Comparison of the Effect of Asphyxia, Hypoxia, and Acidosis on Intestinal Blood Flow and O₂ Uptake in Newborn Piglets

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ABSTRACT. The aim of our study was to compare the effects of asphyxia and the two components of asphyxia, *i.e.* hypoxia and acidosis, on intestinal blood flow and oxygen consumption in anesthetized newborn piglets less than 3 days old. The first series of experiments, consisting of four groups of piglets, showed that blood flow to the proximal and distal small intestine and colon (as determined by the microsphere technique) significantly decreased after piglets were subjected to a sustained hypoxic hypoxemia (PaO₂ 50% of control) or asphyxia (acidosis plus hypoxia) for 90 min. A sustained acidosis (arterial pH = 7.0–7.15 for 90 min), however, decreased blood flow only to the proximal small intestine, and sham operation did not significantly alter any intestinal blood flow. All animals subjected to asphyxia and two of five of the animals subjected to hypoxia alone in this series, produced gross and microscopic intestinal lesions similar to those seen in human newborn with necrotizing enterocolitis. Acidosis alone, however, did not produce any pathologic lesions. The second series of experiments showed that the 90-min hypoxic hypoxemia decreased blood flow to both the mucosa and muscularis layers of the small intestine. The third series of experiments, consisting of four groups of piglets, determined the effects of 60-min acidosis, hypoxic hypoxemia, asphyxia, or sham operation on venous outflow and oxygen consumption of the isolated *in situ* terminal ileum. Acidosis or sham operation altered neither ileal blood flow nor oxygen consumption. Hypoxia or asphyxia, however, decreased ileal oxygen consumption without significantly decreasing blood flow. Our study indicates that hypoxia, a component of asphyxia, plays a more significant role than does acidosis in asphyxia-induced intestinal ischemia and pathology, and that hypoxic hypoxemia plays a more significant role than does ischemia or acidosis in asphyxia-induced decrease in ileal oxygen consumption. (*Pediatr Res* 20: 929–932, 1986)

Abbreviation

NEC, necrotizing enterocolitis

dence of NEC varies from 1 to 7.7% in neonatal intensive care units (8), and NEC has been reported as the cause of death in 3% of premature infants (3). The pathophysiology of NEC is not completely clear, but intestinal ischemia is a possible cause leading to development of NEC (9, 10). Blood flows to the stomach, jejunum, ileum, and colon decrease during asphyxia in 2 to 20-day-old piglets (11, 12). In one of these studies, piglets used were relatively mature compared to human neonates, and the severity of asphyxia studied was more severe than one would find in a clinical situation (12). In addition, both studies (11, 12) determined only the effect of asphyxia, and it is unclear which component of asphyxia, *i.e.* acidosis or hypoxia, plays a significant role in pathogenesis of NEC. The viability of the tissues depends primarily on their oxidative metabolism, but the effect of asphyxia on intestinal oxygen consumption has not been studied. The objectives of our study are to determine 1) which component of asphyxia, *i.e.* hypoxia or acidosis, causes intestinal ischemia and NEC; 2) whether blood flows to different layers of the intestinal wall are equally altered by hypoxia; and 3) the effects of asphyxia, hypoxia, and acidosis on ileal blood flow and oxygen consumption.

METHODS

Cross-breed piglets delivered at term were obtained from the Swine Research Farm at Michigan State University. All piglets (1.5 to 2.5 kg body weight) ($n = 45$) were studied within 72 h of birth. Three series of experiments were performed under pentobarbital sodium (5 mg/kg) anesthesia. In the first and second series of experiments, the blood flow to the proximal and distal small intestine and colon were measured, utilizing the radioactive microsphere technique (13, 14). In the third series of experiments, blood flow and oxygen consumption of the terminal ileum were measured by timed-collection of ileal venous outflow and determinations of arterial and venous oxygen contents. Piglets in the first and third series of experiments were divided into four groups and were subjected to hypoxia, acidosis, hypoxia plus acidosis (asphyxia), or sham operation (control group), whereas the piglets in the second series of experiments were subjected to hypoxia only. The level of hypoxia and acidosis were selected to simulate common clinical situations in premature infants. Hypoxia was produced by ventilating the animal with a mixture of 11% O₂ and 89% N₂ gas via the ventilator to decrease blood pO₂ by 50% of control. Acidosis was produced by intravenous infusion of a dilute HCl to achieve arterial pH of 7.0–7.15, *i.e.* intravenous infusion of 3.7% HCl solution at about 0.5 ml/min. Asphyxia was produced by a combination of the above procedures that produced both hypoxia and acidosis.

Microsphere series. Polyethylene catheters were placed into the left ventricle via the carotid artery for injections of micro-

Many clinical studies (1–7) indicate the association of asphyxia (hypoxia with acidosis) with an onset of acute NEC. The inci-

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spheres, and abdominal aorta via a femoral artery for measurements of arterial blood pressure and heart rate, and for withdrawal of reference samples during microsphere injections. The body temperature was maintained at 37° C rectally throughout the experiment. Three types of carbonized microspheres labeled with either ^{141}Ce (diameter = $14.9 \pm 0.7 \mu\text{m}$), ^{95}Nb ($15.0 \pm 0.8 \mu\text{m}$), or ^{85}Sr (diameter = $14.6 \pm 0.9 \mu\text{m}$) were obtained from the Minnesota Mining and Manufacturing Co. In preparation of the microspheres for injection, the stock solution was agitated with a Vortex mixer and then sonicated with a Bronson ultrasonic cell disruptor to achieve a uniform dispersion of the microspheres. The microspheres (approximately 1×10^5 spheres per kg body weight) were injected into the left ventricle, while a reference arterial blood sample was withdrawn from the aorta at a rate of 1.03 ml/min for 2 min. The number of the microspheres injected was comparable with that used by other investigators in neonatal animals (15–17). The injections did not significantly affect cardiovascular function in our studies and those of others.

One hour after the catheterization, and when arterial blood pressure, pH, pO_2 remained at a steady state for at least 30 min, the first type of microsphere was injected to determine the control blood flow. The aim of the first series of experiments was to determine the effects of acidosis, hypoxia, and asphyxia for 90 min on intestinal blood flow and morphology. The piglets were divided into four groups: acidosis ($n = 4$), hypoxia ($n = 5$), acidosis plus hypoxia (asphyxia, $n = 6$), and sham-operated control ($n = 6$). After subjecting the piglets to arterial blood pH of 7.0–7.15 and/or pO_2 50% that of control for about 90 min, the second type of microsphere was injected to determine the effects of these stresses on intestinal blood flow. Because of variation in the responses to ventilation of the hypoxic gas and/or to infusion of HCl solution among piglets, the time of injection of the second type of microsphere varied from 2 to 4 h after the injection of the first type of microsphere. In the control group, the second microsphere injection was, therefore, made 3 h after the first microsphere injection. The piglets were then allowed to recover from the stresses. Vital signs, blood pH, and gases monitored during the recovery period showed that all these variables had returned to control levels within 60 to 90 min after the termination of the stresses. All piglets were sacrificed 8 to 12 h after the stresses, and the entire segment of the intestinal tract was removed for histopathology and measurement of radioactivity (Packard Auto-Gamma Scintillation Spectrometer, Downers Grove, IL). Blood flow was calculated from the formula: $\text{BF} = \text{RBF} \times 100 \times \text{CS}/\text{CR}$, where BF = blood flow to a tissue in ml/min/g, RBF = reference blood flow (rate of withdrawal from the aorta), CS = counts/g in the tissue sample, CR = total counts in the reference blood sample.

The aim of the second series of experiments was to determine whether blood flows to different layers of the intestinal wall are equally altered by hypoxia. The procedures for catheterization and the first injection of microspheres were the same as those described above. The piglets ($n = 5$) were then subjected to hypoxia for 90 min, and the second and third types of microspheres were injected at 30 and 90 min of the hypoxemic period, respectively. After sacrificing the piglets, the entire small intestine was removed and a blunt instrument was used to separate the gut wall into two layers, *i.e.* the mucosa plus submucosa and muscularis. Radioactivities of all tissues were measured, and the percentage of microspheres distributed to the mucosa-submucosa was calculated to indicate the percent fraction of total gut wall blood flow perfusing the mucosa (13, 18). Reference arterial blood samples were not collected in this series of experiments.

Blood flow and oxygen uptake of the terminal ileum. In the third series of experiments, the effects of hypoxia ($n = 4$), acidosis ($n = 4$), asphyxia ($n = 6$), and sham-operation ($n = 5$) for 60 min on blood flow and oxygen consumption of the terminal ileum were studied. A single vein draining the terminal ileum was cannulated with small gauge tubing after intravenous administration of heparin sodium (500 U/kg). The ileal segment was

then isolated *in situ* in such a manner that all the blood from the segment was drained into a reservoir held at 37° via the venous tubing (19). The venous blood in the reservoir was pumped back to the piglets via a catheter in the femoral vein at a rate equal to the venous outflow. Blood flow was measured by timed collection of the venous outflow. Blood samples were obtained from the femoral artery and venous tubing at various periods during the experiment for the measurement of oxygen content by a Lex-O₂-Con-TL oxygen content analyzer (Lexington Instruments, Waltham, MA). Oxygen consumption was calculated as the product of blood flow and arteriovenous O₂ content difference. Blood pressure, heart rate, and blood gases were monitored as described above.

Data were analyzed using analysis of variance and Turkey's procedure (20). Statistical significance was set at $p < 0.05$.

RESULTS

Systemic arterial pressure (ranged from 81 ± 4 to 104 ± 5 mm Hg among groups) and heart rate (ranged from 176 ± 20 to 198 ± 14 among groups) were not significantly altered by asphyxia, hypoxia, and acidosis produced by our experimental protocol. Blood PaCO_2 ranged between 30 and 42 mm Hg during all experiments and was not significantly altered by the above stresses. The aim of the first series of experiments was to determine the effect of hypoxia, acidosis, or hypoxia plus acidosis (asphyxia) in which blood PaO_2 was maintained at 50% of control levels and/or blood pH at 7.0–7.15 for a duration of 90 min. The resting blood PaO_2 and pH were 70 ± 10 mm Hg and 7.42 ± 0.02 , respectively. As shown in Table 1, both hypoxia and asphyxia significantly decreased blood flow to all sections of the intestine, and the degree of the decrease produced by asphyxia was not significantly different from that produced by hypoxia ($p > 0.05$). Acidosis, however, significantly decreased blood flow to the proximal small intestine without significantly altering blood flow to the remaining intestine. Blood flow to all sections of the intestinal tract was not significantly altered in the sham-operated control piglets over 3-h experimental period. The resting blood flow of the proximal and distal small intestine and colon are within the range reported for newborn piglets by other investigators (11, 12, 16, 21). All piglets subjected to asphyxia and two of five of those subjected to hypoxia alone produced gross and microscopic intestinal lesions similar to those seen in human newborn with acute NEC (10). These lesions were found primarily in the terminal ileum and the colon. The gross examination of the intestine showed congestion of the serosal surface with areas of hemorrhage. Gas bubbles were also present on the serosal surface, some of which measured up to 2 mm in diameter. Congested mucosa obscured the usual mucosal pattern. Microscopic examination demonstrated mucosal and submucosal hemorrhage along with necrosis and intramural air. Severe acidosis alone, however, did not produce any pathologic lesions.

In the second series of experiments, we determined whether the ischemic effect of hypoxia observed in the above experiments was exerted on both mucosal and muscularis layers of the gut wall. The percent distribution of total gut wall to the mucosal layer was not significantly altered 30 and 90 min after exposing the piglets to 50% hypoxia. This indicates that blood flows to both mucosal and muscularis layers were equally decreased by hypoxia.

In the third series of experiments, the effects of acidosis, hypoxia, asphyxia, and sham operation (control) on ileal blood flow and oxygen consumption were studied. The blood pH was significantly decreased to a level of 7.14 in 45 min and the blood PaO_2 to 50% of control in 30 min after starting the stresses (Table 2). Acidosis as well as sham operation did not significantly alter ileal blood flow or oxygen consumption. Hypoxia as well as asphyxia tended to decrease blood flow as the duration of the stress increased. The levels of decrease in blood flow, however, were not statistically significant. In contrast to the insignificant

Table 1. Percent changes in blood flows to proximal and distal small intestine and colon after subjecting the piglets to 50% hypoxia, acidosis (blood pH 7.0–7.15), or hypoxia plus acidosis (asphyxia) for 90 min

	Hypoxia (n = 5)	Acidosis (n = 4)	Asphyxia (n = 6)	Control (n = 6)
Proximal small intestine	$-58.1 \pm 12.8\%^*$	$-53.3 \pm 10.4\%^*$	$-62.8 \pm 7.7\%^*$	-2.3 ± 13.3
Distal small intestine	$-67.8 \pm 18.9\%^*$	$-34.6 \pm 14.8\%$	$-69.3 \pm 5.4\%^*$	-12.9 ± 11.8
Colon	$-55.4 \pm 15.4\%^*$	$-2.6 \pm 33.6\%$	$-54.4 \pm 14.4\%^*$	$+2.4 \pm 9.1$

* Values are significant at $p < 0.05$. Resting blood flow for proximal and distal small intestine and colon were 1.67 ± 0.39 , 1.02 ± 0.28 , and 0.85 ± 0.24 ml/min/g of tissue, respectively.

Table 2. Ileal blood flow and oxygen uptake in the sham-operated control piglets and the piglets subjected to acidosis, hypoxia, and hypoxia plus acidosis (asphyxia)

Time (min)	pH	PaO ₂	Blood flow	Oxygen uptake
A. Control (n = 5)				
0	7.40 ± 0.01	85.4 ± 10.7	45.2 ± 5.5	1.28 ± 0.10
30	7.40 ± 0.04	77.6 ± 11.7	45.2 ± 2.8	1.24 ± 0.12
45	7.40 ± 0.01	76.8 ± 4.7	48.3 ± 7.1	1.23 ± 0.10
60	7.39 ± 0.02	75.8 ± 6.2	48.3 ± 9.2	1.32 ± 0.09
	pH		Blood flow	Oxygen uptake
B. Acidosis (n = 4)				
	7.40 ± 0.05	47.5 ± 12.0	1.05 ± 0.26	
	$7.26 \pm 0.026^*$	46.2 ± 13.5	0.99 ± 0.17	
		$(-2.5 \pm 7.7\%)$	$(-2.2 \pm 10.8\%)$	
	$7.14 \pm 0.026^*$	46.6 ± 18.9	1.02 ± 0.07	
		$(-2.9 \pm 10.7\%)$	$(-2.9 \pm 4.5\%)$	
	$7.04 \pm 0.014^*$	47.2 ± 2.9	1.02 ± 0.22	
		$(-0.6 \pm 1.6\%)$	$(-2.9 \pm 13.9\%)$	
	Time (min)	PaO ₂	Blood flow	Oxygen uptake
C. Hypoxia (n = 4)				
0	69.3 ± 11	49.7 ± 9.6	1.59 ± 0.29	
30	$32.6 \pm 7.5^*$	42.0 ± 13.9	$0.99 \pm 0.39^*$	
		$(-15.5 \pm 7.8\%)$	$(-37.3 \pm 11.0\%)$	
45	$35.3 \pm 6.4^*$	40.8 ± 12.5	$0.83 \pm 0.15^*$	
		$(-17.0 \pm 8.3\%)$	$(-47.0 \pm 4.5\%)$	
60	$36.0 \pm 5.6^*$	37.8 ± 5.6	$0.68 \pm 0.26^*$	
		$(-23.3 \pm 3.9\%)$	$(-56.0 \pm 6.4\%)$	
	pH	PaO ₂	Blood flow	Oxygen uptake
D. Asphyxia (n = 6)				
	7.43 ± 0.03	60.0 ± 2.1	55.2 ± 8.0	1.38 ± 0.12
	$7.24 \pm 0.02^*$	$33.6 \pm 1.5^*$	46.6 ± 3.2	$1.03 \pm 0.14^*$
			$(-15.7 \pm 4.1\%)$	$(-25.3 \pm 3.8\%)$
	$7.14 \pm 0.01^*$	$34.0 \pm 3.5^*$	46.7 ± 5.2	$0.94 \pm 0.12^*$
			$(-15.5 \pm 4.7\%)$	$(-31.7 \pm 9.8\%)$
	$7.02 \pm 0.01^*$	$33.0 \pm 6.0^*$	39.6 ± 5.2	$0.86 \pm 0.05^*$
			$(-28.2 \pm 5.8\%)$	$(-49.2 \pm 9.0\%)$

* Changes from control values are significant at $p < 0.05$. PaO₂ = mm Hg; flow and oxygen uptake = ml/min/100 g tissue weight. Values in parentheses indicate percent changes from control values.

response of blood flow, ileal oxygen uptake significantly decreased 30–60 min after subjecting the piglets to hypoxia or asphyxia.

DISCUSSION

The onset of acute necrotizing enterocolitis in newborn infants is associated with asphyxia (2–4, 9–12). Previous studies have shown that asphyxia in newborn piglets produces intestinal ischemia, which may be a cause of NEC (11, 12). The first objective of our study was to determine which component of asphyxia,

i.e. hypoxia or acidosis, produces intestinal ischemia and NEC. For this purpose, the effects of hypoxia, acidosis, and the combination of these two were compared, utilizing the same protocol. As shown in Table 1, hypoxia decreases blood flow to the proximal and distal small intestine and large intestine, an effect similar to that produced by asphyxia. Acidosis, however, significantly decreases blood flow only to the proximal small intestine. Anatomical examinations on the intestinal tissues obtained 8 to 12 h after the stresses further showed that all animals subjected to asphyxia and two of five of those subjected to hypoxia showed gross and microscopic intestinal lesions similar to those seen in the human newborn with NEC, whereas none of the piglets subjected to acidosis produced such lesions. Our finding that asphyxia or hypoxia alone decreases blood flow to all sections of the intestinal tract agrees with those of the other investigators (11, 12, 22, 23). A decrease in local arterial blood pH has been shown to increase blood flow to almost all organs in the body, including the intestine (24). Our finding that a generalized acidosis, as produced by intravenous infusion of HCl, decreased blood flow to the proximal intestine but did not alter flow to the distal intestine (Table 1), probably results from stimulation of the chemoreceptors by the hydrogen ion (25). The resulting sympathetic vasoconstriction either overwhelms or offsets the vasodilation produced by a direct action of the hydrogen ion.

The second objective of our study was to determine whether the vascular responses of the mucosal and muscularis layers of the intestinal wall to hypoxia are different. The percent fraction of total blood flow perfusing the mucosal or muscularis layer was not significantly altered during 30 and 90 min hypoxia. This indicates that hypoxia exerts its effect equally on mucosal and muscularis vasculatures. To our knowledge, this has not been reported except in 3-day-old lambs; blood flow of the ileal muscularis measured during hypoxia induced 1 h after feeding was greater than that measured before the feeding (22). Blood flow to the ileal mucosa as well as those to the jejunal mucosa and muscularis, however, were unchanged by the hypoxia. Our results agree in part with the above study, and the difference in ileal muscularis flow may be due to differences in the experimental setting, i.e. feeding versus fasting, and difference in species, i.e. piglets vs lambs (ruminants).

The primary function of the circulation is to deliver oxygen and energy substrates to the tissues to maintain their viability and functions. Asphyxia produces both a decrease in blood flow and PaO₂ (11, 12); both conditions can decrease oxygen delivery to the cells, thereby decreasing oxygen consumption. The last objective of our study was to determine the effects of asphyxia, hypoxia, and acidosis on intestinal oxygen consumption. The terminal ileum was selected for the study, as this segment of intestine is most frequently involved in NEC of premature infants (9). As shown in Table 2, sham operation or acidosis did not significantly alter either blood flow or oxygen consumption. Hypoxia or asphyxia for a duration of 30–60 min did not significantly alter blood flow, but significantly and progressively decreased oxygen consumption. This indicates that the decrease in ileal oxygen consumption is primarily due to hypoxic hypoxemia rather than decrease in blood flow.

It has been shown in newborn lambs that moderate hypoxic hypoxemia decreases intestinal (23) and gastrointestinal (22) blood flow without significant change in oxygen consumption.

Severe hypoxemia, however, decreased intestinal oxygen consumption in newborn lambs (23). In the above study the oxygen content of the portal venous or mesenteric venous blood was used to calculate oxygen consumption. The oxygen consumption and blood flow include not only those of the ileum but also those of all organs from which the blood is drained by the portal or mesenteric vein. Furthermore, the responses of blood flow and oxygen consumption in ruminant lambs may be different from responses of single-stomach piglets. However, a recent study (26) has shown that severe hypoxic hypoxemia in newborn piglets also produced an 82% reduction in gastrointestinal oxygen uptake. Intestinal oxygen consumption has been shown to remain unchanged when blood flows were decreased from resting values of 214 and 40 to 160 and 34 ml/min/100 g, respectively, in neonatal lambs (as measured by the microsphere method) (23) and adult dogs (volume collection of blood flow) (27). In our experiments, hypoxia and asphyxia decreased blood flow from resting values of 49–55 to 37.8 and 39.6 ml/min/100 g, respectively (Table 2). The levels of blood flow seem to be adequate to maintain normal oxygen consumption, if no hypoxic hypoxemia were present. In this regard, Nowicki *et al.* (26) have shown that the increase in gastrointestinal oxygen consumption observed 5 min after termination of severe hypoxemia was mainly due to an increase in arteriovenous oxygen content difference; blood flow was not significantly changed.

The resting intestinal blood flow, as measured by the microsphere techniques (Table 1), is higher than that measured by the timed-collection of venous outflow (Table 2). The lower blood flow is most likely due to surgical interventions (laparotomy and catheterization of intestinal vein) required for the timed-collection of venous outflow. There are no published data on resting ileal blood flow in newborn piglets as measured by the timed collection of venous outflow, and therefore no comparison can be made with the data from other investigators. Although there were differences in the resting blood flow values measured by the two techniques, the responses of blood flow to the types of stress were similar, *i.e.* acidosis had no effect, but hypoxia and asphyxia tended to decrease intestinal blood flow progressively. However, the values for the resting oxygen consumption in our study (Table 2) are slightly lower than, but comparable to, those of the total gastrointestinal oxygen consumption in newborn piglets (1.86 ± 0.1 and 1.99 ± 0.19 ml O₂/min/100 g) as reported by Nowicki *et al.* (21, 26, 28).

In conclusion, asphyxia, as produced by 50% decrease in arterial blood pO₂ and acidosis at arterial pH of about 7.0–7.15 for 90 min decreases blood flow to all sections of the intestinal tract and produces pathologic findings similar to those found in human newborn with NEC. Asphyxia for 30–60 min does not significantly alter blood flow of the terminal ileum but significantly decreases its oxygen consumption. The decreased oxygen consumption results primarily from hypoxic hypoxemia. These deleterious effects of asphyxia are due primarily to hypoxia, a component of asphyxia. Acidosis, the other component of asphyxia, appears to play a minor role in these changes.

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