Extra Corporeal Membrane Oxygenation in Newborns

Implications for Brain and Lung

Cover: Upper panel: ECMO treated sheep and their offspring. Lower panel: newborn patient on ECMO.

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Extra Corporeal Membrane Oxygenation in Newborns

Implications for Brain and Lung

Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

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Adrianus Franciscus Jacobus van Heijst

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Promotor

Prof. Dr. R.C.A. Sengers

Co-promotores

Dr. K.D. Liem

Dr. F.H.J.M. van der Staak

Manuscriptcommissie

Prof. Dr. F.K. Lotgering

Prof. Dr. M.H.J. Brouwer

Prof. Dr. D. Tibboel, Erasmus Universiteit Rotterdam

CONTENTS

ABBREVIATIONS

$AaDO_2$: alveolo-arterial difference in partial pressure of oxygen

ACD: alveolar capillary dysplasia

?-SMA: ?-smooth muscle actin

AT%: adventitial thickness expressed as percentage of the external diameter

BAEP: brainstem auditory evoked potential

cHb: intravascular concentration of haemoglobin (in mmol/L)

cHHb: concentration of deoxyhaemoglobin (in µmol/100 g)

cO_2Hb: concentration of oxyhaemoglobin (in µmol/100 g)

ctHb: concentration of total haemoglobin (in µmol/100 g)

CBF: cerebral blood flow

CBFV: cerebral blood flow velocity

CBV: cerebral blood volume (in mL/100 g)

CDH: congenital diaphragmatic hernia

CPP: cerebral perfusion pressure

CVL method: central venous line method

CVP: central venous pressure

CT-scan: computer tomography scan

DLVV-ECMO: double lumen catheter veno-venous extracorporeal membrane oxygenation

ECLS: extracorporeal life support

ECMO: extracorporeal membrane oxygenation

ED: external diameter

EEG: electroencephalogram

ELSO: extracorporeal life support organization

FiO_2: fraction of inspired oxygen

Flow AP: flow in the ECMO system between the bridge and the arterial catheter

Flow VP: flow in the ECMO system between the venous catheter and the bridge

HR: heart rate

i-PPHN: idiopathic persistent pulmonary hypertension of the newborn

IRDS: idiopathic respiratory distress syndrome

kPa: kilo Pascal

MABP: mean arterial blood pressure

MAS: meconium aspiration syndrome

MRI: magnetic resonance imaging

MT%: medial thickness expressed as a percentage of the external diameter

NIRS: near infrared spectrophotometry

OI: oxygenation index

paO_2: arterial partial pressure of oxygen

$paCO_2$: arterial partial pressure of carbon dioxide

PBS: phosphate buffered saline

PPHN: persistent pulmonary hypertension of the newborn

Qao: blood flow in the aorta

Qcar: mean blood flow in the left common carotid artery

Qduct: ductus arteriosus blood flow

Qecmo: ECMO flow

Qpa: blood flow in the common pulmonary artery

Qsyst: systemic blood flow

RCCA: right common carotid artery

RIJV: right internal jugular vein

saO_2: arterial oxygen saturation

sd: standard deviation

SEM: standard error of the mean

SMC: smooth muscle cell

Sp-B: surfactant protein B

SSSP: superior sagittal sinus pressure

svO_2: mixed venous oxygen saturation

svO_2 method: mixed venous oxygen saturation method

svO_2line: inline 'mixed venous' oxygen saturation

VA-ECMO: veno-arterial extracorporeal membrane oxygenation

VV-ECMO: veno-venous extracorporeal membrane oxygenation

WT%: total wall thickness expressed as a percentage of the external diameter

? : change in a variable

GENERAL INTRODUCTION

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BACKGROUND

Extracorporeal life support (ECLS) provides a prolonged but temporary support of cardiac and/or lung function, using mechanical devices. When ECLS is used for respiratory failure, it is called ExtraCorporeal Membrane Oxygenation (ECMO). The ECMO circuit consists of vascular access catheters, connecting tubing, a blood pump, an artificial lung ("oxygenator"), a heat exchanger and monitoring devices. In ECMO in newborns, venous blood is passively drained from the right atrium via a venous catheter inserted into the right internal jugular vein (RIJV). The blood then passes through a pump that maintains adequate flow in the ECMO system. For safety purposes, an intermediate bladder box with servo- system prevents pumping if venous drainage is inadequate. Next, the blood passes the membrane oxygenator where it is oxygenated and the carbon dioxide pressure is regulated. In the membrane oxygenator, a gas mixture of air, oxygen and carbon dioxide passes in the opposite direction to the blood flow. After rewarming in the heat exchanger, oxygenated blood is returned to the patient. This can either take place via the right common carotid artery (RCCA), in veno-arterial extracorporeal membrane oxygenation (VA-ECMO) (figure 1), or via the RIJV into the right atrium, in veno-venous extracorporeal membrane oxygenation (VV-ECMO).

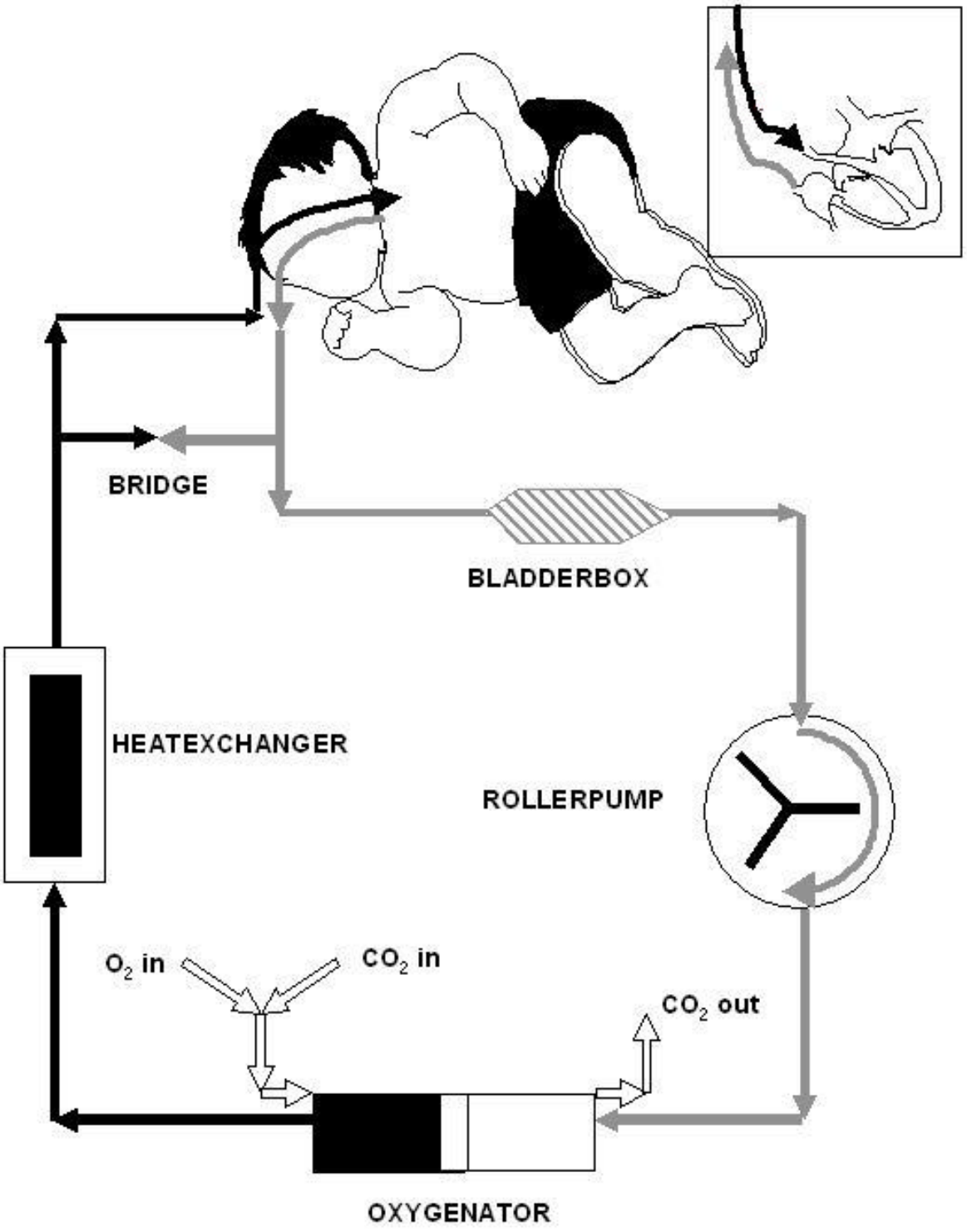
With mechanical support of circulation and gas exchange, the lungs and heart are given a rest period, during which the intensity of artificial ventilation and vaso-active drug administration can be diminished. Partial bypass is continued until the heart or lung function improves, after which blood flow through the extracorporeal circuit is decreased (weaning) and ECMO is ended.

Generally, ECMO is indicated as a rescue treatment in patients with acute reversible respiratory failure, when there is a high risk of dying (50-100%) from the primary disease, despite optimal conventional treatment. The most important indications for ECMO treatment in newborns are respiratory failure and pulmonary hypertension caused by meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), sepsis and idiopathic persistent pulmonary hypertension of the newborn (i-PPHN) (1).

As ECMO is only used in patients who are likely to die without ECMO, the results are usually described in terms of survival. Current survival rates with ECMO treatment reported in the registry of the Extracorporeal Life Support Organization (ELSO) are 80% for neonatal

respiratory failure, 60% for paediatric respiratory failure and 50 % and for adult respiratory failure (1).

Figure 1. Scheme of the VA -ECMO circuit



ECMO has increased survival in selected newborns with severe respiratory insufficiency. Unfortunately, this treatment modality has important complications that cause major morbidity and also determine survival rates. Ten to 30% of patients have major haemorrhagic and/or ischaemic intracranial lesions (2-9). Concern about the short and long-term negative effects of ligation of the RCCA in VA-ECMO led to the development of the VV-ECMO technique, in which ligation of the RCCA is avoided by cannulating a vein to return the oxygenated blood. However, VV-ECMO has the disadvantage of limited oxygenation, as recirculation of oxygenated blood from the 'arterial' infusion side of the cannula into the 'venous' drainage side does not contribute to patient oxygenation.

In addition to cerebral complications, survival rates are also determined by the occurrence of pulmonary complications (10). Severe intracranial abnormalities and pulmonary complications are highly correlated with disturbed neurodevelopmental outcome (2,5,8,11-13). Abnormal developmental outcome was present in 11-24% of the patients in these studies. The presence of major abnormalities in neuro-imaging studies and chronic lung disease increased the risk of adverse neurodevelopmental outcome 27 and 26 times respectively. Patients with intracranial abnormalities on neuro-imaging were 27 times likely to have a delayed development (12,13).

Persistent respiratory problems during ECMO can interfere with weaning the patient from ECMO. Although it is generally possible to wean the patient from ECMO, it remains unclear by which mechanism ECMO improves the underlying disease.

Some technical aspects of ECMO treatment may be related to the occurrence of complications. Our group published about the effects on cerebral oxygenation and haemodynamics of cannulation and VA-ECMO initiation and of opening of the bridge, a safety connection between the arterial and venous side of the ECMO circuit (14,15). Furthermore, our group demonstrated the presence of a patent ductus arteriosus with left to right shunt during VA-ECMO and its relation with a prolonged ECMO duration (run-time) (16). Hereby the time period during which ECMO related complications might occur increases.

STUDY OBJECTIVES

ECMO as a rescue treatment for newborns with severe respiratory insufficiency improves survival. However, the technique is complex and two major aspects determine short and long term outcome: cerebral and lung complications.
It is very important to understand the effects of ECMO on the brain and lungs, in order to be able to optimize its use and prevent complications related to this technique.

Therefore, this thesis had the following aims:

1. To study clinical results, in terms of survival and complications, of VA-ECMO treatment in newborns with severe respiratory failure.
2. To study the effect of VA-ECMO on cerebral oxygenation and haemodynamics.
3. To devise a method to quantify the amount of recirculation during VV-ECMO.

DETAILED OBJECTIVES OF THE STUDY

Part 1 describes the clinical results of ECMO treatment at the University Medical Centre Nijmegen.

1. More than 18,000 newborns have been treated with ECMO worldwide. Since the introduction of ECMO at our centre in 1999, 186 newborns have received treatment because of severe respiratory failure. Are our results comparable with those obtained at other centres? (Chapter 2).
2. The beneficial effect of ECMO is generally described as “lung rest”, but it is unclear what this concept represents. Newborns with severe pulmonary hypertension have an abnormal morphology of the lung vasculature. What is the difference in the morphology of the lung vasculature in patients with pulmonary hypertension treated with ECMO and those not treated with ECMO? (Chapter 3).

Part 2 addresses cerebral oxygenation and haemodynamics during ECMO.

1. VA-ECMO causes changes in cerebral oxygenation and haemodynamics. Does the induction of VA-ECMO have different effects on the left and right cerebral hemispheres? (Chapter 5).

2. Opening of the bridge during VA-ECMO results in changes in cerebral oxygenation and haemodynamics. What causes these changes? What is the effect of opening the bridge at different ECMO flow rates and for different opening times, and can the changes in cerebral oxygenation and haemodynamics be prevented? (Chapter 6).

3. A patent ductus arteriosus with left to right shunt can be present during VA-ECMO. How does a ductus arteriosus with left-to-right shunt during VA-ECMO affect cerebral oxygenation and haemodynamics? (Chapter 7).

Part 3 addresses VV-ECMO

In VV-ECMO, ligation of the RCCA is avoided by cannulating a vein to return the oxygenated blood. Oxygenation is limited with this technique, because recirculation does occur. Is it possible to quantify recirculation during VV-ECMO using an easily applicable, bedside method? (Chapter 9).

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PART 1

'THE NIJMEGEN EXPERIENCE'

CHAPTER 1

ECMO IN NEWBORNS WITH RESPIRATORY FAILURE: INTRODUCTION

ECMO IN NEWBORNS WITH RESPIRATORY FAILURE: INTRODUCTION

HISTORY

The first extracorporeal cardiopulmonary bypass system was developed by John Gibbon in the 1930s (1). In this system, direct blood-gas contact was necessary for oxygenation, which limited the bypass time to about 6 hours because of cell haemolysis, platelet consumption and protein denaturation (2). In 1963, Theodore Kolobow developed the silicone rubber membrane lung, which today is still the oxygenator mainly used for long-term bypass (3).

In 1976, Bartlett was the first to use ECMO successfully in a newborn with respiratory failure due to MAS (4,5). In 1982, Bartlett's group reported on the use of ECMO in 45 newborns (6). These patients were suffering from pulmonary disease, often exacerbated by pulmonary hypertension, and were generally moribund when ECMO was started. ECMO and the short-term follow-up results were considered so encouraging that many others started to apply ECMO treatment for newborn respiratory failure (7-10). Different authors tried to identify patients who would benefit most from rescue treatment with ECMO. Krummel et al, Ortiz et al and Beck et al published criteria to select patients for ECMO treatment (11-13). However, no scientific prove was available that demonstrated better survival with ECMO treatment. For obvious reasons it was not feasible to perform a blind randomised controlled trial comparing conventional treatment to ECMO treatment, because blinding as well as sham operations were impossible in the controls. Experience with ECMO treatment convinced people about its effectiveness. Opportunities were searched for in trials to limit the number of patients who had to be randomised to conventional treatment. Physicians could not accept that children from were dying while an alternative treatment was available.

Two "adapted" randomised studies were published that seemed to prove the benefit of ECMO therapy over conventional therapy in newborns with severe respiratory failure (14,15). However the randomization design of these studies was disputed, which led to the opinion that no approved clinical trials had been undertaken (16).

The ELSO, founded in 1989, participated in a National Institute of Health conference in 1990. It was concluded that ECMO use should be continued and that ECMO centres should participate in the ELSO registry, thus making it possible to monitor efficacy and effectiveness (17). Today, the ELSO has 110 centres in 14 countries.

In 1989, ECMO was applied for the first time at our hospital (University Medical Centre Nijmegen) in two newborns with MAS and sepsis, both survived (18). Between 1991 and 1994, ECMO treatment was used within the "Evaluation project for innovative developments in medicine" entitled Extra Corporeal Membrane Oxygenation in newborns (no OG 90-001). As randomisation was considered to be unethical, the ECMO group was compared to a control group of newborns with severe respiratory failure who fulfilled the criteria for ECMO treatment but had not received ECMO because it was not yet available (1988-1991), the so-called historical control group. Results of this project are summarized in table 1: survival in the ECMO group was better than that in the historical control group. The best survival was seen in the group of patients with MAS, while the greatest increase in survival was achieved in the group of patients with CDH.

Table 1. Results of the "Evaluation project for innovative developments in medicine": Extra Corporeal Membrane Oxygenation in newborns (OG-90-001)

Diagnosis	ECMO survival	Conventional therapy survival	Odd's ratio	p value
MAS	87% (n=31)	50% (n=22)	0.15	0.005
CDH	65% (n=23)	4% (n=24)	0.02	<0.001
Other	72% (n=25)	39% (n=38)	0.25	0.02
Total	76% (n=79)	32% (n=84)	0.15	<0.001

MAS = meconium aspiration syndrome, CDH = congenital diaphragmatic hernia

In 1996, the UK collaborative ECMO group published a large randomised trial on survival in ECMO in newborns in (19). Newborns with severe respiratory failure were randomised to either ECMO treatment at one of the five ECMO centres or conservative treatment at the participating centres. The results are summarized in table 2. Survival until discharge in all the diagnoses groups of newborns with severe respiratory failure was better in the ECMO group than in the conventional treatment group. Cost-effectiveness was also evaluated and it was concluded that ECMO was likely to be as cost-effective as other life-extending technologies (20).

The Cochrane group evaluated the trials of Bartlett et al, O'Rourke et al, the UK trial and also a fourth trial the results of which were presented at a conference (14,15,19,21,22). There were fewer deaths before discharge in ECMO patients than in controls (Relative Risk 0.44, 95% CI: 0.31-0.61, $p<0.00001$). Mortality rates differed by -0.32 (95% CI: -0.44 to -0.20), which meant that ECMO in three newborns was needed to prevent one death. The risk of death

before discharge was reduced the most in infants without the diagnosis CDH (RR 0.33, 95% CI: 0.21-0.53, p<0.00001), but even in infants with CDH the risk of death was reduced (RR 0.72, 95% CI: 0.54-0.96, p=0.03). The Cochrane group concluded that the use of ECMO in newborns with severe, but potentially reversible, respiratory insufficiency resulted in significantly improved survival, without an increased risk of severe disability in survivors. However, in terms of death or disability, the advantage of ECMO treatment over conventional treatment in CDH patients had disappeared at 4 years follow-up in the UK trial (23).

Over the past 28 years, ECMO has evolved from an experimental therapy for moribund newborns to a life-saving technology for a selected group of newborns with reversible or treatable disorders and intractable hypoxaemia, hypotension and/or clinical deterioration that is unresponsive to maximal conservative treatment (24).

Table 2. Results of the UK collaborative randomised trial of extracorporeal membrane oxygenation in newborns

	Deaths*/number treated		
Primary diagnosis	ECMO	Conventional management	Relative risk (95% CI); p value
CDH	13/18	17/17	0.72 (0.54-0.96); p<0.05
MAS	6/32	16/37	
I-PPHN	2/15	10/16	0.41 (0.24-0.67); p<0.001
Other	7/28	11/22	
Total	28/93	54/92	0.52 (0.36-0.73); p<0.001

* = Death before discharge, MAS = meconium aspiration syndrome, CDH = congenital diaphragmatic hernia, I-PPHN = idiopathic persistent pulmonary hypertension of the newborn

PATIENT SELECTION

Patient selection for ECMO treatment is based on the principle that the risk of death or severe morbidity with conventional therapy is greater than the risk associated with ECMO treatment. In general, underlying lung disease must be reversible within the ECMO run-time. The most important disorders in newborns with severe respiratory failure are MAS, sepsis/pneumonia and CDH, often aggravated by severe persistent pulmonary hypertension of the newborn (PPHN). This latter disorder may be present without any of the other underlying disorders: idiopathic persistent pulmonary hypertension of the newborn (I-PPHN). ECMO allows time

for recovery and avoids the risks associated with prolonged intensive mechanical ventilation (24).

ECMO treatment is not offered to patients with a compromised health state, i.e. patients with pre-existing cerebral defects, irreparable congenital heart disorders, non-functional kidneys, lethal and untreatable metabolic diseases, malformation syndromes, major anatomical anomalies and severe chromosomal aberrations (trisomy 13 and 18). Patients with pre-existing irreversible organ damage are also excluded (24).

ECMO is not offered to patients born at a gestational age of less than 34 weeks or with a birth weight of less than 2 kg, because of the increased risk of intracranial haemorrhage (25-27).

As it is necessary to administer heparin during ECMO treatment, uncontrollable bleeding or coagulopathy is considered a relative contra-indication (24). Intensive artificial ventilation for longer than 10 days is also a relative contra-indication, because it may have caused irreversible lung damage.

In their original paper, Bartlett et al used ECMO as a last resort treatment in moribund patients (4). Over the years, different physiological and clinical variables have been used to select patients who might benefit from ECMO treatment for their high mortality rate diseases (11-13). Currently, two main variables are used as criteria for ECMO treatment: the oxygenation index (OI) and the alveolar-arterial difference in partial pressure of oxygen ($AaDO_2$), (table 3). Additionally, there are criteria based on acute deterioration of the patient and criteria related to pH, mainly for sepsis patients who might not develop severe hypoxaemia, but do have severe acidosis and poor organ perfusion (24).

A set of generally used criteria have emerged in the meantime, which are summarized in the ELSO guidelines for the application of ECMO to newborns (28). The selection criteria at our institute are based on these guidelines (table 3).

Although the original criteria predicted 80% mortality, nowadays these criteria would probably not predict this. In the UK trial, an OI of over 40 for 3 hours was used as a selection criterion for ECMO treatment. Thus, survival rates with conventional therapy (61%) in that study were based on this criterion and did not predict 80% mortality as originally suggested (13,19). Our own study demonstrated mortality rates of 50 to 96% in the control group, depending on the primary disease (table 1). Mathias et al published a study on newborns who met the ECMO criteria and found a mortality of 19% (29). Studies like these emphasize the need to re-evaluate ECMO criteria once new treatment modalities become available for respiratory failure.

Table 3. Selection criteria for ECMO at the University Medical Centre Nijmegen in newborns with severe respiratory failure

Indications

1. $AaDO_2$>80 kPa (600 mm Hg) for more than 8 hours.
2. $AaDO_2$>80.6 kPa (605 mm Hg) for more than 4 hours with peak inspiratory pressure = 38 mbar or mean airway pressure = 22 mbar.
3. Acute deterioration for at least 2 hours with pH<7.15 and PaO_2<5.3 kPa (40 mm Hg).
4. No clinical improvement on maximal conventional therapy for 3 hours with PaO_2<5.3 kPa (40 mm Hg).
5. Signs of barotrauma (at least 4): lung emphysema, pneumothorax or pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema, air leak >24 hours, mean airway pressure >15 mbar.
6. OI>40 for 3-5 hours.
7. In patients with CDH, at least one PaO_2>10.6 kPa (80 mm Hg) must be documented.

Contra-indications

1. Gestational age <34 weeks or birth weight <2000 grams.
2. Underlying lung disease or cause of respiratory insufficiency, that is not reversible within 10-14 days.
3. Mechanical ventilation >10 days.
4. Chromosomal or other congenital or acquired abnormalities incompatible with life.
5. Intraventricular or cerebral parenchymal haemorrhage = grade II.
6. Coagulopathy or bleeding complication for which heparin administration is contra-indicated.

$AaDO_2$ = Alveolo-arterial difference in partial oxygen pressure difference (mm Hg).

$AaDO_2 = Patm - P_{H2O} - (paO_2+paCO_2)FiO_2$, where Patm = atmospheric pressure, P_{H2O} = vapour pressure (being 47 mm Hg at 37°C), paO_2 = arterial partial pressure of oxygen, $paCO_2$ = arterial partial pressure of carbon dioxide, FiO_2 = fraction of inspired oxygen.

OI = Oxygenation index = [Mean Airway Pressure x FiO_2 x 100]/paO_2. MAP in mbar, paO_2 in mm Hg.

CLINICAL MANAGEMENT OF NEWBORNS ON VENO-ARTERIAL ECMO

After a patient has been found to fulfil the ECMO criteria in the absence of contra-indications, the paediatric surgeon inserts appropriate cannulas. In VA-ECMO, the arterial cannula is inserted through the RCCA into the junction of the innominate artery and aortic arch. The venous cannula is inserted through the RIJV into the right atrium. The cannulas are then connected to the ECMO system and ECMO can be started. ECMO flow is increased gradually

until adequate oxygenation of the patient has been reached and ventilator settings can be reduced to so-called “rest-settings”, typically a frequency of 17-24/min, inspiratory pressure 22-26 mbar, positive end-expiratory pressure 4-8 mbar and FiO_2 of 0.30. Usually haemodynamic stability improves to such an extend after ECMO initiation that cardiotonic drug administration can be weaned and stopped.

In the initial phase of ECMO, the goal of treatment is to maintain an adequate ECMO flow. This will ensure adequate oxygenation of the patient (arterial blood gas and “mixed venous” saturation) and normal organ function (pH, blood pressure, diuresis). It may be necessary to maintain a high ECMO flow rate in many patients initially, because the chest radiograph shows deterioration during the first 1-2 days (white-out). After 24 to 48 hours, the lung function generally improves, as indicated by increases in arterial partial pressure of oxygen (paO_2) values, lung compliance, end-tidal partial pressure of carbon dioxide values and in paO_2 after increasing the fraction of inspired oxygen (FiO_2) of the ventilator to 100% (“the hyper-oxygenation test”). Then by decreasing the ECMO flow rate, weaning can be started by 10-20 mL/min per hour as long as paO_2 values remain adequate. When an ECMO flow of 50 mL/min has been reached and adequate oxygenation of the patient can be maintained for 6-8 hours (idling), the patient is decannulated. If the ECMO flow cannot be diminished to 50 mL/min, some adaptation of the ventilator settings with higher frequency, pressures and FiO_2 may have to be accepted, in order to enable decannulation of the patient.

In CDH patients, the diaphragmatic defect is closed during ECMO treatment, once an ECMO flow of 50 mL/min is reached. During and directly after surgery, the ECMO flow is maintained at a higher level for 24-36 hours to prevent recurrent pulmonary hypertension, where after the patient was weaned again and decannulated.

Newborns with respiratory failure usually have two distinct abnormalities: pulmonary parenchymal disease with a mismatch in ventilation and perfusion, and pulmonary vascular disease with pulmonary hypertension. The latter disorder can cause right to left shunt at the ductus arteriosus and at the atrial level thereby causing hypoxaemia (30,31).

The syndrome of PPHN is associated with abnormalities in the structure of the small arteries in the lung (32-26). It is important to understand the effects of ECMO on the neonatal lung, the recovery of PPHN and the underlying parenchymal lung disease. Generally, the beneficial effect of ECMO is described as lung rest (37-38). Despite the large number of newborns treated with ECMO worldwide, only a few data are available about the evolution of the abnormal vascular wall structure during ECMO. Shehata et al studied vascular morphology in

CDH patients after ECMO treatment and found partial regression of the abnormal vascular wall structure.

The next two chapters describe the results of ECMO treatment in newborns at the University Medical Centre Nijmegen, and those of a study on lung vascular morphology after ECMO treatment.

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CHAPTER 2

TWELVE AND A HALF YEARS OF EXPERIENCE WITH EXTRACORPOREAL MEMBRANE OXYGENATION TREATMENT IN 186 NEWBORNS WITH CARDIO-RESPIRATORY INSUFFICIENCY

Twelve-and-a-half years of experience with extracorporeal membrane oxygenation treatment in 186 newborns with cardiorespiratory insufficiency

Arno van Heijst[1], Frans van der Staak[2], Djien Liem[1], Henriette Wilbers[1], Rob Sengers[1]

Departments of Paediatrics[1] and Paediatric Surgery[2], University Medical Centre Nijmegen, Nijmegen, the Netherlands

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ABSTRACT

Between 1991 and 2003, 186 newborns were treated with extracorporeal membrane oxygenation at the University Medical Centre Nijmegen, the Netherlands. Diagnoses were meconium aspiration syndrome (n=78, survival 95%), congenital diaphragmatic hernia (n=58, survival 65%), sepsis/pneumonia (n=28, survival 79%), idiopathic persistent pulmonary hypertension of the newborn (n=20, survival 75%) and idiopathic respiratory distress syndrome (n=2, survival 100%). Extracorporeal membrane oxygenation was started at an earlier postnatal age in congenital diaphragmatic hernia than in meconium aspiration syndrome, sepsis and idiopathic persistent pulmonary hypertension of the newborn, and earlier in meconium aspiration syndrome than in idiopathic persistent pulmonary hypertension of the newborn. There were no statistically significant differences in extracorporeal membrane oxygenation run times between diagnosis groups.

Thirty-five newborns died (19%), due to respiratory failure (n=21), intracranial haemorrhage (n=8), alveolocapillary dysplasia (n=3) and surfactant protein B deficiency (n=1). There were two late deaths (> 6 weeks after extracorporeal membrane oxygenation treatment) related to the underlying abnormality. Survivors and non-survivors differed on entry diagnosis, extracorporeal membrane oxygenation run time and birth weight.

Important complications during extracorporeal membrane oxygenation treatment were disseminated intravascular coagulation (19%), need for circulatory support with inotropic medication (16%) and problems with the cannula position (15%).

Important factors related to death were pH < 7.20 and cerebral haemorrhage.

Thirteen patients had a cerebral haemorrhage, while 17 had an ischaemic lesion, without predominance for either cerebral hemisphere.

In 8 patients, a patent ductus arteriosus with left to right shunt was detected during or after extracorporeal membrane oxygenation.

Conclusion: extracorporeal membrane oxygenation is a rescue treatment for a selected group of newborns with cardiorespiratory insufficiency that is unresponsive to maximal conventional treatment. Overall survival at our centre was 81%, which is comparable with other centres. Complications form an important limiting factor for favourable outcome.

INTRODUCTION

ECMO is a rescue treatment for newborns with severe cardiorespiratory insufficiency when conventional treatment, including artificial ventilation, inotropic support, surfactant administration and nitric oxide inhalation, has failed to maintain adequate oxygenation and there is a high predicted mortality (1-3). ECMO was introduced at our clinic in 1989 (4). So far, we have been using the VA-ECMO technique on all newborns treated with ECMO. Venous blood is drained from the right atrium and pumped a by roller pump to a membrane oxygenator. Gas exchange takes place in the membrane oxygenator: venous blood is oxygenated and the carbon dioxide pressure of the blood is regulated. Before the oxygenated blood is returned to the arterial circulation, it passes a heat exchanger to normalize the blood temperature. VA-ECMO offers temporary support for lung function and cardiac function, generally over a maximum period of 2 to 3 weeks. The most important indications for ECMO treatment in newborns with respiratory failure are MAS, CDH, sepsis/pneumonia and i-PPHN.

We describe the results of VA-ECMO treatment in 186 newborns at the University Medical Centre Nijmegen over the period 1991 and 2003.

PATIENTS AND METHODS

Patients

The first two newborns were treated with ECMO at our centre in 1989 (4). From 1991 to 1994, ECMO treatment was offered within the "Evaluation project for innovative developments in medicine" ExtraCorporeal Membrane Oxygenation in newborns (no OG 90-001) and later as a regular treatment method. Between 1991 and 2003, 186 newborns that fulfilled one or more of the selection criteria for ECMO treatment and did not have any contra-indications were treated with ECMO (5,6).

After the initiation of ECMO, there was a stabilization period of 24-48 hours. Then the newborn was weaned until an ECMO flow of 50 mL/min was reached. When oxygenation was adequate at this flow rate, the patient was decannulated. In CDH patients, the diaphragmatic defect was closed during ECMO treatment, once an ECMO flow of 50 mL/min was reached. During and directly after surgery, the ECMO flow was maintained at a higher

level for 24-36 hours to prevent recurrent pulmonary hypertension, where after the patient was weaned again and decannulated (7). Heparin administration during ECMO to prevent clotting in the ECMO circuit was dosed based on determination of the activated clotting time or heparin activity in the blood.

Registration of the results of ECMO treatment

To report our results of ECMO treatment to the ELSO we have been using the ELSO Documentation Form (8). On this form, the diagnosis for ECMO treatment, gestational age, sex, age at the start of ECMO and ECMO run time are documented. In CDH patients, time of diagnosis, prenatal or postnatal, is recorded. Survival rates until discharge or transfer are calculated. Complications that occur during ECMO treatment are also documented in this form. Furthermore, in CDH patients, we record the place of birth. In non-surviving infants, causes of death are described. During the ECMO run, ultrasound of the head is performed daily. Also computer tomography (CT) scanning or magnetic resonance imaging (MRI) scan of the brain are performed in survivors after ECMO treatment. Lesions can be classified as haemorrhagic or ischaemic. They were further classified by us according to their localization: left or right hemisphere, bilateral, or in the posterior fossa.

STATISTICS

Survival rates were compared between the different diagnoses groups and also with those reported by the ELSO (Fisher's exact test). Survival rates were compared in prenatally and postnatally diagnosed CDH patients (Fisher's exact test) and survival was also calculated according to place of birth (Fisher's exact test/Chi-square test). Mean ages at the start of ECMO were compared between the different diagnosis groups (Kruskall Wallis non-parametric ANOVA test with Dunn's multiple comparison test). ECMO run times were compared between the different diagnosis groups (one way ANOVA). Survivors and non-survivors were compared on ECMO run time, birth weight and gestational age (unpaired *t*-test). The distribution of haemorrhagic and ischaemic cerebral lesions over the left and right hemisphere was compared as well as these two lesions combined (Fisher's exact test). The relation between diagnosis and the occurrence of haemorrhagic or ischaemic lesions was tested (chi-square test). Infants with and

without cerebral lesions were compared on gestational age and birth weight (unpaired t-test). P values = 0.05 were considered significant.

RESULTS

Diagnosis and survival

Results are presented as mean ± sd.

The total group of 186 newborns treated with ECMO comprised 116 boys and 70 girls. Table 1 summarizes all the diagnoses and survival rates after ECMO treatment in our patients and survival data according to the ELSO. Survival varied from 65% in CDH to 95% in MAS and was significantly better in MAS than in CDH, sepsis and PPHN.

The diagnosis of CDH was made prenatally in 15 patients and postnatally in the remaining 43. Survival rates in the CDH patients diagnosed prenatally and postnatally were 60% and 67%, respectively (p=0.75). Place of birth had no effect on the survival of CDH patients. Survival rates of patients born at home, at a general hospital and at a 3rd level centre were 75%, 59% and 71%, respectively (p=0.53). Survival rates of CDH patients born at our ECMO centre (62%) were comparable with those born elsewhere (67%; p=0.80).

Age at the start of ECMO

ECMO was started significantly earlier after birth in CDH patients (24±17 hrs, mean ± standard deviation (sd)) than in patients with MAS (46±46 hrs; p<0.001), sepsis (78±90 hrs; p<0.001) and i-PPHN (77±78 hrs; p<0.001), while in MAS patients it was started earlier than in i-PPHN (p<0.05). All the CDH patients, except for one, were on ECMO on day 3 after birth. In two patients, ECMO was started after surgical correction of the diaphragmatic defect; in all the others ECMO was initiated in order to achieve pre-operative cardiorespiratory stabilization before surgery. In the other diagnosis groups, 74% of the patients were on ECMO on day 3 after birth.

Table 1. Diagnosis and survival in 186 newborns treated with ECMO for respiratory insufficiency

Diagnosis	Number	Survival (nr)	Survival (%)	ELSO (%)
MAS	78	74	95* #	94
CDH	58	38	65	53
Sepsis	28	22	79	75
i-PPHN	20	15	75	79
IRDS	2	2	100	84
Total	**186**	**151**	**81**	**-**

MAS = meconium aspiration syndrome, CDH = congenital diaphragmatic hernia, i-PPHN = idiopathic persistent pulmonary hypertension of the newborn, IRDS = idiopathic respiratory distress syndrome, ELSO = Extracorporeal Life Support Organization, Survival = survival to discharge or transfer

*: $p<0.05$ MAS compared to sepsis and PPHN, #: $p<0.01$ MAS compared to CDH

nr = number, % = percentage

ECMO run time

There were no significant differences in ECMO run time between the different diagnosis groups: 153±56 hours in MAS, 176±71 hours in CDH, 166±67 hours in sepsis and 172±48 hours in i-PPHN patients. Differences in ECMO run times between the diagnosis groups were however not significant ($p=0.17$).

ECMO run time was significantly shorter in survivors (154±50 hours) than in non-survivors (214±93 hours; $p<0.01$).

Mortality

Thirty-five newborns died. Causes of death are summarized in table 2. Persistent respiratory insufficiency was the major cause of death, especially in the group of CDH patients. These patients often had severe rebound pulmonary hypertension and signs of multi-organ failure, such as hypotension and oliguria. In the CDH group, 2 patients died more than 6 weeks after ECMO treatment (late deaths), one because of ischaemic intestinal necrosis with perforation and another one because of respiratory insufficiency. In 8 patients with intracranial haemorrhage, ECMO was withdrawn to prevent progression of the haemorrhage during heparin administration or because of expected poor prognosis. In the i-PPHN group, 4 out of the 5 patients that died had rare, untreatable diseases: 3 patients had alveolar capillary dysplasia (ACD) and 1 had surfactant protein B (Sp-B) deficiency.

Apart from the differences in diagnosis and ECMO run time, survivors differed from non-survivors on birth weight (3393±591g and 3094±496g, respectively; $p<0.01$). There was no difference in gestational age between survivors (276±15d) and non-survivors (274±17d; $p=0.41$).

Table 2. Causes of death in 36 newborns treated with extracorporeal membrane oxygenation for cardiorespiratory insufficiency

Diagnosis	Number	Persistent respiratory insufficiency	ICH	Sp-B def	ACD	Late death
MAS	4	*1*	*3*			
CDH	20	*15*	*3*			*2*
Sepsis	6	*4*	*2*			
i-PPHN	5	*1*		*1*	*3*	
IRDS	0					
Total	**35**	***21***	***8***	***1***	***3***	***2***

MAS = meconium aspiration syndrome, CDH = congenital diaphragmatic hernia, i-PPHN = idiopathic persistent pulmonary hypertension of the newborn, IRDS = idiopathic respiratory distress syndrome, ICH = intra-cranial haemorrhage, Sp-B def = surfactant protein B deficiency, ACD = alveolar capillary dysplasia, late death = patients that died more than six weeks after ECMO treatment from primary disease related causes.

Complications

The most frequent complications of ECMO treatment in our population are listed in table 3. Disseminated intravascular coagulation was the most common (19%). Other major complications were the need for circulatory support with inotropic medication during ECMO, problems with the cannula position, surgical site bleeding, hypo- or hyperglycaemia, culture proven infections and clots in the ECMO system, especially in the bridge. The most important factors related to death were the occurrence of metabolic acidosis with $pH<7.20$ during the ECMO run, cerebral haemorrhage, infections and surgical site bleeding. The latter complication occurred in 45% of the CDH patients.

Table 3. Complications of ECMO treatment

Complication	%	Survival (%)
DIC	19	70
Inotropes on ECMO	16	77
Cannula problems	15	79
Surgical site bleeding	45*	56
Clots in bridge	14	73
Glucose > 13.3 mmol/l	14	74
Glucose < 2.2 mmol/l	11	81
Culture proven infection	11	57
Cerebral infarction	9	59
Cerebral haemorrhage	7	38
pH < 7.20	4	14

% = percentage of ECMO runs, DIC: disseminated intravascular coagulation

*: percentage of surgical site bleeding in CDH patients, as this only occurred in CDH patients.

Cerebral imaging

Ultrasound investigations of the brain were performed daily in all 186 patients. A CT-scan or MRI-scan was not done on 33 patients that died. In another 18 patients, care providers decided not to do a CT-scan or MRI-scan because they had normal ultrasound findings. Results of head ultrasound, CT-scan and MRI-scan studies of the brain are presented in table 4. Haemorrhagic lesions were observed in 13 patients (7.0%) and infarctions in 17 patients (9.1%). There was no significant difference between the occurrence of lesions in the left and right hemispheres; in both hemispheres 8 lesions (4.3%) occurred (p=1.0). Also, there was no significant difference in the distribution of haemorrhagic and ischaemic lesions over the right and left cerebral hemispheres (p=0.72 for both). Bilateral lesions were present in 11 patients (5.9%) and posterior fossa lesions in 3 patients (1.6%). Altogether 16.1% of the patients had a haemorrhagic or ischaemic lesion during or after ECMO treatment. In the survivors, 3.3% had a cerebral haemorrhage, while 6.6% had an infarction.

There was no relation between diagnosis and the occurrence of haemorrhagic or ischaemic lesions (p=0.09 and p=0.36, respectively). Infants with and without cerebral haemorrhage did not differ on gestational age (276±16d versus 271±18d; p=0.31) or birth weight (3287±671g versus 3343±577g; p=0.77). Also infants with and without ischaemic lesions were comparable on gestational age (275±16d versus 281±15d; p=0.13) and birth weight (3353±586g versus 3357±575g; p=0.91).

Table 4. Localization of cerebral haemorrhagic and ischaemic lesions

Haemorrhage	**Nr**	**Survival**	**Withdrawn**	**Infarction**	**Nr**	**Survival**
Left hemisphere	5	2	3	Left hemisphere	3	0
Right hemisphere	3	1	2	Right hemisphere	5	4
Bilateral	3	0	3	Bilateral	8	6
Posterior fossa	2	2	0	Posterior fossa	1	0
Total	13	5	8	**Total**	17	10

Nr: number, withdrawn: patients from whom ECMO treatment was withdrawn because of the cerebral lesion that occurred

Patent ductus arteriosus

Although echocardiography investigations were not performed routinely during or after ECMO, 8 patients (4.3%) were found to have a patent ductus arteriosus with left-to-right shunt, which was considered to be haemodynamically important. Six of these patients had a diagnosis of CDH. In 5 patients the patent ductus was detected during the ECMO run and in 3 it was detected afterwards. The ductus closed with conservative treatment (fluid restriction and adequate oxygenation) in 3 patients, it was ligated in 4 patients and in 1 patient it was closed with indomethacin.

DISCUSSION

Number of patients

We treated 186 patients between 1989 when ECMO treatment in the Netherlands was introduced, and 2003. As we only had 1 set of ECMO equipment until 1995, the annual number of patients treated with ECMO has remained fairly constant. Other ECMO centres have reported a decrease in numbers since the introduction of new treatment modalities, such as surfactant administration, high frequency ventilation and nitric oxide inhalation (9-12). The worldwide annual number of neonatal respiratory ECMO runs peaked in 1992 at 1517 treatments, but decreased to 853 treatments in 2001 (13). The constant number of patients treated over the years at our centre is possibly explained by an increase in referrals from other neonatal intensive care units after the official recognition of ECMO centres in the Netherlands.

The proportion of newborns with idiopathic respiratory distress syndrome (IRDS) worldwide has decreased markedly from 15% in 1988 to 4% in 1997. As a consequence, the proportion of CDH patients has increased from 18% to 26% (12). In our population, there were only 2 patients with IRDS; the last one was treated in 1998. MAS was the most frequent indication for ECMO treatment in our group, which is in agreement with the international literature (12). Wilson et al reported changing patient demographics in the ECMO population and suggest an increasing need for cardiac ECMO (9). This is supported by the ELSO data: 165 cardiac runs in 1990 compared to over 500 in 2000. Over the past few years, we have treated 12 cardiac patients apart from the 186 newborns with respiratory failure described here, mainly following cardiac surgery. With the increasing complexity of cardiac surgery, in our ECMO centre we can confirm the trend suggested by Wilson.

Survival rates

Survival rates in our group are comparable with those reported by other centres and registered by the ELSO. In our CDH group, survival of patients with a prenatal diagnosis born at a 3rd level centre was comparable with that of the group born elsewhere. However, confounding factors can have been present. In the Netherlands, there is no routine prenatal screening programme. Thus, the prenatal diagnosis of CDH is mainly made on the basis of incidental screening for other diseases, or on so-called 'fun scans'. Consequently, these cases are not necessarily the ones with the most severe CDH abnormalities and worst outcome. The fact that only a minority of the CDH patients were detected prenatally also determined the place of birth and might have influenced survival in relation to birth location as well. Also, it is not clear which percentage of the CDH patients, born in other centres, were referred for ECMO.

Age at the start of ECMO

Significant differences were found between the different diagnoses groups in the postnatal age at which ECMO was started. In CDH patients, ECMO was started earlier than in all the other diagnosis groups while in MAS patients it was started earlier than in patients with PPHN. Schoeman et al reported that the median age at the start of ECMO in CDH patients was 2 days (14). The fact that in the CDH group all the patients except for one were on ECMO on the third day of life in our opinion confirms the presence of respiratory insufficiency at an early stage in many CDH patients and necessitates the early referral of

these patients. This is supported by our previous study on ECMO criteria in CDH patients. Our group suggested that ECMO should be started earlier than is currently stipulated in classical ECMO criteria (5). Kössel et al stated that in newborns pretreated with high frequency ventilation and nitric oxide inhalation the decision to start ECMO based on an OI>40 needs to be adapted to an OI>25 after 72 hours of such treatment (15).

ECMO run time

There was no significant effect of diagnosis on ECMO run time. However, ECMO run time was significantly increased in non-survivors compared to survivors, with a difference in the mean ECMO run time of almost 60 hours. Apart from the difference in ECMO run time, survivors and non-survivors differed in birth weight and entry diagnosis, as was also described by Stolar et al (14).

Causes of death

Watson et al described that the major cause of death in ECMO patients is the underlying disease process leading to cardiopulmonary failure and that mortality is not affected by technical complications (16). We also observed this in our patients. Short and Walker stated that the major cause of death in infants who are receiving ECMO is cerebral injury (17). In 8 of our patients, ECMO was withdrawn because of severe intracranial haemorrhage at a time when they were not actually weanable and therefore died. In this study, the cause of death in these patients was then classified as intracranial haemorrhage. Late death, more than 6 weeks after ECMO treatment, can occur especially in CDH patients. Schoeman et al reported five late deaths, secondary to chronic lung disease (n=3) and infection (n=2) in 11 CDH patients treated with ECMO (18). In our group of CDH patients, we had 2 late deaths related to the underlying disease. Patients with i-PPHN may have underlying diseases, such as Sp-B deficiency, ACD and congenital pulmonary lymphangiectasia, that are not treatable with any form of therapy (19-22). Four of the 5 deaths in our i-PPHN group were due to these diseases: 3 from ACD, 1 from Sp-B deficiency. There were 5 sets of siblings with ACD in the 45 patients described by Tibbals and Chow, which suggests that the disease can have a genetic basis (23). We had 2 siblings with ACD, one was treated with ECMO and one was not. In patients with ACD, oxygenation status improved during ECMO, but this did not lead to their survival (20,21). Sp-B deficiency is also considered to be lethal; it is usually caused by a

121ins2 mutation in the Sp-B gene. Ballard et al described a patient with a form of Sp-B deficiency that had a milder course. This patient demonstrated a point mutation in exon 7 of the Sp-B gene (24).

Complications

ECMO treatment has potentially severe complications. The most important are haemorrhagic complications. It has been suggested that these are related to the administration of heparin and to an increase in fibrinolytic activity after the initiation of ECMO (25). Heparin is administered because the contact of blood with foreign surfaces causes activation of the clotting system. Despite the use of heparin, thrombus formation still occurs. Nineteen per cent of our patients showed signs of disseminated intravascular coagulation. Glass et al reported that about 50% of the patients that died after ECMO treatment had haemorrhagic complications (26).

We also observed haemorrhagic complications, especially in CDH patients. In these patients, the defect in the diaphragm is closed during the ECMO run and bleeding may occur from the surgical site. Haemorrhages can be so severe that the ECMO run has to be ended to control the blood loss. If this is necessary before the underlying respiratory problem has been completely resolved, the patient will die of respiratory failure. The introduction at our centre of the anti-fibrinolytic drug tranexaminic acid in the peri- and early post-operative phase to CDH patients resulted in a significant decrease in haemorrhagic complications (27).

Mechanical complications occurred less frequently and could always be solved. Owing to the invasive character of this treatment with the insertion of catheters into blood vessels and decreases in plasma immunoglobulin concentration, there is an increased risk of infections (28,29). Cultures were positive in 11% of our patients but many more were suspected of having an infection based on laboratory investigations and clinical symptoms.

Infections may contribute to rebound pulmonary hypertension and multi-organ failure and are a risk factor for non-survival (30,31). Steiner et al found that the risk of acquiring a nosocomial bloodstream infection on ECMO was increased in patients treated for longer than 10 days (32). Other important factors related to death were haemodynamic instability, presenting as metabolic acidosis, and cerebral haemorrhage. Cheung et al demonstrated that plasma lactate levels and a low pH were both related to death and neurodevelopmental disability or delay (33). Low survival rates in patients with a cerebral haemorrhage are partially determined by the withdrawal of ECMO therapy to prevent progression of the

haemorrhage during heparin administration or because it is expected that the patient has a poor prognosis.

Cerebral lesions

Lazar et al reported a range of between 10 and 35% for intracranial lesions, while Bulas et al mentioned an incidence of even 52% for intracranial haemorrhage and infarction (34,35). In contrast, the ELSO registry documented 9.2% for central nervous system infarctions and 5.4% for haemorrhages (13). The latter rates are comparable with our data. We did not find a predominance of cerebral lesions in either hemisphere. Some authors found differences between the left and right hemispheres, whereas others did not (36-42). Haemorrhages in the posterior fossa have also been described by others (40,42,43-45). Several authors found that the majority of cases of intracranial haemorrhage occurred within 72 hours after the start of ECMO (43,46,47).

It has been reported that preterm infants and infants with a low birth weight treated with ECMO are at increased risk for intracranial haemorrhage (42,48). However, in our group there was no difference in gestational age or birth weight between the patients with and without intracranial haemorrhage. Bulas et al found that an increase in time spent on ECMO, increased the risk for ischaemic lesions (42). This could not be confirmed in our group (ischaemic lesions: 161±65hrs, others 162±67hrs; p=0.85, unpaired t-test). They also observed an increased risk of haemorrhagic lesions in sepsis patients and an increased risk of non-haemorrhagic lesions in CDH patients. These findings were not confirmed in our population. In addition, we also could not demonstrate a relation between ischaemic lesions and gestational age or birth weight.

Patent ductus arteriosus

As mentioned above we did not study the presence of a patent ductus arteriosus with left to right shunt systematically during ECMO. However, 5 patients were found to have a patent ductus with left-to-right shunt during ECMO and 3 more afterwards. In these latter patients, it is likely that the ductus was present during ECMO treatment. In an earlier study on 29 newborns, we observed a patent ductus with left to right shunt in 62% at some time during the ECMO run. These patients had a significantly longer ECMO run time than the patients without a ductus with left to right shunt (49). Also the potential stealing effect on the cerebral

circulation of a patent ductus with left to right shunt warrants further studies on this theme (50). Furthermore, it is not clear how a haemodynamically important ductus arteriosus should be treated, conservative, surgically or with medication.

CONCLUSION

ECMO is a rescue treatment for newborns with severe respiratory insufficiency. It improves survival rates in a selected group of patients. However, the occurrence of complications impairs the outcome.

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CHAPTER 3

MORPHOMETRIC ANALYSIS OF THE LUNG VASCULATURE AFTER EXTRACORPOREAL MEMBRANE OXYGENATION TREATMENT FOR PULMONARY HYPERTENSION IN NEWBORNS

Morphometric analysis of the lung vasculature after extracorporeal membrane oxygenation treatment for pulmonary hypertension in newborns

Arno van Heijst[1], Remco Haasdijk[1], Freek Groenman[2], Frans van der Staak[3], Christina Hulsbergen-van de Kaa[4], Ronald de Krijger[5], DickTibboel[2]

Departments of Neonatology[1], Paediatric Surgery[3] and Pathology[4], University Medical Centre Nijmegen, Nijmegen, The Netherlands. Department of Paediatric Surgery[2] and Pathology[5], Erasmus Medical Centre-Sophia Children's Hospital, Rotterdam, The Netherlands

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ABSTRACT

The morphology of persistent pulmonary hypertension in the newborn is represented by increased medial and adventitial thickness in the lung vasculature. This study describes the morphometry of the lung vasculature after extracorporeal membrane oxygenation treatment in newborns with persistent pulmonary hypertension due to meconium aspiration syndrome, sepsis, or idiopathic.

Three groups were studied: newborns with persistent pulmonary hypertension treated with extracorporeal membrane oxygenation (n=9), newborns with persistent pulmonary hypertension not treated with extracorporeal membrane oxygenation (n=12), and age matched controls without persistent pulmonary hypertension of the newborn (n=11). Formalin fixed and paraffin embedded lung specimens obtained at autopsy were stained with Elastic von Gieson or Masson trichrome staining followed by morphometric measurements. In intra-acinar arteries with an external diameter less than 150 μm, the arterial medial, adventitial, and total wall thickness, expressed as percentage of the external diameter, and their cross sectional areas were calculated.

Newborns with persistent pulmonary hypertension, compared to controls, demonstrated an increased percentage of medial thickness, percentage of adventitial thickness and percentage of total wall thickness and an increased medial, adventitial and total wall cross sectional area. Newborns treated with extracorporeal membrane oxygenation, compared those not treated so, showed a decreased percentage of medial thickness and medial cross sectional area in arteries with an external diameter less than 75 μm, and a decreased percentage of medial thickness and a decreased medial, adventitial, and total wall cross sectional area in arteries with an external diameter between 75 and 150 μm.

Extracorporeal membrane oxygenation treatment for persistent pulmonary hypertension of the newborn, due to meconium aspiration syndrome, sepsis, or idiopathic, reduces the abnormal morphometry of the small intra-acinar arteries. The underlying mechanisms contributing to this improved morphometry are yet unknown.

INTRODUCTION

The clinical syndrome of PPHN is characterized by central cyanosis due to right-to-left shunting through the oval foramen and/or ductus arteriosus (1). Right-to-left shunting develops as consequence of persistence of a high pulmonary vascular resistance. Classically, and mainly based on morphologic data, three different anatomic types of lung vascular abnormalities have been documented in case of PPHN; underdevelopment, maldevelopment and maladaptation (2-4). First, underdevelopment of the lung vasculature in combination with hypoplasia of the lung occurs in CDH. The second type of pulmonary vascular abnormalities is present in maldevelopment of pulmonary vessels in utero, like in MAS and i-PPHN. Finally, vascular abnormalities can be present in maladaptation of the pulmonary arteries to postnatal life, where there is a failure to decrease pulmonary vascular resistance after birth, like in sepsis and pneumonia (2,3,5).

Despite the different aetiologies, the lung vascular morphology in all three forms of pulmonary hypertension in newborns is similar, showing an increased medial and adventitial thickness (3,5-9). In MAS, i-PPHN, and sepsis the number of intra-acinar arteries is normal and the vessels have a normal external diameter (ED). There is however extension of the muscle coat into normally non-muscular arteries (5,7,10). However, in CDH the situation is far more complicated because of lung hypoplasia with a decreased number of bronchial generations in which the vasculature is also hypoplastic with a decreased number of intra-acinar arteries. These intra-acinar arteries have a decreased ED in which the medial wall thickness is increased. Extension of the muscle coat in the smaller arteries can either be normal, or increased to distal into normally non-muscular arteries (2).

The treatment of PPHN consists nowadays of a combination of different therapies including artificial ventilation, either conventional or high frequency oscillatory ventilation, inhalation of nitric oxide, and recently the use of phosphodiesterase inhibitors like sildenafil (4,11-13).

ECMO can be used as a rescue treatment for PPHN, when conservative therapy fails (14). Generally, the effect of ECMO is described as 'lung rest' (15-17). Although the beneficial effect of ECMO with regard to changes in the pulmonary vasculature is unclear, it is thought that ECMO therapy "breaks" the circle of increasing pulmonary hypertension and right-to-left shunting (18).

In a series of CDH cases that, following successful decannulation from ECMO, died 12-48 hours later because of therapy resistant or recurrent pulmonary hypertension, our group formerly found a decrease in adventitial thickness of small pulmonary arteries after ECMO

treatment. The medial smooth muscle cell (SMC) hyperplasia was however not altered (8). As described, the vascular changes in CDH patients can be different from those in patients with MAS, sepsis, or i-PPHN. To our knowledge the effect of ECMO treatment in newborns with pulmonary hypertension due to MAS, sepsis or idiopathic has not been documented in a systematic way before. We hypothesized that ECMO has an effect on the abnormal morphology of the vascular wall in patients with pulmonary hypertension (2,3,5). We studied the morphology of the lung vasculature after ECMO treatment in patients with PPHN due to MAS, sepsis or idiopathic, and compared this with patients with PPHN that were not treated with ECMO and control patients without PPHN.

PATIENTS AND METHODS

Study group

We studied thirty-two consecutive lung autopsy specimens of newborns. Materials were retrieved from the archives of the Institute of Pathology, University Medical Centre Nijmegen, Nijmegen and the Department of Pathology, Josephine Nefkens Institute Erasmus MC, Rotterdam. Tissue specimens were obtained from patients after parental consent for autopsy during the period 1991-2001. All newborns had a gestational age above 34 weeks and a birth weight of at least 2,000 gram.

Patients were divided into three groups: (a) patients suffering from pulmonary hypertension due to MAS (n=3), sepsis (n=5) or i-PPHN (n=1) treated with ECMO after conservative treatment had failed (ECMO group, n=9); (b) patients suffering from pulmonary hypertension due to MAS (n=6), sepsis (n=3) or i-PPHN (n=3) treated with conservative therapy only (non-ECMO group, n=12); (c) a control group of patients (n= 11) who died shortly after birth from asphyxia due to placental abruption and did not receive intensive therapy.

In all patients of the ECMO group and the non-ECMO group the presence of pulmonary hypertension was confirmed by cardiac ultrasonography with right-to-left shunting together with the existence of a difference of 10% or more between pre-ductal and post-ductal transcutaneous oxygen saturation (8).

In four patients of the ECMO group, ECMO was withdrawn because of cerebral complications, the other five patients all were early post-ECMO deaths, median value 9 days, range 1-17 days after decannulation. The patients in the non-ECMO group all suffered from

severe pulmonary hypertension but were not treated with ECMO because of the presence of a contra-indication for ECMO treatment: intracranial haemorrhage (n=7) or asphyxia with resulting brain damage (n=5). The patients in the control group showed no clinical features of pulmonary hypertension and had no lung abnormalities on histological examination. In these patients therapy was withdrawn at the median age of 2 days, range 1-4 days, because of the severe neurologic abnormalities and poor prognosis.

The entry-criteria for ECMO treatment were: gestational age of at least 34 weeks, birth weight at least 2000 g, artificial ventilation for less than 10 days, $AaDO_2$ greater than 600 mm Hg for more than 8 hours.

Ventilation modes in the non-ECMO group and ECMO group were either conventional ventilation (peak inspiratory pressures of 30-38 mbar, positive end-expiratory pressures of 4-8 mbar, frequency 45-85/min, FiO_2 1.0) or high frequency oscillation ventilation (mean airway pressure 16-22 mbar, amplitude 30-60 cm H_2O, frequency 10 Hz, FiO_2 1.0). The control group was ventilated with mild conventional ventilation; peak inspiratory pressure of 12-16 mbar, positive end-expiratory pressure of 3-5 mbar, frequency 20-40/min, FiO_2 0.21-0.40. Inhalation of nitric oxide became available as a treatment mode for pulmonary hypertension in 1996 and was used in 5 patients of the ECMO group and in 7 patients of the non-ECMO group.

All autopsy lung specimens, obtained within 24 hours after death, were routinely fixed by immersion in 4% buffered formalin, and embedded in paraffin. Serial 4 µm sections were processed for histopathological and immunohistochemical examination. As our study material was routinely harvested at the time of autopsy, no predetermined protocol including inflation fixation was used (19-22).

All slides were evaluated for diagnosis by an independent investigator, blinded for the clinical history of the individual patients.

Histological staining

Serial sections were mounted on polylysine-coated glass slides and stained with Masson trichrome staining, which stains elastic fibers dark blue/black, collagen fibers green and smooth muscle red or Elastic von Giesson's staining, which stains elastic fibers dark violet, collagen fibers red, and smooth muscle brownish yellow.

Immunohistochemistry

Formalin fixed, paraffin embedded sections of lung tissues, were mounted on super-frost glass slides. Immunohistochemistry was performed using a standard avidin-biotin complex method. Deparaffinised slides were treated with 3% hydrogen peroxide in phosphate buffered saline (PBS, 30 minutes) to block the endogenous peroxidase activity, followed by rinsing with PBS. Slides were then placed in a Sequenza Immunostaining Workstation (Shandon Scientific Ltd, Astmoor, Runcorn, USA). Slides were pre-incubated for 10 minutes with 20% normal horse serum to block non-specific binding, then incubated for 60 minutes at room temperature with mouse monoclonal anti-human ?-smooth muscle actin (a-SMA) antibodies (clone 1A4: Sigma, St. Louis, MO, USA) as a primary antiserum in dilution of 1:15,000 in monoclonal diluent (DPC, Los Angeles, USA). After rinsing with PBS, slides were incubated for 30 minutes with biotinylated horse-anti-mouse antibody 1:200 (Vector Laboratories) in polyclonal diluent (PLD-100, DPC, Los Angeles, USA). After further rinsing with PBS, slides were incubated for 45 minutes with peroxidase conjugated avidin-biotin complex 1:50 (Vector Laboratories) in PLD-100 (DPC, Los Angeles, USA), and visualised with diaminobenzidin in PBS (5 minutes) as the chromogen. Slides were counter-stained with Mayer's haematoxylin for 20 seconds. Negative controls were prepared by omission of the primary antiserum.

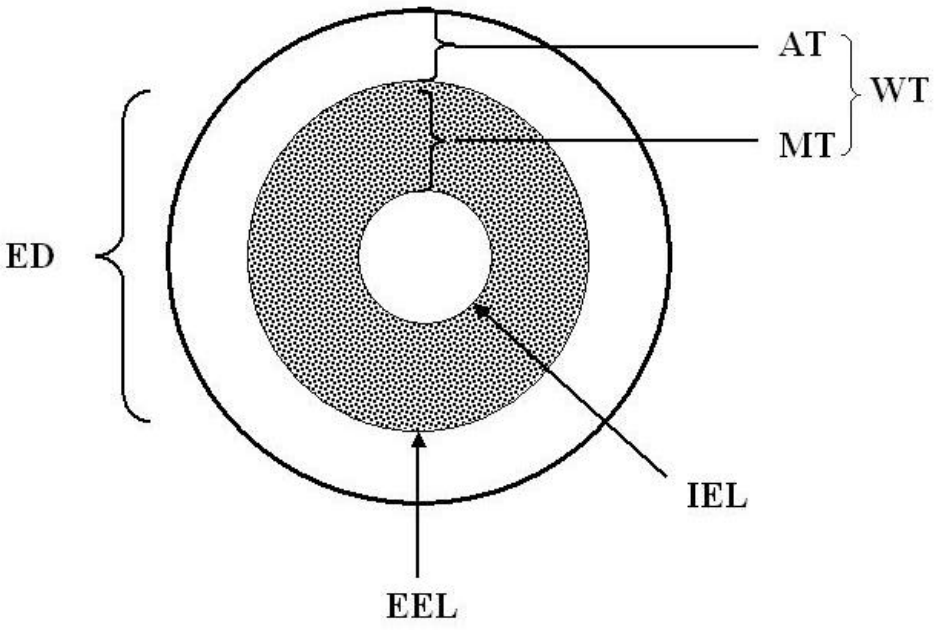
Masson trichrome staining or Elastic von Giesson's staining and ?-SMA immunostaining were compared on serial sections to check that the media is co-localised with ?-SMA in pulmonary arteries before starting the morphometric measurements.

Morphometry

Pulmonary arteries were identified based on their position and structure. They mainly run along the terminal and respiratory bronchioles and at the alveolar duct level and are characterized by a distinct inner and outer elastic lamina (9,23). Arteries fulfilling these criteria, and with an external diameter (ED) measured between the external elastic laminae of up to 150 µm, and having a complete muscular coat, were measured. The diameter of less than 150 µm was chosen, because these arteries are considered to be the pressure regulating arteries (2). Only arteries that were cut at approximately right angles, so that the maximal ED exceeded the minimal ED by less than 50%, were analysed with the use of a calibrated

eyepiece. Measurements of the arterial wall layers in microns were done on Masson trichrome or elastic von Gieson's stained sections. Medial thickness in microns was calculated as the distance from the external elastic lamina to the internal elastic lamina along the shortest diameter of the artery. Adventitial thickness in microns was calculated along the shortest arterial diameter. Total wall thickness in microns consisted of medial thickness plus adventitial thickness, since the thickness of the intima was minimal in all cases. Total wall thickness, medial thickness and adventitial thickness, were expressed as a percentage (%) of ED (respectively WT%, MT% and AT%), to relate them to the arterial vessel size (19-22). To exclude the effect of vasoconstriction on medial, adventitial and total wall thickness, the cross sectional areas of medial, adventitial and total wall thickness were therefore also calculated (expressed as μm^2) (22,24). The measured variables are demonstrated in figure 1.

Figure 1. Diagram of the measured morphometric variables



IEL: internal elastic lamina; EEL: external elastic lamina; WT: total wall thickness in µm; MT: medial thickness in µm; AT: adventitial thickness in µM; ED: external arterial diameter. In this study, MT, AT and WT are expressed as (1) percentage (%) of the ED, where MT% = [MT x 2 x 100]/ED, AT% = [AT x 2 x 100]/ED and WT% = [WT x 2 x 100]/ED and (2) cross sectional area in μm^2. The medial cross sectional area is defined as the area contained by the EEL minus the area contained by the IEL. The adventitial cross sectional area is defined as the area contained by the entire artery minus the area contained by the EEL. The wall thickness cross sectional area is defined by the area contained by the entire artery minus the area contained by the IEL.

Because in previous studies, the most dramatic vascular wall changes were demonstrated in arteries with an ED less than 75 µm, the small arteries were divided in two groups; a group of arteries with ED less than 75 µm and a group with ED between 75 and 150 µm (2,5,22).

Statistical Analysis

Study groups were compared for gender, gestational age and birth weight with Chi-square test and unpaired Student's t-test respectively. Furthermore the age at the moment of death in the non-ECMO group was compared with the age at start of ECMO treatment in the ECMO group (unpaired Student's t-test).
Values of WT%, MT%, AT%, and total wall cross sectional area, medial cross sectional area, and adventitial cross sectional area from the three study groups were calculated and presented as mean (? standard deviation). Data from the three study groups were compared using the unpaired Student's t-test. P values ? 0.05 were considered statistically significant.

RESULTS

There were no significant differences in demographic data between the studied groups, as they were comparable for gender, gestational age, and birth weight (table 1). Mean (?sd) ECMO treatment duration was 182 (±114) hours. The non-ECMO group was ventilated for 7 (±8) days and the control group for 1 (±1) day. There was no significant difference in post-natal age at the moment of death in the non-ECMO group (7±8 d) and the moment of start of ECMO treatment in the ECMO group (4±4 d).

Table 1. Gender, gestational age, birth weight for the 3 study groups

	Gender (F:M)	Gestational age (days)	Birth weight (grams)
Control group	4:7	277 ? 18	3284 ? 486
Non-ECMO group	4:8	273 ? 15	2978 ? 558
ECMO group	3:6	275 ? 16	3248 ? 520

Values for gestational age and birth weight: mean ? standard deviation. F = female, M = male.

The mean number of investigated arteries per case was 34. The mean values (?sd) for WT%, MT%, AT%, total wall cross sectional area, and medial and adventitial cross sectional area of the small pulmonary arteries with an ED<75 µm and an ED between 75 and 150 µm are presented in figures 2 and 3.

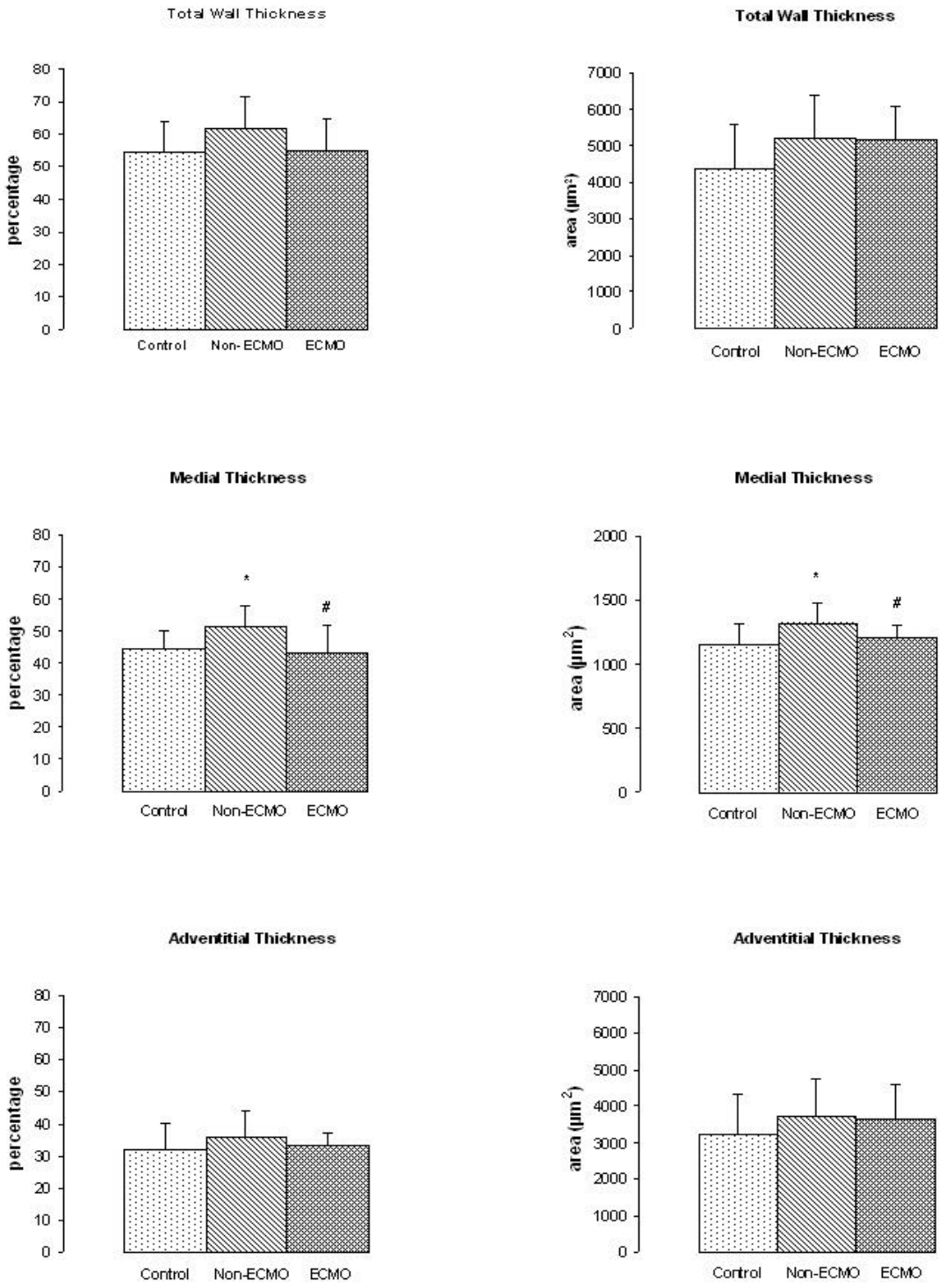
Pulmonary arteries with an ED<75 µm (figure 2)

There were differences in WT%, wall thickness cross sectional area, AT%, and adventitial cross sectional area between the studied groups. The highest values were found in the pulmonary arteries of infants in the non-ECMO group, and the lowest values in the control group. However, these differences were not statistically significant.
The MT% and the medial cross sectional area in the non-ECMO group were significantly increased compared to the control group. In the ECMO group, the MT% and the medial cross sectional area were significantly decreased compared to the non-ECMO group ($p<0.05$).

Pulmonary arteries with an ED 75-150 µm (figure 3)

In the non-ECMO group, all studied variables were increased significantly compared with the control group ($p<0.01$, except for AT%, $p<0.05$). The ECMO group demonstrated a decreased WT% and wall thickness cross sectional area compared to the non-ECMO group, where the decrease in wall thickness cross sectional area was significant ($p<0.01$). WT% in the ECMO group was not significantly different from that in the control group.
The MT% in the ECMO group was decreased compared to the non-ECMO group, but not significantly, and was still increased compared to the control group ($p<0.05$). The medial thickness cross sectional area in the ECMO group was significantly decreased compared to the non-ECMO group ($p<0.01$).
Finally, the AT% in the ECMO group was comparable with that of the control group, but did not demonstrate a difference with the non-ECMO group. However, the adventitial cross sectional area in the ECMO group was significantly decreased compared to the non-ECMO group ($p<0.05$).

Figure 2. Morphometric parameters in pulmonary arteries with external diameter<75 µm

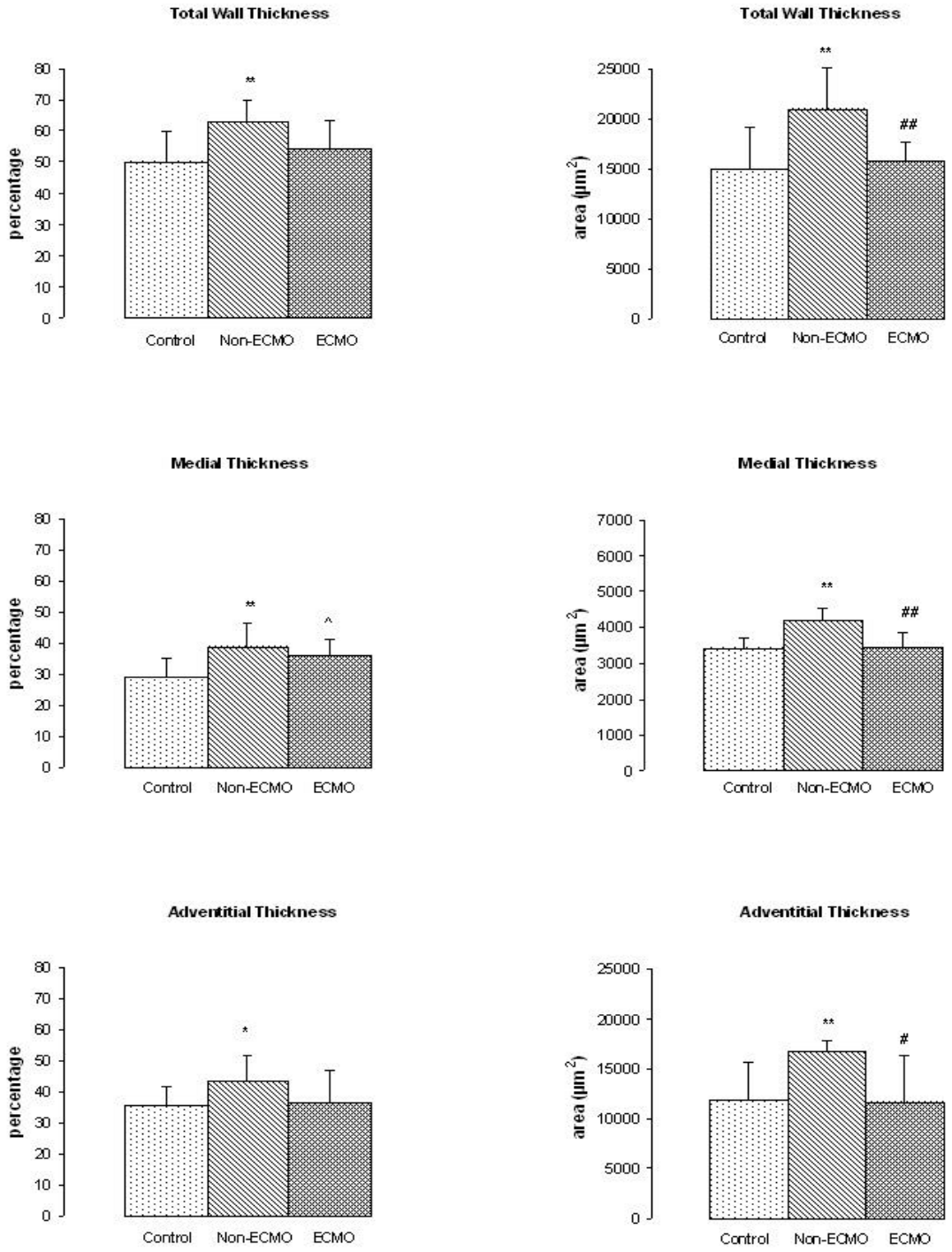


Bars represent mean values, error bars represent standard deviation. Percentage: variable expressed as percentage of the external diameter.

Control: control group, non-ECMO: patients with pulmonary hypertension not treated with ECMO, ECMO: patients with pulmonary hypertension treated with ECMO.

*; $p<0.05$ Non-ECMO group versus control group. #; $p<0.05$ ECMO group versus non-ECMO group.

Figure 3. Morphometric parameters in pulmonary arteries with external diameter between 75 and 150 µm



Bars represent mean values, error bars represent standard deviation. Percentage: variable expressed as percentage of external diameter. Control: control group, Non-ECMO: patients with pulmonary hypertension not treated with ECMO, ECMO: patients with pulmonary hypertension treated with ECMO.

*; p<0.05 Non-ECMO group versus control group, **; p<0.01 Non-ECMO group versus control group, #; p<0.05 ECMO group versus Non-ECMO group, ##; p<0.01 ECMO group versus Non-ECMO group, ^; p<0.05 ECMO group versus control group.

DISCUSSION

In this study we demonstrated that in patients with severe pulmonary hypertension, either idiopathic or secondary to MAS or sepsis, there were significant changes in pulmonary arterial wall morphology compared to controls with the same postconceptional age. WT% and cross sectional area, MT% and cross sectional area, and AT% and cross sectional area in pulmonary arteries with an ED 75-150 µm, and also MT% and cross sectional area in pulmonary arteries with an ED<75 µm were significantly increased.

When looking at the vascular wall morphology in these patients after ECMO treatment, there was a significant decrease in MT% and cross sectional area in pulmonary arteries with ED<75 µm and a significant decrease in wall thickness cross sectional area, medial cross sectional area and adventitial cross sectional area in arteries with an ED 75-150 µm. In uninjected fixated arteries, the media cross sectional area is thought to be a better measurement than MT%, because medial area does not vary with the degree of distension of the artery, whereas the MT% does (25-27).

The observed changes suggest a beneficial effect of ECMO therapy on disturbed lung vascular morphology in newborns with severe pulmonary hypertension. The decreased vascular wall thickness in ECMO treated patients compared to non-ECMO treated patients results in an increased arterial lumen in vessels with a comparable ED (10). Since vascular resistance is inversely related to the fourth power of the intraluminal radius, even a small decrease in the medial diameter, causing a small increase in vascular lumen, may have an important effect on arterial resistance and pressure (2,5). Also, decreases in advential thickness are suggested to increase the compliance in small pulmonary arteries (2).

In both this study and that of Shehata et al in CDH patients, adventitial and wall thickness thinning was found in infants after ECMO treatment. Shehata et al also suggested that adventitial thinning, which is followed by an increase of vascular compliance of the pressure regulating small pulmonary arteries, is a possible mechanism for a temporary decrease of the vascular resistance in CDH patients (8).

However, this study reveals an important difference between non-CDH and CDH cases. We demonstrated a decrease in medial thickness and cross sectional area after ECMO treatment in pulmonary arteries of patients with MAS, sepsis and i-PPHN. Both Shehata et al and Thibeault and Haney could not demonstrate an effect of ECMO on medial thickness in CDH patients, only evaluating patients that died (8,28). An explanation for differences between our study and theirs can be that pulmonary hypertension in CDH has a different pathogenesis than

non-CDH causes of pulmonary hypertension. CDH is a developmental disorder with antenatal anatomical abnormalities. MAS, sepsis and i-PPHN are considered as maldevelopment or maladaptation occurring in the transitional circulation around birth. In CDH as well as in MAS, sepsis and i-PPHN, an increase in medial and adventitial thickness is documented. However, in MAS, sepsis and i-PPHN there is a normal ED and a normal number of intra-acinar arteries, in contrast to CDH patients, in whom there is a decrease in ED and number of intra-acinar arteries (2,3). The difference in timing of the occurrence of the vascular abnormalities in CDH and non-CDH patients with pulmonary hypertension may determine the differences between these groups. Lung hypoplasia in CDH is generally considered to start in the first trimester of pregnancy. As a consequence, the vascular pathology is considered to be the result of an early fetal developmental anomaly (29,30). Although it is suggested that the vascular changes in MAS and i-PPHN do already occur before birth, it is unlikely that they develop in the first trimester (2,3,7).

Probably, these differences in lung vasculature and timing influence the reaction to ECMO treatment and might explain why in CDH no decrease in medial thickness was seen after ECMO treatment. In some CDH cases the absence of changes of the pulmonary vasculature probably refers to an already fixed and irreversible pathology of the media. This is supported by the lack of response on inhaled nitric oxide therapy in CDH patients (31).

Our results may represent an underestimation of the real effect of ECMO on lung vascular morphology, as nine of 12 patients of the non-ECMO group did not yet fulfil criteria for ECMO treatment at the moment of death. This suggests a milder amount of pulmonary hypertension in these patients than in patients of the ECMO group when ECMO was started. Therefore, lung vascular morphologic abnormalities could be less pronounced at the moment of death in these patients than in those of the ECMO group at the moment of start of ECMO treatment. If all patients in the non-ECMO group would have fulfilled the ECMO criteria, the differences found between the non-ECMO group and ECMO group might have been more significant. Another possibility for underestimation of the effect of ECMO treatment may be that the patients in the ECMO group died and therefore did not completely “recover” from their abnormal vascular morphology. It is impossible to correlate our findings with lung vascular morphology in patients after successful ECMO treatment and survival, since all cases studied were autopsy cases. No data are available showing the median time on ECMO necessary to reverse abnormal vascular morphology in newborns with pulmonary hypertension towards a normal pulmonary vascular architecture. Laberge and Wilson, discussing the results found by Shehata et al, suggested that reversal of the abnormal vascular

morphology in pulmonary hypertension is not an effect of ECMO, but rather of postnatal age. These arguments are speculative, as Shehata et al found the same morphometric results in CDH patients after a short period of ECMO treatment as after a prolonged period (8). We also found no differences in the studied morphometric parameters between newborns that died after a short (119±88 hrs) or long (287±57 hrs) ECMO run time, but conclusions are difficult to draw because the groups were relatively small.

From the results in this study it could be argued that ECMO does not cause a reversal of abnormal lung vascular morphology, but only prevents a further deterioration, when ECMO treatment is not started as could have occurred in the non-ECMO group. As stated above it seems unlikely that the vascular abnormalities in patients of the non-ECMO group were more severe than in patients of the ECMO group. Therefore it is likely that ECMO influenced the medial and adventitial abnormalities in patients with pulmonary hypertension due to MAS, sepsis or i-PPHN.

The regression of the abnormal vascular morphology after ECMO treatment points to a mechanism that explains the beneficial effect of ECMO in patients with severe pulmonary hypertension. Further studies are needed to unravel the underlying processes involved in this regression. To study the exact effects of ECMO on lung vascular morphology, lung biopsies are needed before and after ECMO treatment, which is however not possible for obvious ethical reasons (32). In patients with pulmonary hypertension sustained hypoxia may be the mechanism for abnormal vascular remodeling, as persistent ongoing hypoxia is a trigger for cell proliferation (33,34). Experimental models suggest an important role of both SMC's and adventitial fibroblasts during the natural history of vascular remodeling in pulmonary hypertension (33,35). Detailed molecular analysis focussing on maturational changes of the medial SMC population of the arterial media is warranted.

An adequate animal model for pulmonary hypertension in which the animals can be subjected to ECMO is necessary to obtain a better insight into reversal of the pathologic vascular remodeling which exists in pulmonary hypertension (36). An alternative way of evaluating the molecular background of the abnormal lung vascular morphology might include laser capture micro-array in combination with RNA protein isolation to quantify changes in gene products known to be involved in muscle cell proliferation and vascular remodeling (37).

Genes regulating for instance matrix metalloproteinases might not be switched on or off or at an abnormal time point. In animal models, matrix metalloproteinases are involved in vascular remodeling during pulmonary hypertension, by influencing collagen deposition, SMC proliferation and apoptosis (38,39). To determine differences in matrix metalloproteinases

effect between patients in the non-ECMO and ECMO group, extracellular matrix composition may be studied (38,40,41). Alternatively, in PPHN there might be an imbalance between proliferation and apoptosis, a usually occurring feature in preparation to the ability to dilate at the transition for postnatal life. Geraci et al showed an imbalance between genes regulating cell growth and genes regulating apoptosis in patients with primary pulmonary hypertension (37).

In summary, we demonstrated that ECMO therapy caused a reduction in abnormal vascular morphology in small pulmonary arteries of patients suffering from MAS, sepsis, or idiopathic pulmonary hypertension. The effect of ECMO therapy in these patients with pulmonary hypertension, often described as lung rest, can be "translated" into a documented reversal of the vascular wall abnormalities that are present in pulmonary hypertension. The molecular mechanisms underlying this process are currently under investigation in our laboratory.

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PART 2

CEREBRAL OXYGENATION AND HAEMODYNAMICS DURING VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION

CHAPTER 4

INTRODUCTION TO ECMO AND THE BRAIN

INTRODUCTION TO ECMO AND THE BRAIN

Although ECMO has increased survival in selected newborns with severe respiratory insufficiency, it has several complications that can lead to major morbidity. Imaging studies revealed major haemorrhagic or ischaemic intracranial abnormalities in 10 to 30% of patients (1-8). The presence of intracranial abnormalities is highly correlated with adverse neurodevelopmental outcome (4,9-13). It is therefore extremely important to determine risk factors for cerebral haemorrhagic and ischaemic lesions. Prevention of these lesions will improve survival and neurodevelopmental outcome.

Pre-ECMO events as well as ECMO-related events may play a role in the occurrence of intracranial haemorrhagic and ischaemic lesions (table 1).

Table 1. Risk factors for haemorrhagic and ischaemic intracranial lesions in ECMO treated patients

	Haemorrhage	**Ischemia**
Pre-ECMO	Birth trauma	Asphyxia
	Hypercapnia	Hypotension
	Hypertonic solutions	Hypocapnia
		Seizures
ECMO	Ligation right internal jugular vein	Ligation right common carotid artery
	Heparinization	Micro-thrombi
	Thrombocytopenia	
	Coagulopathy	
	Hypertension	
	Reperfusion	

In the pre-ECMO period factors that can contribute to cerebral damage include birth trauma, hypoxia, hypercapnia, acidosis, ischaemia, hypotension, seizures and rapid infusions of colloid or hypertonic solutions (14). Additional risk factors arise during ECMO treatment, such as ligation of the RCCA and RIJV, systemic heparinization, thrombocytopenia, coagulopathy, systolic hypertension, and micro-thrombi from the ECMO circuit (15).

Before starting ECMO, all the patients have hypoxaemia for several hours or even a few days. To maintain oxygen transport to the brain and oxygen metabolism of the brain, cerebral blood flow (CBF) is increased (16-18) Prolonged hypoxaemia compromises cerebral oxygen transport and metabolism, especially when cardiac output is affected by hypoxia. In this compromised brain, the RIJV and the RCCA are ligated. Normally, after RCCA ligation, blood flow to the right cerebral hemisphere is maintained by collateral circulation via the

circle of Willis. Short et al demonstrated that even after exposure to hypoxia, RCCA ligation in the newborn lamb did not result in differences in CBF between the left and right hemispheres. They also demonstrated that CBF, cerebral oxygen transport and cerebral oxygen metabolism remained unchanged (17).

In order to have adequate CBF over a wide range of cerebral perfusion pressures (CPP), it is important that cerebral autoregulation is intact (19). Systemic insults in the pre-ECMO period, such as asphyxia, hypoxia and hypercapnia, may disrupt cerebral autoregulation and render the microcirculation vulnerable to alterations in systemic blood pressure (20,21).

In the lamb model, Short et al demonstrated that cerebral autoregulation was disturbed by pre-ECMO hypoxia combined with blood vessel ligation, and by VA-ECMO itself (18,22). The combination of exposure to hypoxia and VA-ECMO treatment disturbed cerebral autoregulation even more profoundly than either hypoxia or VA-ECMO alone (23). This autoregulation disturbance was characterized by a shift of the lower limit of the autoregulation plateau to a higher CPP value (a shift to the right) than in the control animals. The effect of the shift in autoregulatory threshold was greater in the right cerebral hemisphere than in the left. At this CPP point where autoregulation was lost, this caused differences in CBF between the hemispheres. The shift in autoregulatory threshold increases the risk of ischaemic cerebral injury at a CPP level where this is not usually expected. Cerebral oxygen consumption was indeed decreased at CPP below this higher autoregulatory threshold, thus indicating a potential cause for cerebral injury.

Tweed et al demonstrated in the lamb that after exposure to hypoxia, CBF autoregulation was also lost at the higher end of the autoregulatory curve (21). The loss of autoregulation makes the brain vulnerable to changes in arterial blood pressure, with hypotension resulting in ischaemic lesions and hypertension resulting in hyperaemia and haemorrhages.

Sell et al and Boedy et al reported hypertension in a high percentage of their patients treated with ECMO, in association with the occurrence of intracranial haemorrhages (24,25). Pharmacological control of the hypertension resulted in a reduction in the incidence of intracranial haemorrhages, suggesting a relation between hypertension and the occurrence of intracranial haemorrhages.

As in the studies of Short et al there were differences in CBF between the right and left hemispheres at the point where cerebral autoregulation was lost, RCCA ligation and VA-ECMO initiation may be risk factors for right-sided cerebral lesions (18,22). Schumacher et al found indeed an increase in right-sided cerebral lesions after VA-ECMO treatment (26). ECMO patients also have an increased risk of posterior fossa haemorrhages (2,27). Short et al

demonstrated an increase in CBF in the cerebellum of the lamb after recovery from hypoxia and suggested that the increased risk of posterior fossa haemorrhages was related to reperfusion injury (18). Taylor and Walker suggested that venous outflow obstruction from ligation and cannulation of the right internal jugular vein plays a role in the occurrence of posterior fossa haemorrhages (28). Increased venous pressure may disrupt the blood-brain barrier and alter the cerebral autoregulation curve by shifting the lower end of the autoregulatory curve to a higher level (29,30).

Besides loss of autoregulation and blood vessel ligation as causes of cerebral lesions in newborns treated with VA-ECMO, administration of heparin is another risk factor.

Although heparin does not cause intracranial haemorrhage directly, it may lead to rapid progression of it (6,31). Patients who need ECMO often have pre-existing coagulation factor deficiencies while coagulation factor concentrations can decrease further during the first 24 hours of ECMO (32,33). In addition, activation of the fibrinolytic system, thrombocytopenia and altered thrombocyte function during ECMO may aggravate existing haemorrhagic lesions (34-36). Hirthler et al found that instability of coagulation variables was an early predictor of intracranial haemorrhages (37). This suggests that stability in the clotting system is necessary to prevent haemorrhagic complications.

The ECMO system contains thrombogenic materials. Contact of blood with foreign surfaces activates the contact system and the complement system, resulting in thrombus formation, which can be suppressed by heparin administration during ECMO (38,39). Nevertheless, thrombus formation does still occur. Clots in the ECMO system are reported in 20% of the patients (40). If clots in the ECMO system are reinfused into the arterial circulation, they may cause ischaemic cerebral lesions.

Hyperventilation, used to lower pulmonary hypertension, may be another pre-ECMO factor that contributes to cerebral damage (41,42). Hyperventilation causes a decrease in the arterial partial pressure of carbon dioxide ($paCO_2$) and subsequent vasoconstriction in the cerebral circulation, which reduces CBF. Walker et al and Liem et al demonstrated that cerebrovascular reactivity to carbon dioxide was intact in animal models, during ECMO (43,44). At the start of ECMO, the $paCO_2$ level may show acute normalization and lead to an increase in CBF, another potential risk factor for haemorrhages (45).

In summary, ECMO infants are not only at risk for cerebral injury secondary to their critical pre-ECMO state, but also from the ECMO therapy itself.

The animal studies described above indicate that recovery from hypoxia, with or without ECMO, is a vulnerable period in which physiological alterations, such as hypotension or

hypertension, may hold risk of brain injury. If these results in animals can be extrapolated to the newborn human infant, VA-ECMO may increase this risk. Therefore, stabilization of the infants during the initial recovery period on ECMO and treatment of events such as hypotension and hypertension should be undertaken in an expedient manner. When using a technique as complicated as ECMO, it is necessary to understand the factors that cause morbidity, to be able to optimize the use of ECMO and thus improve the long-term outcome of ECMO patients.

In an earlier study, our group demonstrated a marked increase in cerebral perfusion during the induction of VA-ECMO, but it was not possible to draw conclusions about differences in effect on the left and right cerebral hemispheres (46). This question is studied in chapter 5.

In addition, our group observed changes in cerebral oxygenation and haemodynamics when the bypass bridge was opened during VA-ECMO (47). This bridge is a safety connection between the drainage and infusion tubing of the ECMO system. It is used in emergency situations, when the patient has to be temporarily disconnected from the ECMO circuit. If necessary, the tubings leading to and from the patient can be clamped off and the bridge opened, thus allowing to maintain circulation in the ECMO circuit. During ECMO treatment, the bridge is opened and flushed every 15 minutes to prevent the development of thrombi due to blood stasis.

Chapter 6 addresses the cause of the changes in cerebral oxygenation and haemodynamics when the bypass bridge is opened, effects of opening the bridge at different ECMO flow rates and opening times, and ways to prevent these changes.

In chapter 7, we used an animal model to study how the patent ductus arteriosus with left-to-right shunt affected cerebral oxygenation and haemodynamics during VA-ECMO.

Motivation for this study was the presence of a left to right shunt through the ductus in newborns during VA-ECMO and its relation with a prolonged ECMO run time (48). In pre-term infants, a patent ductus with left-to-right shunt may cause stealing of blood from the cerebral circulation, which might be related to the occurrence of cerebral lesions (49-52).

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CHAPTER 5

OXYGENATION AND HAEMODYNAMICS IN THE LEFT AND RIGHT CEREBRAL HEMISPHERES DURING INDUCTION OF VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION

Oxygenation and haemodynamics in the left and right cerebral hemispheres during induction of veno-arterial extracorporeal membrane oxygenation

Arno van Heijst[1], Djien Liem[1], Jeroen Hopman[1], Frans van der Staak[2], Rob Sengers[1]

Departments of Paediatrics[1] and Paediatric Surgery[2], University Medical Centre Nijmegen, Nijmegen, The Netherlands

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ABSTRACT

Objective: Oxygenation and haemodynamics in left and right cerebral hemispheres were measured during induction of veno-arterial extracorporeal membrane oxygenation.

Study design: Using near infrared spectrophotometry, effects of right common carotid artery and right internal jugular vein ligation and start of veno-arterial extracorporeal membrane oxygenation on concentrations of oxyhaemoglobin, deoxyhaemoglobin and the cerebral blood volume were evaluated in 10 newborn infants. Mean cerebral blood flow velocity in the major cerebral arteries was compared before and after the start of veno-arterial extracorporeal membrane oxygenation (pulsed Doppler ultrasonography).

Results: Right common carotid artery ligation caused a decrease in oxyhaemoglobin concentration and an increase in deoxyhaemoglobin concentration. Right internal jugular vein ligation caused no changes. Sixty minutes after the start of veno-arterial extracorporeal membrane oxygenation, oxyhaemoglobin concentration and cerebral blood volume had increased, and deoxyhaemoglobin concentration had decreased. There were no differences between the hemispheres. Mean cerebral blood flow velocity had increased in the left internal carotid artery, and it increased equally in both middle cerebral arteries. Flow direction was reversed in the right internal carotid artery. Three patients had asymmetric cerebral lesions, not related to differences in the studied variables between the cerebral hemispheres.

Conclusion: The initiation of veno-arterial extracorporeal membrane oxygenation causes changes in cerebral oxygenation and haemodynamics but without a difference in effect on left and right cerebral hemispheres.

INTRODUCTION

ECMO is a rescue therapy for newborns with severe cardiorespiratory insufficiency. Major complications of this treatment are the occurrence of haemorrhagic and ischaemic cerebral lesions, leading to neurological and neurodevelopmental dysfunction (1,2). Since the introduction of ECMO there has been concern about the effect of ligation of the RCCA and the RIJV on the perfusion of the brain. Conflicting data exist on the predominant occurrence of cerebral lesions in the right hemisphere, related to this ligation (3-9). Schumacher et al and Campbell et al found an increase in left-sided seizures, lateralized neuromotor findings, and right-sided ischaemic cerebral lesions (3,4). Lott et al demonstrated long lasting decreased blood flow in the right internal carotid artery and a reduction in the amplitude of right hemispheric long latency evoked potentials (5). Mendoza et al demonstrated the preference of ischaemic lesions to the right hemisphere and of haemorrhagic lesions in the left hemisphere (6). Others demonstrated an equal distribution of cerebral lesions on neuroimaging studies, no lateralized neurologic findings, and satisfactory collateral flow on Doppler flow studies (7-9). In a lamb model, RCCA and RIJV ligation after 2 hours of hypoxia caused a disturbed autoregulation with significant differences in CBF between the right and left hemisphere (10). Previously we demonstrated marked changes in cerebral oxygenation and haemodynamics during introduction of VA-ECMO, using single-channel near infrared spectrophotometry (NIRS) (11). In this present study the effects of ligation of the RCCA and RIJV and the initiation of VA-ECMO on left and right cerebral hemisphere perfusion and oxygenation are evaluated using a two-channel NIRS.

METHODS

Study population and ECMO procedure

After obtaining informed parental consent, we studied 10 VA-ECMO patients who had severe cardiorespiratory failure and hypoxaemia despite adequate conventional treatment, using mechanical ventilation, sedation, muscle paralysis, vaso-active drugs, surfactant and nitric oxide inhalation. All infants met the established entry criteria for ECMO (12). The study population consisted of 4 males and 6 females, gestational age 37 to 42 weeks and birth

weight 3000 to 3670 g. The underlying diseases were CDH (n=4), MAS (n=3), sepsis (n=2) and i-PPHN (n=1). The study was approved by the University Hospital Ethics Committee.

During cannulation, the infants were anaesthetized using fentanyl and midazolam and paralysed with pancuronium. After starting standard VA-ECMO (13), the flow rate on bypass was gradually increased over several minutes until an appropriate level was reached (range: 165-210 mL/kg.min) to maintain the arterial oxygen saturation (saO_2) between 90 and 100% as measured by pulse oximetry.

Subsequently, the artificial ventilation was set at 'rest settings' and was continued during the measurement period, with a peak inspiratory pressure of 22-26 cm H_2O, a positive end expiratory pressure of 4 cm H_2O and FiO2 of 0.30. To prevent clot formation, systemic heparinization was established. During the measurement period, medication administered before VA-ECMO was continued.

Near Infra-Red Spectrophotometry (NIRS)

This technique is based on the continuous spectrophotometric measurement of oxygenation-dependent changes in the absorption of near infrared light by haemoglobin (14). Details of our NIRS measurement have been described earlier (15). Briefly, three wavelengths of near infrared light (905, 850 and 767 nm) were transmitted through the skull with a three-branch fiberoptic bundle and received by two separate optodes. Using the described algorithm, absolute changes (?) in concentration of oxyhaemoglobin (cO_2Hb), deoxyhaemoglobin (cHHb) and total haemoglobin (ctHb), as the sum of the changes in concentration of oxyhaemoglobin and deoxyhaemoglobin, were calculated from changes in absorption of near infrared light at the three wavelengths mentioned (16). To investigate the changes in cerebral oxygenation and haemodynamics in both cerebral hemispheres, the 2 receiving optodes were placed over the left and right parietotemporal region, one above each hemisphere. The transmitting optode was placed over the posterior fontanel. In this way, changes in the concentrations of oxyhaemoglobin ($?cO_2Hb$), deoxyhaemoglobin (?cHHb) and total haemoglobin (?ctHb) could be registered separately over a substantial part of the left and right cerebral hemisphere. In all infants, the interoptode spacing between transmitter and receivers was greater than 2.5 cm to ensure a constant path length multiplying factor, which was 4.39 (17). $?cO_2Hb$ and ?cHHb reflect changes in cerebral oxygen supply, if perfusion and oxygen consumption remain constant. ?ctHb represent changes in cerebral blood volume (CBV).

Doppler ultrasound

Measurements of the mean cerebral blood flow velocity (CBFV) in major cerebral arteries were performed using pulsed Doppler ultrasonography (ATL HDI 3000, ATL ultrasound Inc, Bothell, WA, USA). CBFV in the supraclinoid internal carotid artery was measured by placing the transducer on the anterior fontanel. Measurement of CBFV in the middle cerebral artery in the Sylvian sulcus was performed by placing the transducer 1 to 2 cm in front of the right ear above the zygomatic process (18). Using this approach, the insonation angle was assumed to be negligible (less than 10^{o}). Mean CBFV was calculated using the built-in calculation program. Measurements were performed just before application of the NIRS optodes at approximately 30 mins before cannulation and just after removal of the NIRS optodes at approximately 60 mins after ECMO was started. The changes in mean CBFV after induction of VA-ECMO were expressed as percentages of their precannulation levels.

Measurement of physiological variables

Heart rate (HR), mean arterial blood pressure (MABP) measured by an umbilical arterial catheter, and saO_2 measured non-invasively by pulse oximetry using the right hand, were recorded continuously, using a neonatal monitor (HP Model 68S, Hewlett Packard, Boeblingen, Germany). This monitor was connected to a data acquisition system (Poly®, Inspector Research System, Amsterdam, The Netherlands) with a sampling frequency of 1 Hz. Blood samples for determination of paO_2, $paCO_2$, and the intravascular concentration of haemoglobin (cHb) were drawn from an umbilical arterial catheter just before cannulation and at 60 mins after ECMO was started.

Follow-up

In all patients the occurrence of cerebral haemorrhagic and ischaemic lesions was studied daily during ECMO treatment using ultrasonography. After ECMO treatment, CT-scan or MRI-scan of the brain was performed in all surviving newborns. In addition, brainstem auditory evoked potentials (BAEP) and electroencephalogram (EEG) were conducted.

Data analysis

From each continuously recorded variable (cO_2Hb, cHHb, ctHb, saO_2, MABP and HR), we selected data for a stable 30-secs period from six episodes: (A) just before the start of the cannulation procedure, (B) just before ligation of the RCCA, (C) after RCCA ligation, just before insertion of the arterial cannula, (D) just before RIJV ligation, (E) after RIJV ligation, just before insertion of the venous cannula and (F) at 60 mins after starting ECMO.

For each variable, the mean value for this 30-secs period was calculated. The differences in the mean values for the 30-secs period between C and B and between E and D were calculated to determine the effects of RCCA and RIJV ligation respectively. Because all signals had stabilized 60 mins after starting ECMO, we compared F and A to determine the overall effect of ECMO induction. The effects were analyzed with the Wilcoxon signed-rank test.

The changes in mean CBFV, cHb, pH, paO_2 and $paCO_2$ at 60 mins after starting ECMO, related to their precannulation values, were also calculated and analyzed with the Wilcoxon's signed rank test or one-sided nonparametric test, when appropriate.

The CBV (mL/100 g) can be calculated from the following formula:

$$CBV \; ? \; \frac{4 \; ? \; ctHb}{0.69 \; ? \; cHb}$$

where ctHb is the concentration of total haemoglobin in cerebral tissue, expressed in µmol/100 g and cHb is the intravascular concentration of haemoglobin in mmol/l; 0.69 is the cerebral to large vessel haematocrit ratio and 4 is a correction factor, as ctHb is calculated from changes in light absorption using extinction coefficients based on the tetrahaeme molecule, whereas determination of cHb in blood samples is based on the monohaeme molecule (19).

Because the cHb changes after starting ECMO, the change in CBV (?CBV) cannot be simply calculated from changes in ctHb.

Therefore:

$$CBV + \; ? \, CBV = \; \frac{4 \; ? \; (ctHb \; ? \; ? \, ctHb)}{0.69 \; ? \; (cHb \; ? \; ? \, cHb)}$$

and

$$? \, CBV = \; \frac{? \, ctHb \; ? \; 0.17 \; ? \; ? \, cHb \; ? \, CBV}{0.17 \; ? \; (cHb \; ? \; ? \, cHb)}$$

However, because the initial CBV value in the individual infant is unknown, it is not possible to calculate ? CBV exactly. Wyatt et al found a CBV value of 2.2 ± 0.4 mL/100 g in newborn infants with a normal brain (20). As moderate to severe hypoxaemia 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 (21). To determine the changes in CBV we used a precannulation CBV value of 4 mL/100 g and with this value calculated ? CBV (21).

For those variables from NIRS data or Doppler examination that showed statistically significant changes, we compared these changes between the left and right cerebral hemisphere with the Wilcoxon's signed rank test.

Furthermore, we tested whether the newborns with asymmetric cerebral lesions had greater differences between the left and right hemisphere for the different variables than the newborns without asymmetric lesions. The difference in effect between left and right cerebral hemisphere of the different variables was divided in two groups: values within the interquartile range (between 25^{th} and 75^{th} percentile) and values outside this interquartile range. In a 2x2 contingency table this was tested against the occurrence of asymmetric cerebral lesions (Fisher's exact test). For all analyses, the level of significance was chosen at 0.05.

RESULTS

Clinical Outcome

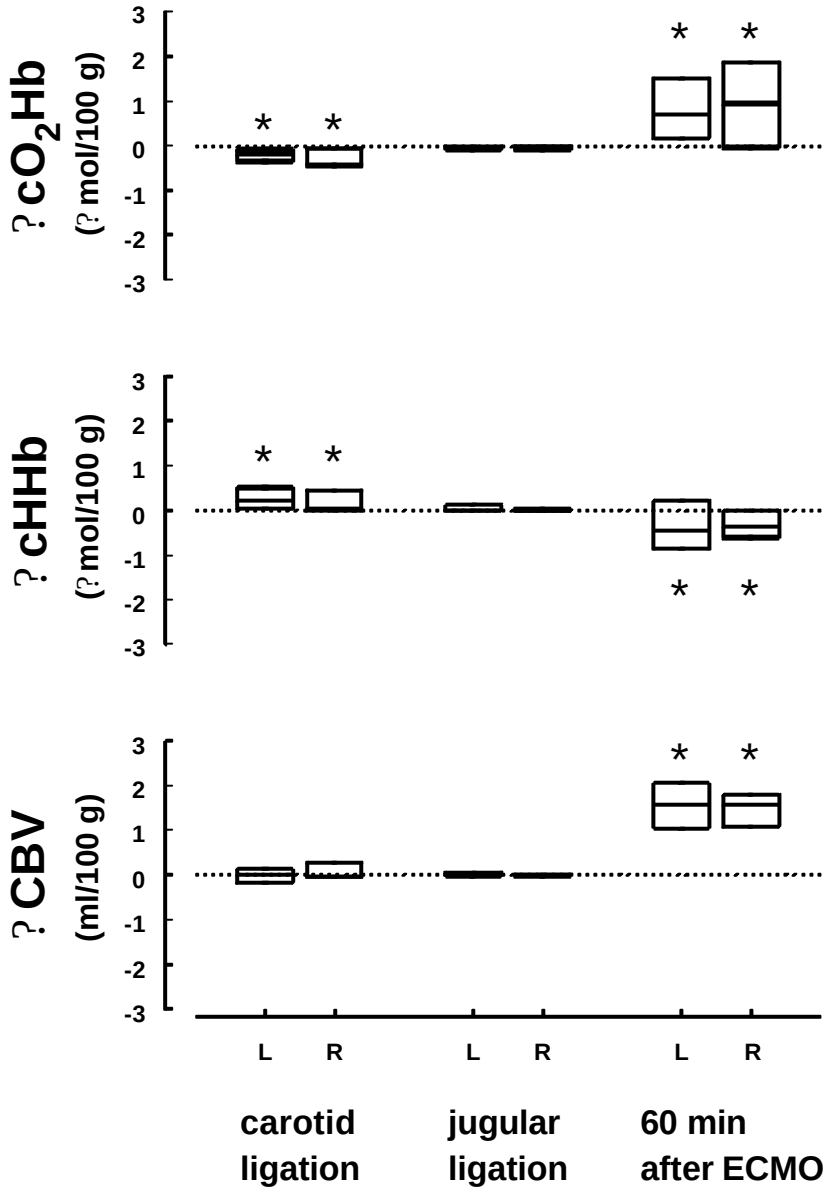
All 10 patients could be successfully weaned from ECMO. One patient with CDH died because of severe respiratory insufficiency after the ECMO run. Neuro-imaging during and after ECMO treatment showed a left sided small periventricular haemorrhagic lesion in one infant, and a second infant had a haemorrhagic infarction in the area of the right middle cerebral artery. Furthermore BAEP showed delayed central conduction on the right side in a third patient.

Blood vessel ligation (figure 1)

After RCCA ligation there was a significant decrease in cO_2Hb and a significant increase in cHHb in both cerebral hemispheres. CBV did not change. Median values [interquartile

ranges] of ? MABP; 0.2, [-1.5, 0.9] mm Hg, ? saO_2; 0 [-1, 1] % and ? HR; -1 [-2, 0] beats per min, were not significant.

Figure 1. Absolute changes in NIRS variables during cannulation and after VA -ECMO initiation



?cO_2Hb = changes in concentration of oxyhaemoglobin, ?cHHb = changes in concentration of deoxyhaemoglobin, ?CBV= changes in cerebral blood volume, L= left hemisphere, R = right hemisphere. Because absolute precannulation values are unknown, changes are compared with precannulation values, defined to be zero µmol/l or mL/100 g brain tissue, respectively. Horizontal lines represent median values; boxes cover interquartile ranges. *: $p<0.05$ compared to precannulation values.

RIJV ligation did not cause any significant changes in NIRS variables. Again, ? MABP; 0.9 [-1.3, 3.9] mm Hg, ? saO_2; -1 [-2, 1] %, and ? HR; -1 [-4, 1] beats per min, were not significant. There were no differences in the observed changes between left and right cerebral hemisphere. The occurrence of asymmetric cerebral lesions and the difference in effect between left and right cerebral hemisphere had no relation in any of the studied variables.

Table 1. Changes in variables 60 minutes after starting ECMO as compared to precannulation values

	Absolute precannulation values	Changes 60 min after starting ECMO
saO_2 (%)	79 (62-95)	15 (1-31)*
MABP (mm Hg)	52 (43-65)	19 (10-21)*
HR (beats/min)	169 (164-176)	-18 (-25, -5)*
paO_2 (mm Hg)	54.0 (36.7-71.3)	+46.1 (+28.3, +69.7)*
$paCO_2$ (mm Hg)	42.7 (36.7-45.0)	+1.8 (-2.2, +5.8)
PH	7.31 (7.25-7.38)	+0.01 (-0.03, +0.05)
cHb (mmol/l)	8.9 (8.4-9.2)	-2.0 (-2.6, -1.5)*

Values are median (interquartile range), * $p < 0.05$

saO_2 = arterial oxygen saturation, MABP = mean arterial blood pressure, HR = heart rate, paO_2 = arterial partial pressure of oxygen, $paCO_2$ = arterial partial pressure of carbon dioxide, cHb = intravascular concentration of haemoglobin.

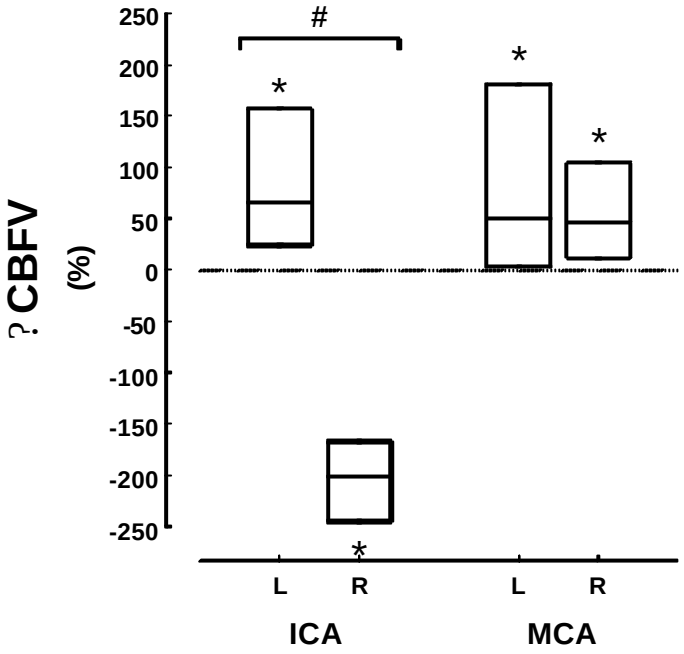
ECMO effect

Immediately after starting ECMO, cO_2Hb increased in both cerebral hemispheres. Also, saO_2 and MABP increased, whereas cHHb decreased in both cerebral hemispheres (figure 1, table 1). In all 10 infants, CBV was increased 60 min after starting ECMO, in the right and in the left cerebral hemisphere (figure 1). In addition, HR had decreased, and cHb was lower due to haemodilution by the priming solution of the ECMO system (table 1).

Induction of VA-ECMO caused a significant increase in mean CBFV in both the left and right middle cerebral arteries and in the left internal carotid artery. In the right internal carotid artery there was a reversed blood flow direction, from positive to negative (figure 2). The magnitudes of ?cO_2Hb and ?cHHb were not significantly different between the right and left cerebral hemispheres. For the changes in mean CBFV after ECMO initiation, there was a significant difference between left and right internal carotid artery ($p<0.05$) (figure 2).

The occurrence of asymmetric cerebral lesions and the difference in effect between left and right cerebral hemisphere showed no relation in any of the measured variables.

Figure 2. Effect of initiation of VA -ECMO on cerebral blood flow velocity



?CBFV= change in the mean cerebral blood flow velocity, ICA = internal carotid artery, MCA = middle cerebral artery, L = left hemisphere, R = right hemisphere. Changes are presented as percentage increase compared with precannulation values. Horizontal lines represent median values; boxes covers interquartile ranges. *: $p<0.05$ compared to precannulation values. #: $p<0.05$ comparing ?CBFV in left and right ICA.

DISCUSSION

With the onset of VA-ECMO, important haemodynamic changes occur. Ligation of the RCCA and RIJV, nonpulsatile bypass flow, hypertension, and normalization of the arterial blood gases may all influence CBFV (22). VA-ECMO may alter cerebral autoregulation significantly, and more severe in the right than in the left hemisphere, and it can be an important risk factor for right-sided cerebral ischaemia (10,23).

NIRS with the two-channel technique offers the opportunity to study blood vessel ligation effects continuously and separately in each cerebral hemisphere.

Although adequate collateral blood flow to the right hemisphere is maintained during VA-ECMO, transient blood flow interruptions and cerebral oxygenation changes causing ischaemic brain lesions at the moment of RCCA ligation can not be ruled out (7,24,25). A temporary decrease in CBFV in the right middle cerebral artery after ligation of the RCCA was demonstrated (18,26). With NIRS, we found that ligation of the RCCA caused a decrease

in the cO_2Hb and an increase in cHHb in both cerebral hemispheres, which could be related to the occurrence of hypoxaemic lesions. The changes observed after RCCA ligation can be explained by a decreased total oxygen delivery because blood flowing through the left common carotid artery is distributed to both hemispheres. Also, oxygen extraction can increase because of prolonged transit time of blood through the brain and as a compensation for diminished oxygen supply, explaining the decrease in cO_2Hb and increase in cHHb. Although earlier results and ours suggest a potential ischaemic moment after RCCA ligation, we found no differences in NIRS variables between the right and left cerebral hemispheres (18,26).

Some authors reported CBFV changes caused by venous outflow obstruction after ligation of the RIJV and related this to the occurrence of cerebrovascular injury (27,28). We saw no acute effect of RIJV ligation on cO_2Hb, cHHb, and CBV. If RIJV ligation would result in venous outflow obstruction, an increase in CBV could be expected.

One hour after the start of VA-ECMO we demonstrated an increase in cO_2Hb and CBV and a decrease in cHHb. Mean CBFV had increased in both middle cerebral arteries and in the left internal carotid artery, and blood flow direction had reversed in the right internal carotid artery. The increase in cO_2Hb is expected from the VA-ECMO procedure itself because oxygenation increases, as demonstrated by the increased paO_2 and saO_2 values. CBV can increase as arterial inflow increases, as represented by increase in CBFV. This can be explained as reactive hyperperfusion after prolonged hypoxaemia before ECMO, or as a compensation for diminished cerebral oxygen delivery due to haemodilution caused by the ECMO procedure (11). However, this could not be confirmed in animal experiments (29).

We chose an initial CBV value of 4 mL/100 g to calculate ?CBV after ECMO initiation. When calculating ?CBV assuming an initial CBV of 2.2 mL/100 g as suggested by Wyatt et al (20), a significant elevation of CBV in both hemispheres was also found, showing that the initial value of CBV is not important to demonstrate that there is an increase in CBV after ECMO initiation.

Both increased CBV and increased CBFV can be related to the occurrence of cerebral haemorrhages. In this study we could not demonstrate a difference in increase in CBV and mean CBFV between the left and right cerebral hemisphere, apart from mean CBFV in the internal carotid artery. Blood flow direction in the right internal carotid artery during VA-ECMO could be forward as well as backward, depending on the collateral circulation originating from the circle of Willis through the anterior and posterior communicating arteries or from the right external carotid artery to the right internal carotid artery (4,24,25). Changes

of flow direction in the right internal carotid artery demonstrate adequate collateral circulation through the circle of Willis and have no effect on hemispheric perfusion because mean CBFV in the left and right middle cerebral arteries was equal 60 mins after the start of ECMO. Others found a symmetric CBFV in the anterior cerebral artery, another distal artery, during VA-ECMO (7,22).

After RCCA and RIJV ligation and also 60 minutes after initiation of VA-ECMO, the 3 newborns with asymmetric brain lesions did not have greater left to right hemispheres differences in NIRS variables or CBFV than those without these lesions.

Although we could not demonstrate a difference in effect on left and right hemispheres, the observed effects may have a relation with the occurrence of cerebral lesions. This study was not aimed at investigating aetiologic factors for the occurrence of haemorrhagic or ischaemic lesions during ECMO. The aetiologic mechanism for cerebral lesions is most likely multifactorial.

NIRS measures absolute changes in oxygenation and CBV, not absolute values. However, the magnitude of the NIRS changes can be compared with usual physiologic challenges, e.g. changes in $paCO_2$. During hypercapnia in piglets on ECMO after hypoxia, a mean ?cO_2Hb of 0.16 µmol/100 g.kPa and a mean ?CBV of 0.10 mL/100 g.kPa occurred (30). Wyatt et al calculated changes in CBV in relation to changes in $paCO_2$ in term infants to be 0.51 mL/100g.kPa (31). Compared with this, the changes in NIRS variables found in the current study seem to be physiologically relevant.

To our knowledge only CBFV Doppler ultrasonography studies on the effect of RCCA ligation and ECMO initiation exist; no studies exist on cerebral oxygenation and CBV. Our study is the first to use NIRS to study the effects of cannulation and initiation of VA-ECMO on each cerebral hemisphere separately. We observed changes in cO_2Hb, cHHb, CBV and mean CBFV, but we observed no asymmetric effect on cerebral oxygenation and haemodynamics. We could not demonstrate that the newborns with asymmetric cerebral lesions had greater differences in changes of the studied variables between left and right hemispheres than those without cerebral lesions.

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CHAPTER 6

HAEMODYNAMIC CHANGES DURING OPENING OF THE BRIDGE IN VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION

Haemodynamic changes during opening of the bridge in veno-arterial extracorporeal membrane oxygenation

Arno van Heijst[1], Djien Liem[1], Frans van der Staak[2], John Klaessens[1], Cees Festen[2], Ton de Haan[3], Wil Geven[4], Margot van de Bor[1]

Department of Paediatrics[1], Department of Paediatric Surgery[2], Department of Medical Statistics[3], University Medical Centre Nijmegen, Nijmegen, The Netherlands, Department of Paediatrics, University Hospital Groningen[4], Groningen, The Netherlands

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ABSTRACT

Objective: To investigate the cause of the haemodynamic changes occurring during opening of the bridge in veno-arterial extracorporeal membrane oxygenation.

Design: Prospective intervention study in animals.

Setting: Animal research laboratory of a university medical centre.

Subjects: Eight anaesthetized lambs installed on veno-arterial extracorporeal membrane oxygenation.

Interventions: During veno-arterial membrane oxygenation the bridge was randomly opened during 1, 2.5, 5, 7.5, 10 and 15 secs at flow rates of 500, 400, 300, 200, 100 and 50 mL/min. Flows in the extracorporeal circuit between venous cannula and bridge and bridge and arterial cannula, mean arterial blood pressure, mean left carotid artery blood flow, central venous pressure, superior sagittal sinus pressure, inline 'mixed venous' oxygen saturation, heart rate, and arterial oxygen saturation were measured continuously. Using near infrared spectrophotometry, changes in concentrations of cerebral oxygenated and deoxygenated haemoglobin and cerebral blood volume were also measured. Values during bridge opening were compared with values before opening. The same variables were determined with a roller pump on the bridge with a flow over the bridge at various flow rates.

Measurements and Main Results: Bridge opening resulted in a change of flow direction between the venous cannula and the bridge and between the bridge and the arterial cannula. A biphasic response with initial decrease and secondary increase occurred in mean arterial blood pressure and mean left carotid artery flow. Central venous pressure, superior sagittal sinus pressure, deoxygenated haemoglobin concentration, and cerebral blood volume increased, whereas concentration of cerebral oxygenated haemoglobin decreased. These effects occurred in each combination of flow rate and opening time. These effects could be abolished by installing a roller pump on the bridge.

Conclusions: Bridge opening in veno-arterial extracorporeal membrane oxygenation resulted in significant cerebral haemodynamic changes caused by an arteriovenous shunt over the bridge. The decreased cerebral perfusion may contribute to the occurrence of cerebral ischaemia, and the venous congestion may result in intracranial haemorrhages. These could be prevented by installing a roller pump on the bridge.

INTRODUCTION

ECMO is a rescue therapy for neonates with severe respiratory failure for which the mortality rate is high if treated with conventional therapy only (1). Since the first patient treated by Bartlett in 1976, more than 15,000 newborns have been treated with ECMO, the majority of them with VA-ECMO (2,3).

Although the overall survival rate for newborns treated with ECMO is 80%, complications occur in a high percentage of these patients (4). The most important complication is cerebral damage caused by haemorrhage or ischaemia, an important determining factor for mortality and impaired neurodevelopmental outcome in the survivors (5-7).

Other than the primary disease, the ECMO technique itself may have an aetiologic role in the development of complications. The understanding of the effects of ECMO on physiologic processes is important for the prevention of possibly dangerous complications. Our group previously reported on the disturbance of cerebral oxygenation and haemodynamics in relation to the opening of the bypass bridge during VA-ECMO (8). The bridge is a part of the VA-ECMO circuit that connects the venous and arterial sides of the system, enabling the continuation of circulation through the circuit while bypassing the patient in case of emergencies. To prevent clotting, the clamp on the bridge should be released every 15 mins during the ECMO procedure (9,10). In piglets and newborn infants, we found that opening of the bridge results in a decrease in CBV and cerebral oxygen supply, because of a decrease in CBF and then a compensatory increase in cerebral oxygen extraction and vasodilation.

The present study was undertaken to determine the following: (a) the changes that are responsible for the previously described disturbance of cerebral oxygenation and haemodynamics; (b) the effect of various opening times and flow rates on the magnitude of the haemodynamic disturbances; and (c) whether the haemodynamic changes could be abolished by using a continuously functioning pump on the bridge.

MATERIALS AND METHODS

The study was performed in 8 lambs (weight, 3.9-4.9 kg; age, 2-7 days) obtained from local farmers. The study was approved by the Ethical Committee on Animal Research of the University of Nijmegen. The care and handling of the animals were in accordance with the guidelines issued by the National Institutes of Health.

General anaesthesia was induced by intravenous administration of 0.2 mg/kg midazolam and 10 ?g/kg fentanyl, and muscle relaxation was obtained with 0.05 mg/kg pancuronium. After endotracheal intubation, mechanical ventilatory support was started with a Babylog 8000 (Dräger, Lübeck, Germany) to maintain normal arterial blood gases (pH 7.40-7.45; paO_2 70-90 mm Hg [9.3–12 kPa]; $paCO_2$ 30-40 mm Hg [4–5.3 kPa]). During mechanical ventilatory support, anaesthesia was maintained using continuous intravenous infusion of midazolam (0.1-0.2 mg/kg per hr), fentanyl (5-10 ?g/kg.hr) and pancuronium (0.02 mg/kg.hr). HR was monitored via electrodes placed on the chest. The temperature was measured with a rectal probe and maintained between 38.5°C and 39.5°C. A catheter was placed in the aorta through the right femoral artery for continuous measurement of MABP, (HP 78206C, Hewlett Packard, Boeblingen, Germany). Through the other femoral artery a 7.5 Fr fiberoptic oxymeter catheter (Viggo Spectramed, Oxnard, CA, USA) was inserted into the abdominal aorta for online continuous monitoring of saO_2 ($HemoprO_2$ SP 1455, Viggo Spectramed, Oxnard, CA, USA). Through the right femoral vein, another 7.5 Fr catheter was placed into the inferior caval vein with the tip in the right atrium to monitor the central venous pressure (CVP), (HP 78205C, Hewlett Packard, Boeblingen, Germany). Superior sagittal sinus pressure (SSSP) was monitored through a catheter placed in the superior sagittal sinus after trepanation of the skull. Mean blood flow in the left common carotid artery (Qcar) was measured using an electromagnetic flow meter (Scalar MDL 1401, Scalar Medical, Delft, The Netherlands). Changes in Qcar were used as a measure for changes in CBF. A close relationship between Qcar and CBF determined with radionuclide labeled microsphere method was demonstrated by van Bel et al (11).

The ECMO circuit was primed with full fresh sheep blood before cannulation. The RCCA was cannulated with an arterial catheter (Elecath 10 Fr, Electro-Catheter, Rahway, NJ, USA) and the RIJV with a venous catheter (Biomedicus 12 Fr, Medtronics, Eden Prairie, MN, USA). Thereafter, the animal was placed on VA-ECMO. During the cannulation procedure a loading dose of heparin was administered (150 IU/kg) and continued intravenously (100 - 200 IU/kg per hr) to maintain activated clotting time between 200 and 250 seconds (Hemochron, Edison, NJ, USA).

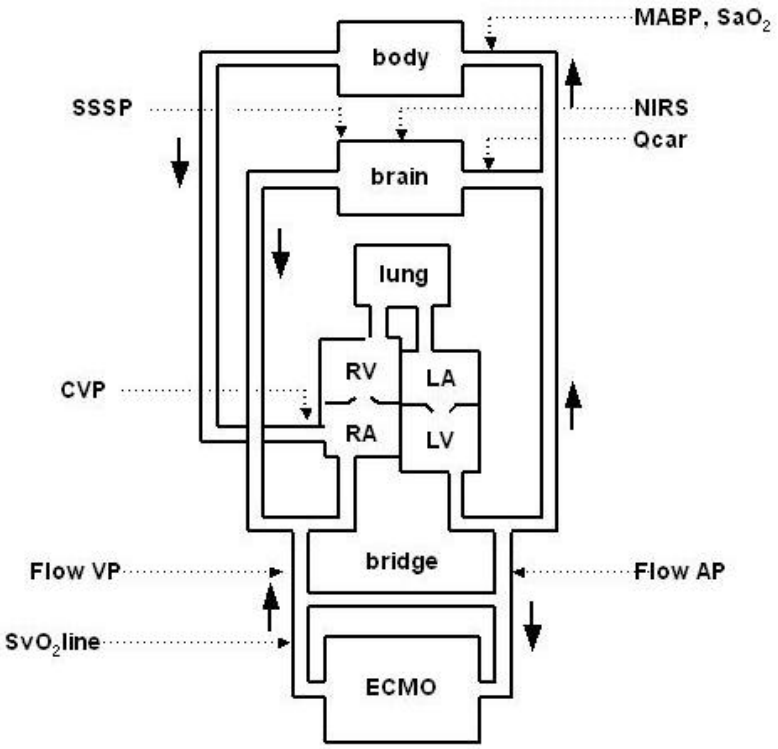
The ECMO circuit itself consisted of a custom packed ¼ inch flexible polyvinylchloride tubing (Baxter, Uden, The Netherlands), with a silicone reservoir, “the bladderbox” (Seabrook Medical System, Værløse, Denmark), a 0.6 m^2 membrane oxygenator (Scimed Life Systems, Minneapolis, MN, USA), a heat exchanger (Cincinnati Sub Zero, Cincinnati, OH, USA) and a rollerpump (Polystan A/S, Denmark). Inline 'mixed venous' oxygen saturation (svO_2line) was continuously monitored between the bridge and the bladderbox (Oxysat, Baxter-Bentley, Irvina,

CA, USA). Two ultrasonic flow meters (Transonic Systems, Ithaca, NY, USA) were placed for the continuous measurement of the actual flow in the circuit: one between the venous catheter and the bridge (Flow VP), and one between the bridge and the arterial catheter (Flow AP). When Flow VP is positive, the blood flow direction is from the animal to the bridge, when Flow VP is negative, the blood flow direction is from the bridge into the animal. When Flow AP is positive, the blood flow direction is from the bridge into the animal, when Flow AP is negative, the blood flow direction is from the animal to the bridge (figure 1).

Cerebral oxygenation and haemodynamics were studied with NIRS. The NIRS equipment used was developed by the Department of Biomedical Engineering and Medical Physics at the University of Keele (UK) and produced by Radiometer (Copenhagen, Denmark) (12). The technique is based on the spectrophotometric measurement of changes in the absorption properties of haemoglobin in the near infrared region, depending on its oxygenation state (13). Details of our NIRS measurement procedure have been extensively described before (8,14). Changes in cO_2Hb and cHHb were calculated from changes in the absorption of near infrared light at wavelengths 904, 845 and 775 nm. The concentration changes are expressed in ?mol/100 gr brain. ?cO_2Hb and ?cHHb reflect changes in cerebral oxygen supply (15). Changes in the ctHb were calculated as the sum of ?cO_2Hb and ?cHHb. Changes in ?CBV, expressed in mL/100 gr, were calculated from the formula: ?CBV = 4. ?ctHb/0.69.cHb, where cHb is the intravascular concentration of haemoglobin in mmol/L, 0.69 is the cerebral-arterial haematocrit ratio, and 4 is a correction factor, because ctHb is calculated from changes in light absorption using an extinction coefficient based on the tetrahaeme molecule, whereas cHb determination is based on the monohaeme molecule (16).

After cannulation and initiation of the ECMO procedure, the ECMO flow was gradually increased to 500 mL/min. The ventilation was adjusted to maintain normal arterial blood gas values, and the animal was allowed to stabilize. Subsequently the bridge was randomly opened during 1, 2.5, 5, 7.5, 10 and 15 seconds. The ECMO flow and opening time followed a Latin square design in each lamb in such way that each opening time is equally often followed by another opening time. The duration of stabilization periods between the measurements was 5 mins. The same procedure was repeated at ECMO flow rates of 400, 300, 200, 100 and 50 mL/min. The NIRS variables were recorded at a sample rate of 1 Hz using a specially designed data acquisition program. The other measured variables were recorded continuously using a data acquisition program Poly® (Inspector Research System, Amsterdam, The Netherlands) at a sample rate of 100 Hz.

Figure 1. Scheme showing the experimental model



RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle, svO_2line = inline 'mixed venous' oxygen saturation, Flow VP = flow between the venous catheter and the bridge, CVP = central venous pressure, SSSP = superior sagittal sinus pressure, MABP = mean arterial blood pressure, saO_2 = arterial oxygen saturation, NIRS = near infrared spectrophotometry measurement, Qcar = mean blood flow in the left common carotid artery, Flow AP = flow between the bridge and the arterial catheter, ECMO = extracorporeal membrane oxygenation circuit. Arrows indicate normal blood flow direction.

Because release of the clamp on the bridge resulted in significant haemodynamic changes, we modified the bridge and constructed a small roller pump that was placed on the bridge. With this pump on the bridge, repeated opening of the bridge was no longer necessary. There was continuous refreshment of blood in the bridge. Measurements of all the above-described variables were repeated in the same eight animals with this pump on the bridge and an ECMO flow rate of 100 mL/min and 500 mL/min and flow over the bridge of 10 mL/min and 50 mL/min, respectively. These data were compared with a zero flow rate over the bridge (bridge closed).

At the end of the experiments, the lambs were killed by administration of an overdose of pentobarbital.

DATA ANALYSIS

Before analysis, the data of CVP and SSSP were filtered with a 0.3-Hz low pass filter to reduce signal noise caused by breathing movements. For each variable, we selected data from two episodes around each bridge opening. During a period of 30 secs just before opening of the bridge, the mean (baseline) and standard deviation (sd) of each variable were calculated. During a period of 120 seconds after the opening of the bridge we selected the first positive peak (maximum) and/or negative peak (minimum) and eventually the second peak that exceeded the baseline level by more than 2 sd's for more than 2 secs. When no positive or negative peak was found a value of 0 was taken.

The differences in the values between the positive or negative peaks after opening the bridge and the mean values before opening the bridge were calculated to assess the effect of the bridge opening. The beginning of the change in Flow AP was considered to represent the actual beginning of the bridge opening.

For analysing the data, a statistical method that took into account the dependency of the observations in one lamb was required. Therefore, the mixed linear model approach was used (17,18). For all analyses, a factorial model, with factors ECMO flow rate and opening time, with random intercept for each lamb was used. This means that the correlation between different observations within one lamb is the same for all pairs of measurements. First, a possible (statistical) interaction between ECMO flow rate and opening time was investigated. A significant interaction was not found for any of the variables. Hence, only results of analyses without the interaction between ECMO-flow and opening time were presented. To correct for multiple testing within each set of hypotheses a Bonferroni correction was applied. Statistical significance required $p = 0.05$.

RESULTS

Table 1 shows the mean haemodynamic changes at various flow rates and opening times. Haemodynamic changes occurred in all combinations of opening times and ECMO flows. For those variables that showed statistically significant changes, these changes were present in each individual combination of flow and opening time.

Figures 2 and 3 illustrate the haemodynamic changes in one experiment at an ECMO flow rate of 500 mL/min and opening time 2.5 secs.

Table 1. Mean haemodynamic changes (± sd) during bridge opening in veno-arterial extracorporeal membrane oxygenation

Variable	**Absolute value ± sd before bridge opening**	**Changes at first peak (mean ± sd)**	**Changes at second peak (mean ± sd)**
Flow VP (mL/min)	50-500[a]	-1128 ± 90[##]	
Flow AP (mL/min)	50-500[a]	-775 ± 59[##]	
MABP (mm Hg)	107.0 ± 10.8	-21 ± 4[##]	+12 ± 4[#]
Qcar (mL/min)	97 ± 52	-26 ± 9[##]	+20 ± 6 [#]
CVP (mm Hg)	2.7 ± 2.9	+2.5 ± 0.6[##]	
SSSP (mm Hg)	11.9 ± 7.5	+2.2 ± 1.0[#]	
svO_2line (%)	52 ± 7	+32 ± 2[##]	
cHHb (µmol/100 gr brain)	na	+0.23 ± 0.11[##]	
cO_2Hb (µmol/100 gr brain)	na	-0.18 ± 0.08[##]	
CBV (mL/100 gr brain)	na	+0.15 ± 0.08[##]	

Flow VP = flow between venous catheter and bridge (when Flow VP is positive, the blood flow direction is from the animal to the bridge, when Flow VP is negative, the blood flow direction is from the bridge into the animal), Flow AP = flow between bridge and arterial catheter (when Flow AP is positive, the blood flow direction is from the bridge into the animal, when Flow AP is negative, the blood flow direction is from the animal to the bridge). MABP = mean arterial blood pressure, Qcar = mean blood flow in the left common carotid artery, CVP = central venous pressure, SSSP = superior sagittal sinus pressure, svO_2line = inline 'mixed venous' oxygen saturation, cHHb = concentration of deoxyhaemoglobin, cO_2Hb = concentration of oxyhaemoglobin, CBV = cerebral blood volume.

[a] flow varied from 50 mL/min to 500 mL/min (see methods)

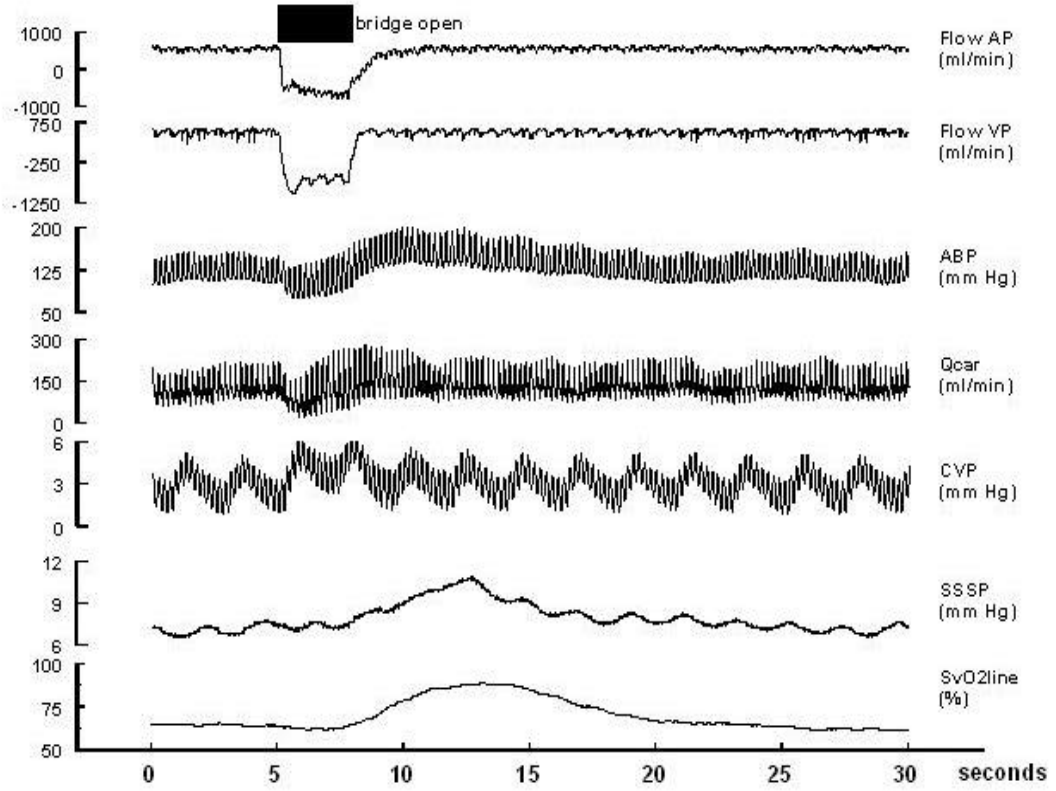
# $p < 0.05$, ## $p < 0.01$, na: not available

Flows in the ECMO circuit

On the venous side of the circuit, Flow VP showed an immediate and sharp decrease after opening of the bridge. The flow direction changed from positive to negative, which means that the Flow VP was reversed toward the animal. After a short negative peak, the flow stabilized, but remained negative during the opening of the bridge. After closing the bridge, the flow returned to its original direction immediately.

On the arterial side of the circuit, Flow AP also showed an immediate and sharp decrease after bridge opening. The flow direction changed from positive to negative, which means that Flow AP was reversed out of the animal. During bridge opening, the flow remained negative. After closure of the bridge, the flow direction returned to its original direction again.

Figure 2. Registration of curves during 2.5-sec bridge opening at a flow rate of 500 mL/min



Flow AP = flow between the bridge and the arterial catheter, Flow VP = flow between the venous catheter and the bridge, ABP = arterial blood pressure, Qcar = left carotid artery blood flow, CVP = central venous pressure, SSSP = superior sagittal sinus pressure, SvO_2line = inline 'mixed' venous oxygen saturation.

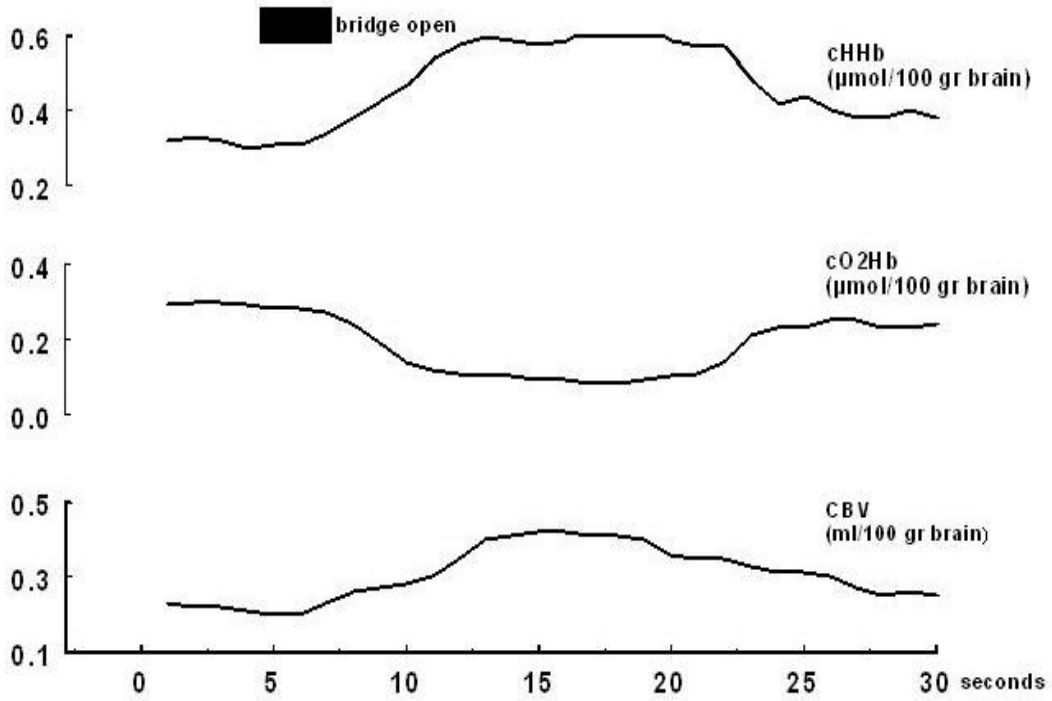
MABP and Qcar

After opening of the bridge, MABP and Qcar showed a biphasic pattern. Initially there was a decrease in MABP as well as in Qcar. After bridge closure, MABP and Qcar increased to higher values than the pre-opening values.

CVP and SSSP

A significant increase in CVP and SSSP was observed after opening of the bridge.

Figure 3. Registration of NIRS variables during 2.5-sec bridge opening at flow rate of 500 mL/min



cHHb = concentration of deoxyhaemoglobin, cO_2Hb = concentration of oxyhaemoglobin, CBV = cerebral blood volume.

svO_2line

After opening of the bridge there was a slow increase in svO_2line.

NIRS signals

After bridge opening, cHHb increased, which resulted in a positive peak, and cO_2Hb decreased, resulting in a negative peak. After a slight decrease of CBV, that was not significant, there was a gradual increase after bridge opening with a statistically significant positive peak shortly after bridge closure.

Table 2. Effect of decreasing flow and opening time on haemodynamic changes during opening of the bridge in VA-ECMO

Variable	Decreasing flow: 500 to 400, 300, 200, 100 and 50 mL/min	Decreasing opening time: 15 to10, 7.5, 5, 2.5, 1 sec(s)
? Flow VP (mL/min)	p<0.01	N.S.
?Flow AP (mL/min)	p<0.01	N.S.
? MABP (mm Hg)	p<0.01	N.S.
? Qcar (mL/min)	p<0.01	N.S.
? CVP (mm Hg)	N.S.	p<0.05
? SSSP (mm Hg)	N.S.	N.S.
? svO_2line (%)	p<0.01	p<0.01
?cHHb (µmol/100 gr brain)	p<0.01	p<0.01
? cO_2Hb (µmol/100 gr brain)	p<0.01	p<0.01
?CBV (mL/100 gr brain)	N.S.	p<0.05

? = change, Flow VP = flow between venous catheter and bridge, Flow AP = flow between bridge and arterial catheter, MABP = mean arterial blood pressure, Qcar = mean left carotid artery blood flow, CVP = central venous pressure, SSSP = superior sagittal sinus pressure, svO_2line = inline 'mixed venous' oxygen saturation, cHHb = concentration of deoxyhaemoglobin, cO_2Hb = concentration of oxyhaemoglobin, CBV = cerebral blood volume.

When p<0.05, decreasing flow or opening time leads to a significant lesser change of that variable.

Heart rate and arterial oxygen saturation

HR and saO_2 did not change significantly during bridge opening.

Effect of ECMO flow rate and opening time

For most variables, there was a significant effect of the ECMO flow rate on the magnitude of the measured haemodynamic changes (table 2), indicating that the haemodynamic changes became less apparent with a decreasing ECMO flow rate. Shortening of the opening time only led to less pronounced changes in CVP, svO_2line, cHHb, cO_2Hb and CBV. For all other measured variables there was no effect of shortening the opening time.

Measurements with pump on the bridge

No significant changes were observed when we used the pump on the bridge with flow rates of 10 mL/min and 50 mL/min in combination with ECMO flow rates of 100 mL/min and 500

mL/min. No complications like clot formation or rupture of the tubing of the bridge were seen during a 2-hr use of this pump on the bridge.

DISCUSSION

Important changes of blood flow on both arterial and venous sides of the cerebral vascular system occurred during bridge opening. At the moment of opening, the arterial and venous sides of the ECMO circuit are linked, creating an arteriovenous shunt over the bridge in which blood flows from a high-pressure area (arterial side) to a low-pressure area (venous side). The net result is a flow from the aorta to the right atrium through the arterial cannula, the bridge, and the venous cannula.

As MABP decreases and CVP and SSSP increase during the bridge opening, CPP decreases. Intact cerebral autoregulation is necessary to maintain an adequate CBF. In normal circumstances, CBF is maintained over a wide range of CPP by cerebral autoregulation (19,20). However, autoregulation can be disturbed during the recovery phase after prolonged hypoxia in newborn lambs (21,22). All infants treated with ECMO have experienced profound hypoxia in the pre-ECMO period and might therefore be at risk for a disturbed cerebral autoregulation. In the absence of an adequate cerebral autoregulation, the decreased CPP could lead to ischaemic brain lesions.

The aetiology of intracranial haemorrhages and ischaemic lesions occurring during ECMO is multifactorial and includes the following: 1) secondary haemorrhage after infarction and systemic heparinization; 2) cerebral perfusion disturbances caused by either blood gas or blood pressure disturbances; or 3) cerebral circulation changes caused by ligation of the jugular vein (23-29). This study demonstrates that bridge opening results in changes in brain perfusion. The venous factor may contribute to the onset of posterior fossa haemorrhages, which occur rather frequently in ECMO treated infants (30,31).

Also, the increase of svO_2line demonstrates that oxygenated blood flows from the arterial side of the circuit to the venous side. After bridge closure, the arterial blood that was drained into the bridge and the venous limb of the ECMO circuit will pass the oxygen saturation monitor, causing a rise in svO_2line.

Statistically significant haemodynamic changes occurred in every combination of ECMO flow rate and opening time. In a clinical ECMO run, opening of the bridge occurs intermittently for the prevention of clot formation. The bridge is opened at regular intervals during the whole run

depending on local protocols. The haemodynamic changes become less pronounced as the ECMO flow rate is diminished and for some of them as the opening time is shortened. As these changes occurred in every combination of ECMO flow rate and opening time, they cannot be prevented. Therefore, bridge opening of any duration at any flow rate might be harmful. Moreover, the opening time must be long enough to fill the bridge with new blood.

The mean decrease and secondary increase in Qcar was substantial, 25% and 20% respectively. Wyath et al demonstrated that mean CBV was 2.2±0.40 (sd) mL/100 g in normal infants and 3.00±1.04 (sd) mL/100 g in infants with brain injury (32). In our study the change in CBV after bridge opening was 0.15 mL/100 g, which also is a substantial change (5-7%) compared to normal values. These changes in cerebral perfusion could be one of the factors contributing to intracranial haemorrhages.

There is one report regarding an ECMO system in which the bridge between the arterial and venous tubing is altered. Gangitano et al used two high flow 3-way stopcocks instead of a bridge (33). The stopcocks are connected to luer connectors in the arterial and venous tubing. In situations in which the patient is off ECMO, the stopcocks control direction of flow and serve as the connection between the two sides of the circuit. Snyder et al used an automatic clamping device for intermittent manual clamping that was parallel to the membrane lung to permit continuation of circulation when the lung needs to be replaced (34). This automated clamping device can also be used as a bridge, but the haemodynamic changes that we observed will still occur. A partial bridge clamp, allowing blood to pass continuously across the bridge can probably prevent these changes. However, this can have the disadvantage of turbulent blood flow resulting in haemolysis and clot formation.

In this study, when using a small pump on the bridge, a small continuous arteriovenous shunt was created to prevent intermittent unclamping of the bridge. It was demonstrated that the use of this system in the ECMO circuit prevented disturbances of the haemodynamic variables of the animals. More information is needed regarding the possibility of any deleterious effects when it is being used for longer periods of time.

CONCLUSIONS

Bridge opening during VA-ECMO results in a massive shunt of blood from the arterial side of the circuit to the venous side, causing significant changes in blood pressure and cerebral oxygenation and haemodynamics. Although the cause of cerebral complications in ECMO

patients is multifactorial, recurrent fluctuations in cerebral oxygenation and haemodynamics might be a factor that contributes to these complications. These changes can be prevented by using a small continuously running pump on the bridge.

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CHAPTER 7

DUCTUS ARTERIOSUS WITH LEFT-TO-RIGHT SHUNT DURING VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION: EFFECTS ON CEREBRAL OXYGENATION AND HAEMODYNAMICS

Ductus arteriosus with left to right shunt during veno-arterial extracorporeal membrane oxygenation: effects on cerebral oxygenation and haemodynamics

Arno van Heijst[1], Frans van der Staak[2], Jeroen Hopman[1], Ronald Tanke[1], Rob Sengers[1], Djien Liem[1]

Department of Paediatrics[1] and Paediatric Surgery[2], University Medical Centre Nijmegen, Nijmegen, The Netherlands

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ABSTRACT

Objective: To investigate the effect on cerebral oxygenation and haemodynamics of a patent ductus arteriosus with left-to-right shunt during veno-arterial extracorporeal membrane oxygenation in a lamb model.

Design: Prospective intervention study in animals.

Setting: Animal research laboratory of a university medical centre.

Subjects: Six anaesthetized newborn lambs with patent ductus arteriosus and left-to-right shunt, installed on veno-arterial extracorporeal membrane oxygenation.

Interventions: Six lambs of 140 days gestational age were prepared to keep the ductus arteriosus open by infiltration of the vessel wall with formaline 10%. The animals were installed on standard veno-arterial extracorporeal membrane oxygenation. With a mechanical occluder, the ductus was closed.

Measurements and mean results: Changes of mean arterial blood pressure and carotid artery blood flow were measured simultaneously. Using near infrared spectrophotometry, we calculated changes in cerebral concentration of oxyhaemoglobin and deoxyhaemoglobin (reflecting changes in cerebral oxygen supply) and total haemoglobin (reflecting changes in cerebral blood volume). Also, cerebral oxygen delivery before and after ductus closure as calculated. Before ductus closure there was a left-to-right shunt with a mean (? standard error of the mean) of 41 ? 20% of the total body blood flow. Closure of the ductus resulted in an immediate increase in mean arterial blood pressure and left carotid artery blood flow. The concentration of oxyhaemoglobin increased and the concentration of deoxyhaemoglobin decreased, representing an increased cerebral oxygen supply. The concentration of total haemoglobin was unchanged, representing unchanged cerebral blood volume. There was an increase in cerebral oxygen delivery.

Conclusions: In this lamb model a considerable left-to-right shunt over the ductus during veno-arterial extracorporeal membrane oxygenation reduced cerebral circulation and oxygenation.

INTRODUCTION

ECMO is a rescue therapy for newborn infants with severe respiratory failure. Most of these patients suffer from pulmonary hypertension with right-to-left shunt over the ductus arteriosus (1). Soon after initiation of VA-ECMO, blood pressure in the pulmonary artery decreases and the shunt over the ductus arteriosus reverses from right-to-left into a left-to-right shunt (2).
Earlier we studied shunt direction through the ductus arteriosus during VA-ECMO in 29 newborns. Before the initiation of VA-ECMO 82% of the patients showed either right-to-left shunt or a bidirectional shunt over the ductus, corresponding with initially existing pulmonary hypertension. After 12 hrs of ECMO treatment, 43 % of the patients showed left-to-right shunt. In total, 62% of all patients showed left-to-right shunt within the first 72 hrs of treatment. All ductus were closed spontaneously 72 hrs after the initiation of VA-ECMO (3,4). It is well known that a patent ductus arteriosus with left-to-right shunt in preterm infants can compromise cerebral circulation, with a decrease in blood flow velocity in cerebral arteries and an increase in pulsatility index as measured by echo-Doppler (5-9). The occurrence of both ischaemic and haemorrhagic cerebral lesions is a major complication of ECMO treatment. To our knowledge, the influence of the patent ductus arteriosus on cerebral circulation during VA-ECMO has not been studied before.
The aim of this study was to investigate the effect of a patent ductus arteriosus with left-to-right shunt during VA-ECMO on cerebral oxygenation and haemodynamics in an animal model. We used an existing lamb model in which, after birth, the ductus was kept open artificially (10). When the animal is placed on VA-ECMO there will be a left-to-right shunt over the ductus because the lamb has normal lungs with low pulmonary vascular resistance. The ductus can be closed mechanically. From the changes in cerebral perfusion and oxygenation that occur after ductus closure, one can get information about the effects of the left-to-right shunt itself. With this model we tried to mimic that part of the ECMO treatment in which, after a decrease in pulmonary vascular pressure, a left to right shunt occurs, before the ductus closes.
The lamb model is a frequently used model in ECMO research and also for studies on CBF and oxygenation (11).

MATERIAL AND METHODS

Subjects

This study was performed in 6 newborn lambs. Mean bodyweight of the lambs was 4.3 kg (range 3.1-5.1 kg). The Ethical Committee on Animal Research of the University of Nijmegen approved surgical and experimental procedures. The care and handling of the animals were in accordance with National Institutes of Health guidelines. Six pregnant mixed breed ewes obtained from local farmers were operated at 140 days of gestation (term 147 days). Anaesthesia was induced with pentobarbital 30 mg/kg intravenously and maintained with 2% enflurane and a 1:1 mixture of nitrous oxide and oxygen administered by mechanical ventilation (Engstrom ER 300 Respirator, LKB Medical AB, Bromma, Sweden). HR was monitored (Hewlett Packard 78330A Monitor, Hewlett Packard, Boeblingen, Germany) by using needle electrodes placed on the chest. After shaving and disinfecting the abdominal skin, we performed a paramedian laparotomy. After hysterotomy, the upper part of the lamb was partially delivered. A thoracotomy through the left fourth intercostal space of the lamb was performed and the left lung retracted to expose the aorta, pulmonary artery, and ductus arteriosus. These vessels were dissected from their surrounding tissue. The ductus wall was infiltrated with formaline 10% to destroy the muscular layer, preventing contraction of the muscular layer and closure of the ductus. The formaline was coloured with methylene blue, which offered the possibility to check the extension of the infiltration of the total length of the ductus wall (10). A silicon vessel loop (Surg-I-Loop; Scanlon, St. Paul, MN, USA) was positioned around the ductus without narrowing its lumen. The ends of the vessel loop were put through a sheet and fixed with a clamp, so that the ductus arteriosus could easily be closed from outside the thorax by pulling the vessel loops out of the sheath.

Flow probes (Transonic cardiac output A probes; Transonic Systems Inc, Ithaca, NY, USA) were attached around the ascending aorta and the common pulmonary artery, both just above the arterial valves, to measure blood flow in the aorta (Qao) and common pulmonary artery (Qpa), respectively. Both the leads of the probes and the sheath containing the vessel loop around the ductus were exteriorized from the thorax. The leads of the flow probes were connected to a flow meter (Transonic Medical Flowmeter HT 207; Transonic Systems Inc, Ithaca, NY, USA). The thorax was closed. After endotracheal intubation of the lamb, mechanical ventilation was started (Babylog 8000, Dräger, Lübeck, Germany) to maintain

normal arterial blood gas values: pH 7.40-7.45, paO_2 70-90 mm Hg [9.3-12 kPa], $paCO_2$ 30-40 mm Hg [4-5.3 kPa].

Catheters were inserted through the femoral artery and vein with the tips in the abdominal aorta for blood sampling and monitoring of the MABP, (HP 78206C, Hewlett Packard, Boeblingen, Germany), and in the inferior vena cava for administration of medication. Anaesthesia of the lamb was induced using midazolam (0,2 mg/kg), fentanyl (10µg/kg) and pancuronium (0.1 mg/kg) and maintained with midazolam (0.2 mg/kg.hr), fentanyl (2-5 µg/kg.hr) and pancuronium (0.02 mg/kg.hr). Then the umbilical cord was ligated and the lamb was put on a table.

An electromagnetic flow meter (Scalar MDL 1401; Scalar Medical, Delft, The Netherlands) was installed around the left common carotid artery to measure Qcar. Changes in Qcar reflect changes in CBF (12).

The RCCA was cannulated with an arterial catheter (Biomedicus 10 Fr) and the RIJV with a venous catheter (Biomedicus 12 Fr; Medtronic, Grand Rapids, MI, USA). The tip of the arterial catheter was positioned in the brachiocephalic trunk and that of the venous catheter in the right atrium. During the cannulation procedure, a loading dose of heparin was administered (150 IU/kg) and continued intravenously (100-200 IU/kg.hr) to maintain activated clotting time between 200 and 250 secs (Hemochron, Edison, NJ, USA). The ECMO catheters were connected to a standard VA-ECMO system that was primed with full fresh sheep blood prior to cannulation. The ECMO circuit itself consisted of a custom packed 1/4 inch flexible polyvinylchloride tubing (Baxter, Uden, The Netherlands) with a silicone reservoir, the "bladderbox" (Seabrook Medical System, Værløse, Denmark), a 0.6 m^2 membrane oxygenator (Scimed Life Systems, Minneapolis, MN, USA), a heat exchanger (Cincinnati Sub Zero, Cincinatti, Ohio, USA) and a rollerpump (Polystan A/S, Denmark). ECMO flow (Qecmo) was measured by a flow probe around the tubing system (Transonic Medical Volume Flowmeter HT 107, Transonic Systems Inc, Ithaca, NY, USA). The HR was monitored (Hewlett Packard 78330A Monitor, Hewlett Packard, Boeblingen, Germany) by using needle electrodes on the chest. Rectal temperature was kept between 38.5 and 39.5°C with a servo controlled heating mattress.

Cerebral oxygenation and haemodynamics were studied by NIRS. The NIRS equipment used was developed by the Department of Biomedical Engineering and Medical Physics, University of Keele (UK), and produced by Radiometer (Copenhagen, Denmark) (13). The technique is based on continuous spectrophotometric measurement of oxygenation-dependent changes in the absorption properties of haemoglobin in the near infrared region (14). Details

of our NIRS measurement procedure have been extensively described before (15-17). ?cO_2Hb and ?cHHb were calculated from the changes in the absorption of near infrared light at wavelengths 904, 845 and 775 nm. The concentration changes are expressed in µmol/100 g of brain. ?cO_2Hb and ?cHHb reflect changes in cerebral oxygen supply (13). ?ctHb was calculated as the sum of ?cO_2Hb and ?cHHb, and reflects changes in CBV.

Oxygen delivery to the brain was calculated 5 min before ductus closure and 15 min thereafter. Oxygen delivery is equal to Qcar x oxygen content, where Qcar is used as actual brain blood flow. Oxygen content is calculated as: (grams Hb/dl x 1.36 mL O_2/g Hb x % oxygen saturation) + (0.0031 x paO_2). From the changes in Qcar and oxygen content, changes in oxygen delivery can be calculated and compared with changes in NIRS variables.

Also, changes in pH, paO_2 and paCO_2 could be investigated from the arterial blood gas analysis. Furthermore, cHb was determined 5 mins before and 15 mins after ductus closure.

Experimental procedure

After ECMO started, the flow rate was increased gradually until further increment was impossible because of insufficient venous return. Ventilator settings were adjusted to maintain normal arterial blood gas values: pH 7.40-7.45, paO_2 70-90 mm Hg [9.3-12 kPa], and paCO_2 30-40 mm Hg [4-5.3 kPa]. Ventilator settings were comparable with so called rest-settings used in our clinic during VA-ECMO: ventilator frequency 15/min, inspiratory pressure 24 mbar, positive end-expiratory pressure 4 mbar, and FiO_2 0.30-0.40. These settings were not changed during the experimental procedure.

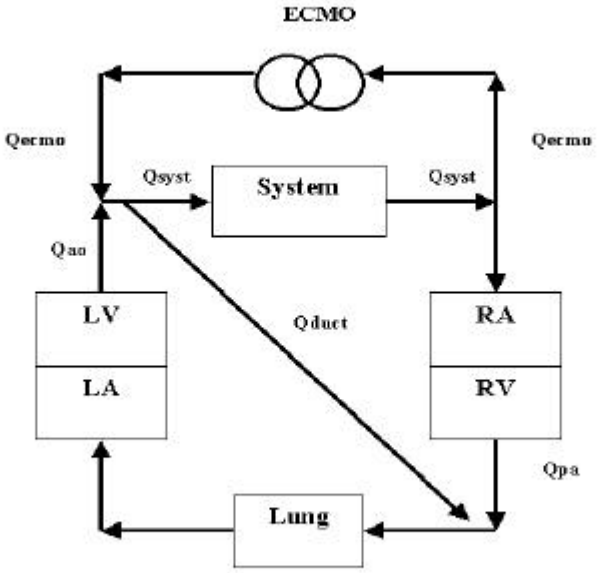
After stabilization, ECMO was continued for two hours during which blood flows were measured from the ECMO circuit, the pulmonary artery and the ascending aorta. Then the vessel loop was attached by using the mechanism described before. This caused an abrupt closure of the ductus. Measurements were continued for 15 minutes after closure of the ductus. At the end of the experiment, all lambs and mother animals were killed with an overdose of pentobarbital. Autopsy of the lambs was performed to exclude congenital heart disease with intracardial shunts and to confirm total closure of the ductus after tightening of the vessel loops. All measured variables were recorded in a data acquisition system (Poly®; Inspector Research System, Amsterdam, The Netherlands) at a sampling frequency of 1 Hz.

Flow measurement and determination of ductus shunt flow

When there is no ductus blood flow (Qduct), Qao is equal to Qpa (figure 1). In this case, total systemic blood flow (Qsyst) can be defined as the sum of ECMO flow (Qecmo) and Qpa (Qsyst = Qecmo + Qpa). In case of ductus flow with left to right shunt, Qao is greater than Qpa and Qduct = Qao-Qpa.

In this experiment, Qpa, Qao and Qecmo were measured so that Qduct could be calculated, and related to Qsyst. In this calculation, coronary perfusion and possible atrial shunting are left out of consideration.

Figure 1. Schematic drawing of the flow in the great vessels and ductus arteriosus during extracorporeal membrane oxygenation



ECMO = extracorporeal membrane oxygenation, Qsyst = systemic blood flow, Qduct = ductus blood flow, Qao = blood flow in the aorta, Qecmo = ECMO flow, Qpa = blood flow in the common pulmonary artery, RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle.

Data analysis

The baseline level of all variables was obtained by calculating their mean values during a 30-sec period before closure of the ductus (t = 0 secs). These values were compared with mean values obtained on a 5 s period at 15, 30, 45, 60, and 90 secs, and 2, 5, 10 and 15 mins after ductus closure.

Results are reported as mean ± standard error of the mean (SEM). Changes in Qcar were expressed as percentage ± SEM compared with baseline level. For each variable, changes as a function of time were determined by analysis of variance with Student-Newman-Keuls post-test for multiple comparisons when a significant difference was found. To compare oxygen delivery to the brain, pH, paO_2 and $paCO_2$ in arterial blood gas and cHb before and after ductus closure, we performed a paired non-parametric test (Wilcoxon signed rank test). We considered p ? 0.05 to be statistically significant.

RESULTS

Infiltrating the ductus wall with formaline could create a substantial left-to-right shunt over the ductus arteriosus during VA-ECMO. Qecmo was 389±27 mL/min and Qpa was 473±162 mL/min. The mean left-to-right shunt was 354±118 mL/min, which was 41±20% of Qsyst.

After closure of the ductus there was a significant increase in MABP and Qcar. This was accompanied by a significant increase in cO_2Hb and a significant decrease in cHHb; ctHb did not show any significant changes (figure 2)

All significant changes occurred already at 15 secs after ductus closure and persisted until 15 mins thereafter. There were no significant changes in HR. Data beyond 15 mins could not be presented because in some animals other necessary interventions had to be done like endotracheal suctioning, volume suppletion because of bladder box alarm, and blood transfusion. Then, the observed changes in variables were not necessarily the consequence of ductus closure.

In those animals in which undisturbed observations could be done, the observed changes in Qcar, MABP and NIRS variables persisted for over 30 mins.

Oxygen delivery to the brain increased from 9.4 ? 1.1 mL of oxygen/min before ductus closure to 11.8 ? 1.3 mL of oxygen/min after ductus closure ($p<0.05$).

Figure 2. The effect of ductus closure during veno-arterial extracorporeal membrane oxygenation

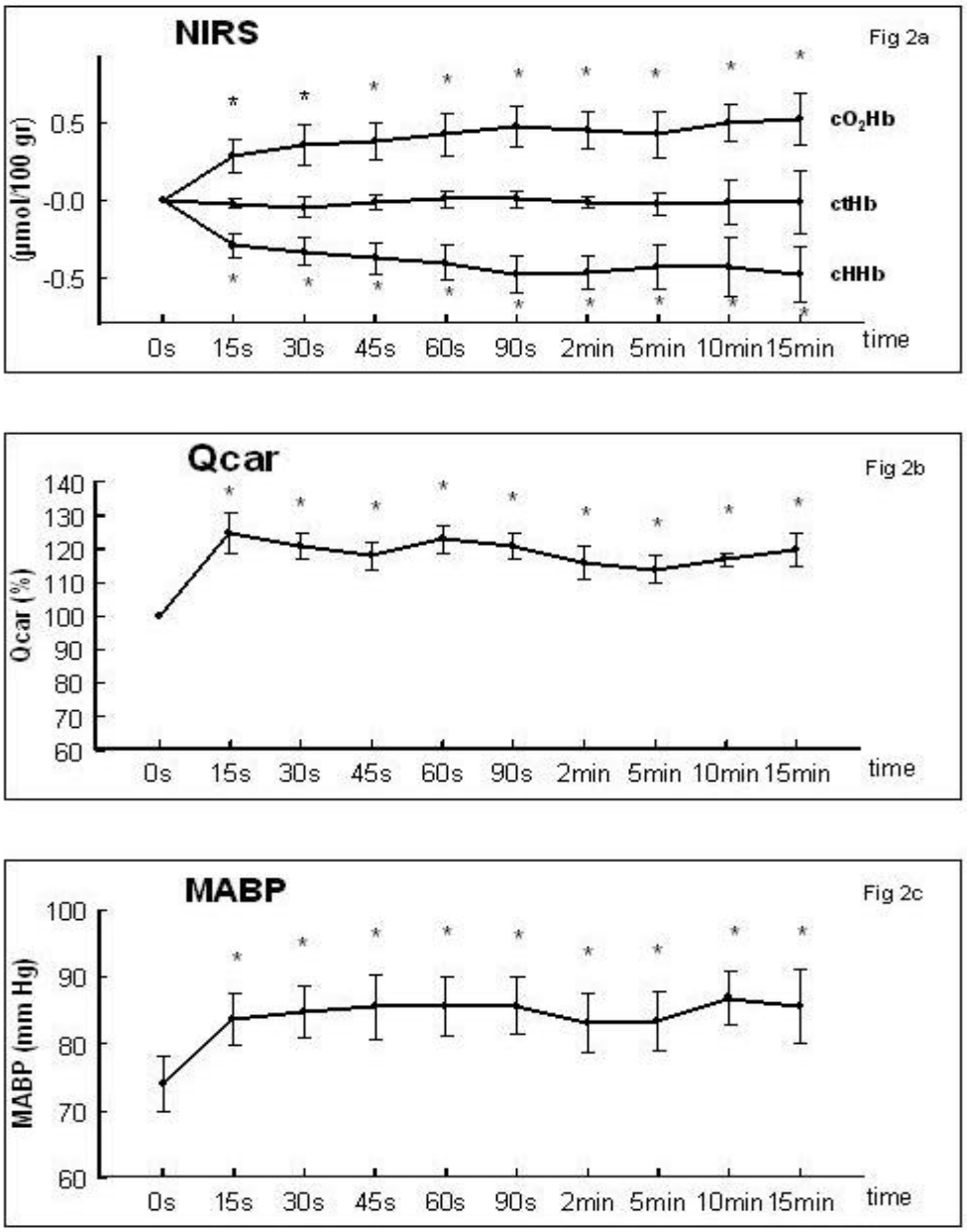


Figure 2a, effect on NIRS variables; Figure 2b, effect on mean left carotid artery blood flow (Qcar); and Figure 2c, effect on mean arterial blood pressure (MABP). NIRS = variables of near infrared spectrophotometry, cO_2Hb = concentration of oxyhaemoglobin, ctHb = concentration of total haemoglobin, cHHb = concentration of deoxyhaemoglobin, Qcar = mean left carotid artery blood flow, MABP = mean arterial blood pressure, 0 s = value before ductus closure, t:15 s to 15 min = values after ductus closure. Values are mean ± SEM. *$p < 0.05$ compared with $t = 0$.

Blood gas analysis before and after ductus closure revealed no significant differences for pH, $paCO_2$ and paO_2. Also, cHb did not change (table 1). Ventilator settings were unchanged during the study period.

Autopsy of the lambs confirmed total closure of the ductus in all lambs and excluded congenital heart disease with intracardial shunts.

Table 1. Mean values (? SEM) of pH, $paCO_2$, paO_2, haemoglobin concentration (cHb), and cerebral oxygen delivery before and after ductus closure

	5 Mins before ductus closure	15 Mins after ductus closure
pH	7.42 ? 0.04	7.39 ? 0.04
$paCO_2$ (Torr)	39.5 ? 0.5	38.9 ? 0.5
paO_2 (Torr)	125 ? 16	122 ? 16
cHb (mmol/l)	5.6 ? 0.2	5.7 ? 0.2
Cerebral oxygen delivery (mL O_2/min)	9.4 ? 1.1	11.8 ? 1.3*

* $p < 0.05$

DISCUSSION

This study aimed to investigate the effect of a patent ductus arteriosus with left-to-right shunt during VA-ECMO on cerebral oxygenation and haemodynamics in a lamb model. It has been demonstrated that during VA-ECMO when the ductus arteriosus is patent, a considerable left-to-right shunt over the ductus can be present. Usually the ductus is closed spontaneously at 48 hrs after birth in 80-90% of all healthy full term newborns. In the remaining group, the ductus normally closes within the next 48 hrs. This means that in humans, beyond the fourth day of life practically every ductus is closed (18,19). In newborns treated with VA-ECMO for severe respiratory insufficiency and pulmonary hypertension, a period with left-to-right shunt over the ductus can be expected when the pulmonary arterial pressure decreases (2-4). A patent ductus with left-to-right shunt during ECMO has been reported in the literature. Becker et al described one newborn out of 500 treated with ECMO where ductus ligation had to be performed (20). However, they stated that many infants were treated empirically for a patent ductus arteriosus with fluid restriction and furosemide. Burch et al demonstrated a left-to-right shunt at the ductus level in nine of 12 infants. In two of them, ductus ligation was necessary to facilitate weaning from ECMO (21). Bartlett et al described that in 11 of their first 45 and 16

of their first 100 patients, ductus ligation was necessary while on ECMO (2,22). Martin and Short demonstrated an increase in left-to-right shunt during ECMO (1). Earlier we demonstrated a left-to-right shunt over the ductus in up to 62% of the newborns treated with VA-ECMO. This shunt was often already present in the first 24 hrs after initiation of ECMO (3). The fact that this left-to-right shunt can be important is supported by our observation that patients with a left-to-right shunt during VA-ECMO had a significant longer ECMO run time than patients without this shunt (4). This possibly reflects increased lung flow during left-to-right shunt over the ductus. Also, Burch et al demonstrated that there was a smaller decrease in left ventricular size than expected during VA-ECMO, suggesting that this is related to increased left ventricular preload from left-to-right shunt (21).

In newborns, a patent ductus arteriosus with large left-to-right shunt compromises the cerebral circulation. There is a diastolic runoff of blood through the patent ductus resulting in a decrease in CBFV and an increase of pulsatility index (5-8). In patients with a large ductus left-to-right shunt, diastolic CBF can be reduced, absent or backward (9). On the other hand, both spontaneous ductus closure and ligation of the patent ductus are associated with an increase in MABP, a significant decrease in pulsatility index, an increase in diastolic and mean blood flow velocities in cerebral vessels, and an increase in CBV, also demonstrating the compromised cerebral circulation as long as a ductus with left-to-right shunt exists. (7,23-27).

This study in lambs demonstrated that ligation of the ductus during VA-ECMO had similar effects on MABP, cerebral haemodynamics and oxygenation with an increase in Qcar, cO_2Hb and cerebral oxygen delivery. The increase in Qcar, cO_2Hb and cerebral oxygen delivery after closure of the ductus does not necessarily mean that the cerebral circulation is compromised as long as the ductus is open. Cerebral perfusion could be adequate at that moment but increase further after closure of the ductus. Although the techniques of NIRS, Qcar measurement, and oxygen delivery calculations that we used cannot prove compromised cerebral circulation when a ductus with left-to-right shunt is present, the high percentage of ductus flow in relation to systemic flow makes it very likely that a stealing effect on the cerebral circulation, as described in preterm infants is present. Further clinical studies during VA-ECMO in newborns should be done to answer this question. We speculate that if the cerebral circulation is compromised by a ductus left-to-right shunt, this can contribute to the occurrence of cerebral lesions, a major complication of ECMO (28).

The question arises how far this model with a lamb with healthy lungs applies to clinical practice. As mentioned earlier, this model mimics part of the clinical ECMO course in which

pulmonary hypertension diminishes after starting ECMO and a ductus right-to-left shunt can reverse into left-to-right shunt. The shunt direction depends on pulmonary vascular pressure. Although in a lamb model with healthy lungs this might be different from the situation in newborns with lung disease, the occurrence of a ductus left-to-right shunt during clinical VA-ECMO is demonstrated, thereby confirming that also in these newborns, pulmonary vascular pressure can decrease (3). Further clinical studies are necessary to determine shunt size in relation to systemic perfusion during VA-ECMO treatment in newborns, to see if our findings can be confirmed.

It is difficult to give an idea about the physiologic importance of the observed changes in Qcar, MABP, cO_2Hb, and oxygen delivery, since with the variables studied one cannot draw conclusions about oxygen metabolism in the brain, rather only about oxygen delivery to the brain. But we think that the observed changes indicate that there is a risk factor for compromised cerebral oxygenation as long as there is a left-to-right shunt through the ductus.

Over the last years there has been increasing use of VV-ECMO in newborns. However, left-to-right shunt during VV-ECMO will have the same effects on systemic circulation as observed during VA-ECMO (29). Theoretically, the left-to-right shunt can be less important during VV-ECMO since the pulmonary circulation is not empty, causing an intrinsic pulmonary arterial pressure. Also, during VV-ECMO, the patient is ventilated with higher pressures, which can be transmitted to the pulmonary circulation. Both these factors can contribute to higher pulmonary artery pressures and thus smaller left-to-right shunt than during VA-ECMO.

In our animal model, the increase in Qcar was not accompanied by an increase in CBV, as represented by ctHb. This can be explained by an increased cerebral venous outflow, which is as much as the increased arterial inflow. The increased cerebral venous outflow may be the result of decreased pressure in the right atrium and right ventricle due to diminished afterload of the right ventricle when left-to-right shunting through the ductus to pulmonary artery has been stopped after ductus ligation.

Some other factors could also influence cerebral haemodynamics and oxygenation. Blood gas analysis revealed no changes in $paCO_2$, pH and paO_2, thereby excluding these factors as a cause of the observed changes after ductus closure. A decrease in cHb, leading to a decrease in arterial oxygen content, could cause a compensatory increase in CBF. However, there were no changes in cHb after closure of the ductus.

The anaesthetic medication used in this study is comparable with the medication used in our clinic during clinical ECMO treatment. This medication might also affect the cerebral

circulation. Yaster et al however demonstrated that fentanyl in newborn lambs did not influence CBF (30). In infants, the combination of fentanyl and midazolam caused only a slight decrease in CBFV (31). The effects of midazolam in newborn sheep are unknown. We believe that the use of these drugs in this study did not influence the results. Also, there was a stable situation during the measurement period.

The point of discussion is whether the ductus should be closed at the time that a left-to-right shunt exists and by what means. The most frequently used method for ductus closure in preterm infants is by indomethacin. Indomethacin itself causes an acute significant reduction of CBF and CBV (15,32-36). This effect can be counteracted by the increased cerebral perfusion after closure of the ductus, but this may take considerably more time, leaving a time window of diminished CBF. Indomethacin administration is therefore not an attractive therapeutic intervention for ductus closure in ECMO patients.

Indomethacin also causes a diminished reactivity to carbon dioxide, preventing the cerebral vascular bed from responding to changes in pCO_2 (36,37). Furthermore, indomethacin causes altered platelet function potentially increasing the haemorrhagic complications of ECMO treatment (38,39). Ibuprofen is known not to have the side effects of indomethacin and could therefore be an alternative when ductus closure has to be performed (40). Although in this animal study ductus ligation has been shown to increase MABP and cerebral oxygen delivery, ligation is not very attractive to be done in a heparinized ECMO patient.

We think that the results of this study have to be confirmed in newborns treated with VA-ECMO. Especially the relation between patency of the ductus arteriosus with left-to-right shunt and CBF should be investigated. Based on our earlier study in which we demonstrated ductus closure 72 hours after the start of ECMO treatment, we recommend that during VA-ECMO treatment in newborns, the patency of the ductus should be investigated by Doppler-echocardiography 72 hours after the initiation of ECMO (3,4). When a patent ductus with left-to-right shunting is present and weaning from ECMO is still impossible, therapy with ibuprofen should be considered. Before the time point of 72 hrs, there is sufficient reason to avoid a large patent ductus arteriosus with left-to-right shunt during VA-ECMO, considering the potential effects on the brain.

CONCLUSION

This study in newborn lambs demonstrated that closure of a patent ductus with left-to-right shunt during VA-ECMO is associated with a significant increase in MABP, CBF, and cerebral oxygen delivery, suggesting a compromised cerebral circulation as long as the ductus is open and left-to-right shunt is present. It has important clinical implications: left-to-right shunting over a patent ductus during VA-ECMO could be one of the contributing factors for cerebral complications during VA-ECMO.

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PART 3

VENO-VENOUS EXTRACORPOREAL MEMBRANE OXYGENATION

CHAPTER 8

INTRODUCTION TO VENO-VENOUS ECMO

INTRODUCTION TO VENO-VENOUS ECMO

In ECMO, blood is diverted from a major systemic vessel, pumped through a gas exchange device and returned to the body via a major blood vessel. Two distinct ECMO methods can be distinguished: VA-ECMO in which the drainage site is a vein and the return vessel is an artery, and VV-ECMO in which the drainage and reinfusion vessels are both veins. VV-ECMO has the primary advantage that it avoids cannulation and ligation of a major artery, e.g. the RCCA. Concern about the short and long-term effects of VA-ECMO on the brain resulted in the development of VV-ECMO (1).

In newborns, a double lumen catheter is predominantly used for VV-ECMO: double lumen catheter veno-venous extracorporeal membrane oxygenation (DLVV-ECMO). In this technique a catheter with two lumina is inserted into the right atrium, via the RIJV. Blood is drained through one port of the double lumen catheter, oxygenated in the membrane oxygenator and reinfused into the right atrium through the other port.

Important differences between the VA-ECMO and VV-ECMO techniques are summarized in table 1.

VA-ECMO has significant disadvantages: cannulation and ligation of a major artery, risk of emboli infusion into the systemic circulation, decrease in pulmonary blood flow, compromised cardiac output due to increased afterload and perfusion of the coronary arteries with relatively hypoxaemic blood delivered from the right ventricle (11).

Major disadvantages of VV-ECMO are the lack of direct circulatory support and the limited oxygenation.

In VA-ECMO heart and lung function are partially replaced by artificial organs, i.e. the membrane oxygenator and the roller pump. Oxygenated blood that has passed through the lungs mixes with blood from the left ventricle in the aorta. The oxygen content in the arterial blood of the patient is determined by the amount of oxygen delivered by the ECMO circuit plus the amount in the blood after passing through the heart and lungs; it can be augmented by increasing the ECMO flow rate. Usual saO_2 values are over 95%. Total systemic blood flow is the sum of the ECMO flow and the flow through the patient's heart and lungs.

In VV-ECMO, blood is oxygenated in the ECMO circuit and is returned to the venous circulation (right atrium) where it mixes with venous blood from the different organ systems. Thus, the oxygen content in the right atrium is raised and the carbon dioxide content is lowered. Oxygen content of the arterial blood of the patient is determined by the oxygen content in the right ventricular blood, plus possible augmentation after passage through the

lungs when lung function improves. Total systemic blood flow is determined by the patient's cardiac output, not by the ECMO flow. The paO_2 and saO_2 are equal to the values in mixed venous blood, in the absence of lung function. Owing to the principle of VV-ECMO, saO_2 is not likely to be above 90% and will usually be less, e.g. 80-85%. Thus, oxygenation is limited, because deoxygenated and oxygenated blood mix.

Table 1. Comparison between veno-venous and veno-arterial extracorporeal membrane oxygenation (2-10)

	VA-ECMO	DLVV-ECMO
Cannulation	Internal jugular vein + Right common carotid artery	Internal jugular vein
Circulation	Direct circulatory support	No direct circulatory support
	Decreased RV preload, pulmonary blood flow, LV output, increased LV afterload	No changes in RV preload, pulmonary blood flow, LV output, and LV afterload
	Decreased pulsatility	Normal pulsatility
	Coronary perfusion with hypoxaemic blood from LV	Coronary perfusion with oxygen enriched blood from LV
Oxygen saturation	Depends on extracorporeal flow, usually >95%	80-90% common at maximal flow
Variables for determination of oxygenation	"Mixed venous oxygen saturation"	Cerebral venous oxygen saturation
	Arterial blood gas analysis	Arterial blood gas analysis
	Calculated oxygen consumption	Pre-membrane oxygenation trend
Emboli from ECMO system	Into systemic circulation (brain)	Into pulmonary circulation

RV=right ventricle, LV=left ventricle

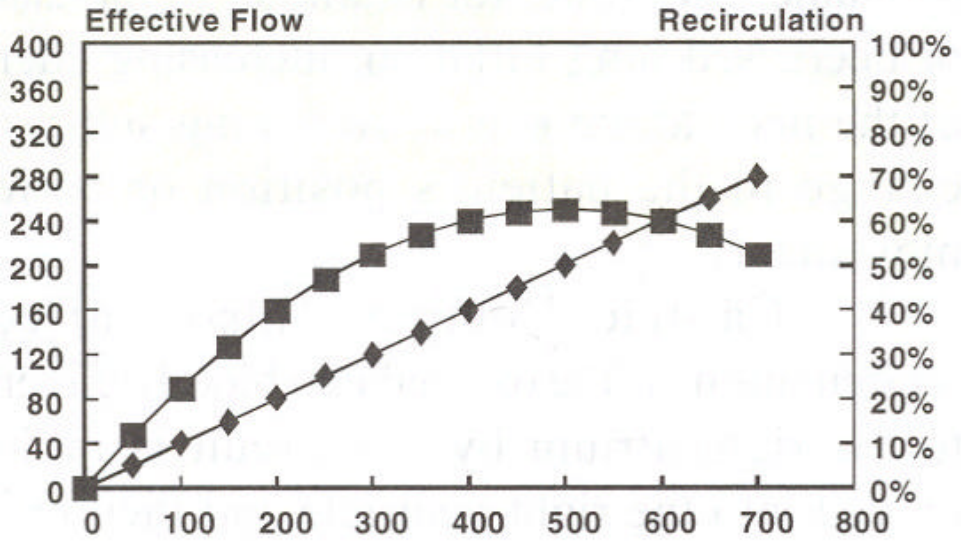
Another factor that limits the patient's oxygenation during VV-ECMO is recirculation: a fraction of the reinfused oxygenated blood drains back into the ECMO system and cannot contribute to the patient's oxygenation. The recirculation fraction is defined as the portion of oxygenated blood from the circuit that flows directly from the reinfusion lumen into the drainage lumen of the catheter and returns to the circuit, instead of entering the patient's circulation (9).

Several factors influence the recirculation fraction (9). First, the recirculation fraction increases with increasing ECMO flow. The relation between the recirculation fraction and ECMO flow is linear in the range of ECMO flows used clinically (12,13). This means that when the ECMO flow is increased, there is an initial increase in oxygen delivery to the patient, but any further increase in ECMO flow beyond the optimal flow rate causes a decrease in oxygen delivery due to increased recirculation.

The effective ECMO flow = Total flow – (Total flow∗recirculation fraction).

Figure 1 illustrates the concept of the recirculation fraction and effective flow.

Figure 1. The effect of recirculation (?) on effective pump flow (¦)



X axis: ECMO flow (mL/min), Y axis left side: effective flow (mL/min), Y-axis right side: recirculation fraction (%). Recirculation increases with increasing ECMO flow. When the total flow is zero, the effective flow is zero. At a given maximal flow, the recirculation fraction is 100%, which means that the effective flow becomes zero again. The optimal flow lies between these two flow rates (9).

The catheter position also determines the recirculation fraction and can change during the ECMO run, because of altered lung inflation or patient movements. Another factor that influences the recirculation fraction is cardiac output. If cardiac output is high, oxygenated blood reinfused into the right atrium will move rapidly towards the right ventricle and make it less likely to be drained back into the ECMO circuit again.

The right atrial volume also influences recirculation. With a larger right atrium, there is less chance that oxygenated blood will be recirculated and more opportunity for mixing with venous blood.

Inadequate oxygenation in a patient on VV-ECMO may be caused by a high amount of recirculation. It is then important to be informed about the recirculation fraction, also enable evaluation of the effects of interventions to decrease it.

It is difficult to determine the recirculation fraction during VV-ECMO. In chapter 9 a method is devised to quantify recirculation during VV-ECMO with an easily applicable bedside method.

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CHAPTER 9

RECIRCULATION IN DOUBLE LUMEN CATHETER VENO-VENOUS EXTRACORPOREAL MEMBRANE OXYGENATION MEASURED BY ULTRASOUND DILUTION TECHNIQUE

Recirculation in double lumen catheter veno-venous extracorporeal membrane oxygenation measured by ultrasound dilution technique

Arno van Heijst[1], Frans van der Staak[2], Anton de Haan[3], Djien Liem[1], Cees Festen[2], Wil Geven[4], Margot van de Bor[1]

Department of Paediatrics[1], Department of Paediatric Surgery[2], Department of Medical Statistics[3], University Medical Centre Nijmegen, Nijmegen, The Netherlands, Department of Paediatrics[4], University Hospital Groningen, Groningen, The Netherlands

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ABSTRACT

Recirculation is a limiting factor for oxygen delivery in double lumen catheter veno-venous extracorporeal membrane oxygenation.

This study compares three different methods for the determination of the recirculation fraction during double lumen catheter veno-venous extracorporeal membrane oxygenation at flow rates of 150, 125, 100, 75 and 50 mL/kg.min in 9 lambs: 1) an ultrasound dilution method, in which the change in ultrasound velocity in blood after injection of a saline bolus as a marker is used for determination of recirculation; 2) the 'mixed venous oxygen method' using real mixed venous blood oxygen saturation, the best standard, for determination of recirculation fraction; and 3) the 'central venous line method', in which the oxygen saturation of a blood sample of the inferior vena cava is considered to represent mixed venous oxygen saturation.

In all methods, the recirculation fraction increased with increasing flow rate. The correlation coefficient between the ultrasound dilution method and the 'mixed venous oxygen method' was 0.68 ($p<0.01$); the mean difference between these two methods was –2.4 % ($p=0.6$). The correlation coefficient between the ultrasound dilution method and the 'central venous line method' was 0.48 ($p<0.01$); the mean difference between these two methods was –18.1 % ($p<0.01$). The correlation coefficient between the 'mixed venous oxygen method' and the 'central venous line method' was 0.51 ($p<0.01$); the mean difference between these two methods was –15.7 % ($p<0.01$). The ultrasound dilution method is a useful method for the measurement of the recirculation fraction in double lumen catheter veno-venous extracorporeal membrane oxygenation and is easier to use than the other methods.

INTRODUCTION

In 1976, Bartlett and colleagues performed the first successful ECMO treatment in a newborn (1). Since then, more than 15,000 newborns have been treated with ECMO, with an overall survival rate of 80% (2).

Initially the VA-ECMO procedure was used, in which blood is drained from the right atrium and, after oxygenation, is returned to the aorta through a cannula inserted into the RCCA. Ligation of this artery caused concern regarding the short- and long-term sequelae on the brain.

To avoid the need for ligation of the RCCA, the VV-ECMO procedure was developed, and 2,500 newborns have been treated in this fashion. In the most commonly used technique, a double lumen catheter is introduced into the right atrium through the RIJV. The catheter has two lumina, one for drainage of blood from the patient (venous limb) and one for returning oxygenated blood into the patient (arterial limb) (3). Although the cannulas are designed to minimize recirculation, this inevitably occurs in the DLVV-ECMO procedure and is a factor that limits oxygen delivery to the patient. Recirculation is the phenomenon in which a fraction of the oxygenated blood that has just been infused into the patient through the arterial limb of the catheter, is immediately drained into the venous limb, thus not contributing to oxygenation of the patient. The recirculation fraction can be calculated from the following formula (3):

$$\text{Recirculation fraction} = \frac{\text{Oxygen saturation of the pre-oxygenator blood - Mixed venous oxygen saturation}}{\text{Oxygen saturation of the post-oxygenator blood -Mixed venous oxygen saturation}}$$

In clinical practice, the pre- and post-oxygenator oxygen saturation can be measured easily, but mixed venous oxygen saturation (svO_2) cannot be measured directly, since there is no possibility of taking blood samples from the pulmonary artery. Although svO_2 is considered to be represented by the saturation of the blood that is drained from the right atrium, during the DLVV-ECMO procedure, it is influenced by recirculation and, thus, not reliable.

There are two methods for obtaining information about the svO_2 during DLVV-ECMO (4). In the first, the oxygen flow to the membrane is stopped; therefore, extracorporeal oxygen transfer to the blood is blocked. With ventilator support, the same oxygen saturation in arterial

blood is then achieved. The oxygen saturation of the blood that is drained from the patient is then considered to represent svO_2 (svO_2 method). This method is considered to be the best standard for the determination of recirculation fraction. In the second method, the oxygen saturation of blood taken from a major vein, not influenced by recirculation (for example the inferior caval vein), is considered to represent the svO_2 (CVL method).

In haemodialysis, recirculation can also occur and limit the dialysis capacity. Different methods have been described to determine the recirculation fraction in haemodialysis: the blood urea nitrogen method, the chemo-illuminescence method, and different dilution methods based on changes in electrical impedance or optical and thermal changes (5-9). In 1995, Depner et al and Krivitski described an ultrasound dilution method for measuring recirculation in haemodialysis (10,11). This method is based on the detection of dilution of the blood with saline. Saline, injected in the arterial limb of the circuit, causes a change in the ultrasound velocity of blood and in case of recirculation, is detected again in the venous limb. The fraction of the arterially injected indicator that returns in the venous limb represents recirculation.

The aim of this study was to compare different methods of assessing recirculation in DLVV-ECMO, the SvO_2 method, CVL method, and the ultrasound dilution method, at different ECMO flows.

METHODS

Preparation

The study was performed in 9 lambs (weight, 4.3–6.5 kg), obtained from local farmers. The study was approved by the Ethical Committee on Animal Research of the University of Nijmegen. General anaesthesia was induced by intravenous administration of midazolam (0.2 mg/kg) and fentanyl (10 µg/kg), and muscle relaxation was obtained with pancuronium (0.05 mg/kg). After endotracheal intubation, assisted ventilation was started with a Babylog 8000 (Dräger, Lübeck, Germany) to maintain normal arterial blood gas values (pH 7.40-7.45; paO_2 70–90 mm Hg [9.3-12 kPa]; $paCO_2$ 30–40 mm Hg [4.0–5.3 kPa]). During assisted ventilation, anaesthesia was maintained using continuous intravenous infusion of midazolam (0.1–0.2 mg/kg.hr), fentanyl (5–10 µg/kg.hr) and pancuronium (0.02 mg/kg.hr). The heart rate was monitored by means of electrodes placed on the chest. The temperature was measured with a

rectal probe and maintained between 38.5 and 39.5 ?C. Through the right femoral vein, a 7.5 Fr catheter was placed in the inferior caval vein for collection of blood samples to determine the oxygen saturation according to the CVL method. The position of this catheter was controlled by X-ray. The ECMO circuit was primed with full fresh sheep blood prior to cannulation. The RIJV was cannulated with a 15 French double lumen venous catheter (Jostra, Hirrlingen, Germany), with the tip of the catheter positioned in the right atrium. The position was controlled by X-ray. Thereafter, the animal was placed on DLVV-ECMO. During the cannulation procedure, a loading dose of heparin was administered (150 IU/kg) and continued intravenously (100–200 IU/kg.hr) to maintain activated clotting time between 200 and 250 seconds (Hemochrom, Edison, NJ, USA).

The ECMO circuit itself consisted of a custom packed ¼ inch flexible polyvinylcloride tubing (Baxter, Uden, The Netherlands), with a silicone reservoir, the "bladderbox" (Seabrook Medical Systems, Værløse, Denmark), a 0.6 m^2 membrane oxygenator (Scimed Life Systems, Minneapolis, MN, USA), a heat exchanger (Cincinnati Sub Zero, Cincinnati, OH, USA), and a roller pump (Jostra HL20, Jostra, Hirrlingen, Germany). Two stopcocks were inserted in the ECMO circuit to draw blood samples before and after the oxygenator, so that pre-oxygenator and post-oxygenator oxygen saturations could be determined (Synthesis 25, Instrumentation Laboratory Milano, Italy). Two ultrasound flow/dilution probes (Transonic Hemodialysis Monitor, Transonic Systems Inc, Ithaca, NY, USA) were clipped on the ECMO circuit, one on the arterial limb and one on the venous limb of the double lumen catheter. The probes were connected to the HD01® Hemodialysis Monitor System (Transonic Systems, Ithaca, NY, USA), which consists of a monitor and a laptop computer (Compaq, Houston, USA), preloaded with ultrasound dilution measurement software. There was an injection port in the arterial limb of the double lumen catheter 20 cm before the flow/dilution sensor, for the injection of isotonic saline. The sensor is calibrated by the factory specifically for the tubing set, to maximize measurement accuracy.

After cannulation and initiation of VV-ECMO, the ECMO flow was gradually adjusted to 150 mL/kg.min.

Determination of recirculation fraction using the ultrasound dilution method

Measurement of recirculation in haemodialysis with the ultrasound dilution method is based on detection of the dilution of blood with saline from changes in the average cross-sectional

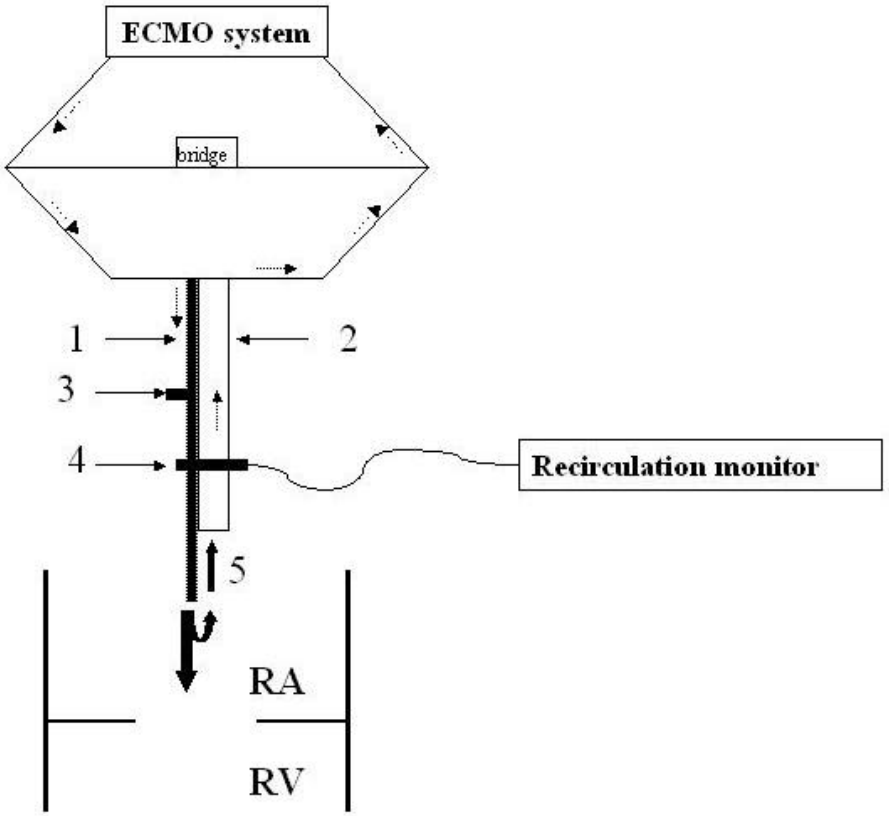
velocity of an ultrasound beam that illuminates the blood flowing through the tubing of the haemodialysis circuit (10).

When this technique is adapted for DLVV-ECMO, sensors are placed around the arterial and venous limb of the double lumen catheter. These sensors can measure blood flow through the ECMO circuit continuously by using the transit-time method (12). They can also detect a reduction in the ultrasound conductivity of blood caused by an injection of saline, primarily by dilution of the blood protein content. The velocity of an ultrasound signal through blood (1560 – 1590 m/sec) differs from the ultrasound velocity through isotonic saline (1533 m/s) (10). The sensors are connected to monitoring equipment and a computer program (model HD01, Transonic Systems, Ithaca, NY), to calculate the recirculation fraction (figure 1). Voltage changes that correspond to the mean cross sectional ultrasound velocity across the tubing are transmitted to the computer system for analysis and display of peak areas on the screen.

A 5 mL bolus of isotonic saline is injected into the arterial limb of the double lumen catheter and causes dilution of blood, which can be detected by the ultrasound dilution sensor as a dilution curve, because it causes a change in the velocity of the ultrasound signal. The change in ultrasound velocity (ultrasound dilution) is linearly correlated with the dilution of whole blood by normal saline. In the absence of recirculation, the entire bolus will flow into the right atrium and then into the body. If recirculation is present, a portion of the bolus will enter the venous limb of the cannula and pass the sensor on that limb, again creating a dilution curve. The monitor records both the actual flow in the cannula and the dilution curves that result from the saline passing through the sensors. The recirculation coefficient is the ratio of the indicator recirculated into the venous limb of the cannula to the injected amount of saline and, therefore, the ratio between the venous and arterial dilution curves is the recirculation fraction. The software algorithms use the dilution curves in combination with the tubing flow measurements to calculate and display the percentage of recirculation.

During this experiment, a bolus of 5 mL isotonic saline was injected three times into the arterial limb of the double lumen catheter and recirculation was measured using the ultrasound dilution method. With the two sensors were placed in series on the arterial limb of the catheter, the injected saline passes both sensors and 100% recirculation is detected. This arrangement was used as a calibration method for the ultrasound dilution method.

Figure 1. Diagram of the system for determination of recirculation fraction using ultrasound dilution method



1 = 'arterial' reinfusion limb of the double lumen veno-venous catheter, 2 = venous drainage limb of the double lumen veno-venous catheter, 3 = point for injection of 5 mL saline, 4 = two ultrasound flow sensors, placed around the 'arterial' and 'venous' limb of the double lumen veno-venous catheter, 5 = fraction of blood that recirculates into the ECMO system, RA = right atrium, RV = right ventricle, bridge = safety connection between the arterial and venous side of the ECMO system. Arrows indicate direction of blood flow.

Determination of the recirculation fraction using the svO_2 and the CVL methods

Immediately after determination of the recirculation fraction with the ultrasound dilution method, a blood sample was taken from the venous line in the inferior caval vein to determine the oxygen saturation in this blood sample, which was then used as a representation of svO_2 (CVL method). Blood samples were also taken from the ECMO circuit before and after the oxygenator. In these samples, oxygen saturation was determined as oxygen saturation of the pre-oxygenator blood and post-oxygenator blood, respectively. Oxygen flow to the membrane oxygenator was then stopped, so that the transfer of oxygen to the blood through the extracorporeal circuit was interrupted. Ventilation was adjusted to achieve the same oxygen saturation as before stopping oxygen flow to the membrane oxygenator, so that svO_2 could be

determined. When saturations in pre-oxygenator and post-oxygenator blood samples were equal, this proved that there was no longer oxygen transfer over the membrane oxygenator. This saturation was then considered to represent svO_2 (svO_2 method). From the formula described above, recirculation could then be calculated according to the CVL and svO_2 methods.

The mean value of the three recirculation fraction measurements with the ultrasound dilution method was used for comparison with the results of the two other methods.

At ECMO flow rates of 125, 100, 75, and 50 mL/kg.min the recirculation fraction was again determinated with the three different methods.

STATISTICS

For comparison of the three methods of recirculation measurement, Pearson's correlation coefficients (r) and p-values were calculated; p ? 0.05 was considered significant. Because the correlation coefficient only determines the strength of a relation between two variables, and not the agreement between them, we also used the method described by Bland and Altman to assess agreement between the different measurement methods (13). The mean difference and standard deviation were calculated and compared using paired Student's t-test. Furthermore we looked at the repeatability of the ultrasound dilution method, since three measurements were done with this method.

RESULTS

Table 1 shows the results of the recirculation fractions determined with the three measurement methods at different flow rates.

With all three methods, the recirculation fraction increased with increasing flow rates. With the ultrasound dilution method, smaller recirculation fractions were detected than with the other two methods. The CVL method detected the highest fractions.

Table 1. Recirculation fraction at different flow rates in 9 animals

Flow rate (mL/kg.min)	Ultrasound dilution method (%)	svO_2 method (%)	CVL method (%)
150	36.0 ? 12.8	45.0 ? 6.9	62.5 ? 6.9
125	32.8 ? 9.3	39.3 ? 9.5	54.8 ? 13.5
100	24.6 ? 9.4	31.7 ? 8.2	39.1 ? 17.6
75	20.2 ? 6.5	24.5 ? 12.6	29.5 ? 15.7
50	13.0 ? 4.0	12.4 ? 10.0	29.6 ? 15.7

Mean values ? standard deviation

Correlation analysis revealed positive relationships between recirculation fractions as determined with 1) the ultrasound dilution method and the svO_2 method; 2) the ultrasound dilution method and CVL method; and 3) svO_2 method and CVL method (table 2).

Table 2. Correlation coefficients and mean differences for three different measurement methods in recirculation fraction during DLVV ECMO in 9 animals

Variable	Correlation coefficient	Mean Difference (- 2 sd, + 2 sd)
Ultrasound dilution versus svO_2 method	r=0.68; p<0.01	-2.4%; p=0.6 (-26.4, +21.6%)
Ultrasound dilution versus CVL method	r=0.48; p<0.01	-18.1 %; p<0.01 (-50.3, +14.1 %)
svO_2 versus CVL method	r=0.51; p<0.01	-15.7 %; p<0.01 (-49.5 %, +18.1 %)

svO_2 method = mixed venous oxygen method, CVL method = central venous line method, sd = standard deviation.

Using linear regression, recirculation determined with the ultrasound dilution method could be calculated as: recirculation (%) = 1.88+0.23xECMO flow (mL/min); r=0.99, p<0.01. With the svO_2 method, recirculation (%) = 1.42+0.32xECMO flow (mL/min); r=0.99, p<0.01. With the CVL method, recirculation (%) =6.66+0.36xECMO flow (mL/min); r=0.96, p<0.05.

Also the mean differences and p-values for the comparison of the different measurement methods are presented. The limits of agreement between 2 methods vary between the mean +2 sd and the mean -2 sd (13).

The mean difference between the ultrasound dilution method and svO_2 method was small and not significant, whereas the differences between the ultrasound dilution method and the CVL method and between the svO_2 method and the CVL method were larger and statistically significant.

The coefficient of repeatability for the ultrasound dilution method, as defined by Bland and Altman, was 6 %.

DISCUSSION

As expected, there was an increase in recirculation fraction with increasing ECMO flow rates in all three methods (4). Using the method as described by Bland and Altman, the differences between the ultrasound dilution method and svO_2 method were not significantly different, indicating that, on average, agreement exists between the methods, whereas when the other methods were compared, the mean differences were significantly different and did, therefore, not agree with each other (13).

The ultrasound dilution method is validated for recirculation measurements in haemodialysis and has proven to be a reliable method for the determination of the recirculation fraction (8,10,14,15). Depner et al compared the recirculation fraction as determined with the ultrasound dilution method and the blood urea nitrogen method and found a correlation coefficient of 0.91 ($p<0.001$) (10). When they looked at the difference between two repeated measurements with the ultrasound dilution method, the mean difference (± sd) between measurements was 3.9% (± 2.8%). Leblanc et al measured recirculation in adults during haemodialysis with a 10 French internal jugular vein twin catheter. They found values between 5 and 11% with a shunt flow varying between 200 and 400 mL/min (15). Traditionally, the blood urea nitrogen method is used in haemodialysis to calculate recirculation. Because with this method measurement errors and cardiopulmonary recirculation occur, it seems to overestimate recirculation (16). Tattersall et al demonstrated no recirculation during haemodialysis in 16 patients with the ultrasound dilution method, whereas an average of 12.5 % recirculation fraction was calculated with the traditional blood urea nitrogen technique (17).

In VV-ECMO, a gold standard for calculation of recirculation fraction does not exist, which makes it impossible to determine the reliability of one of these investigated methods. From a physiological point of view, the svO_2 method was considered the best. However, the svO_2 method has certain disadvantages: ECMO is interrupted by stopping the oxygen delivery to the membrane oxygenator. With adaptation of the assisted ventilation, the same arterial blood oxygen saturation then has to be achieved in order to measure svO_2. This approach cannot be carried out in infants with severe respiratory disease. For determination of the oxygen

saturation of the pre-oxygenator and post-oxygenator blood, different blood samples have to be taken at the same moment, making it prone to failure. Apart from not being an easy applicable bedside method, this method is time consuming and does not provide instantaneous results.

Nevertheless, in this experimental setting, such a measurement can be achieved. Therefore, it is the most useful to compare the CVL and ultrasound dilution methods against the svO_2 method.

When the different methods for assessing the recirculation fraction measurement were compared, there was only a non-significant difference in mean values between the ultrasound dilution method and the svO_2 method.

The lack of agreement between the CVL method and the two other measurement methods can be explained by the fact that oxygen saturation in the inferior caval vein does not represent adequately true mixed venous oxygen saturation (18, 19). The ultrasound dilution method for the determination of recirculation has several advantages over the other two methods. The major advantage is that this method can be used without interruption of the ECMO procedure. In addition, the ultrasound dilution method measures recirculation fraction more directly then the other two methods, since it measures the effect of blood dilution in the two limbs of the double lumen catheter. It avoids the determination of a third factor, svO_2, which is necessary with the other two methods. Furthermore, it provides the ability to visually inspect the dilution curves on the computer screen. Detection of recirculation by dilution of blood caused by a bolus of normal saline injected into the arterial limb of the double lumen catheter has advantages over other dilution indicators such as cardiogreen, because patients already receive saline and saline is innocuous.

In our study the coefficient of repeatability was 6%, which is comparable with the 9.1% found in the study of Lindsay et al (7).

Recirculation is a limiting factor for oxygen delivery in DLVV-ECMO. As expected, increasing ECMO flow in this study also leads to an increase in recirculation fraction and may decrease the efficacy of the oxygenation (4). Information on the recirculation fraction is important for obtaining an optimal oxygenation of the patient being treated with DLVV-ECMO. The ultrasound dilution method provides a rapid, simple, reliable and non-invasive method for assessing recirculation.

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PART 4

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION

This thesis presents the results of clinical and pathophysiological studies on ECMO in newborns with respiratory failure.

ECMO improved survival in selected newborns with severe respiratory failure and pulmonary hypertension (1). The overall survival rate in our patient group was comparable with survival rates reported internationally in the ELSO registry (chapter 2). Although survival rates of newborns with CDH in our patient group were slightly higher than those recorded by the ELSO registry, this difference was not significant. The major cause of death in our patient group was an untreatable respiratory problem, especially in the CDH group. At present it is impossible to predict which patients will survive with ECMO, especially for CDH patients, in whom respiratory failure is the main cause of death.

Intracranial haemorrhage was an important reason to discontinue ECMO before the underlying respiratory problem had been resolved and this inevitably led to death. Other authors also described the relation between pulmonary and cerebral complications and survival (2,3). Long-term neurodevelopmental outcome after ECMO treatment is also associated with pulmonary and neurological complications (4-9). It is therefore very important to study the effects of ECMO treatment on the lung and brain, in order to gain insight in the mechanisms by which complications can occur. Understanding the pathophysiology of complications will aid the development of measures to prevent them.

Newborns needing ECMO treatment have severe respiratory failure in combination with pulmonary hypertension. These life-threatening disorders usually arise due to underlying diseases such as MAS, CDH, and sepsis, but pulmonary hypertension can also occur without one of these underlying diseases; so-called idiopathic persistent pulmonary hypertension. In newborns with pulmonary hypertension the morphology of the lung vasculature is abnormal. Their small pulmonary arteries show increased medial and adventitial thickness (10-13).

The beneficial effect of ECMO on pulmonary hypertension is generally described as “ lung rest”. However, it is unclear what this represents. Shehata et al described a decrease in adventitial thickness after ECMO treatment in CDH patients. They suggested that this caused an increase in compliance and a subsequent decrease in vascular resistance (14). In the study described in chapter 3, that compared newborns with pulmonary hypertension caused by MAS, sepsis or idiopathic and treated with ECMO to similar non-ECMO treated patients, we demonstrated a decrease in percentage medial thickness of the small pulmonary arteries plus a

decrease in the cross-sectional area of the media, adventitia and total wall. This suggests that ECMO treatment had a positive effect by reversing the abnormal vascular wall structure known to exist in these patients.
Stenmark et al suggested that medial myocytes and adventitial fibroblasts play an important role in the abnormal vascular remodeling (15-17). It remains unclear which mechanisms achieve the reduction in abnormal vascular structure. To gain better understanding of these mechanisms, more insight is needed into molecular processes. In chapter 3, we discussed the potential role of genes in regulating matrix metalloproteinases, or an imbalance between proliferation and apoptosis as a cause of abnormal vascular structure in pulmonary hypertension. More knowledge about the mechanisms involved in the structural vascular remodeling will probably enable the development of therapies to replace the need for ECMO to survive.

In our patient group, cerebral complications, i.e. haemorrhages or infarctions, were seen in 7.0% and 9.1% of the patients, respectively (chapter 2). Schumacher et al and Mendoza et al demonstrated lateralized cerebral lesions after VA-ECMO treatment, but in our patient group, there was no predominance of cerebral lesions in the left or right cerebral hemisphere (18,19).
Chapter 5 describes a study in which NIRS and Doppler ultrasound were used to determine whether ligation of the right common carotid artery and right internal jugular vein and the initiation of VA-ECMO caused differences in oxygenation and perfusion between the left and right cerebral hemispheres. Based on the results of this study and our clinical data (chapter 2), it seems unlikely that there is a relation between the predominance of cerebral lesions in either hemisphere and the procedure of ECMO initiation.
Nevertheless, important changes in cerebral oxygenation and haemodynamics did occur. A decrease in cerebral oxygenation was observed in both cerebral hemispheres after ligation of the right common carotid artery. This finding combined with the results of the studies of Raju et al and Matsumoto et al, who both demonstrated a temporary decrease in cerebral blood flow velocity after ligation of the right common carotid artery, suggests that ligation of the right common carotid artery is potentially followed by a hypoxic ischaemic moment (20,21). This is in agreement with Peek and Firmin who stated that cerebral infarction in the watershed area is most likely to occur during the 3-5 minutes it takes for cerebral perfusion to be re-established (22). Our study also showed that ECMO initiation caused an increase in cerebral blood volume, cerebral blood flow velocity and mean arterial blood pressure. The increase in cerebral blood flow could not be explained by changes in $paCO_2$, in contrast with the study of

Lohrer et al (23). Simultaneous increases in cerebral blood flow and mean arterial blood pressure suggested that cerebral autoregulation in these patients had either shifted outside the range of autoregulation in the autoregulation curve or, more likely, was disturbed. If their autoregulation was intact, we would not expect any change in the cerebral blood volume and blood flow velocity as long as the cerebral perfusion pressure remains within the autoregulatory range.

Disturbed autoregulation makes the brain very vulnerable to hypo- or hyperperfusion due to blood pressure changes and this can potentially cause ischaemic or haemorrhagic lesions.

It was not possible to measure absolute values with NIRS and demonstrate ischaemia of cerebral tissue (24). NIRS was unable to measure oxygenation and cerebral blood volume in the whole cerebral hemisphere. Therefore, we could not exclude that differences in oxygenation and circulation can be present between the left and right hemispheres in specific areas of the brain (25).

The aetiology of cerebral lesions in ECMO patients is probably multifactorial and it is often impossible to identify a specific cause in a given patient. Certain (technical) aspects of ECMO might cause cerebral lesions. For example, bridge opening and the patent ductus arteriosus have effects on cerebral oxygenation and haemodynamics. The bridge, a safety connection between the drainage and infusion tubing of the ECMO system, is usually opened every 15 minutes to prevent the development of thrombi due to blood stasis. In chapter 6, we used an animal model to study the effect of opening of the bridge during VA-ECMO. We observed an arteriovenous shunt over the bridge, followed by a sudden drop in cerebral oxygenation and perfusion with every combination of ECMO flow rate and opening time. This means that in our patient group, these phenomena occurred over 600 times per patient based on a mean ECMO run-time between 153 and 176 hours. Such repeated negative effects on cerebral oxygenation and perfusion might result in cerebral vascular lesions. In another study on newborns on VA-ECMO, Doppler ultrasound showed that opening the bridge caused the cerebral blood flow velocity in the anterior cerebral artery to drop to zero (unpublished results), which underlines the importance of the haemodynamic changes observed in our animal study. Above described changes can be prevented by placing a small pump on the bridge to limit the arteriovenous shunt. In the present clinical situation, the “old” bridge has been replaced by a system with two stopcocks. The stopcocks are located at the junction where the bridge connects to the drainage and infusion tubing. Now, the bridge can be filled with saline instead of blood as was the case in the original situation. This avoids the need for

intermittent opening of the bridge and thus prevents any potentially negative effects on the cerebral circulation.

In chapter 7 we showed that during VA-ECMO, cerebral oxygenation and perfusion can be compromised by a patent ductus arteriosus with a left to right shunt. Previously, our group has demonstrated that a left to right ductal shunt occurred in 62% of the newborns on VA-ECMO, and that it was associated with longer ECMO run times (26). Further studies are needed to investigate the exact importance of a patent ductus arteriosus with left to right shunt in the development of cerebral and other potential complications during VA-ECMO. If a patent ductus arteriosus with left to right shunt is clearly related to the occurrence of complications, a therapeutic intervention to close the ductus should be considered. It is also necessary to define factors that predispose to the occurrence of a patent ductus arteriosus with a large left to right shunt in VA-ECMO.

Over the past few years, the use of VV-ECMO has increased as an alternative for VA-ECMO. VV-ECMO has several advantages over VA-ECMO. The most important is that ligation of the right common carotid artery is no longer necessary. Thus, normal arterial perfusion of the brain is maintained and the potential ischaemic moment of carotid artery ligation is avoided. However, it is still necessary to cannulate the right internal jugular vein. Taylor et al and O'Conner et al suggested that ligation of the right internal jugular vein caused venous outflow obstruction and that this was related to the occurrence of cerebrovascular injuries (27,28). Walker et al also demonstrated disturbed autoregulation in a VV-ECMO animal model. However, the changes in autoregulation were less severe than in VA-ECMO, and no right to left differences in cerebral blood flow were observed (29). A randomized study is needed to determine whether newborns treated with VV-ECMO have fewer cerebral lesions than newborns treated with VA-ECMO. In a retrospective cohort study, Zahraa et al compared VV-ECMO to VA ECMO in non-neonatal, paediatric cases and found no difference in central nervous system complications (30).

A major disadvantage of VV-ECMO is limited oxygenation due to the recirculation of blood. Finding a way to quantify recirculation accurately would offer the opportunity to evaluate the effectiveness of interventions to decrease it. Then VV-ECMO can be applied more effectively and it may be possible to shorten the run-time and decrease complications. In chapter 9 we employed the ultrasound dilution technique as a bedside method to determine the recirculation fraction. We were able to monitor recirculation adequately. This enables the evaluation of

manoeuvres to decrease recirculation and optimize the patient's oxygenation. Thus, an important problem of VV-ECMO can now be handled feasibly.

In summary, this thesis demonstrated:

1. ECMO increased survival rates in newborns with severe respiratory insufficiency and pulmonary hypertension. Survival rates at our ECMO centre were comparable with international data.
2. The major causes of death in newborn ECMO patients were associated with pulmonary and cerebral complications.
3. The positive effect of ECMO on the reversal of pulmonary hypertension in newborns with MAS, sepsis or iPPHN can be explained by improvement in the vascular wall structure of the small pulmonary arteries.
4. The initiation of VA-ECMO caused changes in cerebral oxygenation and haemodynamics, but there were no differences in effect between the left and right cerebral hemispheres.
5. Repeated opening of the safety connection between the venous and arterial sides of the VA-ECMO system, the so-called bridge, to prevent thrombus formation, resulted in repeated significant drops in cerebral oxygenation and perfusion. These effects could be prevented with an alternative bridge.
6. A patent ductus arteriosus with left to right shunt during VA-ECMO can compromise cerebral oxygenation and haemodynamics.
7. An ultrasound dilution technique quantified recirculation during DLVV-ECMO adequately, and offered a method to evaluate manoeuvres to decrease recirculation.

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FUTURE PERSPECTIVES

ECMO has proven to be an effective treatment for newborns with severe, but reversible respiratory insufficiency. However, serious complications can occur.

At present, we know too little about the pathophysiological mechanisms involved in the development and reversal of the pulmonary vascular abnormalities associated with pulmonary hypertension. Furthermore, greater insight into pathophysiological processes of ECMO will help to avoid cerebral complications.

On the basis of findings in this thesis, we recommend the following issues for further study:

- ?? Which factors determine that some newborns with respiratory insufficiency and pulmonary hypertension respond to conservative therapy, whereas others need ECMO treatment to survive? In newborns with pulmonary hypertension which factors influence reversal of the abnormal lung vasculature?
- ?? What is the impact of a patent ductus arteriosus with left-to-right shunt during VA-ECMO on the circulation?
- ?? How does VV-ECMO initiation, with the theoretical advantage that the right common carotid artery does not need to be ligated, affect cerebral oxygenation and haemodynamics?
- ?? Will ECMO patient care expand to other indication areas in the future? Internationally, there has been a shift from newborn respiratory ECMO insufficiency candidates towards other indications for ECMO treatment, mainly post-cardiosurgery circulatory support. Twelve patients with circulatory failure have been treated at our institute during the past seven years. This brings up new questions about the pathophysiology of the failing heart and thus opens new opportunities for research.

SUMMARY/SAMENVATTING

SUMMARY

Extracorporeal membrane oxygenation (ECMO) is a treatment that can be applied to (nearly) term babies with severe respiratory failure who cannot be oxygenated adequately with optimal conventional treatment. During ECMO, the blood is oxygenated outside the body, in an artificial lung, a so-called membrane oxygenator.
This thesis addresses the effects of ECMO on the lungs and brain and is divided into four parts.

Part 1 describes "The Nijmegen experience" with ECMO at the UMC St Radboud in Nijmegen, The Netherlands.
Chapter 1 gives a general introduction to the developmental history of the ECMO technique, patient selection and treatment.
Chapter 2 presents the results of ECMO treatment in 186 newborns over a period of 12.5 years. Indications for ECMO treatment were meconium aspiration syndrome, congenital diaphragmatic hernia, sepsis/pneumonia and idiopathic pulmonary hypertension. Survival varied between 65% and 95%, depending on the diagnosis. Thirty-five newborns died. Major causes of death were respiratory insufficiency and intracranial haemorrhage. A total of 13 patients (7.0%) had intracranial haemorrhage, while 17 (9.1%) had cerebral infarction. There was no difference in the incidence of cerebral lesions between the left and right cerebral hemispheres.
In ***chapter 3***, morphometric analysis was performed on the lung vasculature of newborns after ECMO treatment. Other studies showed that newborns with pulmonary hypertension have abnormal morphometry of the pulmonary vasculature, with increased medial and adventitial thickness. The morphometry of the pulmonary vasculature of newborns, who were treated with ECMO for pulmonary hypertension due to meconium aspiration syndrome, sepsis or idiopathic pulmonary hypertension, was compared to that of newborns with pulmonary hypertension who did not receive ECMO and a control group of newborns without pulmonary hypertension. Analyses were performed on lung tissue specimens obtained at post-mortem.
Compared to the control group, the newborns with pulmonary hypertension had increased medial thickness, adventitial thickness and total wall thickness in relation to the external diameter of the vessel. In addition, there was an increase in cross sectional area of the media, adventitia and total wall thickness in transverse section in vessels with an external diameter of less than 150 µm. Newborns with pulmonary hypertension who were treated with ECMO had

decreased medial thickness in relation with the external vessel diameter and decreased medial cross sectional area in transverse section in vessels of less than 75 µm, compared to newborns with pulmonary hypertension who did not receive ECMO. Furthermore, there was a decrease in medial thickness in relation with the external diameter and decreased cross sectional area of the media, adventitia and total wall thickness in transverse section in blood vessels with an external diameter of between 75 and 150 µm.

On the basis of these findings, we concluded that ECMO treatment for pulmonary hypertension decreased the abnormal morphometry that developed in the small pulmonary blood vessels. The underlying mechanisms responsible for this are as yet unknown.

Part 2 describes the effects of ECMO on cerebral oxygenation and haemodynamics.

Chapter 4 gives an introduction to these topics and outlines the risk factors for the development of cerebral lesions in newborns treated with ECMO.

Veno-arterial ECMO involves ligation of the right internal jugular vein and the right common carotid artery. In the literature, discussion is ongoing about whether or not there is an increased incidence of lesions in the right cerebral hemisphere with the application of veno-arterial ECMO.

Chapter 5 describes the effects of the initiation of veno-arterial ECMO on the oxygenation and haemodynamics of the left and right cerebral hemispheres in a study in newborns.

Ligation of the right common carotid artery caused a decrease in cerebral oxygenation. However, this decrease was of the same magnitude in both cerebral hemispheres. Ligation of the right internal jugular vein did not cause any change in cerebral oxygenation. After the initiation of ECMO, an increase was observed in cerebral oxygenation and in cerebral blood volume, once again to the same extend in both hemispheres. In addition, increases of equal magnitude were seen in the blood flow velocities in the left and right medial cerebral arteries. As expected, ligation of the right common carotid artery led to reversal of the blood flow direction in this vessel. In three out of the 10 patients we examined, asymmetrical cerebral lesions were found. However, these did not prove to be related to differences in study variables between the right and left cerebral hemispheres.

The initiation of veno-arterial ECMO caused changes in cerebral oxygenation and haemodynamics, but there were no differences between the left and right cerebral hemispheres.

Chapter 6 describes the haemodynamic effects that occur with opening of the bypass bridge during veno-arterial ECMO in a study on lambs. The bridge connects the arterial and venous

sides of the veno-arterial ECMO system. In emergency situations, this bridge can be opened and the blood flow from the ECMO system to the patient can be stopped. Thus, the circulation within the ECMO circuit can be maintained. The bridge normally remains closed, but it needs to be opened intermittently to avoid clot formation from blood stasis. In the lamb, opening the bypass bridge gave rise to an arterio-venous shunt and reversal of the blood flow direction in the ECMO circuit. Thus, the blood flowed out on the arterial side and re-entered on the venous side. This led to a decrease in mean arterial blood pressure and mean blood flow velocity in the left common carotid artery. In addition, there were increases in cerebral venous pressure, the pressure in the superior sagittal sinus, the cerebral concentration of deoxygenated haemoglobin and the cerebral blood volume. The concentration of oxygenated haemoglobin in the cerebrum decreased. Opening the bypass bridge therefore resulted in significant cerebral haemodynamic changes that might contribute to the development of cerebro-vascular complications.

These changes occurred irrespective of the ECMO pump flow rate or duration that the bridge was kept open, but could be avoided by adapting the bridge construction.

Chapter 7 describes the effects on cerebral oxygenation and haemodynamics of a patent ductus arteriosus with left-to-right shunt during veno-arterial ECMO. In the fetus, the ductus arteriosus is a connection between the pulmonary artery and the aorta. Newborns with pulmonary hypertension often have right-to-left shunt over this duct. During ECMO treatment, pulmonary hypertension decreases and the right-to-left shunt over the duct can reverse into a left-to-right shunt.

In the lamb, the ductus arteriosus was kept open artificially (to produce left-to-right shunt) and ECMO was started. Subsequently, the duct was closed. Closing the duct led to increases in cerebral oxygenation, mean arterial blood pressure, blood flow velocity in the left common carotid artery and cerebral oxygenation.

The findings suggested that during veno-arterial ECMO with left-to-right shunt over the ductus arteriosus, there was decreased cerebral circulation and oxygenation.

Part 3 describes aspects of veno-venous ECMO.

Chapter 8 gives an introduction to veno-venous ECMO and discusses the advantages and disadvantages in comparison with veno-arterial ECMO. In veno-venous ECMO, there are limitations regarding the level of oxygenation than can be achieved. This is due to the occurrence of recirculation, because a certain amount of the oxygenated blood that enters the patient via the cannula drains directly back into the ECMO system and does not contribute to oxygenating the patient.

Chapter 9 describes the ultrasound dilution method as a technique to measure the amount of recirculation during veno-venous ECMO. In a study on lambs, the amount of recirculation was measured during veno-venous ECMO using a double lumen catheter while the ECMO pump was set at different flow rates. The results of the ultrasound dilution method were compared to those obtained using two other methods described in the literature (the so-called "mixed venous oxygen method" and the "central venous line method"). All three methods revealed that the amount of recirculation increased with increasing ECMO pump flow rates. The results of the ultrasound dilution method were closest to those of the "mixed venous oxygen method", which is considered to be the best standard. In contrast with the "mixed venous oxygen method" and the "central venous line method", the ultrasound dilution method was easy to apply and it therefore appears to be a good method to quantify the amount of recirculation during veno-venous ECMO.

Part 4 presents the General Discussion and recommendations for further research.

In conclusion, we found that the survival rates of patients treated with ECMO at our centre were in agreement with those of other centres. Major causes of mortality were pulmonary and cerebral complications.

The beneficial effect of ECMO on pulmonary hypertension in newborns with the meconium aspiration syndrome, sepsis or idiopathic pulmonary hypertension can be explained by a decrease in the abnormal structure of the vessel walls in small pulmonary arteries.

The initiation of veno-arterial ECMO caused changes in cerebral oxygenation and haemodynamics, but there were no differences between the left and right cerebral hemispheres.

Repeated opening of the bypass bridge, necessary to prevent thrombus formation, resulted in significant changes in cerebral oxygenation and perfusion.

An open duct with left-to-right shunt during veno-arterial ECMO could lead to compromised cerebral oxygenation and haemodynamics.

With the aid of the ultrasound dilution method, the amount of recirculation during veno-venous ECMO could be adequately quantified and this offers a method to evaluate interventions that aim to reduce the amount of recirculation when the level is too high.

SAMENVATTING

Extracorporele membraan oxygenatie (ECMO) is een behandeling die wordt toegepast bij (bijna) voldragen pasgeborenen met ernstige respiratoire insufficiëntie, bij wie met optimale conventionele behandeling geen adequate oxygenatie bereikt kan worden. Bij ECMO vindt de oxygenatie van bloed plaats buiten het lichaam in een kunstlong, geheten de membraanoxygenator.
Dit proefschrift bestudeert de effecten van ECMO op de long en de hersenen en is in 4 delen ingedeeld.

Deel 1 beschrijft de ervaringen van onze kliniek met ECMO behandeling.
In ***hoofdstuk 1*** wordt een algemene inleiding gegeven over de ontstaansgeschiedenis van de techniek van ECMO, de selectie van patiënten en de behandeling.
Hoofdstuk 2 beschrijft de resultaten van ECMO behandeling gedurende 12.5 jaar in 186 pasgeborenen. Indicaties voor ECMO behandeling waren meconium-aspiratie-syndroom, congenitale hernia diafragmatica, sepsis/pneumonie en idiopathische pulmonale hypertensie. De overleving varieerde, afhankelijk van de diagnose, tussen 65% en 95%. Vijfendertig pasgeborenen overleden. Belangrijke oorzaken van overlijden waren respiratoire insufficiëntie en intracraniële bloeding. In totaal hadden 13 (7.0%) patiënten een intracraniële bloeding en 17 (9.1%) een cerebraal infarct. Er was geen verschil in de incidentie van cerebrale laesies tussen de linker of rechter hemisfeer.
Hoofdstuk 3 beschrijft de morfometrische analyse van de longvaten in pasgeborenen na behandeling met ECMO. Bekend is dat er bij pulmonale hypertensie van de pasgeborene sprake is van een abnormale morfometrie van de pulmonale bloedvaten, met toegenomen dikte van de media en adventitia. De morfometrie van pulmonale vaten van pasgeborenen die behandeld zijn met ECMO voor pulmonale hypertensie door meconium-aspiratie-syndroom, sepsis of idiopathisch, werd vergeleken met die van pasgeborenen met pulmonale hypertensie die geen ECMO behandeling kregen en met een controle groep van pasgeborenen zonder pulmonale hypertensie. Hierbij werd gebruik gemaakt van longpreparaten die verkregen zijn bij obducties.
Pasgeborenen met pulmonale hypertensie hadden, in vergelijking met de controle groep, een toegenomen mediadikte, adventitiadikte en totale wanddikte ten opzichte van de externe diameter van het vat. Verder bestond er een toegenomen oppervlakte van media, adventitia en totale wanddikte op een dwarse doorsnede, in longvaten met een externe diameter kleiner dan

150 µm. Pasgeborenen met pulmonale hypertensie die met ECMO waren behandeld hadden in vergelijking met niet met ECMO behandelde pasgeborenen met pulmonale hypertensie, een verminderde mediadikte ten opzichte van de externe diameter en een verminderd oppervlakte op de dwarse doorsnede in vaten met een externe diameter kleiner dan 75 µm. Verder hadden zij een verminderde mediadikte ten opzichte van de externe diameter en een verminderd oppervlak van media, adventitia en totale wanddikte op de dwarse doorsnede in vaten met een externe diameter tussen 75 en 150 µm.
Uit deze bevindingen concluderen wij dat ECMO behandeling voor pulmonale hypertensie de afwijkende morfometrie die bestaat in de kleine longvaten, vermindert. De onderliggende mechanismen welke hier toe bijdragen zijn nog onbekend.

Deel 2 beschrijft de effecten van ECMO op de cerebrale oxygenatie en hemodynamiek. ***Hoofdstuk 4*** geeft hierover een inleiding, waarbij risicofactoren voor het ontstaan van cerebrale laesies bij pasgeborenen die met ECMO worden behandeld worden beschreven.
Bij veno-arteriële ECMO worden zowel de rechter vena jugularis interna als de rechter arteria carotis communis onderbonden. Er bestaat in de literatuur discussie over de vraag of er meer cerebrale laesies voorkomen in de rechter hemisfeer door de toepassing van veno-arteriële ECMO.
Hoofdstuk 5 beschrijft de effecten van initiatie van veno-arteriële ECMO op de oxygenatie en hemodynamiek van de linker en rechter cerebrale hemisfeer in een studie bij pasgeborenen. Ligatie van de rechter arteria carotis communis veroorzaakte een afname van de cerebrale oxygenatie. Deze afname was echter in beide cerebrale hemisferen even groot. De ligatie van de rechter vena jugularis interna veroorzaakte geen veranderingen in de cerebrale oxygenatie. Na de start van ECMO werd er een toename gezien van de cerebrale oxygenatie en het cerebrale bloedvolume, opnieuw even groot in beide cerebrale hemisferen. Ook was er een even grote toename van de bloedstroomsnelheden in de rechter en linker arteria cerebri media. Zoals verwacht mocht worden trad er door de ligatie van de rechter arteria carotis communis een omkering van de bloedstroomrichting hierin op. Bij drie van de tien onderzochte patiënten was er sprake van asymmetrische cerebrale laesies, welke echter niet gerelateerd bleken te zijn aan verschillen tussen rechter en linker cerebrale hemisfeer in de bestudeerde variabelen. De initiatie van veno-arteriële ECMO veroorzaakte veranderingen in cerebrale oxygenatie en hemodynamiek zonder verschil in effect tussen de linker en rechter cerebrale hemisfeer.
Hoofdstuk 6 beschrijft de hemodynamische veranderingen gedurende opening van de brug bij veno-arteriële ECMO in een studie in lammeren. De brug is een verbinding tussen de arteriële

en veneuze zijde van het veno-arteriële ECMO systeem. In noodsituaties kan deze verbinding worden geopend en kan de bloedstroom vanuit het ECMO systeem richting patiënt worden afgesloten. Op deze manier kan er circulatie in het ECMO systeem blijven bestaan. De brug is dus normaal gesproken afgesloten, maar moet intermitterend geopend worden om te voorkomen dat zich hier stolsels vormen door stase van bloed. Opening van de brug resulteerde, door het ontstaan van een arterio-veneuze shunt, in een verandering van de bloedstroomrichting in het ECMO circuit. Hierbij stroomde het bloed aan de arteriële zijde het lam uit en aan de veneuze zijde in. Hierdoor trad een afname op in de gemiddelde arteriële bloeddruk en gemiddelde bloedstroomsnelheid in de linker arteria carotis communis. Verder stegen de centraal veneuze druk, de druk in de sinus sagitalis superior, de cerebrale concentratie van gedeoxygeneerd hemoglobine en het cerebrale bloedvolume. De concentratie van geoxygeneerd hemoglobine in het cerebrum nam af. Opening van de brug resulteerde dus in significante cerebrale hemodynamische veranderingen, die zouden kunnen bijdragen aan het optreden van cerebrale vasculaire complicaties. Deze veranderingen traden op bij iedere openingstijd en ECMO pomp snelheid, maar konden worden voorkomen met een aangepaste brug constructie.

Hoofdstuk 7 beschrijft de effecten van een ductus arteriosus met links-rechts shunt tijdens veno-arteriële ECMO op de cerebrale oxygenatie en hemodynamiek. De ductus arteriosus is een verbinding tussen de arteria pulmonalis en de aorta. Bij pasgeborenen met pulmonale hypertensie bestaat er vaak een rechts-links shunt over deze ductus. Tijdens ECMO behandeling zal de pulmonale hypertensie verminderen en kan de rechts-links shunt over de ductus Botalli veranderen in een links-rechts shunt. In deze studie werd bij lammeren de ductus kunstmatig opengehouden zodat er een links-rechts shunt bestond, waarna veno-arteriële ECMO werd gestart. Vervolgens werd de ductus gesloten. Sluiting van de ductus leidde tot een toename van de cerebrale oxygenatie, gemiddelde arteriële bloeddruk, bloedstroomsnelheid in de linker arteria carotis communis en cerebrale zuurstofvoorziening. Dit suggereert dat in de periode van links-rechts shunt over de ductus arteriosus tijdens veno-arteriële ECMO er sprake is van een verminderde cerebrale circulatie en oxygenatie.

Deel 3 beschrijft aspecten van veno-veneuze ECMO.

Hoofdstuk 8 geeft een inleiding over veno-veneuze ECMO, waarbij de voor- en nadelen ten opzichte van veno-arteriële ECMO worden besproken. Bij veno-veneuze ECMO is er een beperking in de mate van oxygenatie die kan worden bereikt. Dat komt doordat er recirculatie optreedt, waarbij een deel van het geoxygeneerde bloed dat vanuit de cannule de patiënt in

gaat, direct weer wordt gedraineerd naar het ECMO systeem en niet bijdraagt aan de oxygenatie van de patiënt.

Hoofdstuk 9 beschrijft de ultrasound dilutiemethode als techniek om de hoeveelheid recirculatie tijdens veno-veneuze ECMO te bepalen. In een studie in lammeren tijdens veno-veneuze ECMO met behulp van een dubbellumencatheter werd de hoeveelheid recirculatie gemeten bij verschillende ECMO pompsnelheden met de ultrasound dilutie methode en vergeleken met twee andere, in de literatuur beschreven methodes (de 'gemengd veneuze zuurstof methode' en de 'centraal veneuze lijn methode'). Voor alle drie de genoemde methodes werd gevonden dat de hoeveelheid recirculatie toenam met een toenemende ECMO pomp snelheid. De resultaten van de ultrasound dilutie methode kwamen het beste overeen met die van de 'gemengd veneuze zuurstof methode', welke wordt gezien als de beste standaard methode. De ultrasound dilutie methode kan, in tegenstelling tot de 'gemengd veneuze zuurstof methode' en de 'centraal veneuze lijn methode' gemakkelijk worden toegepast en lijkt daarom een goede methode om de hoeveelheid recirculatie tijdens veno-veneuze ECMO te kwantificeren.

Deel 4 beschrijft de algemene discussie en voorstellen voor toekomstig onderzoek.

In conclusie kan worden geconstateerd dat de overleving van patiënten die in ons centrum met ECMO zijn behandeld overeenkomt met die in andere centra. Belangrijke oorzaken van mortaliteit zijn pulmonale en cerebrale complicaties.

Het gunstige effect dat ECMO heeft op pulmonale hypertensie in pasgeborenen met meconium aspiratie syndroom, sepsis of idiopathisch kan worden verklaard door een afname van de afwijkende structuur van de vaatwand van de kleine long arteriën.

De initiatie van veno-arteriële ECMO veroorzaakt veranderingen in cerebrale oxygenatie en hemodynamiek, maar zonder verschil in effect tussen de linker en rechter cerebrale hemisfeer. Herhaalde opening van de brug, nodig om thrombusvorming te voorkomen, resulteerde in significante veranderingen in de cerebrale oxygenatie en perfusie.

Een open ductus Botalli met links-rechts shunt tijdens veno-arteriële ECMO kan leiden tot een gecompromitteerde cerebrale oxygenatie en hemodynamiek.

Met behulp van de ultrasound dilutie methode kan recirculatie tijdens veno-veneuze ECMO adequaat worden gekwantificeerd en dat biedt een methode voor de evaluatie van handelingen die worden uitgevoerd om de hoeveelheid recirculatie te verminderen als deze te hoog is.

DANKWOORD EN CURRICULUM VITAE

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CURRICULUM VITAE

Arno van Heijst, werd op 20 juli 1960 geboren in Mierlo. Na in 1978 zijn VWO diploma te hebben behaald aan het Pius X College in Almelo, begon hij in dat jaar aan de studie Geneeskunde aan de Katholieke Universiteit Nijmegen. Het artsexamen werd met succes afgelegd in 1985. In 1986 was hij werkzaam als arts-assistent thoraxchirurgie in het Academisch Ziekenhuis Leiden (Hoofd: Prof. Dr. HA Huysmans). Hier werd zijn belangstelling gewekt voor intensive care geneeskunde en extracorporele circulatie, niet wetende dat die twee zaken later nog eens samen zouden komen. Vanaf december 1985 werd de militaire dienstplicht vervuld. Het grootste deel van die tijd was hij werkzaam als arts-assistent anesthesiologie in het Militair Hospitaal Anton Mathijssen te Utrecht (Hoofd: Dr. A van den Bogaert).

Van maart 1988 tot oktober 1988 was hij werkzaam als AGNIO kindergeneeskunde in het Academisch Ziekenhuis Nijmegen (Hoofd: Prof. Dr. GB Stoelinga). In oktober 1998 werd begonnen met de specialistenopleiding Kindergeneeskunde. Van 1 oktober 1988 tot 1 maart 1990 in het Canisius-Wilhelmina Ziekenhuis te Nijmegen (Opleider: Dr. PMV van Wieringen). Van 1 maart 1990 tot 1 oktober 1993 in het Academisch Ziekenhuis Nijmegen (Opleiders: Prof. Dr. GB Stoelinga en Prof. Dr. RCA Sengers). Op 1 oktober 1992 werd reeds begonnen met de deelspecialisatie Neonatologie (Opleiders: Dr. H Boon en Prof. Dr. LAA Kollée). Op 1 oktober 1994 werd deze opleiding beëindigd en vanaf dat moment is hij werkzaam als staflid op de afdeling Neonatologie van (inmiddels) het Universitair Medisch Centrum St Radboud te Nijmegen. Sinds 1 juni 1997 is hij coördinator van het neonatale ECMO programma.