RESEARCH ARTICLE

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Changes in cerebral haemodynamics, regional oxygen saturation and amplitude-integrated continuous EEG during hypoxia-ischaemia and reperfusion in newborn piglets

Abstract Perinatal asphyxia models are necessary to obtain knowledge of the pathophysiology of hypoxia-ischaemia (HI) and to test potential neuroprotective strategies. The present study was performed in newborn piglets to obtain information about simultaneous changes in cerebral oxygenation and haemodynamics and electrocortical brain activity during a 60-min period of HI and up to 2 h of reperfusion using near infrared spectrophotometry (NIRS) and the amplitude-integrated EEG (aEEG). HI was induced by occluding both carotid arteries and decreasing the fraction of inspired oxygen (FiO_2) to 0.08–0.12 for 60 min. The mean arterial blood pressure (MABP) and heart rate increased, the oxygenated haemoglobin (O_2Hb) decreased, and the deoxygenated haemoglobin (HHb) increased, but total haemoglobin (tHb) remained stable during the 60-min HI period. The regional oxygen saturation (rSO_2) was significantly decreased during the whole HI period, as was the electrocortical brain activity. Upon reperfusion and reoxygenation, the MABP normalised to baseline values but the heart rate remained increased. O_2Hb and HHb recovered to baseline values and tHb remained unchanged. As indicated by the unchanged tHb values during the HI period, it was suggested that compensatory cerebral perfusion occurred during this period, probably via the vertebrobasilar arterial system. Furthermore, in this model a clear hyperperfusion period directly upon reperfusion and reoxygenation is not present. rSO_2 showed a quick recovery to baseline values, but the aEEG-measured electrocortical brain activity remained reduced following HI. In conclusion, the rSO_2 and aEEG showed a different time profile following perinatal asphyxia. The stable tHb during HI and reperfusion in this model differs from observations in human neonates.

Keywords Hypoxia-ischaemia · Brain · Newborn · Near infrared spectrophotometry · Amplitude-integrated EEG

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Introduction

The reperfusion and reoxygenation period following perinatal asphyxia has been increasingly recognised to be an important cause of additional brain cell injury after the hypoxia-ischaemia (HI) insult (Rosenberg et al. 1989; Mujsce et al. 1990; Palmer et al. 1993; Shadid et al. 1998). Pharmaceutical intervention studies, investigating potential neuroprotective effects of different compounds after HI (Groenendaal et al. 1999), were performed in an experimental model of perinatal asphyxia in newborn piglets. Transient carotid artery occlusion was combined with a reduced fraction of inspired oxygen (FiO_2) to induce severe HI, leading to secondary energy failure 24–48 h afterwards (Lorek et al. 1994; Penrice et al. 1997). Cerebral oxygenation and haemodynamics and electrocortical brain activity during the actual HI insult and upon reperfusion have not been simultaneously measured so far. This knowledge, however, might be important for the validation of this particular neonatal HI model as a reliable method to simulate severe perinatal asphyxia in the human newborn baby.

Therefore, the aim of this study was to obtain information about cerebral oxygenation and haemodynamics, and electrocortical brain activity using the carotid occlusion model in newborn piglets during and after HI. To examine changes in cerebral oxygenation and haemodynamics, we used near infrared spectrophotometry (NIRS) (Pryds et al. 1990; Wolf et al. 1998). For evaluation of changes in electrocortical brain activity, we used a filtered, one-channel, continuous amplitude-integrated EEG (aEEG) (Maynard et al. 1969), which is frequently used in intensive care units for long-term monitoring of brain activity (Greisen

1994). Furthermore, this aEEG provides a tool in the evaluation of HI encephalopathy in full-term neonates and the evaluation of anticonvulsive treatment (Hellstrom-Westas et al. 1995; Toet et al. 1999).

Materials and methods

Animal preparation

Eleven newborn Dutch store piglets were used. Age (mean ± SD) was 2.3±1.4 days and body weight 1520±360 g. In accordance with Dutch laws, the Animal Care Committee of Utrecht University approved the animal care protocols. Animals were placed on a heating blanket and a heating lamp was used to maintain rectal temperature at between 38.5° and 39.5°C. Following induction with 4% isoflurane and a nitrous oxide/oxygen mixture (79:21), general anaesthesia was maintained with isoflurane (1.5–2.0%) in the same mixture. After intubation the piglets were mechanically ventilated using a continuous flow, pressure-controlled ventilator (Amsterdam Infant Ventilator mk3, Hoek Loos, Amsterdam, The Netherlands) equipped with an end-tidal CO_2 probe. An intravenous catheter was inserted in a superficial abdominal vein for continuous infusion of glucose 5%/NaCl 0.45% (5 ml/kg/h). After local anaesthesia with lidocaine 2% before each skin incision, a catheter was advanced surgically in the right femoral artery and used for monitoring of arterial blood pressure and sampling of arterial blood gases. The blood was heparinised with 2.5 U/ml (2 ml/h). Inflatable occluders (OC2a, In Vivo Metric, Healdsburg, CA) were placed around both common carotid arteries for induction of HI. After surgery, atropine (0.2 ml) was administered intravenously. Pancuronium bromide (0.5 mg/kg i.v.) was used for muscle paralysis throughout the experiment to avoid artefacts on the aEEG from muscle movements.

Assessment of cerebral oxygenation and haemodynamics and regional oxygen saturation

To examine changes in cerebral oxygenation and haemodynamics, we used NIRS (Critikon Cerebral RedOx Monitor Model 2020, Johnson & Johnson Medical Ltd., Norderstedt, Germany) (Jobsis 1977). The head of the newborn piglet is relatively transparent to near infrared light. Haemoglobin (Hb) is a natural chromophore and has an oxygenation dependent absorption in this wavelength region. By selection of the appropriate wavelength, an algorithm has been developed to convert absorption changes into changes of oxygenated Hb (O_2Hb), deoxygenated Hb (HHb) and total Hb (tHb=O_2Hb+HHb). Assuming a stable haematocrit, the changes in tHb will reflect the changes in cerebral blood volume (Pryds et al. 1990; Wyatt et al. 1990). Earlier studies also showed a good relationship between changes in cerebral blood volume and changes in ^{133}Xe-measured cerebral blood flow in preterm babies (Pryds et al. 1990) and with carotid-artery-assessed changes in global cerebral blood flow in a perinatal HI model in newborn lambs (Shadid et al. 1999). Although NIRS-measured tHb certainly does not measure actual cerebral blood flow, we consider distinct changes in tHb to be indicative of changes in global perfusion of the brain. The Critikon 2020 estimates actual tHb using a sensor with two receiving detectors at different distances (10 and 35 mm). This double detector sensor reduces the influence of skull and skin (Wolf et al. 1999) and decreases the variation due to position of or pressure exerted on the sensor (Wolf et al. 1997). Estimation of absolute O_2Hb, HHb and tHb (in micromoles) is then possible (Wolf et al. 1997); (Gavilanes et al. 2001). It has to be taken into account that cerebral haemoglobin concentrations, measured with the Critikon 2020, return significantly higher values than the directly measured cerebral haemoglobin concentrations, although the method showed a strong positive correlation (Wolf et al. 1998). Additionally, the regional oxygen saturation (rSO_2) of the brain was calculated (=O_2Hb/tHb).

Assessment of electrocortical brain activity

To assess the electrocortical brain activity, the aEEG (Cerebral Function Monitor, Lectromed, Oxford Instruments, Oxford, UK) was used as described previously (Maynard et al. 1969; Hellstrom-Westas et al. 1995). The cerebral function monitor has a special filter, which sharply attenuates frequencies below 2 and above 15 Hz, giving an amplitude-integrated registration with the main EEG frequencies, but with few disturbances from artefacts. The aEEG signal was obtained from a pair of needle electrodes, placed at the P3 and P4 position of the 10–20 International System, i.e. in the left and right parietal region of the piglet's head with a frontal reference electrode. The aEEG was recorded on a semilogarithmic scale (0–100 µV). The paper speed was 1 mm/min. Simultaneously with the amplitude curve, an impedance curve recorded the reliability of the signal, and showed artefacts from movements, experimental procedures, or loose electrodes. An increase in the mean voltage of the aEEG during HI or the presence of seizures could be recognised within 1 min, so that ventilatory settings could be adjusted, when appropriate.

Physiological measurements

O_2Hb, HHb, tHb, rSO_2, arterial SO_2, aEEG, mean arterial blood pressure (MABP), heart rate and rectal temperature were recorded continuously throughout the experiment, digitised with a frequency of 10 Hz, and stored on a personal computer. Arterial pH, base excess, arterial PO_2 and PCO_2, as well as glucose concentration, were measured every 30 min throughout the HI period and hourly during reperfusion. Serum lactate was measured before HI and at the end of 1 h of HI. For statistical evaluation, for representation in the figures and for comparisons with the various variables, the patterns of O_2Hb, HHb tHb, rSO_2 and aEEG were averaged every 10 min.

Experimental protocol

Animals were normoventilated for a 1-h baseline period before induction of HI. Piglets were exposed to HI by inflating the cuffs around both carotid arteries and decreasing the FiO2 for 1 h. FiO2 was reduced until the background of the aEEG was decreased to 10 µV or less. Ten minutes after the start of HI, inhalation of isoflurane was suspended until 10 min after reperfusion and reoxygenation to exclude the effect of isoflurane on cerebral haemodynamics and aEEG, but ventilation with a nitrous oxide/oxygen mixture was continued. After 60 min of HI, the carotid occluders were deflated and the FiO2 was normalised, carefully avoiding hyperoxaemia. Metabolic acidosis was not corrected following HI. Ten minutes after the start of reperfusion, isoflurane was resupplied and continued during the remaining study period.

Statistical analysis

Data were analysed non-parametrically and are expressed as means ± SD. Physiological variables, NIRS and aEEG data were analysed non-parametrically using the one-sample repeated measures design according to Friedman, followed by Wilcoxon signed rank tests when appropriate. A P value <0.05 was considered statistically significant.

Results

Physiological data

The physiological data are summarised in Table 1. MABP increased significantly during HI, but decreased upon reperfusion and reoxygenation to values not sig-

Table 1 Values (means ± SD) of mean arterial blood pressure (*MABP*), heart rate (*HR*), rectal temperature (*Temp*), hemoglobin (*Hb*), arterial oxygen saturation (*O2 sat*), arterial pH and base excess (*BE*), blood glucose and lactate during hypoxia-ischaemia (*HI*) and reperfusion

	Baseline	30 min HI	60 min HI	30 min reperfusion	60 min reperfusion	90 min reperfusion	120 min reperfusion
MABP (mmHg)	47±9	70±17**	64±13*	47±9	44±7	44±8	46±7
HR (bpm)	156±23	222±48***	254±36***	204±30**	192±24**	192±26**	193±27**
Temp. (°C)	38.7±0.6	38.9±0.8	39.0±0.5	39.1±0.5	39.3±0.4*	39.3±0.4*	39.2±0.4*
Hb (mmol/l)	4.3±0.5	4.7±0.5	4.6±0.6	4.2±0.7	5.0±0.4		4.5±0.6
O2 sat. (%)	95.5±2.4	45.2±18.3***	24.8±17.6***	96.2±1.9	96.8±2.3	96.8±2.1	97.3±2.4
pH	7.41±0.07	7.38±0.07	7.25±0.14***	7.25±0.15*			7.41±0.06
PCO_2 (mmHg)	41.1±9.0	42.1±8.5	45.6±11.8	46.1±10.4			43.7±6.8
BE (mM)	0.9±2.9	−0.4±2.7	−6.9±6.1***	−6.9±7.6*			2.2±4.2
Glucose (mM)	6.6±1.4	7.8±1.6	10.4±4.8	9.5±4.1			7.6±1.0
Lactate (mM)	4.4±1.9		10.3±3.0**				

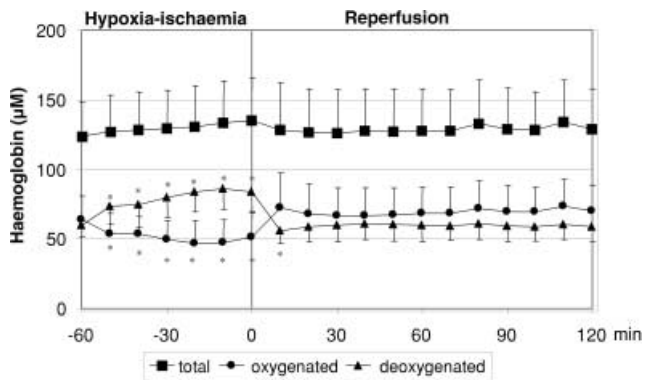*$P<0.05$, **$P<0.01$, ***$P<0.005$ vs baseline (Wilcoxon signed ranks test)

Fig. 1 Pattern (means ± SD) of oxygenated hemoglobin (O2Hb), deoxygenated hemoglobin (HHb) and total hemoglobin (tHb) of the newborn piglets during hypoxia-ischaemia and subsequent reperfusion. *$P<0.05$ vs baseline

Fig. 2 Pattern (means ± SD) of regional oxygen saturation (*rSO2*) in the brain of newborn piglets during hypoxia-ischaemia and reperfusion. *$P<0.05$ vs baseline

Fig. 3 Pattern (means ± SD) of amplitude-integrated EEG (*aEEG*) in newborn piglets during hypoxia-ischaemia and reperfusion. *$P<0.05$, #$P<0.01$ vs baseline

nificantly different from baseline. Heart rate also increased during HI and remained increased during the whole post-HI study period. No relevant changes in rectal temperature were demonstrated during the study period. Arterial pH and base excess after 60 min of HI were significantly lower as compared to baseline values, but both parameters recovered within 2 h post-HI. As expected arterial saturation and PO_2 values were significantly lower during HI, whereas arterial PCO_2 values did not change during the experiment and were in the normal range (arterial PO_2 values not shown). Blood glucose levels did not change during the experiment, but plasma lactate levels at 60 min of HI increased significantly from baseline.

Cerebral oxygenation and haemodynamics

Figure 1 shows the patterns of absolute concentrations of O2Hb, HHb and tHb at baseline, during 60 min of HI, and up to 2 h post-HI in the investigated newborn piglets. O2Hb values were significantly decreased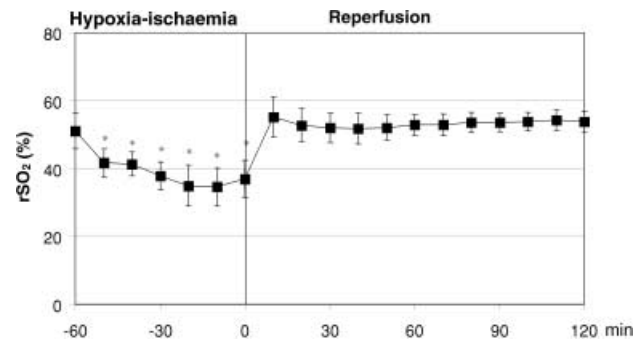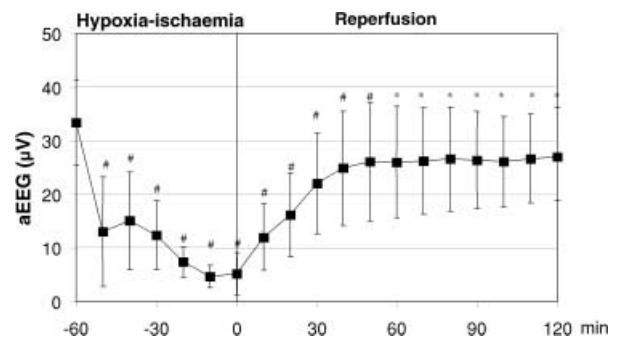 from baseline values during HI. Upon reperfusion and reoxy-genation, O2Hb quickly recovered to baseline values. HHb increased significantly during HI, but recovered after 10 min of reperfusion and reoxygenation to baseline values. tHb did not change from baseline and was stable throughout the experiment.

rSO2 (Fig. 2) decreased significantly from baseline values during HI, mainly due to the decrease in O2Hb (tHb was stable), but recovered within minutes to baseline values upon reperfusion and remained stable during the entire post-HI period.

Electrocortical brain activity

The aEEG decreased significantly from baseline values during HI and during the whole reperfusion and reoxygenation period (Fig. 3).

Discussion

Temporary occlusion of both carotid arteries combined with hypoxia has been used in newborn piglets as a model of perinatal asphyxia in human neonates (Lorek et al. 1994). In this model the pathophysiology of the brain during HI, upon and after reperfusion and reoxygenation, as well as the impact of therapeutic interventions can be studied (Lorek et al. 1994; Penrice et al. 1997; Thornton et al. 1998; Groenendaal et al. 1999). To the best of our knowledge, this is the first study providing simultaneous data about systemic haemodynamics, cerebral oxygenation and haemodynamics, and electrocortical brain activity in this model of perinatal HI in newborn piglets during both the HI insult and the early reperfusion and reoxygenation phase.

Animals were paralysed with pancuronium bromide in order to reduce the effects of muscle artefacts on aEEG recordings. Earlier studies showed a correlation between cerebral blood flow regulation and pancuronium bromide (Chemtob et al. 1992). However, in the present study pancuronium bromide was only administered once, before the start of the measurements. Furthermore, doses of 0.3 mg/kg pancuronium bromide i.v. did not influence the cerebral blood flow in newborn piglets (Pourcyrous et al. 1992).

The study design was set up identically to previously conducted studies inside the magnet for the effect of pharmaceutical treatment on cerebral energy state during HI (Groenendaal et al. 1999). Piglets did not receive intravenous anaesthetics in order to reduce the influence of anaesthetics on brain cell transmission and injury (Zhan et al. 2001). Nevertheless, the piglets were sedated during the experiment with nitrous oxide and isoflurane to provide the necessary comfort. During the HI insult isoflurane was discontinued 10 min after start of HI. At that time the aEEG was reduced to a mean of 13 μV, demonstrating depressed electrocortical activity. Previously, we have observed no signs of pain perception during the HI insult in piglets without muscle paralysis (personal observation). After discontinuation of isoflurane after 10 min of HI, there was a moderate increase in heart rate and a more pronounced effect on MABP. During reinstitution of isoflurane upon reperfusion the heart rate remained fairly constant, but the MABP decreased. Therefore, the discontinuation of isoflurane had the most profound effects on MABP. The changes in heart rate and mABP were considered as a result of the HI insult itself, as demonstrated in earlier studies in anaesthetised lambs (Marks et al. 1996) and piglets (Bauer et al. 1999).

In this study we found that absolute tHb values did not change during HI and the reperfusion/reoxygenation period as compared to baseline values. The O_2Hb values significantly decreased and the HHb values significantly increased during HI, both recovering to baseline values after 10 min in the reperfusion and reoxygenation period. The rSO_2 decreased significantly during HI, but also quickly recovered upon reperfusion. The reader might be surprised that the rSO_2 is higher than the arterial O_2 during HI. A likely explanation is the too high values generated by the algorithm of the NIRS instrument, as mentioned in "Materials and methods," which also affect the rSO_2 readings. Even though NIRS does not give correct absolute values, the qualitative trend of the traces is correct (Wolf et al. 1998).

The above-mentioned NIRS-measured pattern indicates a stable cerebral blood volume in this perinatal asphyxia model during HI, as tHb remained unchanged without large fluctuations in haemoglobin (Table 1). Therefore, no gross changes in global cerebral blood flow are expected. However, the oxygenation of the piglet's brain was decreased during HI, as indicated by the decrease in rSO_2. The maintenance of cerebral blood volume, despite occlusion of both carotid arteries, was probably caused by compensatory perfusion via the vertebrobasilar arterial system (Haaland et al. 1995). This assumption is further supported by the observation that occlusion of both carotid arteries without reduction of FiO_2 has little or no influence on brain energy state, measured with phosphorous magnetic resonance spectroscopy (personal observation).

Our model differs from the clinical situation during severe perinatal asphyxia, in which initially cerebral hyperperfusion occurs during the HI period (Low 1995). In the case of ongoing severe hypoxia, the preferential hyperperfusion to vital organ systems is not sufficient to adequately meet oxygenation of the brain and myocardium, leading to decreased contractility of the heart and aggravation of brain cell injury. Earlier experimental studies in newborn animals closely mimicking severe perinatal asphyxia in neonates confirmed this particular haemodynamic pattern (McPhee et al. 1985; Dorrepaal et al. 1997; Bennet et al. 1999; Shadid et al. 1999). In the present study the tHb remained constant, and did not increase significantly during HI. A possible explanation for the lack of hyperperfusion during HI might be the fact that although the vertebrobasilar arterial system can support compensatory perfusion, it works inadequately to supply the preferential hyperperfusion of the brain.

A second important difference was the absence of an early rise in cerebral hyperperfusion directly upon reperfusion and reoxygenation in our model. This is normally seen in the clinical setting after severe perinatal asphyxia and is also reported from several animal HI experiments, mimicking asphyxia (McPhee et al. 1985; Leffler et al. 1989; Dorrepaal et al. 1997; Shadid et al. 1998; Bennet et al. 1999).

To validate this observation in the present study we serially performed dynamic susceptibility contrast imaging (DSCI) according to the method of Rempp et al. (1994) in a pilot study of six additional newborn piglets

to estimate changes in cerebral perfusion directly after the HI period. Three piglets were subjected to the present HI model, and three piglets were exposed to hypoxic-hypoxia without carotid artery occlusion (FiO_2: 0.06–0.08) for 1 h. The latter three piglets showed all a two- to threefold increase in brain perfusion within minutes following reperfusion, in contrast to the piglets that were subjected to hypoxia-ischaemia with carotid occlusion. Although we have no clear explanation for this lack of immediate post-HI brain hyperperfusion in our model, it might be explained by the slow reopening of the common carotid arteries after the 60-min occlusion period. This was observed during the MR experiments of the above-described DSCI study, in which additional MR angiography was performed. A slow reopening of the carotid arteries was observed after deflation of the vascular occluders, until full dilation occurred only after 10 min after cuff deflation. Alternative explanations might be the use of isoflurane, which is known to influence vascular tone and arterial blood pressure (Stevens et al. 1971; Ullman 2000). This is, however, less likely because isoflurane was only restarted 10 min after the end of HI, whereas the peak of cerebral hyperperfusion will be expected within a few minutes post-HI (Leffler et al. 1989). It might be argued that the HI stress might be less severe in our model than during clinically occurring severe perinatal asphyxia. Considering the prolonged reduction in the aEEG and the occurrence of secondary energy failure in earlier studies of our group (Peeters et al. 2000; Koster et al. 2001) and in comparable studies using combined carotid occlusion and FiO_2 reduction in newborn piglets (Lorek et al. 1994), this explanation is not likely. Therefore, the delayed aforementioned opening of the carotid arteries is the most satisfactory explanation.

Finally, the pattern of the aEEG was investigated. Firstly, an immediate drop in aEEG is present at the start of the HI period, while arterial PO_2 and rSO_2 values are still high. This phenomenon might be explained by a decrease in neuronal cell metabolism to protect the cortical brain cells against further injury, as reported in earlier studies (Harkonen et al. 1969; Duffy et al. 1972; Shadid et al. 1999). Furthermore, after 10 min of HI a stabilisation of the mean voltage of the aEEG is present, probably as a result of a transient increase in MABP caused by the discontinuation of isoflurane. Thirdly, the aEEG remained reduced during the whole reperfusion and reoxygenation period, whereas the O_2Hb and rSO_2 showed a rapid improvement to baseline levels at that time. This suggests lower oxygen utilisation of the brain during this period of reperfusion and reoxygenation. Earlier studies in the developing brain strongly indicated a relation between severity of brain damage and the duration of suppression of electrical brain activity (Williams et al. 1992). It was reported in a clinical study in severely asphyxiated full-term babies (Toet et al. 1999) that the aEEG in the early neonatal period (first 3 h of life) predicted the severity of post-HI encephalopathy. In the present study the reduced electrocortical brain activity

and lower oxygen utilisation might thus suggest potential long-term brain damage in these newborn piglets.

In conclusion, simulation of perinatal asphyxia with transient carotid artery occlusion combined with hypoxia showed no compensatory hyperperfusion of the brain during actual HI, probably because the compensatory perfusion via the vertebrobasilar system was inadequate. The cerebral hyperperfusion directly upon reperfusion and reoxygenation, normally seen after severe HI, also did not occur in this HI model.

Our study indicates that the present model is useful for examining changes in aEEG similar to those in the human newborn brain after perinatal HI. The present model should be used with caution when post-HI changes of cerebral blood volume are the focus of interest.

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