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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, tcPO2, 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 ΔcHb (representative of changes in cerebral blood volume) with ΔMABP and a negative correlation with ΔtcPo2 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. The principle of ECMO is based on prolonged partial cardiopulmonary bypass. The survival rate is over 80%, but cerebrovascular injury is an important complication. 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. We reported preliminary observations of marked changes in cerebral oxygenation and hemodynamics during induction of ECMO. In this report, we present further data and describe the relationship between changes in cerebral oxygenation and hemodynamics and changes in some physiologic variables during induction of ECMO.
CEREBRAL OXYGENATION AND HEMODYNAMICS IN ECMO

Measurements were started just before the cannulation procedure. When the intravascular hemoglobin concentration (cHb) is uninteroptode spacing. As the optical pathlength is wavelength multiplying factor, which has been stated to be 4.39 times the oxygenation.

moglobin (ActHb), and (oxidized - reduced) cytochrome aa3

ECMO was failure to maintain normoxemia despite adequate

weeks, birth weight 2100 to 4330 g). The study was approved by

changed, ActHb reflects changes in cerebral blood volume (CBV).

Ac02Hb and AcHHb reflect changes in cerebral O2 supply,

infrared light at the 3 wavelengths mentioned. The transmitting

muscle paralysis, and vasoactive drugs. All infants met the estab­

the right parietotemporal region. In all infants, the in ter op to de

limited by egress of blood from the venous cannula. Subsequently,

infants were anesthetized with fentanyl.- Standard venoarterial

infrared region, depending on their oxygenation state. The NIRS equipment used was developed by the Department of Biomedical Engineering and Medical Physics, University of Keele, and produced by Radiometer (Copenhagen, Denmark). Details of our NIRS measurement have been described elsewhere. 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 (ΔHHb), total hemoglobin (ΔHgb), 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°, as described elsewhere.
RESULTS

After carotid ligation, significant decreases in c02Hb and MABP were found, whereas cHbHb 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, c02Hb, and MABP were observed, whereas cHbHb decreased. At 60 minutes after starting ECMO, the variables had stabilized in most infants. By then, values of c02Hb, saO2, tcPo2, MABP, and Pao2 were significantly higher than the precanulation values. The cHbHb 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 ActHb and the changes in other variables at 60 minutes after starting ECMO. The best model ($R^2 = .67$) had the independent variables AcHb, AMABP, ActHb, AtcPco2, AtcPo2, and AsaO2 for AcO2Hb, AcHb, AMABP, ActHb, AtcPco2, and AsaO2 at 60 minutes after starting ECMO. The best model ($R^2 = .67$) had the independent variables AcHb, AMABP, ActHb, AtcPco2, AtcPco2, and APaco2. The next two best models ($R^2 = .66$) differed from the best model by substituting APaco2 for AtcPco2 and AsaO2 for $P < .05$. There was no statistically significant correlation between ActHb and AsaO2, $P < .05$. There was no statistically significant correlation between AcHb and AsaO2, $P < .05$ 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,19 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.3,20 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.14,21,22 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 $cO_2Hb$ reduction with a concomitant $cHHb$ increase was observed. This may reflect increased $O_2$ 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 $O_2$ 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 congestion23 and contribute to the occurrence of cerebral vascular lesions during ECMO.24 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 $O_2$ supply ($cO_2Hb$). Nevertheless, cCyt.aa3 did not change, reflecting unchanged cerebral $O_2$ 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 $cO_2Hb$, as the enzyme remains almost completely oxidized until severe hypoxemia occurs.13 However, data on cCyt.aa3 should be interpreted with caution because the algorithm
Induction of ECMO in normoxemic animals has been shown in animals. There is no clear-cut explanation caused by differences in the species used, in the correlation between CBF and CBV changes has been shown not to alter CBF or to increase. There is no clear-cut explanation caused by differences in the species used, in the correlation between CBF and CBV changes has been shown not to alter CBF or to increase. There is no clear-cut explanation caused by differences in the species used, in the correlation between CBF and CBV changes has been shown not to alter CBF or to increase.

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Second, the regression models showed a clear relation between AMABP and ActHb as a representation of ACBV. Changes of CBV following changes of MABP are considered to result from disturbed autoregulation, which occurs in distressed newborn infants. However, impairment of cerebral autoregulation occurs in normoxic newborn lambs undergoing venoarterial ECMO. Disruption of the blood flow-metabolism couple in the brain occurs in pigs undergoing normothermic nonpulsatile cardiopulmonary bypass, indicating “luxury perfusion syndrome,” but not in those undergoing pulsatile cardiopulmonary bypass. 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.

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.

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

### TABLE 2. Changes of the Measured Variables at 60 Minutes After Starting Extracorporeal Membrane Oxygenation (ECMO) as Compared with Precannulation Values (n = 24)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Precannulation</th>
<th>Changes 60 min After Starting ECMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>cO2Hb μmol/100 g</td>
<td>Not available</td>
<td>1.80† (0.62 to 3.41)</td>
</tr>
<tr>
<td>chHb μmol/100 g</td>
<td>Not available</td>
<td>-0.72† (-3.27 to -0.20)</td>
</tr>
<tr>
<td>ctHb μmol/100 g</td>
<td>Not available</td>
<td>0.13 (-0.77 to 0.58)</td>
</tr>
<tr>
<td>cCyt.aa2 μmol/100 g</td>
<td>Not available</td>
<td>-0.01 (-0.06 to 0.05)</td>
</tr>
<tr>
<td>HbO2 %†</td>
<td>76.5 (66.25 to 88.42)</td>
<td>16.60† (4.57 to 30.37)</td>
</tr>
<tr>
<td>tcPao2 mm Hg</td>
<td>27.98</td>
<td>47.63† (18.82 to 64.99)</td>
</tr>
<tr>
<td>ttcPao2 mm Hg</td>
<td>41.02</td>
<td>0.15</td>
</tr>
<tr>
<td>MABP mm Hg</td>
<td>34.80 to 50.95</td>
<td>11.82† (7.01 to 25.32)</td>
</tr>
<tr>
<td>HR beats/min</td>
<td>159.04</td>
<td>-5.16</td>
</tr>
<tr>
<td>PaO2 mm Hg</td>
<td>35.25 (24.37 to 49.87)</td>
<td>59.25† (29.75 to 104.25)</td>
</tr>
<tr>
<td>PaCO2 mm Hg</td>
<td>38.25 (32.62 to 50.62)</td>
<td>-4.25 (-10.5 to 4.87)</td>
</tr>
<tr>
<td>pH</td>
<td>7.34 (7.24 to 7.46)</td>
<td>-0.07 - 0.06</td>
</tr>
<tr>
<td>cHb m Hg</td>
<td>8.75 (7.80 to 9.15)</td>
<td>-1.95† (-2.55 to -0.60)</td>
</tr>
</tbody>
</table>

* Values are median (interquartile range). Abbreviations: PaO2, arterial partial pressure of oxygen; PaCO2, arterial partial pressure of carbon dioxide; cHb, intravascular hemoglobin concentration; cHbO2, intravascular oxygenated hemoglobin concentration; other abbreviations as in Table 1.
† Significant changes (P ≤ .05).
‡ n = 23.
§ n = 21.

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, 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. 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). A high correlation between CBF and CBV changes has been shown in animals. There is no clear-cut explanation for the increases of 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 CBF or to increase or decrease 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 ΔcPO2 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 hypoxemic newborn piglets, significant cerebral hyperperfusion has been shown after restoration of normoxemia.

Second, the regression models showed a clear relation between AMABP and ActHb as a representation of ACBV. Changes of CBV following changes of MABP are considered to result from disturbed autoregulation, which occurs in distressed newborn infants. However, impairment of cerebral autoregulation occurs in normoxic newborn lambs undergoing venoarterial ECMO. Disruption of the blood flow-metabolism couple in the brain occurs in pigs undergoing normothermic nonpulsatile cardiopulmonary bypass, indicating “luxury perfusion syndrome,” but not in those undergoing pulsatile cardiopulmonary bypass. 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.

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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 Beatrice Fonds grant (no. 92.132). We are also grateful to Mr. M. Gerrits 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 Preconditioning Values, cm/s</th>
<th>Changes 60 min After Starting ECMO, %</th>
<th>Absolute Preconditioning Values, cm/s</th>
<th>Changes 60 min After Starting ECMO, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal carotid artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>21.0</td>
<td>57.47††</td>
<td>1.92</td>
<td>-68.37††</td>
</tr>
<tr>
<td></td>
<td>(17.0 to 27.0)</td>
<td>(34.09 to 103.70)</td>
<td>(1.25 to 2.56)</td>
<td>(-70.53 to -44.33)</td>
</tr>
<tr>
<td>Left</td>
<td>20.0</td>
<td>100.61†</td>
<td>1.88</td>
<td>-59.60†</td>
</tr>
<tr>
<td></td>
<td>(16.0 to 26.0)</td>
<td>(52.49 to 166.67)</td>
<td>(1.28 to 2.44)</td>
<td>(-72.60 to -41.18)</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>23.5</td>
<td>18.57</td>
<td>1.83</td>
<td>-65.92†</td>
</tr>
<tr>
<td></td>
<td>(20.0 to 35.0)</td>
<td>(-14.29 to 44.00)</td>
<td>(1.50 to 2.65)</td>
<td>(-75.12 to -59.24)</td>
</tr>
<tr>
<td>Left</td>
<td>23.5</td>
<td>29.26†</td>
<td>1.59</td>
<td>-51.46†</td>
</tr>
<tr>
<td></td>
<td>(21.0 to 31.0)</td>
<td>(5.56 to 42.86)</td>
<td>(1.13 to 1.87)</td>
<td>(-66.06 to -33.63)</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.