Cerebral Aspects of Neonatal Extracorporeal Membrane Oxygenation: A Review

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Key Words

Extracorporeal membrane oxygenation · Infant neonate · Brain damage · Cerebral hemodynamics · Cerebral oxygenation · Intracranial hemorrhage · Neonatal persistent pulmonary hypertension · Neurodevelopmental outcome · Respiratory failure · Respiratory insufficiency therapy · Cerebral ischemia

Abstract

Background: Neonatal extracorporeal membrane oxygenation (ECMO) is a lifesaving therapeutic approach in newborns suffering from severe, but potentially reversible, respiratory insufficiency, mostly complicated by neonatal persistent pulmonary hypertension. However, cerebral damage, intracerebral hemorrhage as well as ischemia belong to the most devastating complications of ECMO. **Objectives:** The objectives are to give insights into what is known from the literature concerning cerebral damage related to neonatal ECMO treatment for pulmonary reasons. **Methods:** A short introduction to ECMO indications and technical aspects of ECMO are provided for a better understanding of the process. The remainder of this review focuses on outcome and especially on (potential) risk factors for cerebral hemorrhage and ischemia during ECMO treatment. **Results:** Although neonatal ECMO treatment shows improved outcome compared to conservative treatment in cases of severe respiratory insufficiency, it is related to dis-

turbances in various aspects of neurodevelopmental outcome. Risk factors for cerebral damage are either related to the patient's disease, ECMO treatment itself, or a combination of both. **Conclusion:** It is of ongoing importance to further understand pathophysiological mechanisms resulting in cerebral hemorrhage and ischemia due to ECMO and to develop neuroprotective strategies and approaches.

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Introduction

Extracorporeal membrane oxygenation (ECMO) has become a rescue therapy for neonates with severe, but potentially reversible, respiratory failure when maximal conventional therapy has failed. Without ECMO, in these children mortality is high [1, 2]. Over 22,000 neonates have been treated with ECMO with an overall survival rate of 80% [3, 4]. In addition to earlier supportive studies, the most important study proving the efficiency of ECMO came from the UK collaborative ECMO Trial Group [5]. Newborns with severe respiratory failure were randomized to either ECMO or conservative treatment in one of the five participating centers. In all diagnosis groups of newborns, survival was better in the ECMO group compared to conventional treatment. Additionally, ECMO was likely to be as cost-effective as other life-extending technologies [6]. In 2008 the Co-

chrane group concluded that neonatal ECMO resulted in improved survival, without an increased risk of severe disability in survivors [7]. The effect of ECMO was less in newborns with congenital diaphragmatic hernia. Further studies were advised to optimize timing for the initiation of ECMO and to determine which infants will benefit most. As cerebral injury, intracranial hemorrhage (ICH) as well as ischemia belong to the most devastating complications of ECMO, the goal of this review is to give an overview of the relation between neonatal ECMO and the cerebrum.

Methods

All three authors included specific articles for this review. Next to a selection of articles used for their own decades of research in the area of ECMO and the brain, an extensive literature search was performed in the PubMed database using *extracorporeal membrane oxygenation, (infant) newborn and/or neonate, cerebral injury, intracranial hemorrhage, cerebral complications, and brain ischemia and outcome*. Finally, the list of publications registered by the Extracorporeal Life Support Organization was used.

Technical Aspects of ECMO

During neonatal ECMO an external circuit temporarily supports lung function of the newborn with an artificial oxygenator. Venous blood is passively drained from the right atrium through the venous cannula of the ECMO circuit, which is inserted into the right internal jugular vein. Blood then passes the bladderbox. In case of inadequate venous drainage from the right atrium the bladderbox will slow down and finally interrupt the ECMO pump. The ECMO pump actively pumps the blood at a regulated variable ECMO flow rate through a membrane oxygenator. Before the blood is returned to the patient, it is rewarmed by a heat exchanger. In case of veno-arterial ECMO (va-ECMO), the blood will be returned to the aortic arch through an arterial cannula inserted in the right common carotid artery. If veno-venous ECMO (vv-ECMO) is used the blood will return through the same venous cannula (which in this case is a double lumen cannula) into the right atrium. Clot formation due to the artificial materials has to be avoided by heparinization of the patient throughout the ECMO treatment.

Cerebral Aspects Related to Neonatal ECMO

Neonatal ECMO Criteria Are Related to the Brain

The decision to initiate ECMO is formed by a delicate balance between an effective rescue therapy aimed on survival and complications of the ECMO treatment, especially cerebral injury. Most nonsurvivors of ECMO treatment die from ICH and not from their primary respiratory disease. Exclusion criteria are mainly based on the fact that, once present, they increase the risk for ECMO-related complications, especially (intracranial) hemorrhage. As an illustration, table 1 shows the selection criteria and (relative) contraindications for the initiation of ECMO as used at our Department of Neonatology of the Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands. Criteria fit closely to those described by the international Extracorporeal Life Support Organization [8]. Inclusion and exclusion criteria are aimed to initiate ECMO in newborns with an estimated mortality of 80% with maximal conservative therapy. However, with therapies like surfactant, high-frequency oscillation (HFO) ventilation and the use of inhaled nitric oxide (iNO), predicted mortality without ECMO is less than 80% for certain diagnoses. In the UK trial, the control group had a mortality rate, depending on the underlying disease, of 43% in meconium aspiration syndrome to 100% in congenital diaphragmatic hernia. To avoid a delay in the use of ECMO because of an inadequate response to prior iNO treatment and other techniques like HFO, it has been suggested to lower the current ECMO criteria in patients suffering from severe hypoxic respiratory failure, who are already treated with iNO and HFO ventilation [2, 9]. Schumacher et al. [10] showed a shorter length of hospitalization, better cost-effectiveness and better (neurological) outcome at 1 year of age when neonates were randomized to lower threshold criteria to initiate ECMO.

Neonatal ECMO and (Neurological) Outcome

Cerebral injury, ICH as well as ischemia are revealed by imaging studies in 10% up to as high as 52% of the neonates [11–13]. Although ECMO has increased survival rates, the occurrence of hemorrhagic and ischemic cerebral lesions resulting in future neurological and neurodevelopmental dysfunction are of major concern [14, 15]. An important study describing the relation between severity of neonatal brain injury as detected by ultrasound and CT scan and neuropsychological and neurobehavioral outcome at the age of 5 years was performed by Glass et al. [16]. Disability was found to range from 10% in children with no radiologic brain abnormalities up to 57% in

Table 1. Inclusion criteria for neonatal ECMO at the Department of Neonatology, Radboud University Nijmegen Medical Centre

1	AaDO ₂ >600 mm Hg (80 kPa) for more than 8 h
2	AaDO ₂ >605 mm Hg (80.6 kPa) for more than 4 h with peak inspiratory pressure ≥38 mbar or mean airway pressure ≥22 mbar
3	Acute deterioration for at least 2 h with pH <7.15 and PaO ₂ <40 mm Hg (5.3 kPa)
4	No clinical improvement on maximal conventional therapy for 3 h with PaO ₂ <40 mm Hg (5.3 kPa)
5	Signs of barotrauma (at least 4): lung emphysema, pneumothorax or pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema, air leak >24 h, mean airway pressure >15 mbar
6	OI >40 for 3–5 h
7	In patients with congenital diaphragmatic hernia, at least once a documented PaO ₂ >80 mm Hg (10.6 kPa)

(Relative) contraindications

1	Gestational age <34 weeks or birth weight <2,000 g
2	Underlying lung disease or cause of respiratory insufficiency that is not expected to be reversible within 10–14 days
3	Mechanical ventilation >10 days
4	Chromosomal or other congenital or acquired abnormalities incompatible with life, including severe asphyxia
5	Intraventricular or cerebral parenchymal hemorrhage ≥ grade II
6	Coagulopathy or bleeding complication for which heparin administration is contra-indicated

AaDO₂ = Alveolar-arterial difference in partial oxygen pressure; AaDO₂ = (patm – pH₂O) × FiO₂ – (PaO₂ + PaCO₂), where patm = atmospheric pressure (mm Hg); pH₂O = vapor pressure (being 47 mm Hg at 37°C); PaO₂ = arterial partial pressure of oxygen (mm Hg); PaCO₂ = arterial partial pressure of carbon dioxide (mm Hg); FiO₂ = fraction of inspired oxygen; OI = oxygenation index = (MAP × FiO₂ × 100)/PaO₂, where MAP = mean airway pressure (mbar).

those with severe radiologic brain abnormalities. In the control group, healthy newborns, disability was detected in 2% of cases. A few studies concern the short-term outcome of newborns treated with ECMO, like feeding problems, growth and persistent pulmonary problems [17–19]. For the purpose of this review, we will concentrate on long-term neurodevelopmental and neuropsychological outcome. Most long-term follow-up studies show mild to major neurological impairment in 15 up to 25% of ECMO survivors. Impairment involves different kinds of neuro-

logical development, cognitive development, IQ and neuromotor development. More subtle signs of neurological involvement occur at higher rates in ECMO survivors. Learning problems at school age appear to be as high as 50% and ECMO parents reported behavioural problems more often compared to normal controls [15–18, 20–24]. In a Dutch follow-up study after va-ECMO, treated children were found to be highly at risk for developmental problems, most prominently in the motor domain as compared to normal reference populations [25].

In all long-term follow-up studies the selection of the control group is very important, especially as neonates treated with ECMO are generally severely ill and suffered from episodes of hypoxia and/or hemodynamic instability prior to ECMO treatment. Although several authors use near-miss ECMO patients to compare with, the best control group can probably be found in the follow-up studies of the UK collaborative randomized trial of neonatal ECMO [5, 20, 26, 27]. In their studies, the UK ECMO trial group found an improved survival at 1, 4 and 7 years of age in ECMO-treated newborns compared to those treated with conventional therapy. Even though 1 in every 4 patients treated with ECMO showed signs of impairment, there seemed to be a favorable outcome at 4 and 7 years of age in those newborns treated with ECMO. In addition, ECMO showed to be cost-effective compared to conventional treatment based on the 7-year results in the UK [28]. An important limitation of all follow-up studies is that they are mainly or exclusively based on neonates treated with va-ECMO, while in the meantime vv-ECMO was introduced, to initiate when possible instead of va-ECMO. This type of ECMO does not require ligation of the carotid artery, a concern for increasing the risk for cerebral injury. There are however no studies available comparing the long-term outcome between both forms of ECMO in neonates. For short-term differences in outcome only one study is available in the literature: Vanholt et al. [29] compared neonates treated with vv-ECMO and va-ECMO over a 5-year episode and found significantly more ICH in va-ECMO-treated newborns. This was however a nonrandomized and retrospective study in which patients' characteristics were significantly different between both groups, especially for birth weight and gestational age, which were significantly lower in the va-ECMO group.

Neonatal ECMO and Risk Factors for Brain Damage

The origin of cerebral injury in ECMO-treated newborns is probably a combination of factors, including pre-ECMO, patient and disease-related factors as well as fac-

Table 2. Overview of topics discussed as related to or (potential) risk factor for brain injury during neonatal ECMO

Topics related to brain injury	Topics as (potential) risk factor for brain injury
Gestational age	Disturbed cerebral autoregulation
Postconceptional age	Cannulation of the right common carotid artery
Acidosis/lactate level	Venous congestion
Sepsis/primary diagnosis	Loss of arterial pulsatility
Coagulopathy	Bloodstream contact with plasticizers
Heparinization	Inflammatory response to ECMO
Elevated activated clotting time	Venoarterial bridge
Low platelet count requiring transfusion	Bladderbox alarms
Longer ECMO treatment	Intravascular volume administration
iNO before ECMO	

tors related to the ECMO treatment itself and a combination of both [30]. A very interesting review concerning many of these aspects was written by Short [14]. Literature concerning risk factors for cerebral injury can be divided into two categories. The first category contains (case-control) studies looking for risk factors, like primary diagnosis, in patients who did develop cerebral lesions, with or without a control group. Studies of the second category focus more on possible pathophysiological risk factors in patients and on technical aspects and consequences of ECMO, like the changes in pulsatility of the cerebral blood flow (CBF) pattern during va-ECMO. An overview of topics discussed in both categories is shown in table 2. Several of the studies of the first category are important to mention: Hardart et al. [31, 32] determined gestational age, postconceptional age, acidosis, sepsis, coagulopathy and treatment with epinephrine as independent pre-ECMO factors associated with ICH in neonates who were treated with ECMO. These factors could probably explain why ECMO outcome depends on primary diagnosis as was also seen in the UK ECMO trial mentioned before. Dela Cruz et al. [33] demonstrated that an elevated activated clotting time and low platelet counts requiring transfusion were statistically associated with an increase in the development of ICH. The relation between activated clotting time and ICH reflects the role of anticoagulation, which is necessary to avoid clot formation in the ECMO system. Hirthler et al. [34] reviewed that instability of activated clotting time and platelet count are early predictors of ICH. In general the equilibrium between anticoagulation and clotting complications is difficult to manage. Clotting complications might result in embolization of (micro)clots to different organs, including the brain. Major ischemic lesions seem to be related

to longer ECMO treatment and more conservative use of heparin [35, 36]. Finally, lactate level before ECMO treatment was found to be a useful marker for the development of ICH during ECMO [37]. Again, this stresses that primary disease and severity of disease are important risk factors and partially explains the difference in outcome between for example severe sepsis/pneumonia and meconium aspiration syndrome. Our ECMO group studied the influence of iNO treatment before the initiation of ECMO on bleeding and clotting complications and the course of ECMO. iNO before ECMO is usually part of the treatment because of its specificity as a pulmonary vasodilator [38]. However, iNO has systemic effects as well, including alteration in platelet function [39]. Next to this, the use of iNO might result in a delayed initiation of ECMO, possibly resulting in a longer ECMO treatment course and more (cerebral) complications. In two retrospective studies we found a significant relationship between prior iNO use and clotting complications and/or disseminated intravascular coagulation, which might be a risk factor for ischemic cerebral events. We did not find a significant relationship with bleeding complications, including ICH. In our study the use of iNO did not result in a delay in the initiation of ECMO nor in an increase in the duration of ECMO treatment [40, 41].

Since randomized controlled studies are difficult to perform because of practical and ethical considerations, the second category of studies contains mainly observational aspects and concerns in neonates treated with ECMO. One interesting aspect, probably influenced by both patient factors like severity of illness and hypoxia as well as by the ECMO treatment itself, is the disturbance of cerebral autoregulation (AR). In normal, healthy newborns, cerebral AR maintains the CBF over a wide range

of cerebral perfusion pressures with a contraregulation response occurring with a delay of 2 s after sudden changes in blood pressure. It has been shown, however, that AR is disturbed in severely ill term infants [42–45]. Additional studies in newborn lambs showed that prolonged hypoxia and/or the ECMO treatment itself will significantly disturb the cerebral AR [46–49]. As a result, the capillary vasculature of the brain might be at increased risk in case of systemic blood pressure changes. This could be an additional risk for ischemic complications due to hypoperfusion as well as for hemorrhagic complications due to hyperperfusion.

Cannulation of the right common carotid artery and internal jugular vein became a concern. Some authors describe predominance of cerebral lesions in especially the right hemisphere of the brain, while in other studies this predominance, possibly related to ligation of the right common carotid artery and right internal jugular vein, could not be confirmed [50–56]. It has to be stressed that all studies mentioned concern neonates treated with va-ECMO. Data from large studies in vv-ECMO are actually not available. Theoretically, in the presence of an intact circle of Willis, ischemia of the right cerebral hemisphere will never occur. However, incompleteness of the circle of Willis has been found in 0.6% of normal brains, possibly an additive risk factor for ischemic lesions of the right hemisphere [57]. Reassuring data concerning the cannulation came from two studies. In the first, Short et al. [58] showed that 4 h of hypoxia in lambs before cannulation caused a 100% increase in CBF, with maintenance of oxygen transport to the brain and cerebral oxygen metabolism. These parameters were not altered by cannulation of the right common carotid artery and/or the right internal jugular vein. A second study by Klein et al. [59] found no statistically significant or persistent differences on MRI performed directly after ligation between rats in which either the jugular vein and/or the carotid artery were ligated compared to control rats. Less reassuring studies, considering the cannulation procedure, occurred as well. Our group found alterations in cerebral oxygenation after carotid artery ligation in human newborns, possibly reflecting an increased O_2 extraction due to increased transit time of the blood resulting from the diversion of arterial blood supply from the left common carotid artery to the right hemisphere. After jugular vein ligation, no changes were found. At 60 min after the initiation of ECMO there was a significant increase in CBV velocity (CBFV) and cerebral blood volume (CBV) [60]. In a consecutive study, van Heijst et al. [61] confirmed these data. Changes were measured in the right and left

cerebral hemisphere separately, but differences between right and left were not found. These findings combine well with two studies, both demonstrating a temporary decrease in CBFV after ligation of the right common carotid artery [62, 63]. Finally, Hunter et al. [64] performed a study in which the CBF of lambs was measured by laser Doppler flowmetry during va-ECMO as well as vv-ECMO. Ligation of the right common carotid artery resulted in temporary (1 min) decrease in CBF to the right cerebral cortex. It can at least be concluded that there are concerns about possible negative effects for the brain related to ligation of the right common carotid artery. Besides this, there is a lack of knowledge about the long-term consequences of permanent ligation of the right common carotid artery, for example at a later age when vascular atherosclerotic changes appear. All these factors together stimulated the development of vv-ECMO, using a double-lumen cannula, inserted in the right atrium of the patient. It has to be stressed, however, that vv-ECMO might have its own risks for the brain. There is especially fear for venous congestion due to obstruction caused by the thicker double lumen venous cannula. This is supported by three, somewhat older, studies, two of which describe a high frequency of ICH in the posterior fossa of the brain [65, 66]. The third study found a high incidence of subarachnoid space enlargement at the interhemispheric fissure and frontal, temporal and parietal convexity (68%) and ventricular enlargement (35%) in patients treated with vv-ECMO. In this same study, ICH occurred in 7 out of 31 neonates (22%) [67]. A direct comparison with va-ECMO is difficult as from the ELSO registry data it becomes clear that there are differences in populations treated with vv-ECMO compared to those treated with va-ECMO. One of the major reasons is the fact that less cardiac support can be given in vv-ECMO. However, a possible positive effect of vv-ECMO compared to va-ECMO might be the maintenance of pulsatile arterial flow to the brain. Once va-ECMO is initiated, Taylor et al. [68] found the systolic phase broadened and diastolic flow velocities markedly increased, as measured by Doppler imaging of the pericallosal portion of an anterior cerebral artery. This resulted in a decrease of the pulsatility index [PI, in which $PI = (systolic\ CBFV - diastolic\ CBFV) / systolic\ CBFV$] most clearly at higher ECMO flow rates. There was also an increase in true CBF expressed by the area under the time-velocity curve. Although clinical relevance and importance of these findings remain unclear, as is the case for many observational studies, this loss of arterial pulsatility might be additionally harmful for the vulnerable brain [14]. One of the underlying mechanisms

might be the increased disturbance of cerebral AR in va-ECMO compared to vv-ECMO as demonstrated by Ingyinn et al. [69, 70]. Vascular reactivity to acetylcholine was measured in middle cerebral arteries from lambs exposed to ECMO. Intraluminal acetylcholine infusion resulted in vasodilation in vessels from control and pulsatile vv-ECMO animals, while vasoconstriction was observed in vessels exposed to nonpulsatile va-ECMO. This indicates altered endothelial reactivity in vv- and va-ECMO. There are still conflicting data about the influence of nonpulsatile flow on cerebral perfusion [71, 72]. However, in the literature there is some evidence for more benefit from pulsatile circulation on CBF and increased vital organ flow [73, 74].

A concern for va-ECMO as well as for vv-ECMO could be the extensive contact of blood with the plasticizers containing tubings of the ECMO system, which might result in exposure of the brain to potential toxic agents [75, 76]. In addition, it has to be mentioned that the initiation of ECMO results in an important inflammatory response in the newborn with a release of mediators that might lead to cerebral damage. The white matter of the brain is especially vulnerable and therefore one could speculate that this could result in a high incidence of disturbed neurological development, most prominently in the motor domain [25].

Whether va-ECMO is used or vv-ECMO, it seems to be rational to further study treatment-related factors that might contribute to the occurrence of complications in the vulnerable brain. A good example is the use of the veno-arterial bridge (va-bridge) between the arterial and venous side of the va-ECMO system. Historically this va-bridge was filled with blood and opened and closed several times per hour to avoid clotting in it. Studies of our ECMO group showed significant changes in cerebral oxygenation and hemodynamics related to the use of the va-bridge. In piglets and newborn infants, Liem et al. [77], using near infrared spectrophotometry (NIRS), found that opening of the va-bridge resulted in a decrease in CBV and cerebral oxygen supply. After this initial decrease there is a compensatory increase in cerebral oxygen extraction and vasodilation. In a consecutive study in lambs, van Heijst et al. [78] described that opening of the va-bridge during va-ECMO resulted in a massive shunt of blood from the arterial side of the circuit to the venous side, causing significant changes in blood pressure, cerebral oxygenation and hemodynamics in lambs. In a more recent study, these changes were shown in a different way by using echo Doppler of the pericallosal artery during opening and closure of the va-bridge [79]. Opening of the

bridge resulted in very acute and large changes in CBF, sometimes even resulting in a negative CBF in the pericallosal artery, which is an end artery for a part of the brain supplied by the anterior cerebral artery. Although a direct causal relation between changes in cerebral oxygenation and hemodynamics because of the use of the blood-filled va-bridge and cerebral injury is not proven, changes can easily be avoided if the va-bridge is filled with normal saline instead of blood and connected with stopcocks to the venous and arterial cannula. In this way the va-bridge does not have to be opened intermittently, avoiding fluctuations in cerebral hemodynamics.

Three more studies of our group concern the possible harmful relation between bladderbox alarms, intravascular volume administration and cerebral lesions. The bladderbox controls venous drainage of blood from the right atrium. If the venous drainage becomes inadequate to maintain the established flow of the ECMO system, the bladderbox will give an alarm, slow down the pump and finally cause an acute interruption of the pump. Intravascular volume is often administered to restore the circulation through the ECMO system and the patient. In a retrospective case-control study we found a statistically significant relationship between the total number and volume of intravascular volume administrations and the development of ICH during treatment with va-ECMO [80]. We hypothesized that either the bladderbox alarms or the intravascular volume administration might cause potentially harmful fluctuations in cerebral oxygenation and hemodynamics. In a second study, using NIRS in lambs, we found that simulated bladderbox alarms during va-ECMO result in statistically significant fluctuations in cerebral oxygenation and hemodynamics, which might be an additional risk factor for cerebral injury [81]. As fluctuations were most profound when bladderbox alarms were resolved with intravascular volume administration, a third study was performed in human newborns on va-ECMO, in which the effect of volume administration on cerebral oxygenation and hemodynamics was studied using NIRS. Intravascular volume administration resulted in statistically significant fluctuations of cerebral oxygenation and hemodynamics [submitted for publication]. Most bladderbox alarms and consecutive intravascular volume administrations occur in the first 72 h of ECMO treatment. This is also the period in which most ICH is diagnosed. Studies above were all performed using a roller pump. An option to reduce described fluctuations could be the use of a centrifugal pump (without a bladderbox), however possible effects on the brain have to be studied for such pumps too.

Future Perspectives

Future research about cerebral damage in relation to ECMO treatment should consider several points. First of all it should be focused on gaining a better understanding of pathophysiological and technical aspects related to cerebral complications. One of these aspects is the role of venous congestion next to CBV in the occurrence of ICH and ischemia. Other technical aspects of ECMO to be studied for their potential effect on cerebral injury are centrifugal versus roller pumps.

The place of ECMO in the treatment cascade of severe neonatal respiratory insufficiency is another important point. Is it time to go beyond death as an outcome measure of ECMO? Should long-term neurodevelopmental

outcome, hospital length of stay and hospital cost be further evaluated with early intervention of this lifesaving therapy instead of using ECMO as a 'rescue therapy'? Should we come to more individualized ECMO criteria?

An interesting point is the fact that vv-ECMO is considered to be more gentle for the brain, but that there is still a lack of evidence that vv-ECMO does really result in less cerebral complications and improved long-term outcome. The ultimate study would be a multicenter trial in which patients are randomized to va- or vv-ECMO.

Finally, it is important that future research should consider possible brain-protective strategies like (head) cooling and neuroprotective drugs during ECMO treatment. From this point of view, results of a current randomized controlled trial by Field et al. [82] seem to be interesting.

References

- 1 Lequier L: Extracorporeal life support in pediatric and neonatal critical care: a review. *J Intensive Care Med* 2004;19:243–258.
- 2 Rais-Bahrami K, Short BL: The current status of neonatal extracorporeal membrane oxygenation. *Semin Perinatol* 2000;24:406–417.
- 3 Bartlett RH, Gazzaniga AB, Jefferies MR, Huxtable RF, Haiduc NJ, Fong SW: Extracorporeal membrane oxygenation cardiopulmonary support in infancy. *Trans Am Soc Artif Intern Organs* 1976;22:80–93.
- 4 ELSO Registry Report, June 2008: Extracorporeal Life Support Organization. Ann Arbor, ELSO, 2008.
- 5 UK Collaborative ECMO Trial Group: UK collaborative randomized trial of neonatal extracorporeal membrane oxygenation. *Lancet* 1996;348:75–82.
- 6 Roberts TE: Economic evaluation and randomized controlled trial of extracorporeal membrane oxygenation: UK collaborative trial. The Extracorporeal Membrane Oxygenation Economics Working Group. *BMJ* 1998;317:911–915.
- 7 Mugdoff M, Elbourne D, Field D: Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants (Cochrane Review). *Cochrane Database Syst Rev* 2008;16:CD001340.
- 8 Van Meurs K, Hintz S, Sheehan A: ECMO for Neonatal Respiratory Failure; in van Meurs K, Lally KP, Peek G, Zwischenberger JB (eds): *ECMO Extracorporeal Cardiopulmonary Support in Critical Care*, ed 3. Ann Arbor, Extracorporeal Life Support Organization, 2005, pp 273–296.
- 9 Kössel H, Bauer K, Kewitz G, Karaca S, Ver-smold H: Do we need new indications for ECMO in neonates pretreated with high-frequency ventilation and/or inhaled nitric oxide? *Intensive Care Med* 2000;26:1489–1495.
- 10 Schumacher RE, Roloff DW, Chapman R, Snedecor S, Bartlett RH: Extracorporeal membrane oxygenation in term newborns. A prospective cost-benefit analysis. *ASAIO J* 1993;39:873–879.
- 11 Lazar EL, Abramson SJ, Weinstein S, Stolar CJ: Neuroimaging of brain injury in neonates treated with extracorporeal membrane oxygenation: lessons learned from serial examinations. *J Pediatr Surg* 1994;29:186–190.
- 12 Graziani LJ, Gringlas M, Baumgart S: Cerebrovascular complications and neurodevelopmental sequelae of neonatal ECMO. *Clin Perinatol* 1997;24:655–675.
- 13 Bulas D, Glass P: Neonatal ECMO: neuroimaging and neurodevelopmental outcome. *Semin Perinatol* 2005;29:58–65.
- 14 Short BL: The effect of extracorporeal life support on the brain: a focus on ECMO. *Semin Perinatol* 2005;29:45–50.
- 15 Hofkosh D, Thompson AE, Nozza RJ, Kemp SS, Bowen A, Feldman HM: Ten years of extracorporeal membrane oxygenation: neurodevelopmental outcome. *Pediatrics* 1991;87:549–555.
- 16 Glass P, Bulas DI, Wagner AE, et al: Severity of brain injury following neonatal ECMO and outcome at age 5 years. *Dev Med Child Neurol* 1997;39:441–448.
- 17 Van Meurs KP, Robbins ST, Reed VL, et al: Congenital diaphragmatic hernia: long-term outcome in neonates treated with extracorporeal membrane oxygenation. *J Pediatr* 1993;122:893–899.
- 18 Glass P, Wagner AE, Papero PH, Rajasingham SR, Civitello LA, Kjaer MS, Coffman CE, Getson PR, Short BL: Neurodevelopmental status at age five years of neonates treated with extracorporeal membrane oxygenation. *J Pediatr* 1995;127:447–457.
- 19 Walsh-Sukys MC, Bauer RE, Cornell DJ, Friedman HG, Stork EK, Hack M: Severe respiratory failure in neonates: mortality and morbidity rates and neurodevelopmental outcomes. *J Pediatr* 1994;125:104–110.
- 20 Bennett CC, Johnson A, Field DJ, Elbourne D, UK Collaborative ECMO Trial Group: UK collaborative randomized trial of neonatal extracorporeal membrane oxygenation: follow-up to age 4 years. *Lancet* 2001;357:1094–1096.
- 21 Khambekar K, Nichani S, Luyt DK, Peek G, Firmin RK, Field DJ, Pandya HC: Developmental outcome in newborn infants treated for acute respiratory failure with extracorporeal membrane oxygenation: present experience. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F21–F25.
- 22 Hanekamp MN, Mazer P, van der Cammen-van Zijp MH, van Kessel-Feddema BJ, Nijhuis-van der Sanden MW, Knuijt S, Zegers-Verstraeten JL, Gischler SJ, Tibboel D, Kollée: Follow-up of newborns treated with extracorporeal membrane oxygenation: a nationwide evaluation at 5 years of age. *Crit Care* 2006;10:R127.
- 23 Schumacher RE, Palmer TW, Roloff DW, La Claire PA, Bartlett RH: Follow-up of newborns treated with extracorporeal membrane oxygenation for newborn respiratory failure. *Pediatrics* 1991;87:451–457.
- 24 Rais-Bahrami K, Wagner AE, Coffman C, Glass P, Short BL: Neurodevelopmental outcome in ECMO vs. near-miss ECMO patients at 5 years of age. *Clin Pediatr (Phila)* 2000;39:145–152.
- 25 Nijhuis-van der Sanden MW, van der Cammen-van Zijp MH, Janssen AJ, Reuser JJ, Mazer P, van Heijst AF, Gischler SJ, Tibboel D, Kollée LA: Motor performance in five-year-old extracorporeal membrane oxygenation survivors: a population-based study. *Crit Care* 2009;13:R47.

- 26 The UK Collaborative ECMO Group: The collaborative UK ECMO trial: follow up to 1 year of age. *Pediatrics* 1998;101:E1.
- 27 McNally H, Bennett CC, Elbourne DL, Field DJ; UK Collaborative ECMO Group: UK collaborative randomized trial of neonatal extracorporeal membrane oxygenation: follow-up to age 7 years. *Pediatrics* 2006;117:e845–e854.
- 28 Petrou S, Bischof M, Bennett C, Elbourne D, Field D, McNally H: Cost-effectiveness of neonatal extracorporeal membrane oxygenation based on 7-years of results from the United Kingdom Collaborative ECMO Trial. *Pediatrics* 2006;117:1640–1649.
- 29 Varnholt V, Lasch P, Sartoris J, Koelfen W, Kachel W, Lorenz C, Wirth H: Prognosis and outcome of neonates treated either with venoarterial (va) or veno-venous (vv) ECMO. *Int J Artif Organs* 1995;18:569–573.
- 30 Short BL, Bulas D: Neonatal ECMO and the Brain; in van Meurs K, Lally KLP, Peek G, Zwischenberger JB (eds): *ECMO Extracorporeal Cardiopulmonary Support in Critical Care*, ed 3. Ann Arbor, Extracorporeal Life Support Organization, 2005, pp 307–317.
- 31 Hardart GE, Hardart KM, Arnold JH: Intracranial hemorrhage in premature neonates treated with extracorporeal membrane oxygenation correlates with conceptual age. *J Pediatr* 2004;145:184–189.
- 32 Hardart GE, Fackler JC: Predictors of intracranial hemorrhage during neonatal extracorporeal membrane oxygenation. *J Pediatr* 1999;134:156–159.
- 33 Dela Cruz TV, Stewart DL, Winston SJ, Weatherman KS, Phelps JL, Mendoza JC: Risk factors for intracranial hemorrhage in the extracorporeal membrane oxygenation patient. *J Perinatol* 1997;17:18–23.
- 34 Hirthler MA, Blackwell E, Abbe D, et al: Coagulation parameter instability as an early predictor of intracranial hemorrhage during extracorporeal membrane oxygenation. *J Pediatr Surg* 1992;27:40–43.
- 35 Bulas DI, Glass P, O'Donnell RM, Taylor GA, Short BL, Vezina GL: Neonates treated with ECMO: predictive value of early CT and US neuroimaging findings on short-term neurodevelopmental outcome. *Radiology* 1995;195:407–412.
- 36 Fink SM, Bockman DE, Howell CG, Falls DG, Kanto WP Jr: Bypass circuits as the source of thromboemboli during extracorporeal membrane oxygenation. *J Pediatr* 1989;115:621–624.
- 37 Nozik-Gracyk EN, Melionies JN, Kern FH, Hansell DR, Ungerleider RM, Greeley WJ: Elevated serum lactate correlates with intracranial hemorrhage in neonates treated with extracorporeal life support. *Pediatrics* 1995;95:914–917.
- 38 Kinsella JP, Abman SH: Inhaled nitric oxide: current and future uses in neonates. *Semin Perinatol* 2000;24:387–395.
- 39 Weinberger B, Laskin DL, Heck DE, Laskin JD: The toxicology of inhaled nitric oxide. *Toxicol Sci* 2001;59:5–16.
- 40 De Mol AC, van Heijst AFJ, Brouwers M, de Haan AFJ, van der Staak FHJM, Liem KD: Abnormalities of coagulation related to the use of iNO prior to extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 2007;3:261–263.
- 41 De Mol AC, van Heijst AFJ, de Haan AFJ, van der Staak FHJM, Liem KD: The effect of inhaled nitric oxide on the course of extracorporeal membrane oxygenation and the occurrence of hemorrhagic complications. *ASAIO J* 2009;55:213–216.
- 42 Greisen G: Autoregulation of cerebral blood flow in newborn babies. *Early Hum Dev* 2005;81:423–428.
- 43 Aaslid R, Lindegaard KF, Sorteberg W, Nornes H: Cerebral autoregulation dynamics in humans. *Stroke* 1989;20:45–52.
- 44 Panerai RB, Kelsall AWR, Rennie JM, Evans DH: Cerebral autoregulation dynamics in premature newborns. *Stroke* 1995;26:74–80.
- 45 Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL: Responses of cerebral arteries and arterioles to acute hypotension and hypertension. *Am J Physiol* 1978;234:371–383.
- 46 Boylan GB, Young K, Panerai RB, Rennie JM, Evans DH: Dynamic cerebral autoregulation in sick newborn infants. *Pediatr Res* 2000;48:12–17.
- 47 Tweed A, Cote J, Lou H, Gregory G, Wade J: Impairment of cerebral blood flow autoregulation in the newborn lamb by hypoxia. *Pediatr Res* 1986;20:516–519.
- 48 Short BL, Walker LK, Traystman RJ: Impaired cerebral autoregulation in the newborn lamb during recovery from severe, prolonged hypoxia, combined with carotid artery and jugular vein ligation. *Crit Care Med* 1994;22:1262–1268.
- 49 Ashwal S, Majcher JS, Longo L: Patterns of fetal lamb regional cerebral blood flow during and after prolonged hypoxia: studies during the posthypoxia recovery period. *Am J Obstet Gynecol* 1981;139:365–372.
- 50 Campbell LR, Bunyapen C, Holmes GL, Howell CG Jr, Kanto WP Jr: Right common carotid artery ligation in extracorporeal membrane oxygenation. *J Pediatr* 1988;113:110–113.
- 51 Schumacher RE, Barks JD, Johnston MV, et al: Right-sided brain lesions in infants following extracorporeal membrane oxygenation. *Pediatrics* 1988;82:155–161.
- 52 Taylor GA, Short BL, Fitz CR: Imaging of cerebrovascular injury in infants treated with extracorporeal membrane oxygenation. *J Pediatr* 1989;114:635–639.
- 53 Mendoza JC, Shearer LL, Cook LN: Lateralization of brain lesions following extracorporeal membrane oxygenation. *Pediatrics* 1991;88:1004–1009.
- 54 Hahn JS, Vaucher Y, Bejar R, Coen RW: Electroencephalographic and neuroimaging findings in neonates undergoing extracorporeal membrane oxygenation. *Neuropediatrics* 1993;24:19–24.
- 55 Lago P, Rebsamen S, Clancy RR, Pinto-Martin J, Kessler A, Zimmerman R, Schmelling D, Bernbaum J, Gerdes M, D'Agostino JA: MRI, MRA and neurodevelopmental outcome following neonatal ECMO. *Pediatr Neurol* 1995;12:294–304.
- 56 Bulas DI, Taylor GA, O'Donnell RM, Short BL, Fitz CR, Vezina G: Intracranial abnormalities in infants treated with extracorporeal membrane oxygenation: update on sonographic and CT findings. *Am J Neuroradiol* 1996;17:287–294.
- 57 Alpers BJ, Berry RG, Paddison RM: Anatomical studies of the circle of Willis in normal brain. *AMA Arch Neurol Psychiatry* 1959;81:409–418.
- 58 Short BL, Bender K, Walker LK, Traystman RJ: The cerebrovascular response to prolonged hypoxia with carotid artery and jugular vein ligation in the newborn lamb. *J Pediatr Surg* 1994;29:887–891.
- 59 Klein MD, Lessin MS, Whittlesey GC, Chang CH, Becker CJ, Meyer SL, Smith AM: Carotid artery and jugular vein ligation with and without hypoxia in the rat. *J Pediatr Surg* 1997;32:565–570.
- 60 Liem KD, Hopman JCW, Oeseburg B, de Haan AFJ, Festen C, Kollée LAA: Cerebral oxygenation and hemodynamics during induction of extracorporeal membrane oxygenation as investigated by near infrared spectrophotometry. *Pediatrics* 1995;95:555–561.
- 61 Van Heijst A, Liem D, Hopman J, van der Staak F, Sengers R: Oxygenation and haemodynamics in the left and right cerebral hemispheres during induction of veno-arterial extracorporeal membrane oxygenation. *J Pediatr* 2004;144:223–228.
- 62 Raju TN, Kim SY, Meller JL, Srinivasan G, Ghai V, Reyes H: Circle of Willis blood velocity and flow direction after common carotid artery ligation for neonatal extracorporeal membrane oxygenation. *Pediatrics* 1989;89:343–347.
- 63 Matsumoto JS, Babcock DS, Brody AS, Weiss RG, Ryckman FG, Hiyama D: Right common carotid artery ligation for extracorporeal membrane oxygenation: cerebral blood flow velocity measurement with Doppler duplex US. *Radiology* 1990;175:757–760.
- 64 Hunter CJ, Blood AB, Bishai JM, Hickerson AD, Wall DD, Peverini RL, Power GG, Hopper AO: Cerebral blood flow and oxygenation during venoarterial and venovenous extracorporeal membrane oxygenation in the newborn lamb. *Pediatr Crit Care Med* 2004;5:475–481.
- 65 Taylor GA, Short BL, Fitz CR: Imaging of cerebrovascular injury in infants treated with extracorporeal membrane oxygenation. *J Pediatr* 1989;83:465–470.
- 66 Bulas DI, Taylor GA, Fitz CR, Revenis ME, Glass P, Ingram JD: Posterior fossa intracranial hemorrhage in infants treated with extracorporeal membrane oxygenation: sonographic findings. *Am J Roentgenol* 1991;156:571–575.

- 67 Brunberg JA, Kewitz G, Schumacher RE: Venovenous extracorporeal membrane oxygenation: early CT alterations following use in management of severe respiratory failure in neonates. *Am J Neuroradiol* 1993;14:595–603.
- 68 Taylor GA, Catena LM, Garin DB, Miller MK, Short BL: Intracranial flow patterns in infants undergoing extracorporeal membrane oxygenation: preliminary observations with Doppler US. *Radiology* 1987;165:671–674.
- 69 Ingyinn M, Lee J, Short BL, Viswanathan M: Venoaerterial extracorporeal membrane oxygenation impairs basal nitric oxide production in cerebral arteries of newborn lambs. *Pediatr Crit Care Med* 2000;1:161–165.
- 70 Ingyinn M, Short BL, Rais-Bahrami K, Viswanathan M: Altered cerebrovascular responses after exposure to venoaerterial extracorporeal membrane oxygenation: role of the nitric oxide pathway. *Pediatr Crit Care Med* 2006;7:368–373.
- 71 Hindman B: Cerebral physiology during cardiopulmonary bypass: pulsatile versus non-pulsatile flow. *Adv Pharmacol* 1994;31:607–616.
- 72 Edmunds LH Jr: Pulseless cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1982;84:800–804.
- 73 Rider AR, Schreiner RS, Undar A: Pulsatile perfusion during cardiopulmonary bypass procedures in neonates, infants and small children. *ASAIO J* 2007;53:706–709.
- 74 Undar A: Pulsatile versus nonpulsatile cardiopulmonary bypass procedures in neonates and infants: from bench to clinical practice. *ASAIO J* 2005;51:6–10.
- 75 Karle VA, Short BL, Martin GR, Bulas DI, Getson PR, Luban NL, O'Brien AM, Rubin RJ: Extracorporeal membrane oxygenation exposes infants to the plasticizer, di(2-ethylhexyl)phthalate. *Crit Care Med* 1997;25:696–703.
- 76 Schneider B, Schena J, Troug R, Jacobson M, Kevy S: Exposure to di(2-ethyl)phthalate in infants receiving extracorporeal membrane oxygenation. *N Engl J Med* 1989;320:1563.
- 77 Liem KD, Kollée LA, Klaessens JH, Geven WB, Festen C, De Haan AF, Oeseburg B: Disturbance of cerebral oxygenation and hemodynamics related to the opening of the bypass bridge during veno-arterial extracorporeal membrane oxygenation. *Pediatr Res* 1995;38:124–129.
- 78 Van Heijst A, Liem D, van der Staak F, Klaessens J, Festen C, De Haan T, Geven W, van de Bor M: Hemodynamic changes during opening of the bridge in veno-arterial extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 2001;2:265–270.
- 79 De Mol AC, van Heijst AFJ, van der Staak FHJM, Liem KD: Disturbed cerebral circulation during opening of the veno-arterial bypass bridge in extracorporeal membrane oxygenation. *Int J Artif Organs* 2008;31:266–271.
- 80 De Mol AC, Gerrits LC, van Heijst AFJ, Straatman H, van der Staak FHJM, Liem KD: Intravascular volume administration: a contributing risk factor for intracranial hemorrhage during extracorporeal membrane oxygenation. *Pediatrics* 2008;121:e1599–e1603.
- 81 De Mol AC, Gerrits LC, van Heijst AFJ, Menssen J, van der Staak FHJM, Liem KD: The effect of bladderbox alarms during veno-arterial extracorporeal membrane oxygenation on cerebral oxygenation and hemodynamics in lambs. *Pediatr Res* 2009;66:688–692.
- 82 Field DJ, Firmin R, Azzopardi DV, Cowan F, Juszczak E, Brocklehurst P, NEST Study Group: Neonatal ECMO Study of Temperature (NEST) – a randomized controlled trial. *BMC Pediatr* 2010;10:24.