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Gastrointestinal Blood Flow and O_2 Uptake in Piglets: Recovery from Hypoxemia

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ABSTRACT. Gastrointestinal (GI) blood flow, O_2 transport, and O_2 uptake were measured during recovery from severe hypoxemia in newborn piglets. Hypoxemia was induced by lowering the inspired O_2 concentration to 0.05 for 15 min. This resulted in an 82% decrease in GI O_2 uptake. Recovery measurements were obtained 5 and 65 min after restoration of normoxia. During early recovery (5 min), GI O_2 uptake increased above prehypoxemia baseline, presumably to "repay" the O_2 deficit incurred during hypoxemia. This was mediated by an increase in the arteriovenous O_2 content difference, as GI blood flow did not increase above prehypoxemia baseline. During late recovery (65 min), GI blood flow, O_2 delivery, and arteriovenous O_2 content difference decreased below prehypoxemia baseline. This resulted in a 52% decrease in GI O_2 uptake below prehypoxemia baseline. Therefore, early recovery was characterized by an appropriate increase in GI O_2 uptake; however, late recovery was characterized by a significant reduction in GI O_2 transport and uptake. Circulatory homeostasis was not reestablished during the late recovery period. (*Pediatr Res* 19: 1197–1200, 1985)

Abbreviations

GI, gastrointestinal
(a-v) Δ O_2, arteriovenous O_2 content difference

A decrease in O_2 availability below the level necessary to sustain aerobic metabolism results in accumulation of an O_2 deficit. Following restoration of the O_2 supply, tissue O_2 uptake increases above the normoxic resting level, effecting a "repayment" of the O_2 deficit (1, 2). This sequence has been identified in mature intestine subjected to ischemic O_2 deprivation (3).

Severe hypoxemia in the newborn produces a decrease in GI blood flow and (4–7) O_2 uptake (5, 6). It would be anticipated, therefore, that restoration of normoxia would be accompanied by an increase in blood flow and O_2 uptake above prehypoxemia levels. However, the newborn mesenteric circulation is limited in its capacity to increase blood flow, via local vasodilation, in response to increased O_2 demands (8, 9). A preliminary report demonstrated that the newborn piglet GI tract does not exhibit a hyperemia or increased O_2 uptake during recovery from hypoxemia (6). Hence, the posthypoxemia circulatory adjustment in the newborn may not parallel those in the mature GI tract. The purpose of this investigation was to characterize the newborn mesenteric circulation during recovery from severe hypoxemia.

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MATERIALS AND METHODS

Animal preparation. Newborn piglets (2 days of age) were fasted for 6 h before study. This species was selected because of its nonruminant GI physiology and developmental similarity to the human neonate (10). Using NO_2 and lidocaine anesthesia, a tracheostomy was performed, and catheters were placed into the left ventricle, upper and lower abdominal aorta, and portal vein (via the umbilical vein). The portal vein catheter was used to sample the O_2 content of venous blood draining from the GI tract. The O_2 content of portal vein blood sampled in this fashion correlates well with that obtained simultaneously from the common mesenteric vein, and the correlation holds true over a wide range of O_2 contents (9). Following catheterization, NO_2 was discontinued, and muscle paralysis achieved with pancuronium bromide (0.1 mg/kg). The piglet was ventilated with a Bourns LS104 ventilator during data collection.

Experimental protocol. Heart rate, blood pressure, and arterial blood gas tensions were stable for 2 h before the onset of data collection. The study consisted of four measurement periods. During each period, cardiac output, GI blood flow, and arterial and portal vein O_2 content determination were made. A baseline measurement was made under normoxic conditions. Hypoxemia was induced by lowering the inspired O_2 concentration to 0.05 with N_2, and continued for 15 min. No other adjustments were made with the ventilator. The hypoxemia measurement was obtained and then the inspired O_2 concentration returned to 21%. Early and late recovery measurements were made 5 and 65 min following restoration of normoxia. Hematocrit was determined before and after the study. All blood removed for sampling was replaced with age- and hematocrit-matched piglet blood.

Methodology. Blood flow and cardiac output were measured with microspheres (15 ± 2 μm diameter) using the method of Heymann *et al.* (11). The microspheres were labeled with one of four nuclides: ^{57}Co, ^{113}Sn, ^{103}Ru, or ^{46}Sc (New England Nuclear, Boston, MA). The order of isotopes administered in each study was randomly varied. Approximately 9×10^5 microspheres were injected into the left ventricle over 20 s, while, simultaneously, an arterial reference sample was withdrawn at a constant rate (1.03 ml/min for 2 min) through the abdominal aorta catheter. Tissue was fixed in 10% formalin for 24 h and then placed in plastic counting vials. Tissue and blood radioactivity was measured using a Packard γ spectrometer (Packard Instruments, Downers Grove, IL) and blood flow data generated with an IBM PC. The program was corrected for isotope spillover and decay. Regional blood flows were calculated with the equation:

$$\text{Blood flow} = \left(\frac{\text{cpm tissue}}{\text{cpm reference blood}}\right) \times \text{rate reference withdrawal (11)}$$

Cardiac output was calculated with the equation:

$$\text{Cardiac output} = \left(\frac{\text{cpm injected}}{\text{cpm reference blood}}\right) \times \text{rate of reference withdrawal (11)}$$

To facilitate cardiac output determination the radioactivity (cpm) of each microsphere injection was determined prior to injection. The criteria necessary to ensure accuracy of blood flow measurements to within ±5% were met during the study (11). Sampling of lung tissue from each piglet indicated no left to right shunting of blood across the ductus arteriosus.

O_2 contents were measured with a Lex-O_2-Con O_2 analyzer (Lexington Instruments, Waltham, MA) and arterial blood gas tensions measured with standard electrodes (Instrumentation Laboratories, Waltham, MA). Heart rate, mean arterial blood pressure, and pulse pressure were continuously measured with Statham p23d transducers and recorded on a Gould 2600S recorder (Gould Electronics, Cleveland, OH).

Data analysis. GI blood flows were calculated per tissue weight, and are expressed as $ml \cdot min^{-1} \cdot 100\ g^{-1}$. In addition, the percentage of total GI blood flow distributed to each region of the GI tract was calculated using nonweighted blood flow data.

GI O_2 delivery and uptake were determined from measured data using the Fick equation:

$$\text{GI } O_2 \text{ delivery} = \text{GI blood flow } (Q_{GI}) \times \text{arterial } O_2 \text{ content } (CaO_2)$$

$$\text{GI } O_2 \text{ uptake} = Q_{GI} \times (CaO_2 - \text{portal vein } O_2 \text{ content})$$

These data were calculated per tissue weight, and are expressed as $ml\ O_2 \cdot min^{-1} \cdot 100\ g^{-1}$. The percentage of total GI O_2 delivery distributed to each region was also determined, using nonweighted blood flow data. (a-v) $\Delta\ O_2$ was calculated as the difference between arterial and portal vein O_2 contents, and is expressed as $ml\ O_2 \cdot 100\ ml^{-1}$.

The statistical significance of hypoxemia and recovery measurements were determined by analysis of variance, using the prehypoxemia measurement (hereafter, baseline) as control measurement. A $p < 0.05$ was accepted as significant.

RESULTS

The piglets weighed 1.14 ± 0.12 kg. The entire GI tract weight was 42.3 ± 16.9 g, distributed regionally as follows: stomach 5.3 ± 1.0 g; proximal small bowel 20.4 ± 8.9 g; distal small bowel 11.4 ± 5.7 g; and colon 5.2 ± 2.2 g. Arterial blood gas and O_2 content data are shown in Table 1. During hypoxemia a 78% reduction in arterial O_2 content was achieved, while values obtained during recovery were similar to baseline.

During the baseline measurement, the distribution of GI blood flow to each region was as follows: stomach 11 ± 4%; proximal small bowel 62 ± 6%; distal small bowel 16 ± 4%; colon 10 ± 5%. Despite changes in GI blood flow during the study, the regional distributions did not change.

Hypoxemia resulted in a decrease in GI blood flow and cardiac output (Fig. 1). The reduction in blood flow occurred in all regions of the GI tract (Fig. 2). During early recovery (5 min after restoration of normoxia), cardiac output and total and regional GI blood flows returned to baseline. During late recovery, GI blood flow decreased 32% below baseline, despite maintenance of cardiac output. On a regional basis, only blood flow to the proximal small bowel had decreased during late recovery.

GI O_2 delivery decreased during hypoxemia, returned to baseline in early recovery, and decreased again during late recovery (Fig. 3). When examined on a regional basis, O_2 delivery to all regions of the GI tract decreased during hypoxemia, but only O_2 delivery to the proximal small bowel was reduced during late recovery. This observation was valid whether O_2 delivery was expressed per tissue weight or as a percentage of total GI O_2 delivery distributed to each region. The (a-v) $\Delta\ O_2$ decreased during hypoxemia, increased more than 2-fold in early recovery, and decreased again in late recovery (Fig. 3). GI O_2 uptake paralleled the changes noted in (a-v) $\Delta\ O_2$ (Fig. 3).

DISCUSSION

Early recovery was characterized by return of cardiac output and GI blood flow to prehypoxemia baseline values. Unlike the response observed in the mature intestine (3), a significant posthypoxemia increase in mesenteric blood flow did not occur. The newborn mesenteric circulation exhibits limited capacity to regulate GI blood flow in response to increased tissue O_2 de-

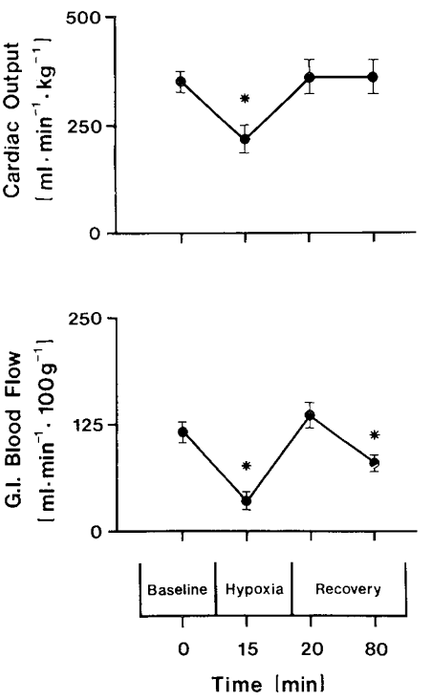

Fig. 1. Cardiac output and gastrointestinal blood flow. Mean ± SEM ($n = 8$). * $p < 0.05$ *versus* baseline.

Table 1. *Arterial blood gas and O_2 content in study subjects*

	Baseline	Hypoxia	Recovery	
			5 min	65 min
pH	7.47 ± 0.03*	7.36 ± 0.06	7.21 ± 0.05†	7.39 ± 0.04
pCO_2 (mm Hg)	32 ± 4	30 ± 3	30 ± 4	30 ± 4
pO_2 (mm Hg)	85 ± 4	18 ± 3†	92 ± 6	85 ± 4
CaO_2 ($ml\ O_2 \cdot 100\ ml^{-1}$)	11.8 ± 0.8	2.6 ± 0.3†	11.0 ± 0.7	10.5 ± 0.7

* Mean ± SEM ($n = 8$).

† $p < 0.05$ compared to baseline.

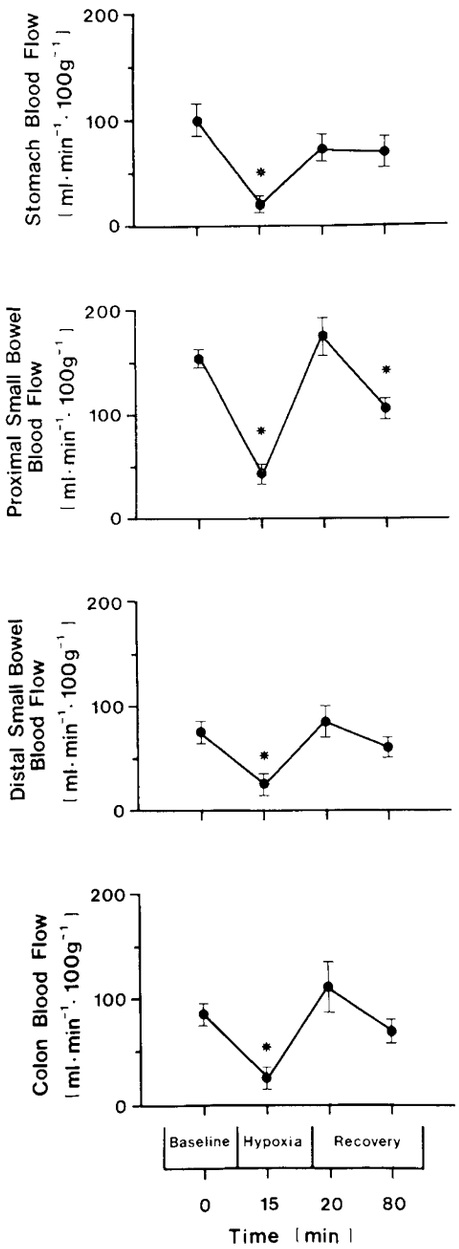

Fig. 2. Regional GI blood flow. Mean ± SEM (n = 8). *$p < 0.05$ *versus* baseline.

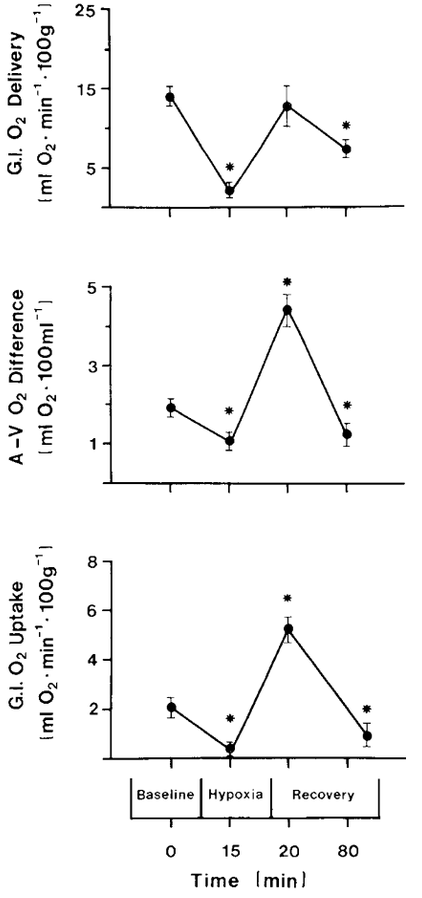

Fig. 3. GI O_2 delivery, a-v O_2 difference, and O_2 uptake. Mean ± SEM (n = 8). *$p < 0.05$ *versus* baseline.

mands (8, 9). During the postprandial period, another circumstance in which GI O_2 demands are increased, the newborn manifests only a modest increase in GI blood flow (9). The resting GI blood flow of the newborn is substantially higher than that reported in mature GI tracts (8, 9). Edelstone and Holzman (8) speculated that the newborn mesenteric circulation is at near maximal vasodilation in the resting state, with little capacity for increased blood flow if tissue O_2 demands increase (8). The present data support this speculation.

Despite the lack of a mesenteric hyperemia, GI O_2 uptake did increase above prehypoxemia baseline during early recovery. This was mediated by an increase in the (a-v) Δ O_2 across the GI tract. Regulation of (a-v) Δ O_2 is accomplished by opening or closing precapillary sphincters, altering the number of perfused capillaries. This adjusts the total surface area available for O_2 diffusion and metabolite exchange (12, 13). Control of (a-v) Δ O_2 is an integral mechanism in the maintenance of GI O_2 uptake (12, 14). This is particularly important in the newborn because of the limited capacity to regulate GI blood flow and O_2 delivery. Our observation is consistent with studies in which the newborn GI tract response to changes in O_2 availability or O_2 demand is mediated primarily by adjustment of (a-v) Δ O_2 (7, 8, 15, 16).

Late recovery was characterized by reduction in GI blood flow and O_2 delivery below prehypoxemia baseline levels. When examined on a regional basis, the reduction in GI blood flow and O_2 delivery was localized to the proximal small bowel. Cardiac output remained unchanged and mean arterial blood pressure was also stable. Therefore, the reduction in GI blood flow was secondary to an increased mesenteric vascular resistance. The mechanism responsible for this observation cannot be determined from the present data, although some speculation is feasible. Damage to the GI tract and/or mesenteric vasculature may have occurred during, or after, severe hypoxemia, leading to a reduction in blood flow. There is evidence vascular damage can occur during reoxygenation (15, 16). Alternatively, it is possible the late mesenteric vasoconstriction represented a physiological response; *i.e.* redistribution of cardiac output may have occurred during the late recovery period, in a fashion similar to that which has been described during hypoxemia (17, 18). Additional data are necessary to clarify the basis for the present observation.

In a preliminary report, Szabo *et al.* (6) observed no significant reduction in piglet GI blood flow 70 min after resolution of a hypoxemia stress. This contrasts with the 32 ± 3% decrease in GI blood flow reported here during late recovery. There may be two explanations for this discrepancy. Szabo *et al.* (6) reduced pO_2 to 29 ± 1 mm Hg, compared to 18 ± 2 mm Hg induced in

the present study. These values fall on the steep portion of the piglet Hb dissociation curve, resulting in expected saturations of 58 and 30%, respectively (19). The degree of hypoxemia induced in the present study was more profound, which may have been a factor in the pronounced circulatory changes. Also, the baseline GI O_2 uptake observed by Szabo *et al.* (6) was 3.6 ± 0.4 ml $O_2 \cdot min^{-1} \cdot 100\ g^{-1}$, which is substantially higher than the prehypoxemia baseline GI O_2 uptake observed in the present investigation. This may have been secondary to the duration of fasting prior to study, as GI O_2 uptake increases significantly during digestion (16). It is unlikely that the difference reflects anesthetic effect, as similar anesthesia was used in both studies. The response of the mesenteric circulation to changes in O_2 availability or tissue O_2 demand is affected by the resting state of the circulation (14). Hence, the observations of Szabo *et al.* (6) might reflect the higher baseline GI O_2 uptake. If this is correct, it implies that the existence of an increased GI O_2 uptake may afford some protection against the circulatory adjustments observed in the late recovery period after hypoxemia.

Previous studies have demonstrated that a reduction in GI O_2 delivery results in an increase in (a-v) Δ O_2 (12, 13). However, in the present study (a-v) Δ O_2 decreased when GI O_2 delivery decreased, during hypoxemia, and late recovery measurements. The (a-v) Δ O_2 quantifies O_2 diffusion from capillary to cell. While the GI tract is capable of regulating (a-v) Δ O_2 by altering the number of perfused capillaries (12, 13), the diffusive process itself remains passive. The driving force for O_2 diffusion is the pO_2 gradient between capillary and cell (12, 13), therefore, if the capillary pO_2 is severely decreased, such as would occur during profound hypoxemia, the diffusive process would be diminished, and (a-v) Δ O_2 would decrease (9). This is the likely explanation for the reduction in (a-v) Δ O_2 which was observed during hypoxemia, and the reason why (a-v) Δ O_2 failed to increase during the reduced O_2 delivery noted at that time. During late recovery, however, systemic pO_2 and arterial O_2 content were restored to normal and GI O_2 delivery, while diminished compared to baseline, was most probably not decreased to a degree sufficient to limit capillary pO_2 and thus O_2 diffusion. An alternative explanation is necessary to reconcile the reduction in (a-v) Δ O_2 which ccurred during late recovery. We speculate that this could have occurred because of damage to capillaries during and after hypoxemia. Granger et al. (15) observed a loss of intestinal capillary integrity following O_2 deprivation and reoxygenation. During O_2 deprivation, metabolism of ATP results in a large pool of hypoxanthine and, during reoxygenation, abundant O_2 is made available. These substrates are metabolized by xanthine oxidase to produce superoxide anion and hydroxyl radicals, which alter capillary integrity (16). Regulation of (a-v) Δ O_2 is dependent on control of capillary perfusion and maintenance of capillary integrity (12, 13). Therefore, damage to capillaries might disrupt normal regulation of capillary perfusion.

GI O_2 uptake decreased during late recovery, due to the decreases in O_2 delivery and (a-v) Δ O_2. The methodology used in this study did not allow quantification of regional (a-v) Δ O_2 or GI O_2 uptake, as the venous effluent from the GI tract was measured only at the portal vein. It is not reasonable, therefore, to conclude that O_2 uptake was lower in one particular region. However, O_2 delivery was decreased only in the proximal small bowel, and it is feasible to speculate that this region might have been more severely affected in terms of diminished O_2 uptake.

The present data were obtained while the piglets were artificially ventilated. Comparison of baseline values for GI blood flow, O_2 transport, and O_2 uptake presented herein with that reported in fasting, spontaneously breathing piglets (20) reveals no differences in these variables. However, the cardiovascular responses to hypoxemia can be affected by artificial ventilation (21), and it is important to qualify the data presented herein with the experimental model utilized.

In summary, the adjustments of the newborn mesenteric circulation during recovery from severe hypoxemia change over time. In early recovery, GI O_2 uptake increased over prehypoxemia baseline, mediated by an increase in (a-v) Δ O_2. Late recovery was characterized by a reduction in GI blood flow and O_2 transport, and thus GI O_2 uptake. Restoration of mesenteric circulatory homeostasis did not occur within the time frame evaluated in this study.

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