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Comparison of Short- and Long-Duration Oxygen Treatment after Cerebral Asphyxia in Newborn Piglets

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ABSTRACT

We tested whether reoxygenation with 100% O_2 for 5 min after experimental asphyxia in newborn piglets was as efficient as 100% O_2 for 20 min compared with room air. Forty-one anesthetized piglets, 1–3 d old, were randomized to cerebral hypoxemia-ischemia-hypercapnia (HIH) or control ($n = 5$). HIH was achieved by ventilation with 8% O_2, temporary occlusion of the common carotid arteries, and adding of CO_2. After 25 min, reoxygenation-reperfusion was started with 100% O_2 for 20 min (group 1, $n = 12$), 100% O_2 for 5 min (group 2, $n = 12$), or 21% O_2 (group 3, $n = 12$). All piglets were observed for 2 h. During reoxygenation-reperfusion, significantly higher blood pressure and more complete restoration of microcirculation (laser Doppler flow) in the cerebral cortex was found in both groups reoxygenated with 100% O_2 compared with 21% O_2 (regional cerebral blood flow ≥100% *versus* 70% of baseline, $p = 0.04$). Reoxygenation with 100% O_2 for 5 min was as efficient as 20 min. Oxygen delivery in cortex was significantly higher in groups 1 and 2 compared with group 3 ($p = 0.03$), but there were no significant differences in cerebral metabolic rate for oxygen. In the striatum, no significant differences in flow or extracellular glutamate, glycerol, and lactate/pyruvate ratio were found between the groups. In conclusion, after experimental asphyxia, newborn piglets can be reoxygenated as efficiently with 100% O_2 for only 5 min as 100% O_2 for 20 min compared with room air. **(*Pediatr Res* 56: 125–131, 2004)**

Abbreviations

BE, base excess
Cao_2, arterial O_2 content
$Cvsso_2$, sagittal sinus O_2 content
CBF, cerebral blood flow
$CMRO_2$, metabolic rate for oxygen
DO_2, oxygen delivery
HIH, hypoxemia-ischemia-hypercapnia
MABP, mean arterial blood pressure
OER, oxygen extraction ratio
$Paco_2$, arterial CO_2 tension
Pao_2, arterial O_2 tension
ROS, reactive oxygen species

The optimum way to reoxygenate asphyxiated newborns is still not known. Infants in need of resuscitation are often exposed to high concentrations of O_2. The possibility of increasing the load of toxic ROS by giving additional O_2 during resuscitation is, however, still of major concern (1). Several experimental and clinical studies from our group (2–7) have shown that asphyxiated newborns may be reoxygenated as efficiently with 21% O_2 as with 100% O_2. However, in two recent animal studies using a model of combined cerebral hypoxemia-ischemia in newborn piglets, we found significantly higher MABP and better restoration of microcirculation in cerebral cortex after initial reoxygenation for the first 30 min with 100% O_2 compared with 21% O_2. In the first study (8), in which piglets were exposed to 20 min of combined hypoxemia-ischemia alone, we also found significantly higher levels of excitatory amino acids in the striatum after reoxygenation with 21% O_2. In the second study (in press), a moderate hypercapnia was added to the hypoxic-ischemic insult to more closely simulate perinatal asphyxia. This seemed to result in a less severe insult, as no significant differences in biochemical markers were found between the groups, whereas differences in MABP and microcirculation in cerebral cortex still persisted.

Exposure to O_2 during resuscitation can be limited in two ways, either by reducing the concentration or by limiting the time of exposure. The purpose of the present study was to test whether initial reoxygenation after combined HIH in newborn piglets with 100% O_2 for only 5 min was as efficient as 20 min

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compared with reoxygenation with 21% O_2. Outcome measures were MABP, changes in microcirculation in cerebral cortex and striatum (laser Doppler flow), and biochemical markers (glutamate, glycerol, and lactate/pyruvate ratio) in the striatum (*in vivo* microdialysis). To monitor oxygen metabolism we calculated cerebral OER and relative changes in DO_2 and $CMRO_2$ in the cortex.

METHODS

Animal preparation. Forty-nine piglets (1–3 d old, 1.1–2.5 kg) were delivered from a local farmer on the day of the experiments. Eight piglets were excluded because of low Hb at baseline (<5 g/dL, $n = 4$), low basal Pa_{O_2} (<9.0 kPa, $n = 2$), and death during the asphyxic insult ($n = 2$).

Anesthesia was induced by halothane, an ear vein was cannulated, halothane was discontinued, and the piglets were given pentobarbital sodium 20 mg/kg and fentanyl 50 μg/kg i.v. as a bolus injection. Anesthesia was maintained with a continuous fentanyl infusion (25–50 μg/kg/h) and a continuous midazolam infusion (0.25 mg/kg/h). Midazolam was temporarily discontinued during HIH. Pancuronium was given every hour (0.1 mg/kg i.v.). A continuous i.v. infusion containing 0.7% NaCl and 1.25% glucose was given at a rate of 10 mL/kg/h. Blood glucose levels were maintain between 4 and 10 mM.

A tracheotomy was performed, and a pressure-controlled ventilator (Dräger Babylog 8000 Plus, Drägerwerk AG, Lübeck, Germany) ventilated the piglets at a rate of 30 breaths/min. Normoventilation (Pa_{CO_2} 4.5–6.0 kPa) was maintained during the stabilizing and reoxygenation-reperfusion period by adjusting the tidal volume with a constant inspiratory time of 0.5 s and a positive end-expiratory pressure of 3 cm H_2O. Before HIH was induced, all piglets were ventilated with 21% oxygen. Inspired fraction of O_2 and end tidal CO_2 were continuously monitored (Datex Normocap Oxy, Datex, Helsinki, Finland). Rectal temperature was kept between 38 and 39.5°C with a heating blanket.

Both femoral arteries were cannulated for continuous measurements of MABP and blood sampling. The common carotid arteries on both sides were exposed through a small incision in the neck at the level of the fourth cervical vertebra.

The piglets were placed with the head fixed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, U.S.A.). The scalp was removed and three holes, one 3 mm in diameter and two 3 × 6 mm, were drilled through the skull. Small dural incisions were made and one microdialysis probe was implanted into the striatum (8 mm anterior, 4.5 mm lateral, and 19 mm vertical to the bregma) on the right side. Opposite the microdialysis probe, a laser Doppler probe was implanted into the striatum on the left side. A second laser Doppler probe was implanted into the frontal cerebral cortex on the right side (16 mm anterior, 5 mm lateral to the bregma, and 5 mm vertical from the surface of the cortex). The coordinates for the cerebral striatum and cortex have been verified through neuropathological postmortem examination in earlier studies (9). A 3-mm diameter hole was drilled in the midline of the skull about 5 mm posterior of the bregma, and a cannula (Venflon, outside diameter 0.8 mm) was inserted through the intact dura into the superior sagittal sinus.

At the end of the experiment, the piglets were killed with a bolus injection of pentobarbital sodium, and brains were sliced to confirm the position of the probes.

Experimental protocol. After a 60-min recovery period from surgery, the piglets were randomized to four groups. Group 1 was subjected to 25 min of combined HIH followed by reperfusion and reoxygenation with 100% O_2 for the first 20 min and then 21% O_2 for another 100 min ($n = 12$). Group 2 was subjected to 25 min of combined HIH followed by reperfusion and reoxygenation with 100% O_2 for the first 5 min and then 21% O_2 for 115 min ($n = 12$). Group 3 was subjected to combined HIH for 25 min followed by reperfusion and reoxygenation with 21% O_2 for 120 min ($n = 12$). Group 4 (control) received no HIH and was normoventilated with 21% O_2 for a total of 145 min ($n = 5$). Hypoxemia was induced by ventilation with 8% O_2 in N_2, hypercapnia by adding CO_2 to the inspiratory gas (Pa_{CO_2} aimed at 8.0–9.0 kPa), and ischemia by temporary occlusion of the common carotid arteries on both sides with small, nontraumatizing metallic clamps. At the start of reoxygenation-reperfusion, clamps were released and the CO_2 was discontinued.

Blood samples. Blood samples from the femoral artery and sagittal sinus were taken before HIH (baseline), just before start of reoxygenation-reperfusion and then after 5, 10, 20, 30, 45, 60, 90, and 120 min of reoxygenation-reperfusion. Temperature-corrected blood gases and acid/base status were measured with a blood gas analyzer AVL Omni 1–9 (AVL LIST GmbH, Graz, Austria). Hb and arterial and venous oxygen saturation were measured with an OSM 3 Hemoximeter (Radiometer, Copenhagen, Denmark). A 3-fold volume of normal saline replaced the withdrawn blood.

Microdialysis. Microdialysis probes (CMA 10, CMA, Stockholm, Sweden) with a membrane length of 4 mm and a molecular mass cutoff of 20,000 D were perfused at 3 μL/min with an unbuffered electrolyte solution as previously described (5). Samples for measurements of glutamate, lactate, pyruvate, and glycerol were collected at 10-min intervals and analyzed using CMA 600 Microdialysis Analyzer (CMA), based on enzyme reagents and colorimetric analysis. Glutamate and glycerol measurements are presented as the concentrations measured in the microdialysis fluid. This concentration is always lower than the actual concentration in the extracellular fluid, and is dependent on perfusion flow rate, surface area of the probe, and molecular cutoff. Due to contamination of the vials, microdialysis results were excluded in two animals (one in group 1 and one in group 2).

Laser Doppler flowmetry. Measurements of changes in cerebral microcirculation in cortex and striatum were performed with 2 LDF 100A Laser Doppler Flow Modules (BIOPAC Systems, Inc., Santa Barbara, CA, U.S.A.). The flowmeter emits a temperature-stabilized semiconductor laser light with a wavelength of 780 ± 10 nm, which is directed to the tissue by an optical fiber through a micro-needle probe (TSD 145, length 25 mm, diameter 480 μm). The magnitude and frequency distribution of the Doppler-shifted light is proportional to the number and velocity of red blood cells (*i.e.* blood perfusion)

that are moving through the illuminated area of the tissue with a measurement depth of about 1 mm. The Doppler shift is independent of movement direction. Blood flow is computed by determining the product of blood volume and velocity and gives only a relative, not an absolute, value that is expressed in arbitrary units (10). Backscatter signal (tissue remittance) for each probe was recorded throughout the experiment to ensure adequacy and stability of the reading. The signal was considered inadequate if backscatter signal was <5%. Micro-needle probes were new and precalibrated by the manufacturer. In all animals a (close to) zero reading was obtained immediately after death.

Calculations. Arterial (Cao_2) and venous sagittal sinus ($Cvsso_2$) O_2 content were calculated as $Cao_2 = (1.39 \times Hb \times$ arterial saturation) + ($Pao_2 \times 0.003$), and $Cvsso_2 = (1.39 \times Hb \times$ venous sagittal sinus saturation) + ($Pvsso_2 \times 0.003$).

Relative changes in DO_2 were calculated as DO_2 = CBF (% of baseline) × Cao_2.

OER was calculated as OER = ($Cao_2 - Cvsso_2$)/Cao_2 (or $CMRO_2/DO_2$).

Relative changes in $CMRO_2$ was calculated as $CMRO_2$ = CBF (percentage of baseline) × ($Cao_2 - Cvsso_2$).

Due to problems in aspirating blood from the sagittal sinus at the end of the insult/start of reoxygenation-reperfusion, calculations of oxygen metabolism had to be excluded in six animals (two in each HIH group).

Statistics. Values are presented as mean ± SD. The three HIH groups were compared at baseline and at end of HIH to investigate whether there were any differences between the groups before the start of reoxygenation-reperfusion by using a one-way ANOVA followed by a Games/Howell *post hoc* test. When comparing two time points in the same group, a paired *t* test with or without Welch's correction (for unequal variance) was used. A repeated measures ANOVA followed by a Games/Howell *post hoc* test was used to compare values for the groups during the reoxygenation-reperfusion period. The control group was used to assess the stability of the model, and was not directly compared with the HIH groups. Two-sided *p* values < 0.05 were considered significant. All analyses were done with the statistical computer program StatView 5.0 (Abacus Concepts, Berkeley, CA, U.S.A.).

Approval. The study was approved by the Norwegian Animal Experimental Board.

RESULTS

There were no significant differences between the three HIH groups in any measured variable at baseline or at the start of reoxygenation-reperfusion.

Blood gases and blood pressure. Except for a significantly higher Pao_2 ($p < 0.001$) in groups 1 and 2 compared with group 3 during the period the two groups received additional O_2, there were no significant differences between the groups in pH, Pao_2, $Paco_2$, or BE (Table 1). At the start of reoxygenation-reperfusion, $Paco_2$ was 8.4 ± 0.6 kPa, with no significant differences between the groups ($p = 0.5$).

During reoxygenation-reperfusion, there were significant differences in MABP (Fig. 1) between all groups ($p = 0.005$). MABP was highest in group 2 and lowest in group 3. At the end of the observation period, MABP was 77 ± 10 mm Hg in group 1, 85 ± 13 mm Hg in group 2, and 67 ± 12 mm Hg in group 3, which was significantly lower than baseline in both group 1 ($p = 0.003$) and group 3 ($p = 0.0002$).

Laser Doppler flowmetry. Changes in microcirculation in the striatum and cortex are shown in Figure 2. Data are presented as percentage of baseline. Baseline values in arbitrary units were, in the striatum, 291 ± 127 in group 1, 303 ± 116 in group 2, and 279 ± 156 in group 3; and, in the cortex, 372 ± 150 in group1, 335 ± 106 in group 2, and 392 ± 144 in group 3. In the striatum, blood flow decreased by 80% during HIH. During reoxygenation-reperfusion, flow was rapidly restored without any significant differences between the groups. There was, however, a considerable overshoot during the first 20 min of reoxygenation-reperfusion, especially in the two O_2-treated groups, with flow values up to three times baseline in some animals. At the end of the observation period, blood flow was not significantly different from baseline in any group.

In the cortex, blood flow also decreased by 80% during HIH. During reoxygenation-reperfusion, blood flow values returned to or exceeded baseline values within 5 min in the two groups receiving additional O_2, whereas values in the room air group

Table 1. *pH, Pao_2, Pco_2, and BE (mean ± SD)*

				Reoxygenation-reperfusion			
		Baseline	End HIH	5 min	20 min	60 min	120 min
pH	Group 1	7.42 ± 0.12	7.02 ± 0.15	7.18 ± 0.17	7.21 ± 0.16	7.30 ± 0.10	7.34 ± 0.09
	Group 2	7.44 ± 0.11	7.08 ± 0.11	7.24 ± 0.14	7.25 ± 0.12	7.36 ± 0.08	7.40 ± 0.04
	Group 3	7.43 ± 0.15	7.05 ± 0.11	7.16 ± 0.12	7.23 ± 0.09	7.34 ± 0.07	7.39 ± 0.05
Pao_2 (kPa)	Group 1	11.5 ± 1.7	4.4 ± 0.9	59.6 ± 9.9*	54.6 ± 13.9*	11.1 ± 1.8	10.9 ± 1.5
	Group 2	12.5 ± 2.4	4.0 ± 0.8	57.7 ± 5.6*	12.9 ± 2.2	11.8 ± 1.9	11.7 ± 1.7
	Group 3	10.9 ± 0.9	4.6 ± 0.9	13.4 ± 1.4	12.0 ± 1.5	11.1 ± 1.8	10.7 ± 1.3
$Paco_2$ (kPa)	Group 1	5.1 ± 0.4	8.5 ± 0.5	4.9 ± 0.5	5.2 ± 0.3	5.3 ± 0.3	5.3 ± 0.5
	Group 2	5.1 ± 0.3	8.3 ± 0.4	4.9 ± 0.3	5.3 ± 0.2	5.3 ± 0.9	5.2 ± 0.3
	Group 3	5.2 ± 0.3	8.3 ± 0.8	5.0 ± 0.4	5.0 ± 0.2	5.2 ± 0.3	5.2 ± 0.3
BE (mmol/L)	Group 1	0.2 ± 3.9	−14.4 ± 7.5	−14.8 ± 7.4	−12.3 ± 7.1	−6.9 ± 6.1	−4.3 ± 5.4
	Group 2	1.0 ± 3.8	−12.1 ± 5.5	−11.3 ± 6.7	−9.8 ± 6.1	−4.1 ± 4.3	−1.1 ± 3.4
	Group 3	0.7 ± 3.2	−13.8 ± 5.0	−14.5 ± 5.3	−12.1 ± 4.2	−5.1 ± 4.2	−1.9 ± 3.6

* $p < 0.0001$ group effect.

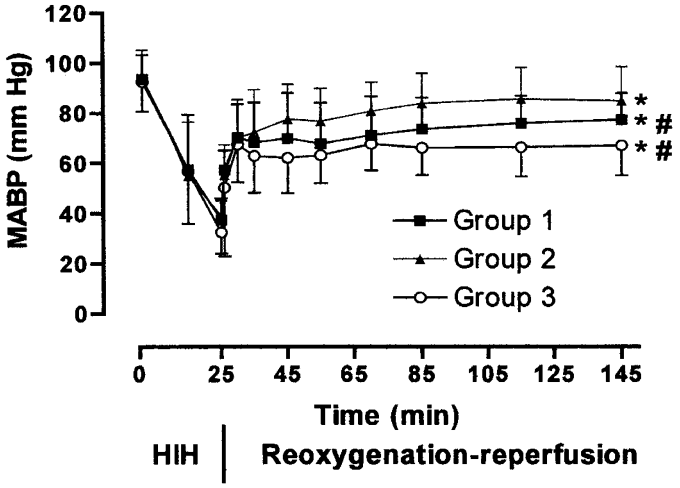

Figure 1. MABP during HIH and reoxygenation-reperfusion. Mean ± SD. Group 1 was reoxygenated with 100% O_2 for the initial 20 min, group 2 with 100% O_2 for the initial 5 min, and group 3 was reoxygenated with 21% O_2. *$p < 0.05$ group difference. #$p < 0.05$ *vs* baseline for the group.

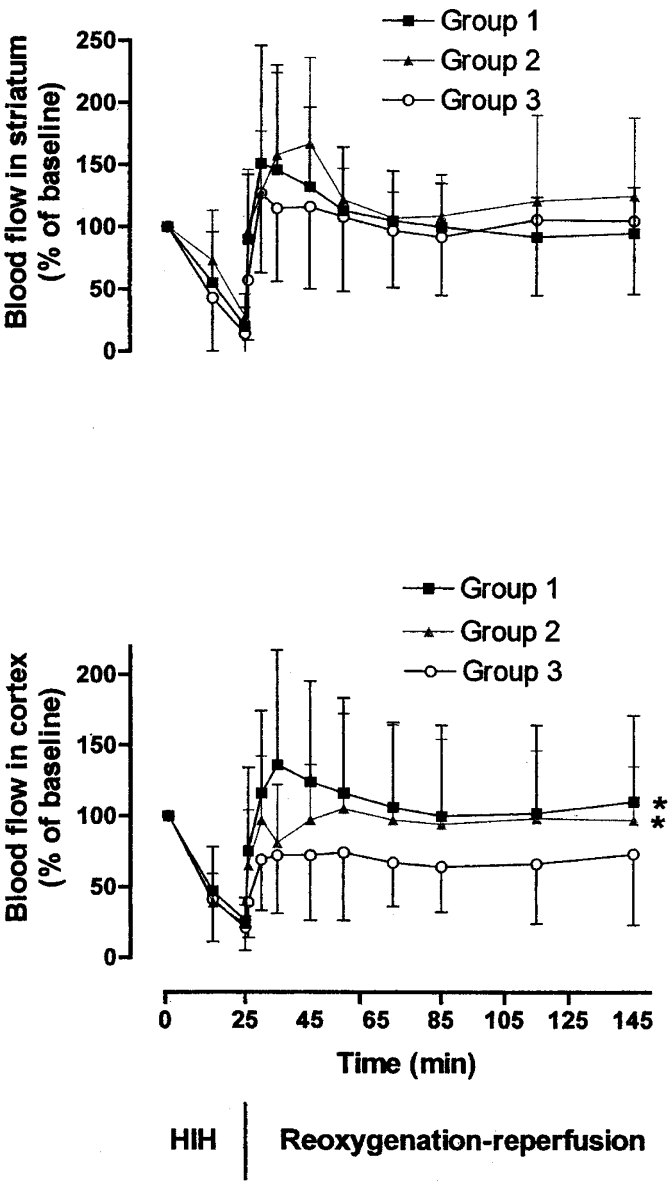

Figure 2. Changes in microcirculation in the striatum and cortex during HIH and reoxygenation-reperfusion. Mean ± SD. Group 1 was reoxygenated with 100% O_2 for the initial 20 min, group 2 with 100% O_2 for the initial 5 min, and group 3 was reoxygenated with 21% O_2. *$p < 0.05$ group effect.

reached approximately 70% of baseline. Repeated measures ANOVA for the whole reoxygenation-reperfusion period showed a significant group effect ($p = 0.04$), with significantly higher blood flow in groups 1 and 2 compared with the room air group. At the end of reoxygenation-reperfusion, blood flow was not significantly different from baseline in any group.

Oxygen metabolism. Cerebral OER and relative changes in cortical DO_2 and $CMRO_2$ are shown in Figure 3. DO_2 in cortex was significantly higher ($p = 0.03$) during reoxygenation-reperfusion in the two groups receiving additional O_2 compared with the room air group. There was a near-significant difference in OER between the groups during reoxygenation-reperfusion ($p = 0.056$), with the highest values in the room air group. There were no significant differences in changes in $CMRO_2$ between the groups ($p = 0.18$) during reoxygenation-reperfusion. At the end of the observation period, values were not significantly different from baseline.

Glutamate in striatum. Extracellular concentrations of glutamate in the striatum (Fig. 4) increased 4- to 5-fold during HIH and the first 10 min of reoxygenation-reperfusion. Values then started to decrease toward baseline values in all animals, but, in two animals in group 2 and three animals in group 3, a second increase occurred during the last 60 min of reoxygenation-reperfusion. The overall change from baseline to the end of reoxygenation-reperfusion was, however, not significantly different between the groups.

Glycerol and lactate/pyruvate ratio in striatum. Extracellular concentrations of glycerol in the striatum (Fig. 4) increased 2- to 3-fold during HIH and further during reoxygenation-reperfusion without significant differences between the groups. At the end of the observation period, values were significantly higher than baseline for all groups ($p < 0.05$). Lactate/pyruvate ratio (Fig. 4) increased 12–16 times baseline values during HIH, and started to decrease immediately during reoxygenation-reperfusion without any significant differences between the groups.

Control group. All measured variables were stable throughout the observation period in the five control animals (data not shown).

DISCUSSION

In this study, we found significantly higher MABP and more complete restoration of microcirculation in the cerebral cortex in both groups reoxygenated with 100% O_2 compared with 21% O_2. Reoxygenation with 100% O_2 for 5 min was as efficient as 20 min. DO_2 in cortex was significantly higher in the two groups receiving additional oxygen compared with the room air group, and OER was near significantly higher in the room air group. In the striatum, however, no significant differences in flow or biochemical markers were found between the groups.

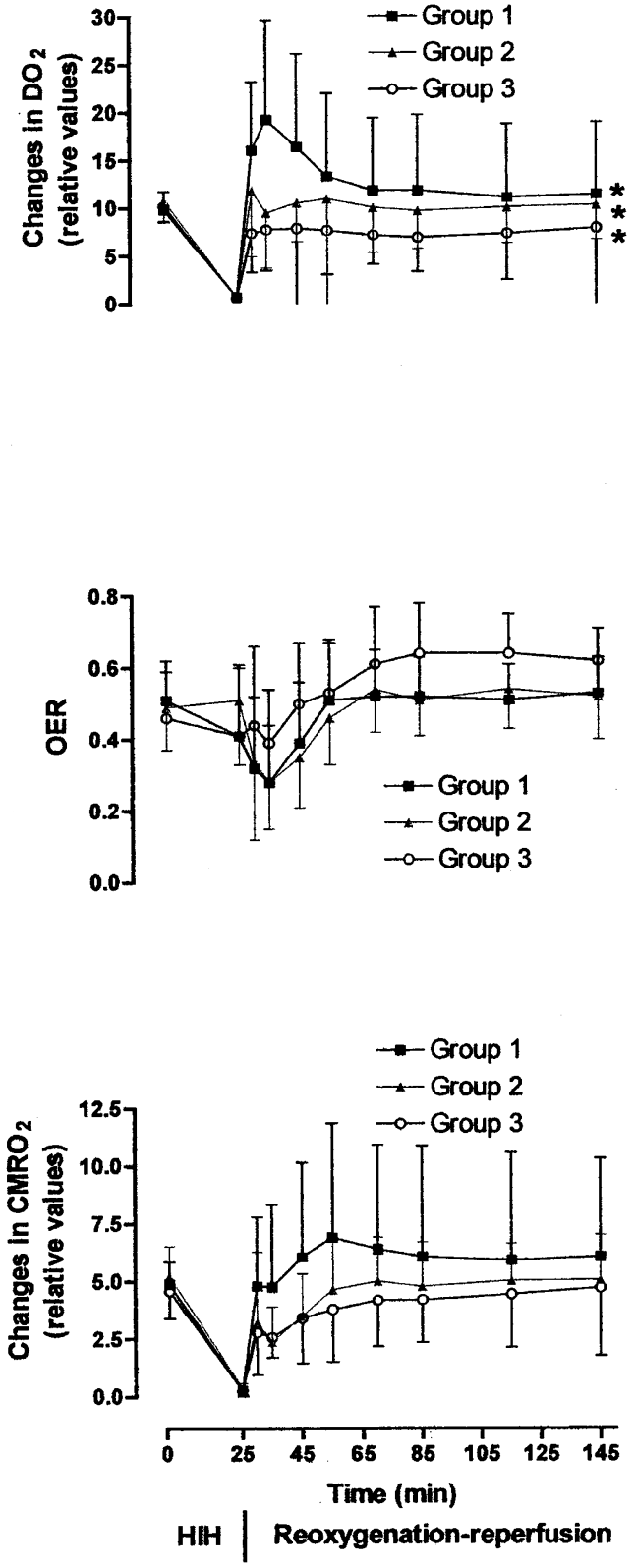

Figure 3. Relative changes in DO_2, OER, and $CMRO_2$ in the cortex during HIH and reoxygenation-reperfusion. Mean ± SD. Group 1 was reoxygenated with 100% O_2 for the initial 20 min, group 2 with 100% O_2 for the initial 5 min, and group 3 was reoxygenated with 21% O_2. Relative changes in DO_2 was calculated as DO_2 = CBF (% of baseline) × Cao_2. OER was calculated as OER = (Cao_2 − $Cvsso_2$)/Cao_2 (or $CMRO_2/DO_2$). Relative change in $CMRO_2$ was calculated as $CMRO_2$ = CBF (percentage of baseline) × (Cao_2 − $Cvsso_2$). *$p < 0.05$ group effect.

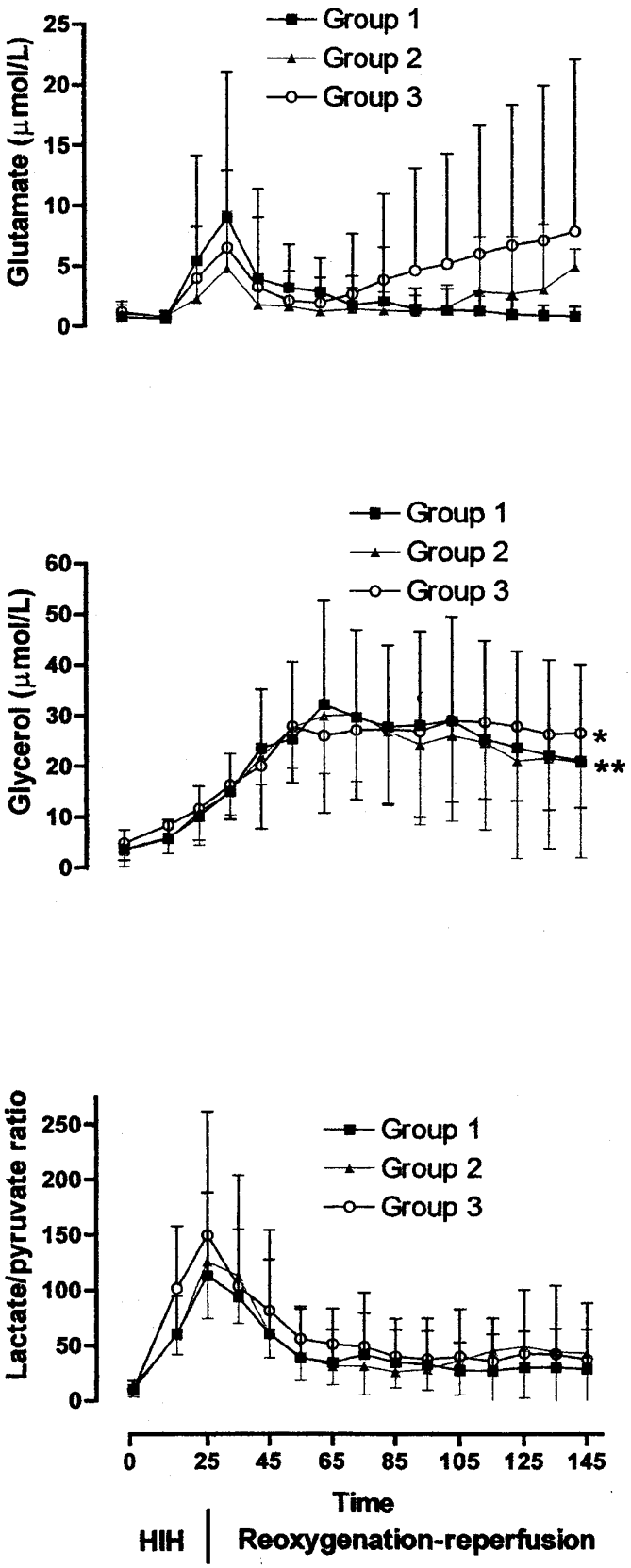

Figure 4. Extracellular concentrations of glutamate, glycerol, and lactate/pyruvate ratio in the striatum during HIH and reoxygenation-reperfusion. Mean ± SD. Group 1 was reoxygenated with 100% O_2 for the initial 20 min, group 2 with 100% O_2 for the initial 5 min, and group 3 was reoxygenated with 21% O_2. *$p < 0.05$ *vs* baseline for the group.

The findings of higher flow in the cortex after reoxygenation with 100% compared with 21% O_2, are in accordance with findings in two of our previous animal studies using comparable models (8, in press). In the two groups receiving additional O_2, microcirculation in cortex rapidly returned to or exceeded baseline values during reoxygenation-reperfusion, whereas values in the room air group reached approximately 70% of baseline. Threshold values for regional CBF after asphyxia have not been established. The findings of significantly higher DO_2 in the two groups receiving 100% O_2 and the nearly significantly higher OER in the 21% O_2 group may indicate a borderline, but perhaps sufficient, cortical perfusion after reoxygenation with 21% O_2 compared with 100% O_2 in this model. Maintaining normal $CMRO_2$ is necessary for normal brain function. The brain can maintain a stable $CMRO_2$ either by increasing CBF or by increasing O_2 extraction. If CBF is inadequate, OER will increase until this compensatory mechanism is exhausted and $CMRO_2$ finally falls. In this study, changes in $CMRO_2$ were not significantly different between the groups, and values at the end of the observation period were not significantly different from baseline in any group, findings that perhaps indicate that even reoxygenation with room air only is safe in this model. OER is normally around 0.45 both in newborn piglets (11), human adults (12), and neonates (13), and values exceeding 0.75 are conventionally accepted as indicating tissue ischemia (14). However, results from studies in a middle cerebral artery occlusion-reperfusion primate model (15) indicate that $CMRO_2$ is a better predictor of reversible or irreversible brain damage than CBF and OER. In the present study, only relative changes in CBF were measured, and care must be taken when CBF results and calculated variables are interpreted.

The finding of perhaps greatest interest in the present study was that reoxygenation with 100% O_2 for only 5 min was as efficient as 20 min for all variables measured. Somehow, a brief exposure to oxygen for 5 min seems to trigger the same mechanisms that restore blood pressure, microcirculation, and oxygen metabolism in cortex more completely than in piglets reoxygenated with 100% O_2 for 20 or 30 min (8) compared with room air. Under normal conditions, hyperoxia induces cerebral vasoconstriction (16), but this oxygen reactivity may be lost when tissue is at risk of ischemia (17). It is known that free oxygen radicals are potent vasoregulators and can have a dilating effect on both cerebral arterioles and arteries (18, 19). Endothelial cells play a key role in the regulation of vascular tone, and a very fine balance exists between relaxing and contracting factors during asphyxia and reoxygenation-reperfusion (*i.e.* production and action of ROS, nitric oxide, and peroxynitrite). We did not measure any of these substances in the present study, but high oxygen tension contributes substantially to the accumulation of ROS, and significantly higher cerebral NO concentrations have been demonstrated during reoxygenation with 100% compared with 21% O_2 after hypoxia in piglets (20).

The cerebral cortex, basal ganglia, and brainstem are areas at special risk during hypoxic-ischemic insults in both term babies and piglets (21–23). Animal studies have shown that the mature fetus reacts to an asphyxic insult by increasing and redistributing CBF, especially to the brainstem and central parts of the brain (24–26), but as the insult persists, a reduction in CBF occurs (25). After the insult, a transient hyperperfusion may be seen (27). We have not measured changes in microcirculation in the striatum in this model before, but our findings are in accordance with previous results reported from a different study where no differences in flow in the striatum were found after reoxygenation with 100% compared with 21% O_2 in newborn piglets (28). Regional differences in mechanisms for regulation of CBF could possibly explain differences in response to 100% O_2 and room air during reoxygenation-reperfusion in different parts of the brain. It has been suggested that the relative vasoconstriction in cerebral cortex during and after acute asphyxia may be sympathetically mediated, whereas vasodilatation in central parts of the brain may be consistent with chemical control (26, 29).

A transient hyperperfusion was seen both in the cortex and striatum, especially in the two oxygen-treated groups. This reactive hyperemia after asphyxia has been of some concern, as it in some studies has been associated with a fall in $CMRO_2$ despite a marked increase in DO_2 (30). This was not the case in the present study, and recent positron emission tomography studies in both humans and animals have indicated that early hyperperfusion following ischemia is not necessarily detrimental *per se* (31).

Extracellular concentrations of glycerol, lactate/pyruvate ratio, and glutamate are well-known markers of cell membrane damage, ischemia, and energy failure in the brain (32). No significant differences between the groups were found during reoxygenation-reperfusion. This could reflect the finding of generally good restoration of flow in the striatum in all groups. In this model, room air resuscitation therefore seems to give an adequate reoxygenation at least in the striatum. In the present study, biochemical markers were, however, not measured in the cortex. This would have been of great interest, inasmuch as significant differences in flow and DO_2 but not $CMRO_2$ were found between the two oxygen-treated and the room air group.

The repeated findings of significantly higher MABP after reoxygenation with 100% compared with 21% O_2 in this model have been somewhat unexpected. No such differences have been demonstrated in the numerous previous studies from our group using the model of global hypoxemia without clamping of cerebral vessels. However, hyperoxia has been shown to cause increased systemic vascular resistance in both dogs (33) and humans (34). Our study was not designed to look specifically at cardiovascular function during asphyxia and reoxygenation-reperfusion. Further studies addressing this issue are therefore needed.

In conclusion, significantly higher MABP and more complete restoration of microcirculation and DO_2 in the cerebral cortex were found in both groups reoxygenated with 100% O_2 compared with 21% O_2 after experimental asphyxia in newborn piglets. There were no significant differences in $CMRO_2$ between the groups. In the striatum, no significant differences in flow or biochemical markers were found. Reoxygenation with 100% O_2 for 5 min was as efficient as 20 min, a finding that indicates that exposure to additional O_2 during resuscitation at least can be limited in time in this model.

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