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0031-3998/96/3902-0209$03.00/0
PEDIATRIC RESEARCH
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Vol. 39, No. 2, 1996
Printed in U.S.A.

The Influence of Extracorporeal Membrane Oxygenation on Cerebral Oxygenation and Hemodynamics in Normoxemic and Hypoxemic Piglets

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ABSTRACT

The objective of this study was to compare the effect of extracorporeal membrane oxygenation (ECMO) on cerebral oxygenation and hemodynamics in normoxemic and hypoxemic piglets. Six hypoxemic and six normoxemic piglets were put on venoarterial ECMO after cannulation of the right common carotid artery and external jugular vein with careful priming to avoid hemodilution. Changes in cerebral concentrations of oxyhemoglobin (cO_2Hb), deoxyhemoglobin (cHHb), (oxidized-reduced) cytochrome aa_3 (cCyt.aa_3), and blood volume (CBV) were continuously measured by near infrared spectrophotometry. Heart rate, arterial O_2 saturation (Sao_2), arterial blood pressure, pulsatility ratio of systemic circulation (calculated as systolic-diastolic/mean arterial blood pressure), central venous pressure, intracranial pressure, and left common carotid artery blood flow (LCaBF) were simultaneously measured. We found that the cannulation procedure resulted in increased CBV, cHHb, and LCaBF in both groups. At 60 and 120 min after starting ECMO, the values of cO_2Hb, CBV, and LCaBF in both groups were significantly higher than precannulation values, while the pulsatility ratio decreased. In the hypoxemic groups cHHb decreased and Sao_2 increased as well. No significant changes of other variables were found. Between hypoxemic and normoxemic groups no significant differences in the response of CBV and LCaBF at 60 and 120 min were found. We conclude that in piglets cannulation for ECMO resulted in cerebral venous congestion and compensated increase in LCaBF. After starting ECMO, the cerebral O_2 supply increased due to increased arterial O_2 content. It was accompanied by similar increase of CBV in both groups, probably as a result of hyperperfusion, which seems to be related to the ECMO procedure itself. (***Pediatr Res* 39: 209–215, 1996**)

Abbreviations

ECMO, extracorporeal membrane oxygenation
NIRS, near infrared spectrophotometry
CBF, cerebral blood flow
LCaBF, mean blood flow in left common carotid artery
CBV, cerebral blood volume
***c*O$_2$Hb,** oxyhemoglobin concentration
***c*HHb,** deoxyhemoglobin concentration
***c*tHb,** total Hb concentration
***c*Cyt.*aa*$_3$,** (oxidized-reduced) cytochrome aa_3 concentration
***c*Hb,** arterial Hb concentration
Sao$_2$, arterial O_2 saturation
MABP, mean arterial blood pressure
CVP, central venous pressure
ICP, intracranial pressure
Pao$_2$, partial pressure of arterial O_2
Paco$_2$, partial pressure of arterial CO_2

Cerebrovascular injury is one of the important complications during ECMO in newborn infants (1, 2). Because most of the intracranial abnormalities were detected during the first days of ECMO (3), changes in cerebral circulation and oxygenation during induction of ECMO might play a role in the pathogenesis of this complication. These changes might be related to the pre-ECMO condition or the ECMO procedure itself. Alteration in cerebral hemodynamics during ECMO has been described in animal models (4–7). In a previous study using NIRS we have shown that CBV increases in newborn infants after starting ECMO, and that this was most likely caused by an increase in CBF (8). It is not clear whether this disturbance of cerebral hemodynamics is directly related the ECMO procedure itself or if it is a result of prolonged hypoxemia before ECMO. Therefore, in this study, the differences in cerebral oxygenation and hemodynamics changes during induction of ECMO between hypoxemic and normoxemic piglets were investigated.

Received February 3, 1995; accepted July 31, 1995.
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MATERIAL AND METHODS

Animal preparation. Twelve piglets (age 2–3 wk, weight 7.6–8.5 kg) from a local farm were used for this study. The porcine model was used because of its close physiologic resemblance to the human infant, easy availability, low cost, and suitability for ECMO experiments (9, 10). Initially a mixture of droperidol and fentanyl (0.25 mg/kg and 0.005 mg/kg, respectively) was administered intramuscularly for sedation. After 30 min, anesthesia was induced by i.v. midazolam (1.5 mg/kg), atropine (0.25 mg), and fentanyl (0.2 mg/kg). Orotracheal intubation was subsequently performed and the piglets were put on the ventilator (Babylog 8000, Dräger, Lübeck, Germany). Anesthesia was maintained using i.v. fentanyl (0.2 mg/kg/h), midazolam (0.4 mg/kg/h), and droperidol (0.1 mg/kg/h). The piglets were paralyzed with pancuronium (loading dose 0.2 mg/kg, maintaining dose 0.15 mg/kg/h). The ventilator settings were adjusted to maintain normoxemia: Sao_2 > 95%, Pao_2 at 75–100 mm Hg (10–13.3 kPa), and $Paco_2$ at 30–40 mm Hg (4–5.3 kPa). Rectal temperature was maintained between 38 and 39°C using a servo-controlled heating mattress. Heart rate was monitored (HP 78330A, Hewlett Packard, Boeblingen, Germany) using conductive adhesive electrodes on the chest wall.

Catheters were inserted through the femoral artery and vein and the tips were positioned in the abdominal aorta for blood sampling and measurement of arterial blood pressure (HP 78206C, Hewlett Packard, Boeblingen, Germany), and in the inferior vena cava near the right atrium for fluid and medication administration and measurement of CVP (HP 78205C, Hewlett Packard, Boeblingen, Germany). Through the other femoral artery a fiber optic oximeter catheter (Spectracath STP 7.5 Fr, Viggo Spectramed, Oxnard, CA) was inserted, and the tip was advanced into the abdominal aorta for on-line continuous monitoring of Sao_2 ($HemoprO_2$ SP1455, Viggo Spectramed, Oxnard, CA). Mean blood flow in the LCaBF was continuously recorded by an electromagnetic flowmeter (Scalar MDL 1401, Scalar Medical, Delft, The Netherlands) using a 2.5-mm diameter probe. After the neck incision, the cisterna magna were punctured with a hollow needle through the foramen magnum, and a catheter was placed through the needle for continuous monitoring of ICP (HP 78205C, Hewlett Packard, Boeblingen, Germany). The needle was withdrawn after successful positioning of the catheter, as shown by a pulsatile signal on the monitor.

Near infrared spectrophotometry. The NIRS equipment used was developed by the Department of Biomedical Engineering and Medical Physics, University of Keele (UK) and produced by Radiometer (Copenhagen, Denmark) (11). This method is based on continuous spectrophotometric measurement of oxygen-dependent changes in the absorption properties of Hb and cytochrome aa_3 in the near infrared region (12). Our NIRS measurement procedure has been published earlier (13). Briefly, near infrared light at 3 wavelengths (904, 845, and 775 nm) was transmitted through the skull by fiber optic bundles. The transmitting and receiving optodes were fixed to the skull as previously described (14). Each optode was positioned between the midline of the skull and the ear. Interoptode spacing was always >2.5 cm, to ensure a constant path length multiplying factor (15), which has been stated to be 4.39 times the interoptode spacing (16). Because the extent of light attenuation caused by scattering and oxygenation-independent absorption by tissue is unknown, but considered constant, only concentration changes (Δ) in cO_2Hb, cHHb, and cCyt.aa_3 can be calculated from changes in absorption of near infrared light at these three wavelengths using the described algorithm (11, 17) and the obtained optical path length. (The designated hemoglobin abbreviations used are according to the guidelines of the (U.S.) National Committee for Clinical Laboratory Standards (NCCLS), Document C25-P, Vol. 10, No. 2, 1990.) Using a value of 1.05 for brain-specific mass, these concentration changes are expressed in micromoles/100 g. Therefore, during NIRS measurement only relative changes of these variables are obtained as a trend. ΔcO_2Hb and ΔcHHb reflect changes in cerebral O_2 supply, whereas ΔcCyt.aa_3 reflects changes in cerebral O_2 sufficiency (18). Changes in concentration of total Hb (ΔctHb) were calculated as the sum of ΔcO_2Hb and ΔcHHb. Changes in CBV (ΔCBV), expressed in milliliters/100 g, were calculated from the formula $\Delta CBV = (4 * \Delta c\text{tHb})/(0.69 * c\text{Hb})$, where cHb = arterial Hb concentration in millimoles/L, 0.69 = cerebral-arterial hematocrit ratio (19), and 4 = correction factor, since ctHb is calculated from changes in light absorption using an extinction coefficient based on the tetraheme molecule, whereas cHb determination is based on the monoheme molecule.

Experimental protocol. After stabilization and before starting ECMO the piglets were randomized in 2 groups:

Normoxemic group (n = 6). The ventilator setting was unchanged to maintain normoxemia for at least 2 h.

Hypoxemic group (n = 6). The fraction of inspired O_2 concentration of the ventilator was lowered to 0.16–0.18 to maintain moderate hypoxemia for at least 2 h: Pao_2 35–40 mm Hg (4.7–5.3 kPa) and Sao_2 60–80%. A more profound hypoxemia was avoided, because it would have resulted in a high mortality rate of the animal before ECMO can be started.

Standard venoarterial ECMO was performed after cannulation of the right common carotid artery and the external jugular vein using a 10 and 12 Fr cannula, respectively. The tip of the arterial cannula was positioned just cranial to the junction of the right common carotid artery and the brachiocephalic trunk and that of the venous cannula in the right atrium. Priming of the ECMO system was carried out by using pigs donor blood in such a way that the Hb level was similar to that of the animal. After starting ECMO the flow rate was increased gradually over several minutes until further increment was impossible due to limited blood egress from the venous cannula. The range of the flow rate obtained was 65–100 mL/kg/min. The fraction of inspired O_2 concentration of the membrane oxygenator was adjusted to maintain Sao_2 > 95% and Pao_2 at 75–100 mm Hg (10–13.3 kPa). In hypoxemic groups the fraction of inspired O_2 concentration of the ventilator was turned again to the prehypoxemic level. Acidosis was corrected when necessary and extra carbon dioxide was supplied to the membrane oxygenator to maintain $Paco_2$ at 30–40 mm Hg (4–5.3 kPa). In some piglets administration of blood or colloid was necessary just after starting ECMO to maintain arterial

blood pressure in the normal range. Systemic heparinization was performed to maintain an activated clotting time at 200–220 s.

At the end of the experiment the piglets were each terminated by an overdose of pentobarbital. Autopsy was performed to verify the position of the cannulas, which were correctly positioned in all cases and the presence of cerebral hemorrhage.

Physiological measurement. The following variables were continuously recorded at a sampling frequency of 1 Hz: heart rate, arterial blood pressure, CVP, Sao_2, ICP, LCaBF, ΔcO_2Hb, ΔcHHb, ΔcCyt.aa_3, and ΔCBV. To express the pulsatility of the systemic circulation analogous to the pulsatility index usually calculated in Doppler ultrasound investigations, the pulsatility ratio was calculated as (systolic-diastolic)/MABP (20). From the arterial blood pressure recording only the MABP was used for subsequent analysis. Recording was commenced after application of NIRS measurement system and continued until 120 min after starting ECMO. Arterial blood samples for determination of pH, Pao_2, $Paco_2$, and cHb (Blood Gas Manager 1312 and Co-oximeter 482, Instrumentation Laboratory, Milan, Italy) were drawn before induction of hypoxemia, just before cannulation, and at 60 and 120 min after starting ECMO.

Data analysis. Before analysis, CVP and ICP data were filtered with a 0.3-Hz low pass filter to reduce signal noise caused by breathing movements.

In the hypoxemic group the differences in the mean values over a 30-s period of each continuously recorded variable just before cannulation (A) and just before start of hypoxemia (E = reference point) were calculated to evaluate the effect of hypoxemia (Fig. 1). The results were analyzed using the paired t test.

From each continuously recorded variable in both groups, data of a 30-s period were obtained from four episodes: A (reference point), just before the start of the cannulation procedure; B, after cannulation, just before starting ECMO; C, at 60 min after starting ECMO; and D, at 120 min after starting ECMO (Fig. 1). The differences in the mean values over these 30-s periods between B and A, between C and A, and between D and A were calculated to determine the effect of cannulation and ECMO induction, respectively. First, the changes of all variables were analyzed using Hotelling's T^2 test (multivariate paired t test) to protect the overall confidence level. Thereafter only the statistically significant variables were analyzed further with the paired t test. The presented p values in the results are those from the paired t test. Next to the baseline values of the variables, the mean and SD of the changes within subjects are presented.

To compare the changes between the two groups, first a repeated measures analysis (analysis of variance) was performed to protect the overall confidence level. Thereafter, only the statistically significant variables (the overall difference between the groups or the interaction between time and group or both being statistically significant) were further analyzed with two sample t tests. For all statistical analyses, the level of significance was chosen at 0.05.

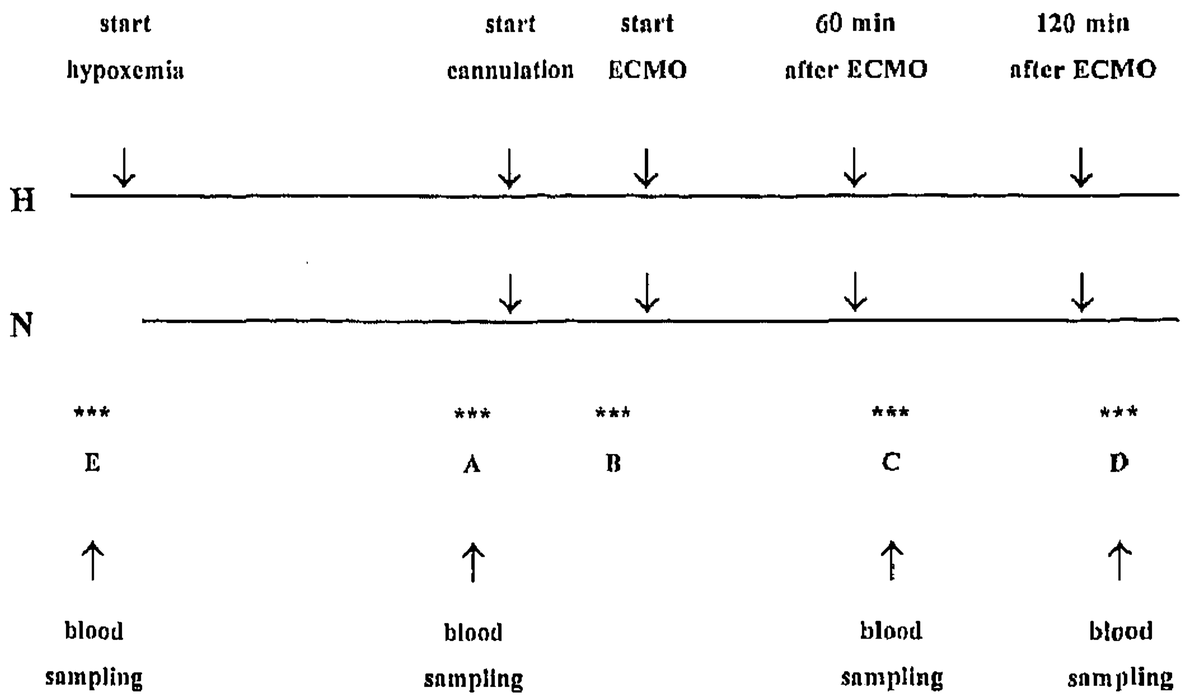

Figure 1. Schematic representation of data selection from continuous data registration and blood sampling (see text). H, hypoxemic group; N, normoxemic group.

RESULTS

After a 2-h duration of hypoxemia (mean ΔSao_2, 21.3%; mean ΔPao_2^- 62.2 mm Hg) there was a significant decrease in cO_2Hb with concomitant increase in cHHb, CBV, LCaBF, and ICP (Table 1). Surprisingly, an increase in cCyt.aa_3 was observed.

After cannulation increases in LCaBF, CBV, and cHHb only were detected in both groups (Tables 2 and 3).

After starting ECMO, LCaBF measurement in one hypoxemic piglet failed due to technical failure. In another hypoxemic piglet, data on Sao_2 were not available due to a calibration error. In the third hypoxemic piglet ICP at 120 min after starting ECMO was extremely increased and, from the autopsy, this animal turned out to be the one with extended arachnoidal hemorrhage. This ICP value was therefore discarded from the statistical analysis. Due to inaccurate O_2 supply to the membrane oxygenator, the Pao_2 in one normoxemic piglet at 120 min was extremely high.

Immediately after starting ECMO, significant changes of some variables were observed, which were finally stabilized

Table 1. *Changes at 2 h after induction of hypoxemia as compared to normoxemic values (n = 6)*

	Pre-hypoxemia values (E)	Changes after hypoxemia ($A - E$)
cO_2Hb (μmol/100 g)	NA	−0.83 (0.29)*
cHHb (μmol/100 g)	NA	1.67 (0.31)*
cCyt.aa_3 (μmol/100 g)	NA	0.03 (0.01)*
CBV (mL/100 g)	NA	0.71 (0.26)*
LCaBF (mL/min)	58.2 (15.9)	16.5 (11.6)*
MABP (mm Hg)	90.8 (12.0)	−5.8 (8.3)
CVP (mm Hg)	5.0 (0.7)	0.9 (0.7)*
Heart rate (beats/min)	117.2 (24.8)	21.5 (9.3)*
ICP (mm Hg)	14.6 (4.2)	4.0 (0.5)*
Sao_2 (%)	94.8 (4.0)†	−21.3 (5.1)*†
Pao_2 (mm Hg)	102.2 (13.0)	−62.2 (14.1)*
$Paco_2$ (mm Hg)	37.4 (2.3)	−0.6 (3.8)
pH	7.43 (0.03)	0.01 (0.02)
cHb (mmol/L)	6.6 (0.6)	0.2 (0.2)

Values are mean (SD). NA = not available.
* Significant changes ($p \leq 0.05$, paired t test).
† n = 5.

Table 2. *Changes in normoxemic piglets (n = 6) after cannulation and at 60 and 120 min after starting ECMO as compared to the precannulation values*

	Precannulation values (*A*)	Changes after cannulation (*B* − *A*)	Changes after starting ECMO: At 60 min (*C* − *A*)	Changes after starting ECMO: At 120 min (*D* − *A*)
cO_2Hb (μmol/100 g)	NA	−0.01 (0.10)	1.06 (0.40)*	0.78 (0.43)*
*c*HHb (μmol/100 g)	NA	0.18 (0.16)*	−0.09 (0.41)	0.16 (0.31)
*c*Cyt.aa_3 (μmol/100 g)	NA	0.01 (0.01)	0.02 (0.03)	0.03 (0.04)
CBV (mL/100 g)	NA	0.16 (0.12)*	0.87 (0.32)*	0.82 (0.44)*
LCaBF (mL/min)	75.5 (13.8)	33.6 (8.9)*	50.9 (28.2)*	52.8 (18.5)*
MABP (mm Hg)	98.5 (14.2)	5.1 (5.4)	9.1 (14.5)	12.9 (4.8)*
Pulsatility ratio	0.51 (0.09)	−0.01 (0.06)	−0.15 (0.04)*	−0.20 (0.09)*
CVP (mm Hg)	6.9 (2.1)	0.2 (0.3)	1.3 (1.1)	1.0 (1.5)
Heart rate (beats/min)	129.3 (23.0)	4.0 (9.4)	−9.2 (22.3)	−6.7 (21.2)
ICP (mm Hg)	13.3 (2.9)	2.3 (1.7)	2.4 (3.3)	0.6 (3.2)
Sao_2 (%)	99.3 (0.1)	0.1 (0.2)	0.0 (0.1)	0.0 (0.1)
Pao_2 (mm Hg)	104.8 (5.4)	—	−2.8 (33.4)	29.0 (108.9)
$Paco_2$ (mm Hg)	38.7 (2.8)	—	0.6 (4.7)	2.0 (6.8)
pH	7.42 (0.03)	—	0.03 (0.09)	0.01 (0.09)
*c*Hb (mmol/L)	6.6 (0.6)	—	0.0 (0.5)	0.0 (0.5)

Values are mean (SD). NA = not available.
* Significant changes ($p \leq 0.05$, paired *t* test, performed only if Hotelling's T^2 test is significant).

Table 3. *Changes in hypoxemic piglets (n = 6) after cannulation and at 60 and 120 min after starting ECMO as compared to the precannulation values*

	Absolute values precannulation (*A*)	Changes after cannulation (*B* − *A*)	Changes after starting ECMO: At 60 min (*C* − *A*)	Changes after starting ECMO: At 120 min (*D* − *A*)
cO_2Hb (μmol/100 g)	NA	−0.08 (0.10)	2.68 (0.86)*	2.66 (0.69)*
*c*HHb (μmol/100 g)	NA	0.59 (0.53)*	−1.83 (0.58)*	−1.82 (0.51)*
*c*Cyt.aa_3 (μmol/100 g)	NA	0.01 (0.02)	−0.01 (0.03)	0.01 (0.07)
CBV (mL/100 g)	NA	0.42 (0.40)*	0.68 (0.42)*	0.67 (0.45)*
LCaBF (mL/min)	74.7 (14.1)	29.7 (13.9)*	49.8 (10.4)*†	50.1 (17.7)*†
MABP (mm Hg)	85.0 (8.4)	−1.4 (3.4)	24.8 (9.6)*	28.1 (9.2)*
Pulsatility ratio	0.62 (0.08)	−0.03 (0.07)	−0.17 (0.07)*	−0.23 (0.11)*
CVP (mm Hg)	5.9 (0.9)	−0.3 (1.0)	0.2 (1.3)	0.2 (1.7)
Heart rate (beats/min)	138.7 (22.1)	25.4 (25.0)	−14.8 (18.8)	−19.9 (35.1)
ICP (mm Hg)	18.6 (4.4)	0.9 (2.2)	−1.7 (2.4)	−3.8 (3.3)†
Sao_2 (%)	73.5 (7.8)†	−7.3 (7.5)†	22.7 (6.2)†	21.1 (6.5)†
Pao_2 (mm Hg)	40.0 (3.7)	—	57.7 (27.8)*	61.0 (8.9)*
$Paco_2$ (mm Hg)	36.8 (2.5)	—	−0.8 (2.7)	1.4 (2.9)
pH	7.44 (0.02)	—	0.01 (0.02)	0.01 (0.04)
*c*Hb (mmol/L)	7.0 (0.6)	—	0.1 (0.4)	0.2 (0.4)

Values are mean (SD). NA = not available.
* Significant changes ($p \leq 0.05$, paired t test, performed only if Hotelling's T^2 test is significant).
† $n = 5$.

after 60 min. By then the values of cO_2Hb, CBV, and LCaBF were significantly higher than the precannulation values (Tables 2 and 3 and Fig. 2). In the hypoxemic groups there was also a decrease in *c*HHb and an increase in MABP, Sao_2, and Pao_2. In both groups a significant decrease of the pulsatility ratio was found. No significant changes in the other variables were found. As shown in Tables 2 and 3 and Figure 2, these changes still persisted at 120 min after starting ECMO. However, at 120 min the value of the MABP increase in the normoxemic group and ICP decrease in the hypoxemic group reached statistical significance.

Comparing the normoxemic and the hypoxemic groups, statistically significant differences were found for ΔcO_2Hb and ΔcHHb (at 60 and 120 min after starting ECMO), ΔSao_2 (after cannulation and at 60 and 120 min after starting ECMO), ΔMABP (after cannulation and at 120 min after starting ECMO), and ICP (at 120 min after starting ECMO). No significant differences were found in the response of CBV and LCaBF at 60 and 120 min.

In one hypoxemic piglet a diffuse extended and in one normoxemic piglet a small localized arachnoidal hemorrhage was found during autopsy.

DISCUSSION

As expected, the cerebral O_2 supply was increased (increased cO_2Hb and decreased *c*HHb) in hypoxemic piglets after starting ECMO. However, no significant change of *c*Cyt.aa_3 was observed. Because previous hypoxemia did not result in significant reduction of *c*Cyt.aa_3, it can be expected

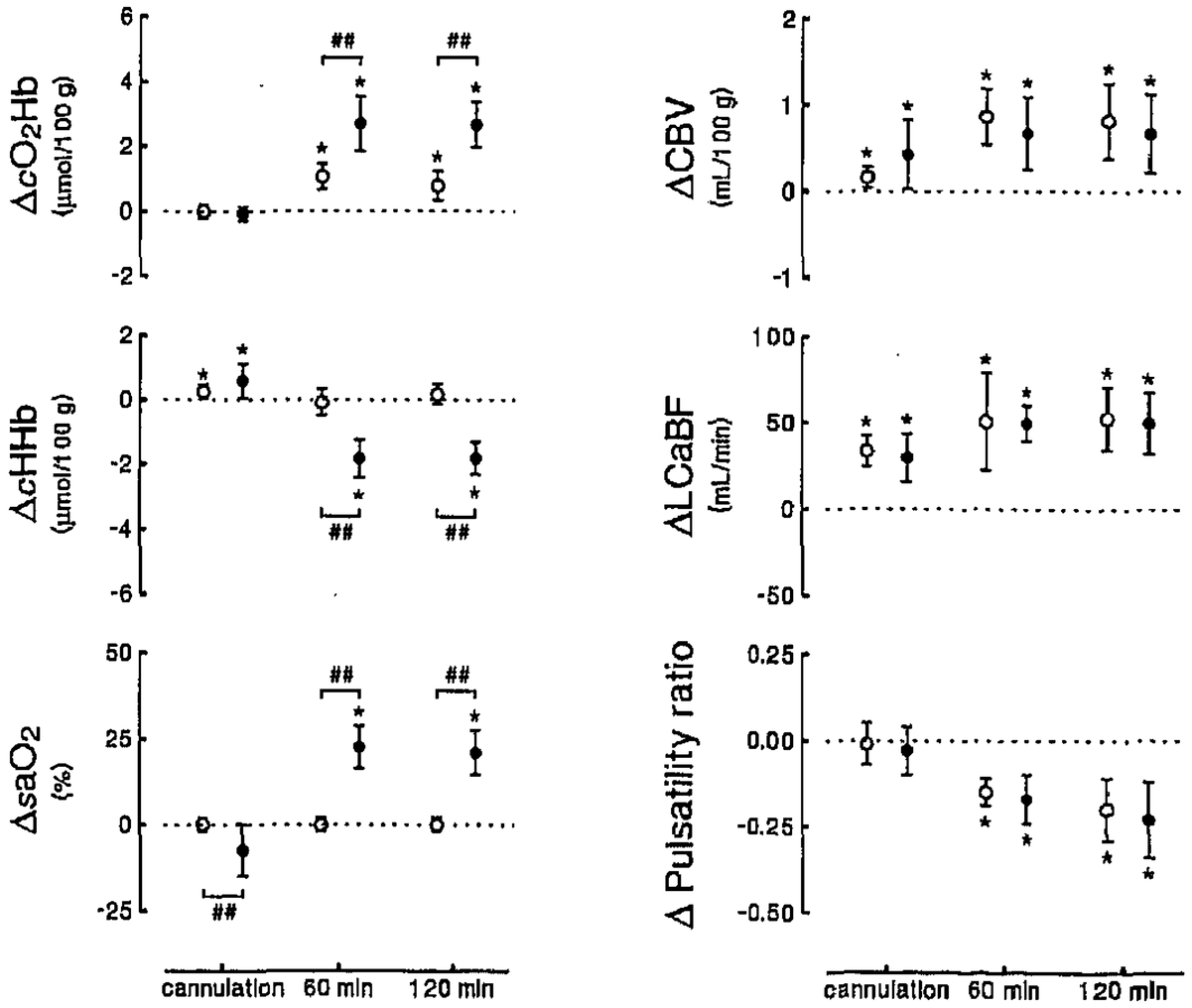

Figure 2. Changes of cO_2Hb, cHHb, Sao_2, CBV, LCaBF, and pulsatility ratio after cannulation and at 60 and 120 min after starting ECMO in normoxemic (*open circle*) and hypoxemic (*closed circle*) piglets. Mean ± SD values are shown. * = Significant change, related to precannulation level; ## = significant difference between both groups.

that recovery to normoxemia will not influence cCyt.aa_3 as well. However, the spread of the ΔcCyt.aa_3 value was very large. Because the Cyt.aa_3 signal is weak, it is very sensitive to major changes in the tissue, such as tissue edema, which seems to occur during nonpulsatile circulation (21).

Concomitant with increased cerebral O_2 supply, a significant increase in CBV occurred, which may be caused by increased CBF or decreased venous outflow (22). Decreased venous outflow is unlikely to occur, because during ECMO venous blood is continuously drained from the right atrium. Increased CBF is the most likely explanation, which is supported by the fact that the increase in cO_2Hb was more than the decrease in cHHb. A positive relationship between CBF and CBV has been described (23). The further increase in LCaBF after starting ECMO might also indicate increased CBF. However, the common carotid artery in pigs is not the only supplying artery of the brain, and moreover it supplies also the extracerebral circulation of the head (24). Therefore, in piglets changes in LCaBF will not necessarily reflect changes in CBF (25). So far these findings are similar to our previous observations in ECMO-treated newborn infants (8). In that report the increased CBV was presumed to be a result of three possible mechanisms: *1*) reactive hyperperfusion after restoration of normoxemia, *2*) disturbed autoregulation due to prolonged hypoxemia before ECMO and/or decreased arterial pulsatility, or *3*) compensation for hemodilution related to the ECMO procedure.

In normoxemic piglets, although significantly less than in hypoxemic ones, an increase in cerebral O_2 supply was observed after starting ECMO. The same increase in CBV as well as a further increase in LCaBF in the hypoxemic group was also observed. Therefore, the increased CBV and LCaBF after starting ECMO seems not to be related to the hypoxemic condition before ECMO. However, the hypoxemia in our piglets was not as severe and long as in the infants before they fulfill the ECMO entry criteria. Furthermore, in the infants the hypoxemia was frequently associated with perinatal asphyxia and metabolic changes due to severe therapeutic efforts. Therefore, reactive hyperperfusion due to restoration of normoxemia as well as disturbed autoregulation due to hypoxemia as possible causes of the increase in CBV cannot be completely excluded. Compensation for hemodilution can also be excluded, because cHb was unchanged in both groups due to careful priming of the ECMO circuit.

It is likely that the ECMO-related increases in CBV and LCaBF are the result of hyperperfusion induced by the ECMO system itself. Interaction between extracorporeal circulation and organ systems has been investigated in many cardiopulmonary bypass studies, but comparison with ECMO is not very useful because, in contrast with ECMO, most of these studies were performed during hypothermia with pulseless circulation. However, during ECMO, reduced arterial pulsatility is induced due to the use of a roller pump. We found a similar decrease of the pulsatility ratio in both normoxemic and hypoxemic groups. There is some evidence that arterial pulsatility may participate in the regulation of vascular tone and microcirculation, but there are many conflicting data on its effect on cerebral circulation (21, 26). During nonpulsatile flow in the canine brain, dilatation of venules and sludging of red cells in capillaries were observed (27), which might be expected to result in increased CBV. Normothermic nonpulsatile cardiopulmonary bypass in cats resulted in increased CBF and dilatation of cortical arterioles, indicating a "luxury perfusion syndrome" (28). During normothermic nonpulsatile cardiopulmonary bypass in pigs, an increase in the ratio between CBF and cerebral glucose consumption was observed, which was also an indication of a luxury perfusion syndrome, probably due to the disturbance of the regulation of cerebral vascular tone (29). Although it has been shown to occur during ECMO in normoxemic newborn lambs (7), impairment of autoregulation in our piglets is unlikely, because in contrast to the CBV and LCaBF changes, the MABP response was different between normoxemic and hypoxemic groups. Another possible etiologic factor is the release of microemboli from the extracorporeal system. During cardiopulmonary bypass, a substantial number of embolic events occur (30, 31). Microemboli might result in capillary occlusion and reactive hyperperfusion. On the other hand, hyperperfusion could be due to release of many endotoxin-related inflammatory mediators caused by exposition of blood to "foreign" materials (32, 33), which is already initiated during priming of the extracorporeal circuit (34). Finally, some chemical compounds may be excreted by the ECMO system (35), which could alter the microcirculation.

It is remarkable that, despite evidence of hyperperfusion, no significant ICP changes were found. A decrease of ICP after starting ECMO in normoxemic and hypoxemic newborn lambs has been reported (4). We have no explanation for this observation, but speculate that the regulation of cerebrospinal fluid circulation may be independent of that of cerebral blood circulation.

For venoarterial ECMO, ligation of the common carotid artery and the right internal jugular vein was necessary. There was concern about its potential hazard to the brain, but data

from the literature are conflicting (2, 36). Doppler ultrasound studies in newborn infants have shown that perfusion of the right cerebral hemisphere was maintained after ligation of the right common carotid artery (37, 38). The unchanged cO_2Hb after cannulation in our piglets might indicate unchanged cerebral O_2 supply. However, evidence of alterations in cerebral venous drainage after jugular ligation were found (39). In newborn lambs with the carotid artery and jugular vein ligated, recovery to normoxemia after prolonged hypoxemia resulted in cerebellar hyperperfusion and disrupted autoregulation (40, 41). In our piglet model, CBV was increased after the cannulation procedure. We did not analyze the influences of carotid and jugular ligation separately, but because *c*HHb increased in both groups, increased CBV was presumably the result of cerebral venous congestion due to jugular ligation, which is in accordance with reports from the literature (39, 40). However, in our previous NIRS study, during ECMO cannulation in newborn infants no change in CBV was observed (8). We have no clear explanation for the difference in CBV response after cannulation between newborn infants and piglets, but it might be due to differences in the ventilation pressure. Because the piglet lungs were normal, they were ventilated with lower positive pressure than in the infants. Higher ventilation pressure might impede cerebral venous return, resulting in increased CBV (42), which might abolish the effect of cannulation. Species differences in the cerebral venous system might also play a role.

The consequence of these hemodynamic changes during induction of ECMO is unknown. However, it can be speculated that cerebral hyperperfusion as well as venous congestion in combination with vulnerable capillary endothelium due to prolonged hypoxemia may easily result in capillary rupture. Venous congestion may result in decreased regional CBF, resulting in parenchymal infarction (39). In combination with heparinization and thrombocyte depletion during ECMO both conditions may result in development of cerebral hemorrhage or hemorrhagic infarction, an important complication during ECMO (1, 2). In one of the hypoxemic piglets an extended arachnoidal hemorrhage occurred within 2 h after induction of ECMO. However, further investigations on the relationship between cerebral vascular injury and perturbation of cerebral hemodynamics during ECMO is necessary to judge the clinical importance of this hyperperfusion during ECMO.

Normally, after induction of hypoxemia, contraregulatory mechanisms such as an increase in CBF or increase in cerebral O_2 extraction can be expected to occur. An increase in LCaBF was observed, but as it has been discussed earlier, in piglets it does not necessarily reflect increased CBF (25). Theoretically the observed CBV increase may be caused by increased arterial inflow (=CBF) or decreased venous outflow (22). Physiologically, increased CBF is more likely than decreased venous outflow. However, cO_2Hb decreased, but there was a larger increase in *c*HHb, which might be the result of increased cerebral O_2 extraction as a compensation for decreased cerebral O_2 supply, probably due to insufficient increase in CBF to fully compensate the loss in arterial O_2 content. If this contraregulatory mechanisms are effective, adequate cerebral O_2 sufficiency can be maintained, but an increase in $c\text{Cyt.}aa_3$ was observed. Since the algorithm for calculating $\Delta c\text{Cyt.}aa_3$ is derived from experiments on rat brains after exchange transfusion with fluorocarbon, the results of $c\text{Cyt.}aa_3$ should be interpreted with caution (23). However, using NIRS in the same animal model, it has been shown that moderate hypoxemia resulted in some exposures and inconsistently in increased $c\text{Cyt.}aa_3$ (43). Decrease in $c\text{Cyt.}aa_3$ was observed only after severe hypoxemia when the fraction of inspired O_2 concentration was lower than 6%, which was also accompanied by cerebral energy loss as assessed simultaneously by nuclear magnetic resonance (43). In neonatal piglets this enzyme seems to react differently to hypoxemia than it does in adult animals (18). In hypoxemic condition the enzyme will change toward much higher affinity for its substrate, which might result in increased $c\text{Cyt.}aa_3$. Apparently, this ability still seems to be present in this 2–3-wk-old piglets. Therefore, the response of $c\text{Cyt.}aa_3$ during moderate hypoxemia in our piglets seems to be reliable.

In conclusion, the cerebral hemodynamic changes after induction of ECMO is not different in pre-ECMO-induced normoxemic and hypoxemic piglets. To answer the question whether cerebral hemodynamics during ECMO are influenced by severe hypoxemia, another animal study is needed, in which more profound hypoxemia and circulatory changes before ECMO are induced.

Acknowledgments. The authors thank the staff of the Animal Laboratory for assistance with animal preparation, J. Evers for technical support, M. Gerritse for assistance in data analysis, and S. Houston for linguistic support.

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