Cerebral Oxygenation and Hemodynamics During Induction of Extracorporeal Membrane Oxygenation as Investigated by Near Infrared Spectrophotometry

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ABSTRACT. Objective. To investigate cerebral oxygenation and hemodynamics in relation to changes in some relevant physiologic variables during induction of extracorporeal membrane oxygenation (ECMO) in newborn infants.

Methods. Twenty-four newborn infants requiring ECMO were studied from cannulation until 60 minutes after starting ECMO. Concentration changes of oxyhemoglobin (cO2Hb), deoxyhemoglobin (cHHb), total hemoglobin (cHb), and (oxidized-reduced) cytochrome aa3 (cCyt.aa3) in cerebral tissue were measured continuously by near infrared spectrophotometry. Heart rate (HR), transcutaneous partial pressures of oxygen and carbon dioxide (tcPo2 and tcPCo2), arterial O2 saturation (saO2), and mean arterial blood pressure (MABP) were measured simultaneously. Intravascular hemoglobin concentration (cHb) was measured before and after starting ECMO. In 18 of the 24 infants, mean blood flow velocity (MBFV) and pulsatility index (PI) in the internal carotid and middle cerebral arteries were also measured before and after starting ECMO using pulsed Doppler ultrasound.

Results. After carotid ligation, cO2Hb decreased whereas cHHb increased. After jugular ligation, no changes in cerebral oxygenation were found. At 60 minutes after starting ECMO, the values of cO2Hb, saO2, tcPCo2, and MABP were significantly higher than the pre-cannulation values, whereas the value of cHHb was lower. There were no changes in cCyt.aa3, tcPCo2, and HR, whereas cHHb decreased. The MBFV was significantly increased in the major cerebral arteries except the right middle cerebral artery, whereas PI was decreased in all measured arteries. Cerebral blood volume, calculated from changes in cHb and cHb, was increased in 20 of 24 infants after starting ECMO. Using multivariate regression models, a positive correlation of ∆cHb (representative of changes in cerebral blood volume) with ∆MABP and a negative correlation with ∆tcPCo2 were found.

Conclusions. The alterations in cerebral oxygenation after carotid artery ligation might reflect increased O2 extraction. Despite increase of the cerebral O2 supply after starting ECMO, no changes in intracellular O2 availability were found, probably because of sufficient preservation of intracellular cerebral oxygenation in the pre-ECMO period despite prolonged hypoxemia. The increase in cerebral blood volume and cerebral MBFV may result from the following: (1) reactive hyperperfusion, (2) loss of autoregulation because of prolonged hypoxemia before ECMO and/or decreased arterial pulsatility, or (3) compensation for hemodilution related to the ECMO procedure. Pediatrics 1995;95:555-561; extracorporeal membrane oxygenation, near infrared spectrophotometry, cerebral oxygenation, cerebral hemodynamics, autoregulation.

ABBREVIATIONS. ECMO, extracorporeal membrane oxygenation; PaO2, arterial partial pressure of oxygen; PaCO2, arterial partial pressure of carbon dioxide; NIRS, near infrared spectrophotometry; saO2, arterial oxygen saturation; cO2Hb, oxyhemoglobin concentration; cHHb, deoxyhemoglobin concentration; cHb, total hemoglobin concentration; cCyt.aa3, (oxidized - reduced) cytochrome aa3 concentration; cHb, intravascular hemoglobin concentration; CBV, cerebral blood volume; MBFV, mean blood flow velocity; PI, pulsatility index; HR, heart rate; MABP, mean arterial blood pressure; tcPo2, transcutaneous partial pressure of oxygen; tcPCo2, transcutaneous partial pressure of carbon dioxide; CBF, cerebral blood flow.

Extracorporeal membrane oxygenation (ECMO) is used to treat newborn infants with severe respiratory failure who do not respond adequately to conventional treatment.1,2 The principle of ECMO is based on prolonged partial cardiopulmonary bypass. The survival rate is over 80%, but cerebrovascular injury is an important complication.2,3 Generally, the ECMO patient is hypoxemic for hours before ECMO is started. Induction of ECMO may result in significant changes in cerebral circulation caused by ligation of the right common carotid artery and internal jugular vein, decreased arterial pulsatility because of cardiopulmonary bypass, and rapid changes in arterial partial pressures of oxygen (PaO2) and carbon dioxide (PaCO2). However, in humans the effects of these changes on cerebral oxygenation and hemodynamics and their role in the pathophysiology of cerebrovascular injury have not been investigated extensively.

Near infrared spectrophotometry (NIRS) offers the possibility of noninvasive and continuous bedside investigation of cerebral oxygenation in newborn infants.4,5 We reported preliminary observations of marked changes in cerebral oxygenation and hemodynamics during induction of ECMO.5,6 In this report, we present further data and describe the relation between changes in cerebral oxygenation and hemodynamics and changes in some physiologic variables during induction of ECMO.
CEREBRAL OXYGENATION AND HEMODYNAMICS IN ECMO

Study Population

After obtaining informed parental consent, we studied 24 ECMO patients (17 male and 7 female, gestational age 35.1 to 40.9 weeks, birth weight 2100 to 4330 g). The study was approved by the University Hospital ethics committee. The indication for ECMO was failure to maintain normoxemia despite adequate conventional treatment using mechanical ventilation, sedation, muscle paralysis, and vasoactive drugs. All infants met the established entry criteria for ECMO; infants with cerebral hemorrhage or cerebral malformation were excluded. The underlying diseases were congenital diaphragmatic hernia (n = 9), meconium aspiration syndrome (n = 6), sepsis (n = 5), and persistent pulmonary hypertension from other causes (n = 4). During cannulation, the infants were anesthetized with fentanyl. Standard venoarterial ECMO was performed.1 After starting ECMO, flow rate of the bypass was increased gradually during several minutes until reaching a level (ranging from 136 to 205 mL/kg/min) needed to maintain arterial O2 saturation (SaO2) between 90% and 100% as measured by pulse oximetry. This flow rate is considerably higher than recommended,1 but proved to be necessary and was not limited by egress of blood from the venous cannula. Subsequently, the ventilator was set at a lower level for pressure, rate, and fraction of inspired O2 concentration to minimize barotrauma and O2 toxicity. Systemic heparinization was established. Medication administered before ECMO was continued during the measurement period.

Near Infrared Spectrophotometry

This technique is based on the spectrophotometric measurement of changes in the absorption properties of hemoglobin and cytochrome aa3 in the near infrared region, depending on their oxygenation state.8 The NIRS equipment used was developed by the Department of Biomedical Engineering and Medical Physics, University of Køge, and used by Radiometer (Copenhagen, Denmark).5 Details of our NIRS measurement have been described elsewhere.8 Briefly, near infrared light at 3 wavelengths (904, 845, and 775 nm) was transmitted through the skull by fiberoptic bundles. Using the described algorithm, concentration changes of oxyhemoglobin (ΔO2Hb), deoxyhemoglobin (ΔHb), total hemoglobin (ΔHbT), and oxidized – reduced cytochrome aa3 (ΔCyt.aa3) were calculated from changes in absorption of near infrared light at the 3 wavelengths mentioned. The transmitting and receiving optodes were fixed to the skull at an angle of approximately 90°, one at the anterior fontanelle and the other at the right parietotemporal region. In all infants, the interoptode spacing was greater than 2.5 cm to ensure a constant pathlength multiplying factor,10 which has been stated to be 4.39 times the spacing was greater than 2.5 cm to ensure a constant pathlength

Fig. 1. Schematic representation of data selection from the continuous data registration (see text). ECMO, extracorporeal membrane oxygenation.

METHODS

Near Infrared Spectrophotometry

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Measurement of Physiologic Variables

Using a neonatal monitor (Sirecust 404N, Siemens, Erlangen, Germany), heart rate (HR) and (umbilical) mean arterial blood pressure (MABP) were recorded continuously. The abdominal transcutaneous partial pressures of oxygen (tcPO2) and carbon dioxide (tcCO2) (Transend, Sensormedics Corp, Anaheim, CA) and SaO2 at the foot by pulse oximetry (N 200, Nellcor Inc, Hayward, CA) were also measured continuously. Data on tcPCO2 and tCO2 in three infants and data on SaO2 in one infant were not available because of technical failure. Blood samples for determination of PaO2, PaCO2, and Hb were drawn from the umbilical artery catheter just before cannulation and at 60 minutes after ECMO was started. Blood gas values and Hb were not corrected during this period.

Data Analysis

From each continuously recorded variable (cO2Hb, cHb, cCyt.aa3, SaO2, tC02, tC02, MABP, and HR), we obtained data on a 30-second period from six episodes: (A) just before the start of the cannulation procedure, (B) just before carotid ligation, (C) post-carotid ligation just before insertion of the arterial cannula, (D) just before jugular ligation, (E) post-jugular ligation just before insertion of the venous cannula, and (F) at 60 minutes after starting ECMO (see Fig 1). The differences in the mean values over the 30-second period between C and B, between E and D, and between A and F were calculated to determine the effects of carotid ligation, jugular ligation, and ECMO induction, respectively. First, the changes of the variables were analyzed with a multivariate version of the signed-rank test to protect the overall confidence level. Thereafter, statistically significant variables were analyzed further with the signed-rank test. The P values presented in the results are those from the (univariate) signed-rank test. The changes in MBFV, and PI at 90 minutes and in Hb and cHb at 60 minutes after starting ECMO, related to their precanulation values, were also calculated. Each difference was statis-
CAROTID LIGATION

CBV = (4 • cHb)/(0.69 • cHb),

where cHb is expressed in mmol/L, and cHb in mmol/100 g: 0.69 = cerebral-large vessel hematocrit ratio and 4 = correction factor, as cHb is calculated from changes in light absorption using extinction coefficients based on the tetraheme molecule, whereas cHb determination in blood samples is based on the monoheme molecule.

Because cHb changes after starting ECMO, ΔCBV cannot simply be calculated from ΔcHb. Therefore,

\[ \text{CBV} + \Delta \text{CBV} = 4 \cdot (\text{cHb} + \Delta \text{cHb})/0.69 \cdot (\text{cHb} + \Delta \text{cHb}), \]

and

\[ \Delta \text{CBV} = (\Delta \text{cHb} - 0.17 \cdot \Delta \text{cHb} \cdot \text{CBV})/0.17 \cdot (\text{cHb} + \Delta \text{cHb}). \]

However, because the initial CBV in the individual infant is unknown, it is impossible to calculate ΔCBV exactly. Wyatt et al. found a CBV of 2.2 ± 0.4 mL/100 g in newborn infants with normal brains. As moderate to severe hypoxemia is the main feature in the pre-ECMO condition, the initial CBV in these infants could be expected to be higher as a result of cerebral vasodilation. Assuming that the pre-ECMO CBV in these hypoxemic infants is between 2 and 6 mL/100 g, only the direction of ΔCBV could be estimated:

If ΔcHb is positive: ΔCBV is positive when
\[ (\Delta \text{cHb}/0.17 \cdot \Delta \text{cHb}) > 6 \]
and negative when
\[ (\Delta \text{cHb}/0.17 \cdot \Delta \text{cHb}) < 2. \]

If ΔcHb is negative: ΔCBV is positive when
\[ (\Delta \text{cHb}/0.17 \cdot \Delta \text{cHb}) < 2 \]
and negative when
\[ (\Delta \text{cHb}/0.17 \cdot \Delta \text{cHb}) > 6. \]

The distribution of ΔCBV direction among these infants was analyzed by the sign test.

In an attempt to describe the relation between ΔcHb and the changes in selected physiologic variables (ΔcHb, ΔMABP, ΔsaO2, ΔtcPO2, ΔtcPCO2, ΔatcPO2, and ΔHR) at 60 minutes after starting ECMO, we assessed possible linear regression models with ΔcHb as a dependent variable and the changes in these selected physiologic indices as independent variables. Because not all physiologic variables were recorded in each infant, regression models could be assessed in only 20 of 21 infants. For the three most suitable models, the regression coefficients (β) and the squared multiple correlation coefficients (R²) are given. Furthermore, to show the relative contribution to the explanation of the variation in ΔcHb, the partial R² (taking into account all other variables in the model) is given.

RESULTS

After carotid ligation, significant decreases in cO2Hb and MABP were found, whereas cHb increased. The other variables showed no significant changes. Jugular ligation revealed only an increase in MABP (Table 1; Fig. 2).

Immediately after starting ECMO, increases in saO2, tcPO2, cO2Hb, and MABP were observed, whereas cHb decreased. At 60 minutes after starting ECMO, the variables had stabilized in most infants. By then, values of cO2Hb, saO2, tcPO2, MABP, and PaO2 were significantly higher than the precanulation values. The cHb was significantly decreased because of hemodilution by the ECMO priming solution (Table 2; Fig. 2).

After starting ECMO, MBFV increased significantly in the major cerebral arteries except the right middle cerebral artery (Table 3). However, the direction of the blood flow in the right supraclinoid internal carotid artery was reversed in all infants. The PI values decreased significantly after starting ECMO (Table 3).

The CBV increased in 15 of 24 infants after starting ECMO, which was statistically significant (P < .01). In the other nine infants, CBV decreased (n = 2) or did not change (n = 7).

After assessing each possible regression model, we found that a model with five independent variables appeared to be most suitable to describe the relation between ΔcHb and the changes in other variables at 60 minutes after starting ECMO. The best model (R² = .67) had the independent variables ΔcHb, ΔMABP, ΔtcPO2, ΔtcPCO2, and ΔPaO2. The next two best models (R² = .66) differed from the best model by substituting ΔPaCO2 for ΔtcPCO2 and ΔsaO2 for ΔPaO2, respectively. As could be expected, there was a strong correlation between ΔcHb and the changes in other variables at 60 minutes after starting ECMO. The best model had the independent variables ΔcHb, ΔMABP, ΔtcPO2, ΔtcPCO2, and ΔPaO2.

In these models, after correction for the influence of the remaining independent variables, there was a positive correlation of ΔcHb with ΔMABP and a negative correlation with ΔtcPCO2 (P < .05). There was no statistically significant correlation between ΔcHb and ΔsaO2, ΔHR, ΔPaO2 or ΔPaCO2 after this correction.

DISCUSSION

Venoarterial ECMO requires ligation of the right common carotid artery. When the collateral circulation through the circle of Willis is completely normal,
perfusion of the right cerebral hemisphere will be sufficiently preserved. However, because incompleteness of the circle of Willis has been described in 0.6% of normal brains, there is a risk of cerebral infarction in the right hemisphere. Conflicting data on lateralization of cerebral lesions in former ECMO patients have been reported. In our study, ctHb was unchanged after carotid ligation, reflecting unchanged CBV. Assuming unchanged cerebral venous outflow, cerebral arterial inflow must remain unchanged as well. This is demonstrated by our and other Doppler ultrasound studies showing maintained antegrade blood flow in the right middle cerebral artery. Reversed blood flow in the right internal carotid artery, as found in our study, is evidence of collateral flow as well. The technique of NIRS may be useful to monitor cerebral hemodynamics during an occlusion test of the right common carotid artery before its definite ligation. When collateral circulation through the circle of Willis reveals inadequacy by showing a fall in CBV, venovenous ECMO should be considered. The advantage of NIRS compared with (color) Doppler ultrasound is the possibility for hands-free continuous monitoring, even during the surgical cannulation procedure.

After carotid ligation, a cO2Hb reduction with a concomitant cHHb increase was observed. This may reflect increased O2 extraction in the brain, caused by increased transit time of the blood resulting from diversion of the arterial blood supply to the right hemisphere. This is supported by the observation that, in contrast to the other major cerebral arteries, the right middle cerebral artery did not show a significant increase in MBFV. This compensatory mechanism is probably sufficient, because there is no significant change in cCyt.aa3, reflecting unchanged cerebral O2 availability. However, there is doubt about the reliability of the cytochrome aa3 signal, which will be discussed later.

Ligation of the right internal jugular vein might result in cerebral venous congestion and contribute to the occurrence of cerebral vascular lesions during ECMO. However, in our study ctHb and thus CBV did not change after jugular ligation; therefore, it might be concluded that the collateral venous system is sufficient for draining the cerebral venous blood. The improvement of arterial oxygenation after starting ECMO results in increased cerebral O2 supply (cO2Hb). Nevertheless, cCyt.aa3 did not change, reflecting unchanged cerebral O2 availability, which means sufficient preservation of intracellular oxygenation and energy metabolism in the cerebral tissue in the pre-ECMO period despite prolonged hypoxemia. In newborns, cCyt.aa3 seems to behave more independently from cO2Hb, as the enzyme remains almost completely oxidized until severe hypoxemia occurs. However, data on cCyt.aa3 should be interpreted with caution because the algorithm
used for calculating ΔCyt.aa₃ is derived from experiments on rat brains after exchange transfusion with fluorocarbon. Therefore, the data might be affected by noise due to residual hemoglobin after fluorocarbon exchange,25 as well as from scattering by fluorocarbon, which is different from that of erythrocytes.

After induction of ECMO, we observed an increase in CBV, which may result from increased arterial inflow or decreased venous outflow.26 Venous outflow decrease is unlikely to occur because during ECMO, venous blood is drained continuously from the right atrium. Increased arterial inflow is more likely the cause of increased CBV, as MBFV in the major cerebral arteries increases significantly, reflecting increased cerebral blood flow (CBF).27 A high correlation between CBF and CBV changes has been shown in animals.28 There is no clear-cut explanation for the increases in CBF and CBV after induction of ECMO. Data from the literature are contradictory. Induction of ECMO in normoxic animals has been shown not to alter CBF29 or to increase30 or decrease31,32 CBF. These conflicting results may be caused by differences in the species used, in the bypass flow rate, and in the duration of ECMO before CBF was measured. However, because many physiologic conditions change during ECMO induction, the cause of hemodynamic changes will be multifactorial.

Some factors could influence cerebral hemodynamics during induction of ECMO. First, changes in arterial blood gas values are probably not responsible for the increases in CBV and CBF found in our study. No changes in arterial PaCO₂ and acid-base balance were found. Increased arterial PaO₂ would be expected to result in decreases of CBF and CBV. In the selected regression models, the inverse relation between ΔcHb, as a representation of ΔCBV, and ΔcPaO₂ was confirmed. On the other hand, the increases of CBV and MBFV may also be caused by reactive hyperperfusion due to prolonged hypoxemia before ECMO. In hypoxic newborn piglets, significant cerebral hyperperfusion has been shown after restoration of normoxemia.33

Second, the regression models showed a clear relation between ΔMABP and ΔcHb as a representation of ΔCBV. Changes of CBV following changes of MABP are considered to result from disturbed autoregulation,26 which occurs in distressed newborn infants.34 However, impairment of cerebral autoregulation occurs in normoxic newborn lambs undergoing venoarterial ECMO.35 Disruption of the blood flow-metabolism couple in the brain occurs in pigs undergoing normothermic nonpulsatile cardiopulmonary bypass,36 indicating "luxury perfusion syndrome," but not in those undergoing pulsatile cardiopulmonary bypass.36 It seems, therefore, that the ECMO procedure itself is a potential cause of impaired autoregulation. It introduces a reduced arterial pulsatility caused by the use of a roller pump, as reflected by the decreased PI in our patients. This might impair the autoregulatory function, as it has been postulated that the pulse pressure may participate in autoregulation of capillary beds.36

Third, significant hemodilution during induction of ECMO will result in a decrease of arterial O₂ content. Therefore, CBF will increase to maintain cerebral O₂ delivery.18

It seems that these changes in cerebral hemodynamics after starting ECMO result from both the ECMO procedure itself and the prolonged pre-ECMO hypoxemia. Because fluctuations of cerebral hemodynamics in severely distressed infants might be harmful for the brain, they must be avoided. Further studies are necessary to identify all of the factors responsible for the perturbation of cerebral hemodynamics during ECMO.

In conclusion, NIRS is a valuable tool for studying cerebral oxygenation and hemodynamics during induction of ECMO. We found alterations in cerebral oxygenation reflecting increased O₂ extraction after carotid ligation, but not after subsequent jugular ligation. Despite the increase in the cerebral O₂ supply after starting ECMO, intracellular O₂ availability was unchanged, probably reflecting sufficient preservation of cerebral intracellular oxygenation and energy metabolism in the pre-ECMO period despite prolonged hypoxemia. The observed increases in CBV and cerebral MBFV may result from the following: (1) reactive hyperperfusion, (2) loss of autoregulation...
because of prolonged hypoxemia before ECMO and/or decreased arterial pulsatility, or (3) compensation for hemodilution related to the ECMO procedure.

**ACKNOWLEDGMENTS**

We thank the nursing staff of the neonatal intensive care unit and all members of the ECMO group for their contribution to this study, which was supported by a Princes Beatrix Fonds grant (no. 92.132). We are also grateful to Mr. M. Gerritse for his valuable help in data analysis and Mrs. S. Houston for her linguistic support.

**REFERENCES**


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**TABLE 3.** Changes in Mean Blood Flow Velocity (MBFV) and Pulsatility Index (PI) Values at 90 Minutes After Start of Extracorporeal Membrane Oxygenation (ECMO) (n = 18)

<table>
<thead>
<tr>
<th>MBFV</th>
<th>Absolute Precession Values, cm/s</th>
<th>Changes 60 min After Starting ECMO, %</th>
<th>PI</th>
<th>Absolute Precession Values, cm/s</th>
<th>Changes 60 min After Starting ECMO, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal carotid artery</td>
<td>Right</td>
<td>21.0</td>
<td>57.47††</td>
<td>1.92</td>
<td>-68.37††</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>20.0</td>
<td>100.6††</td>
<td>1.88</td>
<td>-59.60††</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>Right</td>
<td>23.5</td>
<td>18.57</td>
<td>1.83</td>
<td>-65.92††</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>23.5</td>
<td>-14.29 to 44.00</td>
<td>1.50 to 2.65</td>
<td>-75.12 to -59.24</td>
</tr>
</tbody>
</table>

† Values are median (interquartile range).
†† Significant changes (P ≤ .01).
†‡ Reversed flow.


NOTICE

Crigler-Najjar Syndrome

A Small Research Conference on this syndrome is to be held in 1996 to discuss new therapies which *might* be available.

I would appreciate hearing from physicians caring for such patients in order to inform them of the meeting and make the proceedings available to them. A newsletter and registry of individuals interested in this topic will be established if there is sufficient interest. **Contact:** Jerold F. Lucey, MD, FAAP, Prof. of Pediatrics, Editor of *Pediatrics*, Medical Center Hospital of Vermont (Fletcher Allen Health Care), Burlington, VT 05401. Telephone: (802) 862-8778.