Early cerebral metabolic and electrophysiological recovery during controlled hypoxemic resuscitation in piglets

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1Department of Pediatric Research and Institute for Surgical Research, The National Hospital, N-0027 Oslo, Norway; 2Department of Neonatology, The National Hospital, DK-2100 Copenhagen Ø, Denmark; and 3Department of Pediatrics, Lund University Hospital, S-22185 Lund, Sweden

Feet, Björn A., Nikolai C. Brun, Lena Hellström-Westas, Niels W. Svenningsen, Gorm Greisen, and Ola D. Saugstad. Early cerebral metabolic and electrophysiological recovery during controlled hypoxemic resuscitation in piglets. J. Appl. Physiol. 84(4): 1208–1216, 1998.—We tested the hypothesis that controlled hypoxemic resuscitation improves early cerebral metabolic and electrophysiological recovery in hypoxic newborn piglets. Severely hypoxic anesthetized piglets were randomly divided into three resuscitation groups: hypoxic, 21% O₂, and 100% O₂ (8 in each group). The hypoxic group was mechanically ventilated with 12–18% O₂ adjusted to achieve a cerebral venous O₂ saturation of 17–23% (baseline; 45 ± 1%). Base excess (BE) reached −22 ± 1 mM at the end of hypoxia. During a 2-h resuscitation period, no significant differences in time to recovery of electroencephalography (EEG), quality of EEG at recovery, or extracellular hypoxanthine concentrations in the cerebral cortex and striatum were found among the groups. BE and plasma hypoxanthine, however, normalized significantly more slowly during controlled hypoxemic resuscitation than during resuscitation with 21 or 100% O₂. We conclude that early brain recovery during controlled hypoxemic resuscitation was as efficient as, but not superior to, recovery during resuscitation with 21 or 100% O₂. The systemic metabolic recovery from hypoxia, however, was delayed during controlled hypoxemic resuscitation.

METHODS

Animal preparation. The study was approved by the Norwegian Animal Experimental Board. The care and handling of the animals were in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes of March 18, 1986. Twenty-eight domestic piglets (2–5 days old; 1.3–2.1 kg) were delivered from a local farmer on the day of the experiments. Anesthesia was induced with halothane (3% halothane mixed with O₂). When surgical anesthesia was ob-
tained, halothane was reduced to 1–1.5% mixed with 30% O2.
The piglets were tracheotomized, and a 3.5-mm endotracheal tube was inserted. A humidifier (Hygrobaby, DAR, Mirandola, Italy) was connected to the endotracheal tube. A volume-controlled respirator (Servo 900 B, Elema-Schönander, Stockholm, Sweden) mechanically ventilated the piglets at 30 breaths/min. End-tidal CO2 was continuously measured (Engstrom eliza, Engstrom Medical). A peripheral ear vein was cannulated, and the piglets were given fentanyl (50 µg/kg iv). Further anesthesia was maintained with fentanyl infusion (50 µg·kg⁻¹·h⁻¹) and 0.3–0.5% halothane (except during the hypoxic period, when halothane was discontinued). The piglets were paralyzed with pancuronium bromide (0.2 mg/kg iv), and this was repeated every hour (0.1 mg/kg iv).

A continuous peripheral intravenous infusion containing 0.7% NaCl and 1.25% glucose was given at a rate of 10 ml·kg⁻¹·h⁻¹. Blood glucose was measured regularly by using a Haemo-Glukotest (Boehringer Mannheim, Mannheim, Germany), and the infusion was altered to maintain blood glucose between 4 and 10 mM. The right femoral artery and vein were cannulated and were connected to a strain-gauge transducer, and mean arterial blood pressure (MAP) was measured via skin electrodes. Body temperature was monitored with a rectal probe and was kept between 38 and 39°C by use of a heating blanket.

The piglets were then placed in the prone position, and the head was positioned in a stereotaxic holder (David Kopf Instruments, Tujunga, CA). The scalp was removed to expose the skull. A hole with a diameter of 3 mm was drilled in the midline of the skull ~2 cm anterior to the bregma, and a cannula (Venflon, inner diameter 0.8 mm, 22 gauge, Ohmeda, Helsingborg, Sweden) was inserted through the intact dura into the sagittal sinus. Another four 3-mm holes were drilled through the skull. The dura was penetrated, two microdialysis probes were implanted into the striatum (8 mm anterior, 4.5 mm lateral, and 19 mm vertical to the bregma, one probe on each side), and another two microdialysis probes were implanted into the cerebral cortex (6 mm posterior and 10 mm lateral to the bregma, and 6 mm vertical from the surface of the cerebral cortex, one probe on each side). Several pilot studies were performed before the present study to accurately decide the coordinates for the cerebral striatum and cortex. The insertion of the striatal probes was guided by the location of the nucleus caudatus. The location of the microdialysis probes is demonstrated in Fig. 1.

The NIRS optodes were applied directly onto the skull. The detector fiber was placed in the midline in line with the posterior angle of the orbit, and the source fiber was placed posterior to the detector, resulting in an interoptode distance of ~2 cm.

Two channels of EEG, one from each hemisphere, were recorded. Platinum needle electrodes (Grass subdermal electrodes, West Warwick, RI) were placed over both hemispheres ~3 cm apart and as close as possible to the microdialysis probes and the NIRS optodes, in positions corresponding to the Fp₁–Fp₂ and Fp₃–Fp₄ positions (International 10–20 system). At the end of the experiment, the piglets were killed with a bolus injection of pentobarbital sodium.

Experimental protocol. After the surgical procedure, the piglets were normoventilated [arterial PCO₂ (PaCO₂) kept between 34 and 45 Torr] with 21% O₂ during a 60-min stabilization period. The hypoxic period was then started by ventilation of the piglets with 6% O₂-balance N₂. The O₂ content of the inspired gas was monitored with an O₂ monitor (Penlon Intermed, Penlon, Oxon, UK). To imitate perinatal asphyxia, a moderate hypercapnia (PaCO₂ between 52 and 60 mmHg) was induced during hypoxia by simultaneous addition of CO₂ to the inspired gas. Tidal volume and ventilatory rate of the ventilator were kept unaltered during the hypoxic period. Hypoxia was continued until EEG became isoelectric and MAP decreased to <25 mmHg, or until base excess (BE) decreased to less than −25 mM. The piglets were then randomized to resuscitation with either a low F₁O₂, resulting in SSBO₂ values between 17 and 23% O₂ (hypoxic group; n = 8), 21% O₂ (100% O₂ group; n = 8), or 100% O₂ (100% O₂ group; n = 8). The decision to start resuscitation was always taken without knowledge as to which group the animal was allocated. CO₂ supplementation was only given during the hypoxic period, and the piglets were kept normoventilated during resuscitation by adjusting the tidal volume of the ventilator. However, to avoid unfavorable high intrapulmonary pressures, the tidal volumes were never increased over the baseline settings. Resuscitation was continued for 2 h.

Four piglets were excluded because of sudden death during hypoxia (1 piglet, before randomization) or errors in drug administration (3 piglets, randomized to 1 piglet/group). The decision to exclude an animal from the study was always taken by a colleague who was not informed as to which group the animal was allocated.

Microdialysis. Microdialysis probes (CMA 10, CMA/Microdialysis, Stockholm, Sweden), with a membrane length of 3 mm and a molecular mass cutoff of 20,000 Da, were perfused at 2 µl/min with an unbuffered electrolyte solution ([in mM] 148 NaCl, 1.2 CaCl₂, 0.85 MgCl₂, and 2.7 KCl). The dialysis samples were collected at 10-min intervals in polypropylene vials and frozen at −70°C for later analysis. The efficiency values of each microdialysis probe (relative recovery) were determined in vitro for the compounds measured. Hypoxantine data are presented after correction for this relative recovery. After each experiment the probes were perfused
with Evans blue; thereafter, the brain was sliced to confirm the position of the probes.

NIRS. NIRS quantitatively monitors changes in cerebral tissue concentrations of oxy- and deoxyhemoglobin (HbO₂ and deoxy-Hb, respectively), with an average tissue penetration of 8–9 mm and a subsecond time resolution (12). Measurement techniques using NIRS for estimation of tissue Hb saturation and blood volume have previously been developed (10, 34). By selection of appropriate wavelengths, algorithms have been developed for the calculation of changes in the chromophores (33) that were used in the present study. NIRS was performed by using a Radiometer prototype instrument (Radiometer, Copenhagen, Denmark). Measurements were performed by using four wavelengths (774, 806, 845, and 910 nm). The optodes were applied directly onto the skull, with the detector placed in the midline in line with the posterior angle of the orbit and the source fiber placed posterior to the detector, resulting in an interoptode distance of ~2 cm. The attenuation because of scattering is assumed to be constant, whereas changes in absorbed light depend on changes in the concentrations of the chromophores HbO₂ (ΔHbO₂) and deoxy-Hb (Δdeoxy-Hb). Wavelength-dependent pathlength factors were used (35). NIRS signals were recorded with a 4.0-s averaging time, and for each measurement period the mean concentration change from initial baseline values was derived for the oxygenation index (OI; ΔHbO₂ - Δdeoxy-Hb) and total hemoglobin (thb; ΔHbO₂ + Δdeoxy-Hb).

EEG. EEG was continuously recorded from two channels, one from each hemisphere. A battery-powered EEG tape recorder (Oxford 9000, Medilog system, Oxford, UK) was used as a preamplifier, with the bandwidth set at 0.5–100 Hz. After amplification, the EEG was digitized with an analog-to-digital converter (PCM-1 Digital VCR Instrumentation Recorder Adaptor, Medical Systems, Greenvale, NY). From the analog-to-digital converter, the EEG was further conducted into a computer, by using a software system (Work Bench PC for Windows, Sunnyvale, CA), for on-line monitoring of the EEG on the computer screen. The EEG was also recorded on standard C-120 tape cassettes on a Medilog tape recorder for later analysis. Before hypoxia (baseline EEG), all piglets had continuous EEG, with mixed frequencies and main amplitudes varying between 50 and 200 µV. After the hypoxia was started, the time for the EEG to become isoelectric was estimated from the on-line monitoring and was also later confirmed by blind evaluation of the Medilog tapes. The time to EEG recovery during resuscitation and the type of EEG pattern at the end of resuscitation were later evaluated visually on the Oxford Medilog System, but the evaluation was blind regarding the resuscitation group to which the piglet was allocated. Recovery of EEG was defined as EEG activity of amplitude >25 µV on three occasions within a 5-s period. The background EEG patterns at the end of resuscitation were categorized as follows (see also Fig. 2): 1) baseline, i.e., EEG background similar to the baseline pattern before hypoxia, with small changes in frequency (mainly slowing) accepted and no seizure activity present; 2) abnormal EEG, i.e., low-voltage EEG (continuous EEG with mixed frequencies but amplitude <50% of baseline EEG) or burst suppression (discontinuous EEG background with periods of high-voltage bursts intermixed with periods of very-low-voltage activity), with seizure activity present; and 3) no return of EEG activity, i.e., no discernible EEG activity above 5 µV at the end of the resuscitation period.

Blood samples. Arterial blood samples from the femoral artery [PaO₂ and arterial O₂ saturation (SaO₂)] and cerebral venous blood samples from the sagittal sinus [PssO₂ and SssO₂, (venous PO₂ and O₂ saturation, respectively)] were taken at baseline (before hypoxia), after 5 and 15 min, and then every 5 min after EEG became isoelectric and throughout hypoxia. Additional samples were taken just before resuscitation, after 5, 10, 15, and 30 min, and then every 30 min for 2 h. Temperature-corrected blood gases were measured with an automatic blood-gas system (AVL 945, AVL Biomedical Instruments, Schaffhausen, Switzerland), and HbO₂ saturations were measured with a CO-Oximeter (482, Instrumentation Laboratory, Lexington, MA). Blood for hypoxanthine analysis was collected into prechilled EDTA tubes and centrifuged for 10 min at 2,500 g. Plasma was transferred to polypropylene tubes and frozen at −70°C until analysis. The withdrawn blood was replaced with a double volume of 0.9% NaCl.

Analysis of hypoxanthine. Hypoxanthine in plasma and microdialysis fluid was analyzed by high-performance liquid chromatography as previously described (6).

Statistics. Values are presented as means ± SE, with the exception of the time for the EEG to become isoelectric during hypoxia and the time for the EEG to reappear during resuscitation. These values are given as median (25–75 percentile). The groups were compared at baseline and at the end of hypoxia to investigate whether there were any differences among the groups before start of resuscitation by using one-way ANOVA followed by the Bonferroni correction for post hoc t-test comparison (P = P ∗ 3). A repeated-measures ANOVA design was used to compare values for the three groups during the resuscitation period. The start-of-resuscitation values were used as covariates to correct for potential
preintervention bias. If the repeated-measures ANOVA demonstrated a significant group-by-time effect, the maximal increase/decrease (absolute numbers) from the end of hypoxia to the end of resuscitation was compared by using one-way ANOVA. If the repeated-measures ANOVA demonstrated a significant group effect, a simple contrast analysis between the groups was performed. The maximal effect of early resuscitation was evaluated by using paired t-tests to compare the baseline value with the maximum value within the first 15 min of resuscitation, except for microdialysis data, for which the maximal value within 60 min was used. Kaplan-Meier’s log-rank test was performed to evaluate differences in EEG disappearance (time) and EEG recovery among the groups, and the Kruskal-Wallis test was performed to evaluate differences in quality of EEG recovery among the groups. Spearman’s rank-correlation test was performed to describe the relationship among the maximum values of extracellular hypoxanthine concentrations, OI, and cerebral venous SssO2 during resuscitation and the EEG pattern at the end of resuscitation. Two-sided P values <0.05 were considered significant. All calculations were done by statistical software (Statistical Package for the Social Sciences, Windows Release 7.0, SPSS, Chicago, IL), and graphs were produced by a graphics program (GraphPad Prism, version 2.01, San Diego, CA).

RESULTS

The total duration of hypoxia was 36 ± 5, 40 ± 6, and 33 ± 4 min in the hypoxic, 21% O2, and 100% O2 groups, respectively (P = 0.61). There were no significant differences among all three groups in any measured variable at baseline or at the end of the hypoxic period.

Physiological variables. PaO2 decreased rapidly during hypoxia, and, after 5 min of hypoxia, PaO2 was 19 ± 2, 17 ± 1, and 18 ± 1 Torr in the hypoxic, 21% O2, and 100% O2 groups, respectively. SaO2, PssO2, and SssO2 peaked during early resuscitation in all groups (Fig. 3). PaO2, SaO2, PssO2, and SssO2 were significantly higher during resuscitation in the 100% O2 group compared with the hypoxic and 21% O2 groups, and SaO2 and SssO2 were significantly higher in the 21% O2 group than in the hypoxic group (group difference by repeated-measures ANOVA). PaCO2 was, at the end of hypoxia, 56, 56, and 61 Torr in the hypoxic, 21% O2, and 100% O2 groups, respectively, and was normalized during the first minutes of resuscitation (Table 1). No significant differences in PaCO2 were found among the groups.

BE (Fig. 4) reached −22.4 ± 1.4, −20.4 ± 2.6, and −22.8 ± 2.2 mM in the hypoxic, 21% O2, and 100% O2 groups, respectively, at the end of hypoxia. ANOVA for repeated measures showed both a significant group difference (P < 0.01) and a significant group-by-time difference (P < 0.01) among the groups. During the 2-h resuscitation period, BE normalized significantly more slowly in the hypoxic group compared with the values in the 21% O2 and 100% O2 groups (to −13.4 ± 2.1 vs. −5.0 ± 2.1 and −4.7 ± 1.4 mM, respectively, P < 0.05).

MAP fell markedly toward the end of hypoxia and increased rapidly during early resuscitation to maximum values not significantly different from baseline in all groups (Table 1). Repeated-measures ANOVA showed a group difference (P < 0.01), but not a group-by-time difference, in MAP among the groups. MAP was significantly lower during resuscitation in the hypoxic group compared with the values in the 21% O2 and 100% O2 groups.

Hematocrit was stable throughout the study, and no differences were found among the groups (data not shown). pH and inspired concentrations of O2 are shown in Table 1.

Hypoxanthine in arterial plasma. Hypoxanthine concentrations in arterial plasma increased five- to sixfold during hypoxia (Fig. 5). During resuscitation, plasma hypoxanthine concentrations decreased continuously but normalized significantly more slowly in the hypox-
are means ± SE; n = 8 piglets/group. MAP, mean arterial pressure; PaCO2, arterial PCO2. *P < 0.05 vs. hypoxemic group (group difference by repeated-measures ANOVA).

Results are means ± SE; n = 8 piglets/group. MAP, mean arterial pressure; PaCO2, arterial PCO2. *P < 0.05 vs. hypoxemic group (group difference by repeated-measures ANOVA).

Changes in cerebral tissue oxygenation. OI increased rapidly during early resuscitation and reached, within the first minutes, significantly higher values than baseline in both the 21% O2 and 100% O2 groups but significantly lower values than baseline in the hypoxemic group (Fig. 8). During resuscitation, OI in the 100% O2 group was significantly higher than in the 21% O2 group, and it was further significantly higher in the 21% O2 group than in the hypoxemic group.

Changes in cerebral blood volume. tHb increased markedly during hypoxia (Fig. 9). During resuscitation, tHb increased further and reached maximum values within the first minutes of resuscitation. During the rest of the resuscitation period, tHb decreased toward baseline values, and ANOVA for repeated measures did not show any significant differences among the groups.

EEG. EEG became isoelectric in all piglets during hypoxia. During resuscitation, EEG recovered in all piglets except in two from the hypoxemic group. The median (25–75 percentile) time for the EEG to become isoelectric during hypoxia was 19 (12–33), 30 (23–37), and 13 (7–34) min in the hypoxemic, 21% O2, and 100% O2 groups, respectively (P = 0.35). EEG reappeared during resuscitation after 14 (4–106), 2 (1–13), and 12

### Table 1. MAP, PaCO2, inspired O2 concentration, and pH for resuscitation groups of newborn piglets

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>End of Hypoxia</th>
<th>Resuscitation, min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>MAP, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxemic</td>
<td>82 ± 5</td>
<td>63 ± 7</td>
<td>58 ± 3</td>
</tr>
<tr>
<td>21% O2</td>
<td>83 ± 4</td>
<td>76 ± 3</td>
<td>68 ± 2</td>
</tr>
<tr>
<td>100% O2</td>
<td>82 ± 4</td>
<td>91 ± 5</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>Hypoxemic</td>
<td>39 ± 1</td>
<td>50 ± 4</td>
<td>43 ± 5</td>
</tr>
<tr>
<td>21% O2</td>
<td>39 ± 1</td>
<td>56 ± 2</td>
<td>44 ± 2</td>
</tr>
<tr>
<td>100% O2</td>
<td>40 ± 2</td>
<td>60 ± 4</td>
<td>52 ± 4</td>
</tr>
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(2–52) min in the hypoxemic, 21% O2, and 100% O2 groups, respectively (P = 0.17).

During resuscitation, the EEG in the hypoxemic group returned to baseline in four piglets. The EEG was abnormal in two piglets and did not recover in another two. In the 21% O2 group, seven EEGs returned to baseline, and only one was abnormal. In the group resuscitated with 100% O2, five piglets had EEGs that returned to baseline and three had abnormal EEGs. There was no significant difference among the three groups in quality of the EEG at the end of the resuscitation period (P = 0.22).

Correlations among variables. During resuscitation, the maximal value of the OI strongly correlated with the maximal value of the cerebral venous SssO2 (r = 0.84, P < 0.001), but no significant correlation was found between the maximal OI and the EEG pattern at the end of resuscitation. The maximal concentration of extracellular hypoxanthine in the cerebral cortex correlated well with the maximal concentration in the cerebral striatum (r = 0.70, P < 0.001). No significant correlation was found between the EEG pattern at the end of resuscitation and the maximal concentration of extracellular hypoxanthine in the cerebral cortex or the cerebral striatum during resuscitation.

DISCUSSION

In the present study, controlled hypoxemic resuscitation normalized EEG and extracellular hypoxanthine concentrations in the cerebral cortex and striatum as efficiently as, but not in a manner superior to, resuscitation with 21% O2 or 100% O2. BE and plasma hypoxanthine, however, normalized significantly more slowly during hypoxemic resuscitation than during resuscitation with 21% O2 or 100% O2, indicating a delayed systemic metabolic recovery from hypoxia during hypoxemic resuscitation.

Gradual reintroduction of O2 during early resuscitation has demonstrated improved functional and metabolic recovery of the nervous system in several animal studies. Graded postischemic reoxygenation of rabbit spinal cord demonstrated a highly protective effect on vascular membrane permeability (15), a reduction in histological damage (7, 8), and an improvement in metabolic and functional recovery after 4 days (5). Graded postischemic reoxygenation reduced the inhibition of cerebral cortical protein synthesis in dogs,
suggesting a reduction in posts ischemic damage to nervous tissue (3). By contrast, hypoxic reperfusion after cerebral ischemia in swine did not improve the recovery of somatosensory evoked potentials after 2-h survival (30). However, all of these studies investigated single- organ ischemia-reperfusion, whereas we investigated global hypoxia and resuscitation. In the present study, the delayed recovery of BE and plasma hypoxanthine in the hypoxemic group despite similar cerebral recovery indicates that organs other than the brain may have suffered during this resuscitation form. This is not surprising because blood flow to vital organs during hypoxia is increased at the expense of less important organs (11). Possible systemic responses like altered blood flow, altered substrate supply to the brain, and altered function of both the brain and other organs may therefore have influenced the outcome in our study. The significantly lower MAP during controlled hypoxemic resuscitation suggests a cardiovascular insufficiency in this group.

Resuscitation with 8.5 or 12% O2 for 15 min after 9 min of cardiac arrest in adult dogs did not provide any protection from neurological dysfunction beyond that offered by normoxic resuscitation (37). Actually, resuscitation with 8.5% O2 tended to give a greater neurological deficit and a reduced overall survival compared with that in normoxically resuscitated dogs. In contrast to our controlled hypoxemia model, the hypoxemic resuscitation in that model was given with a fixed FIO2, without attention to cerebral oxygenation. Furthermore, the above-mentioned studies used an adult animal model, whereas we investigated resuscitation of newborns.

The present results confirm previous studies from our group in finding that resuscitation with 21% O2 is as efficient as resuscitation with 100% O2 (16, 18, 19). Furthermore, adverse effects of resuscitation with high concentrations of O2 have been suggested (6, 13, 36). In a recent study in newborn piglets, our laboratory found a significantly higher increase in extracellular hypoxanthine concentrations in the cerebral cortex during the initial period of resuscitation with 100% O2 compared with use of 21% O2 (6). These results suggested a more severe impairment of energy metabolism in the cerebral cortex or increased blood-brain barrier damage during resuscitation with 100% O2 compared with resuscitation with 21% O2. This could, however, not be confirmed in the present study. This may be explained by the use of different anesthesia and different hypoxia models in these two studies. For instance, mild hypercapnia during hypoxia-ischemia, as used in the present study, has been shown to be protective of the immature rat brain compared with normocapnia (32).

Ventilation with 6% O2 introduced a rapid and severe hypoxemia in the present study. The first arterial blood samples were taken 5 min after hypoxia started, and the PaO2 at this time point was 18 ± 1 Torr. The EEG activity during hypoxia was, however, present for a rather long period, and the median time for the EEG to become isoelectric was 24 (12–34) min. This suggests that the change in EEG pattern reflects an impaired O2 supply to the neuronal environment rather than a possible programmed response to hypoxia for preservation of cellular integrity. In a similar hypoxia model using 10- to 72-h-old piglets, the EEG background activity 1 h after the hypoxic episode correlated well \( (r = 0.86) \) with the pathology score for cerebral cortical/white matter after 72 h (27). Therefore, EEG is suggested to be an appropriate marker of brain function during hypoxia and resuscitation in newborn piglets.

NIRS was demonstrated in the present study to be a valuable technique in measuring changes in cerebral oxygenation. The cerebral blood volume consists, under normal conditions, of \( \sim \frac{1}{3} \) arterial blood and \( \frac{2}{3} \) venous blood. During hypoxia and early resuscitation, the cerebral blood volume increases (as measured by \( \text{Tb} \)) and this increase in cerebral blood volume is assumed to consist mainly of venous blood (25). Finally, normally \( >90\% \) of the O2 available in blood is bound to Hb. Consequently, the \( \text{OI} \) correlated well with the \( S_{\text{SO2}} \), in the present study.

Usually, supplementary O2 is given during the first minutes of resuscitation of asphyxiated newborn infants. However, we have disputed the necessity of this practice (21, 22). The \( \text{OI} \) and the cerebral venous O2 contents in the present study increased within the first minutes of resuscitation to significantly higher levels than baseline in the 21% O2 group, suggesting a luxury perfusion with an adequate oxygenation of the brain in this period, even when room air was used for resuscitation.

In rhesus monkeys, the basal ganglia are severely damaged during anoxia, whereas cortical damage is most prominent during hypoxia (14). Striatum has, however, been suggested to be a brain region particularly vulnerable to hypoxia (2). In newborn infants, brain injury after hypoxia may occur in most parts of the brain (26). The microdialysis technique allows us to measure extracellular concentrations of hypoxanthine and xanthine from the piglet cerebral cortex and striatum. The insertion of microdialysis probes induces only limited damage to the blood-brain barrier (28) and the surrounding cells in the piglet cerebral cortex (6). The concentration of a substrate in the extracellular fluid depends on the production and utilization by the cells and the delivery and elimination through the blood vessels. A possibly different cerebral blood flow, as well as different blood-brain barrier damage among the resuscitation groups, may therefore have influenced the microdialysis results in this study. Hypoxanthine reflects the intracellular energy status and was used as a marker of hypoxia.

Halothane was, in the present study, given in low doses (0.3–0.5%) to minimize the cardiodepressive side effects simultaneously as sleep was ensured. The analgesic part of the anesthesia was taken care of by fentanyl. If halothane had been given as the only anesthetic in the present study, the doses of halothane would have had to be increased to 1.0–1.2% [the minimum alveolar concentration of 1 in newborn piglets during physiological conditions is 0.8% (20)], and the side effects of halothane would thereby have be-
come severely increased. In addition, halothane was withdrawn during hypoxia because the effects of halothane are known to increase during severe hypoxemia (4). Furthermore, as with most anesthetics, both halothane and, to a lesser degree, fentanyl, reduce the cerebral metabolic rate of O₂ (1, 23). The cerebral blood flow increases during halothane anesthesia (23) but is almost unchanged during fentanyl anesthesia (1). However, it is unlikely that the identical use of anesthetics in this study should disturb the comparison among the groups.

Our hypoxia-resuscitation model in newborn piglets is a simplified model of a very complex system, and care should be exercised in drawing clinical conclusions on the basis of our data. The full-term human brain is, however, comparable to that of a newborn piglet (29).

In conclusion, early cerebral metabolic and electrophysiological recovery during controlled hypoxic resuscitation was as efficient as, but not superior to, recovery during resuscitation with 21% O₂ or 100% O₂. The systemic metabolic recovery from hypoxia, however, was delayed during controlled hypoxic resuscitation. Resuscitation with 21% O₂ was found to be as efficient as resuscitation with 100% O₂ in this newborn piglet hypoxia model.

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