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

BJÖRN A. FEET, 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 groups (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.

Asphyxiated newborn infants are routinely resuscitated with high concentrations of O2. The necessity and possible adverse effects of this practice have been questioned (21, 22).

In several animal studies (16, 18, 19), and in a pilot clinical study (17), resuscitation of newborns with 21% O2 has been found to be as efficient as resuscitation with 100% O2. Furthermore, adverse effects of resuscitation with high concentrations of O2 have been suggested. For instance, dogs resuscitated with 21% O2 demonstrated significantly better neurological outcome at 12 and 24 h after 9 min of normothermic cardiac arrest than dogs resuscitated with 100% O2 (36).

During early resuscitation after severe hypoxia, blood flow to vital organs normally increases (19). The organ blood flow greatly exceeds tissue demands for O2 on the basis of measurements of high venous Po2 and decreased arteriovenous O2 differences. This indicates that venous (and presumably tissue) O2 are not the sole, or primary, determinants of reactive hyperemia. Because the production of free radicals may be proportional to Po2 (9, 24), a burst of free radical production may be related to the increase in PO2 that accompanies both reactive hyperemia and a high inspired fraction of O2 (FiO2). This burst of free radicals may increase brain damage (31). A gradual reintroduction of O2 during early resuscitation has therefore been suggested and may theoretically reduce the free O2 radical production and thereby reduce possible damage to the brain and other organs.

In the present study the O2 supply during hypoxemic resuscitation was reduced to a level close to the minimal O2 requirements of the piglet brain. This controlled hypoxemic resuscitation model was based on our recent hypoxic threshold study in newborn piglets (unpublished observations). During stepwise increasing hypoxia, electroencephalographic (EEG) suppression and the onset of accumulation of hypoxanthine in the cerebral cortex appeared at an FIO2 of 0.08–0.10, corresponding to a cerebral venous sagittal sinus O2 saturation (SssO2) of 10–13%. In the present study the piglets in a hypoxic group were ventilated with 12–18% O2 adjusted to achieve an SssO2 values of 17–23%, levels giving a safety margin to the hypoxic threshold but still being much lower than baseline values of 45 ± 1%. By contrast, the O2 supply in previous hypoxemic resuscitation studies has been given without attention to the cerebral oxygenation. The animals in these studies have been ventilated with either fixed low FIO2 during the first minutes (5, 7, 8, 15, 37) or with FIO2 adjusted to maintain arterial Po2 (PoaO2) within certain limits (30).

The purpose of the present study was to test the hypothesis that controlled hypoxemic resuscitation [guided by cerebral venous SssO2 and near-infrared spectrophotometry (NIRS)] improves early brain recovery by reducing available substrate (O2) necessary for oxidant injury in severely hypoxic newborn piglets. Brain recovery was evaluated by EEG and accumulation of extracellular hypoxanthine in the cerebral cortex and striatum.

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, Miranda, 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 (Engström Eliza, Engström 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-Glukostat (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 recorded continuously by using a recorder (TA 5000, Gould Recording Systems, Cleveland, OH). Heart rate was monitored 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, outer 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 nucudaudatus. 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–Fp3 and Fp2–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 Torr) 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 Fio2, resulting in SsatCO2 values between 17 and 23% O2 (hypoxic group; n = 8), 21% O2 (21% 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 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. Hypoxanthine 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

...was 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).

Fig. 2. Electroencephalography (EEG) patterns at baseline (before hypoxia) and at 60 and 120 min after start of resuscitation in 3 piglets (A–C). All piglets demonstrated a continuous EEG at baseline. During resuscitation, piglet A demonstrated a continuous EEG with a slight decrease in fast-frequency activity (no seizures present; "recovery to baseline EEG"). A discontinuous burst-suppression pattern during resuscitation was demonstrated in piglet B ("abnormal recovery"). Piglet C demonstrated an EEG pattern with low-voltage activity (amplitude <50% of baseline) at 60 min and a burst suppression-like pattern (suppression periods containing low-voltage activity) at 120 min after start of resuscitation ("abnormal recovery").
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.

RESULTS

The total duration of hypoxia was 36 ± 5, 40 ± 6, and 33 ± 4 min in the hypoxemic, 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 hypoxemic, 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 end of hypoxia, 56, 56, and 61 Torr in the hypoxemic, 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 hypoxemic, 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 hypoxemic 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 hypoxemic 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-
Hypoxic group compared with the 21% O₂ and 100% O₂ groups (P < 0.05).

Extracellular hypoxanthine in cerebral cortex and striatum. Extracellular hypoxanthine concentrations in the cerebral cortex and striatum increased three- to fourfold during hypoxia (Fig. 6 and 7). During early resuscitation, extracellular hypoxanthine concentrations increased further and reached maximum values after 30–60 min of resuscitation. During the rest of the resuscitation period, extracellular hypoxanthine concentrations decreased toward baseline values, and no significant differences were found among the groups. Xanthine in cerebral cortex, cerebral striatum, and plasma followed a pattern similar to that of hypoxanthine (data not shown).

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 hypoxic, 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>
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<tr>
<td></td>
<td></td>
<td></td>
<td>5</td>
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<tr>
<td>MAP, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxic</td>
<td>82 ± 5</td>
<td>26 ± 2</td>
<td>63 ± 7</td>
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<tr>
<td>21% O₂</td>
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<td>91 ± 5</td>
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<tr>
<td>PaCO₂, Torr</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>39 ± 1</td>
<td>56 ± 4</td>
<td>50 ± 4</td>
</tr>
<tr>
<td>21% O₂</td>
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<td>60 ± 4</td>
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<tr>
<td>Inspired O₂ concentration, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxic</td>
<td>21 ± 0</td>
<td>6 ± 0</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>pH</td>
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<tr>
<td>Hypoxic</td>
<td>7.42 ± 0.02</td>
<td>6.82 ± 0.04</td>
<td>6.83 ± 0.04</td>
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<tr>
<td>21% O₂</td>
<td>7.45 ± 0.01</td>
<td>6.86 ± 0.07</td>
<td>6.83 ± 0.06</td>
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<tr>
<td>100% O₂</td>
<td>7.41 ± 0.01</td>
<td>6.77 ± 0.06</td>
<td>6.75 ± 0.05</td>
</tr>
</tbody>
</table>

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).

Fig. 4. Base excess (BE) during hypoxia and resuscitation. Values are means ± SE; n = 8 piglets/group. **P < 0.01 vs. hypoxemic group (group difference by repeated-measures ANOVA). § BE normalized significantly more slowly (P < 0.05) in hypoxemic group compared with 21% O₂ and 100% O₂ groups.

Fig. 5. Hypoxanthine in arterial plasma during hypoxia and resuscitation. Values are means ± SE; n = 8 piglets/group. § Hypoxanthine normalized significantly more slowly (P < 0.05) in hypoxemic group compared with 21% O₂ and 100% O₂ groups.
(2–52) min in the hypoxic, 21% O₂, and 100% O₂ groups, respectively (P = 0.17).

During resuscitation, the EEG in the hypoxic 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 hypoxic 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 hypoxic resuscitation than during resuscitation with 21% O₂ or 100% O₂, indicating a delayed systemic metabolic recovery from hypoxia during hypoxic 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 postischemic damage to nervous tissue (3). By contrast, hypoxemic 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 hypocapnia 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 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 ~ 1/3 arterial blood and 2/3 venous blood. During hypoxia and early resuscitation, the cerebral blood volume increases (as measured by THb in the present study; Fig. 9), 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 OI correlated well with the SSO₂ 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 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 been...
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 hypoxicemic 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 hypoxicemic resuscitation. Resuscitation with 21% O₂ was found to be as efficient as resuscitation with 100% O₂ in this newborn piglet hypoxia model.

The authors thank Professor Thore Engeland for valuable statistical advice, Professor Kari Skullerud for confirming the accurate position of the cerebral striatum, and Pilvi Ilves and Roger Odegaard for technical assistance.

B. A. Feet is a research fellow with the Norwegian Council on Cardiovascular Diseases. This work was also supported by the Rgf Geir Gjertsen Foundation, The Beckett Foundation, The Nansen Foundation, Swedish Medical Research Foundation Grant 4732, and the Axelsson-Johnson Foundation.

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Received 22 July 1997; accepted in final form 19 November 1997.

REFERENCES


