Effects of Ischemia and Reperfusion on Intrinsic Vascular Regulation in the Postnatal Intestinal Circulation¹

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ABSTRACT. The purpose of these experiments was to determine the effect of 1 h of total ischemia followed by 2 h of reperfusion on intrinsic vascular regulation within intestine from 3- and 35-d-old swine. Intrinsic vascular regulation was defined as the ability of *in vitro* segments of small intestine to bring about adjustments of blood flow and the arteriovenous O₂ content difference across the intestinal segment of sufficient magnitude to preserve tissue O₂ uptake in response to a 35% reduction in arterial perfusion pressure. This response was elicited before (control conditions) and after ischemia-reperfusion (post-I/R). In older subjects, the efficacy of blood flow regulation was attenuated post-I/R, insofar as blood flow fell in response to pressure reduction. However, this group demonstrated a rise in arteriovenous content difference after pressure reduction under control and post-I/R conditions that were of sufficient magnitude to preserve tissue O₂ uptake. In younger subjects, blood flow regulation was absent under control conditions and post-I/R. The arteriovenous O₂ content difference increased in response to pressure reduction under control conditions but failed to do so post-I/R; consequently, tissue oxygenation decreased in response to arterial pressure reduction post-I/R in 3-d-old intestine. We conclude that ischemia-reperfusion affects intrinsic vascular regulation in postnatal intestine and that this effect is age-dependent. Intestine from older subjects maintains the intrinsic capacity to preserve tissue oxygenation in response to a hypotensive challenge despite the insult of ischemia-reperfusion, whereas intestine from younger subjects does not maintain this capacity. (*Pediatr Res* 33: 400-404, 1993)

Abbreviations

(a-v)O₂, the arteriovenous O₂ content difference across the intestinal segment
post-I/R, after ischemia and subsequent reperfusion
P_vO₂, partial pressure of O₂ within intestinal venous effluent

vasoactive stimuli, an effect that might attenuate central neurohumoral regulation of regional circulations (1). Also, ischemia and reperfusion can disrupt intrinsic vascular regulation, *i.e.* vascular regulation governed by effector mechanisms that reside entirely within regional circulations and whose function does not depend on central vasoactive stimuli (2). Thus, Tsao and Lefer (3) noted loss of intrinsic coronary vascular reactivity within *in vitro* rat hearts after ischemia and reperfusion, and Kim *et al.* (4) observed similar findings in isolated coronary vessels.

Ischemic disruption of intrinsic vascular regulation may be highly relevant to the postnatal intestinal circulation. The newborn intestine frequently experiences ischemic stress during episodes of antepartum or intrapartum asphyxia, or during postnatal hypoxia or hypotension (5, 6). Furthermore, intrinsic vascular regulation within the intestinal circulation plays a vital role in preservation of intestinal oxygenation (7). Damage to these mechanisms might impair subsequent regulation of gut O₂ uptake; thus, episodes of ischemia and reperfusion sustained by the gut around the time of birth might imperil subsequent gut viability and function by reducing the inherent capability of the intestine to regulate tissue oxygenation.

The goal of this experiment was to determine whether ischemia and subsequent reperfusion affect the efficacy of intrinsic vascular regulation within postnatal swine intestine. To this end, efficacy of intrinsic vascular regulation was defined as the ability of *in vitro* intestinal segments to bring about adjustments in blood flow and (a-v)O₂ of sufficient magnitude to preserve tissue oxygenation after a 35% reduction in arterial perfusion pressure. Studies of intestinal segments obtained from 3- and 35-d-old swine were conducted to determine whether the effects of ischemia and reperfusion on intrinsic vascular regulation are age-dependent.

MATERIALS AND METHODS

Experimental preparation. All procedures used in the handling of experimental animals conformed to standards listed in the NIH's *Guide for the Care and Use of Laboratory Animals*. The experimental preparation and study design were approved by the Institutional Animal Care and Use Committee of Children's Hospital. Farm-bred swine served as experimental subjects for these experiments. Subjects in the 3-d-old group were obtained on the 1st or 2nd postnatal day and were fasted for 12 h before study, whereas subjects in the 35-d-old group were obtained 1 d before use and fasted 18 h before study. These durations of fasting are sufficient to ensure a resting, or postabsorptive, state in swine intestine at these postnatal ages (8).

Experimental subjects were anesthetized (pentobarbital sodium 35 mg/kg intraperitoneally), heparinized (500 U/kg), and ventilated to maintain normal blood gas tensions. A segment of distal jejunum-proximal ileum approximately 35 cm in length was isolated from the remainder of the gut and cleansed by

Ischemia and subsequent reperfusion injure blood vessels and impair vascular function. Manifestations of this damage include loss of vascular response to adrenergic and other neurohumoral

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repetitive luminal infusion of warm (38°C) saline and air. The single artery-vein pair serving this segment was quickly cannulated (15-s interruption of blood flow), and extracorporeal perfusion of the segment was initiated. The intestinal segment was removed from the experimental subject and placed in a humidified Plexiglas chamber; thereafter, the experimental subject was euthanized (Uthol 1 mL/kg i.v.). A temperature probe placed into the gut lumen was connected to a servo-controlled overhead heating element. Luminal temperature was maintained at 38°C throughout the experiment.

Arterial perfusion of the intestinal segment was achieved by means of an extracorporeal perfusion apparatus. Blood for this apparatus was obtained from a second animal, approximately 90 d old and 40 kg, hereafter called the donor subject. Donor subjects were anesthetized (pentobarbital sodium 35 mg/kg intraperitoneally), heparinized (500 U/kg), and ventilated via an endotracheal tube to maintain normal blood gas tensions. Approximately 1500 mL of whole blood were withdrawn from the donor through a 40- μ m filter and placed into a 2-L collecting flask. Thereafter, the donor subject was euthanized (Uthol solution, 1 mL/kg i.v., Butler, Columbus, OH). The collecting flask was placed within a circulating water bath maintained at 39°C, which in turn was placed over a stirplate. This arrangement allowed continual warming and mixing of the blood therein. Blood in the collecting flask was continuously circulated through a 0.6-m² membrane oxygenator (SciMed, Minneapolis, MN) at 200 mL/min. The oxygenator was gassed with 95% compressed air and 5% CO₂ so that gas tensions within the collecting flask remained approximately at PO₂ 16.0 kPa and PCO₂ 5.3 kPa. A small volume of blood (approximately 20 mL/min) was continuously withdrawn from the collecting flask and directed to a sealed arterial reservoir, and thereafter to the intestinal segment. Like the collecting flask, the arterial reservoir was positioned within a water bath and over a stirplate to facilitate warming and mixing of the blood therein. Blood flow from the arterial reservoir to the intestinal segment was achieved by pressurizing the reservoir with 95% air and 5% CO₂ by means of a low-range air-pressure regulator (Bellofram, type 10R, Burlington, MA). Reservoir pressure directly determined the arterial pressure delivered to the intestinal segment and could be varied within 1 to 2 mm Hg. The venous effluent from the intestinal segment was directed to a venous reservoir and thereafter pumped back to the collecting flask at approximately 20 mL/min.

A cannulating electromagnetic flowmeter (1.5-mm internal diameter Gould, Oxnard, CA) was placed between the intestinal segment and venous reservoir to measure total intestinal blood flow. Zero flow was determined by transient occlusion of the venous circuit distal to the flowmeter. Arterial and venous pressures were determined by pressure transducers connected to the perfusion circuits by T-tubes. Blood sampling ports in the arterial and venous circuits allowed withdrawal of blood samples without interruption of blood flow. Blood gas tensions and blood O₂ content were measured with a Corning 168 analyzer (Corning Medical, Medfield, MA) and Lex-O₂-Con (Hospex, Chestnut Hill, MA), respectively.

The stability of the *in vitro* intestinal preparation was validated in a series of four preliminary studies, conducted in two 3-d-old and two 35-d-old subjects. After steady state conditions were attained and baseline samples taken, a 35% pressure reduction was applied and maintained until new steady state conditions were noted. Thereafter, arterial pressure was returned to baseline and the preparation allowed to stand, without manipulation, for approximately 3 h. A second pressure reduction was then applied.

Experimental protocol. Twenty subjects were used in the experimental protocol, 10 each in the 3-d-old (age range 2 to 4 d) and 35-d-old groups (age range 30 to 40 d). Intestinal segments were perfused at mean arterial pressures that duplicated *in vivo* conditions, i.e. 70 mm Hg (9.3 kPa) for 3-d-old subjects and 85 mm Hg (11.3 kPa) for 35-d-old subjects (9). Venous pressure was maintained at 0 mm Hg (0 kPa) throughout the experiment

by adjusting the height of the venous reservoir with respect to the tissue. Perfusion was initiated and maintained until the preparation attained steady state conditions, defined as momentary fluctuation of blood flow of less than 5% from baseline. Values noted during perfusion at these age-appropriate arterial pressures are hereafter designated baseline circulatory parameters.

The experimental protocol consisted of two reductions of arterial pressure, one before ischemia (control) and one after ischemia-reperfusion (post-I/R). Arterial and venous blood samples were obtained and hemodynamic variables recorded during perfusion at baseline arterial pressure. Arterial pressure was then reduced by 35% and maintained at that level until new steady state conditions were attained (5 to 7 min); thereafter, repeat blood samples and measurement were attained, and pressure was restored to baseline. These observations served as control data. Total gut ischemia was induced by clamping the arterial circuit. After 60 min, perfusion was restored and arterial pressure reset, as necessary, to its age-appropriate baseline value. Two h after restoration of perfusion, post-I/R data were attained by obtaining samples and measurements before and after reduction of arterial pressure by 35%, as described previously.

Statistical analysis. The null hypothesis tested herein was as follows: ischemia-reperfusion has no effect on the efficacy of intrinsic vascular regulation within intestine from 3- or 35-d-old swine. To this end, three measures of intrinsic vascular regulation were evaluated: change in blood flow, change in (a-v)O₂, and change in tissue O₂ uptake, each after a 35% reduction in arterial perfusion pressure. Effective intrinsic regulation was defined as adjustment of flow and (a-v)O₂ sufficient in magnitude and direction to preserve tissue O₂ uptake in the face of arterial pressure reduction. To test the null hypothesis, a three-way analysis of variance was performed that incorporated group (3- versus 35-d-old), condition (control versus post-I/R), and time (baseline arterial pressure versus reduced arterial pressure) as main effects. If the *F* statistic was significant, *post-hoc* tests were performed to determine the sites of difference.

RESULTS

The four preliminary studies revealed excellent stability of the *in vitro* intestinal preparation over the time frame encompassed by the experimental protocol. Values for blood flow, (a-v)O₂, and O₂ uptake remained steady within intestine from younger and older subjects, furthermore, the effect of a 35% arterial pressure reduction on the measured variables did not change after approximately 3 h of perfusion (data not shown). The membrane lung and extracorporeal perfusion apparatus afforded excellent stability in arterial gas tensions and pH (Table 1). Values for arterial pH, PO₂, and PCO₂ did not change from the baseline values listed in Table 1 throughout the course of the experiments.

As expected, baseline circulatory parameters within 3- and 35-d-old swine intestine were age-dependent under control conditions (Table 2). Three major differences were noted between age groups. First, intestinal vascular resistance was lower in younger subjects, so that blood flow and O₂ delivery were greater in this group despite perfusion at a lower arterial pressure. Second, younger subjects extracted a smaller percentage of delivered O₂.

Table 1. O₂ status of arterial blood during first baseline measurement, under control conditions*

	3-d-old	35-d-old
pH	7.40 $\pm$ 0.02	7.41 $\pm$ 0.03
PO ₂ (kPa)	15.2 $\pm$ 0.5	16.1 $\pm$ 0.6
PCO ₂ (kPa)	5.1 $\pm$ 0.5	5.1 $\pm$ 0.2
O ₂ content (mM O ₂ /L)	4.92 $\pm$ 0.08	4.91 $\pm$ 0.12
Hematocrit (%)	34 $\pm$ 1	35 $\pm$ 1

* Values are mean $\pm$ SEM; *n* = 10 for both groups.

Table 2. Baseline circulatory parameters noted within *in vitro* intestinal segments from 3- and 35-d-old swine under control conditions and after 1-h ischemia and 2-h reperfusion (post-I/R)*

	3-d-old		35-d-old	
	Control	Post-I/R	Control	Post I/R
Arterial pressure (mm Hg)	68 ± 1	71 ± 1	86 ± 1†	85 ± 1
Blood flow (mL/min/100 g)	111 ± 9	95 ± 10	54 ± 2†	90 ± 7‡
Vascular resistance (mm Hg/mL/min/100 g)	0.66 ± 0.06	0.84 ± 0.12	1.60 ± 0.07†	1.01 ± 0.10‡
O ₂ delivery (mM O ₂ /min/100 g)	54.7 ± 4.9	48.4 ± 5.4	26.8 ± 1.6†	45.4 ± 3.5‡
(a-v)O ₂ (mM O ₂ /L)	0.93 ± 0.07	0.86 ± 0.08	1.28 ± 0.09†	0.82 ± 0.08‡
O ₂ uptake (mM O ₂ /min/100 g)	9.65 ± 0.34	7.65 ± 0.50‡	6.89 ± 0.44‡	6.90 ± 0.37

Values are mean ± SEM; *n* = 10 for both groups. Conversion of pressure data from mm Hg to kPa can be achieved with the factor mm Hg = 0.1333 kPa.

† *p* < 0.05 vs 3-d-old.

‡ *p* < 0.05 vs control.

This difference was manifest by a lower (a-v)O₂ and higher P_vO₂ (Table 3) in intestine from 3-d-old than from 35-d-old subjects. Finally, the net amount of O₂ used by the intestine, *i.e.* O₂ uptake or consumption, was greater in younger than in older subjects.

Ischemia-reperfusion changed baseline circulatory parameters in an age-dependent fashion (Table 2). Intestine from 3-d-old subjects demonstrated reduction in O₂ uptake, post-I/R; other circulatory parameters remained unchanged, except for P_vO₂ (Table 3), which increased. This increase reflected the concomitant reduction in O₂ uptake, *i.e.* more O₂ appeared within the intestinal venous effluent because less was being used by the gut. In contrast to younger subjects, intestine from 35-d-old subjects demonstrated reduced vascular resistance and increased blood flow and O₂ delivery post-I/R. Despite the increased rate of O₂ delivery, gut O₂ uptake noted after 2 h of reperfusion was unchanged from control because of a proportional reduction in (a-v)O₂. P_vO₂ increased in older subjects post-I/R. More O₂ appeared within the intestinal venous effluent post-I/R because more was being delivered, whereas the same amount was being used.

The effects of ischemia and reperfusion on intrinsic vascular regulation was different in intestine from 3- and 35-d-old subjects (Fig. 1). Older subjects demonstrated a significant decrease in blood flow in response to pressure reduction post-I/R but not under control conditions. However, (a-v)O₂ increased and P_vO₂ decreased (Table 3) after pressure reduction under both control and post-I/R conditions; thus, the intestine extracted a greater percentage of delivered O₂ in response to arterial pressure reduction in this group. Consequent to this adjustment, tissue O₂ uptake was unaffected by pressure reduction in intestine from older subjects under either experimental condition. Younger subjects demonstrated a significant decrease in blood flow after pressure reduction under control conditions and post-I/R. In contrast to older subjects, however, (a-v)O₂ increased, and P_vO₂ decreased in response to pressure reduction only under control conditions. Post-I/R, significant change in either of these variables was not observed; thus, extraction of delivered O₂ failed to increase in response to pressure reduction post-I/R in younger

subjects. This failure caused a significant compromise in tissue O₂ uptake in this group after arterial pressure reduction.

DISCUSSION

Like most organs, the intestine demonstrates an inherent capacity to regulate its circulation in response to reduced systemic O₂ availability or increased tissue O₂ use (7). This capacity is generally attributed to a vascular effector system (or perhaps systems) intrinsic to the gut parenchyma and its attendant microcirculation (2). The mechanistic basis for intrinsic vascular regulation has not been established in a definitive sense. The most compelling explanation for this phenomenon, outlined as the O₂ delivery version of the metabolic theory of local blood flow regulation (or simply metabolic theory), is that the gut parenchyma produces a feedback signal in proportion to its state of O₂ sufficiency that interacts within the microcirculation to regulate local O₂ transport (9). This interaction determines the rate of O₂ diffusion from capillary to cell by adjustment of two discrete elements within the microvasculature: resistance vessels and precapillary sphincters. Resistance vessels govern the flow of blood and O₂ into the microcirculation, and so regulate capillary PO₂ and hence the capillary-cell PO₂ gradient that drives the O₂ diffusion process. Precapillary sphincters govern the number of perfused capillaries and so regulate the surface area available for O₂ diffusion. According to the metabolic theory, arterial pressure reduction causes a transient reduction in blood flow and thus O₂ delivery to the gut; this action causes capillary PO₂ to decrease and so compromises O₂ diffusion from capillary to cell, resulting in cellular hypoxia (9–11). This effect elicits release of the feedback signal, which relaxes resistance vessels and opens precapillary sphincters; the net effect of these actions is restoration of O₂ diffusion from capillary to cell and thus restoration of cellular PO₂. The effects of ischemia-reperfusion on intrinsic vascular response to pressure reduction within postnatal intestine can be interpreted within the context of the metabolic theory.

The principal effect of ischemia-reperfusion on intrinsic vascular regulation noted in intestine from 35-d-old subjects was an apparent loss of blood flow regulation insofar as flow decreased in response to pressure reduction post-I/R. Control of blood flow is determined by resistance vessels; thus, one interpretation of these data is that ischemia-reperfusion damaged these microvascular elements. Another explanation is equally feasible. The metabolic theory contends that adjustment of resistance vessel tone only occurs when reduction in capillary PO₂ limits O₂ diffusion from capillary to cell (9, 11). Stated otherwise, if capillary PO₂ is elevated, the need for active resistance vessel control is minimal insofar as the capillary-cell PO₂ gradient is sufficient to drive the diffusion process; under this circumstance, regulation of capillary surface area provides a sufficient means to assure adequate tissue oxygenation (9, 11, 12). This circum-

Table 3. PO₂ in intestinal venous effluent (kPa) in both groups under each experimental condition*

	Control		Post-I/R	
	Baseline	Decreased pressure	Baseline	Decreased pressure
3-d-old (<i>n</i> = 10)	7.9 ± 0.2	6.7 ± 0.3†	8.7 ± 0.3‡	8.1 ± 0.3
35-d-old (<i>n</i> = 10)	6.2 ± 0.2	5.6 ± 0.1†	8.1 ± 0.2‡	7.2 ± 0.2†

* Values are mean ± SEM.

† *p* < 0.05 vs baseline.

‡ *p* < 0.05 post-I/R baseline vs control baseline.

Fig. 1. Blood flow, (a-v)O₂, and O₂ uptake within *in vitro* segments of small intestine from 3-d-old (○) and 35-d-old (●) swine before (B) and after (IP), a 35% reduction in arterial pressure. Data are given as mean ± SEM. *, $p = 0.05$ vs respective baseline (three-way analysis of variance with *post-hoc*).

stance is precisely that which characterized older intestine post-I/R: venous PO₂, an approximation of capillary PO₂ (11), had increased from 6.2 to 8.1 kPa because the basal rate of O₂ delivery had increased, whereas the rate of O₂ use had remained constant. Accordingly, it is quite possible that the loss of resistance vessel regulation merely reflected the change in baseline circulatory conditions that had occurred post-I/R, rather than damage to vascular control elements within the microcirculation. This explanation is consistent with published observations, wherein it was demonstrated that the intensity of resistance vessel regulation in 35-d-old swine intestine is a function of venous PO₂ (13).

Despite the absence of resistance vessel regulation in older subjects post-I/R, tissue oxygenation was preserved during pressure reduction because (a-v)O₂ increased. This rise in (a-v)O₂ was likely the consequence of two events. First, the decrease in capillary PO₂ that occurred after pressure reduction under both control and post-I/R conditions likely caused a small decrease in cellular PO₂, thus stabilizing the capillary-cell PO₂ gradient

(11). Small reductions of cell PO₂ are quite feasible because the PO₂ within the intestinal parenchyma is generally well above the "critical PO₂ level" necessary for preservation of cellular function (11). Second, it is likely that precapillary sphincters opened and that the capillary surface area increased (9, 11, 14). Neither cell PO₂ nor perfused capillary density were measured in this investigation, such that the aforementioned explanation is entirely speculative. However, it is clear that one or both of these events had to occur to maintain tissue oxygenation after arterial pressure reduction, insofar as these events represent the sole means by which the diffusive flux of O₂ from capillary to cell could have been preserved under this circumstance (11).

The effect of ischemia-reperfusion on intrinsic vascular regulation in intestine from 3-d-old subjects was clearly different from that noted in the older group. Blood flow regulation was absent in this group under both control and post-I/R conditions; these data are consistent with published observations (13, 15). The principal effect of ischemia-reperfusion noted in younger subjects was to attenuate the increase in (a-v)O₂ noted in response to pressure reduction under control conditions. Within the framework of the metabolic theory, (a-v)O₂ is determined by the capillary-cell PO₂ gradient, the capillary surface area, and the diffusion distance from capillary to cell (9, 11). How might ischemia-reperfusion have affected these variables? It is clear from venous PO₂ data that capillary PO₂ was not the rate-limiting factor post-I/R, insofar as values for this variable were higher under post-I/R conditions than under control conditions. Unless cell PO₂ increased post-I/R, it appears that the capillary-cell PO₂ gradient was sufficient to drive the diffusion process at this time. Capillary surface may not have increased in response to pressure reduction because of damage to mechanisms controlling precapillary sphincters. Finally, the diffusion distance from capillary to cell might have increased post-I/R consequent to interstitial edema formation. Although these explanations are speculative, it is clear that regulation of O₂ diffusion from capillary to cell in response to pressure reduction was attenuated within gut from younger subjects post-I/R and that this attenuation caused significant compromise in intestinal oxygenation.

Several caveats regarding these data are important to note. First, by design, the present observations exclusively represent the effects of ischemia-reperfusion on intrinsic vascular regulation within postnatal intestine. It is possible, if not probable, that other vascular effectors, such as adrenergic or peptidergic neurons, and humoral vasoactive substances, might be activated after localized intestinal ischemia. Alternatively, the mechanisms by which these extrinsic control systems exert their effect within the intestine might be damaged by ischemia-reperfusion. These actions could play an important role in determining the net effect of ischemia-reperfusion on subsequent intestinal vascular function. In this context, it is interesting to note that Papparella *et al.* (16) observed reduction of blood flow after ischemia-reperfusion within intact young swine, in contrast to our observation that flow did not change post-I/R within denervated, *in vitro* intestine from swine of a similar age. Second, the use of an extracorporeal perfusion circuit mandates blood heparinization, an action that would diminish the probability of thrombus formation post-I/R. Microvascular thrombus formation may play an important role in perpetuation of ischemia and in subsequent attenuation of vascular responses. Thus, although attenuation of intrinsic vascular regulation post-I/R may contribute to subsequent loss of intestinal viability and function, it is probable that other pathophysiology also contributes to the changes noted within the gut post-I/R.

We conclude that 1 h of total ischemia followed by 2 h of reperfusion impairs intrinsic vascular regulation within postnatal intestine but that the net effect of this impairment on intestinal oxygenation is age-dependent. Intestine from 35-d-old subjects demonstrates loss of blood flow regulation, yet this tissue is still able to preserve tissue oxygenation by adjustment of (a-v)O₂.

Intestine from 3-d-old subjects fails to regulate (a-v) O_2 post-I/R and thus loses the ability to preserve tissue oxygenation.

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Announcement

Meeting

The Society for Behavioral Pediatrics will conduct its 11th Annual Scientific Meeting and Workshops on September 9-13, 1993 at the Providence Marriott in Providence, RI. *For further information and registration forms, please contact Ms. Noreen Spota at (215) 248-9168.*