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Intestinal Blood Flow and Oxygen Consumption: Responses to Hemorrhage in the Developing Piglet

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ABSTRACT. Age-related differences in the intestinal hemodynamic and oxygenation responses to arterial hemorrhage were studied in anesthetized and ventilated 1-d, 3-d, 1-wk, and 2-wk-old piglets. Steady-state values of superior mesenteric blood flow, venous pressure, and arteriovenous oxygen difference were obtained before and after 5 and 10 mL/kg arterial hemorrhage. With 5 mL/kg hemorrhage, intestinal blood flow fell significantly below baseline values, but oxygen extraction increased to maintain oxygen uptake at control levels in all age groups. In contrast to 2-wk-old piglets, the intestine of 1-d, 3-d, and 1-wk-old animals could not compensate for the greater reduction in blood flow produced by 10 mL/kg hemorrhage, resulting in a significant reduction in oxygen uptake. Thus, the intestine of developing piglets up to 1 wk of age appears to be at greater risk for tissue hypoxia induced by arterial hemorrhage than that of older animals. (*Pediatr Res* 26: 102–105, 1989)

The intestine of the premature infant may be subjected to numerous stresses in the perinatal period, such as hypothermia, hypotension, hypoxia, and enteral alimentation. The role of these stresses in the development of neonatal necrotizing enterocolitis remains unknown, but mesenteric ischemia has often been invoked as the common denominator in the pathogenesis of this devastating disease of prematurity (1, 2). Because of this association between necrotizing enterocolitis and mesenteric ischemia, the intestinal vascular responses to hemorrhage have been studied in neonatal (3, 4) and fetal animals (5). In the intestine of fetal lambs (5) and neonatal pigs (3, 4) blood flow decreases significantly after acute hemorrhage. Local blood flow reductions of this magnitude in adult animals are usually not associated with a fall in intestinal oxygen consumption inasmuch as oxygen extraction rises sufficiently to offset the reduced flow (6). Whether such compensatory mechanisms exist in the newborn intestine remains an important unresolved issue that is potentially relevant in the problem of necrotizing enterocolitis.

Thus, the objectives of this study were to characterize the responses of intestinal blood flow and oxygen consumption to graded arterial hemorrhage in the piglet and to determine whether the intestine of the newborn is more susceptible to tissue hypoxia than that of older piglets after hemorrhage.

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MATERIALS AND METHODS

Fasted Hampshire/Yorkshire piglets of either sex were studied at one day ($n = 6$; wt = 1.4 ± 0.1 kg), 3 d ($n = 5$; wt = 1.7 ± 0.2 kg), 1 wk ($n = 5$; wt = 2.9 ± 0.2 kg), and 2 wk ($n = 6$; wt = 3.3 ± 0.2 kg) of age. After intramuscular injection of ketamine hydrochloride (20 mg/kg) and xylazine (2 mg/kg), the animals were anesthetized with intravenous pentobarbital sodium (15 mg/kg). Maintenance doses of pentobarbital sodium (5 mg/kg) were given as necessary during the experiment.

Surgical procedure. A tracheostomy was performed immediately after administration of pentobarbital sodium. The animal was artificially ventilated (Harvard Apparatus intermediate ventilator, South Natick, MA) at a tidal volume and respiratory rate to maintain normal arterial blood gases and pH (Corning Blood Gas Analyzer, Corning Medical, Medfield, MA). Cannulas were inserted into the left carotid artery to monitor systemic arterial pressure and into the right external jugular vein for administration of lactated Ringers solution for hydration. Both left and right femoral arteries were cannulated for removal of arterial blood during hemorrhage and for perfusion of the arterial cuvette of an arteriovenous oxygen difference analyzer (AVOX Systems, San Antonio, TX) (7), respectively. Body temperature was maintained at 38°C during the experiment via a heating pad and an infrared heating lamp.

The abdomen was opened along the midline, the spiral colon was removed, and the duodenum was ligated proximal to its retroperitoneal segment as previously described (8). The superior mesenteric artery was isolated with care taken to avoid damage to the perivascular nerves. An intravenous injection of heparin sodium (5 000–10 000 USP units) was given immediately before temporary occlusion of the superior mesenteric artery. This temporary occlusion facilitated cannulation of the mesenteric vein via the portal vein. The venous outflow drained into a reservoir before being returned to the piglet through the right external jugular vein. Interposed in the venous circuit was a T tube to measure intestinal venous pressure and a calibrated flow probe to monitor intestinal blood flow. The signal from the flow probe was used to drive a square-wave electromagnetic flowmeter (Carolina Medical Electronics, King, NC). A portion of the venous outflow was also used to provide intestinal venous blood for the arteriovenous oxygen difference analyzer. Systemic arterial and superior mesenteric venous oxygen content measurements were made at the beginning and end of each experiment with a Lex-O_2-Con apparatus (Hospex, Chestnut Hill, MA). Heparin-treated blood from a donor piglet was used to prime all extracorporeal circuits. The intestines were covered with saline-soaked gauze and plastic wrap to minimize evaporative water loss. Pressures, blood flow, and arteriovenous oxygen difference measurements were continuously monitored on a physiologic recorder (Model 7D, Grass Instrument Co., Quincy, MA).

Experimental protocol. Inasmuch as blood volume increases linearly with body wt until 2 wk of age in the piglet (9, 10) hemorrhage was defined in terms of volume of blood withdrawn per kg body wt. All hemodynamic and oxygenation parameters were allowed to stabilize for at least 30 min. Systemic arterial pressure, and intestinal blood flow, arteriovenous oxygen difference, and venous pressure were continuously monitored for 10 min after removal of 5 mL/kg arterial blood (15–30 s). An additional 5 mL/kg arterial blood (10 mL/kg, total hemorrhage) was withdrawn and all parameters were monitored for an additional 10 min. Values used in data analysis were those recorded immediately before removal of blood and those at the end of each 10 min equilibration period.

Data analysis. At the completion of the experiment, the small intestine was removed, opened, washed, patted dry, and weighed. The results are expressed per unit mass of tissue. Oxygen uptake was calculated as the product of arteriovenous oxygen difference and intestinal blood flow and expressed as $mL \cdot min^{-1} \cdot 100\ g^{-1}$. The time required for blood to reach the arteriovenous oxygen difference analyzer was determined. Calculations of oxygen uptake were based on these time-corrected values. Total vascular resistance was calculated by dividing the arteriovenous pressure gradient by the intestinal blood flow.

All values are expressed as mean ± SEM. A two factor, repeated measures, analysis of variance was used to determine if differences existed among age groups for each dependent variable, followed by Duncan multiple range tests if the ANOVA revealed differences ($p < 0.05$) among age groups at each level of hemorrhage.

RESULTS

With both 5 and 10 mL/kg arterial hemorrhage (equivalent to removal of 5 and 10% of total blood vol, respectively), the systemic blood pressure (Fig. 1) fell significantly below control values. The percentage fall in blood pressure was significantly more in 1-d-old (−15.3 ± 3.0% and −30.2 ± 4.2% for 5 mL/kg and 10 mL/kg, respectively) and 3-d-old (−18.0 ± 3.2% and −30.8 ± 4.5%) piglets compared to that in 2-wk-old (−7.4 ± 0.9% and −15.3 ± 2.1%) animals.

The effect of hemorrhage on intestinal hemodynamics and oxygenation is illustrated in Figure 2. The fall in intestinal blood flow (Fig. 2*A*) was significantly more in 1 d than in all older age groups during 10 mL/kg hemorrhage. All age groups demonstrated increases in intestinal arteriovenous oxygen difference

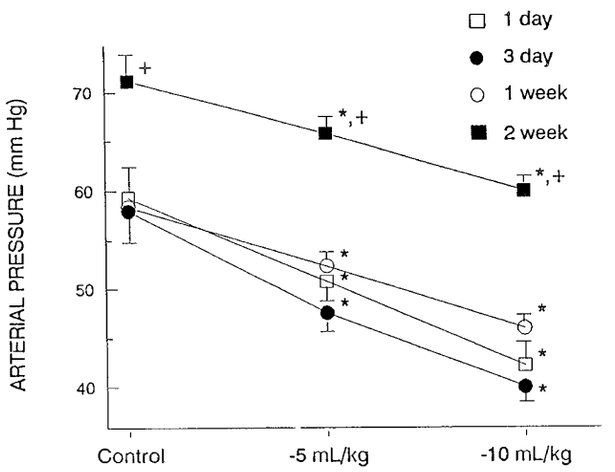

Fig. 1. Systemic blood pressure during control and after 5 and 10 mL/kg arterial hemorrhage in 1-d, 3-d, 1-wk, and 2-wk-old piglets. * signifies $p < 0.05$ *versus* control values within an age group, whereas + indicates $p < 0.05$ *versus* all younger age groups within a level of hemorrhage.

with hemorrhage (Fig. 2*B*), although the increase was significantly lower in 1-wk-old animals compared to other age groups. Intestinal vascular resistance increased with hemorrhage in all but the 3-d-old intestine (Fig. 2*C*). Figures 2*D* and 3 illustrate that after 5 mL/kg hemorrhage, all age groups maintained intestinal oxygen uptake at levels which were not significantly different from baseline values. With 10 mL/kg hemorrhage, however, intestinal oxygen uptake in 1-d, 3-d, and 1-wk-old animals fell, whereas in 2 wk olds it did not change significantly from control (Fig. 3).

Control arterial oxygen content measurements were 14 ± 1, 12 ± 1, 11 ± 1, and 15 ± 1 mL O_2/dL in 1-d, 3-d, 1-wk, and 2-wk-old animals, respectively.

DISCUSSION

When interpreting the results of these experiments, one should be cognizant that this was an acute preparation in which the animals were subjected to stresses of anesthesia and abdominal surgery in addition to hemorrhage. By cannulating the left carotid artery, one of the baroceptor mechanisms has also been eliminated. Nonetheless, the stresses imposed were the same for each age group so that the results should be comparable as regards developmental changes.

Although little is known about the effects of acute hemorrhage on intestinal oxygenation, intestinal perfusion is significantly reduced during hemorrhage. For example, hemorrhage of 10% of the blood vol in anesthetized adult dogs causes an 18% decrease in arterial blood pressure, a 30% fall in intestinal blood flow, and a 29% increase in intestinal vascular resistance (11). More severe hemorrhage causes progressively larger declines in arterial pressure and intestinal blood flow until a point is reached (approximately 35% of blood volume) at which most animals suffer irreversible shock and death (12, 13). In fetal lambs, removal of 15% of the fetal-placental blood volume causes a 10% decrease in arterial blood pressure, a 15% decrease in gastrointestinal blood flow, and a 4% increase in gastrointestinal vascular resistance (5). The smaller changes in intestinal hemodynamic parameters in the fetus may be due to the ability of the umbilical-placental circulation to accommodate for a reduction in blood volume via redistribution of blood into the fetal body. Hemorrhage of 10 mL/kg (approximately 10% of blood vol) in 2- to 4-d-old piglets causes a 22% decrease in blood pressure, a 45% decrease in intestinal blood flow, and a 70% increase in intestinal vascular resistance (3). By 1 wk of age (3), the changes are similar to those of adult dogs (11) with arterial blood pressure decreasing by 19%, intestinal blood flow decreasing by 35%, and intestinal vascular resistance increasing by 29%.

In adult rats, these intestinal vascular changes during hemorrhage are a result of neural vasoconstriction of both the precapillary and postcapillary vasculature that overwhelms the local vasodilatory response (14). In neonatal swine there is evidence for the presence at birth of sympathetic vasoconstrictor tone in the mesenteric circulation (15). Indeed, one might speculate that the developing intestine may undergo sustained vasoconstriction with hemodynamic stress, as evidenced by the absence of autoregulatory escape of the piglet mesenteric vasculature from norepinephrine infusion in animals less than 2 wk of age (16).

The effect of hemorrhage on intestinal oxygen consumption has not been studied, but with local reduction in intestinal blood flow in adult dogs, flow must fall >30% before oxygen uptake begins to be compromised (6). The purpose of our study was to characterize the responses of intestinal blood flow and oxygen consumption to graded arterial hemorrhage in the piglet and to determine whether the intestine of the newborn is more susceptible to tissue hypoxia than that of older piglets after hemorrhage. The most important finding of this study was that the intestine of piglets less than 2 wk of age is unable to maintain oxygen uptake after hemorrhage. Despite the hypotensive stress imposed in our study, the capacity of the intestine of piglets less than 2

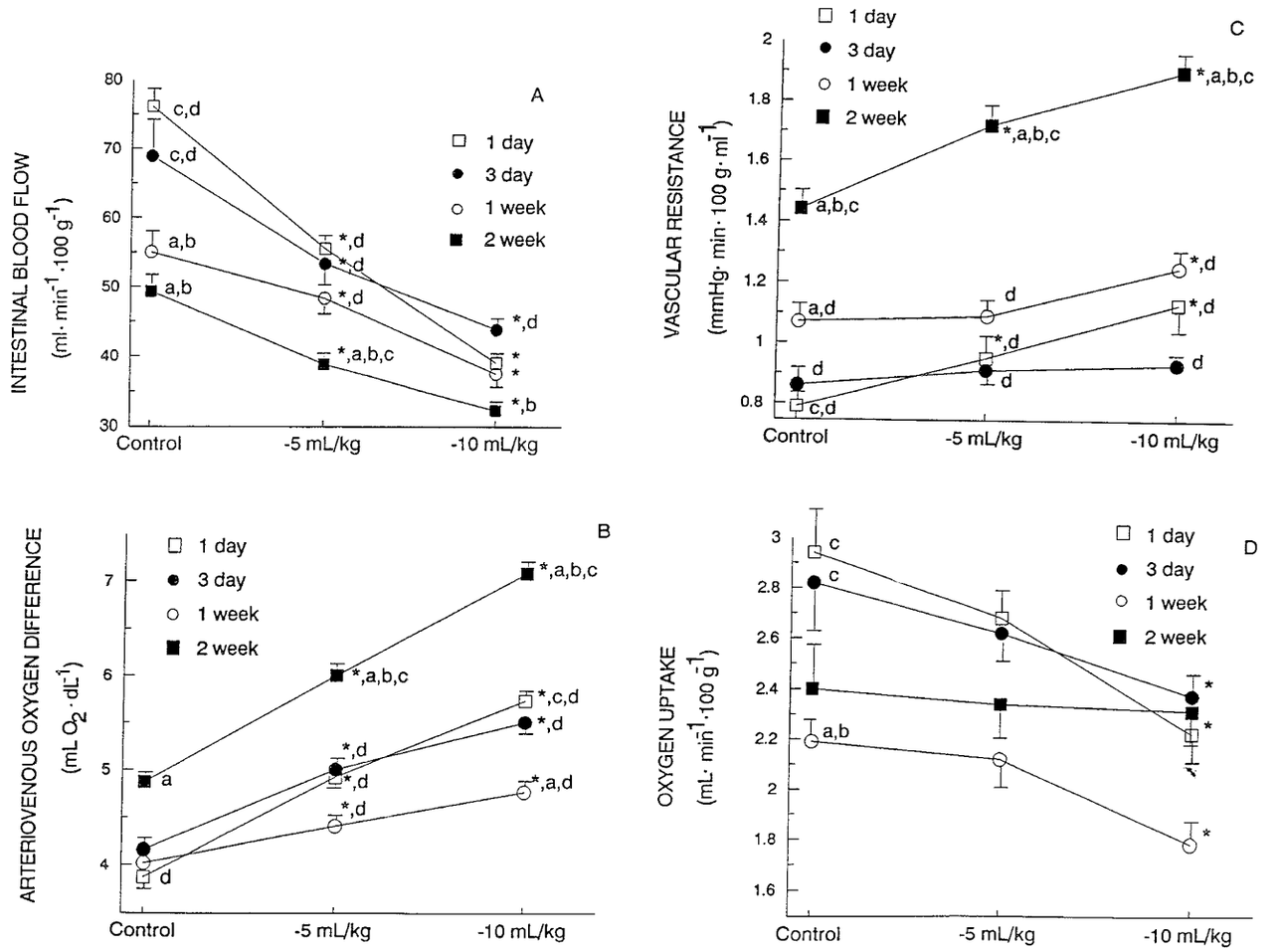

Fig. 2. Intestinal blood flow (*A*), arteriovenous oxygen difference (*B*), vascular resistance (*C*), and oxygen uptake (*D*) during control and after 5 and 10 mL/kg arterial hemorrhage in 1-d, 3-d, 1-wk, and 2-wk-old piglets, * signifies $p < 0.05$ *versus* control values within an age group, whereas *a* indicates $p < 0.05$ *versus* 1 d, *b versus* 3-d, *c versus* 1-wk, and *d versus* 2-wk-old values.

wk of age to maintain adequate oxygenation was reduced by approximately 20% as compared to the intestine of 2-wk-old animals which was able to maintain oxygen consumption at the control level. Nowicki and Miller (17) have also shown that with local reduction of perfusion pressure in a denervated, isolated ileal loop preparation, intestinal blood flow and oxygen uptake are less effectively maintained in 3-d-old than in 35-d-old piglets. Thus, irrespective of whether extrinsic (neural and hormonal) influences are maintained or eliminated, the newborn intestine cannot maintain oxygen uptake during reduced perfusion pressure.

Bulkley *et al.* (18) have shown that mucosal damage, as measured by ^{131}I-albumin clearance from blood to lumen increases significantly in isolated, perfused segments of canine jejunum after blood flow is reduced to levels at which oxygen uptake is decreased by more than 50%. These findings indicate that the ability of the small intestine to maintain oxygen consumption during low flow states may be an important factor in providing protection from mucosal damage. Whether the mucosa of newborn animals is more susceptible to ischemic insults than the mucosa of older animals is unknown. The newborn intestine is, however, at significantly higher risk of damage than the intestine of older animals based on its inability to maintain oxygen uptake in the face of hypovolemic stress or reduction in local perfusion pressure. One might speculate that the developing intestine may be especially susceptible during times of increased oxygen demand such as with feeding.

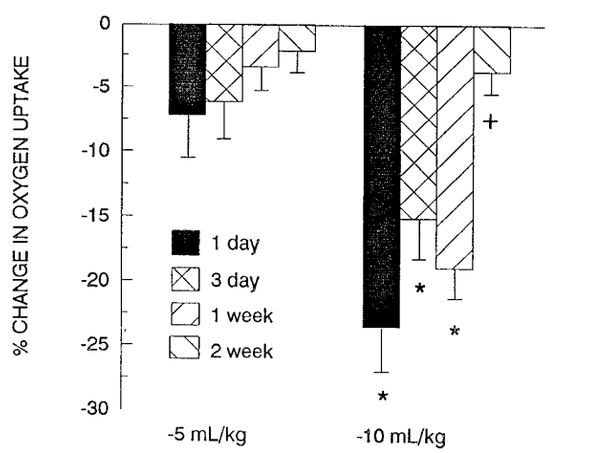

Fig. 3. Percentage change in intestinal oxygen uptake after 5 and 10 mL/kg arterial hemorrhage in 1-d, 3-d, 1-wk, and 2-wk-old piglets. * signifies $p < 0.05$ *versus* no change, whereas + indicates $p < 0.05$ *versus* all younger age groups within a level of hemorrhage.

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