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The Effect of Asphyxia on Superior Mesenteric Artery Blood Flow in the Premature Sheep Fetus

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Background/Purpose: The aim of this study was to determine superior mesenteric artery blood flow changes during and after an asphyxial insult in utero in chronically instrumented unanaesthetised premature fetal sheep.

Methods: Fetal sheep at 0.7 gestation (103 to 104 days) underwent 25 minutes of complete umbilical cord occlusion ($n = 6$) or sham occlusion ($n = 6$). Fetal heart rate, blood pressure, superior mesenteric artery (SMA) blood flow and vascular resistance, electroencephalographic activity, and nuchal electromyographic activity were measured from 6 hours before occlusion until 3 days after occlusion. Fetal gastrointestinal tissue was taken for histological assessment.

Results: During occlusion, cardiovascular response was characterised by 3 phases: initial redistribution of blood flow away from the gut to maintain vital organ function, subsequently partial failure of this redistribution, and finally near

terminal cardiovascular collapse with profound hypotension and gastrointestinal hypoperfusion. Postasphyxia there was a secondary period of hypoperfusion that was mediated by increased vascular resistance, not hypotension. There was no evidence of injury on standard histological assessment after 3 days of recovery.

Conclusions: SMA blood flow is not only significantly reduced during asphyxia, but also for several hours after an asphyxial insult. The authors speculate that these perturbations of gastrointestinal blood flow could compromise gut wall integrity potentially leading to increased vulnerability to necrotising enterocolitis.

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INDEX WORDS: Fetal, asphyxia, superior mesenteric artery blood flow, premature, sheep, gut.

THE CARDIOVASCULAR RESPONSES of the near-term fetus to episodes of reduced oxygen supply have been well described.^{1,2} Gastrointestinal blood flow is maintained during moderate hypoxia and asphyxia, but there is a marked fall in gastrointestinal blood flow during a severe asphyxial insult.³⁻⁶ The changes in gastrointestinal blood flow during the hours after an asphyxial insult are unknown. Further, little is known about the blood flow responses of the immature fetal gut to asphyxia. Iwamoto et al⁷ reported that there was no significant change in gastrointestinal blood flow during graded umbilical cord occlusion in the 0.6 to 0.7 gestation fetus. This apparent failure to redistribute combined ventricular

output (CVO) at this age traditionally has been attributed to immature cardiovascular development.^{1,7} In contrast, however, we recently have shown that the 0.6 gestation fetus is capable of redistributing blood flow away from the periphery during asphyxia and that this severe asphyxial insult leads to a secondary period of significant peripheral hypoperfusion during the first 12 hours after the insult.⁸

It was the purpose of this study, therefore, to examine in the premature fetal sheep the hypotheses that gastrointestinal blood flow is reduced actively during asphyxia and that after this severe asphyxial insult gastrointestinal blood flow would be significantly perturbed.

MATERIALS AND METHODS

Subjects and Experimental Preparation

All procedures were approved by the Animal Ethics Committee of The University of Auckland. Twelve singleton Romney/Suffolk fetal sheep were instrumented at 98 to 99 days of gestation (term, 147 days) under general anaesthesia (2% halothane in O₂) using sterile techniques.^{8,9} Catheters were placed in the left femoral artery and vein, right axillary artery, and the amniotic sac. A 2S ultrasound blood flow probe (Transonic Systems Inc, Ithaca, NY) was placed around the superior mesenteric artery to record gastrointestinal blood flow. Two pairs of electroencephalographic (EEG) electrodes (AS633-5SSF, Cooner wire Co, Chatsworth, CA) were placed on the dura over the parasagittal parietal cortex (5 mm and 10 mm anterior to bregma and 5 mm lateral) and secured with cyanoacrylate glue. A reference electrode was sewn over the occiput. Electromyographic (EMG) electrodes were placed in

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the nuchal muscle and electrocardiogram (ECG) electrodes were sewn across the chest to record the fetal ECG. An inflatable silicone occluder was placed around the umbilical cord of all fetuses (In Vivo Metric, Healdsburg, CA). All fetal leads were exteriorised through the maternal flank, and a maternal long saphenous vein was catheterised. Antibiotics (80 mg gentamicin) were administered into the amniotic sac before closure of the uterus and to the ewes (5 mL of streptopen) intramuscularly before the start of surgery.

After surgery, sheep were housed together in separate metabolic cages with access to water and food *ad libitum*. They were kept in a temperature-controlled room ($16 \pm 1^\circ\text{C}$; humidity, $50 \pm 10\%$), in a 12-hour light-dark cycle. A period of 4 to 6 days postoperative recovery was allowed, during which time antibiotics were administered daily to the ewe (600 mg crystapen intravenously for 4 days and 80 mg gentamicin, intravenously daily for the first 2 days). Fetal arterial blood was taken daily from the brachial artery for blood gas analysis for the assessment of fetal health. Catheters were maintained patent by continuous infusion of heparinised saline (20 U mL^{-1} at 0.15 mL h^{-1}).

Experimental Design

Experiments were conducted at 103 to 104 days' gestation. Fetal mean arterial pressure (MAP), corrected for maternal movement by subtraction of amniotic fluid pressure, fetal heart rate (FHR), superior mesenteric artery blood flow (SMABF), fetal EEG and nuchal EMG activity were recorded continuously from 6 hours before occlusion to 72 hours postocclusion. Data were stored to disk by custom software for off-line analysis (Labview for Windows, National Instruments Ltd, Austin, Texas).

Fetuses were assigned randomly to either the sham occlusion group ($n = 6$) or the occlusion group ($n = 6$). Fetal asphyxia was induced in the occlusion group by rapid inflation of the umbilical cord occluder for 25 minutes with sterile saline of a defined volume known to completely inflate the occluder. Successful occlusion was confirmed by observation of a rapid flattening of the EEG.¹⁰ The sham group underwent sham occlusion for 25 minutes. In both groups, fetal arterial blood was taken 15 minutes before asphyxia; 5 and 20 minutes during asphyxia; and 2, 4, 6, 10, 24, 48, and 72 hours postasphyxia for pH and blood gas determination (845 blood gas analyzer and co-oximeter; Ciba-Corning Diagnostics, MA) and for glucose and lactate measurements (YSI model 2300, Yellow Springs, Ohio).

On completion of the experiment at 72 hours the ewe and fetus were killed by an overdose of pentobarbitone sodium. Samples of the fetal duodenum, jejunum, ileum, and colon were taken for histological examination. All tissue specimens were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned ($4 \mu\text{m}$) and stained with

H&E. The degree of intestinal injury was evaluated by an observer masked to the experimental groups (JQ) using a grading system that describes development of necrosis on a scale from 0 to 8 in which grade 0 means normal mucosa and grade 8 means transmural infarction.¹¹

Data Analysis and Statistics

Off-line analysis was performed using an analysis programme written using Labview for Windows (National Instruments Ltd). Superior mesenteric artery vascular resistance (SMAVR) was calculated using the formula (mean arterial pressure – mean venous pressure)/blood flow (mm Hg min mL^{-1}).

Statistical analysis was performed using SPSS for Windows (SPSS, Chicago, IL). Data are presented as mean $\pm$ SEM. Statistical significance was accepted when P was less than .05. The effect of asphyxia on the biophysical parameters was determined by 2-way analysis of variance (ANOVA). Time was treated as a repeated measure to allow for repeated sampling. When statistical significance was found between groups or between group and time, analysis of covariance (ANCOVA) was used to compare selected time points, using the baseline period as a covariate. For the analysis of the occlusion and 1 hour postocclusion data, the baseline period was taken as the mean of the hour before occlusion, whereas for the analysis of the long-term recovery data (1 to 72 hours postocclusion) the baseline period was taken as the mean of the 6 hours before occlusion.

RESULTS

Blood Composition Measurements

All fetuses had normal blood gas, acid base, and glucose and lactate status, according to the standards of our laboratory, before each experiment. Values and statistical comparisons for arterial pH, blood gases, and glucose and lactate levels for the control and occlusion groups up to 10 hours postasphyxia are presented in Table 1. Between 24 and 72 hours post-asphyxia there were no significant differences between groups for pH, PaCO_2 , glucose, and lactate levels. PaO_2 , however, was significantly elevated in the occlusion group fetuses at each of the 3 days postasphyxia ($P < .05$) and at 72 hours was $30.0 \pm 1.1 \text{ mm Hg}$ versus $25.8 \pm 1.6 \text{ mm Hg}$ ($P < .05$).

Table 1. Fetal Arterial Data for Control (C) and Occlusion (O) Groups

		Control	5 Minutes	20 Minutes	30 Minutes Post	2 Hours Post	4 Hours Post	6 Hours Post	10 Hours Post
pH	C	7.388 ± 0.0	7.385 ± 0.0	7.380 ± 0.0	7.387 ± 0.0	7.389 ± 0.0	7.390 ± 0.0	7.380 ± 0.0	7.382 ± 0.0
	O	7.384 ± 0.0	$7.042 \pm 0.0\ddagger$	$6.818 \pm 0.0\ddagger$	$7.288 \pm 0.0\ddagger$	$7.335 \pm 0.0^*$	7.403 ± 0.0	$7.425 \pm 0.0^*$	7.395 ± 0.0
PaCO_2 (mm Hg)	C	48.1 ± 1.8	46.9 ± 1.4	48.6 ± 1.7	46.7 ± 1.4	47.6 ± 1.8	48.9 ± 2.3	48.8 ± 2.0	49.7 ± 1.6
	O	47.0 ± 1.3	$95.8 \pm 4.2\ddagger$	$141.2 \pm 6.1\ddagger$	44.63 ± 1.3	45.42 ± 0.8	46.1 ± 0.4	$43.3 \pm 1.0^*$	48.3 ± 1.0
PaO_2 (mm Hg)	C	23.5 ± 1.8	23.7 ± 0.8	23.6 ± 0.8	23.1 ± 0.9	23.2 ± 0.1	23.1 ± 1.0	23.4 ± 0.7	23.3 ± 0.9
	O	24.9 ± 1.0	$6.0 \pm 0.4\ddagger$	$8.8 \pm 1.0\ddagger$	$27.2 \pm 0.8\ddagger$	$27.2 \pm 1.2^*$	25.3 ± 1.1	26.0 ± 1.2	27.0 ± 0.8
Glucose (mmol/L)	C	1.02 ± 0.1	1.02 ± 0.2	1.02 ± 0.1	1.0 ± 0.1	1.08 ± 0.1	1.03 ± 0.0	1.07 ± 0.1	1.19 ± 0.2
	O	1.03 ± 0.1	$0.36 \pm 0.1\ddagger$	$0.61 \pm 0.1\ddagger$	$1.44 \pm 0.2^*$	1.21 ± 0.1	1.30 ± 0.1	1.32 ± 0.1	1.52 ± 0.2
Lactate (mmol/L)	C	0.81 ± 0.1	0.7 ± 0.1	0.83 ± 0.1	0.79 ± 0.0	0.86 ± 0.1	0.84 ± 0.1	0.86 ± 0.1	1.14 ± 0.2
	O	0.68 ± 0.1	$3.95 \pm 0.3\ddagger$	$6.32 \pm 0.2\ddagger$	$4.43 \pm 0.4\ddagger$	$3.90 \pm 0.7\ddagger$	$2.63 \pm 0.5^*$	1.7 ± 0.4	2.02 ± 0.4

NOTE. Data are mean $\pm$ SEM.

* $P < .05$.

† $P < .01$.

‡ $P < .005$.

§ $P < .001$ (between group comparisons, data compared by ANCOVA).

Fig 1. The effect of 25 minutes of asphyxia induced by complete umbilical cord occlusion on fetal MAP, FHR, SMABF, and SMAVR. Data from the asphyxia group only shown. The shaded region denotes the period of asphyxia. Values are 1-minute averages, mean $\pm$ SEM. (*) $P < .05$, (***) $P < .005$, (****) $P < .001$ asphyxia group versus control group (ANCOVA; $n = 6$ in each group). The horizontal bars show the time periods over which data had the same significance.

Changes Observed During Asphyxia

Fetal MAP, FHR, SMABF, and SMAVR responses during occlusion are shown in Fig 1 (control group data not shown because there were no significant changes after sham occlusion). Umbilical cord occlusion led to a pattern of bradycardia with initial hypertension, followed by profound hypotension. MAP fell to 8.7 ± 0.7 mm Hg by 25 minutes of occlusion (v 36 ± 1.2 mm Hg in the control group; $P < .001$), and FHR fell to 54 ± 3.1 beats per minute (bpm; v 195.3 ± 3.4 bpm in the control group; $P < .001$). SMABF exhibited a triphasic pattern. Blood flow initially fell to 0.8 ± 0.1 mL min^{-1} by 3 minutes of occlusion compared with 14.7 ± 3.4 mL min^{-1} in the

control group ($P < .005$). SMABF then rose, transiently returning to levels not significantly different from the control group between 8 and 16 minutes, before falling again in parallel with the fall in MAP. By 25 minutes, SMABF was 3.4 ± 0.9 mL min^{-1} versus 13.1 ± 2.7 mL min^{-1} in the control group ($P < .05$). SMAVR increased between 1 and 5 minutes peaking at 4 minutes ($P < .05$). SMAVR then returned to control values during the rest of the occlusion period. Both EEG and nuchal EMG activity were rapidly and profoundly depressed during the entire period of occlusion ($P < .001$ for each variable; data not shown).

Changes Observed During the 3 Days After Asphyxia

Figure 2 shows the changes in SMABF after sham asphyxia in the control group and asphyxia in the occlusion group. Postocclusion, SMABF transiently returned to control group values within 3 minutes. Between

Fig 2. This figure shows the time sequence of the changes in superior mesenteric artery blood flow (SMABF) in the control group (top panel) and occlusion group (bottom panel) before (4 hours) and for 10 hours after either occlusion or sham occlusion. Data are 1-minute averages, mean $\pm$ SEM. The arrow denotes when occlusion occurred. The postocclusion data start with the last minute of occlusion. (*) $P < .05$ occlusion group versus control group by ANCOVA. For clarity the significant data points are denoted as $P < .05$. The horizontal bars show the time periods over which data had the same significance.

35 and 105 minutes there was a spontaneous secondary fall in SMABF in all fetuses ($P < .05$). The nadir of the fall occurred at 74 minutes postocclusion ($4.9 \pm 1.0 \text{ mL min}^{-1}$ v $15.5 \pm 3.2 \text{ mL min}^{-1}$ in the control group, $P < .05$). This period of hypoperfusion was interrupted by a transient rise back to control values, peaking at 206 minutes postocclusion at $14.2 \pm 3.1 \text{ mL min}^{-1}$ (v $13.7 \pm 2.8 \text{ mL min}^{-1}$ in the control group). This was followed by a further fall in SMABF in all fetuses. In this second phase of delayed hypoperfusion, SMABF was significantly lower than control between 5 hours 40 minutes and 7 hours 20 minutes. The nadir in flow at 6 hours 20 minutes was $7.6 \pm 1.3 \text{ mL min}^{-1}$ (v $14.7 \pm 3.2 \text{ mL min}^{-1}$ in the control group, $P < .05$). Thereafter, SMABF returned to control group values until the end of recordings at 72 hours. Postocclusion there was a significant increase in SMAVR between 41 minutes and 2 hours, peaking at 66 minutes ($P < .01$) and again between 5 hours and 40 minutes and 6 hours and 50 minutes

($P < .05$; data not shown). Thereafter, SMAVR returned to control group values.

Figure 3 shows the postocclusion changes in nuchal EMG activity, MAP, and FHR in the occlusion group and control group. MAP returned to control group values by 3 minutes and was significantly elevated between 35 minutes and 2 hours, peaking at 54 minutes ($42.2 \pm 2.2 \text{ mm Hg}$ v $36.7 \pm 1.7 \text{ mm Hg}$ in the control group, $P < .05$). Thereafter, MAP was not significantly different from the control group. There was a rebound tachycardia between 8 and 14 minutes with FHR peaking at 9 minutes ($231.7 \pm 12.7 \text{ bpm}$ v $190.0 \pm 5.5 \text{ bpm}$; $P < .05$). FHR also was significantly elevated between 2 hours 30 minutes and 3 hours with FHR peaking at $229.8 \pm 14.4 \text{ bpm}$ (v $190.7 \pm 5.2 \text{ bpm}$ in the control group; $P < .05$). Thereafter, FHR was not significantly different from the control group.

EEG activity remained significantly depressed until a mean of 7 hours 45 minutes ($P < .005$; data not shown),

Fig 3. This figure shows time sequence of the changes in nuchal EMG activity, MAP and FHR in the occlusion group (A) and control group (B) before (4 hours) and for 10 hours after either occlusion or sham occlusion. Data are 1-minute averages, mean $\pm$ SEM. The arrow denotes when occlusion occurred. The postocclusion data start with the last minute of occlusion. (*) $P < .05$ occlusion group versus control group by ANCOVA. For clarity the significant data points are denoted as $P < .05$. The horizontal bars show the time periods over which data had the same significance.

corresponding with the onset of epileptiform activity in 4 of the 6 occlusion group fetuses. These epileptiform events were correlated with episodic nuchal EMG activity, and resolved at a mean of 21 hours 30 minutes. EEG activity subsequently remained significantly depressed for the remainder of the study ($P < .01$). No seizures were observed in the control group. Nuchal EMG activity remained depressed until 40 minutes after occlusion ($P < .05$). Nuchal EMG activity was transiently depressed again between a mean of 6 hours 35 minutes and 7 hours 50 minutes ($P < .05$). Nuchal activity then returned to control group values.

Histology

Histological evaluation by light microscopy of the H&E-stained sections did not show intestinal damage in the asphyxiated or control animals after 3 days of recovery.

DISCUSSION

Results of both animal and clinical studies suggest that the pathogenesis of necrotising enterocolitis (NEC) involves, in part, exposure of the gastrointestinal tract to hypoperfusion during an hypoxic or asphyxial insult.¹²⁻¹⁵ Such an asphyxial insult may occur either during labour or, perhaps more likely, before labour during fetal life. In addition, periods of hypotension or bradycardia during the early postnatal care of premature newborns also may have potential to cause gastrointestinal hypoperfusion. The current study has described the changes in gastrointestinal blood flow during and after severe asphyxia in utero in the premature fetus. We report for the first time that the premature fetal gut is involved in the acute redistribution of blood flow during asphyxia, and that subsequent to reperfusion, there is a secondary prolonged phase of perturbation of gastrointestinal blood flow. We speculate that this represents a phase of endothelial dysfunction and vulnerability.

Twenty-five minutes of umbilical cord occlusion did not result in gastrointestinal injury on standard histological assessment after 3 days of recovery. This finding is complementary with observations made in the developing chicken embryo subjected to repetitive episodes of asphyxia.¹⁶ These data and those of the current study are consistent with the hypothesis that such an insult may represent an early predisposing factor in the chain of events leading to NEC.

We previously have shown that the premature fetus at 0.6 gestation is able to mount an acute cardiovascular defense to asphyxia similar to that observed at full term.^{8,17,18} The responses include redistribution of CVO, hypertension, and bradycardia.¹⁸⁻²⁰ The current data confirm this finding. The key maturational difference compared with the full-term fetus is that the premature fetus is

able to survive a much longer duration of asphyxia. This capacity of the preterm fetus to survive long periods of reduced oxygen supply is caused by such factors as greater glycogen stores, greater anaerobic capacity in many tissues, and lower basal metabolic activity.^{21,22} Paradoxically, this capacity to survive allows the fetus to be exposed to extended periods of profound hypotension and hypoperfusion.

In the current study, the 0.7 gestation fetus was able to survive 25 minutes of asphyxia. During asphyxia the fetal cardiovascular response was characterised by 3 phases: initial redistribution of blood flow away from the gut to maintain vital organ function, subsequent failure of this redistribution, and finally near-terminal cardiovascular collapse. The initial fall in SMA blood flow to almost zero was mediated by a significant increase in vascular resistance at a time when blood pressure was rising and is likely to be regulated by the same neural mechanisms that mediate redistribution of CVO in the full-term fetus.²³ This redistribution of blood flow away from the gut was, however, only sustained for a few minutes. During most of the insult gastrointestinal blood flow was essentially pressure-passive, paralleling changes in arterial blood pressure, with low levels of SMA vascular resistance. The mechanisms mediating this failure of redistribution of blood flow are unknown, but we observed a similar pattern in femoral blood flow in the 0.6 gestation fetus.⁸ We speculate that the intense initial peripheral vasoconstriction may have resulted in exacerbated local tissue hypoxia and acidosis, which, in turn, led to rebound vasodilatation at this time. The fall in blood pressure was steepest during this phase, and it is likely that the failure of the redistribution of blood flow hastened the onset of hypotension. Thus, one consequence of the failure of SMA vasoconstriction was greater perfusion of the gut during asphyxia, at the expense of central organs. The final phase marked the onset of circulatory collapse as demonstrated by sustained, profound hypotension with a corresponding progressive significant fall in SMA blood flow.

After the end of occlusion, blood pressure, heart rate, and SMA blood flow all rapidly recovered, and there was a brief period of hypertension and tachycardia. This is consistent with other fetal, neonatal, and adult data on immediate haemodynamic changes after asphyxia.^{8,9,17,18,24-26} There was, however, no rebound hyperperfusion of the gut, although SMA blood flow initially did return to control values. An overall increase in vascular resistance appeared to inhibit rebound hyperperfusion. After initial reperfusion, within 20 minutes there was a secondary fall in SMA blood flow. This hypoperfusion was not related to hypotension because blood pressure was still significantly elevated. Rather, the fall in SMA blood flow was associated with a significant rise in

vascular resistance suggesting an actively mediated process.

It has been suggested that the perturbation of ischemia-reperfusion may lead to dysfunction of organ vasculature caused by either a reduced capacity to produce vasodilators such as nitric oxide and a rise in vasoconstrictors such as endothelin or a reduced ability to respond to vasodilators (endothelial dysfunction).^{12,27,28} In the adult, local ischaemia-reperfusion typically is accompanied in the affected organs by significant changes in basal and reactive vascular function during the first 24 to 48 hours.²⁹ We also have observed changes in blood flow after asphyxia in the premature fetus at 0.6 gestation.⁸ The pattern in SMA blood flow in the 0.7 gestation fetus was, however, very different to that observed in femoral blood flow at 0.6 gestation because femoral blood flow took much longer to fall postasphyxia (the nadir occurring at 8 hours). This may be related to maturational changes in the mechanisms controlling blood flow at 0.6 versus 0.7 gestation or, more likely, that asphyxia has a profound and differential effect on the mechanisms controlling SMA blood flow.

The immature intestine has been suggested to be more vulnerable to endothelial dysfunction. Nowicki³⁰ showed that mesenteric artery endothelial production of nitric oxide (NO) after ischaemia was reduced in the 3-day-old piglet, whereas production was increased in the 35-day-old pig. These data are supported by the recent observation that NO synthase inhibition causes a significantly greater fall in SMA blood flow in the premature fetus compared with later in development.³¹ From this study it

was suggested that NO plays a greater role in the regulation of fetal gastrointestinal blood flow in the premature fetus than later in gestation.

The pattern of SMA blood flow we observed during the first 9 hours postocclusion is unique and highly consistent. The fall in SMA blood flow was reversed transiently between 2 and 5 hours suggesting that the endothelial dysfunction can be overridden. This rise in SMA blood flow between the periods of postasphyxial hypoperfusion was not related to a rise in blood pressure, but was associated with a significant fall in SMA vascular resistance. It is of interest that this increase in SMA blood flow was associated with a delayed period of sustained tonic nuchal EMG activity. When this muscle activity subsided, SMA blood flow once again fell. The etiology of this increased nuchal EMG activity is not known, but it was not associated with EEG changes; the EEG remained depressed at this time. It also was not associated with an evident increase in general metabolic activity as determined from blood gases, glucose and lactate values, although local gastrointestinal metabolism may have increased. It was associated with a rise in FHR and thus an increase in CVO.³² Whether the neural mechanisms mediating this increased nuchal muscle activity are also related to the control of heart rate and gastrointestinal blood flow or whether SMA blood flow increases as a function of almost constant fetal body movements cannot be determined from the current study. The return of SMA blood flow to control values at 9 hours was associated with the onset of episodic nuchal EMG activity and EEG epileptiform activity.

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