Med* 152:659-666
- Dudgeon DL, Spoon D, Randall P 1981 The effects of gastric hyperosmotic glucose feedings on regional perfusion in the neonatal piglet. *J Pediatr Surg* 16:854-858
- Szabo JS, Mayfield SR, Oh W, Stonestreet BS 1985 Effects of hypoxemia on postprandial GI blood flow and oxygen consumption in newborn piglets. *Clin Res* 32:906A
- Thompson DG, Richelson E, Malagelada J-R 1982 Perturbation of gastric emptying and duodenal motility through the central nervous system. *Gastroenterology* 83:1200-1206
- Bean JW, Sidky MM 1957 Effects of low oxygen on intestinal blood flow, tonus, and motility. *Am J Physiol* 189:541-547