

Intrauterine Growth Restriction Ameliorates the Effects of Gradual Hemorrhagic Hypotension on Regional Cerebral Blood Flow and Brain Oxygen Uptake in Newborn Piglets

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ABSTRACT

Data are scant regarding the development of cerebrovascular autoregulation in intrauterine growth-restricted (IUGR) newborns. We tested the hypothesis that IUGR improves the ability of neonates to withstand critical periods of gradual hemorrhagic hypotension by optimizing cerebrovascular autoregulation. Studies were conducted on 1-d-old anesthetized piglets divided into groups of normal weight (NW, $n = 14$, body weight = 1518 ± 122 g) and IUGR ($n = 14$, body weight = 829 ± 50 g) animals. Physiologic parameters, including regional cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO₂), were similar in NW and IUGR piglets under baseline conditions. Controlled arterial blood loss [hemorrhagic hypotension (HH)] induced a stepwise reduction of the mean arterial blood pressure of 49 ± 3 mm Hg (mild HH), 39 ± 3 mm Hg (moderate HH), and 30 ± 3 mm Hg (severe HH) in seven NW and seven IUGR piglets ($p < 0.05$). In NW piglets, cortical CBF and CMRO₂ was reduced already at moderate HH ($p < 0.05$). A similar CMRO₂ reduction occurred during severe HH in NW and IUGR piglets ($p < 0.05$). In addition, during mild and moderate HH, primarily in IUGR piglets, an increase in regional

CBF of brainstem, cerebellum, and thalamus was shown compared with baseline values ($p < 0.05$). Furthermore, under these conditions, cerebral cortex blood flow was maintained in newborn IUGR animals. In contrast, NW piglets exhibited a significant reduction in CBF ($p < 0.05$) during moderate HH. Thus, IUGR resulted in an improved ability to withstand critical periods of gradual oxygen deficit as shown by improved cerebrovascular autoregulation during hemorrhagic hypotension. (*Pediatr Res* 56: 639–646, 2004)

Abbreviations

ABP, arterial blood pressure
CBF, cerebral blood flow
CMRO₂, cerebral metabolic rate of oxygen
HH, hemorrhagic hypotension
IUGR, intrauterine growth restriction
MABP, mean arterial blood pressure
NW, normal-weight
PID-controller, proportional differential integral controller

Asymmetric IUGR (type II) is still an unresolved problem in perinatal medicine. Perinatal mortality is markedly increased (1–3), as well as the incidence of perinatal asphyxia, because placental insufficiency is the main cause of IUGR (4).

The perinatal morbidity and mortality of neonates after IUGR is mainly caused by postasphyxial encephalopathy (4). The most dangerous complication is brain injury secondary to hypoxic-ischemic disease, which is the predominant form of all brain injuries encountered in the perinatal period (5). Periods of arterial hypotension are frequently involved in the initial

period of acute perinatal asphyxia (6). Cerebrovascular autoregulation protects against brain hypoperfusion, provided arterial pressure does not fall below the lower limit of the autoregulatory range. The efficiency of autoregulation to prevent hypoperfusion generally improves with increasing fetal age and maturity of the brain (7–9). This implies that the immature brain is susceptible to ischemia during hypotension (10). Therefore, poor autoregulation may place the immature brain at risk for injury (11,12).

The slow down of fetal growth late in gestation after intrauterine malnutrition, although resulting in IUGR, can be regarded as a compensatory process, which enables the fetus to survive (13,14). Growth reduction is primarily achieved by altering the endocrine milieu, possibly by reducing the endocrine and paracrine IGF-I activity (15) in response to impaired transplacental nutrient transfer (16). Reduced substrate consumption enables—at least at times—the prevention of a life-

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threatening imbalance between nutritional supply and demand. Therefore, the period of adequate compensation, characterized by reduced growth due to restricted nutrient availability, but widely compensated placental respiratory function (17), reflects a functional state in which contradictory effects of acceleration or delay in organ maturation including brain functional development may occur (18–22). Moreover, it should be considered that further disturbances in hormonal homeostasis during fetal life are apparently involved in permanent alterations of organ structure or function. Among others, an excess of glucocorticoids during fetal life may be associated postnatally with an altered programming of the hypothalamo-pituitary-adrenal axis (23), disturbed brain dopamine metabolism (21,24), and altered cerebrovascular function (25).

Furthermore, an improved capacity of newborn IUGR piglets to withstand severely disturbed renal oxygenation has been reported (26). Until now, the effects of IUGR on the cerebral autoregulatory response and cerebral oxygen uptake during gradual reduction of the cerebral perfusion pressure have not been determined. Therefore, we estimated regional CBF and CMRO₂ during gradual HH in newborn normal-weight and IUGR piglets. We used a morphometrically well-characterized state of IUGR in newborn piglets (27) and included animals with optimal vital conditions early after birth. We speculate that IUGR may improve the ability of the neonate to withstand critical periods of brain oxygen availability by gradual HH.

METHODS

All surgical and experimental procedures were approved by the committee of the Thuringian State Government on Animal Research. Animals were obtained from a breeding farm. Delivery was observed and the viability of neonatal piglets assessed immediately after birth so that only animals with a viability score ≥ 7 (28) were included in the study. Immediately before the onset of the experiments, animals were carried to the laboratory in a climate-controlled transport incubator (environmental temperature, 33–34°C; time for transportation, 30–60 min). Animals were divided into NW piglets ($n = 14$; age, 11–26 h; body weight, 1518 \pm 122 g) and IUGR piglets ($n = 14$; age, 13–28 h; body weight, 829 \pm 50 g) according to their birth weight. The birth weight distribution of the breed of piglets used here (German Landrace) has been described previously (27).

Anesthesia and surgical preparation. The piglets were initially anesthetized with 1.5% isoflurane in 70% nitrous oxide and 30% oxygen by mask. The anesthesia was maintained throughout the surgical procedure with 0.8% isoflurane. Cutaneous incisions were made after s.c. instillation of a local anesthetic (Xylocitin 2%, Jenapharm, Jena, Germany). A central venous catheter was introduced through the left external jugular vein and was used for the administration of drugs and for volume substitution [heparinized isotonic saline solution (1 IU heparin/mL): 5 mL/h]. An endotracheal tube was inserted through a tracheotomy. After immobilization with i.v. pancuronium bromide (0.2 mg/kg body weight/h), the piglets were artificially ventilated (Servo Ventilator 900C, Siemens-Elema, Sweden). The artificial ventilation was adjusted to maintain normoxic and normocapnic blood gas values. Polyurethane

catheters (inner diameter, 0.5 mm) were advanced through both umbilical arteries into the abdominal aorta to record the arterial blood pressure and to withdraw reference samples for the colored microsphere technique. Another polyurethane catheter (inner diameter, 0.3 mm) was inserted into the superior sagittal sinus through a midline burr hole (3 mm in diameter and located 4 mm caudal to the bregma) and advanced to the confluence sinuum to obtain brain venous blood samples. The left ventricle was cannulated retrogradely *via* the right common carotid artery with a polyurethane catheter (inner diameter, 0.5 mm). The arterial, left ventricular, and the central venous catheters were connected with pressure transducers (P23Db, Statham Instruments Inc., Hato Rey, Puerto Rico). Correct positioning of the catheter tips was checked by continuous pressure trace recordings and by autopsy at the end of the experiment. Body temperature was monitored by a rectal temperature probe, and was maintained throughout the general instrumentation at 38 \pm 0.3°C using a warmed pad and a feedback-controlled heating lamp. Physiologic parameters were recorded on a multichannel polygraph (MT95K2, Astro-Med, W. Warwick, RI). The arterial blood pressure was monitored continuously, and arterial blood samples were withdrawn and analyzed at regular intervals to monitor blood gases and whole blood acid-base parameters.

Experimental protocol. After the surgical preparation had been completed, the anesthesia was reduced to 0.25% isoflurane in 70% nitrous oxide and 30% oxygen and the piglets were allowed to stabilize for 1 h. After control values were obtained, randomly chosen NW piglets (group 3, $n = 7$) and IUGR piglets (group 4, $n = 7$) were connected with the external ABP controller to adjust MABP sequentially at three different levels (starting with MABP-50: ~ 50 mm Hg, followed by MABP-40: ~ 40 mm Hg, and MABP-30: ~ 30 mm Hg) in each animal. Each level of gradually reduced MABP was maintained for about 30 min. A complete series of values was recorded at the 25th min of every steady state period. Blood volume replacement was given after each blood withdrawal using stored heparinized blood obtained from a sibling donor piglet. The remaining NW piglets (group 1, $n = 7$) and IUGR piglets (group 2, $n = 7$) were submitted to all experimental procedures except the induced ABP changes and served as untreated control animals.

Gradual ABP reduction controlled by an external PID-controller. A detailed description of the procedure of mean arterial blood pressure adjustment at externally given set-points using an external blood pressure control loop has been given elsewhere (29,30). In brief, ABP (controlled quantity) was controlled by a PID-controller running on a personal computer, by altering the blood volume by arterial blood infusion or withdrawal, respectively. An infusion/withdrawal pump was the controlling element. Because there are several nonlinear and non-stationary properties in the controlled physiologic system, the parameters of the external technical controller were searched by trial and error. Stable control of ABP was obtained by means of the integrating property of the controller in particular. The integration time constant of $K_I = 6.94 \text{ mm Hg} \cdot \text{min}^{-1}$ was found to be appropriate during all states investigated.

Measurements. The regional CBF was measured by means of the reference sample color-labeled microsphere (Dye-Trak, Triton Technology, San Diego, CA) technique, which represents a valid alternative to the radionuclide-labeled microsphere method for organ blood flow measurement in newborn piglets without the disadvantages arising from radioactive labeling (31). Application of this technique in piglets and methodological considerations have been presented and discussed in detail elsewhere (31,32). Briefly, in random color sequence, a known amount of colored polystyrene microspheres was injected into the left ventricle. A blood sample was withdrawn from the thoracic aorta as the reference sample. At the end of each experiment, the piglet brains were obtained. To retrieve the microspheres, each tissue sample was digested and then filtered under vacuum suction through an 8- μ m-pore polyester-membrane filter. Colored microspheres were quantified by their dye content. The dye was recovered from the microspheres by adding dimethylformamide. The photometric absorption of each dye solution was measured by a diode-array UV/visible spectrophotometer (Model 7500, Beckman-Coulter, Inc., Fullerton, CA). Calculations were performed using MISS software (Triton Technology, San Diego, CA). The number of microspheres was calculated using the specific absorbance value of the different dyes. All reference and tissue samples contained >400 microspheres.

The heart rate, ABP, arterial and brain venous pH, P_{CO_2} , P_{O_2} , oxygen saturation, and Hb values were measured immediately before the microsphere injection. Blood pH, P_{CO_2} , and P_{O_2} were measured with a blood gas analyzer (model ABL50, Radiometer, Copenhagen, Denmark), and blood Hb and oxygen saturation were measured using a hemoximeter (model OSM2, Radiometer) and corrected to the body temperature of the animal at the time of sampling.

The absolute flows to the tissues measured by the colored microspheres were calculated by the formula: $\text{flow}_{\text{tissue}} = \text{number of microspheres}_{\text{tissue}} \cdot (\text{flow}_{\text{reference}} / \text{number of microspheres}_{\text{reference}})$. Flows were expressed in milliliters per minute per 100 g tissue by normalizing for tissue weight. Blood O_2 content (cO_2) was calculated using the following equation:

$$cO_2 [\text{mL} \cdot \text{dL}^{-1}] = \\ cHb [\text{g} \cdot \text{dL}^{-1}] \times sO_2 [\text{mmol} \cdot \text{mmol}^{-1}] \\ \times 1.39 [\text{mL} \cdot \text{g}^{-1}] + (P_{O_2} [\text{mmHg}] \\ \times \alpha O_2 [\text{mL} \cdot \text{dL}^{-1} \cdot \text{mmHg}^{-1}])$$

to obtain the sum of oxygen that is physically dissolved and chemically bound to Hb [cHb: Hb concentration; sO_2 : O_2

saturation; $1.39 (\text{mL} \cdot \text{g}^{-1})$: theoretical oxygen capacity of Hb; αO_2 : solubility of O_2 in blood = $cHb \times 0.000054$ (Hb-dependent O_2 solubility) + 0.0029 (solubility of O_2 in plasma)]. Because the sagittal sinus drains the cerebral cortex, the cerebral white matter, and some deep gray structures (basal ganglia, thalamus, and hippocampus) (33), the blood flow measured to the forebrain included these structures. The $CMRO_2$ was obtained by multiplying the blood flow to the forebrain by the cerebral arteriovenous O_2 content difference. Cerebral oxygen extraction was calculated as the ratio between cerebral arteriovenous O_2 content difference and arterial O_2 content.

Statistical analysis. Data are reported as means \pm SD. Initial comparison was done for all parameters studied using two-way ANOVA with one factor, "treatment," which considered possible effects of gradual ABP reduction. The second factor, "stages," considered repeated measures along the experimental approach. Because in a majority of cases an interaction between the two factors was shown, we reduced the following statistical analysis on separate evaluations of the parameters without considering their correlations. Consequently, comparisons between groups were made with one-way ANOVA. Posthoc comparisons were made with Tukey's test for all pairwise multiple comparisons. Comparisons of measurements between baseline and different stages of gradual ABP decrease within the groups and CBF values of different brain regions were made with one-way ANOVA, with repeated measures. A Bonferroni adjustment was performed to evaluate significant differences. Differences were considered significant when $p < 0.05$.

RESULTS

Table 1 summarizes some morphometric parameters of the experimental groups. Naturally occurring growth restriction in swine is asymmetrical, with an increase in the mean ratio of brain weight to liver weight from 0.90–0.97 to 1.60–1.73 ($p < 0.01$). The reduction in brain weight was quite small (90% of NW group). In contrast, the decrease in liver weight (47–55% of NW group) was similar to that in body weight (54–55% of NW group). All differences in organ weight were significant ($p < 0.01$).

During baseline conditions, ABP, heart rate, acid-base balance, blood gas, and metabolic values were within the physiologic range and consistent with other data obtained from anesthetized and artificially ventilated newborn piglets (34,35). Arterial glucose content was mildly but significantly lower in IUGR piglets ($p < 0.05$). Other physiologic values such as $CMRO_2$ and regional CBF were also similar in NW and IUGR piglets (Table 2, Figs. 1 and 2).

Table 1. Organ weights of newborn piglets following normal growth [groups 1 (untreated, $n = 7$) and 3 (gradual HH-treated, $n = 7$)] or IUGR [groups 2 (untreated, $n = 7$) and 4 (gradual HH-treated, $n = 7$)]

	Body weight (g)	Brain weight (g)	Liver weight (g)	Brain liver ratio	Brain body weight ratio
Group 1	1467 \pm 85	33.0 \pm 0.4	37.3 \pm 6.0	0.90 \pm 0.12	0.023 \pm 0.001
Group 2	804 \pm 46*	29.5 \pm 0.2*	17.5 \pm 3.0*	1.73 \pm 0.30*	0.037 \pm 0.002*
Group 3	1568 \pm 138	33.5 \pm 0.7	35.2 \pm 5.3	0.97 \pm 0.14	0.021 \pm 0.001
Group 4	854 \pm 42*	29.8 \pm 0.2*	19.4 \pm 4.3*	1.60 \pm 0.35*	0.035 \pm 0.001*

Values are means \pm SD.

* $p < 0.01$, comparison between normal weight newborn piglets and IUGR ones.

Table 2. Effect of hemorrhagic hypotension on arterial blood gases, acid-base balance, and metabolic parameters in normal weight (NW, group 1, untreated; group 3, gradual HH-treated) and IUGR (group 2, untreated; group 4, gradual HH-treated) piglets

	Baseline	MABP-50	MABP-40	MABP-30
Heart rate (min ⁻¹)				
Group 1	170 ± 23	175 ± 31	191 ± 36	208 ± 13
Group 2	164 ± 16	185 ± 36	195 ± 28	211 ± 19
Group 3	202 ± 33	242 ± 31*	273 ± 14*	259 ± 14*
Group 4	202 ± 32	263 ± 25*	245 ± 27*	238 ± 12*
Arterial Pco ₂ (mm Hg)				
Group 1	40 ± 2	41 ± 2	40 ± 2	40 ± 1
Group 2	40 ± 1	40 ± 2	40 ± 3	39 ± 3
Group 3	41 ± 4	43 ± 5	42 ± 8	44 ± 8
Group 4	40 ± 2	43 ± 8	42 ± 6	38 ± 8
Arterial pH				
Group 1	7.46 ± 0.02	7.46 ± 0.03	7.45 ± 0.02	7.44 ± 0.02
Group 2	7.48 ± 0.03	7.47 ± 0.03	7.45 ± 0.06	7.46 ± 0.05
Group 3	7.45 ± 0.05	7.34 ± 0.09*	7.20 ± 0.17*	7.22 ± 0.10*
Group 4	7.48 ± 0.03	7.33 ± 0.10*	7.30 ± 0.08*	7.25 ± 0.05*
Arterial Po ₂ (mm Hg)				
Group 1	93 ± 10	92 ± 11	94 ± 11	90 ± 20
Group 2	107 ± 21	111 ± 16	114 ± 24	111 ± 25
Group 3	90 ± 15	93 ± 19	83 ± 16	90 ± 13
Group 4	114 ± 33	116 ± 34	97 ± 21	96 ± 24
Arterial O ₂ content (mL · dL ⁻¹)				
Group 1	6.0 ± 1.0	5.9 ± 1.1	6.0 ± 1.1	5.8 ± 0.9
Group 2	6.0 ± 1.5	5.6 ± 0.9	5.4 ± 0.7	5.0 ± 0.5
Group 3	5.9 ± 0.9	3.9 ± 0.5*	3.1 ± 0.4*	2.5 ± 0.4*
Group 4	5.9 ± 1.5	4.1 ± 0.7*	3.1 ± 1.3*	3.0 ± 1.1*
Arterial hemoglobin content (mMol · L ⁻¹)				
Group 1	6.2 ± 0.9	6.1 ± 1.1	6.2 ± 1.1	6.1 ± 0.9
Group 2	6.2 ± 1.5	5.8 ± 0.8	5.5 ± 0.6	5.1 ± 0.5
Group 3	6.2 ± 0.9	4.3 ± 0.6*	3.4 ± 0.5*	2.9 ± 0.5*
Group 4	5.9 ± 1.5	4.1 ± 1.7*	3.3 ± 1.2*	3.2 ± 1.4*
Arterial glucose content (mMol · L ⁻¹)				
Group 1	5.7 ± 1.2	5.7 ± 1.4	5.2 ± 1.0	5.3 ± 1.6
Group 2	3.6 ± 0.8§	3.8 ± 0.8§	3.6 ± 0.8	3.7 ± 0.5
Group 3	5.9 ± 1.4	8.0 ± 3.9	7.1 ± 4.4	5.2 ± 3.1
Group 4	3.6 ± 1.5§	3.6 ± 1.5§	2.8 ± 1.6§	1.9 ± 1.1§
Arterial lactate content (mMol · L ⁻¹)				
Group 1	2.0 ± 0.4	2.2 ± 0.5	2.4 ± 0.6	3.2 ± 1.2
Group 2	2.0 ± 0.4	2.2 ± 0.4	2.4 ± 0.6	3.2 ± 1.2
Group 3	2.7 ± 0.9	8.7 ± 3.4*	12.5 ± 3.4*	14.6 ± 2.9*
Group 4	2.6 ± 1.0	6.8 ± 2.3*	11.1 ± 2.8*	14.4 ± 3.4*

Values are presented as means ± SD.

* Significant differences between untreated control (groups 1, *n* = 7) and treated (group 3, *n* = 7) NW or untreated control (group 2, *n* = 7) and treated (group 4, *n* = 7) IUGR piglets at baseline or different levels of hemorrhagic hypotension (MABP-50: ~50 mm Hg; MABP-40: ~40 mm Hg; MABP-30: ~30 mm Hg; *p* < 0.05).

§ Significant differences between NW and IUGR groups of same treatment; *p* < 0.05.

Controlled arterial blood loss induced a stepwise MABP reduction to 75 ± 10% (MABP-50), 58 ± 8% (MABP-40), and 45 ± 8% (MABP-30) of baseline in NW and IUGR piglets (Fig. 1, *p* < 0.05). This gradual HH induced a marked tachycardia, gradual reduction in arterial Hb content, and a resulting decrease in arterial O₂ content. Furthermore, an increasing metabolic acidosis appeared, which was shown by reduced arterial pH and increased arterial lactate content, whereas arterial Pco₂ remained unaltered (Table 2, *p* < 0.05).

In NW piglets, CMRO₂ was reduced already at moderate HH (Fig. 1, *p* < 0.05). A similar CMRO₂ reduction occurred during severe MABP reduction in NW and IUGR piglets (Fig. 1, *p* < 0.05). Cerebral O₂ extraction was increased throughout the whole period of HH in both treated groups (Fig. 1, *p* < 0.05).

During mild and moderate HH, primarily in IUGR piglets, an increase in regional CBF of brainstem and thalamus was shown (Fig. 2, *p* < 0.05). Furthermore, under these conditions cerebral cortex blood flow was maintained in newborn IUGR animals. In contrast, already under moderate HH (MABP-40), NW piglets exhibited a significant reduction in CBF (*p* < 0.05). A gradual blood pressure reduction to ~45% of baseline (MABP-30) induced similar CBF reduction in NW and IUGR piglets (*p* < 0.05).

DISCUSSION

The main new finding in this study is that IUGR induces an increased ability to prevent a decrease in regional cerebral blood flow and oxygen uptake in newborns during progressive reduction

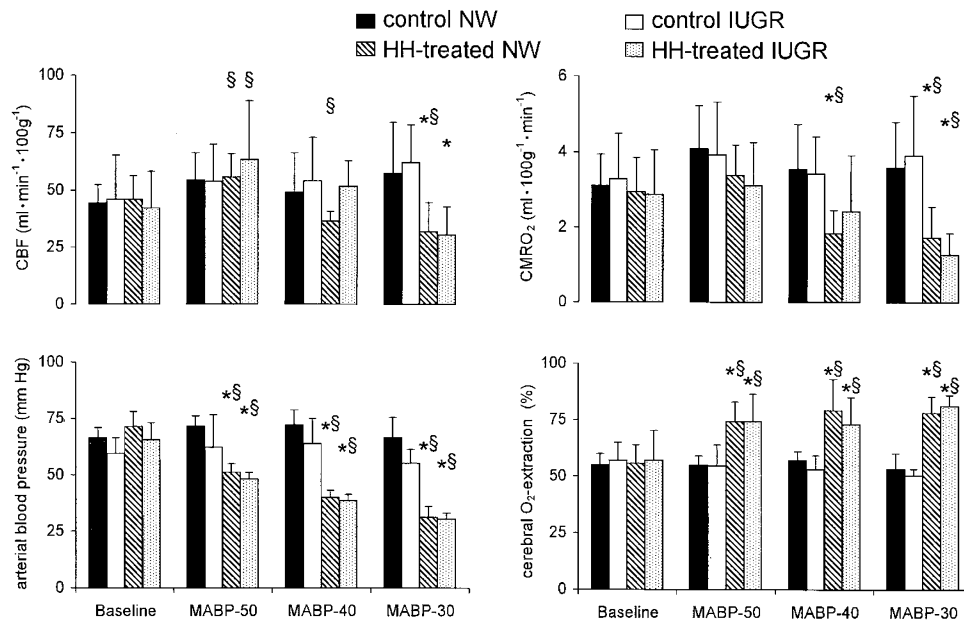


Figure 1. Effect of gradual hemorrhagic hypotension on arterial blood pressure, global CBF, CMRO₂, and cerebral O₂ extraction in NW (*n* = 7, hatched columns) and IUGR piglets (*n* = 7, dotted columns) compared with untreated NW (*n* = 7, filled columns) and untreated IUGR piglets (*n* = 7, blank columns). Values are presented as means + SD. *Comparison with untreated control animals, *p* < 0.05; §comparison within every group with baseline, *p* < 0.05.

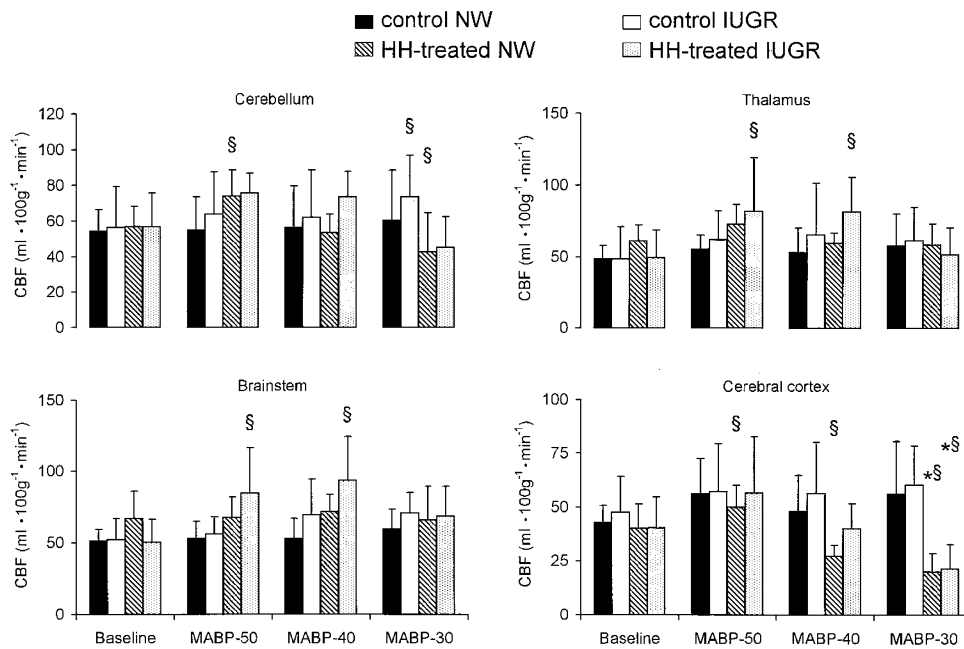


Figure 2. Effect of gradual hemorrhagic hypotension on regional CBF in NW (*n* = 7, hatched columns) and IUGR piglets (*n* = 7, dotted columns) compared with untreated NW (*n* = 7, filled columns) and untreated IUGR piglets (*n* = 7, blank columns). Values are presented as means + SD. *Comparison with untreated control animals, *p* < 0.05; §comparison within every group with baseline, *p* < 0.05.

of the cerebral perfusion pressure. Indeed, at moderate HH (~58% of baseline) global CBF and CMRO₂ were reduced in newborn NW piglets (*p* < 0.05), whereas IUGR animals exhibited no alterations under similar conditions. These differences, however, disappeared with increasing severity of HH.

These findings support our assumption that, in IUGR piglets, adequate regional perfusion is maintained over a broader range due to improved cerebral autoregulation. The newborn IUGR piglet is apparently able to maintain oxygen delivery to brain regions outside the cerebral cortex despite a reduction in

arterial oxygen content owing to progressive blood loss and gradual HH. Therefore, under conditions of progressive cerebral perfusion pressure reduction, an adequate vascular dilation occurred in newborn IUGR piglets, whereas this was obviously insufficient in NW newborn animals.

The underlying mechanisms were not addressed by these experiments. Methodological reasons for the differences between NW and IUGR animals are unlikely because the experimental conditions were similar. However, we cannot fully exclude a different sensitivity of the cerebral vasculature to the

pancuronium bromide used as myorelaxant. In a high dosage with ganglion blocking activity (*i.e.* 0.4 mg/kg), this drug enhances CBF autoregulation, whereas in a dose more selective for the neuromuscular junction (*i.e.* 0.1 mg/kg), it does not alter CBF autoregulation in the newborn piglet (36). We used a dosage of 0.2 mg/kg/h in NW and IUGR piglets. The reported lower limit of the forebrain CBF autoregulatory range in the NW piglets is in accordance with data given in previous reports (8,36–38). Therefore, we assume that the dosage used in the recent study did not alter CBF autoregulation in NW animals. However, we are unable to exclude the possibility that the cerebral vasculature of IUGR animals may be more susceptible to pancuronium bromide, even if no evidence exists previously. Action time of a single dose was similar in NW and IUGR piglets.

Mild sedation by volatile anesthetics and analgesia by nitrous oxide, as used here, appears to be adequate for the experimental approach of this study. Previous studies have shown that there is no detectable influence on the cardiovascular response in newborn piglets (39). Furthermore, CBF and cerebral O₂ uptake values presented in this study were similar to values obtained from newborn piglets that were treated with other drugs for general anesthesia that have been shown not to alter brain oxidative metabolism and were delivered to awake newborn piglets (40,41). CBF distribution throughout the immature brain demonstrates a gradient between the brainstem (highest perfusion values) and forebrain (lowest perfusion values), thereby confirming previous findings (42). In a previous study with extensive surgical interventions, including opening the abdominal cavity, craniotomy, and ureter cannulation after retroperitoneal preparation along with 5 h of experimental performance, sham-operated newborn piglets showed no significant differences in ABP with only a slight increase in heart rate (by 20%). This corresponded to a comparatively moderate increase in circulating catecholamines (epinephrine by 73%, norepinephrine by 66%) (26). This elevation in circulating catecholamines was markedly blunted compared with a rather mild hypoxic exposure. After 45 min of mild normocapnic hypoxia (arterial O₂ saturation = 71 ± 8%, arterial P_{O₂} = 39 ± 7 mm Hg), we found a marked increase in circulating catecholamines (epinephrine by 175%, norepinephrine by 125%) (43). Furthermore, during baseline conditions, data were within the physiologic range, consistent with other data obtained from anesthetized newborn piglets (34,43), and similar to data obtained from newborn nonanesthetized piglets (35).

Mild hypoglycemia apparently did not alter CBF in IUGR piglets (Fig. 1 and 2). This is in accordance with previous findings on the effects of hypoglycemia on CBF: Mild to moderate hypoglycemia induces no more than a modest CBF increase in immature brains (44–46). Furthermore, the enhanced cerebrovascular autoregulation during HH in the newborn IUGR animals appears not to be influenced by hypoglycemia. In adult dogs, it has been shown that moderate hypoglycemia induces no change in CBF at normal cerebral perfusion pressure, but does elevate the lower limit of autoregulation to a CPP of 40 mm Hg (47). Moreover, a reduced cerebrovascular reactivity in newborn piglets (48) and a positive correlation between mean arterial blood pressure and

cerebral cortical blood flow (45) suggests a loss of CBF autoregulation during hypoglycemia.

A mechanistic explanation for an enhanced cerebrovascular autoregulation in IUGR piglets during hemorrhagic hypotension cannot be derived from the present study. In addition, no other studies are known that deal with the mechanisms underlying the regulation of cerebrovascular tone in newborn IUGR individuals. Nevertheless, it is obvious that the regulatory capacity of the cerebral resistance vessels is modified, *i.e.* at a level of reduced perfusion pressure, where a pressure-passive alteration of blood flow appeared in NW piglets, a further relaxation of the vessel wall occurred in IUGR piglets to maintain CBF. Thus, IUGR is apparently associated with a delayed vasodilatory response at gradually reduced cerebral perfusion pressure, which could be provoked by a primarily increased vascular tone of the cerebral resistance vessels. Another possibility for a delayed vasodilatory response may result from attenuated generation of vasodilatory factors. On principal, such response patterns could be due to the chronic effects of enhanced glucocorticoid availability during fetal development of IUGR. Evidence is available that glucocorticoid activity is increased in IUGR fetuses because maternal glucocorticoids are cleared insufficiently by the placenta (see below). In a recent report it was shown that a 24-h pretreatment with glucocorticoid induces an increase in the cerebrovascular tone of newborn piglets (49). The underlying mechanisms appear complex and presumably involve a diminished release of endothelium-derived prostanoids (50) due to inhibition of cyclooxygenase-2 itself and/or induction of phospholipase A2 inhibitory proteins (51,52). Furthermore, it has been shown that glucocorticoids down-regulate the expression of calcium-dependent potassium channels in vascular smooth muscle (53) and may thereby interfere with the carbon monoxide-induced vasorelaxant response shown in newborn piglets (54).

There is evidence that an increased exposure to glucocorticoids occurs in IUGR fetuses due to disturbed placental clearance of maternal glucocorticoids. Because the concentration of circulating corticosteroid is several-fold higher in the sow than in the fetus (55), fetal protection against maternal corticosteroid intoxication is normally affected through conversion of physiologic glucocorticoids to inactive products by placental 11 β -hydroxysteroid dehydrogenase (56–58). This may be altered during IUGR pregnancies. Placental 11 β -hydroxysteroid dehydrogenase activity was markedly reduced in the late gestational period of maternal protein-malnutrition sufficient to cause IUGR in rats (59). Recently, a significant association was found in pigs between fetal or placental size and placental 11 β -HSD net dehydrogenase activity (60). In addition, IUGR rats exhibited elevated liver and brain activities of specific glucocorticoid-inducible marker enzymes (61), suggesting an increased glucocorticoid action in these organs.

The principal response of regional CBF regulation includes an early tendency to CBF increase and subsequently maintained blood flow in brainstem, cerebellum, and thalamus, but decreased CBF in brain cortex, under steady state conditions. Previous findings showed regional differences in the lower autoregulatory limit in newborn piglets with a most pronounced reduction in blood flow to the cerebrum, less to the cerebellum,

and least to the brainstem (8,62). These findings are in contrast to results obtained after a short-term ABP decrease (~2 min), where no regional differences were reported in the lower limit of autoregulation in newborn piglets (63).

In summary, this study shows that autoregulation in the brain cortex has a lower threshold in newborn IUGR piglets than in NW animals. A similar response was shown for forebrain oxygen uptake. However, the cerebral O₂ extraction during gradual HH was not different between NW and IUGR piglets. Causal mechanisms for these differences are unknown. In contrast to the initial assumption, it seems that IUGR newborns are more capable of protecting some brain regions against hypoperfusion during hypotensive periods than NW neonates.

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