0031-3998/09/6501-0057
PEDIATRIC RESEARCH

Vol. 65, No. 1, 2009
Printed in U.S.A.

High Brain Tissue Oxygen Tension During Ventilation With 100% Oxygen After Fetal Asphyxia in Newborn Sheep

VALERIA PEREZ-DE-SA, DORIS CUNHA-GONCALVES, ANDERS NORDH, STEFAN HANSSON, ANDERS LARSSON, DAVID LEY, VINETA FELLMAN, AND OLOF WERNER

Departments of Pediatric Anesthesia and Intensive Care [V.P.-S., A.N., O.W.], Pediatrics [D.L., V.F.], Thoracic Anesthesia and Intensive Care [D.C.-G.], and Obstetrics [S.H.], University Hospital of Lund, Lund, Sweden, SE-22185; Clinical Institute [A.L.], Aarhus University, Aalborg, Denmark, DK-9100; Department of Pediatrics [V.F.], University of Helsinki, 00029 Helsinki, Finland

ABSTRACT: The optimal inhaled oxygen fraction for newborn resuscitation is still not settled. We hypothesized that short-lasting oxygen ventilation after intrauterine asphyxia would not cause arterial or cerebral hyperoxia, and therefore be innocuous. The umbilical cord of fetal sheep was clamped and 10 min later, after delivery, ventilation with air ($n = 7$) or with 100% oxygen for 3 ($n = 6$) or 30 min ($n = 5$), followed by air, was started. Among the 11 lambs given 100% oxygen, oxygen tension (P_{O2}) was 10.7 (1.8–56) kPa [median (range)] in arterial samples taken after 2.5 min of ventilation. In those ventilated with 100% oxygen for 30 min, brain tissue P_{O2} (Pbt_{O2}) increased from less than 0.1 kPa in each lamb to individual maxima of 56 (30–61) kPa, whereas in those given oxygen for just 3 min, Pbt_{O2} peaked at 4.2 (2.9–46) kPa. The maximal Pbt_{O2} in air-ventilated lambs was 2.9 (0.8–5.4) kPa. Heart rate and blood pressure increased equally fast in the three groups. Thus, prolonged ventilation with 100% oxygen caused an increase in Pbt_{O2} of a magnitude previously only reported under hyperbaric conditions. Reducing the time of 100% oxygen ventilation to 3 min did not consistently avert systemic hyperoxia. **(*Pediatr Res* 65: 57–61, 2009)**

Current guidelines from the International Liaison Committee on Resuscitation breathe considerable uncertainty as to how much supplementary oxygen should be given during resuscitation of newborn asphyxiated infants (1). Previous recommendations were to be generous with oxygen, but recent guidelines from a number of countries, *e.g.* Australia, Canada, Finland, the Netherlands, Sweden, and the United Kingdom recommend initial ventilation with air, because of the results from several experimental (2–5) and clinical (6–13) studies indicating that resuscitation with 100% oxygen is harmful. In the clinical studies, the time of exposure to 100% oxygen was typically 5–7 min (8,13), whereas only one animal study (5) has investigated an exposure time to oxygen less than 15 min.

We speculated that very short times of exposure might not allow systemic hyperoxia to develop and so be harmless to the newborn infant, except for a possible negative effect on the lungs. In fact, the pulse oximetric saturation at 3 min after birth is usually below 80% (14,15) in the normal air-breathing infant, suggesting the presence of cardiac or pulmonary right-to-left shunts. One might expect that such shunts would delay the appearance of arterial hyperoxemia in the infant breathing pure oxygen. However, this has been studied neither in normal nor in asphyxiated subjects.

We used a sheep model of term intrauterine asphyxia with postnatal resuscitation, and hypothesized that hyperoxia of arterial blood and of brain tissue could be prevented by limiting the period of ventilation with 100% oxygen to 3 min. We also investigated whether the speed of circulatory recovery, as reflected by the heart rate (HR) and mean arterial blood pressure (MAP) responses, and the speed of recovery of brain oxygenation, as reflected by regional cerebral oxygen saturation (CrS_{O2}), differed between oxygen- and air-resuscitation.

Work on the same animal model has shown that the mRNA expression of some proinflammatory cytokines in the brain is increased in asphyxiated lambs 90 min after exposure to 30 min of 100% oxygen breathing (16), and a secondary aim was to see whether already 3 min with pure oxygen could generate the same inflammatory response.

METHODS

The study was approved by the Animal Ethics Research Committee of Lund University. The animals were cared for and handled in accordance with European Guidelines for Use of Experimental Animals.

Animal preparation and cerebral oxygenation measurements. Datemated ewes were anesthetized and underwent cesarean section at 140–141 gestational days, when pulmonary surfactant function in the lamb is usually normal (17). Term is 145–150 d. The fetus received catheters in an axillary artery and a jugular vein, and was tracheotomized as described previously (16).

The scalp was shaved and an incision made to expose the right parietal bone. A hole of 3-mm diameter was drilled down to the dura mater, and a hollow bolt screwed into the hole. By using an introducer passed through the lumen of the bolt, a flexible microcatheter probe containing a polarographic cell (LICOX; GMS, Mielkendorf, Germany) was placed with its tip in the subcortex so that brain tissue Po_2 (Pbt_{O2}) could be continuously measured. Alongside the Pbt_{O2} probe, a thermocouple probe was placed through the same introducer, and both were connected to a LICOX CMP monitor for automatic temperature-corrected Pbt_{O2} readings. Every 20 s, the Pbt_{O2} and temperature signals were collected and stored in a personal computer using the LICOX for PC Software. The Pbt_{O2} recording was later processed to find the individual's maximum (peak) value.

Received April 29, 2008; accepted August 6, 2008.

Correspondence: Valeria Perez-de-Sa, M.D., Ph.D., D.E.A.A., Department of Pediatric Anesthesia and Intensive Care, Children's Hospital, University Hospital of Lund, Lund, Sweden, SE-221 85; e-mail: valeria.perezdesa@gmail.com

Supported by The Laerdal Foundation, The Swedish Medical Research Council (grant nos 14940, 4732), University Hospital of Lund and Lund's Medical Faculty grants, the Segerfalk Foundation, and the Craaford Foundation.

Abbreviations: BE, arterial base excess; **Bpm,** beats per minute; **CrS_{O2},** regional cerebral oxygen saturation; **Fi_{O2},** inspired fraction of oxygen; **Hb,** hemoglobin; **HR,** heart rate; **MAP,** mean arterial pressure; **Pbt_{O2},** brain tissue partial pressure of oxygen

Measurement of CrS_{O2} by dual wavelength near-infrared spectroscopy, was performed with equipment for clinical use (INVOS® 5100C Cerebral/Somatic Oxymeter, Somanetics Corporation, Troy, MI), using a disposable self-adherent pediatric probe (Pediatric SomaSensor probe, <40 kg, model SPFB-USA, Somanetics Corporation) that was attached to the shaved scalp and secured in place by a fabric net.

Induction of asphyxia and resuscitation. After clamping and cutting the umbilical cord, the lamb was removed from the womb, weighed, sedated, and placed in an open, heated incubator. A catheter was positioned in the abdominal aorta *via* the umbilical cord and used for recording MAP and HR on a Datex-Ohmeda AS/3 Compact Anesthesia Monitor (GE Health Care, Helsinki, Finland). Pressure-regulated volume control ventilation with a Servo 300 ventilator (Siemens-Elema, Solna, Sweden) was initiated exactly 10 min after cord occlusion. Tidal volume was 10 mL/kg, respiratory rate 40/min, I:E ratio 1:1, and end-expiratory pressure 4 cm H_2O. The lambs were randomized to receive an inhaled oxygen fraction (Fi_{O2}) that was either 21% ($n = 7$) throughout or 100% during the first 3 ($n = 6$) or 30 min ($n = 6$) of ventilation. The ventilation with pure oxygen was followed by ventilation with air. One lamb of the 30-min oxygen group was subsequently excluded because of low blood hemoglobin (Hb) concentration; see Results. An observer, blinded to the Fi_{O2}, looked at the arterial pressure curve, to judge whether the circulation showed signs of spontaneous recovery after start of ventilation. If not, 10 μg/kg of adrenaline was injected i.v., and external cardiac massage given for 15 s. After the first half hour, respiratory rate was adjusted to achieve an arterial Pco_2 (Pa_{CO2}) around 6 kPa.

Arterial sampling. A 0.5 mL sample for blood-gas and Hb measurements was obtained from the axillary artery catheter shortly before occluding the umbilical cord (*in utero*), just before start of ventilation (end of asphyxia), and 0.75, 2.5, 5, 10, 15, 29.5, and 60 min after start of ventilation. The samples were analyzed on an ABL 700 blood-gas analyzer (Radiometer, Copenhagen, Denmark). Its settings were adjusted to ovine blood, according to a factory-installed algorithm.

Assessment of circulatory recovery and of recovery of cerebral oxygenation. The time from start of ventilation until HR had increased to 150 bpm was measured. We also assessed the time from start of ventilation until CrS_{O2} reached 30%, *i.e.* a value just above the minimum displayed by the equipment, namely 15%. Because a new CrS_{O2} figure was presented every 6 s, and the HR and MAP every 10 s, interpolation was used to calculate the times to the nearest second.

In a separate analysis, individual HR and MAP curves were aligned, so that the respective points in time when HR reached 150 bpm coincided. The respective mean curves representing each group were then calculated.

Experiments in nonasphyxiated controls. Subsequent to the asphyxia series, four nonrandom controls were ventilated with oxygen to assess cerebral oxygenation during hyperoxemia that was not preceded by asphyxia. Using an infant self-expanding resuscitator bag, manual ventilation with air started with the lamb *in utero*, a few seconds before clamping and cutting the umbilical cord. The lamb was transferred to the open incubator where mechanical ventilation with 100% oxygen was initiated as soon as an aortic catheter had been placed *via* the umbilical cord, for pressure monitoring. After 30 min, the inspired gas was changed to air. Axillary arterial samples for blood-gas and Hb measurements were taken *in utero*, and 0.75, 2.5, 5, 10, 15, 29.5, and 60 min after switching from air- to oxygen-ventilation. The preparation, ventilator settings, sedation, and measurements were otherwise the same as for the asphyxiated animals.

mRNA expression in the brain of proinflammatory cytokines IL-1β, IL-12, and IL-18. After the 60 min arterial sample, the heart was arrested by an i.v. injection of potassium chloride. In 13 asphyxiated animals and three controls, the brain was immediately removed from the skull and split in the midline. In the left half, tissue sections were taken from the temporo-parietal cortex including sub-cortical white matter and from the thalamus, and immediately frozen on dry ice. The samples were stored at −80°C.

Total RNA was extracted from frozen tissue using Trizol® (GIBCO BRL, Invitrogen Corporation, Grand Island, NY) according to the manufacturer's instructions. Gene transcripts were quantified using real-time PCR on ABI PRISM® 7000 sequence detection system (Applied Biosystems, Foster City, CA) as described previously (10). The quantitative value of each sample was normalized to the corresponding value of beta-actin and results expressed as relative values.

Statistics. Between-group differences among asphyxiated lambs were assessed by analysis of variance using Sigma Chemical Co.-Stat 3.5 software (Systat Software GmbH, Ekrath, Germany). In case of non-normal distribution, analysis of variance on ranks was used instead. The difference in peak Pbt_{O2} between the group of asphyxiated lambs that was ventilated with oxygen for 30 min and the nonasphyxiated lambs was assessed with the *t* test.

RESULTS

One asphyxiated lamb, randomized to resuscitation with oxygen for 30 min, was excluded because of a low Hb: 60 g/L. Among the remaining 18 asphyxiated animals, the median (range) for Hb was 136 (119–157) g/L, with no difference between the three groups. Hb was 127 (95–151) g/L in the four nonasphyxiated animals.

Asphyxiated lambs. Table 1 shows arterial blood gases and base excess (BE) by group. *In utero* pH (not shown in the Table) of all 18 subsequently asphyxiated animals was 7.26 (7.10–7.32). There was no significant difference between groups in respect of any of these measures.

During the cord occlusion, median arterial P_{O2} (Pa_{O2}) decreased to 0.74 kPa, and a severe combined respiratory and metabolic acidemia developed, with a median Pa_{CO2} of 17 kPa, and BE of −13 mM. pH decreased to 6.92 (6.81–6.99). Pbt_{O2} became less than 0.1 kPa in all animals, and CrS_{O2} was

Table 1. *Arterial blood gases*

Group	*In utero*	End of asphyxia	45 s	2.5 min	29.5 min	60 min
Asphyxia, air ($n = 7$)						
Pa_{O2} (kPa)	3.0 (1.4–4.0)	0.6 (0.5–1.6)	2 (0.6–3.3)	3.0 (1.1–11)	5.2 (2.7–12)	6.0 (1.9–11)
Pa_{CO2} (kPa)	9.0 (7.8–10)	17 (16–19)	17 (15–17)	13 (8.1–16)	5.5 (4.9–11)	5.1 (3.8–6.5)
BE (mmol/L)	0 (−9 to +2)	−14 (−21 to −8)	−12 (−21 to −9)	−11 (−20 to −9)	−9 (−15 to −1)	−3 (−11–+3)
Asphyxia, oxygen 3 min ($n = 6$)						
Pa_{O2} (kPa)	1.8 (1.6–3.5)	0.9 (0.5–1.0)	3.1 (0.5–4.3)	26 (5.4–56)	5.2 (3.1–10)	4.5 (2.6–8.3)
Pa_{CO2} (kPa)	8.9 (7.8–9.6)	17 (14–19)	15 (8 .0–17)	13 (7.0–15)	6.2 (5.2–7.5)	6.3 (5.3–7.5)
BE (mmol/L)	−1 (−2 to +2)	−12 (−15 to −8)	−13 (−15 to −9)	−13 (−14 to −8)	−5 (−8 to −3)	−1 (−3 to +4)
Asphyxia, oxygen 30 min ($n = 5$)						
Pa_{O2} (kPa)	2.4 (1.5–3.4)	0.9 (0.6–1.3)	2.1 (0.9–3.2)	5.5 (1.8–51)	21 (6.1–65)	3.8 (3.5–5.5)
Pa_{CO2} (kPa)	8.0 (7.2–11)	17 (15–19)	17 (16–18)	15 (7.8–16)	8.2 (5.7–12)	6.2 (5.2–8.4)
BE (mmol/L)	+1 (−2 to +2)	−13 (−14 to −10)	−12 (−15–−10)	−13 (−15 to −11)	−7 (−8 to −6)	−3 (−5 to −2)
No asphyxia, oxygen 30 min ($n = 4$)						
Pa_{O2} (kPa)	1.8 (1.4–2.6)	—	46 (5.6–49)	47 (33–58)	58 (7.4–63)	7.0 (4.0–7.4)
Pa_{CO2} (kPa)	8.4 (6.0–9.1)	—	8.0 (6.7–10)	9.7 (7.6–11)	4.8 (4.4–7.5)	4.6 (4.2–5.4)
BE (mmol/L)	−5 (−8 to −3)	—	−4 (−7 to −2)	−6 (−12 to −2)	0 (−8 to +4)	2 (−1 to +3)

Pa_{O2}, Pa_{CO2}, and base excess (BE) before asphyxia (*in utero*), just before start of ventilation (end of asphyxia), and at various times after start of ventilation in the three groups of asphyxiated lambs. For nonasphyxiated control animals, times are after switching from air- to oxygen-ventilation. Values are median (range).

Table 2. *Times from start of ventilation until heart rate (HR) reached 150 bpm, and until cerebral regional oxygen saturation (CrS_{O2}) reached 30% in asphyxiated lambs*

	Asphyxia			
	Air (n = 7)	Oxygen for 3 min (n = 6)	Oxygen for 30 min (n = 5)	No asphyxia Oxygen for 30 min (n = 4)
Time (s) until HR ≥150 bpm	68 (6–150)	107 (5–182)	58 (23–368)	—
Time (s) until $CrSO_2$ ≥30%	112 (35–590)	54 (35–109)	26 (23–206)	—
Peak Pbt_{O2} (kPa)	2.9 (0.8–5.4)	4.2 (2.9–46)	56 (30–61)*	15 (6.5–22)

Individual maxima for brain tissue oxygen tensions (peak Pbt_{O2}).
Values are median (range).
* Significant difference *vs* no asphyxia ($p = 0.002$).

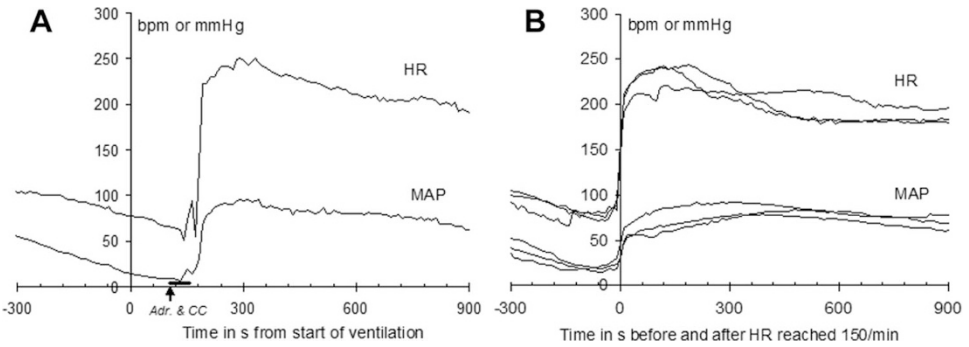

Figure 1. Heart rate and arterial pressure response to resuscitation. (A) HR and MAP in a lamb that was resuscitated with oxygen for 3 min, and then with air ventilation. The *arrow* and *horizontal bar* indicate injection of adrenaline and subsequent cardiac compressions. All lambs had a similar abrupt increase in HR from less than 100/min to more than 200/min, concomitant with a likewise abrupt increase of arterial pressure, signaling that the resuscitation was successful. The time when this occurred varied between individuals, but not between groups (Table 2). (B) Mean curves for HR and MAP in the three groups of asphyxiated lambs. They were obtained by aligning curves from individual lambs, so that the times when HR reached 150/min coincided, and then computing the mean curve. This method was chosen in order that the mean curves should reflect the above-mentioned abrupt increase in HR and MAP.

displayed as the minimum value for the equipment, *i.e.* 15%, in all animals. MAP decreased to a nadir of 14 (7–20) mm Hg in 17 animals and to 32 mm Hg in one. HR decreased to 64 (30–96) bpm. There was no difference between the groups in any of these measures.

The circulation recovered spontaneously when ventilation was started, except in one lamb in the air-only group and in two in each of the two oxygen groups. These five lambs were successfully resuscitated with adrenaline and external cardiac massage. Time to reach a HR of 150 bpm was the same with oxygen-ventilation as with air (Table 2) and curves representing mean HR and MAP were similar in the three groups (Fig. 1). Median time to reach a CrS_{O2} of 30% was 2 min in those air-ventilated and ½–1 min in the two groups given 100% oxygen (Table 2). The difference between groups was not significant ($p = 0.084$).

After 45 s of ventilation, Pa_{O2} had increased slightly in most animals, but there was no arterial hyperoxemia (Table 1). Such was seen at 2 ½ min when Pa_{O2} was over 50 kPa in three lambs ventilated with oxygen. In the samples taken at 5, 10, and 15 min, the median Pa_{O2} was over 55 kPa in lambs allotted to prolonged oxygen breathing (Fig. 2C), and Pbt_{O2} generally increased to peak values over 50 kPa in these (Fig. 2C, Table 2). Among lambs ventilated with pure oxygen for just 3 min, Pbt_{O2} peaked at 46 kPa in one, and was 2.9–5.4 kPa in the other five (Fig. 2B). When oxygen-ventilation was discontinued, Pbt_{O2} decreased to essentially the same levels as in the air-only group (Fig. 2).

Nonasphyxiated controls. At the intrauterine (baseline) stage, arterial oxygenation and Pa_{CO2} were similar to those in the other groups (Table 1), but BE tended to be somewhat more negative. During 30 min of oxygen breathing, Pa_{O2} levels were approximately the same as in those asphyxiated lambs that were ventilated equally long with oxygen (Fig. 2D), whereas peak Pbt_{O2} was significantly less (Table 2).

Cytokines in cerebral tissue. IL-1β, IL-12, and IL-18 (Table 3) did not vary significantly between groups.

DISCUSSION

The main finding of the present study is the extremely high Pbt_{O2} of asphyxiated lambs, exposed to prolonged ventilation with 100% oxygen (Fig. 2C). The peak value was 56 (30–61) kPa, and such a high Pbt_{O2} has been previously seen only under hyperbaric conditions (18). The finding is probably due to a combination of factors, namely high Fi_{O2}, postischemic hyperemia accentuated by metabolic and respiratory arterial acidemia, and reduced metabolism (19) in the post-asphyctic brain. Surprisingly, Lyng *et al.* (20) found a much smaller peak Pbt_{O2} in 1–2-d-old piglets that were asphyxiated by breathing an hypoxic mixture and then resuscitated with 30 min of oxygen-ventilation. In these, Pbt_{O2} only increased to a maximum of approximately 5 kPa. The discrepancy could be the result of differences in equipment and species, different P_{O2} electrode placement in the brain, a Pa_{CO2} following asphyxia which was probably less in their study, and the fact

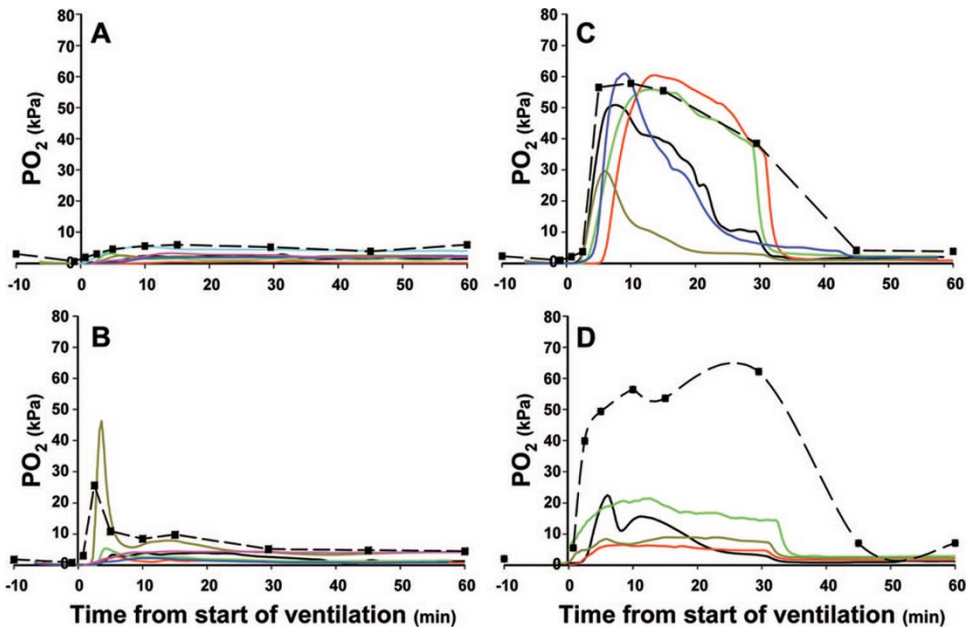

Figure 2. Brain tissue P_{O2} (Pbt_{O2}) and arterial P_{O2} (Pa_{O2}). Individual curves depicting Pbt_{O2} (*continuous lines*) in lambs that were asphyxiated *in utero* and resuscitated after birth, with (A) air-ventilation ($n = 7$) or with 100% oxygen for (B) 3 min ($n = 6$) or (C) 30 min ($n = 5$), and then with air. Group medians for Pa_{O2} (■—■) are also shown. The dot at −10 min represents the Pa_{O2} *in utero*, before occluding the umbilical cord. (D) In a group that was not made asphyctic ($n = 4$), the Pbt_{O2} and Pa_{O2} during 30 min of oxygen ventilation and a subsequent 30 min of air ventilation are displayed.

Table 3. *Cytokine mRNA activity in cerebral tissue*

	Asphyxia			
	Air (n = 5)	Oxygen for 3 min (n = 4)	Oxygen for 30 min (n = 4)	No asphyxia Oxygen for 30 min (n = 3)
$10^{-3} \times$ IL-1β/β-actin				
Cortex/subcortex	25 (10–40)	21 (17–24)	14 (10–31)	21 (11–26)
Thalamus	16 (08–29)	15 (13–40)	19 (15–36)	29 (17–32)
$10^{-3} \times$ IL-12/β-actin				
Cortex/subcortex	10 (0–85)	10 (4–26)	52 (4–81)	7 (0–18)
Thalamus	17 (12–123)	33 (16–46)	9 (24–116)	39 (22–49)
IL-18/β-actin				
Cortex/subcortex	1.01 (0.99–1.68)	1.54 (1.21–1.91)	1.28 (0.86–1.91)	1.17 (0.90–1.21)
Thalamus	1.00 (0.92–1.31)	1.54 (0.73–3.89)	1.45 (0.72–2.07)	1.12 (0.94–1.17)

The result was normalized to β-actin activity. Values are median (range); n = number of analyzed brains.

that they used a postnatal asphyxia model, rather than one involving the transition from intrauterine to postnatal life.

In the present study, we addressed the question whether arterial and cerebral hyperoxia could be avoided by reducing time of exposure to 100% oxygen. As it turned out, Pa_{O2} was above 50 kPa already at 2.5 min in three lambs. Thus, the fluid-filled lungs did not protect the newly delivered lambs from hyperoxemia, except in the arterial sample taken 45 s after start of ventilation. In addition, one lamb in the 3-min oxygen group had an extremely high Pbt_{O2} peak (Fig. 2B). Whether a similar rapid hyperoxygenation could occur in asphyxiated human neonates is not known. Vento *et al.* (8) found a Pa_{O2} of approximately 17 kPa in arterial samples taken approximately 7 min after birth in asphyxiated infants breathing 100% oxygen. A suggestion that brief exposures could be toxic is given by clinical studies comparing oxygen and air ventilation for resuscitation after asphyxia. In these, an increased mortality (21) and signs of oxidative stress (13) were seen in infants given 100% oxygen during a mean time of only 7.5 ± 1.8 min. In addition, an association between neonatal exposure to 100% oxygen for less than 10 min and childhood leukemia has been found (10). In another study, neonatal exposure to supplemental oxygen for more than 3 min was associated with an increased risk of subsequent cancer, although a shorter exposure was not (11).

There was no significant increase in mRNA expression of proinflammatory cytokines after 30 min of 100% oxygen, in contrast to results in a previous paper (16). In that study, cerebral proinflammatory activity was evaluated at 2 h after initiation of resuscitation compared with 1 h in the present study. Sufficient time after hyperoxic exposure may be required for detection of increase in proinflammatory cytokine expression. In addition, the considerably smaller sample size in the present study limits detection of differences between groups.

The INVOS system, that was used to measure CrS_{O2}, is adapted to the light absorption characteristics of human Hb, which are slightly different from those of ovine Hb (22). Nevertheless, the measurement was thought to provide an idea as to how quickly cerebral oxygenation was being restored during resuscitation, and we used the time taken for CrS_{O2} to reach 30% as an indicator. There was a tendency for this time to be shorter with oxygen ventilation than with air (Table 2), but the groups were not significantly different in this respect. The median time until HR had reached 150 bpm was the same with air ventilation as with oxygen (Table 2), and the MAP

responses, too, were similar (Fig. 1). This is consistent with previous studies on the same asphyxia model (16) and with studies in asphyxiated 1–3-d-old piglets (23).

In conclusion, the findings in this model of fetal asphyxia followed by neonatal resuscitation indicate that ventilation with air will restore the circulation as fast as when pure oxygen is used, if ventilation is unobstructed and the lungs normal. Prolonged ventilation with 100% oxygen caused an extreme increase in brain tissue oxygen tension, which emphasizes the need to limit oxygen exposure in the asphyxiated newly born. However, reducing the time of 100% oxygen ventilation to 3 min did not consistently avert systemic hyperoxia.

Acknowledgments. We thank Tina Markus for the analysis of cytokine expression in brain tissue, GE Healthcare Technologies for lending a Datex-Ohmeda AS/3 Compact Anesthesia Monitor, and Research Manager, Juha Virtanen, Ph.D., for technical advice.

REFERENCES

1. The International Liaison Committee on Resuscitation 2006 The International Liaison Committee on Resuscitation (ILCOR) consensus on science with treatment recommendations for pediatric and neonatal patients: pediatric basic and advanced life support. Pediatrics 117:e955–e977
2. Munkeby BH, Børke WB, Bjørnland K, Sikkeland LI, Borge GI, Halvorsen B, Saugstad OD 2004 Resuscitation with 100% O2 increases cerebral injury in hypoxemic piglets. Pediatr Res 56:783–790
3. Graulich J, Hoffmann U, Maier RF, Ruscher K, Pomper JK, Ko HK, Gabriel S, Obladen M, Heinemann U 2002 Acute neuronal injury after hypoxia is influenced by the reoxygenation mode in juvenile hippocampal slice cultures. Brain Res Dev Brain Res 137:35–42
4. Døhlen G, Carlsen H, Blomhoff R, Thaulow E, Saugstad OD 2005 Reoxygenation of hypoxic mice with 100% oxygen induces brain nuclear factor-kappa B. Pediatr Res 58:941–945
5. Solas AB, Munkeby BH, Saugstad OD 2004 Comparison of short- and long-duration oxygen treatment after cerebral asphyxia in newborn piglets. Pediatr Res 56:125–131
6. Saugstad OD, Rootwelt T, Aalen O 1998 Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the Resair 2 study. Pediatrics 102:e1
7. Ramji S, Rasaily R, Mishra PK, Narang A, Jayam S, Kapoor AN, Kambo I, Mathur A, Saxena BN 2003 Resuscitation of asphyxiated newborns with room air or 100% oxygen at birth: a multicentric clinical trial. Indian Pediatr 40:510–517
8. Vento M, Asensi M, Sastre J, Lloret A, Garcia-Sala F, Vina J 2003 Oxidative stress in asphyxiated term infants resuscitated with 100% oxygen. J Pediatr 142:240–246
9. Vento M, Sastre J, Asensi MA, Vina J 2005 Room-air resuscitation causes less damage to heart and kidney than 100% oxygen. Am J Respir Crit Care Med 172:1393–1398
10. Naumburg E, Bellocco R, Cnattingius S, Jonzon A, Ekbom A 2002 Supplementary oxygen and risk of childhood lymphatic leukaemia. Acta Paediatr 91:1328–1333
11. Spector LG, Klebanoff MA, Feusner JH, Georgieff MK, Ross JA 2005 Childhood cancer following neonatal oxygen supplementation. J Pediatr 147:27–31
12. Rabi Y, Rabi D, Yee W 2007 Room air resuscitation of the depressed newborn: a systematic review and meta-analysis. Resuscitation 72:353–363
13. Vento M, Asensi M, Sastre J, García-Sala F, Pallardó FV, Viña J 2001 Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics 107:642–647
14. Kamlin CO, O'Donnell CP, Davis PG, Morley CJ 2006 Oxygen saturation in healthy infants immediately after birth. J Pediatr 148:585–589
15. Rabi Y, Yee W, Chen SY, Singhal N 2006 Oxygen saturation trends immediately after birth. J Pediatr 148:590–594
16. Markus T, Hansson S, Amer-Wåhlin I, Saugstad OD, Hellström-Westas L, Ley D 2007 Cerebral inflammatory response after fetal asphyxia and hyperoxic resuscitation in newborn sheep. Pediatr Res 62:71–77
17. Robertson B 1992 Animal models of neonatal surfactant dysfunction. In: Robertson B, van Golde LM, Batenburg JJ (eds) Pulmonary Surfactant: from Molecular Biology to Clinical Practice. Elsevier Science Publishers B.V., Amsterdam, pp 459–484
18. van Hulst RA, Haitsma JJ, Klein J, Lachmann B 2003 Oxygen tension under hyperbaric conditions in healthy pig brain. Clin Physiol Funct Imaging 23:143–148
19. Thorngren-Jerneck K, Ley D, Hellström-Westas L, Hernandez-Andrade E, Lingman G, Ohlsson T, Oskarsson G, Pesonen E, Sandell A, Strand SE, Werner O, Marsal K 2001 Reduced postnatal cerebral glucose metabolism measured by PET after asphyxia in near term fetal lambs. J Neurosci Res 66:844–850
20. Lyng K, Braakhuis M, Frøen JF, Stray-Pedersen B, Saugstad OD 2005 Inflammation increases vulnerability to hypoxia in newborn piglets: effect of reoxygenation with 21% and 100% O2. Am J Obstet Gynecol 192:1172–1178
21. Saugstad OD 2004 The role of oxygen in neonatal resuscitation. Clin Perinatol 31:431–443
22. Grosenbaugh DA, Alben JO, Muir WW 1997 Absorbance spectra of inter-species hemoglobins in the visible and near infrared regions. J Vet Emerg Crit Care 7:36–42
23. Haase E, Bigam DL, Nakonechny QB, Rayner D, Korbutt G, Cheung PY 2005 Cardiac function, myocardial glutathione, and matrix metalloproteinase-2 levels in hypoxic newborn pigs reoxygenated by 21%, 50%, or 100% oxygen. Shock 23:383–389