Short and Long Term Studies in Neonates treated with Extracorporeal Membrane Oxygenation (ECMO)

Korte en lange termijn studies van neonaten behandeld met
extra corporele membraan oxygenatie (ECMO)

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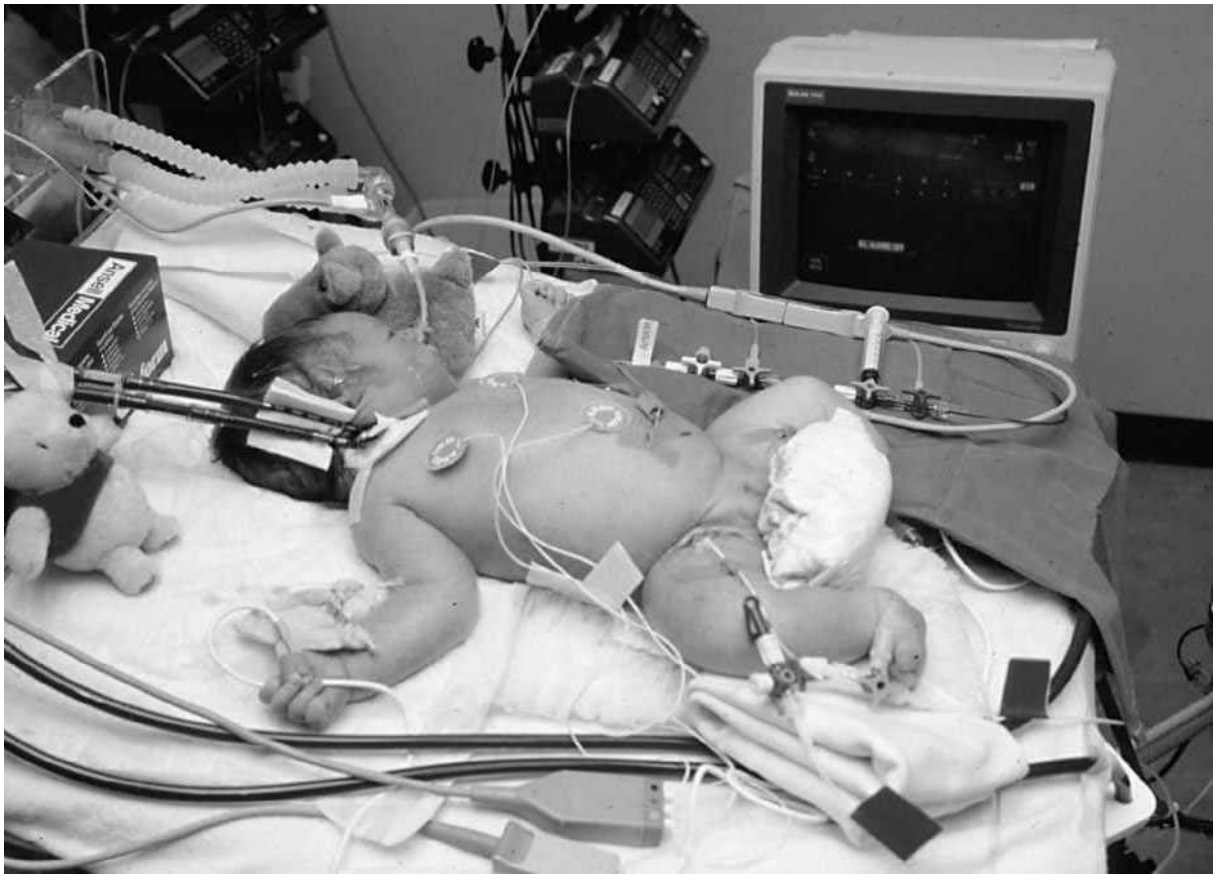
General Introduction

chapter 1

Extracorporeal life support (ECLS) is a technique for providing life support in severe but potentially reversible cardiorespiratory failure. The technique oxygenates blood outside the body, obviating the need for gas exchange in the lungs and, if necessary, provides cardiovascular support.
Initially ECLS was used as a device to take over the functions of the heart and lungs to permit surgical operations on the heart and great vessels. As experience with extracorporeal circulation was gained during the 1950s it appeared that the life supporting technique itself became lethal when used for more than a few hours. The development of the artificial lung machine – the early membrane oxygenators – then demonstrated that it would be possible to conduct prolonged extracorporeal circulation also outside the operating room. A logical next step was to attempt the use of this technique in the care of patients whose respiratory failure was unmanageable with conventional mechanical ventilation.
When used with extra-thoracic cannulation for respiratory support the technique is called extracorporeal membrane oxygenation (ECMO). This enables the lungs to rest with use of minimal ventilator settings, thereby preventing injury from high oxygen concentration and barotrauma. Especially in term newborns with pulmonary disease sustained pulmonary hypertension exacerbated the disease and frequently resulted in death. It appeared that in many of these patients the process was reversible if the patient could be supported through a critical period of adaptation.
In 1976, Bartlett et al. reported the first successful use of ECMO in the management of neonatal respiratory failure. By 1981 they had treated 45 newborns, of whom 25 survived.[1] In 1996 the UK-Collaborative ECMO trial group performed the first and only randomised controlled clinical trial showing a survival benefit of ECMO, without a concomitant rise in severe disability at 1 year of age.[2,3]
To date, ECMO has been used in over 18,000 newborns in 153 centers in 14 different countries.[4]

The ECMO circuit for newborn makes use of two catheters, one placed into the right internal jugular vein, positioned in the right atrium, and the other in the right common carotid artery (veno-arterial or VA ECMO). Blood is drained passively via the venous catheter, and then passed on to a pump, which maintains flow in the circuit. A 'bladder box' and servo system prevent the pump from working if venous drainage becomes inadequate for any reason. Blood then passes the membrane oxygenator where it is oxygenated and the carbon dioxide pressure is regulated. Warmed in a heat exchange column before re-entering the body, blood is returned via the common carotid artery at systemic pressure. This type of ECMO is able to support both pulmonary and cardiac function. (*Fig. 1*) A different type, veno-venous (VV) ECMO in which the drainage and reinfusion vessels are both veins and therefor provide mainly pulmonary support, is becoming increasingly popular. Its particular, theoretical advantage is uninterrupted cerebral arterial blood supply. Moreover, oxygenated blood will enter the pulmonary arterial system and as such could be advantageous in neonates with pulmonary hypertension.

Figure 1



ECMO is most commonly used to support mature newborn infants. Limiting factors are required size of the cannulae and systemic heparinization of the patient during ECMO. In neonates of less than 35 weeks gestational age the risk of intracranial haemorrhage is too high.[5] The smallest cannula capable of providing adequate ECMO flow is an 8 Fr. Therefore it is more difficult to perform cannulation in a child weighing less than 2000 grams. Also, as ECMO is not intended to delay inevitable death, it is important to establish the patient's diagnosis before the initiation of ECMO. Patients with a known lethal congenital anomaly or major uncorrectable cardiac lesion are excluded from ECMO treatment. Apart from these general criteria, Beck et al. developed specific criteria to predict 80% mortality. Especially the AaDO2/time interval was established as a major criterion for institution of ECMO, in a population of infants with severe acute lung disease treated conventionally.[6] Criteria for institution of ECMO in neonates are now derived from the ELSO guidelines.[7]

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).[4] *Table 1* shows the number of ECMO runs for neonatal respiratory failure by diagnosis according to the ELSO registry report, July 2004.[4]

Table 1

Diagnosis	Total Runs	Average Run Time (hrs)	% Survival
CDH	4491	231	53
MAS	6560	129	94
PPHN	2914	144	78
Sepsis	2384	138	75

Survival to discharge or transfer.

Acute care

Newborns treated with ECMO are critically ill. Nutrition is an important factor in the acute care of these patients in view of the fact that children admitted to an ICU may suffer from malnutrition.[8] It is common practice to withhold enteral nutrition from these patients and to feed them with total parenteral nutrition. This practice largely springs from fear of developing necrotising enterocolitis (NEC). In theory NEC may be due to an affected splanchnic circulation, subsequently leading to intestinal ischemia, in patients with hypoxic periods prior to ECMO and hemodynamic alterations during ECMO.[9,10] However, enteral nutrition was shown to be adequate in pediatric ECMO patients without the occurrence of major complications.[11] Data on intestinal permeability, safety and feasibility and the occurrence of complications in newborns receiving enteral nutrition during ECMO are still scarce.

A second factor in the acute care of ECMO patients is drug use. ECMO is known to alter drug disposition through expanded circulation volume, the presence of a non-pulsatile blood flow and reduced plasma protein levels, with effects on pharmacokinetics and pharmacodynamics.[12]
Morphine and midazolam are widely used drugs to provide adequate sedation and analgesia during ECMO. Plasma concentrations of morphine were found to drop during ECMO, especially over the first 10 days.[13] For midazolam, Mulla et al. reported that the distribution volume in ECMO-treated neonates was three to four times greater than that in critically ill neonates not treated with ECMO.[14]
Taking into account that factors such as increased tolerance after prolonged morphine intake also reduce the predictability of the effect of these drugs, morphine and midazolam therapy should be guided by clinical monitoring, preferably by validated pain or comfort scales.[15-17]
Severe (primary of secundary) pulmonary hypertension in neonates is common in the neonatal intensive care setting.[18] Over the years no single therapy has been established to be effective in all cases and this condition is still a major reason for ECMO support. Recent observations suggest that the phosphodiesterase (PDE) inhibitor sildenafil (Viagra) is promising in the treatment of pulmonary hypertension in adults and children.[19,20] However, very little is known of its (side-)effects in neonatal persistent pulmonary hypertension and its use during ECMO.

Long-term outcome

Since the UK-ECMO trial showed a survival advantage of ECMO over conventionally treated neonates with severe respiratory failure, morbidity has become increasingly important.[2] Bennett et al. showed that 13% of the children were moderately to severe disabled at four years of age. They also concluded that the range of morbidity widens with increasing ages when assessment of cognitive skills, co-ordination, behavioural difficulties and sensory loss can be more precise.[21] However, these findings may have been influenced by patient selection.
Pulmonary function testing is also included in the assessment of morbidity after ECMO support. Because ECMO could potentially result in survival of infants with severe respiratory dysfunction – or alternatively could result in survival of infants who might be spared aggressive ventilation and consequent volutrauma – it is essential to investigate their respiratory function independent of the fact whether ECMO results in a survival advantage. Cross-sectional data from different studies suggest that forced expiratory flow in ECMO survivors decreases in the first year of life.[22,23] Longitudinal data during the first year of life are not yet available.

Study Objectives

The main objectives of our studies were:

1. To evaluate the feasibility of enteral nutrition in newborns treated with ECMO.
2. To describe the pharmacokinetics and pharmacodynamics of analgesia and sedation during ECMO.
3. To evaluate the long-term follow-up of neonates treated with ECMO; i.e. overall outcome at the age of 5 years.
4. To evaluate pulmonary sequelae during the first year of life and at 5 and 8 years of age.

ECMO is a complexe technique used mainly in severely ill newborns with respiratory failure. In the knowledge that most ECMO treating centers tend to withhold enteral nutrition from these patients in fear of complications and inadequate intestinal perfusion we evaluated in **Chapter 2** over a five-year period the feasibility and tolerance of a protocol of routine enteral nutrition in neonates requiring ECMO.
In **Chapter 3** the effect of enteral nutrition on gut function during ECMO was evaluated. Since splanchnic circulation is at risk of inadequate perfusion during cardiopulmonary bypass we hypothesized that plasma gut hormone levels in patients on ECMO would be lower with a decreased response to enteral nutrition.
In **Chapter 4** we evaluated whether ECMO increases the risk of developing a chylothorax after congenital diaphragmatic hernia repair.

As a preliminary report of a study on the pharmacokinetic and pharmacodynamic poperties of midazolam and morphine administered during VA-ECMO, **chapter 5** describes the plasma concentrations of midazolam and morphine during ECMO. In the line of drug therapy during ECMO we evaluated in **Chapter 6** the use of sildenafil (Viagra®) in the treatment of neonatal persistent pulmonary hypertension.
We assessed morbidity in ECMO survivors at the age of 5 years, when they start primary school and major decisions for their school careers must be made.
The results of this nationwide extended follow-up program are described in **Chapter 7**. Next, **Chapters 8 and 9** describe pulmonary sequelae of ECMO survivors during the first year of life and at ages 5 and 8 years.
This thesis is completed by a general discussion (**Chapter 10**) and summary.

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Routine enteral nutrition in neonates on Extracorporeal Membrane Oxygenation

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Pediatr Crit Care Med 2005 Vol. 6, No.3

chapter 2

Abstract

Objectives
To evaluate over a 5-yr period the feasibility and tolerance of a protocol of routine enteral nutrition in neonates requiring extracorporeal membrane oxygenation (ECMO).

Design
Retrospective medical chart review.

Setting
Level III children's hospital, pediatric surgical intensive care unit.

Patients
Neonates treated with venoarterial ECMO (VA-ECMO) between January 1997 and January 2002. Patients with congenital diaphragmatic hernia were excluded.

Interventions
None.

Measurements and Main Results
Charts of all neonates treated with VA-ECMO were reviewed. Feasibility was evaluated by recording the time period needed for enteral nutrition to reach 40% of total fluid intake; tolerance was evaluated by reviewing data on enteral nutrition related morbidity. Sixty-seven of the 77 eligible patients received enteral feeding during ECMO. Thirty-six of these patients (54%) received 40% of total fluid intake as enteral nutrition within a median of 3 (range, 2 - 4) days. Over the years there was a trend toward an increasing usage of enteral nutrition from 71% to 94% (p = .07). Enteral nutrition was temporarily discontinued in 16 patients, with 14 showing gastric retentions, one showing discomfort, and one showing aspiration. Symptoms of bilious vomiting, blood-stained stool, or abdominal distention were not present.

Conclusion
Neonates on ECMO in this series tolerated enteral feeding well and did not show serious adverse effects. Overall, it is our experience that routine use of enteral feeding in critically ill neonates on VA-ECMO is feasible.

Introduction

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a type of heart-lung bypass that provides short-term support for selected critically ill patients with acute therapy-resistant respiratory or cardiac failure. ECMO can be used for reversible disorders only. Worldwide, > 20,000 newborns have been treated so far, 18,703 of whom for respiratory failure.[1] Conditions most commonly treated with ECMO in the neonatal period are meconium aspiration syndrome, primary or secondary persistent pulmonary hypertension of the newborn, congenital diaphragmatic hernia, sepsis, and pneumonia.

As critically ill neonates have limited endogenous nutrient stores and relatively high nutritional requirements, early institution of nutritional support is important.[2,3] Enteral nutrition in neonates stimulates intestinal hormone secretion.[4] These hormones may be instrumental in stimulating structural and functional changes occurring in the gut and other organs when adapting to enteral nutrition.[5,6] Moreover, early administration of enteral nutrition, at least in critically ill adults, is known to reduce sepsis-associated morbidity and cost.[7,8]

Parenteral nutrition has been traditionally preferred over enteral nutrition in the neonatal ECMO patient for different reasons. First, splanchnic circulation may be adversely affected by hypoxic periods and the need for vasopressor therapy before ECMO. This may lead to intestinal ischemia, which in its turn increases the chance of developing necrotizing enterocolitis (NEC) and facilitates bacterial translocation and eventually sepsis.[9-11] Second, the hemodynamic alterations present in patients on cardiopulmonary bypass also have a negative effect on gut barrier function.[12,13] And finally, other complications such as aspiration or intestinal distention due to obstruction are thought to occur.

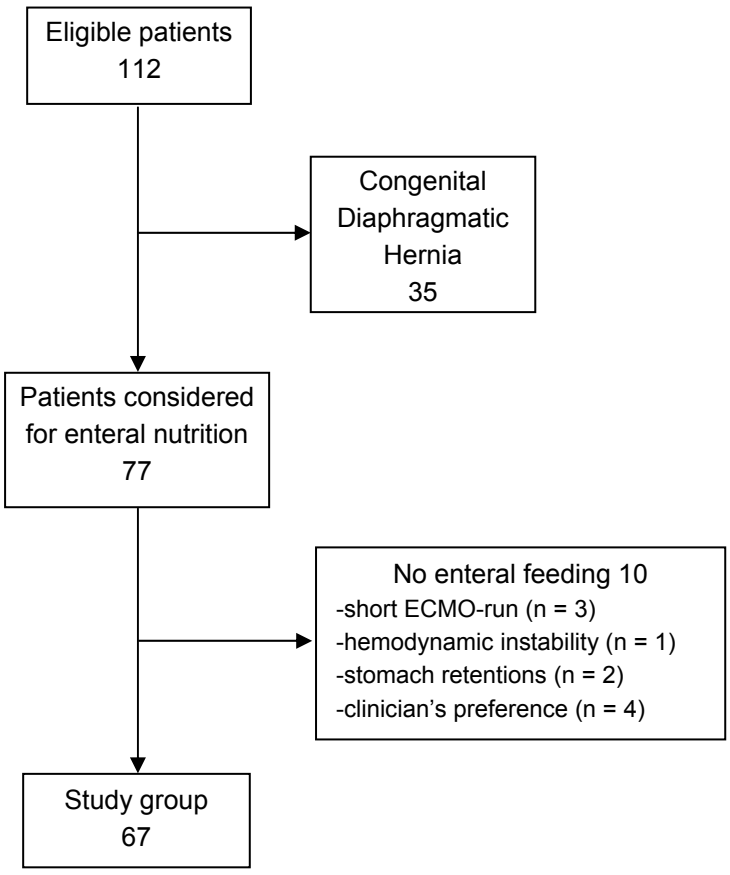
In earlier publications we evaluated intestinal permeability in ECMO patients, as well as gut responses to starvation and reintroduction of enteral feeding, in both premature neonates with NEC and in term-born infants. Intestinal integrity in ECMO patients was compromised but did not deteriorate after introduction of enteral nutrition.[14,15] After these prospective evaluations, we developed a protocol providing for enteral nutrition in neonatal ECMO patients. Except our previous data and those from Pettignano et al.[16] in pediatric ECMO patients, there are no data on the effects of enteral nutrition in newborns during ECMO.[2]

Therefore, we evaluated the use of enteral nutrition in neonates receiving VAECMO at our institution. We hypothesized that enteral nutrition in neonates on ECMO is feasible and tolerated without major complications.

Patients and methods

From January 1997 till January 2002, 112 neonates in our pediatric surgical intensive care unit were treated with VA-ECMO, of whom 82 (73.2%) survived. According to the Dutch law, there is no need for Institutional Review Board approval in cases of a retrospective chart review. Indications for ECMO were derived from the "classic" criteria of the Children National Medical Center ECMO Team, which remained unchanged during the study period.[17] We excluded from analysis 35 patients with a congenital diaphragmatic hernia who received ECMO before surgery because hospital practice dictates continuous suctioning of the nasogastric tube during ECMO and surgical repair following decannulation. In ten of the 77 remaining patients, enteral nutrition was withheld for various reasons. In three of them, once a stable situation was obtained and enteral nutrition could be introduced, weaning from ECMO had already started and the decision was made to start enteral nutrition following decannulation. One remained hemodynamically instable and developed severe intracerebral bleeding, after which the ECMO run had to be stopped and the patient died. Two other patients had ongoing stomach retentions before introduction of enteral nutrition, and in four patients the clinician in charge preferred to withhold enteral nutrition. Hence, 67 patients were included for analysis (*Fig. 1*).

Figure 1 Flow-sheet of included and excluded patients. *ECMO*, extracorporeal membrane oxygenation.



Feeding Regimens

By protocol, all patients received continuous morphine (10 - 20 μg/kg/hr) and midazolam (0.1 - 0.2 mg/kg/hr) infusions. They routinely received infusions with glucose 10%, and total parenteral nutrition was introduced 24 hrs after initiation of ECMO. Total parenteral nutrition consisted of a combination of glucose 10% with 10% amino acids (Aminovenös N-paed 10%, Fresenius, the Netherlands) and lipids 20% (Intralipid 20%, Pharmacia Upjohn, the Netherlands). Hospital protocol dictated half the amounts of amino acids and lipids on the first day, 12 ml/kg/24 hrs and 6 ml/kg/24 hrs, respectively. On the second day, glucose with amino acids was given at 24 ml/kg/24 hrs and lipids 20% at 12 ml/kg/24 hrs. Enteral feeding regimens were not strictly protocolized, but enteral nutrition was usually introduced when a hemodynamically stable situation on ECMO was reached without stomach retention. Stomach retention was then measured every 2 hrs. All patients had nasogastric or occasionally transpyloric feeding tubes in place before initiation of ECMO. The physician in charge decided the volume of enteral nutrition to be given. In principle, the concept of minimal enteral feeding was applied to the first 24 hrs, after which amounts were increased daily taking fluid restrictions into account. In general, the policy regarding fluid intake in neonates on ECMO dictates a maximum of 100 ml/kg/ day (blood- and platelet transfusions not included).

Breast milk was advocated as the primary source of food in all children. If not available, a regular infant formula was given, Nutrilon Premium (Nutricia, Zoetermeer, the Netherlands).

Outcome

We retrieved each patient's birth weight, gestational age, diagnosis, age at initiation of ECMO, duration of ECMO treatment, and time elapsed from the start of ECMO to introduction of enteral nutrition. We also recorded daily intakes of enteral nutrition and maximum administered amounts of vasopressor drugs during enteral nutrition. Approximately 20% of the fluid intake is provided with continuous medication, leaving 80% available for nutrition. Feasibility was evaluated by recording the time period needed for enteral nutrition to reach 40% (half of the amount available for nutrition) of total fluid intake.

Tolerance was evaluated by recording symptoms of stomach retention, bilious vomiting, aspiration, and NEC-related symptoms such as blood-stained stool, abdominal distention, and number of positive blood cultures during ECMO.

Statistical Analysis

Data are presented as median with the interquartile range (IQR). Changes in feasibility over the years were analyzed with a Cox regression analysis using 1997 as year of reference. A univariate analysis of variance was performed to compare time of onset of enteral nutrition over the years.

The influence of various variables on feeding intolerance was evaluated by logistic regression analysis. Factors included in the analysis were Apgar scores at 1 and 5 mins, gestational age, time to beginning enteral feeding, use of vasoactive drugs, morphine dosage, and type of feeding tube. A Spearman correlation was performed to study the relationship between dopamine and volume of stomach retention.

Results

The underlying diagnoses of the 67 enrolled neonates who received enteral nutrition in the period 1997 - 2002 are presented in *Table 1*. Their median gestational age was 40 (IQR, 38 - 42^{+6}) wks with a median birth weight of 3300 (IQR, 2885 - 3700) g. Six of the 67 patients died: five before the age of 30 days and one at the age of 38 days. The median duration of ECMO treatment was 7 (IQR, 5 - 9) days. The median intensive care unit stay was 15 (IQR, 11 - 20) days.

Table 1 Underlying Diagnosis

	No.
Meconium aspiration syndrome	39
Persistent pulmonary hypertension of the Neonate	14
Sepsis	7
Pneumonia	4
Congenital cystic malformation of the lung	2
Pertussis	1
Total	67

Start and Amount of Enteral Nutrition

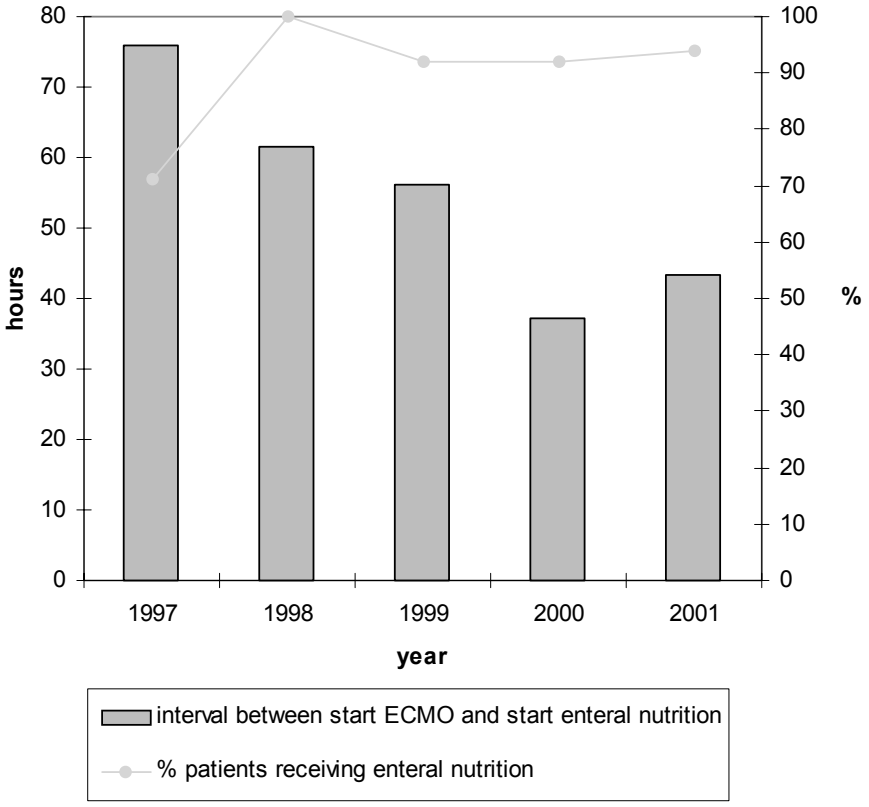
At the start of enteral nutrition, the median ECMO flow was 280 (IQR, 180 - 360) ml/min. Over the 5-yr period, enteral nutrition was started at a median of 45 (IQR, 23 - 41) hrs after start of ECMO. In 58 of the 67 patients (87%), gastric feeding tubes were in place. Nine patients received enteral nutrition through a transpyloric feeding tube.

On the first day of enteral nutrition, feeds were given as an hourly bolus of 1 - 4 ml, in 50% of the cases. However, amount and frequency ranged from 8 times 1 ml to 24 times 10 ml on the first day. The amount was daily increased by clinician preference toward a maximum ranging from 8 times 35 ml to 24 times 15 ml on the fourth day.
Over the course of ECMO therapy, every child received bolus feeds.

Feasibility

Figure 2 shows the mean amounts of enteral nutrition, parenteral nutrition, and continuous medication as a percentage of the total fluid intake per day.

Figure 2 Interval between start of extracorporeal membrane oxygenation (ECMO) and start of enteral nutrition in hours together with the percentage of patients receiving nutrition.

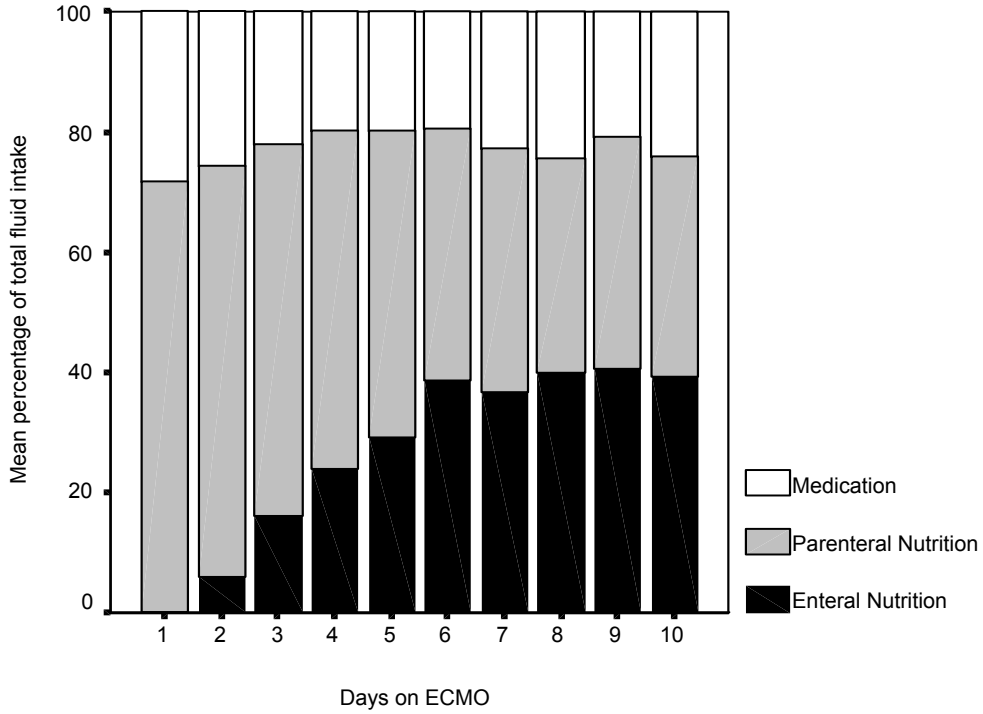


Thirty-six of the 67 (54%) neonates reached 40% of total fluid intake as enteral nutrition, at a median of 3 (range, 2 - 4) days. A Cox regression analysis showed that only in the year 2000, the relative risk for enteral nutrition to reach 40% of the total fluid intake was 5.5 (95% confidence interval, 1.9 - 15.8) times higher than in 1997 (p = .002).
The median interval between start of ECMO and start of enteral nutrition decreased significantly from 67 (IQR, 48 - 88) hrs in 1997 to 37 (IQR, 30 - 43) hrs in 2000 and to 40 (IQR, 34 - 54) hrs in 2001 (analysis of variance, p = .0001). Over the years there was a trend toward an increasing usage of enteral nutrition from 71% to 94% (*Fig. 3*; Chi-quadrate test, p = .07).

Tolerance
In 14 patients, enteral feeding was discontinued because of gastric retentions. They showed a median of 9 (IQR, 5 - 14) ml of retention the moment enteral feeding was discontinued for a median period of 24 (IQR, 12 - 47) hrs (*Table 2*).

In four patients, feeding was not successfully resumed during ECMO. In one other patient, enteral feeding was discontinued for 8 hrs because of discomfort, without stomach retentions. In one other patient, enteral feeding was stopped because milk was aspirated from the endotracheal tube. This did not result in a clinically documented aspiration pneumonia with a prolonged ECMO run.

Figure 3 Parenteral and Enteral nutrition as mean percentages of the total fluid intake. *ECMO*, extracorporeal membrane oxygenation.



Symptoms of bilious vomiting, bloodstained stools, or abdominal distension had not been noted in any of the 67 patients. In all cases, enteral nutrition was discontinued approximately 2 hrs before decannulation and successfully restarted thereafter.

The influence of Apgar scores at 1 and 5 mins, gestational age, time to beginning of enteral feeding, use of vasoactive drugs, morphine dosage, and type of feeding tube on feeding intolerance was evaluated by logistic regression analysis. None of the predictors had a significant influence on feeding intolerance (chisquare 6.165; *df* 8; $p = .63$).

Use of Vasoactive Drugs

Dopamine was given to 80% of patients on enteral nutrition during ECMO. The median amount was 7 (IQR, 3 - 10) μg/kg/min, with a maximum of 20 μg/kg/min.

Table 2 Enteral feeding related morbidity

	No. 67	**Median time-period to stop enteral nutrition in hrs (range)**
Gastric Retentions (median 9 ml, range 4 - 31ml)	14	24 (range 8 - 60)
Discomfort	1	8
Aspiration	1	Not resumed during ECMO
Positive blood cultures with enteric bacterium	1	

Dopamine together with dobutamine (5 μg/kg/min) was given in three of the patients and together with noradrenaline (0.5 μg/kg/min) in four other patients. They were added near the end of an ECMO run.

There was no significant correlation between volume of stomach retention and the dosage of dopamine at the moment enteral nutrition was discontinued because of stomach retentions (Spearman correlation -.06, p = .8).

Sepsis-Related Morbidity
From the daily routinely taken blood cultures of the ECMO system, 13 were positive in 13 different patients. One blood culture revealed *Enterococcus faecalis*. The other 12 blood cultures revealed *Staphylococcus epidermidis*. Three were considered contaminants in the absence of clinical and biochemical signs of sepsis. All other patients were treated with antibiotics successfully. Enteral nutrition was never discontinued because of a positive blood culture.

Discussion

In this study we evaluated feasibility and tolerance of routine enteral nutrition in neonates on VA-ECMO during a 5-yr period. We found that enteral nutrition was well tolerated and that no major complications occurred. Over the years, enteral nutrition was introduced approximately 1.5 day sooner after the start of ECMO and there was a tendency toward a greater proportion of patients receiving enteral nutrition. In 54% of the patients, enteral nutrition reached 40% of the total fluid intake within a median time of 3 (range, 2 - 4) days.

For several reasons (i.e., concern about inadequate gut perfusion, caused by absence of pulsatility, vasoconstrictive effects of many vasopressor drugs used pre-ECMO, and hypoxia), ECMO centers commonly withhold enteral nutrition. However, 80% of our ECMO patients who were fed enterally received dopamine. Clinically, negative effects on gut function in these patients were not noted. Also, the use of inotropic drugs did not correlate with the amount of retention.

To our knowledge there are no reports on feasibility and safety of routine enteral nutrition in newborn ECMO patients. Pettignano et al.[16] reported their experience with enteral nutrition in 13 pediatric ECMO patients with a median age of 72 months. Enteral nutrition was well tolerated, and patients obtained adequate nutrition within 4 days without developing major complications.[16]

Although the majority of the patients described by Pettignano et al. (69%) were treated with venovenous ECMO, preserving pulsatile blood flow to the gastrointestinal tract, all

our patients were treated with VA-ECMO. Still, we noted no major complications such as bloodstained stool or other NEC-related symptoms.

However, enteral feeding was temporarily stopped because of gastric retentions in 14 (21%) neonates. A study conducted in preterm neonates receiving enteral nutrition while low umbilical artery catheters were in place showed a 14% incidence of gastric residuals.[18] A proportion of 15% with feeding intolerance was reported by Pettignano et al.[16] Our patients did not receive any prokinetic medication, unlike the patients in the study of Pettignano et al. In 71% of our patients, enteral feeding could be successfully reintroduced after a median of 24 hrs, still during ECMO. It is questionable whether our policy to withhold enteral feeding for as long as 24 hrs is justified. To answer this question, we need to better document retention volumes in relation to amount of enteral nutrition and also the standard use of prokinetic drugs in this special group of patients.

Fluid intake restriction is a known barrier to adequate nutrition in critically ill children.[19] Neonates on ECMO have a restricted fluid intake of 100 ml/kg/day. Given the fact that approximately 20% of the fluid intake was provided with continuous medication such as furosemide, midazolam, and morphine, 80% was available for nutrition (*Fig. 3*). Providing half of the amount available for nutrition by enteral nutrition seemed a feasible goal. However, this was reached in 54% of the neonates. One might expect that over the years increasing experience should have led to higher proportions reaching this goal; however, this was only true in 2000. The one trend observed over the years was a decrease in the median interval between start of ECMO and start of enteral nutrition.

The incidence of positive blood cultures in our patients was 19%. This was higher than the 6.5% overall incidence of culture-proven infections mentioned in the ELSO registry report.[1] A previous report from us on septic complications in neonates on ECMO did not show any influence of the feeding route, that is, parenteral vs. enteral nutrition.[20] Coagulase- negative staphylococci were the microorganisms cultured most frequently. There was only one positive blood culture with *E. faecalis* in which gut mucosal integrity and bacterial translocation may have played a role.

Conclusions

We found that over a 5-yr period, enteral feeding was well tolerated and not associated with serious adverse effects. Overall, it is our experience that routine use of enteral feeding in critically ill neonates on VA-ECMO is feasible. In fact, they could benefit from the early introduction of enteral nutrition because it plays an important role in the maintenance of gut mucosal integrity and has been associated with improved gastrointestinal immunologic function and reduced septic morbidity, in both adults and children.[7,8,21] An additional advantage is cost reduction.

However, we are aware that the retrospective nonrandomized nature, the lack of a comparison group of parenterally fed neonates, and the absence of available information on caloric intake and uptake in this study could limit the interpretation of the results.

Nevertheless, our findings in these 67 patients lead us to suggest that the introduction of enteral nutrition in neonates on ECMO between 24 and 48 hrs after the start of ECMO is a safe procedure, provided patients do not show gastric retentions. With restriction of a maximum fluid intake of 100 ml/kg in neonates on ECMO, it seems reasonable to achieve approximately 50% of the nutritional fluid intake for enteral nutrition within 3 days. Future studies should focus on the caloric intake and protein uptake in ECMO patients receiving enteral nutrition.

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Gut hormone profiles in critically ill neonates on Extracorporeal Membrane Oxygenation

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chapter 3

Abstract

Objectives
The objective of this study was to gain insight into the hormonal responses to enteral nutrition in critically ill newborns requiring venoarterial extracorporeal membrane oxygenation (ECMO) by analyzing plasma gut hormone levels of gastrin, cholecystokinin and peptide-YY in relation to enteral nutrition.

Methods
In 24 consecutive neonates treated with venoarterial ECMO intestinal hormone secretions were determined by radioimmunoassay at 2-day intervals. Twelve received parenteral nutrition only. In 12 enteral nutrition was introduced later. The findings in these patients were compared with those of 16 measurements in eight non-ECMO treated age-matched controls. Mixed model analysis of variance was used for statistical analysis.

Results
Concentrations of gastrin, cholecystokinin and peptide- YY were significantly higher in ECMO patients receiving enteral nutrition compared with ECMO patients who received parenteral nutrition (62, 3.8 and 59.4 pmol/l versus 46, 3.1 and 34.7 pmol/l, respectively). Overall, plasma hormone levels did not differ from those in age-matched controls.

Conclusions
Intestinal hormone levels showed normal responses after introduction of enteral feeding, comparable with those in age-matched controls without ECMO. These results do not provide an argument for withholding enteral nutrition even in the most severely ill neonates on venoarterial ECMO.

Introduction

Gut hormones are regulatory peptides produced in endocrine cells in the gastrointestinal mucosa that control gastrointestinal function, including motility, intestinal fluid secretion, blood flow, absorption and immunity.[1] They may be instrumental in stimulating structural and functional changes occurring in the gut and other organs when adapting to enteral nutrition.[2-4] Term and preterm infants experience major plasma hormone surges in the neonatal period.[2] However, Lucas et al. found that these did not occur in infants deprived of enteral feeding, suggesting that plasma hormone elevation after birth is related to feeding rather than to postnatal age.[3] In fact, even very small quantities of enteral nutrition induced significant elevations of gut hormones in neonates.[3] They suggested that infants dependent on total parenteral nutrition from birth might benefit from the biologic effects of this ‘‘minimal enteral feeding’’ concept, but further investigations in critically ill term and preterm neonates is warranted.[3]

Centers providing extracorporeal membrane oxygenation (ECMO) in critically ill newborns usually withhold enteral substrate from these neonates and feed them parenterally. ECMO is a method of providing life support in severe but potentially reversible respiratory or cardiac failure, used particularly in mature newborn infants. Conditions most commonly treated with ECMO in the neonatal period are meconium aspiration syndrome, primary or secondary persistent pulmonary hypertension of the newborn, congenital diaphragmatic hernia, sepsis and pneumonia.

Enteral nutrition may be withheld from these patients for various reasons, such as the notion that splanchnic circulation may be adversely affected both by hypoxic periods and by the need for vasopressor therapy before ECMO. The splanchnic circulation is also at risk of inadequate perfusion during cardiopulmonary bypass.[5] Disturbed splanchnic circulation may lead to intestinal ischemia, which in its turn increases the chance of developing necrotizing enterocolitis and facilitates bacterial translocation and eventually sepsis.[6-8] It is not known whether intestinal hormone secretion is also affected in these patients. As ECMO can be considered a very prolonged bypass procedure, it carries a risk of abnormal gut hormone profiles. In fact, plasma hormone levels are expected to be decreased and remain so after enteral nutrition is introduced.

In our ongoing research on gut function in critically newborns and children we evaluated intestinal permeability in ECMO patients. We also evaluated gut responses to starvation and reintroduction of enteral feeding both in premature neonates with NEC and in term born infants. Intestinal integrity, as evaluated by sugar absorption tests, was compromised in ECMO patients but did not deteriorate after introduction of enteral nutrition.[9,10] After these prospective evaluations we developed a protocol using enteral nutrition as a standard in neonatal ECMO patients. Other than our previous data and those from Pettignano et al. in pediatric ECMO patients, there are no data available on gut function or the effect of enteral nutrition during ECMO.[11,12]

The aim of the present study was to gain more insight into the hormonal responses of the gut in neonates requiring venoarterial ECMO. We hypothesized that plasma gut hormone levels in patients on ECMO would be lower with a decreased response to enteral nutrition. Plasma concentrations of gastrin (mainly produced in the gastric antrum), cholecystokinin (CCK, produced in the duodenum and jejunum) and peptide-YY (PYY, produced in the ileum and colon) were analyzed in neonates during enteral nutrition and during parenteral nutrition. Findings from these neonates were compared with findings in age-matched controls.

Materials and methods

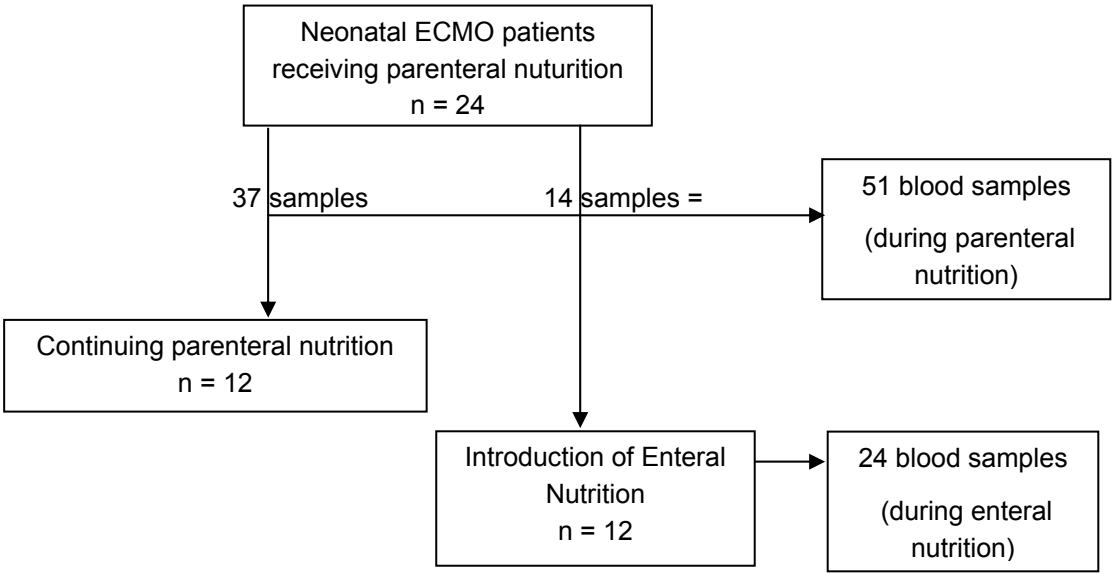
Patients

In 24 consecutive ECMO patients, plasma concentrations of gastrin and CCK and PYY levels were determined in all patients during a period of parenteral nutrition and in 12 of the 24 patients during a period of enteral nutrition after informed consent (*Fig. 1*).

Allocation to enteral or parenteral feeding in this group of 24 patients was not randomized but based on the underlying disease. For instance, patients with congenital diaphragmatic hernia, all subjected to continuous suctioning of the nasogastric tube as part of a delayed surgical approach, were given total parenteral nutrition.

All patients had nasogastric feeding tubes in place before initiation of ECMO. Enteral nutrition was initiated at 24 x 1 ml and was increased each day by 0.5 - 1 $ml.kg^{-1}.h^{-1}$ as tolerated. Breast milk was advocated as the primary source of food in all children. If not available, a regular infant formula was given (Nutrilon Premium; Nutricia, Zoetermeer, the Netherlands).

Figure 1 Flow chart showing number of patients and number of blood samples drawn.



In addition, plasma concentrations of gastrin, CCK and PYY were measured during starvation and during enteral nutrition in eight control patients matched for birthweight and gestational age who underwent thoracic surgery for major congenital anomalies, such as esophageal atresia.

Hormone Analysis

Every other day at 8:00 AM 3-ml arterial blood samples were drawn and collected in glass tubes containing ethylene diamine tetra-acetate. Samples were centrifuged within 30 minutes of sampling and plasma was stored at -80°C until assayed.

Gastrin, CCK and PYY were all measured by radioimmunoassay as described previously.[13-19] The antibody used for measurement of gastrin was raised in rabbits.[15,17] Directed towards the COOH-terminal bioactive site of sulfated and nonsulfated gastrins, it binds gastrin-17 and gastrin-34 with almost equal affinity. Cross-reaction with structurally related cholecystokinin and unrelated peptides was absent or negligible.[15,17] The intra-assay variation was below 10% in the working range of the standard curve. The detection limit of the assay was 0.1 pmol/l of incubation mixture. The antibody used for measurement of CCK was also raised in rabbits.[13,14] It binds with almost equal affinity to biologically active CCK peptides containing the sulfated tyrosine region. It shows less than 2% cross-reactivity with sulfated gastrins and does not bind to unsulfated forms of gastrin or structurally unrelated peptides, like insulin, secretin, pancreatic polypeptide, bombesin and neurotensin. The detection limit of the assay was between 0.5 and 1.0 pmol/l CCK in plasma. The intra-assay precision ranged from 4.6% to 11.5% in the steep part of the standard curve.

PYY was measured in plasma by a recently described, sensitive and specific radioimmunoassay.[18,19] The antibody used in the PYY-assay was raised in hens and binds to PYY_{1-36} and PYY_{3-36} with almost equal affinity.[18] Although there is no detectable cross-reactivity with the structurally related peptide pancreatic polypeptide, cross-reactivity with neuropeptide Y is negligible. The antibody does not cross-react with unrelated peptides.[18] The detection limit of the assay is obtained at a final concentration in the incubation mixture of 0.3 pmol/l. Intra-assay variation ranges from 6% to 11% in the working range of the assay.

Statistical Analysis

All data are presented as median with range unless stated otherwise. The effect of enteral feeding on gut hormone levels, both in ECMO patients and controls, was evaluated by calculating the ratios of the geometric means (enteral feeding versus parenteral feeding). Groups were compared using mixed model analysis of variance. Differences were considered statistically significant when $p < 0.05$.

Results

From a group of 24 ECMO-patients 75 blood samples were taken to determine plasma gastrin, CCK and PYY concentrations. Patient characteristics and underlying diagnoses are presented in *Table 1*. Fifty-one samples were drawn during total parenteral nutrition: 14 of these from 12 patients in whom enteral nutrition was started later (*Fig. 1*). The median postnatal age of these 24 patients at time of sampling was 5 days (range, 1 - 19 days). Twenty-four samples were drawn after start of enteral nutrition in 12 patients (median postnatal age at time of sampling 8 days; range, 3 - 13 days). The median (interquartile range) amount of enteral nutrition as a percentage of the total fluid intake was 10% (6% to 25%) at time of sampling.

Plasma concentrations of gastrin, CCK and PYY were significantly higher in patients fed enterally; $p = 0.04$, $p = 0.047$ and $p = 0.022$, respectively (*Table 2*). *Figures 2* through *4* show the median gut hormone levels per day of age during enteral nutrition and parenteral nutrition. The median age of onset of enteral nutrition was 4 days (range, 3 to 9 days).

Table 1 Patient Characteristics of 24 ECMO-patients

Birthweight, median (grams) (range)	3245 (2150 - 4500)
Gestational age, median weeks (range)	40 + 5 (37 ± 1 - 42 ± 2)
Underlying diagnosis	
Congenital Diaphragmatic Hernia	6
Meconium Aspiration Syndrome	11
Persistent Pulmonary Hypertension of the Neonate	4
Sepsis	2
Pulmonary bleeding	1

Values are number of patients unless otherwise indicated.
ECMO extracorporeal membrane oxygenation.

Table 2 Gut hormone plasma concentrations in 24 ECMO-patients

	Gastrin (pmol/l)	**Cholecystokinin (pmol/l)**	**Peptide-YY (pmol/l)**
Enteral nutrition (n = 24)	62.0 (45.3 - 95.8)	3.8 (2.9 - 4.8)	59.4 (43.0 - 75.6)
Total parenteral nutrition (n = 51)	46.0 (33.0 - 60.0)	3.1 (2.5 - 3.8)	34.7 (26.7 - 54.7)
Ratio of geometric mean	1.4	1.2	1.3
	$p = 0.04$	$p = 0.047$	$p = 0.022$

Plasma levels are expressed as median (range).
ECMO extracorporal membrane oxygenation.

Figure 2 Mean Cholecystokinin plasma levels per day of age

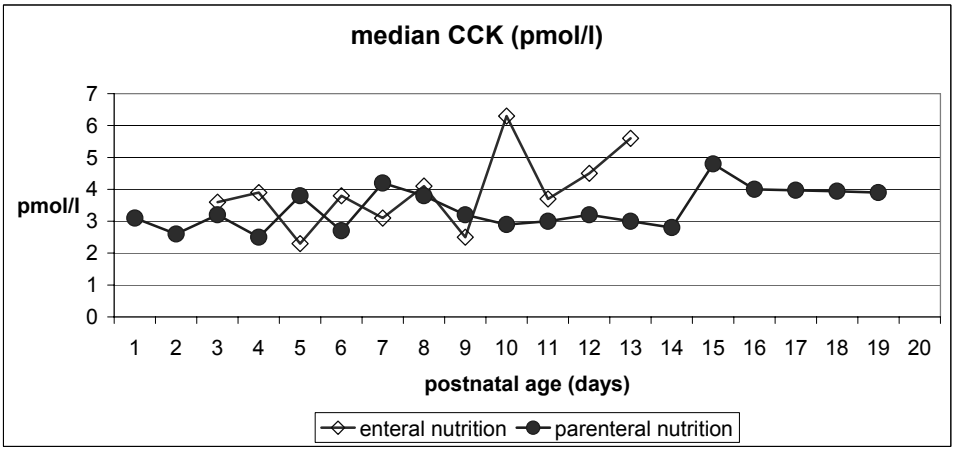


Figure 3 Mean Gastrin plasma levels per day of age

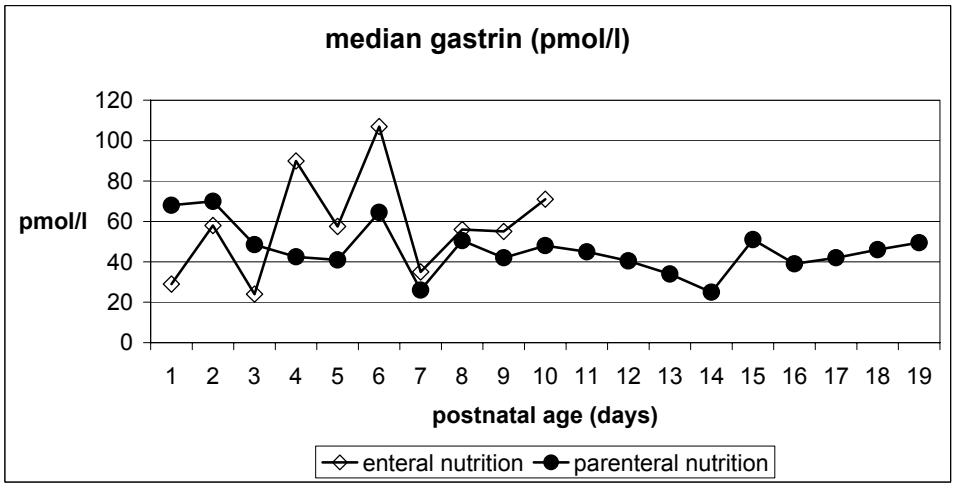
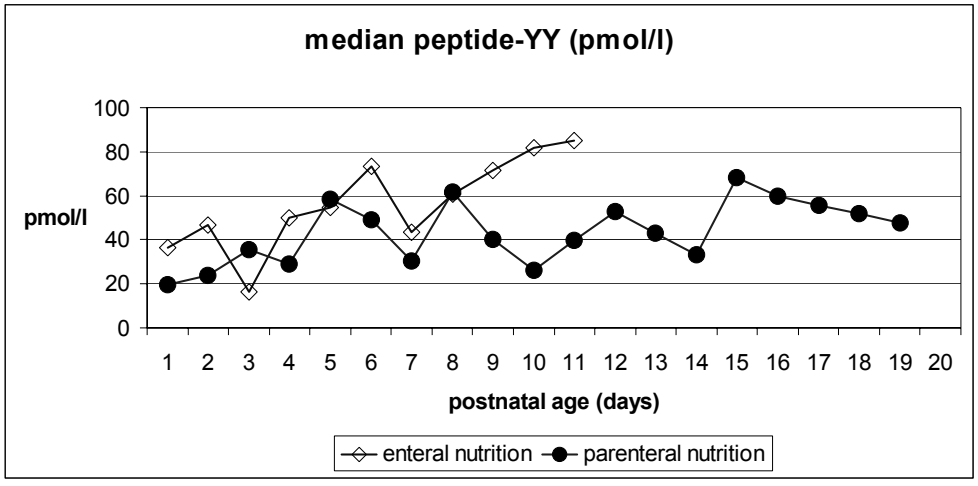


Figure 4 Mean Peptide-YY plasma levels per day of age



Eight of the 12 enterally fed patients (17 measurements) were fed with breast milk, three patients (six measurements) received standard formula and in one measurement the patient was given a combination of breast milk and standard formula. The plasma concentrations of CCK, gastrin and PYY in breast milk-fed patients did not differ significantly from those in patients given standard formula. Median CCK plasma concentration was higher in breast milk-fed patients (3.8 versus 3.4 pmol/l (p = 0.4). Median PYY and gastrin concentrations were lower in breast milk-fed patients (58 versus 61.5 pmol/l (p = 0.9) and 58.2 versus 60.8 pmol/l (p = 1.0) respectively).

Plasma gastrin, CCK and PYY concentrations were also measured after surgery in 16 blood samples from eight age-matched control patients who underwent thoracic surgery. Birthweight and age did not differ from those in the 24 ECMO patients. Nine samples were drawn during starvation and seven during enteral nutrition at a median postnatal age of 6 days (range 1 - 20 days). Median plasma concentrations are presented in *Table 3.* Plasma gastrin, CCK and PYY concentrations were higher in patients fed enterally, but differences were not significant (*Table 3*). During enteral feeding gastrin and PYY concentrations were lower in surgical patients, but CCK concentration was lower in ECMO patients. Plasma gut hormone concentrations in surgical patients showed the same trend as in patients on ECMO; they all increased after start of enteral nutrition. In surgical patients CCK and PYY levels seem to increase more than in ECMO patients; however, without reaching significant difference (CCK, 1.7 versus 1.2; p = 0.6; PYY, 1.9 versus 1.3; p = 0.3).

Table 3 Gut hormone plasma concentrations in 8 thoracic surgery patients

	Gastrin (pmol/l)	**Cholecystokinin (pmol/l)**	**Peptide-YY (pmol/l)**
Enteral nutrition (n = 7)	41 (31 - 106)	3.7 (2.2 - 30.3)	61.1 (21.6 - 147)
Total parenteral nutrition (n = 9)	25 (13 - 620)	2.1 (1.5 - 7.2)	32.6 (17 - 44.4)
Ratio of geometric mean	1.4 p = 0.33	1.7 p = 0.44	1.9 p = 0.057

Plasma levels are expressed as median (range)

Discussion

In this study we measured gut hormone profiles in neonates on ECMO fed enterally and we found a normal pattern in comparison with age-matched controls. Differences between patients fed with breast milk or standard formula were not statistically significant.

However, as allocation to enteral or parenteral feeding in determining plasma hormone concentrations was not randomized but based on the underlying diseases, the results may be biased. Patients with congenital diaphragmatic hernia, for instance, are given total parenteral nutrition during the entire ECMO period because our protocol dictates closure of the diaphragm after successful decannulation.

Few data are available on gut hormone levels in patients with impaired intestinal function. In 1997 Gounaris et al. found these to be low in premature patients with necrotizing enterocolitis.[20] We previously reported increased CCK and PYY levels in premature infants with an ileostomy after necrotizing enterocolitis and reintroduction of enteral nutrition.[10] Median plasma gastrin, CCK and PYY levels of the ECMO patients in our study were in the same range as those in healthy neonates in previous studies.[20-24] However, taking into account the substantial inter-laboratory variation of radioimmunoassay for gastrin, CCK and PYY, comparison with absolute values reported in the literature is not directly feasible.[22,23] For this reason we measured gut hormone levels of age-matched patients after thoracic surgery using the same radioimmunoassay in the same laboratory. These levels were not consistently higher than the gut hormone levels measured in patients on ECMO. Mean hormone levels during total parenteral nutrition and mean gastrin and PYY levels after start of enteral nutrition were even higher in patients on ECMO. A recent study performed at our institution with the use of the same radioimmunoassay revealed similar gut hormone profiles in neonates after bowel surgery for congenital intestinal anomalies and in age-matched controls who underwent surgery for other reasons.[25]

The plasma gut hormone levels in patients receiving enteral nutrition showed great variability. Secretion of gut hormones is influenced by various factors. In adults, the concentration of gastrin increases in response to protein-enriched feeds with a peak concentration within the first hour after a meal. CKK concentrations also rise after a protein or fat enriched meal. Once feeding is interrupted, concentrations decrease to preprandial levels within approximately 30 minutes. PYY-levels increase after a fat enriched meal, although slower, and concentrations of PYY remain higher for a few hours after a meal.[26,27] Studies in newborns by Lucas et al. showed similar findings: plasma concentrations increase with increasing intake, and hormone release in continuously fed infants differs from that in intermittently fed infants, who have a cyclic hormone release.[28] Neonates in this study received different amounts of enteral nutrition varying from 24 x 1 ml to 24 x 15 ml at time of sampling. Although blood samples were taken at a fixed time point in the morning, time between feeding and sampling could still vary. This best explains the variability in plasma concentrations.

In 1993 Marchini et al. found significantly higher CCK levels in breast-fed infants compared with formula-fed infants during the first 5 days of life.[22] We did not find any statistical differences between these groups. Failure to reach statistical significance might be attributable to the fact that ECMO patients did not receive their total intake as enteral nutrition (i.e., 10% of their total fluid intake) and the amount of milk ingested

cannot be excluded as an important factor for the level of hormone secretion. In contrast, in Marchini et al.'s study all patients received total enteral nutrition.

In conclusion, we found no evidence that previous respiratory and circulatory failure and nonpulsatile blood flow during ECMO negatively affected gut hormone secretion in term critically ill neonates. Gut hormone secretion normally increases after the introduction of minimal enteral feeding. Thus, our study does not provide an argument to withhold enteral feeding in critically ill neonates on venoarterial ECMO, as has been common practice in many ECMO centers because of the fear of intestinal ischemia and eventually the development of necrotizing enterocolitis. However, there is no conclusive evidence for this policy. In fact, critically ill neonates may benefit from the early introduction of enteral nutrition, as it is instrumental in the maintenance of gut mucosal integrity and has been associated with improved gastrointestinal immunologic function and reduced septic morbidity both in adults and children.[29-31] A vigorous enteral feeding protocol has been instituted in our hospital in an attempt to replace the use of total parenteral nutrition with its intrinsic morbidity.

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Does V-A ECMO increase the likelihood of chylothorax after congenital diaphragmatic hernia repair?

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chapter 4

Abstract

Background
The authors noticed a relatively large number of patients with congenital diaphragmatic hernia (CDH) repair after extracorporeal membrane oxygenation (ECMO) who had a chylothorax (CT). The data are reviewed.

Methods
The charts of patients from 1990 until 2000 with CDH, treated with or without ECMO, together with the charts of patients treated with ECMO for other reasons and patients with esophageal atresia (EA) repair were reviewed. The diagnosis of CT was made if aspirated fluid appeared chylous and contained more than 90% lymphocytes or if the triglyceride level was more than 1.50 mmol/l.

Results
Eighty-nine patients with CDH were analyzed. Postoperatively, 10% had a CT—21% in CDH patients with ECMO treatment and 6% in CDH patients without ECMO treatment. This difference appeared to be significant ($p < .05$). The presence of a patch as independent variable for the development of CT also showed significance ($p < .05$).

Conclusions
Chylothorax presented in almost all cases as a left-sided fluid accumulation, and a patch was present in the majority of patients with CDH. Therefore, CT should be considered the result of the severity of the defect rather than the consequence of ECMO as a therapeutic modality.

Introduction

Over the years the treatment of congenital diaphragmatic hernia (CDH) has changed its focus from immediate surgery towards a delay in surgery until the child is stable, with increasingly lower mortality rates in recently published series.[1-3]

Extracorporeal membrane oxygenation (ECMO) is used in these children as one of the treatment modalities. This technique of cardiopulmonary bypass allows support of the infant and concomitant lung "rest". It is mainly aimed at overcoming the reversible components of pulmonary hypertension and improving lung compliance. The postoperative course of CDH repair can be complicated by an ipsilateral pleural effusion.[4] This may be because of fluid filling the space resulting from removal of the herniated viscera in combination with a not fully expanded lung. An alternative explanation holds that the effusion is caused by a chylothorax (CT), resulting from trauma to the diaphragmatic lympathics during surgery.[5] We noticed a relatively large number of chylothorax in patients with CDH repair after ECMO. For that reason, we reviewed our data and compared them with the occurrence of a CT after CDH repair without ECMO or after repair of esophageal atresia to evaluate whether ECMO results in a higher risk for the development of CT.

Materials and methods

We conducted a chart review of all patients with CDH admitted to the pediatric surgical intensive care unit at the Erasmus MC-Sophia from January 1, 1990 until January 1, 2001. This unit functions as one of the 2 regional ECMO centers in the Netherlands. We also studied the charts of patients treated with veno-arterial ECMO for reasons other than CDH from the same period. To evaluate the effect of a thoracotomy with potential damage to the lymphatic drainage as a cause of CT in children, newborns with EA also were evaluated. Age, gender, birth weight, side of the hernia, indication for ECMO treatment, duration of ECMO treatment, and the use of prosthetic material for hernia repair, indicating a larger defect, were noted. We created 4 groups of patients: CDH and ECMO treatment, CDH without ECMO treatment, ECMO for reasons other than CDH, and patients after esophageal atresia repair.

The treatment protocol for patients with CDH in our institution has been published before and consists of delayed surgery, inhaled nitric oxide (NO) and high-frequency oscillation (HFO) since 1999.[6] Operative repair is performed routinely after successful decanulation from ECMO.

The diagnosis of a chylothorax (CT) was made if a pleural effusion appeared chylous in enterally fed infants and if the fluid contained more than 90% lymphocytes or if the triglyceride level was more than 1.50 mmol/l.[5,7]

We traced 141 patients admitted for CDH in the study period, including patients with major congenital anomalies, prenatal diagnosis, and those who died within one hour after birth because of extreme pulmonary hypoplasia. Forty-nine (35%) patients died before surgical repair of the CDH. Three charts were not available for review, leaving 89 patients for analysis. Of these patients 65 (73%) were treated without ECMO, and 24 (27%) were treated with ECMO.

In the same time span there were 114 patients treated with ECMO for reasons other than CDH (*Table 1*). In the same period, 118 patients with an EA underwent surgical correction. The charts of 15 patients were not available for review. Three patients died before surgical repair of the EA, leaving 100 patients for analysis. The patient characteristics show that non-CDH ECMO patients were significantly older and had a higher birth weight because of inclusion criteria for ECMO. CDH patients with or without ECMO were comparable for age, birth weight, and gender. EA patients were significantly younger and had lower birth weight than CDH patients (*Table 2*).

Groups were compared, and differences were examined for statistical significance using the X^2 or Fischer's Exact test as appropriate. *p* less than .05 was considered statistically significant.

Table 1 Underlying diagnosis in patients treated with ECMO, excluding CDH

Meconium aspiration syndrome	64 (56%)
Persistent pulmonary hypertension of the newborn	25 (22%)
Sepsis	14 (12%)
Pneumonia	7 (6%)
Other	4 (4%)
Total	114 (100%)

Table 2 Patient characteristics per group

	CDH repair and ECMO	**CDH repair without ECMO**	**EA repair**	**ECMO for other reasons**
Male	15	38	67	60
Female	9	27	33	54
Gestational age (wk)	39 + 1	38 + 5	37 + 2*	39 + 3†
Birth weight (g)	3,087	3,095	2,495*	3,364†

* *Significantly lower than the other three groups*
† *Significantly higher than the other three groups*

Results

Eighty-nine patients with a CDH underwent surgical repair. Sixty-nine of the defects (78%) were left sided, which is similar to that reported by Clark et al.[8] In 41 of the 89 patients (46%) the defect in the diaphragm was closed with a patch. This was in 21 of 24 patients (88%) treated with ECMO and in 20 of the 65 CDH patients (31%) not treated with ECMO (*Fig. 1*). Postoperatively, 9 infants (10%) had a chylothorax—all but one on the side of the hernia. Five of the 24 CDH and ECMO group had a CT (21%). Four of the 65 CDH patients not treated with ECMO had a CT (6.2%; *Fig. 2*). In the five CDH and ECMO patients, the mean age at operative repair was 11 days (range, 3 to 29 days), mean duration of ECMO therapy was 160 hours (range, 95.5 to 308.5 hours). Drainage was first required at a median of 10 days (range, 3 to 22 days) postoperatively. In all cases, treatment consisted of continuous drainage of the CT, with a mean of 9 days (range, 2 to 12 days). Three of the 5 children received a formula containing only medium-chain triglycerides (Caprilon; Nutricia, Zoetermeer, The Netherlands) for approximately 6 weeks, one of them after a 12-day period of cessation of enteral feeding. One child did not receive Caprilon because there was uncertainty about the diagnosis of CT. Once enteral feeding was introduced, and the aspect became more chylous, the drain production had already decreased and stopped spontaneously. Another child did not receive enteral nutrition because in the same period she underwent surgery for a bowel obstruction. Once normal milk formula was introduced, the chylothorax had already disappeared. In the 4 CDH patients without ECMO treatment, the median age at operative repair was 3 days (range, 2 to 138). In 2 cases, the postoperative wound drain was still in situ when chylous production started 2 days postoperatively. In the other 2 cases, drainage was first required at, respectively, 3 and 13 days postoperatively. In all cases, continuous drainage was instituted for a mean of 11 days (range, 4 to 19 days). In one case, enteral feeding was withheld for 10 days after which Caprilon was introduced. In the other 3 cases, enteral feeding was changed to Caprilon. In the group of patients treated with ECMO for other reasons, CT developed in 4 of 114 patients (3.5%), one of them after a cardiothoracic procedure for a tricuspid insufficiency and ASD type II. Four of 100 patients (4%) had a CT after an esophageal atresia repair (*Fig. 2*).

Statistical analysis showed that CDH patients treated with ECMO had a significantly higher chance of having a CT compared with CDH patients not treated with ECMO ($p = .042$) or EA patients ($p = .04$). Statistical analysis with the presence of a patch in CDH patients as an independent variable for the development of a CT also showed a significant difference ($p = .044$).

Figure 1 Incidence of chylothorax in CDH patients with or without a patch

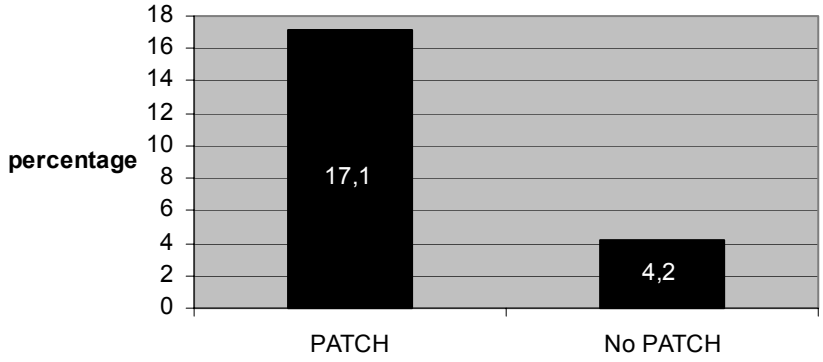
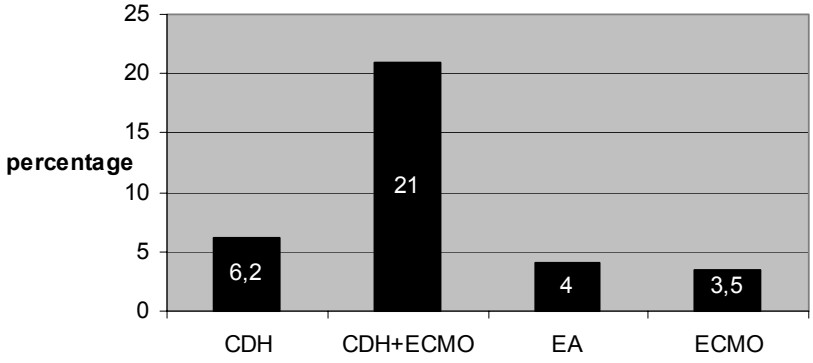


Figure 2 Incidence of chylothorax by group



Discussion

Chylothorax is defined as an accumulation of chyle in the thoracic cavity. The large losses of chylous fluid may lead to deficits in lymphocytes, proteins and immunoglobulins and, thus, to increased morbidity.[7] Chylothorax has been reported after almost every type of thoracic procedure in children. In our series we found an incidence of 10%, which is low compared with previously described (smaller) series.[5,9,10] In the literature, various pathogeneses for the development of a CT after CDH repair are mentioned. Mercer[9] described 5 cases of CT in patients after CDH repair with the presence of a hernial sac. In these cases, it was likely that lymph vessels present in the diaphragm and in the hernial sac were injured during surgery.[9] Our series shows that the development of a CT is as common after EA repair as after CDH repair without ECMO, indicating trauma to the lymphatic ducts as a result of the surgical procedure. However, in our series, only one patient with a very thin hernial sac was identified. Klin et al[11] proposed an alternative pathogenesis for the development of a CT in cases in which a hernial sac is absent, and direct trauma to the lymphatic ducts is less likely to occur. Large visceral herniation to the left thorax may produce significant pressure on the thoracic ducts which, at the level of the fifth thoracic vertebra, branches of toward the left side of the thorax. This back-

pressure phenomenon of the visceral lymphatics may lead to small breaks in the thoracic duct.[11]

According to Trevisanuto et al[12] during ECMO therapy a similar mechanism could be responsible; the catheter positioned in the superior vena cava impedes the venous return and consequently (partially) obstructs the outflow of the thoracic duct into the superior caval vein. This would also increase pressure in the ducts, leading to (micro) perforations. Our data show an increased likelihood of CT in patients with a CDH after ECMO. If this pathogenesis would be the leading cause, one would expect the CT to occur on the right side where the venous cannula is situated. However, in our patients, all but one of the CT occurred on the side of the hernia (*Table 3*). Moreover, infants with CDH who require ECMO often have a larger defect. This is reflected in this study in the number of cases in which the defect was closed with a patch; 88% in CDH patients treated with ECMO and 31% in patients not treated with ECMO. The presence of a patch as an independent variable also showed a significant higher chance of a CT developing in patients after CDH repair. It seems, therefore, more likely that ECMO serves as a selection bias and not as a primary cause for the CT.

Management strategies of a CT include repeated thoracocentesis or continuous drainage, complete cessation of enteral feeding, or the use of medium chain triglycerides formula for a prolonged period. Beghetti et al[13] showed that a standard treatment protocol with conservative management for all children who presented with a CT was effective in 80% of their patients. All our CDH patients with a CT were treated successfully with conservative management. If conservative management fails, surgical ligation of the thoracic duct is a possibility, but indication criteria are controversial.[5,13] Recently, the use of Octreotide as a nonsurgical intervention to decrease chyle production has been suggested.[14-17] Administering Octreotide either as a continuous intravenous infusion or as subcutaneous dosages was reported to be successful in pediatric patients after cardiothoracic surgery. Prospective studies still need to be undertaken on this aspect.

Table 3 Clinical data for the nine patients with CDH and CT

	Case No	Side of Hernia	Side of Chylothorax	Hernial Sac present	Patch
CDH + ECMO	1	Left	Left	-	+
	2	Left	Left	-	-
	3	Left	Right	-	+
	4	Left	Left	-	+
	5	Left	Left	-	+
CDH without ECMO	6	Right	Right	-	-
	7	Left	Left	-	+
	8	Left	Left	+	-
	9	Left	Left	-	+

Chylothorax is a recognized complication after surgery for congenital diaphragmatic hernia. Treatment modalities such as ECMO improve survival of patients with a poor prognosis. Our data show an increase in the likelihood of chylothorax in patients with a CDH when ECMO is used. Our data also show that the presence of a patch increases the likelihood of chylothorax. Because in a large number of infants who require ECMO a patch is present, ECMO is more likely to be a selection bias for the development of a CT than the cause of the CT.

It can not be excluded completely that direct trauma to the lymphatic ducts and a backpressure phenomenon caused by visceral herniation play a role in the pathogenesis of a chylothorax. The role of increased pressure caused by the ECMO cannula is not clear and is not supported by our study. Still, in cases of CDH repair in combination with ECMO treatment, the surgeon and pediatrician should be alert for the development of a chylothorax in the postoperative phase.

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Pharmacokinetics of morphine and midazolam in neonates during veno-arterial Extracorporeal Membrane Oxygenation (ECMO)

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chapter 5

Abstract

Adequate analgesia and sedation are cornerstones of Extracorporeal Membrane Oxygenation (ECMO) treatment protocols. Drug disposition is altered during ECMO. Most frequently used drugs in newborns on ECMO are benzodiazepines such as midazolam for sedation and morphine for analgesia. Studies on pharmacokinetics and pharmacodynamics of both medications are scarce. We conducted a prospective cohort study in neonates on ECMO to assess the pharmacokinetics of midazolam and morphine. This paper concentrates on the descriptive parameters of the patients and the plasma concentrations of morphine and midazolam in a group of 20 term newborns receiving veno-arterial-ECMO. Plasma concentrations of midazolam, 1-OH-midazolam, 1-OH-midazolamglucuronide, morphine, morpine-M3G and morphine-M6G were analysed at separate time points after discontinuation of morphine and midazolam just after cannulation and after reintroduction of the medication. Time to restart of medication was noted as well as the dosages of midazolam and morphine used during ECMO. Plasma concentrations showed great variability. All but two infants needed both midazolam and morphine for adequate sedation and analgesia. Although the pharmacokinetic data are of importance for our understanding of drug metabolism during veno-arterial -ECMO clinical practice and dose adjustment is guided by observational assessment using validated instruments such as the COMFORT-behavior scale and the visual analogue scale for pain.

Introduction

Extracorporeal membrane oxygenation (ECMO) was developed in the early seventies to provide partial heart-lung bypass for the neonate with life-threatening, reversible cardiopulmonary failure unresponsive to more conventional therapies. Adequate analgesia and sedation are cornerstones of ECMO treatment protocols. In general, sedation serves several purposes: to decrease anxiety, induce amnesia, decrease oxygen consumption and carbon dioxide production, prevent the patient from removing lines and promote synchronous breathing with the ventilator. In patients on ECMO sedation and analgesia seem even more critical since inadequate sedation with excessive patient movement may result in a position shift, or even dislodgement of the cannula causing a decrease in venous drainage and arterialized return. The most frequently used drugs for sedation in newborns on ECMO are benzodiazepines such as midazolam. Morphine and fentanyl are the most commonly used analgetics in this group of patients.[1] During ECMO, disposition of drugs is altered due to expanded blood volume and increased volume of distribution, an intrinsic increase in intra- and extracellular volumes, the presence of a non-pulsatile blood flow and reduced plasma protein concentrations with resulting effects on pharmacokinetics and dynamics.[2] Earlier studies on morphine pharmacokinetics reported an increased morphine clearance during ECMO and after discontinuation of ECMO.[3,4] However, Geiduschek et al. did not find a decrease of serum morphine concentrations after initiation of ECMO, but concluded that morphine clearance for infants receiving ECMO is variable.[5] The volume of distribution for midazolam in neonates on ECMO was 3 to 4 times greater compared to that in critically ill neonates not treated with ECMO together with an increased plasma half life.[6]

Although knowledge of the pharmacokinetics of sedation and analgesia during ECMO is increasing, assessment of the effect of sedation and analgesia in ECMO patients remains limited and standards are lacking. We conducted a prospective cohort study in neonates on veno arterial (VA)-ECMO to assess the pharmacokinetics and pharmacodynamics of midazolam and morphine. In this chapter we concentrate on the descriptive parameters of the patients and the plasma concentrations of morphine and midazolam (pharmacokinetics).

Patients and Methods

From September 2002 until September 2003 neonates younger than 7 days of age treated with veno arterial extracorporeal membrane oxygenation were included. Approval for this study was obtained from the hospital ethics review board. Parents were asked to give informed consent for blood sampling, effect observations and use of clinical data for research. Those who were expected to die within 24 hours were excluded.

Sedative and analgesic regimen

According to standard procedures infants received routinely 50 mcg/kg/hr morphine and 0.2 mg/kg/hr midazolam at the time of cannulation. Several minutes after cannulation morphine and midazolam were stopped. We created three groups for the reintroduction of medication; reintroduction of midazolam alone, reintroduction of morphine alone and reintroduction of morphine and midazolam at the same time. There was no formal randomisation, reintroduction of midazolam and/or morphine was decided on by the consultant in charge and morphine or midazolam could be freely added if thought necessary in the course of the ECMO run.

Assessment of pain and sedation

Time to reintroduction was noted. Depth of sedation was assessed every 3 hours using the COMFORT-behavior scale, which rates 6 behavioural items, each scored on a 5-pont scale, resulting in a total score from 6 (no distress) to 30 (severe distress).[7,8] In addition a Bispectral Index monitor (BIS) recorded a BIS-value at 60-minutes intervals (Bispectral A 2000 version 3.12, Aspect Medical Systems, Natick, MA, USA, with pediatric BIS sensors). The BIS values may range from 100 (awake) to 0 (iso-electric EEG). To determine whether restlessness was induced by pain, trained nurses obtained VAS pain scores [9] together with the COMFORT-score.[8]

Blood sampling

Blood samples were taken on predetermined time points after stopping midazolam and morphine and during 24 hours after reintroduction of the medication (*Fig. 1*). Steady state samples were taken thereafter approximately once a day during the ECMO run. Blood samples (500 microliter) were taken from the venous site of the ECMO system and were collected in heparin tubes. After collection the samples were centrifuged and stored at -80 ºC until analysis.

Analytical methods

Midazolam

Midazolam, 1-OH-midazolam and 1-OH-midazolamglucuronide concentrations were e measured in serum using high performance liquid chromatography (HPLC) with ultraviolet detection at 230 nm. Temazepam was used as internal standard. 500 µl 0.05 borate buffer (pH 9.2) was added to 200 µl serum. Following liquid-liquid extraction with 6ml dichloromethane, the organic layer was evaporated to dryness at 37 ºC. The mobile phase was prepared as follows: 400 µl phosphoric acid 85% and 146 µl tri-etylamine were added to 530 ml water. The pH was adjusted to 3.2 with 10% potassium hydroxide and 470 ml acetonitrile was added. The residue was reconstituted in 200 µl of mobile phase and 75 µl was injected onto the analytical column (Lichrosphere 100RP-18 encapped 5 µm, Merck). Total drug concentration of 1-OH-midazolam was measured after enzymatic hydrolysis of 200 µl serum with 100 Ul β-glucuronidase for 24 hours at 37 ºC. The difference between total and unconjugated 1-OH-midazolam was taken as the 1-OH-midazolamglucuronide. The limits of quantification were 11 µg/l for midazolam

and 6 µg/l for 1-OH midazolam using 200 µl of serum. Inter- and intra-assay coefficients of variation were less than 8% and 13% respectively. Total recovery exceeded 90% for both compounds.

Morphine
Serum concentrations were assessed by HPLC. Plasma 0.2 ml was mixed with 0.2 ml of 0.01 M ammonium hydrogen carbonate (pH 9.3) and spiked with 75 µl of appropriate dilutions of stock solutions of internal standards (Morphine-d_3 at 37.5 ng/ml; M3G-d_3 and M6G-d_3 at 18.75 ng/ml). The supernatant was extracted with solid phase columns (BOND ELUT C18,1ml and 100mg). The eluate was evaporated to dryness under nitrogen. The residue was dissolved in 75 µl of mobile phase, a mixture of acetonitrile and 10 mM of ammonium formate (pH 3.0) with formic acid (8/92, v/v) and was splitted with a ratio of 1/5 at the entrance of the mass spectrometer. A quadripole mass spectrometer (PE SCIEX API 150EX, Toronto, Ontario, Canada) equipped with a turbo ionspray interface was used for signal detection.
The intra-assay variability for all concentrations tested was below 10%. The inter-assay coefficient of variation for calibration standards and quality controls was also below 10%.

Data analysis
For this descriptive paper demographic data of the studied population are presented as median (IQR). Plasma concentrations of midazolam and morphine are plotted over two periods; period one after stopping the medication; period two after reintroduction of the medication.

Figure 1 Timing of blood sampling and COMFORT scoring

Time	**0**	**10 min**	**30 min**	**1 hr**	**3 hrs**	**6 hrs**	**12 hrs**	**18 hrs**	**21 hrs**	**24 hrs**
After stopping midazolam and/or morphine			x	x	x	x	x			x
After reintroduction of midazolam and/or morphine	x	x	x	x	x	x	x			x
COMFORT scoring	x			x	x	x	x	x	x	x

Results

Patients characteristics
From September 2002 until September 2003 27 infants received VA-ECMO support. Twenty of them were included in the study, because one died within 24 hours, 4 infants received ECMO when older then one month and the parents of two refused consent.
The characteristics of these 20 patients are presented in *Table 1*.

Table 1 Patient characteristics

	Total group n = 20
Gestational age (wk)	40.1 (38.3 to 41.6)
Birth weight (g)	3195 (2800 to 3650)
Males	9
MAS	10
CDH	6
Sepsis	2
PPHN	2
Apgar score at 1 minute	4 (2 to 7)
Apgar score at 5 minutes	7 (5 to 7)
Oxygenation index prior to ECMO #	38 (21 to 54)
AaDO2 prior to ECMO	599 (522 to 624)
Age at start of ECMO support (hours)	22 (9.5 to 107)
Duration of ECMO support (hours)	110 (74 to 162)

Data given are number of infants or median (IQR)
MAS *Meconium aspiration syndrome*
CDH *Congenital diaphragmatic hernia*
PPHN *Persistent Pulmonary Hypertension of the Newborn*
*Oxygenation index was calculated as: [(Mean airway pressure * FiO2)/PaO2] •100.*

Sedative and analgesic use

After cannulation both morphine and midazolam were discontinued in all patients, except for two cases in which morphine was continued accidentally. The median (IQR) interval between discontinunation of medication and reintroduction was 10 (7.8 to 27) hours.

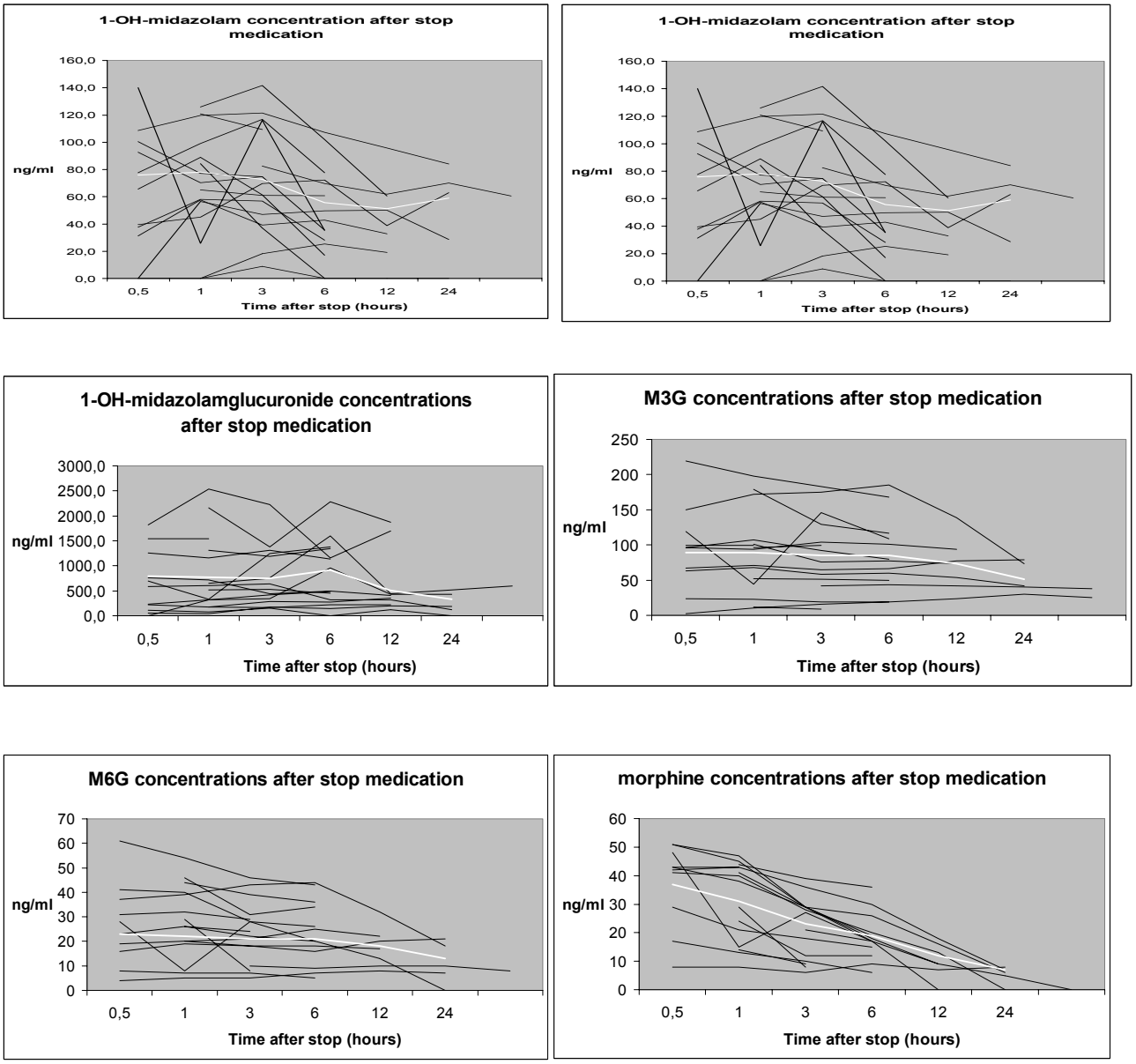
For reintroduction of midazolam and morphine we created three groups. The first group was to consist of 7 patients in whom midazolam alone was reintroduced. However, in 2 cases morphine was never discontinued. Then, in 4 other neonates of the first group morphine was eventually co-started after a median (IQR) period of 22 (18.5 to 24.8) hours because of insufficient sedation with midazolam alone. Thus in fact only one patient received midazolam alone as sedative during ECMO. The second group was to consist of 5 patients in whom morphine alone was reintroduced. However, only one infant in this group was adequately sedated with morphine alone. In the other 4 midazolam was also started after a median (IQR) of 7.5 (7.1 to 27,4) hours. The third group consisted of 8 patients in whom midazolam and morphine were reintroduced at the same time.

Median dosage of morphine used during ECMO support was 11.5 (10.1 to 15.5) µg/kg/hr. Median dosage of midazolam used during ECMO support was 0.15 (0.1 to 0.2) mg/kg/hr.

Plasma concentrations

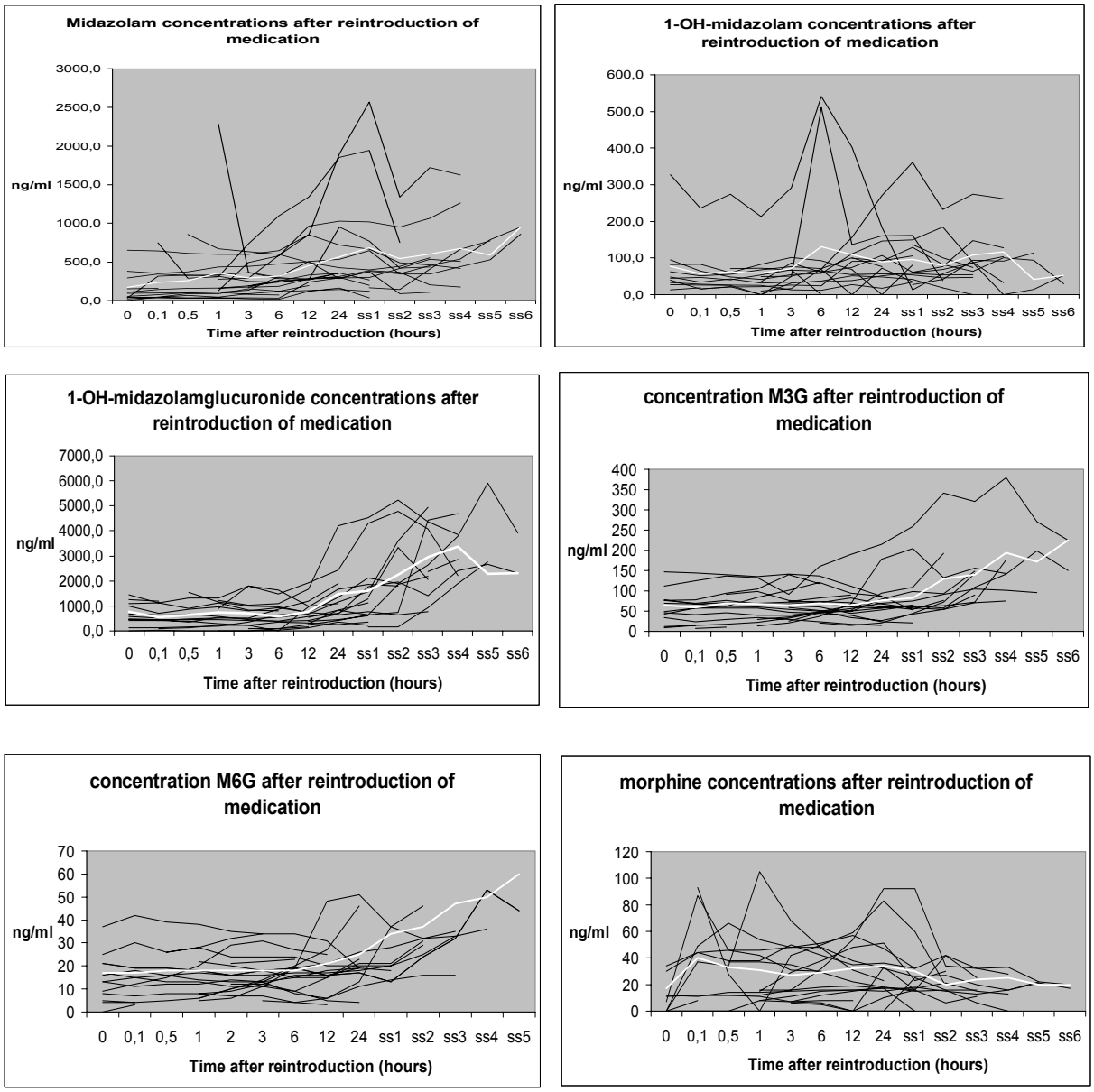
Plasma concentrations were measured after stopping midazolam and morphine and after reintroduction. Plasma concentrations over time of morphine, M3G, M6G, midazolam, 1-OH-midazolam and 1-OH-midazolamglucuronide are presented in *Figures 2 and 3*.

Figure 2 Midazolam, morphine and their metabolite concentrations after discontinuing medication by time of sampling



The white line represents the Mean

Figure 3 Midazolam, morphine and their metabolite concentrations after reintroduction of medication by time of sampling



The whiteline represents the Mean. Ss = steady state samples taken once a day

Discussion

Morphine and midazolam are often used in providing analgesia and sedation in neonates on ECMO. This paper describes the basic characteristics of a prospective cohort study in 20 neonates on VA-ECMO with the intention in the future to assess the pharmacokinetics together with the pharmacodynamics (COMFORT, VAS) of midazolam and morphine in the majority of cases. Midazolam and morphine alone did not provide adequate sedation and analgesia during ECMO. Plasma concentrations of morphine, M3G, M6G,

midazolam, 1-OH-midazolam and 1-OH-midazolamgluconoride showed great variability between patients and over time.

Morphine clearance for infants receiving ECMO has been described previously as variable. Geiduschek et al. found a mean morphine clearance, calculated on days 1, 3, and 5 of ECMO, of 11.7 +/- 9.3 (SD) ml/min/kg (range 2.6 to 34.5).[5] Peters et al. compared morphine clearance during ECMO to postoperative infants not receiving ECMO aged 0-3 years[3]. They found a decreased morphine clearance at the start of ECMO, increasing rapidly within 14 days to equal that of postoperative infants. They also reported a 38.7% between-subject variability of which weight and age information explained 83% of the overall clearance variability.[3] This finding suggests that increased clearance will result in decreased plasma concentrations and that dosing should be adjusted. However Dagan et al. found a lower morphine clearance during ECMO compared to the situation after decannulation.[4] In our patients we noted a progressive increase of both M3G and M6G in combination with a stable morphine plasma concentration. The interpretation of the balance between the anti-analgesic effects of M3G and the even higher analgesic effect of M6G compared to the native compound is dependent on the way caregivers assess levels of pain and/or sedation of the individual newborn.

Mulla et al. described the pharmacokinetics of midazolam in neonates receiving ECMO. Plasma concentration profiles of midazolam over time also showed great variability. Their main finding was that volume of distribution during ECMO increased from 0.8 (± 0.5) to 4.1 (± 5) l/kg. Consequently plasma half life increased.[6] A previous study by Mulla et al. described plasma concentrations of midazolam during ECMO. Mean plasma concentrations at 24, 48 and 72 hours increased, with levels at 48 and 72 hours exceeding those predicted, suggesting accumulation. The authors suggested that in the first 24 hours of ECMO, because of expanded circulating volume and sequestration by the circuit, significantly more midazolam is required to achieve adequate sedation.[10] However, with increasing distribution volume and increasing plasma half-life during ECMO, maintenance doses should be adjusted.

There are no published studies on the use of midazolam and morphine together. There are also no known effects of midazolam on morphine formation clearance to M3G and M6G. A possible reason is that morphine is metabolised in the liver by the enzyme UDP-glucuronosyl transferase (UGT2B7) into M3G and M6G, while midazolam is metabolised by the cytochrome P450 system (i.e. CYP3A4, CYP3A5 and to a much lesser extent by CYP3A7).[11,12] In principle our group of term newborns can be used as a model to evaluate the combined use of sedative and analgesic drugs in this specific age group.

With the variability in clearance and reported plasma concentrations of morphine and midazolam it remains difficult to predict pharmacodynamics. Initial dosing may be guided by age and weight, but changes in clearance and distribution volume (and their variability) during prolonged ECMO suggest that morphine and midazolam therapy

should be adjusted to prevent over- or under-sedation and should by guided by clinical monitoring. Estimating the efficacy in nonverbal patients is difficult. To quantify distress and levels of sedation, behaviour patterns can be measured using the COMFORT-bevavior scale.[8] A Bispectral index monitor (BIS) has also been described in assessing efficacy of sedation with propofol in infants under 2 years of age.[13] However, standards as well as studies on assessing efficacy of sedation and analgesia in neonates on ECMO are lacking.

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Sildenafil (Viagra) in neonatal persistent pulmonary hypertension during ECMO; a New Magic Bullet?

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chapter 6

Abstract

Recent observations of intracellular transport in smooth muscle cells suggest that the phosphodiesterase (PDE) inhibitor sildenafil (Viagra) is promising in the treatment of pulmonary hypertension in adults and children. Very little is known of its efficiency in neonatal persistent pulmonary hypertension (PPHN). We analysed retrospectively the effects of oral sildenafil in 15 consecutive neonates over more than two years with therapy resistant PPHN necessitating ECMO support. Eight survived (53%); seven, all with congenital diaphragmatic hernia, died. Survivors and non-survivors did not show significant differences in reduction of ECMO flow (p = 0.53) 24 hours after initiation of sildenafil or in duration of ECMO support (p = 0.23). The survivors had first received sildenafil significantly earlier after cannulation than the non-survivors; median (IQR) 41 (17 - 90) hours versus 200 (161 - 334) respectively (p < 0.01). Patients with concomitant iNO administration at the start of sildenafil showed greater reduction in ECMO flow over the next 24 hours than patients who received sildenafil only. Two patients were successfully decannulated after previous failure due to rebound pulmonary hypertension. In 12 patients a significant decline in systemic blood pressure over the first 2 hours after initial sildenafil administration of 9 mmHg (median) was established (p = 0.02), not dosage related.

We conclude that sildenafil therapy might be of benefit in individual cases of PPHN and that administration relatively early in the disease proces with concomitant administration of iNO might be favourable. In contrast with earlier studies in animals and adults, significant systemic hypotension was observed.

Introduction

While primary pulmonary hypertension (PPH) in adults and children is rare, pulmonary hypertension (PH) among neonates requiring neonatal intensive care is not a rare disease, with incidences ranging from 0.43 to 6.8 cases per 1000 live births).[1] PH in this group is subclassified according to the likely aetiology. The primary type is referred to as persistent pulmonary hypertension of the newborn (PPHN), or persistent foetal circulation, with pulmonary vascular resistance failing to decrease after birth despite radiographically normal lungs and no evidence of pulmonary parenchymal disease. The secondary type is associated with pulmonary parenchymal disease – as in meconium aspiration and hyaline membrane disease – or with hypoplasia of the lungs – as in congenital diaphragmatic hernia (CDH). Severe PH is also known to occur in infants following cardiothoracic surgery.[2] Severity of illness and likely outcome of neonatal PH are related to the underlying disease and to potential changes in pulmonary vascular architecture, comprising thickening of the adventitial and medial layers and muscularisation of precapillary vessels.[3] In the light of this heterogeneity, it is not surprising that so far no single therapy was found to be effective in all cases. Severe (therapy resistant) primary or secondary PPHN often leads to last resort support with Extracorporeal Membrane Oxygenation (ECMO), which is still unsuccessful in 6 - 46% of all neonates requiring ECMO, depending on the underlying pathology.[4]

Apart from specific measures to treat the underlying condition in secondary PHN, treatment of PHN is based on preventing hypoxia and boosting pulmonary vasodilatation by selectively decreasing pulmonary vascular resistance (PVR) without affecting systemic vascular resistance (SVR). New therapies such as endothelin receptor antagonists, chronic anticoagulation, calcium channel blockers, L-arginine or citrulline therapy, have been mostly designed for and tested in adults. They have led to sustained clinical and hemodynamic improvement as well as better survival in selective patients with PPH. Inhaled nitric oxide (iNO) is currently regarded as the gold standard therapy in PPHN.[5] It improves outcome in hypoxemic infants by reducing the incidences of the combined endpoints death or need for ECMO.[6] However, about 40% of patients fail to respond, to iNO therapy. Those who do respond may develop severe, life threatening, rebound hypoxemia and pulmonary hypertension on withdrawal of NO after long-term therapy.[7]

Continuous IV infusion of the prostacyclin (PGI2) epoprostenol (Flolan) has meanwhile become the mainstay of therapy for patients with PH other than PPHN.[8] Its efficiency has been demonstrated in patients of all ages, but significant drawbacks are the high costs and adverse effects such as major systemic hypotension and tachyphylaxia. Furthermore, administration is difficult because of its very short half-life of 3 - 5 minutes necessitating continuous IV infusion and the risk of acute withdrawal leading to fatal PH. All this makes the use of Flolan in the neonatal population particularly challenging.

Recent interest has turned to phosphodiesterase (PDE) inhibitor therapy. Integral components of cyclic nucleotide signalling, PDEs are crucial for signalling homeostasis, cell adaptation and in crosstalks between different pathways. PDE inhibitors block the hydrolysis of cyclic nucleotides, causing accumulation of cAMP or cGMP. In the lung, cGMP is a final messenger for vascular smooth muscle relaxation. It is metabolised by PDE5, the predominant PDE in normal lungs, which may be upregulated in PPH,[9] causing increased turnover of cGMP. Inhibition of PDE5 is therefore a logical step to increase bioavailability of cGMP and thus support endogeneous vasodilatition. Recent studies have explored the therapeutic potential of PDE5 inhibitor sildenafil (Viagra®) in PH. In adults with PPH, sildenafil was found to significantly improve effort tolerance, cardiac output and quality of life.[10-17] Its long-term safety and efficacy have not been established yet.[18] In animal models of acute and neonatal pulmonary hypertension it was shown to be a selective pulmonary vasodilatator with no effect on systemic arterial pressure.[19-21] Both animal and clinical studies in adults demonstrated that sildenafil, administrated orally, intravenously or in aerolized form, potentiated the effect of iNO and facilitated its withdrawal.[22-25] Current clinical experience with sildenafil in children is restricted to four single case reports,[13,25-27] three case series[11,14,22] and three randomised trials mainly in post-cardiac surgery patients beyond the newborn period.[28,29] Sildenafil was reported to be just as effective as iNO in improving pulmonary vasodilatation, with a combination of the two being more effective than either therapy alone. It was found to attenuate the rebound PHT associated with withdrawal of iNO and no side effects were noted on systemic arterial pressure. Sildenafil was reported to augment the pulmonary vasodilator effects of iNO early after surgery for congenital heart disease, although systemic hypotension was observed.[30] In view of the beneficial effects reported, sildenafil seems a promising agent in the treatment of PPHN.

Nevertheless, populations described in these reports vary, with only few neonates. Thus, in order to learn more about the administration of sildenafil in PPHN and its efficiency and side effects, we retrospectively analysed the administration of sildenafil and its efficiency in 15 neonates with therapy resistant PHN in the course of ECMO treatment. To our knowledge we are the first to do so.

Patients and methods

This analysis includes all neonates treated with sildenafil for PPHN and in need for VA-ECMO support hospitalised at the pediatric surgical intensive care unit (PSICU) of the Sophia Children's Hospital between March 2002 and June 2004.

The treatment algorithm used was based on publications as reviewed by Hansell in 2003.[4] Treatment included maesures for the apparent underlying disorder, adequate ventilation and lung recruitment using conventional artificial ventilation or high frequency oscillation (HFO), and administration of subsequently dopamine, dobutamine and noradrenaline to optimise systemic blood pressure and cardiac performance. Additional

iNO up to 20 ppm was administered as recommended by Clark et al.[6] If treatment failed, veno-arterial ECMO was instituted according to the "classical" criteria of the National Medical Center ECMO Team, which remained unchanged during the study period.[31] Cardiac ultrasound was performed before iNO or after ECMO was started. Sildenafil (Viagra®) administration was started when persistent pulmonary hypertension was assumed in spite of maximal conventional therapy. In the Netherlands sildenafil is available for enteral administration only. After an initial dose of 4 - 8 mg/kg, sildenafil was continued as a daily dose of 1 - 2mg/kg 12 hours after the first dose. Dosage was extrapolated from adult regimes using enteral doses.[32,33]

We considered consistency of sildenafil administration regarding indication, time, route and dosage. Effects and side effects of sildenafil were assessed from the following parameters: survival, time on ECMO, evolution of ECMO flow (ml/kg/min) and the relation with concomitant iNO administration, echocardiography and systemic blood pressure before and after administration of sildenafil, oxygenation index before and after ECMO, and prevalence of rebound PHT during sildenafil administration. In non-survivors, histopathology of the lung was performed and verified for the presence of PHT.

Data analysis
Precise data from continuous electronic data monitoring and registration (PDMS) over the study period were available for retrospective analysis.
Data are presented as median with interquartile range (IQR) due to skewed distribution. Mann-Whitney test or a chi-square test was used to compare data between subsets of the entire study population. The significance level was set at $p < 0.05$.

Results

Patient characteristics
During the study period, 52 neonates received VA–ECMO support. The overall mortalilty rate was 23%. Seventeen neonates had been treated with sildenafil during the same period. However, two of these were excluded from analysis because their maximal medical treatment did not include ECMO. In one, with left-sided CDH, ECMO was contraindicated due to chromosomal abnormality (unbalanced translocation in 12q). This patient eventually died of ventilatory complications. The other patient, with an omphalocele associated with lung hypoplasia, finally developed PH. He was considered as contraindicated for ECMO in view of the extent of chronic lung pathology. He died because of therapy resistant PH, confirmed by lung biopsy.

Characteristics of the remaining 15 patients are shown in *Table 1*. Nine of the 10 patients with CDH had left-sided CDH. Treatment with sildenafil was initiated at a median (range) age of 209 (8 to 3504) hours and at a median (range) time of 126 (-12 to 357) hours after start of ECMO. Oral dosage varied from 4 to 9 mg/kg/d (median 8) in 3 or 4 times daily (*Table 2*).

Table 1 Patient characteristics

	Total group n = 15	**Survivors n = 7**	**Deceased N = 8**
Gestational age (wk)	38^{+4} (38 to 40^{+2})	40 ($38^{=4}$ to 40^{+4})*	38^{+1} (37^{+2} to 39^{+4})
Weight at cannulation (kg)	3.3 (3 to 4)	4 (4 to5)#	3 (2.7 to 3.2)
Males/Females	6/9	2/5	4/4
CDH	10	2	8
PPHN	2	2	0
CCAML	1	1	0
Cardiomyopathy	2	2	0
Age at start of ECMO support (hrs)	24 (12 to 24)	12 (11 to 23)†	24 (24 to 288)†
Duration of ECMO support (hrs)	200 (149 to 302)	195 (122 to 235)‡	262 (152 to 349)‡
Oxygenation index prior to ECMO	49 (24 to 66)	26 (22 to 54)	50 (32 to 79)
Oxygenation index post ECMO	6.3 (3.4 to 15)	3.9 (1.5 to 7.7)§	7.7 (5.4 to 23)§

Data are presented as median (IQR) or number of patients.
CDH *Congenital diaphragmatic hernia*
PPHN *Persistent Pulmonary Hypertension of the Newborn*
CCAML *Congenital cystic adenomatoid malformation of the lung*
* *Survivors had significantly higher gestational age (p = 0.042)*
\# *Survivors had a significantly higher weight at time of cannulation (p = 0.007)*
† *p < 0.01*
‡ *p = 0.2*
§ *p = 0.052*

Table 2 Parameters of sildenafil administration

	Dose (mg/kg/d)	**Frequency (times daily)**	**P (t = 0) (mmHg)**	**P (t = 2) (mmHg)**	**Start after cannulation (hrs)**
Entire population (n = 15)	8.0 (6.0 - 8.0)	3.0 (3.0 - 3.0)	55 † (50 - 60)	46 † (45 - 53)	126 (41 - 204)
Deceased (n = 8)	8.0 (4.5 - 8.0)	3 (3.0-3.0)	53 (48-59) (n = 8)	45 (39 - 48) (n = 6)	200‡ (161 - 334)
Survivors (n = 7)	6.0 (6.0 - 8.0)	3 (3.0-4.0)	60 (55 - 62) (n = 7)	51 (45 - 53) (n = 6)	41‡ (17 - 90)

Data are presented as median (IQR).
P *(t = 0): mean arterial systemic pressure at sildenafil administration*
P *(t = 2): mean arterial pressure 2 hours after sildenafil administration*
† *p = 0.02*
‡ *p < 0.01*

Effects of sildenafil

1. ECMO flow reduction
   ECMO flow at (t = 0) and 24 hours after (t = 24) sildenafil administration was used to calculate flow reduction (*Table 3*). Survivors and non-survivors showed no significant difference in ECMO flow reduction. (p = 0.53).

2. Concomitant iNO administration
   Typically, iNO was stopped at the start of ECMO, but restarted however when ECMO flow did not diminish. Seven patients received iNO and sildenafil concomitantly; 4 survivors versus 3 non-survivors. Median (IQR) time on ECMO in the group without iNO was 279 (164 - 352*)* hours, in the group with iNO 179 (142 - 232) hours (p = 0.19).
   ECMO flows at initiation (t = 0) and 24 hours after (t = 24) sildenafil administration were compared between patients who received sildenafil as well as NO (10 to 20 ppm) and patients who only received sildenafil (*Table 3*). ECMO flow reduction was significantly greater in the former group (p = 0.048).

3. Time on ECMO support
   Median (IQR) ECMO support in the survivors was 195 (122 - 235) versus 262 (152-359) hours in the non-survivors (*Table 1*). This difference was not statistically significant (p = 0.23).

4. Echocardiographic findings
   Six patients (2 survivors, 4 non-survivors) underwent echocardiography both before ECMO and more than 48 hours after sildenafil administration. Amelioration of PH was expressed as reduction of pulmonary artery pressure based on tricuspidal incompetence (TI), ductal shunt velocities and artery Doppler acceleration time. Amelioration was observed in one patient, stable PH was observed in four, and one patient showed an increase in PH.

5. Mode of prescription
   Survivors and non-survivors did not show differences in median dosage (IQR); 6.0 (4.5-8) versus 8.0 (6 - 8) respectively (p = 0.96) or frequency of administration (both 3.0 times daily) (p = 0.40) (*Table 2*). Sildenafil was first administered significantly earlier after cannulation in survivors compared with non-survivors; i.e. median (IQR) 41 (17 - 90) hours versus 200(161 - 334) (p < 0.01)(*Table 3*). Proportions of patients who received both sildenafil and iNO did not differ between non-survivors and survivors (43% versus 50%) (Pearson Chi Square p = 0.78).

6. Prevention of rebound pulmonary hypertension
   In four patients complete weaning of ECMO (flow < 50 ml/min) had been unsuccessful first because of rebound pulmonary hypertension, but was successfully accomplished later on, after administration of sildenafil. Two of them died after all of rebound pulmonary hypertension after decannulation, proven by lung biopsy.

7. Side effects
   Change in mean systemic arterial pressure was calculated over the first 2 hours after initial sildenafil administration. Cardiovascular support for three patients had been changed in between first and final measurements and they were therefore excluded from analysis. The remaining 12 patients showed significantly diminished systemic arterial pressure (p = 0.02) (*Table 2*). Changes in mean systemic arterial pressure did not differ between survivors and non-survivors (p = 0.8). We did not establish a correlation with dosage (p = 0.4).

Histopathology

The eight non-survivors died at a median (IQR) age of 396 (300 - 463*)* hours, 69 (14 - 212) hours after decannulation. Cause of death was mostly PPHN. Histopathology revealed thickening of the adventitial and medial layers and muscularisation of precapillary pulmonary vessels. Two non-survivors died from causes other than circulatory failure; one because of ventilatory failure due to pulmonary parenchymal disease (prominent presence of hyaline membranes in lung autopsy and significant amount of pulmonary hypoplasia), one from sepsis. All non-survivors had CDH.

Table 3 Evolution of ECMO flow after administration of sildenafil (t = 0)

ECMO flow (ml/kg/min)	**t = 0 (hours)**	**t = 24 (hours)**	**t0-t24**
Entire population (n = 15)	24 (12 - 58)	22 (7 - 53)	3 (0 – 18)
Deceased (n = 8)	23 (5 - 50)	12 (0 - 48)	0 (0 – 30)
Survivors (n = 7)	58 (12 - 71)	30 (11 - 59)	4 (1 – 23)
iNO ⊕ (n = 7)	52 (0 - 66)	12 (0 - 48)	17 (0 - 30)†
iNO ∅ (n = 6)	19 (14 - 49)	28 (11 - 56)	0 (-9 - 3)†

Data are presented as median (IQR).
INO ⊕ *Coadministration of iNO and Sildenafil at t = 0*
INO ∅ *no iNO coadministered at t = 0*
† *p = 0.048*

Table 4 Oxygenation index pre- and postECMO

	OI preECMO (%)	**OI postECMO (%)**	**OI pre-postECMO (%)**
Entire population (n = 15)	49 (24 - 66)	6.3 (3.4 - 15)	29 (20 - 55)
Deceased (n = 8)	50 (32 - 79)	7.7 (5.3 - 23)	37 (21 - 75)#
Survivors (n = 7)	26 (22 - 54)	3.9 (1.5 - 7.7)	24 (18 - 47)#
NO ⊕ (n = 7)	65 (48 - 84) *	7 (3.8 - 14)	53 (32 - 80)$
NO ∅ (n = 7)	24 (21 - 49) *	5.6 (2.2 - 25)	20 (16 - 24)$

OI *oxygenation index*
INO ⊕ *Coadministration of iNO and Sildenafil at t = 0*
INO ∅ *no iNO coadministered at t = 0*
p = 0.06
$ *p < 0.01*
* *p < 0.01*

Discussion

In this study we described retrospectively our 2 years experience with enteral administration of sildenafil in 15 neonates for therapy resistant primary or secondary PHN during their time on veno-arterial ECMO.

We used ECMO flow reduction (ml/kg/min) as an indirect parameter to assess decline of pulmonary hypertension due to sildenafil administration. ECMO flow reduction at 24 hours after initial sildenafil administration tended to be higher in the survivors as compared with the non-survivors, but the difference was not significant. All non-survivors had CDH. Previously it was shown that only few CDH patients respond to iNO.[34] Aetiology and pathophysiology of PH in CDH is still not entirely understood and it might be different from other forms of neonatal PH.[35,36] Successful therapy therefore probably needs to be tailored to the individual situation.

Concomitant iNO administration seemed to have an additional effect on reducing PH. This was reflected by the observation that those with concomittant iNO showed greater ECMO flow reduction than did those treated with sildenafil only. Although three of the seven patients who received iNO concomitantly finally died, not PPH but sepsis and ventilatory failure were the cause of death in two of the three. In addition, the group who received iNO showed a significantly higher decrease in oxygenation index from cannulation to decanullation. Previous studies have already suggested that concomitant sildenafil and iNO administration would be more beneficial to PH than either one alone.[21-24]

The survival rate in our study population (47%) is less than that observed in the general neonatal ECMO population. This is not surprising in view of the fact that our study population cannot be considered representative for the general population. Moreover, the non-survivors' significantly lower gestational age and weight at cannulation as compared to the survivors might be considered extra risk factors for the bad evolution, but their immaturity could also be interpreted as the cause for being less susceptible to treatment; in fact they might be 'less-responders'.

Failure of weaning of iNO has been repoerted to become successful after sildenafil administration.[22,23] We noticed successful weaning of ECMO in four patients following sildenafil administration after earlier failure. Still, two of them later died because of rebound PH.

Amelioration of pulmonary hypertension could not be objectified by echocardiography (only in 1 out of 6 patients studied). Yet, little is known about correct estimation of PH by echocardiography during ECMO support as cardiac output is partially taken over by ECMO and TI is difficult to evaluate.[37] Furthermore, measurement of neonatal PH by echocardiography in general is not always straightforward.[38] Although echocardiography was performed in all patients before cannulation for ECMO, it was not standardly

performed after administration of sildenafil. Often clinical evolution, particularly when favourable, did not necessitate echocardiography.

In our population dose variation (4 to 9 mg/kg/d), frequency of administration (3 to 4 times daily) and survival were not correlated. Interestingly is the observation, in the survival group sildenafil was administered significantly earlier after cannulation than in the group of deceased patients, which might indicate that earlier administration in the disease proces is more efficient in reducing pulmonary hypertension. This could correlate with previous animal study observations that sildenafil does not only lower pulmonary vascular resistance by specific pulmonary vasodilatation, but also inhibits remodelling of the pulmonary vasculature.[39,40]

Although not observed in studies concerning sildenafil administration in animals and adults, we found a significant reduction in systemic blood pressure in our population, in line with the findings of a recent study concerning sildenafil administration in neonatal surgery for congenital heart disease.[30] Systemic hypotension can increase the pulmonary to systemic blood pressure ratio and consequently negate the beneficial effects of sildenafil, or even lead to circulatory failure when cardiovascular support already was maximised. Hence, sildenafil might not be a selective pulmonary vasodilatator in neonates. As we only examined differences in systemic tension after the first dose, which was a loading dose, and 3 - 4 times higher than the subsequent doses, fall in systemic tension could be related to the loading dose. However, we did not notice dose dependency. We also did not study the persistency of hypotension, which is an important factor. If persistency of hypotension would be confirmed in following observations and studies, the use of sildenafil in the neonatal population could be considered limited.

Our results should be interpreted cautiously, in view of the retrospective analytic nature of this study. Also, sample size is still small and a control group is absent. Procedures such as echocardiography were not standardised and medical treatment policy for iNO and sildenafil on ECMO were not protocolised. Moreover, we analysed indirect parameters such as ECMO flow, duration of ECMO support and survival as indicatiors of efficiency, but are well aware that these depend on several factors and are not only linked to the presence of PH, which makes interpretation delicate. Then, our study population can not be considered as representative for the general group of neonatal PPH. Firstl, PPH in our study population was highly severe, as reflected by the fact that all neonates required ECMO support that even threatened to fail. Second, the distribution and occurrence of the underlying pathologies do not match the general population and all patients contraindicated for ECMO are not represented.

Finally, we feel that route of administration could be a key factor determining the usefulness of sildenafil in the critically ill neonate. Oral administration, like in our study population, is associated with unpredictable bioavailability, which depends on absorption from the gastro-intestinal tract. The intravenous formulation would therefore seem

potentially more appealing in these patients. However, international multicenter studies are still hampered by the absence of a proper dose finding and safety study. In addition, other potential long-term risks like retinal damage linked to PDE6 inhibition[41,42] and specific issues like tolerance – requiring dose increase with long-term exposure – and rebound effects after withdrawal should be evaluated. Outcome measures should include evaluation of PH by regular echocardiography. Pharmacokinetic studies are necessary to determine optimal dosing of sildenafil in neonates of different gestational ages and weights.

In conclusion, in this small group of neonates with pulmonary hypertension receiving ECMO treatment the concomittant use of iNO and oral sildenafil significantly reduced ECMO flow. Despite the drawbacks of the study, we might conclude therefore that there might be a place for sildenafil in neonatal persistent pulmonary hypertension during the course of ECMO. Further multicenter, randomised controlled clinical trials using the intravenous formulation are warranted.

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Follow-up of newborns treated with Extracorporeal Membrane Oxygenation; a nation-wide evaluation at 5 years of age

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(Submitted)

chapter 7

Abstract

Background
Extracorporeal membrane oxygenation (ECMO) is a supportive cardiopulmonary bypass technique for babies with acute reversible cardiorespiratory failure. We assessed morbidity in ECMO survivors at the age of 5 years, when they start primary school and major decisions for their school careers must be made.

Methods
5-year-old neonatal venoarterial-ECMO survivors from the two designated ECMO centres in the Netherlands (Erasmus MC - Sophia Children's Hospital in Rotterdam, and University Medical Center Nijmegen) were assessed within the framework of an extensive follow-up program. The protocol included medical assessment, neuromotor assessment, and psychological assessment by means of parent and teacher questionnaires.

Findings
Seventeen of the 98 children included in the analysis (17%) were found to have neurological deficits. Six of those 17 (6%) showed major disability. Two of those six had a chromosomal abnormality. Three were mentally retarded and profoundly impaired. The sixth had a right-sided hemiplegia. These six children did not undergo neuromotor assessment. Twenty-four of the remaining 92 (26%) showed motor difficulties: 15% actually had a motor problem and 11% were at risk for this. Cognitive delay was identified in eleven children (14%). The mean IQ score was within the normal range (IQ = 100.5).

Interpretation
Neonatal ECMO in the Netherlands was found to be associated with considerable morbidity at 5 years of age. It appeared feasible to have as many as 87% of survivors participate in follow-up assessment, due to co-operation between two centres and small travelling distances. Objective evaluation of the long-term morbidity associated with the application of this highly invasive technology in the immediate neonatal period requires an interdisciplinary follow-up program with nation-wide consensus on timing and actual testing protocol.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass technique for providing life support in acute reversible cardiorespiratory failure when conventional management is not successful. Most patients receiving ECMO support are neonates suffering from persistent pulmonary hypertension of the newborn (PPHN), primary or secondary to meconium aspiration syndrome, sepsis or congenital diaphragmatic hernia. Worldwide, over 18,700 neonates have been treated with ECMO for respiratory problems, and the overall survival rate was 77% (ELSO Registry Report January 2004).

The UK Collaborative ECMO Trial Group in 1996 presented the results of a randomised controlled clinical trial, showing a significant survival benefit of ECMO, without a concomitant rise in severe disability at 1 year of age.[1,2] Even for the 35 neonates with congenital diaphragmatic hernia (CDH) the risk of death was reduced (RR 0.72, 95% CI 0.54 to 0.06; p = 0.03). However, of the 18 neonates with CDH allocated to ECMO, 14 died (one after discharge) and only three children survived to age 4. All 17 infants in the conventional management arm died before discharge.[3] No other therapeutic intervention (i.e., high frequency oscillatory ventilation, surfactant and inhaled nitric oxide) for neonatal acute respiratory failure has such a positive impact on mortality and morbidity.[4]

Nevertheless, the severity of illness of potential candidates for ECMO, as well as the risks associated with the procedure itself, places the ECMO survivor at high risk of developing brain injury and subsequent function deficits. All patients receiving ECMO support have suffered from severe respiratory failure prior to treatment. Prolonged episodes of severe hypoxaemia may occur, despite the administration of 100% oxygen. The inevitable high ventilatory pressures and hyperventilation may cause alterations in cerebral bloodflow.[5,6] In veno-arterial ECMO the right common carotid artery and right internal jugular vein are cannulated and subsequently ligated after bypass is finished. And finally, the heparin that is administered to prevent the blood from clotting might cause intracranial haemorrhage as a confounder for long-term morbidity. It is not easy, therefore, to predict the long-term outcome of neonates treated with ECMO. The few reports on structural follow-up of ECMO survivors either describe infants up to age 2 or patients from a single centre with wide age distribution.[2,7-14] They point out that logistic problems may prevent patients from being available for predetermined, structural evaluation. Major disabilities in terms of severe developmental delay or neuromotor disabilities were reported in some 20% of ECMO survivors.[2,7,9,11] The range of morbidity widens with evaluation after age 1, when assessment of cognitive skills, co-ordination, behavioural difficulties and sensory loss can be more precise.[15] Long-term longitudinal follow-up of these children seems thus essential for placing ECMO results in perspective. Only two studies describe longitudinal neurodevelopmental evaluation at school age.[15,16] Although surviving children treated for severe life-threatening respiratory failure soon after birth show considerable long-term morbidity, the results of the UK-ECMO trial point to a favourable profile of long-term morbidity in the group assigned to ECMO.[15]

Glass et al. reported a 61% response rate; 25% did not participate because of the long travelling distances in the USA.[16] In the Netherlands neonatal ECMO is provided in two designated centres only, authorised by the Dutch government. All parents of ECMO survivors are invited to enter their child in a redesigned follow-up program. High response rates are feasible because travelling distances are short in the Netherlands and regionalised high-risk perinatal care, including ECMO, is available. The children are scheduled to undergo assessment at ages 6, 12, 18 and 24 months and 5, 8 and 12 years. In this paper we present the follow-up findings at age 5 years, when children are in the first or second year of primary school and major decisions for their future school careers must be made.

Patients and methods

Patients

The study population included 5-year-old neonatal venoarterial ECMO survivors from both ECMO centres in the Netherlands, i.e. the Erasmus MC - Sophia Children's Hospital Rotterdam and University Medical Center Nijmegen. They were seen either between May 2001 and December 2003 (Rotterdam) or between March 1998 and December 2003 (Nijmegen).

Assessment protocol (*Fig. 1*)

Complete assessment included a one-hour medical assessment by a paediatrician/ neonatologist experienced in follow-up evaluation, a one and a half hour neuromotor assessment by a paediatric physiotherapist and a three-hour neuropsychological assessment by a psychologist or psychological test assistant. In Nijmegen a speech therapist assessed speech and language development, in Rotterdam the psychologist who performed the neuropsychological assessment. The complete assessment took place in one day. The sequence of the different assessments could vary for logistic reasons. In addition, one month before assessment parents were invited to complete questionnaires on parental socio-economic status and the child's current general health and behaviour.

Perinatal characteristics such as birthweight, gestational age, age at start of ECMO, duration of ECMO, primary diagnosis, and possible intra-cranial abnormalities were obtained from each centre's ECMO registry and are included in the ELSO registry (ELSO Registry Report January 2004).

Medical assessment

Medical assessment consisted of taking the child's medical history, measurement of growth parameters, and standard physical examination followed by standard neurological examination. Length and weight were expressed as SD score using the Dutch Growth Analyser, version 2.0 (Dutch Growth Foundation). The results of the neurological examination were categorised into normal (no neurological abnormalities), minor neurological dysfunction (neurological abnormalities without influence on normal posture

or movement) and major neurological dysfunction (neurological abnormalities with abnormal posture or movements, including seizure disorders).

Neuromotor assessment

The Movement Assessment Battery for Children (M-ABC) was used to measure motor functioning.[17] A Dutch standardisation study has shown that the original norm scores and cut-off points can also be applied to Dutch children. Good validity and reliability have been demonstrated.[17,18]

The M-ABC was developed for children aged 4 - 12 years. It has four age-related item sets, each consisting of eight items. Three manual dexterity items: a time-related task for each hand separately, a bimanual co-ordination task and a graphical task with the preferred hand. Two ball skill items: a task of catching a moving object and a task of aiming at a goal. Three balance items: static balance, dynamic balance while moving fast and dynamic balance while moving slowly. Scores may range from 0 - 5 for each item. A high score on the M-ABC indicates poor performance. The total impairment score, which is the sum of the item scores, was calculated into a percentile score. A score below the 5th percentile is indicative of a motor problem, a score between the 5th and 15th percentile means borderline performance and a score above the 15th percentile is a normal score.[17]

Exercise test. The children seen in Rotterdam performed a graded, maximum exercise test using a motor driven treadmill. The treadmill was programmed for increases in angle of inclination and speed every 3 minutes according to the Bruce-protocol.[19,20] The Bruce-protocol starts with a speed of 2.7 km per hour at an incline of 10%. The children are encouraged to perform to voluntary exhaustion. The maximal endurance time was used as criterion of exercise capacity and compared to data reported by Cumming and colleagues.[20]

Figure 1 Assessment protocol at 5 years of age

	Time (hours)	Instrument	Nijmegen	Rotterdam
Medical assessment (paediatrician)	1	Physical and neurological examination	x	x
Neuromotor assessment (paediatric physiotherapist)	1.5	Movement ABC	x	x
		Exercise test		x
Neuropsychological assessment (psychologist and speech therapist)	3			
Intelligence		RAKIT/WISC-R	x	x
Concentration		Bourdon-Vos		x
Visual-motor integration		Beery		x
Receptive language development		Reynell	x	x
Expressive language development		Schlichting	x	x
Behaviour		CBCL/TRF	x	x

Neuropsychological assessment

Cognitive development. A short version of the revised Amsterdam intelligence test for children (RAKIT) was used to evaluate cognitive development. The RAKIT is a well-known standardised instrument in the Netherlands for children aged from 4 - 11 years. Good reliability and validity have been demonstrated.[22,23] The short version contains six sub-tests. The raw sub-test scores are converted into standardised scores, which are then transformed into a short RAKIT IQ with a mean of 100 and a standard deviation (SD) of 15. Cognitive delay was defined by a test result of more than -1 SD below the norm (i.e., IQ ≤ 85).

Visual-motor integration. The Developmental Test of Visual-Motor Integration (VMI Beery) for children from 3 - 18 years measures the integration of visual perceptual and motor abilities.[24] Children are asked to copy figures of increasing geometric complexity. The computed raw item scores are transformed into a VMI standard score with a mean of 100 and a SD of 15.

Behaviour. The Dutch versions of the Child Behaviour Checklist (CBCL) and the Teacher's Report Form (TRF) were completed by parents and teachers, respectively.[25,26] Both have been standardised for the Dutch population from 4 - 18 years and rate 120 problem behaviour items on a 3-point scale ranging from 0 = not true, 1 = somewhat true or sometimes true, 2 = very true or often true.[27,28] A total problem score is computed by summing the scores of all items. Two broadband scales were constructed: an Internalising scale including withdrawn behaviour, somatic complaints without physical cause, and anxious-depressive feelings, and an externalising scale including aggressive and delinquent behaviour. Total scores ≥ 60 classify children in the borderline/clinical range.

Language development. Language development was assessed with the Reynell Test and the Schlichting Test. The Reynell test assesses receptive language development of Dutch speaking children between ages 1 and 6 years.[29] Expressive language is not required since the children may respond non-verbally.

The Schlichting Test assesses language expression of Dutch speaking children between ages 1 and 6 years.[30] Two subtests were applied, one testing knowledge of grammatical structure (syntactical development), the other measuring active vocabulary (lexical development).

The numbers of correct answers in the tests were transformed into standard quotient scores with a mean of 100 and a SD of 15. The following categories were discerned: delayed/abnormal development (score < -2 SD), at risk (score -1 to -2 SD) and normal (score > -1 SD).

Data analysis

Data are presented for the entire group and also by diagnosis. When appropriate an independent samples Student *t*-test was performed to analyse differences between the study group and general population norms with $p < 0.05$ for statistical significance.

A chi-square test was performed to test if the motor performance scores in this ECMO population differed significantly from the distribution in the normal population; *p*-values < 0.05 were considered statistically significant.

Results

A total of 144 neonates received VA-ECMO support from January 1996 up to and including December 1998. Thirty-one of them (22%) died before age 5 years, all during first admission at median age 21 days (IQR 11 - 35 days/range 2 - 120)). Fourteen infants were lost to follow-up for various reasons. Of two the present addresses could not be traced, the families of three moved abroad, and parental consent was withheld for five. Four other children failed to appear, even after repeated invitations. Thus, 99 infants participated in the follow-up program (*Fig. 2*.)
However, the parents of one child withheld consent to use data for publication purposes, so eventually we present data of 98 children (Rotterdam 35, Nijmegen 63) (87%).
Their perinatal and ECMO-treatment characteristics are presented in *Table 1*. Their basic characteristics at time of follow-up are presented in *Table 2*.

Figure 2 Flow sheet infants included in follow-up program.

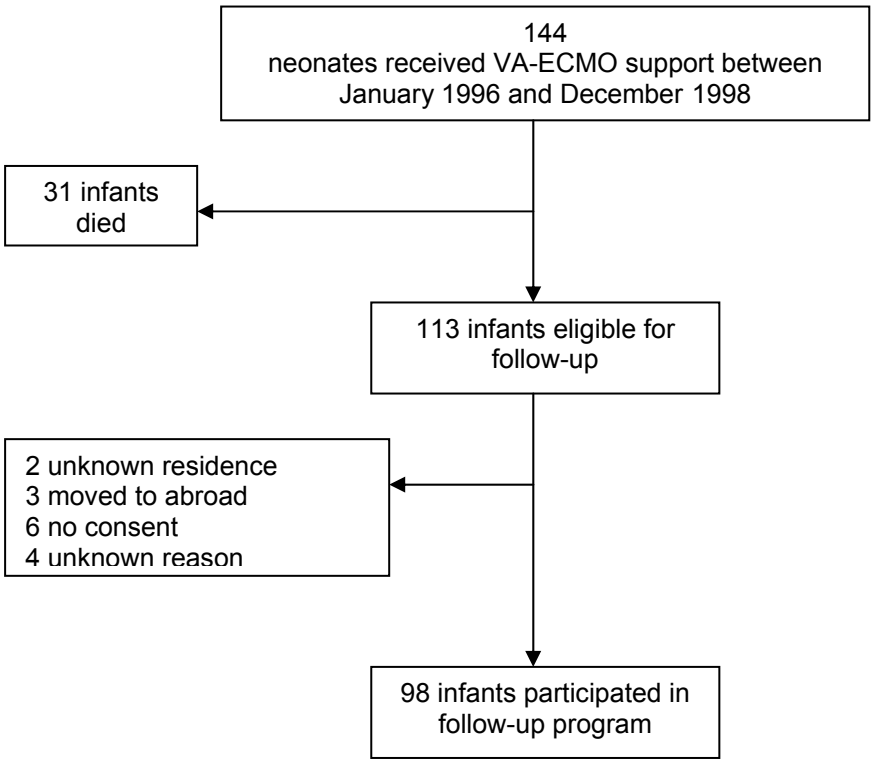

Table 1 Perinatal and ECMO characteristics

Male / Female		60 / 38
Birthweight (kg)		3.3 (2.9 - 3.8)
Gestational age (wk.)		40 (38 - 41)
Apgar score at 1/5 min.		5/7
Primary diagnosis:	MAS	51
	CDH	20
	Sepsis	11
	PPHN	15
	CCAML	1
Outborn (No.):		91
	Home	10
	> 20 km from ECMO centre	51
	< 20 km from ECMO centre	30
Oxygenation index prior to ECMO*		39 (24 - 58)
AaDo2*		622 (606 - 637)
Age at start of ECMO (hours)		28 (17 - 43)
Duration of ECMO support (hours)		155 (127 - 188)
Duration of mechanical ventilation (days)		16 (13 - 22)
Supplemental O2 after ECMO (days)		8 (4 - 16)
Duration of first admission (days)		38 (30 - 55)
Haemorrhagic intracranial abnormalities (No.)		
	Minor: IVH grade 1 and 2	8
	Major: IVH grade 3 and 4	0
Nonhaemorrhagic intracranial abnormalities (No.)		
	Minor: ventricular dilatation and focal atrophy	17
	Major: general atrophy and infarcts	4
Observed infants with epileptic insults (No.)		27
Patients treated with phenobarbital as prophylaxis (No.)		37
Duration of phenobarbital treatment in infants with epileptic insults (days)		49 (21 - 90)

Presented are the perinatal characteristics of the group of 98 children available for analysis. Data given are number (%) of infants or median (IQR).
MAS meconium aspiration syndrome.
CDH congenital diaphragmatic hernia.
PPHN persistent pulmonary hypertension of the newborn.
CCAML congenital cystic adenoid malformation of the lung.
Oxygenation index was calculated as [(Mean airway pressure × FiO2)/PaO2] × 100.
$AaDO_2$ Alveolar arterial oxygen distention gradient and was calculated as P_{atm}- P_{H2O}- PaO_2 - $PaCO_2$ (PaO_2 and $PaCO_2$ in mmHg).
IVH Intraventricular haemorrhage.

Table 2 Basic characteristics of the study group at 5 years of age

		Total group n = 98
Males/females		60/38
Age (months)		62 (3.0)
Weight SD score		-0.5 (1.5)*
Height SD score		-0.4 (1.2)**
Weight for height SD score		-0.4 (1.4)***
SES	High (%)	26 (27)
	Normal (%)	49 (50)
	Low (%)	19 (19)
	Unknown (%)	4 (4)
Ethnic group: White (%)		85 (87)
	African (%)	3 (3)
	Asian (%)	1 (1)
Turkish or Moroccan (%)		9 (9)

Data are presented as number (%) of patients or mean (SD).
SES: socio-economic status.
Mean weight, height and weight for height in SD score for the entire population were all significantly below zero (p = 0.001, ** p = 0.002, *** p = 0.008)*
Children with CDH had significantly lower height and weight than children with MAS (p < 0.001)

Outcome medical assessment

Seventeen children (17%) were found to have a neurological disorder. Six of those (6%) showed major neurodevelopmental disability, including two with a chromosomal abnormality. Of the latter, one was known with Down syndrome and the second (diagnosed with CDH) showed unbalanced translocation of chromosome 11 - 22 (unknown at the time of ECMO). This boy was severely impaired and mentally retarded, and is known to have died at age 6 years. One of the other four children with major neurological disorder had a right-sided hemiplegia caused by nonhaemorrhagic infarction during ECMO. He walked with an orthesis and attended special education. The second had developed a right-sided hemiplegia as a result of left-sided cerebral hemi-atrophy. He was confined to a wheelchair and was mentally retarded. The third (diagnosed with MAS) had severe asphyxia and had been resuscitated in the immediate postnatal period. Still suffering from a seizure disorder, she used a walking frame and was mentally retarded. The fourth suffered from seizures, used a wheelchair and was mentally retarded.

Eleven children (11%) showed minor neurological dysfunction, varying from strength differences in upper and lower extremities to very mild hemiplegia and a mild form of West syndrome (one child).

Mean (SD) weight and height in SD score for the entire population was -0.5 (1.5) and -0.4 (1.2), respectively (*Table 2*). Both were significantly below zero (p = 0.001 and p = 0.002 respectively). Eighteen children (18%) had respiratory complaints. Twelve of them regularly used a combination of beta-sympathicomimetic drugs and inhalation steroids. None of the children needed supplemental oxygen. Two children were followed

because of a muscular ventricular septal defect (VSD), without haemodynamic consequences; one because of atrial septal defect (ASD). One of the twenty children diagnosed with CDH was still on (nightly) tube feeding because of low weight (-3,4 SD) and pulmonary problems, and a second had received tube feeding until his fourth birthday. The child who was known with unbalanced translocation of chromosome 11-22 was fed through a gastrostomy drain and had undergone a Nissen fundoplication because of gastrooesophageal reflux. Another child, not diagnosed with CDH, was fed through a gastrostomy drain as well.

Outcome neuromotor assessment

Excluding the 6 children with major neurodevelopmental disability, 92 of the 98 children were tested using the Movement Assessment Battery for Children (M-ABC). Twenty-four children (26.1%) were classified as having some kind of motor difficulty (percentile score < P 15), which represents a significantly higher proportion than expected (Chi-square: $p < 0.005$).

Fourteen children (15.2%) had scores indicative of a motor problem (percentile score < P 5) (Chi-square: $p < 0.001$), ten (10.9%) had borderline performance (percentile score < P 15; > P 5) and 68 (73.9%) performed normally (percentile score > P 15) (*Table 3*).

A comparison with population norms revealed that the mean (SD) M-ABC score of the total group was significantly below reference value; 8.4 (8,1) versus 5.2 (5.6) $p < 0.001$.[17]

Table 3 Movement-ABC results

		Total group n = 92	MAS n = 49	CDH n = 19	Sepsis n = 11	PPHN n = 12
Total impairment score mean (SD)		8.4 (8,1)*	6.8 (6.6)	13.4 (10,3)	7.5 (7.5)	7 (7.1)
< P 5	motor problem n (%)	14 (15.2%)**	3 (6.1)	7 (36.8)	1 (9.1)	2 (16.7)
P 5 - P 15	borderline n (%)	10 (10.9%)	3 (6.1)	4 (21.1)	2 (18.2)	1 (8.3)
> P 15	normal n (%)	68 (73.9%)***	43 (87.8)	8 (42.1)	8 (72.7)	9 (75)

* *t-test* *significant p < 0.001*
** *Chi square* *significant p < 0.001*
*** *Chi square* *significant p < 0.005*

Table 4 Exercise test

			Total group n = 29	boys n = 15	girls n = 14
Endurance time in minutes (mean (S.D.))				9.0 (1.2)*	9.2 (1.8)
< -2 SD	abnormal	[n(%)]	1 (3.4%)	0	1
-1 SD - -2 SD	suspect	[n(%)]	8 (27.6%)	7	1
> -1 SD	normal	[n(%)]	20 (69.0%)	8	12

Score according to Cumming et al.
** t-test* *significant p < 0.001*

Twenty-nine of the 35 children seen in Rotterdam performed the exercise test according to the Bruce protocol (*Table 4*). Five children with major neurological impairment could not perform the test. One child (diagnosed with CDH) was too anxious to use the treadmill and performed a six-minute walking test instead. Height and weight of the 29 children (15 boys) were expressed as SD-scores. These were not significantly below or above reference value (SD = 0) and there were no significant differences between boys and girls. Comparison of endurance times to the Canadian norms reported by Cumming et al.[20] revealed significantly lower mean (SD) endurance time for the boys; 9.0 (1.2) versus 10.4 (1.9) ($p < 0.005$). Mean endurance time for the girls was not significantly different: 9.2 (1.8) versus 9.5 (1.8) ($p = 0.6$).

Outcome neuropsychological assessment

In order to create a mutually comparable group, three children with chromosomal or syndromal abnormalities as well as 11 children who did not have Dutch as a native language and one with severe hearing problems were excluded from data analysis. One child's data on all neuropsychological tests were lost, leaving 82 children for analysis. For three children all data on cognitive development were missing. Three children could not be successfully tested on expressive language, and one neither on expressive nor on receptive language. In Rotterdam visual-motor integration was tested in 28 out of 35 children. Major neurological impairment precluded testing in five children and data of two other children were missing. Neuropsychological outcome data are presented in *Table 5.*

Cognitive development Eleven children (14.1%) showed cognitive delay. The mean RAKIT score of the total group (IQ = 100.5) did not differ significantly from the Dutch norm.

Language development In the expressive language test, 13 children (16.7%) scored ≥1SD below the norm on grammar and vocabulary. In the receptive language test, six children (7.3%) scored ≥ 1SD below the norm. The mean scores on grammar and receptive language were significantly above the Dutch norm.

Visual-motor integration Seven children (25%) scored ≥ 1SD below the norm. The mean score of the total group did not differ significantly from the Dutch norm.

Behaviour The results of the Child Behaviour Checklist are presented in *Table 6.* Of all children, 12.8% had a total problem score above 63, indicating behavioural problems. Internalising problems occurred slightly more than did externalising problems.

Table 5 Neuropsychological outcome

	Total group (n = 82)
IQ (n = 79)	100.5 (19.7)
70 - 85	4 (5.1%)
51 - 70	3 (3.9%)
≤ 50	4 (5.1%)
Expressive Language (n = 78)	
Grammar	104.2[a] (17.9)
70 - 85	11 (14.1%)
51 - 70	2 (2.6%)
≤ 50	-
Vocabulary	103.2 (19.6)
70 - 85	6 (7.8%)
51 - 70	5 (6.5%)
≤ 50	2 (2.6%)
Receptive Language (n = 81)	104.3[a] (15.3)
70 - 85	1 (1.2%)
51 - 70	5 (6.1%)
≤ 50	-
Visual-Motor Integration (n = 28)	96.6 (13.7)
70 - 85	7 (25%)
51 - 70	-
≤ 50	-

Data are presented as mean (SD) and or as n (% of total number)
[a] *significant difference (p < .05) from the Dutch population norm*

Table 6 Child behaviour checklist

CBCL	**n = 86**
Total problem score	
< 60	72 (83.5%)
60 - 63	5 (5.9%)
> 63	9 (10.5%)
Internal problem score	72 (83.7%)
< 60	7 (8.1%)
60 - 63	7 (8.1%)
> 63	
External problem score	76 (88.4%)
< 60	6 (7.0%)
60 - 63	4 (4.7%)
> 63	

Presented are number of patients (%). The internal scale includes withdrawn behaviour, somatic complaints without physical cause and anxious-depressive feelings. The external scale includes aggressive and delinquent behaviour. Scores ≥ 60 but < 63 are in the borderline range. Scores ≥ 63 are in the clinical range.

Discussion

This report presents nation-wide neurodevelopmental sequelae of 98 VA-ECMO-treated neonates at age 5 years (87% of all survivors). Seventeen children (17%) presented with major or minor neurological disorders. Another 24 (26.1%) presented with some kind of motor difficulty, 14 of whom (15.2%) had an actual motor problem and ten (10.9%) were at risk for that. Cognitive delays were identified in eleven children (14%).

Two of the 17 children with neurological disability had a chromosomal disorder accounting for neurological impairment and one child had West syndrome associated with mental retardation and seizures. Four of the remaining 14 patients (14%) had major and 11 had minor neurological impairment without an underlying disorder. Our findings seem not completely consistent with findings reported by Glass et al.[16] in 103 children: 17% had one or more major disability versus 14% in our group. However, Glass et al. ranked mental disability, as well as motor disability and seizure disorders, also under major disability. Had we included children who scored abnormal in the medical, motor or mental assessment as well, we would have found a similar proportion (17%).

The UK-ECMO Trial Group has reported on the outcome of ECMO-treated neonates at age 4 years.[15] A consistent comparison is hampered by the fact that methods were different. In the UK one paediatrician assessed the children in six clinical domains, including cognitive ability, neuromotor skills, general health, behaviour, vision and hearing. Nineteen percent of the children had test scores outside the normal range. With regard to 'disability', 13% of the children were moderately to severely disabled, which is consistent with the 14% we report.

The rate of motor difficulties in our cohort was 26% (score < P15); 15% had an abnormal motor score (score < P5). This 15% exceeds the 6% reported by Glass et al.[16] Unfortunately, few follow-up studies have used standardised tests such as the M-ABC to assess neuromotor outcome. Even in our study some of the children with minor motor difficulties were assessed normal at neurological examination. However, in the M-ABC assessment they are stressed to move under velocity or accuracy demands. Such circumstances are more sensitive to detect motor performance problems. It is essential therefore that professionals with specific experience should assess the developmental domains in the context of a structured follow-up program.

In our study 29 children performed a maximum exercise test. The maximal endurance time was used as criterion of exercise capacity and we compared outcomes with data presented by Cumming and colleagues.[20] Binkhorst et al. in 1992 published references values for normal exercise performance in Dutch boys and girls aged 4 - 18 years using the Bruce treadmill protocol.[21] However, they included few 4-year-olds, the number of 6-year-olds is unclear, and did not provide means and standard deviations for these ages. This is why we did not use these Dutch reference values. Nevertheless 41% of the children in our study would score below the 5th percentile according to these Dutch

reference values. The question is whether this can be explained by impaired physical condition of ECMO-treated patients or by the fact that the reference values established by Binkhorst et al. insufficiently reflect the exercise performance of contemporary healthy Dutch children. Future studies are needed and will be performed in Erasmus MC – Sophia Children's Hospital in the near future.

Follow-up at age 5 is important because children are in their first or second year of primary school, at the start of their further school career. Eleven children (14%) showed cognitive delay, a proportion comparable to that reported by Glass et al. (13%). The IQ summary scores are comparable as well: 100 in our cohort versus 96. Although in the UK-ECMO trial cognitive ability at age 4 did not show evidence of a difference between the two trial groups, 26% of ECMO-treated children showed cognitive delay defined as an IQ>-1SD.[15]

Behavioural problems beyond the clinical cut-off point were identified in eleven children. These problems might contribute to school failure, even in the absence of cognitive delay.[31]
Language development scores were all above population norms. However, children without Dutch as their native language who had difficulty understanding and speaking Dutch were excluded from these tests. Still, language development seems not affected.

In the absence of a matched control group it remains difficult to establish to what extent ECMO treatment contributes to the outcome. The UK-ECMO trial did show a benefit of ECMO based on the primary outcome of death or severe disability. At age 4 there was no evidence of significant difference regarding cognitive ability and motor disability between the conventional treatment and ECMO groups.[15] The rate of disability (i.e. cerebral palsy) reported in a study of 89 surviving children with moderate to severe perinatal asphyxia at age 8 years was 15%. Ten percent had profound cognitive delay.[32] The intelligence quotient in a group of non-disabled children with mild and moderate perinatal asphyxia was 106 (±14).[32] These proportions are in the same range as the proportions reported in this study.

In conclusion, the outcome figures of ECMO-treated neonates at follow-up at age 5 years presented in this study do not greatly differ from those reported in previous publications on ECMO treated neonates.[15,16] The high response rate of 87 % (vs. 61% by Glass et al.) was feasible for various reasons: co-operation between two centres, small travelling distances as well as the quality of the health care system in the Netherlands. We believe that a successful follow-up programme of severely ill neonates should be structured in consultation with representatives from different disciplines, such as a paediatrician, a paediatric physiotherapist, a psychologist and a speech therapist. Further longitudinal follow-up studies will focus on the relationship between neonatal status and test results at 5 years and on detailed analysis of the different domains. Within the framework of the nation-wide follow-up program longitudinal data at ages 8 and 12 years are expected to become available in due time.

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Lung function during the first year of life in infants following extracorporeal membrane oxygenation (ECMO)

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(Submitted)

chapter 8

Abstract

Neonates with reversible cardio-respiratory failure may be treated with extracorporeal membrane oxygenation (ECMO). We evaluated lung function longitudinally at 6 and/or 12 months of age in a group of ECMO survivors. Functional residual capacity (FRC_p) and forced expiratory flow at FRC ($V'max_{FRC}$) were measured and expressed as Z scores. We studied 45 infants, 35 were evaluated at 6 months and 35 at 12 months; 25 infants completed both measurements. Mean (SEM) FRC_p in Z score was -0.2 (0.2) and 0.1 (0.2) at 6 and 12 months respectively. Mean (SEM) $V'max_{FRC}$ in Z score was significantly below normal values ($p < 0.001$) at 6 and 12 months: -1.3 (0.2) and -1.2 (0.2), respectively. Infants with congenital diaphragmatic hernia (CDH) had a higher mean (SEM) FRC_p in ml/kg compared to infants with meconium aspiration syndrome; 32.3 (2.4) versus 26.6 (1.3) ($p = 0.047$). In CDH infants, FRC_p in Z score was above reference value at 12 months of age ($p = 0.03$).

We conclude that during the first year of life, these infants have normal lung volume and reduced expiratory flow. Flows showed normal development at a level below average. This study is the first, providing data on longitudinal development of lung function post ECMO, in early infancy.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a supportive intensive care technique mainly used for newborn infants with acute reversible cardio-respiratory failure and a high mortality risk with conventional management. Conventional management ranges from pressure controlled ventilation to high frequency ventilation, with or without inhaled nitric oxide (NO). ECMO consists of prolonged cardiopulmonary bypass while resting the lungs and using minimal ventilator settings. It is thought that this promotes lung healing and prevents further injury from high oxygen concentration and barotraumas.[1] The UK ECMO trial conferred a survival advantage of ECMO over conventional management, without a concomitant increase in severe disability.[2,3] However, ECMO may promote survival of infants with severe respiratory dysfunction, who would otherwise have died. This could result in a poor respiratory status in infants treated with ECMO. On the other hand, the (early) institution of ECMO in selected cases avoids prolonged “aggressive” ventilation and its sequelae (inflammatory response, volutrauma), which has been shown to be associated with subsequent alterations in respiratory mechanics.[4,5] Hence, investigation of the respiratory function of survivors is important to assess whether or not ECMO results in a survival advantage.[6] Several groups studied respiratory function in infants during or shortly after ECMO,[7-9] at 6 months[10] or at 12 months.[6] These studies found a reduction in pulmonary function during the first year of life as sequelae of severe respiratory disease, despite ECMO. Longitudinal data are only available for infants during or shortly after ECMO, ranging from 1 day to1month after decannulation[7,8] To our knowledge, no study evaluated lung function in ECMO survivors longitudinally during the first year of life. Therefore, we evaluated lung function in a prospective longitudinal study at 6 and 12 months of age, in a group of ECMO survivors. Furthermore, we studied the relationship between lung function and perinatal patient characteristics.

Methods

Subjects

A follow-up study was conducted in neonates who received veno-arterial ECMO support between February 2001 and September 2003 at the Pediatric Surgical Intensive Care Unit of the Sophia Children's Hospital. ECMO support was given in case of reversible severe respiratory failure and when a mortality risk of 80% was estimated. Indications for ECMO were derived from the “classical” criteria of the National Medical Center ECMO Team, which remained unchanged during the study period.[11] Criteria used to define this mortality risk were an oxygenation index > 40 in 3 to 5 subsequent arterial blood gases, an alveolar arterial oxygen gradient ($AaDO_2$) > 600 during 8 hours with a FiO_2 of 100% and signs of barotrauma. Exclusion criteria for ECMO support were:

a. gestational age < 34 weeks or a birth weight of < 2 kg,
b. intraventricular hemorrhage grade II,
c. known bleeding disorders,

d. high pressure ventilation for more than 10 days prior to ECMO support,
e. any reason to question continuation of conventional management (for example a major congenital or chromosomal anomaly).

Artificial ventilation was administered by conventional mechanical ventilation (CMV) (Babylog 8000, Dräger Medical, Germany) or high-frequency oscillatory ventilation (HFOV) (Oscillatory Ventilator, model 3100A, Sensormedics, the Netherlands). The initial ventilation strategy was not randomized in our study. According to hospital practice surfactant therapy was occasionally used, based on the attendings preference, in the treatment of meconium aspiration syndrome (MAS). As a consequence Surfactant therapy was not randomized in this study. The study was part of a structured clinical follow-up program. According to the Dutch law, approval from a medical ethical committee was therefore not required. All parents gave written informed consent.

Lung function

The technique used in measuring lung function was previously described.[12] In brief, lung function measurements were performed at 6 and 12 months of age, when the infants had no signs of infection or acute respiratory symptoms for at least one week prior to testing. Infants with a known bronchopulmonary dysplasia (BPD), defined as oxygen dependence at age 28 days and a chest radiogram at one month of age typical for BPD, were excluded.[13] To prevent the infants from waking up during the measurements, they were sedated with choral hydrate (50 - 75 mg/kg). First, airway resistance was measured using the interrupter technique (R_{int}) (MicroRint, Micro Medical Ltd, Rochester, UK). Then, functional residual capacity (FRC_p) was measured by means of a modified whole body plethysmograph (Baby Body, Jaeger, Würzburg, Germany). Mean FRC_p of 3 to 5 technically acceptable measurements was expressed as Z score.[14] Finally, forced expiratory flow at FRC ($V'max_{FRC}$), used as a measure of airway patency, was assessed using the end-tidal rapid thoracoabdominal compression (RTC) technique (Custom-made equipment. Department of Experimental Medical Instrumentation, Erasmus University Medical Center, Rotterdam). Equipment and procedures were in accordance with guidelines.[14-16] Mean $V'max_{FRC}$ of 3 to 5 technically acceptable measurements was expressed as Z score.[17]

Analysis

Demographic data of the 25 infants with paired measurements were compared with the 20 infants with single measurements using Mann-Whitney of chi-square test where applicable. Lung function measurements at 6 and 12 months and lung function measurements of MAS and CDH were compared using mixed-model ANOVA (SAS, PROC MIXED). Where applicable, the difference in lung function was evaluated using paired Student's T-test or one sample T-test. The influence of various perinatal variables (gestational age, birthweight, number of surfactant dosages, mean airway pressure, age at start ECMO, duration of ECMO therapy, duration of oxygen and days of ventilation) on level of lung function was evaluated by multiple regression analyses. The significance level was set at $p < 0.05$.

Results

Between February 2001 and September 2003, 69 neonates received ECMO treatment of which 54 infants survived. Lung function measurements were performed from February 2002 until May 2004 in 45 infants. Four patients were lost to follow-up, the parents of one patient did not give consent, two patients were excluded because of BPD together with another patient who was neurological unstable, 1 patient did not sleep during the procedure (*Figure 1*). Except for the two infants with BPD, the oxygenation index and total days of mechanical ventilation did not significantly differ from the study group (data not shown).

Twenty-five infants were measured both at 6 and 12 months of age. Reasons for not completing both measurements were being older than 6 months at the beginning of the study (n = 10) or being younger than 12 months at the end of the study (n = 10).

Figure 1 Flow-sheet of included and excluded infants

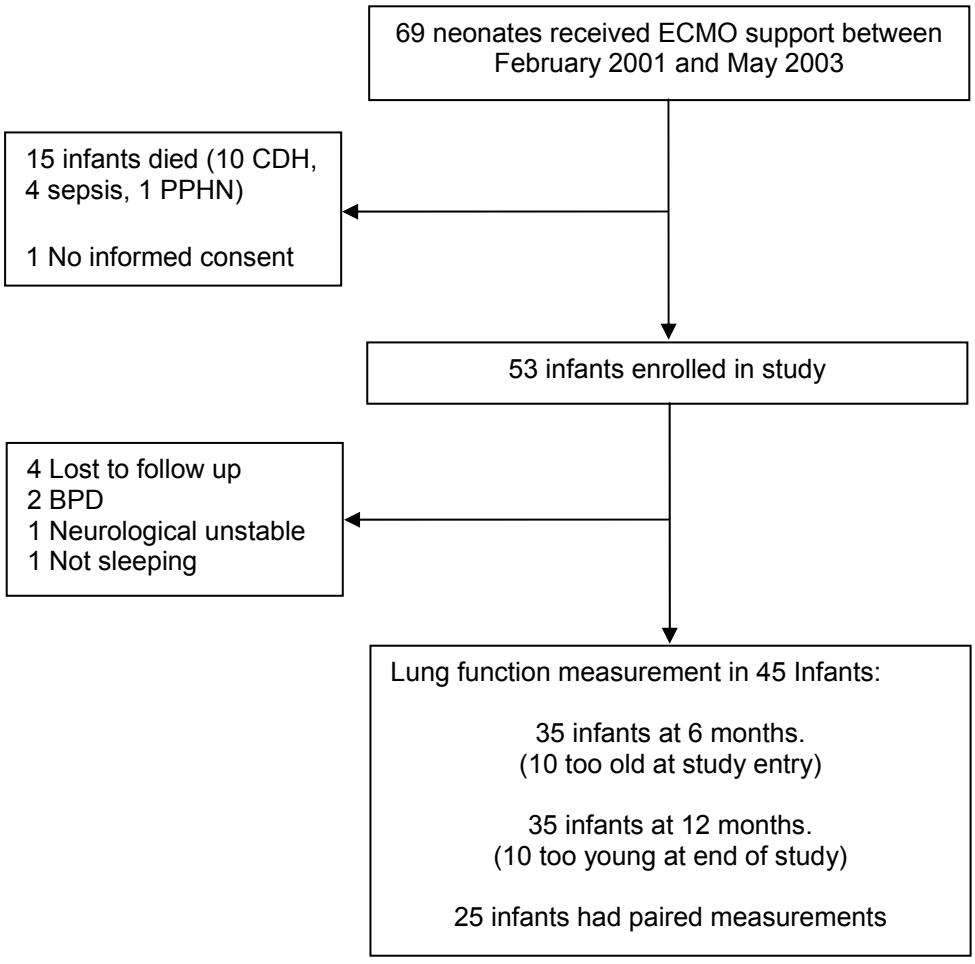


Table 1 Demographic data

	Total group **n = 45**	**Measurement at 6 months** **n = 35**	**Measurement at 12 months** **n = 35**
Gestational age (wk)	40.3 (1.4)	40.3 (1.2)	40.3 (1.4)
Birth weight (g)	3527 (570)	3497 (600)	3464 (499)
Males	23	18	19
MAS	26	21	20
CDH	8	5	7
Sepsis	3	1	3
PPHN	3	3	3
IRDS	5	5	2
Age at start of ECMO support (hours)	24 (5 - 398)	22 (5 - 398)	22 (5 - 252)
MAP prior to ECMO (cm H_2O)	20 (5)	20 (5)	20 (4)
PIP prior to ECMO (cm H_2O)	35 (8)	36 (7)	36 (8)
FiO_2 prior to ECMO	1 (0)	1 (0)	1 (0)
Oxygenation index prior to ECMO*	38 (10 - 167)	39 (10 - 143)	38(10 -167)
Inhaled NO prior to ECMO (ppm)	20 (0 - 40)	20 (0 - 40)	20 (0 - 40)
Duration of ECMO support (hours)	115 (53 - 253)	115 (53 - 238)	118 (53 - 253)
Duration of mechanical ventilation (days)[#]	14 (6 - 47)	14 (6 - 47)	14 (6 - 47)
Duration of oxygen dependence (days)	18 (5 - 76)	21 (8 - 74)	26 (5 - 76)
Surfactant treated newborns	18	14	15

Data given are number of infants or mean (SD) or median (range). Shown are the total group, and the subgroups of infants measured at 6 months, and measured at 12 months of age.

GA *gestational age*
MAS *Meconium aspiration syndrome*
CDH *Congenital diaphragmatic hernia*
PPHN *Persistent Pulmonary Hypertension of the Newborn*
IRDS *Respiratory distress syndrome of infancy*
MAP *Mean Airway Pressure*
PIP *Peak inspiratory pressure*
HFOV *high-frequency oscillatory ventilation*
FiO_2 *Fraction of inspired oxygen*
NO *Nitric oxide (parts per million)*
* *Oxygenation index was calculated as: [(Mean airway pressure * FiO2)/PaO2] •100*
\# *Duration of mechanical ventilation includes mechanical ventilation prior and after ECMO treatment*

Demographic data of the cohort of 45 infants are shown in *table 1*. Except for birthweight the demographic data of the 25 infants with paired measurements were comparable with the 20 infants with single measurements. Reasons for ECMO support were meconium aspiration syndrome (MAS) (n = 26), congenital diaphragmatic hernia (CDH) (n = 8), persistent pulmonary hypertension of the newborn (PPHN) (n = 3), sepsis (n = 3) and respiratory distress syndrome of infancy (IRDS) (n = 5). All CDH infants had undergone surgical repair after decannulation from the ECMO-circuit. The first and second lung function measurements were performed at a mean (SD) age of 6.4 (0.5) and 12.2 (0.6)

months, respectively. The results of the R_{int}, FRC_p and the $V'max_{FRC}$ measurements are shown in *table 2*.

Table 2 Lung function during first year of life in infants following ECMO

	Measurement at 6 months (Mean ± SEM)	**Measurement at 12 months** (Mean ± SEM)	**Mean difference** (95% CI)
Length (cm)	68.2 (0.5)	76,7 (0.5)	
Weight (kg)	7.4 (0.2)	9.5 (0.2)	
R_{int} (kPa/l/s)	3.5 (0.2)	3.2 (0.2)	-0.3 (-0.8 to 0.2)
FRC_p (ml/kg)	26.8 (0.9)	27.8 (1.0)	1.0(-0.5 to 2.5)
FRC_p (Z score)	-0.2 (0.2)	0.1 (0.2)	0.3 (-0.1 to 0.7)
$V'max_{FRC}$ (ml/s)	128.0 (11.7)	189.3 (14.6)	61.2 (36.3 to 86.1)*
$V'max_{FRC}$ (Z score)[†]	-1.3 (0.2)[#]	-1.2 (0.2)[#]	0.05 (-0.3 to 0.4)

Results of lung function measurements in infants following ECMO during the first year of life. At measurement 1 and 2, the mean (SD) corrected age was 6.4 (0.5) and 12.2 (0.6) months, respectively.
R_{int} *airway resistance measured by means of interrupter technique*
FRC_p *functional residual capacity*
$V'max_{FRC}$ *forced expiratory flow at FRC*
* *p < 0.0001*
[#] *Significantly below normal (p < 0.0001)*

For the whole group, mean (SEM) $V'max_{FRC}$ in Z score was significantly below zero which, for Z scores, corresponds to the normal value both at the first and second measurement ($p < 0.001$) (*table 2, figure 2*). Between the two measurements there was a mean (95% CI) change of $V'max_{FRC}$ in Z score of 0.05 (-0.3 to 0.4) ($p = 0.75$). Similar results were seen within the subgroup of 25 infants who completed both measurements: Mean (SEM) $V'max_{FRC}$ in Z score at 6 and 12 months was -1.5 (0.2) and -1.4 (0.2), respectively, with a mean (95% CI) difference of 0.1 (-0.3 to 0.4)($p = 0.67$).

Infants who received ECMO for MAS or CDH were analyzed separately. Their lung function results are shown in *table 3*. At 12 months of age, infants with CDH had a higher mean (SEM) FRC_p in ml/kg as compared to infants with MAS; 32.3 (2.4) and 26.6 (1.3) respectively, with a mean (95% CI) difference of 5.6 (0.2 to 11.0) ($p = 0.047$). FRC_p in Z score in CDH infants was significant above the reference value (Z score = 0) at 12 months of age (Mean (95% CI) difference: 1.3 (0.1 to 2.4) ($p = 0.03$)).

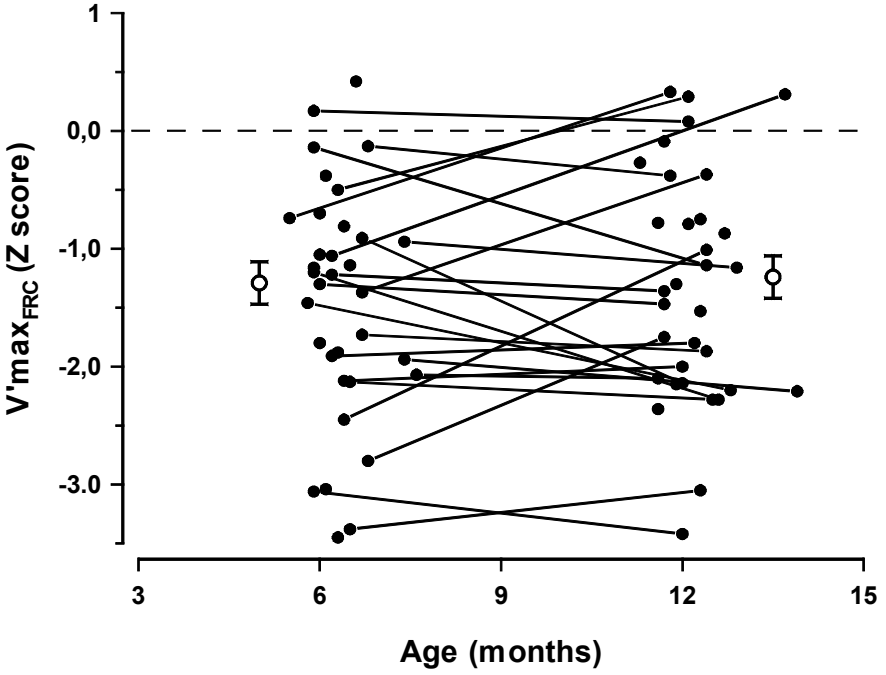
There was a significant correlation between days of mechanical ventilation (prior and after ECMO) and FRC_p in ml/kg and in Z score at 6 months ($r = 0.52$, $p = 0.002$ and $r = 0.54$, $p = 0.002$, respectively) and at 12 months ($r = 0.62$, $p < 0.001$ and $r = 0.66$, $p < 0.001$, respectively) (*Figure 3*) None of the other perinatal patient characteristics, including age at receiving ECMO or the duration of ECMO, correlated with lung function parameters when adjusted for the effect of days of mechanical ventilation.

Table 3 Lung function differences between MAS and CDH

	Measurement at 6 months			Measurement at 12 months		
	MAS n = 21	**CDH** n = 5	**Mean difference** (95% CI)	**MAS** n = 20	**CDH** n = 7	**Mean difference** (95% CI)
$\mathbf{R_{int}}$ (kPa/l/s)	3.8 (0.3)	3.2 (0.5)	-0.5 (-1.7 to 0.5)	3.2 (0.3)	3.3 (0.4)	0.1 (-0.9 to 1.1)
$\mathbf{FRC_p}$ (ml/kg)	26.4 (1.2)	30.4 (2.4)	3.9 (-1.4 to 9.2)	26.6 (1.3)	32.3 (2.4)	5.6 (0.2 to 11.0)*
$\mathbf{FRC_p}$ (Z score)	-0.2 (0.3)	0.7 (0.5)	0.9 (-0.3 to 2.1)	-0.1 (0.3)	1.1 (0.6)#	1.3 (0.0 to 2.6)
$\mathbf{V'max_{FRC}}$ (ml/s)	106.0 (13.8)	122.9 (27.4)	17.0 (-43.1 to 77.1)	177.8 (20.2)	193.3 (34.9)	15.5 (-63.7 to 94.7)
$\mathbf{V'max_{FRC}}$ (Z score)	-1.7 (0.2)	-0.9 (0.4)	0.8 (-0.1 to 1.7)	-1.5 (0.3)	-1.0 (0.4)	0.4 (-0.6 to 1.4)

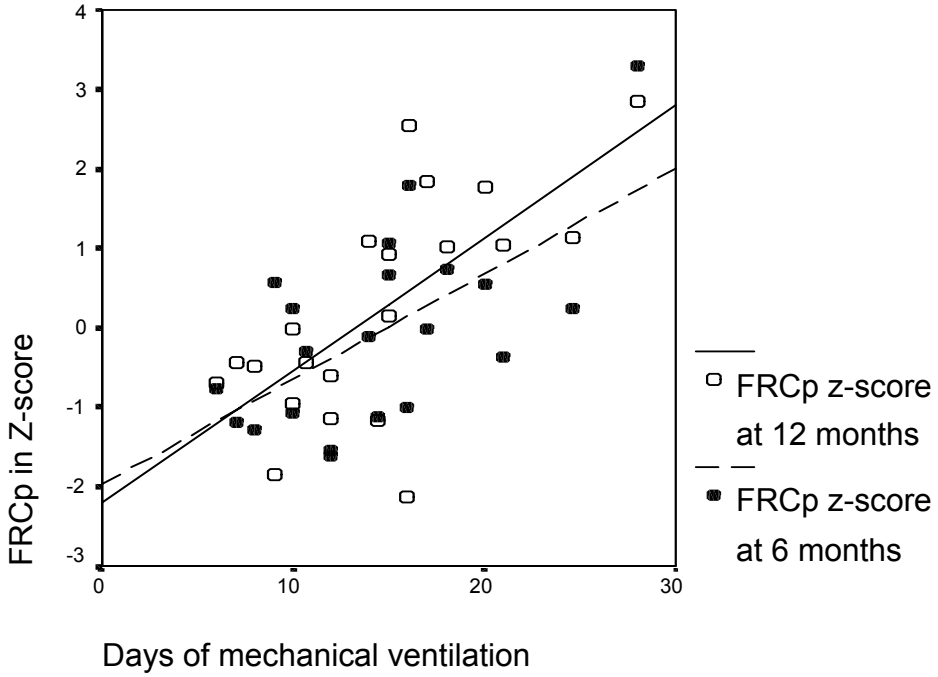
Mean (SEM) lung function data between infants who received ECMO because of meconium aspiration syndrome (MAS) or congenital diaphragmatic hernia (CDH)
* *p = 0.047*
\# *Significantly above reference value (p = 0.03)*

Figure 2 Lung function data of 36 infants following ECMO



Lung function data of 45 infants following ECMO. The first (n = 35) and second (n = 35) measurement were done at a mean (SD) age of 6.4 (0.5) and 12.2 (0.6) months, respectively. Mean (SEM) $V'max_{FRC}$ in Z score was -1.3 (0.2) and -1.2 (0.2) at the first and second measurement respectively. Twenty-five infants completed both measurements (connected datapoints).

Figure 3 Correlation between FRC_p in z-score and days of mechanical ventilation



Correlation between FRC_p in Z score and days of mechanical ventilation. There was a significant correlation between days of mechanical ventilation (prior and after ECMO) and FRC_p in Z score at 6 months (r = 0.54, p = 0.002 resp.) and at 12 months (r = 0.66, p < 0.001).

Discussion

In this study we prospectively evaluated lung function during the first year of life in a cohort of 45 infants who received ECMO support. Furthermore, we studied the relationship between lung function and perinatal patient characteristics. We found normal lung volume and subnormal forced expiratory flow during the first year of life.

To our knowledge, this is the first longitudinal study on the growth of airway function during the first year of life in survivors of ECMO. Two cross-sectional studies were published. Greenspan and colleagues[9] studied pulmonary function in 25 infants prior to ECMO, immediately after decannulation and at time of nursery discharge at approximately 1 month of age. FRC at time of discharge were comparable with our results; i.e. 26 ml/kg. The $V'max_{FRC}$ is best compared when using the normative data by Sly and colleagues.[15] the $V'max_{FRC}$ in Z score at 1 month of age in this study was approximately -0.3 SD. It was not feasible to calculate the $V'max_{FRC}$ in Z score using the normative data by Hoo and colleagues, as no information about length at time of measurement was provided.

Beardsmore and colleagues[6] found a $V'max_{FRC}$ at 12 months of -1.6 SD in Z score (personal communication A. Hoo), using the normative data by Hoo and colleagues.[17]Using the normative data by Sly and colleagues,[15] the $V'max_{FRC}$ is

approximately -1.7 SD. These cross-sectional data from different studies suggest a decrease in forced expiratory flow during the first year of life in ECMO survivors. This is in contrast with our longitudinal data, which shows a normal FRC_p and $V'max_{FRC}$ values at a level below average but without a decrease during the first year of life. It can be speculated that clinics have different criteria for ECMO, and this could explain discrepant follow-up results. For example, we placed infants on ECMO earlier compared with Beardsmore and colleagues (median (IQR) age in hours: 24 (13 - 46) versus 32 (19 - 68).[6] However, this is difficult to substantiate, also because data on the oxygenation index prior to ECMO were not available from the study of Beardsmore and colleagues.

It is not clear what the separate effects are of mechanical ventilation on the one hand, or the underlying disease on the other hand. One could hypothesize that, if infants received ECMO support earlier, the duration of mechanical ventilation and its potential negative effects is reduced which could lead to “improved” lung function. However, we did not find a correlation between lung function and the age (hours after birth) at receiving ECMO. In contrast, we did find a significant correlation between days of mechanical ventilation (prior and after ECMO) and FRC_p in ml/kg and in Z score at 6 and at 12 months. A possible explanation could be that mechanical ventilation leads to peripheral airway damage, which could lead to airtrapping. Conversely, one could reason that the increased lung volume after prolonged ventilation is not the result of this ventilation, but infants with increased lung volume, possibly due to increased gastrapping, were more likely to require prolonged ventilation.

When infants were subgrouped by primary reason for ECMO, infants with CDH had a higher mean FRC_p in ml/kg at 12 months of age, as compared to infants with MAS. In CDH infants, FRC_p in Z score was significant above reference value at 12 months of age. Helms and Stocks found normal lung volumes (FRC_p) in 4 infants and low lung volumes in 5 infants with a surgically repaired CDH at the postnatal age of 2 to 8 weeks.[18] They argued that a normal lung volume in these infants does not necessarily mean that intrauterine lung development has been normal. The development of a normal lung volume later in infancy[19] may be the combined result of alveolar distension and destructive emphysema of a hypoplastic lung.[20,21] Nagaya and co-workers studied lung volume at 3 months of age, by computed tomography scan, and pulmonary perfusion in infants following surgical repair of CDH and ECMO treatment.[22] They found that these infants had low ipsilateral lung volumes (61% of contra-lateral lung volume), which increased during follow-up to 88% of contralateral lung volume. In contrast, the perfusion of the affected side remained low, or decreased to below the initial value. It was concluded that the lung of the affected side has limited ability to develop arterial branches and that enlargement of lung volume may depend on over-expansion or even progressive emphysema, rather than tissue growth.[22] To our knowledge, our study is the first that found an increased lung volume in infants following surgical repair of CDH and ECMO treatment. Possibly, with the introduction of ECMO, more severe cases of CDH have survived, with consequently more severely hypoplastic lungs. We speculate that a high-normal lung volume is most likely explained by hyperinflation of a hypoplasitc lung.

However one must take into account that sample size differences between the two groups may have affected these results.

We did not find a correlation between age at receiving ECMO and any lung function parameter. This is in contrast with Greenspan and coworkers who found that infants who received ECMO late had lower V'max$_{FRC}$ at discharge, as compared with infants who received ECMO earlier.[9] However, as Greenspan and coworkers studied the infants at discharge, at approximately 1 month of age, an effect of age at receiving ECMO on lung function may only be present during the first months of life.

We conclude that during the first year of life, infants who received ECMO support had a normal FRC$_p$ and reduced expiratory flows, with a normal development of flow at a level below average. We interpretate the findings with prudence, considering the lack of a comparison group and the limited number of repeated measurements in these infants with a variety of underlying diagnosis. Still, this study does not only contribute to our understanding of the effects of ECMO in severe respiratory insufficiency, but also provides data on longitudinal growth of lung function in early infancy.

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WH and MNH contributed equally to the manuscript.

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Lung function at ages 5 and 8 years following Extracorporeal Membrane Oxygenation

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chapter 9

Abstract

Extracorporeal membrane oxygenation is a life-saving therapy for neonates with potentially reversible cardio-respiratory failure. Lung function was evaluated in 28 5-year-old and in 14 8-year-old ECMO survivors hypothesising that airway obstruction would already be observable in children at these ages.

Airway resistance was measured using the interrupter technique (R_{int}) during expiration and expressed as Z score at both 5 and 8 years. Together with measurements of FVC, FEV_1, FEV_1/VC-ratio and MEF_{25} using a spirometer. At 8 years helium dilution was used to determine TLC_{he}, residual volume of helium (RV_{he}), $VC_{he,}$, FRC_{he} and RV/TLC-ratio.

Mean (SEM) airway resistance was for both 5 and 8 year olds within normal range; 0.3 (0.3) resp. 0.8 (0.3). After bronchodilatation airway resistance decreased significantly in both age groups to -0.8 (0.3) and -0.8 (0.3) respectively.

Mean (SEM) FEV1/VC ratio and MEF_{25} before bronchodilatation in 8-year-olds showed mild airway obstruction; 86 (2) and 57 (8) respectively. Values were significantly lower than that in 5-year-olds (p = 0.01 and p = 0,03). Diffusion capacity was within the normal range. Despite the limitations of this study these data confirm the presence of long-term pulmonary sequelae despite the use of lung rest during ECMO.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a heart-lung bypass system that can be used as a life-saving treatment modality in neonates with severe but potentially reversible cardio-respiratory failure. Conditions most commonly treated with ECMO in the neonatal period are meconium aspiration syndrome (MAS); primary or secondary persistent pulmonary hypertension of the newborn (PPHN); congenital diaphragmatic hernia (CDH); sepsis; and pneumonia. One of the major problems in treating neonates with severe respiratory failure is that extremely high ventilator settings are required to keep these patients alive. Aggressive ventilation with high oxygen concentrations and damaging pressures can lead to pulmonary barotrauma and oxygen toxicity.[1,2] During ECMO the ventilator can be turned back to mild settings and allow the lungs to 'rest' modifying the severity of chronic lung disease, while the patients vital functions are safely supported. On the other hand, ECMO may promote survival of infants with severe respiratory dysfunction, who would otherwise have died. Survival could then potentially result in a poor respiratory status on the long term. In fact, reported incidences of bronchopulmonary dysplasia (BPD) in newborns treated with ECMO range from 4% to 38%, and there is an association with delayed use of ECMO.[3]

Data on long-term pulmonary outcomes following ECMO are limited. Boykin et al. reported mild lower airway obstruction and air trapping in ECMO survivors at 10 - 15 years of age.[4] Recently Hamutcu et al. also found airway obstruction in a group of 50 ECMO survivors aged 9 - 13 years.[5] Since February 2002 we have been performing lung function tests on a regular basis as part of an extensive prospective follow-program for children treated with ECMO. Pulmonary function is measured at ages 6 and 12 months and at ages 5, 8 and 12 years. In addition we retrospectively studied lung function of ECMO-treated children aged 5 and 8 years. Our hypothesis was that airway obstruction would already be observable in children at these ages.

Patients and methods

The study population included 5- and 8-year-old neonatal venoarterial ECMO survivors. Lung function tests were performed between February 2002 and December 2004.
Clinical data were obtained from the charts, including underlying diagnosis, birthweight, gestational age, oxygenation index prior to ECMO, maximum dosage of inhaled nitric oxide (iNO) prior to ECMO, mean airway pressure (MAP), number of pneumothorax prior to ECMO, age at onset of ECMO in hours, duration of ECMO support in hours, duration of mechanical ventilation and duration of oxygen dependence in days.
At the time of lung function testing a medical history was taken including personal history of atopy and lung disease, presence of respiratory symptoms and use of medication for pulmonary diseases. Physical examination was performed including length, weight, heart rate, blood pressure and auscultation of heart and lungs.

Lung function testing

At 5 and 8 years

Airway resistance was measured using the interrupter technique (R_{int}) during expiration (MicroRint, Micro Medical Ltd, Rochester, UK). R_{int} values are expressed as z-score using reference values by Merkus et al.[6]

Dynamic lung volumes were obtained using a heated Fleisch pneumotachograph (Number 3.1184; Godart Statham, Bilthoven, The Netherlands) connected to a computer or a water-sealed spirometer (Volutest Model VLT; Mijnhardt, Zeist, the Netherlands). FVC, FEV_1, FEV_1 /VC-ratio and maximal expiratory flows at 25% of the FFVC (MEF_{25}) were determined and the best of three consecutive measurements was recorded. All values, except FEV_1/VC-ratio, were expressed as percentage of predicted values.[7]

Measurements were performed before and after inhalation of 1 mg of terbutaline.

At 8 years

A water-sealed spirometer (Expirograph; Godart Statham, Bilthoven, the Netherlands) filled with a known concentration of helium was used to determine TLC_{he}, residual volume of helium (RV_{he}), $VC_{he,}$, FRC_{he} and RV/TLC-ratio. Volumes were expressed as percentage of predicted values except for RV/TLC-ratio.[7]

When children were able to perform the above-mentioned tests, bodyplethysmography (Jaeger Masterlab, Würzburg, Germany) was also performed to determine TLC_{pleth}, RV_{pleth}, and RV/TLC_{pleth}. Volumes were expressed as percentage of predicted values except for RV/TLC. Then carbon monoxide diffusion capacity (D_{Lco}) was measured using a single breath method (Jaeger Masterlab, Würzburg, Germany). Reference values for D_{Lco} and D_{Lco} corrected for alveolar volume (D_{Lco}/V_a) were based on a study by Stam et al.[8]

All lung function tests were performed with subjects in sitting position.

Data analysis

All data are expressed as median (IQR) or mean (± SEM) unless stated otherwise.

Differences before and after bronchodilatation and differences between the two age groups were tested with the Mann-Whitney U test. Significance level was set at $p = 0.05$

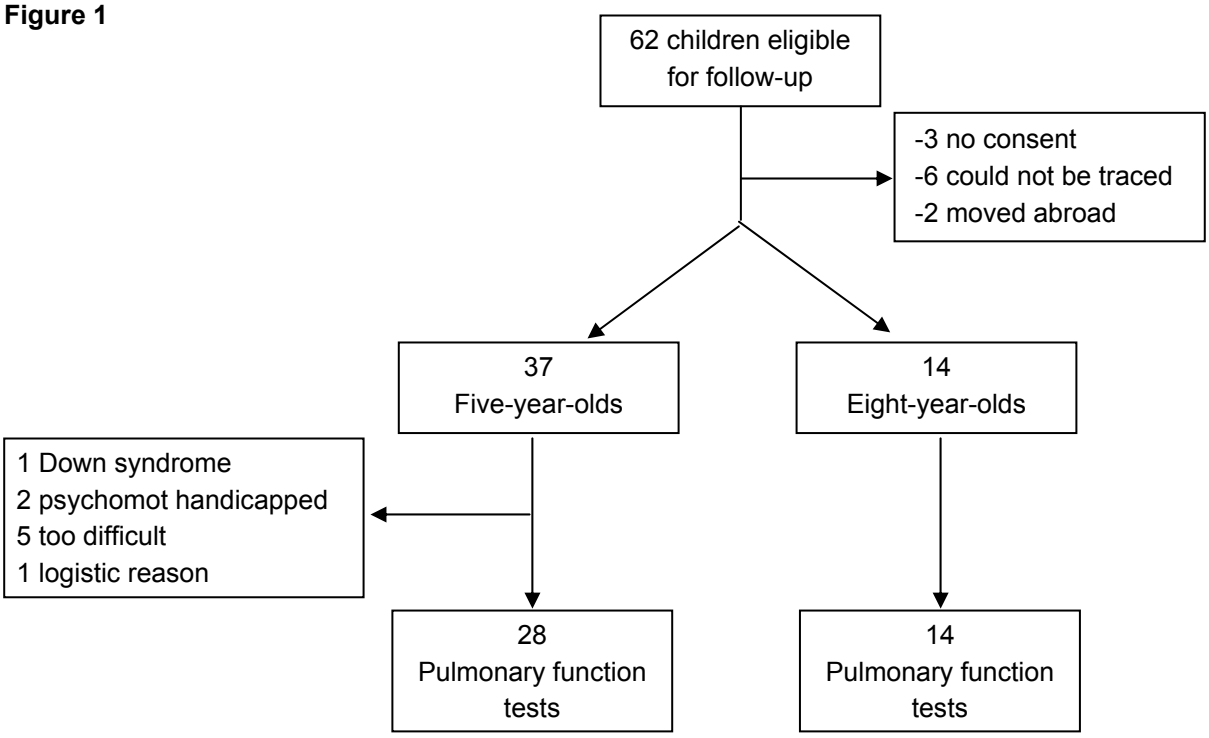
Results

During the study period 40 five-year-old children and 22 eight-year-old children were eligible for follow-up after ECMO. Parents of 3 of the 62 children did not give consent, the families of 2 other children moved abroad and 6 children could not be traced.

Thus, 37 five-year-olds and 14 eight-year-olds visited our outpatient department. Lung function test were not performed, however, in 9 of the five-year-olds, for reasons presented in *Figure 1*.

The perinatal characteristics of the 51 children who performed lung function tests are presented in *Table 1*.

Figure 1



Five children (2 five-year-olds) (12%) had a history of atopy (asthma, eczema, or hay fever) and there was a history of atopy in the parents or siblings of three (2 five-year-olds) children. Three children (2 five-year-olds) had been exposed to prenatal maternal smoking. Eleven children (8 five-year-olds) used bronchodilators or inhaled steroids up to the age of 2. At time of pulmonary function testing seven children (17%) (6 five-year-olds) still used bronchodilators or inhaled steroids. (*Table 2*)

Lung function testing

R_{int}

R_{int} before bronchodilatation with 1mg of terbutalin was measured in 16 five–year-olds and in 10 eight–year-olds; after bronchodilatation in 12 and 9, respectively. In both age groups R_{int} had decreased after bronchodilatation. This decrease was only significant for the eight-year-olds. (p = 0.006) (*Table 3*) Before bronchodilatation R_{int} did not differ between the two age groups (p = 0.08). For the eight-year-olds, Z score before bronchodilatation was significantly above reference values (z score 0) but within the normal range. After bronchodilatation z scores for both groups decreased signifianctly and are below reference values (*Table 3*).

Flow/volume

Flow/volume curves before inhalation of terbutalin were obtained in 20 five-year-olds. One child had already inhaled 1 mg of terbutalin when performing the flow/volume curve so 21 performed after inhalation.

Flow/volume curves were obtained in all 14 eight-year-olds. One child was too tired to perform another session after inhalation of terbutalin.

There was no significant difference in values before and after bronchodilatation.

The FEV1/VC ratio and MEF_{25} in 8-year-olds was significantly lower than that in 5-year-olds before bronchodilatation (p = 0.01 and 0.03 respectively). After bronchodilatation, significant difference between the two age groups sustained for the FEV1/VC ratio. (*Table 4*).

Table 1 Patient characteristics

		5-year-olds n = 28	**8-year-olds** n = 14
Male/female		15/13	7/7
Diagnosis:	MAS	13	10
	CHD	3	3
	Sepsis	5	0
	PPHN	7	1
Birthweight (kg)		3.4 (2.9 to 3.8)	3.4 (3.0 to 3.9)
Gestational age (weeks)		39^{+5} (37^{+5} to 41^{+1})	40^{+3} (39^{+5} to 41^{+4})
No. of children with inhaled NO prior to ECMO (%)		26 (93%)	5 (36%)
Maximum dosage of iNO (ppm)		20 (17 to 33)	30 (20 to 40)
Oxygenation index		29 (16 to 50)	58 (29 to 70)*
MAP (cm H_2O)		20 (15 to 22)	19 (17 to 22)
Maximal FiO_2 (%)		100	100
No. of children with pneumothorax prior to ECMO (%)		5 (18)	5 (29)
Age at start ECMO (hours)		30 (23 to 60)	25 (12 to 43)
Duration of ECMO support (hours)		137 (115 to 190)	119 (115 to 149)
Duration of mechanical ventilation (days)[#]		13 (8 to 21)	9 (7 to 18)
Duration of oxygen dependence (days)		20 (12 to 34)	25 (12 to 42)

Data are presented as numbers of patients (%) or median (IQR).
MAS *Meconium Aspiration Syndrome*
CDH *Congenital Diaphragmatic Hernia*
PPHN *Persistent Pulmonary Hypertension of the Newborn*
FiO_2 *Fraction of inspired oxygen prior to ECMO*
iNO *Inhaled Nitric Oxide. Oxygenation index was calculated from the last known arterial bloodgas value before ECMO as; [(Mean airway pressure x FiO_2)/PaO_2] x 100*
[#] *Duration of mechanical ventilation includes mechanical ventilation prior, during and after ECMO*
* *p = 0.02*

Table 2 Data at follow-up

	5-year-olds	**8-year-olds**
Age at follow-up (yrs)	5.4 (5.3 to 5.5)	8.5 (8.2 to 8.6)
Weight (kg)	21.8 (19.4 to 23.9)	26.8 (22.4 to 33.2)
Weight SD score	0.5 (-0.5 to 1.1)	-0.3 (-1.6 to 0.6)
Height (cm)	116.5 (114 to 119.8)	130.7 (129.6 to 133)
Height SD score	0.4 (-0.6 to 1.0)	-0.8 (-1.5 to -0.04)
History of atopy (n)	2	3
Inhalation medication during first 2 yrs of life (n)	8	3
Inhalation medication at follow-up (n)	6	1

Data are presented as numbers of patients or median (IQR).

Table 3 R_{int}

		Before bronchodilatation	After bronchodilatation
R_{int} (kPa/l/s)	5 years	0.80 (± 0.04)	0.65 (± 0.04)*
	8 years	0.72 (± 0.04)	0.52 (± 0.05)**
R_{int} (Z score)	5 years	0.3 (± 0.3)	-0.8 (± 0.3)##
	8 years	0.8 (± 0.2)#	-0.8 (± 0.3)###

Data are presented as mean (± SEM). 1mg of terbutalin was given for bronchodilatation. R_{int} before bronchodilatation was measured in 16 children at 5 years and in 10 children at 8 years. After bronchodilatation R_{int} was measured in 12 children at 5 years and in 9 children at 8 years.
* *p = 0.05 R_{int} before vs after bronchodilatation in 5 year-olds. (Mann-Whitney U test)*
** *p = 0.006 R_{int} before vs after bronchodilatation in 8 year-olds. (Mann-Whitney U test)*
\# *p = 0.007; significant above reference values (z score 0). (student t test)*
\## *p = 0.04 Z score before vs after bronchodilatation in 5 year-olds (Mann-Whitney U test)*
\### *p = 0.001 Z score before vs after bronchodilatation in 8 year-olds (Mann-Whitney U test)*

Table 4 Dynamic lung volumes

		Before bronchodilatation	After bronchodilatation
FVC	5 years	91 (± 4)	99 (± 4)
	8 years	91 (± 6)	96 (± 6)
FEV_1	5 years	97 (± 4)	105 (± 4)
	8 years	92 (± 6)	100 (± 6)
FEV_1/VC	5 years	92 (± 3)	93 (± 3)
	8 years	86 (± 2)*	89 (± 2)***
MEF_{25}	5 years	80 (± 7)	91 (± 10)
	8 years	57 (± 8)**	72 (± 8)

Values are presented as mean (±SEM). All data are expressed as percentage of predicted except for the FEV_1/VC ratio. Measurements were performed before and after inhalation of 1mg of terbutalin.
There is no significant difference before and after bronchodilatation in both age groups.
Differences between 5 and 8-year-olds before bronchodilatation:
* *p = 0.01*
** *p = 0.03*
Differences between 5 and 8-year-olds after bronchodilatation;
*** *p = 0.03*

Spirometry

Nine 8-year-old children performed a spirometry of which 7 performed a plethysmography. Only 5 children were able to perform a carbon monoxide diffusion capacity. Results are presented in *Table 5*.

Table 5 Helium dilution-spirometry (n = 9) and bodyplethysmography (n = 7) at 8 years

	After bronchodilatation
TLC_{he}	92 (80 - 99)
VC_{he}	102 (95 - 111)
FRC_{he}	81(75 - 94)
RV_{he}	42 (33 - 77)
RV/TLC_{he}	51 (36 - 70)
TLC_{pleth}	102 (90 - 106)
RV_{pleth}	95 (86 - 116)
RV/TLC_{pleth}	106 (82 - 109)
D_{Lco}	94 (86 - 109)
D_{Lco}/V_a	89 (88 - 109)

Data are presented as median (IQR).

Discussion

In this study we evaluated lung function in twenty-eight 5-year-old and fourteen 8-year-old survivors after ECMO support. We found mild airway obstruction in the eldest children. All values were within the normal range in the youngest children. Seventeen percent of all children used bronchodilatation or inhaled steroids.
During the study we noticed that some 5-year-olds had difficulties in performing a complete lung function test. This resulted in scattered data and results should be interpreted with caution. Nystad et al. however did show good feasibility of dynamic spirometry in children of preschool age.[9] Crenesse et al. found that forced expiratory tests are not always feasible in young children, but that 55% of their selected population performed reliable maneuvers, provided that well-trained pediatric medical staff supervised them.[10] There are few studies on pulmonary sequelae including 5-year-old ECMO survivors. A possible explanation for the difficulties may lie in the fact that the tests were part of an extended follow-up program for ECMO survivors, lasting a whole day. Also, Glass et al. in a similar, larger population found 17% of children to have neurodevelopmental disability and 6% motor difficulties.[11] Nevertheless we found no profound bronchial obstruction.

We did find mild obstruction in the 8-year-olds. As our data are not longitudinal data, the question is whether the 8-year-olds were perhaps in worse clinical condition before ECMO or perhaps were on ventilation for a longer time. Comparison of the OI, MAP, duration of ECMO treatment, age at start ECMO treatment, duration of ventilation and oxygen dependence between both age groups was only significant for the OI, measured using the last arterial blood gas before ECMO (p = 0.02). This could perhaps indicate worse clinical conditions before ECMO in a period when NO and HFO was less frequently used. However, a study by Beardsmore and colleagues dating from a later

period showed reduced expiratory flows in ECMO survivors, already present at one year of age.[12]

The group of 8-year-olds included 3 children with a congenital diaphragmatic hernia. Obstruction may be due to different anatomy or residual lung hypoplasia in children with CDH.[13] However, re-analysis without data from these 3 children did not change the outcome significantly. It is the neonatal intensive care treatment that is most likely to contribute to airway obstruction despite the use of lung rest during ECMO.

Our findings are in concordance with those reported by Hamutcu et al. who also found airway obstruction in a group of 48 ECMO survivors at 11 years of age.[5] Airway obstruction was also found in a group of conventionally treated children who suffered from meconium aspiration syndrome.[14] Still our data need to be interpreted cautiously, as we did not use a control group and number of patients is very small.
Only few children were able to perform spirometry and bodyplethysmograpy. Difusion capacity seemed within the normal range. Furthermore, results may indicate minor airtrapping since RV/TLC_{pleth} was high and RV/TLC_{he}. low. However, numbers are too small to draw definite conclusions. Continuation of the follow-up assessment will eventually clarify this.

In conclusion we found mild airway obstruction in 8-year-old ECMO survivors, and not in 5-year-olds. Despite the limitations of this study these data confirm the presence of long-term pulmonary sequelae despite the use of lung rest during ECMO. In the future children will be followed longitudinally as part of an extensive long-term follow-up program for ECMO survivors.

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General discussion

chapter 10

This thesis presents the results of clinical studies evaluating some aspects in the acute phase of ECMO treatment and long-term follow-up of newborns treated with ECMO for respiratory failure.
ECMO is known to have a survival advantage and is used worldwide in selected critically ill patients with acute therapy resistant respiratory or cardiac failure.[1] The majority of patients treated with ECMO are newborns with respiratory failure most of whom receive ECMO for meconium aspiration syndrome (MAS).[2] The incidence of patients with MAS in this thesis however is probably higher compared to the incidence in the United States. For one reason, their changing obstetric practice; i.e. an increased number of cesarean deliveries and a decrease in births after more than 41 weeks, was associated with a four-fold decrease of meconium aspiration syndrome.[3] Second, several new therapies, including high-frequency oscillatory ventilation (HFOV), exogenous surfactant therapy, and inhaled nitric oxide (iNO), have become available for the treatment of neonatal hypoxemic respiratory failure. The need for ECMO therapy decreased from 42.8% to 27.7% following the application of iNO and HFOV being used more frequently. The incidence of MAS in these two groups decreased from 66.6% to 38.5%.[4] Still, those patients who do require ECMO compose a more severe subset of critically ill newborns. As a consequence studies with a large group of infants treated with ECMO for MAS will become more difficult to conduct in the United States.

Nutritional Aspects

In the care of critically ill newborns nutrition is an important factor. During ECMO most children receive parenteral nutrition. Withholding enteral feeding in patients on ECMO is common practice in many centers, based partly on the risk of potential splanchnic ischemia resulting in loss of intestinal integrity, development of necrotising enterocolitis and predisposition for bacterial translocation and sepsis.[5-7] Total parenteral nutrition however is associated with the occurrence of cholestasis.[8] Forty to sixty percent of infants who require long term TPN for intestinal failure develop liver disease varying from cholestasis to hepatic fibrosis and biliary cirrhosis.[9] The pathogenesis is multifactorial. Lack of enteral feeding leading to reduced gut hormone secretion; reduction of bile flow, and biliary stasis may be important mechanisms in the development of cholestasis. According to a review by Kelly, the management strategies for the prevention of TPN-induced liver disease include early enteral feeding, a multidisciplinary approach to the management of parenteral nutrition, and aseptic catheter techniques to reduce sepsis.[9] In chapter 2 we showed that enteral nutrition in neonates on ECMO was well tolerated and that no major complications occurred, especially no symptoms of bilious vomiting, blood stained stools or abdominal distension. Also, when introducing small quantities of enteral nutrition in healthy neonates a significant elevation of gut hormones is observed.[10] Gut hormones are necessary in stimulating structural and functional changes in the gut and other organs when adapting to enteral nutrition.[11] They control gastrointestinal function such as motility, intestinal fluid secretion, blood flow, absorption and immunity.[12] Splanchnic circulation may be adversely affected and intestinal integrity

is compromised, although not deteriorated after the introduction of enteral feeding, in neonates on ECMO.[13] Despite these factors we did find a normal response of intestinal hormone secretion after the introduction of enteral nutrition. These findings do not sustain the arguments to withhold these infants from enteral nutrition.

Apart from the existing fear of a decreased mesenteric blood flow and development of necrotising enterocolitis (NEC), the need for vasopressor drugs pre-ECMO can be another argument to withhold enteral nutrition. Use of vaso-active drugs did not have an influence on feeding intolerance as described in chapter 2, while 80% of our ECMO patients who were fed enterally received dopamine. And, so far there are no documented cases of NEC during ECMO in the literature. As a matter of fact neonates treated with ECMO receiving mother's milk and with a gestational age over 34 weeks, are in a low risk category for developing NEC.

Newborns on ECMO have a restricted fluid intake of 100 ml/kg. This is a known barrier to adequate nutrition in critically ill children.[14] So when reducing costs, reducing the chance of developing parenteral nutrition associated cholestasis in the context of a normal gut hormone response with the use of enteral nutrition, future research should focus on whether these patients have sufficient caloric intake and protein uptake. Indirect calorimetry might be useful in determining energy requirements, especially in critically ill patients on continues flow ventilators and with a FiO2 of less then 40%.[15]

ECMO has become a principal part in the treatment of selected newborns with congenital diaphragmatic hernia (CDH).[16,17] Since operative repair in our hospital is routinely performed after decannulation from ECMO, these children do not receive enteral nutrition during ECMO. Still it is desirable to feed them enterally as soon as possible. However, one of the complications of thoracic surgery is the occurrence of a chylothorax due to damage of the lymphatic ducts possibly resulting in a longer period of cessation of enteral nutrition.[18,19] Trevisanuto et al. suggested that ECMO treatment itself could be responsible for the development of a chylothorax. Due to the venous cannula the superior caval vein (SCV) possibly hinders the venous return and consequently obstructs the outflow of the thoracic duct. The increased pressure may had lead to (micro) perforations of the thoracic duct.[20] In chapter 4 we did find an increased number of chylothorax in ECMO treated CDH patients. The majority of the CT occurred on the side of the hernia and not on the side of the ECMO cannula. Together with the findings that the presence of a patch to close the diaphragm increased the chance of developing a CT it is more likely that ECMO serves as a selection bias then as a primary cause for the development of chylothorax. Treatment modalities for a CT include repeated thoracocentesis or continuous drainage together with prolonged use of TPN during 3 weeks followed by the use of formula for several weeks containing medium chain triglycerids. This conservative management was effective in children with a CT after cardiothoracic surgery in 80%.[19] If conservative management fails, surgical ligation of the thoracic duct is a possibility, but criteria are controversial.[19] Still, in our population ligation of the thoracic duct has not been necessary. Moreover, additional risks may come from

repeated surgery. A new non-surgical intervention such as somatostatin (Octreotide) aimed at decreasing chyle production is increasingly used. Administering Octreotide either as a continuous intravenous infusion or as subcutaneous dosages was reported to be successful in pediatric patients after cardiothoracic surgery and after CDH repair.[21-24]

Overall, there is an important morbidity and evident risk of complications using TPN. Especially in patients with a CT needing prolonged periods of TPN.[18] Our overall recommendation concerning enteral nutrition in neonates on ECMO is;

- Start enteral feeding early, within 24 - 48 hours after start of ECMO.
- Try to reach full enteral intake.
- There are no arguments for minimal enteral feeding since strong evidence for an increased risk of developing NEC is lacking.
- Additional therapy with somatostatin for chylothorax may be helpful.

Drug studies during ECMO

Patients on mechanical ventilation in the ICU are generally heavily sedated. The purposes of sedation are to relieve pain, decrease anxiety, decrease oxygen consumption and carbon dioxide production, prevent the patient from removing lines, and promote synchronized breathing with the ventilator. In patients on ECMO sedation and analgesia seem even more critical since inadequate sedation with excessive patient movement may result in a shift in the position, or even dislodgment of the cannula causing a decrease in venous drainage and arterialised return. Also when ECMO is used for respiratory failure the primary goal is to recover lung function. Ventilation strategies are therefore of great importance. Interventions or treatment that can cause further lung damage should be avoided. As drugs for sedation and analgesia may potentially increase the requirements of mechanical ventilation they may influence the chance of pulmonary recovery. Therefore mode of sedation and pain management is very important. The most frequently used drugs for sedation in newborns on ECMO are benzodiazepines such as midazolam. Morphine and fentanyl are most commonly used for analgesia in this group of patients.[25]

During ECMO disposition of drugs is altered due to expanded blood volume and increased volume of distribution, an intrinsic increase of intra- and extracellular volume, the presence of a non-pulsatile blood flow and reduced plasma protein concentration with resulting effects on pharmacokinetics and dynamics.[26] As described in chapter 5 midazolam and morphine are used as primary sedative and analgesic drugs in our clinic. We found that midazolam and morphine alone did not provide adequate analgesia and sedation during ECMO. Also, plasma concentrations of morphine, M3G, M6G, midazolam, 1-OH-midazolam and 1-OH-midazolamglucuronide showed great variability between patients and over time. Pharmacokinetic studies of morphine during neonatal

ECMO have shown increased as well as decreased metabolic clearance of morphine to their metabolites M3G and M6G, each contributing to both clinical and side effects.[27,28] Geiduschek also reported that morphine clearance showed great variability in infants receiving ECMO and initiation of ECMO did not lead to a significant decrease in serum morphine concentration.[29] No effect is documented of midazolam or fentanyl on morphine formation clearance to M3G and M6G or elimination clearance of these metabolites because of the fact that midazolam and morphine are glucuronidated by different enzyme systems.[30,31] Mulla et al. reported that the volume of distribution of midazolam in ECMO treated neonates was 3 to 4 times greater than in critically ill neonates not treated with ECMO and subsequently more midazolam is required to achieve adequate sedation, especially during the first 10 days.[32] Prolonged use of morphine and midazolam should be guided by clinical monitoring, preferably by validated pain or comfort SCALES as clearance is variable during treatment with ECMO.[28,29,33]

The most important indications for neonatal ECMO are respiratory failure and severe primary or secondary pulmonary hypertension.[34] In the line of treatment of pulmonary hypertension inhaled NO (iNO) is considered the golden standard.[35] ECMO serves as the last resort support with ranging success percentages depending on the underlying pathology.[36] Since there is no single therapy yet proven to be effective in all cases of pulmonary hypertension, new therapies focussing on selective pulmonary vasodilatation are still under investigation. Sildenafil (Viagra®) is one of those therapies. This phosphodiesterase inhibitor relaxes pulmonary smooth cells by inhibiting the degradation of cyclic guanosine monophosphate.[37] Experience is mainly gained in adult patients. Sildenafil was found to be an effective pulmonary vasodilator in adult patients with congestive heart failure and pulmonary hypertension which effect was potentiated by combination with iNO.[38,39] Experience in young children, especially in newborns is limited. We therefore analyzed retrospectively the effects of oral sildenafil in 15 consecutive neonates with therapy resistant PPHN necessitating ECMO support. ECMO flow reduction (ml/kg/min) was used as an indirect parameter to assess decline of pulmonary hypertension due to sildenafil administration. Comparable to findings in adults, we found a favorable effect of sildenafil in combination with iNO. This was reflected by the observation that those with concomitant iNO showed greater ECMO flow reduction than those treated with sildenafil alone. Distinct from adult studies a significant reduction of systemic blood pressure was observed in this study. A decrease in mean arterial blood pressure was only observed after the first dose, which was a loading dose, and 3 - 4 times higher than the subsequent doses. However, analysis showed no dose dependency. Still, in a randomized control trial of infants at risk for pulmonary hypertension after cardiac surgery sildenafil also reduced the systemic blood pressure and systemic vascular resistance and worsened arterial oxygenation and the alveolar-arterial gradient.[40] In the future randomized-controlled trials in neonates are warranted and should focus on pharmacokinetics to determine the optimal dosage and routing of sildenafil together with attention for possible systemic (side-) effects. Unfortunately, recently an international multicenter trial stopped due to the absence of safety data in the newborn population. Moreover in neonates with CDH who form the largest group of

therapy resistant pulmonary hypertension, intestinal absorption is unpredictable with continuous nasogastric drainage. Pharmacokinetics will be difficult to interpret and studies with an intravenous form of sildenafil for PK-PD studies are needed in this group of patients. However, pharmacodynamics will also be difficult to evaluate. Cardiac ultrasound can be used to determine a decrease in pulmonary artery pressure based on tricuspidal incompetence, but this is non-specific and 'far away' from the underlying pathology in CDH patients.[41] In the analysis for expression of vasoactive mediators in newborns with CDH results are not conclusive whether endothelial nitric oxide synthase (eNOS) is decreased or not.[42-45] More consensus was found in an upregulation of endotheline-1; an endothelial derived vasoconstrictor in patients with CDH.[43,46,47] It is questionable whether or not future perspectives in medical treatment of PPHN should focus on blocking vasoconstriction with for instance Bosentan, an orally administered endothelin receptor antagonist instead of stimulating vasodilatation with sildenafil.[48]

Long-term effects

Over the years development of high frequency ventilation (HFV), iNO, surfactant and changing policy in the delivery room, demographic data of neonates treated with ECMO have changed. Over a time period from 1988 to 1998 neonates were exposed to an ever-expanding group of new therapies, they appeared to be healthier based on indices of gas exchange, and were cared for at centers that reported fewer cases per year.[49] Another study in the United States showed a decrease in the number of neonates treated with ECMO for respiratory failure from 1989 to 2001. However, the increased use of iNO an HFV were associated with an increase of the age at ECMO initiation (from 40.5 hours to 68.5 hours) and an increased length of ECMO run from 154.7 hours to 174.5 hours in the last 4 years.[50] Still the overall mortality remained unchanged. There is no doubt that new techniques will still be developed and the number of neonates needing ECMO support for respiratory failure will probably decrease. However, currently approximately 40 patients a year still need ECMO support in the newborn period in the Netherlands. Follow-up studies of neonates treated with ECMO in the UK and United States showed considerable morbidity with major disability in terms of severe developmental delay or neuromotor disabilities up to 20% at 1 to 5 years of age.[51-54] These data are comparable to our findings of a nation wide follow-up study at 5 years of age presented in chapter 7. Therefore follow-up of these infants remains necessary. Especially with increasing age, expectations of the children rise and assessment of different domains can be more precise. In our opinion a successful follow-up program should be structured in consultation with representatives from different disciplines, such as a pediatrician, a pediatric physiotherapist, a psychologist and a speech therapist. In 2000 van Baar et al. presented a systematic and standardized program for neonatal follow-up in the Netherlands.[55] This protocol functioned as a guideline for a standardized protocol developed for the follow-up of ECMO survivors (*Fig. 1*). We added age 12 and 18 years since this is again a major step in school career determining future educational perspectives and job opportunities.

Figure 1 Follow-up protocol for ECMO survivors

Domain	Instrument	Age						
		6 mnths	12 mnths	18 mnths	24 mnths	5 yrs	8 yrs	12 yrs
Physical/ neurological examination		x	x	x	x	x	x	x
Biometry	lenght/weight/ skinfold	x	x	x	x	x	x	x
Lung function	Bodybox/ spirometry	x	x	(x)		x	x	x
Hearing	Audiometry					x	(x)	(x)
Psychomotor development	Bailey 2-30	x	x	x	x			
Neuromotor assessment	Movement ABC					x	x	x
Intelligence	RAKIT/WISC-R					x	x	x
Concentration	Bourdon-Vos						x	x
Visual-motor integration	Beery						x	x
Receptive language development	Reynell				x	x		
Expressive language development	Schlichting				x	x		
Behavior	CBCL/TRF					x	x	x
Quality of life	PedsQL					x	x	x

As part of this follow up program lung function tests were performed at different ages. It remains essential to assess lung function whether or not ECMO results in a survival advantage.[56] So far only cross sectional studies on lung function during the first year of life following ECMO are published suggesting a decrease of lung function during the first year of life.[56,57] In chapter 8, lung function was evaluated longitudinally during the first year of life in infants following ECMO support. We found normal lung volumes and normal expiratory flows with a normal development at a level below average during that year. Furthermore we found higher lung volumes at both 6 and 12 months in infants receiving ECMO for CDH compared with infants receiving ECMO for MAS. Nagaya et al. studied lung volumes in infants following surgical repair of CDH and ECMO treatment at 3 months of age. These infants had low ipsilateral lung volumes (61% of contra-lateral lung volume), which increased during follow-up to 88%. The perfusion however of the affected side remained low, or decreased to beneath the initial value. It was concluded that the lung of the affected side has limited ability to develop arterial branches and that enlargement of lung volume may depend on over-expansion or even progressive emphysema, rather than tissue growth.[58] We suggest that in infants after CDH repair a high-normal lung volume is most likely explained by hyperinflation of hypoplastic lung. However, numbers in this study were very small and future research on lung function in infants after CDH repair is necessary to clarify the presence of increased lung volume. For instance alternative ways to evaluate lung growth in combination of lung function with visualization of the architecture of the lung might be the use of a CT-scan. Especially in the follow up of infants with CDH it is important to evaluate growth potential of the pulmonary blood vessels and airways.

In one year olds we found a forced expiratory flow within normal ranges but at a level below average. This could suggest an increased incidence of airway obstruction at a later age. However from the age of 18 months to 5 years it is impossible to perform a reliable lung function test. Boykin et al. reported mild lower airway obstruction and air trapping in ECMO survivors at 10 - 15 years of age.[59] Recently Hamutcu et al. also found airway obstruction in a group of 50 ECMO survivors aged 9 - 13 years.[60] In chapter 9 we evaluated lung function at an earlier age compared to Hamutcu and Boykin. We found mild lower airway obstruction in 8 year olds. All values were within the normal range in 5-year-olds. Comparison of the OI, MAP, duration of ECMO treatment, age at the start of ECMO treatment, duration of ventilation and oxygen dependence between both age groups showed only a significant higher OI in 8-year-olds. This could perhaps indicate worse clinical conditions before ECMO in a period when NO and HFO was less frequently used.

In the future the one-year old infants of chapter 8 will continue their follow-up program and will perform lung function tests at age 5 and 8 years. These future longitudinal data may enhance our understanding of lung growth and function in this particular group of patients.

Overall conclusions

In summary this thesis demonstrated that:

- Introduction of enteral nutrition in critically ill newborns on ECMO was well tolerated and no major complications occurred.
- Together with the fact that there were normal gut hormone responses following the introduction of enteral nutrition in a theoretically compromised intestinal circulation, these data do not provide arguments to withhold these newborns from enteral nutrition.
- Pharmacokinetic and pharmacodynamic data of sedatives and analgesia are increasingly needed to guide optimal treatment especially in case of combined therapy.
- Sildenafil in combination with iNO may be a promising adjuvant in the treatment for severe therapy resistant PPHN, also during ECMO.
- Follow-up of neonates treated with ECMO at age 5 years shows a considerable morbidity comparable to the UK and Unites States, consolidating the idea that structural follow-up of these infants remains important, preferably with representatives from different disciplines.
- Lung function during the first year of life showed normal lung volume and normal expiratory flow at a level below average with normal growth and development during that year. At ages 5 and 8, lower airway obstruction was only observed in the oldest age group.

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Summary / Samenvatting

chapter 11

Summary

Extracorporeal membrane oxygenation (ECMO) is a technique for providing life support in severe but potentially reversible cardiorespiratory failure. The technique oxygenates blood outside the body, obviating the need for gas exchange in the lungs and, if necessary, provides cardiovascular support. This enables the lungs to rest with use of minimal ventilator settings, thereby preventing injury from high oxygen concentration and barotrauma. ECMO is most commonly used to support (nearly) mature newborn infants with respiratory failure and pulmonary hypertension caused by meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), sepsis and idiopathic persistent pulmonary hypertension of the newborn (idiopathic-PPHN). This thesis addresses clinical studies evaluating several aspects of the acute phase of ECMO treatment and long-term follow-up of newborns treated with ECMO for respiratory failure.

Chapter 1 is a general introduction to the developmental history of ECMO. It presents the studied aspects of the acute phase (chapters 2 to 6) and long-term follow-up (chapters 7 to 9) together with the study aims.

In **chapter 2** we retrospectively evaluated over a five-year period the feasibility and tolerance of a protocol of routine enteral nutrition in neonates requiring ECMO. Feasibility was evaluated by recording the time period needed for enteral nutrition to reach 40% of total fluid intake; tolerance was evaluated by reviewing data on enteral nutrition related morbidity. Sixty-seven of the 77 eligible patients received enteral feeding during ECMO. Thirty-six of these patients (54%) received 40% of total fluid intake as enteral nutrition within a median of 3 (range 2 - 4) days. Over the years there was a trend toward an increasing usage of enteral nutrition from 71% to 94%. Enteral nutrition was temporarily discontinued in 16 patients, with 14 showing gastric retentions, one showing discomfort, and one showing aspiration. Symptoms of bilious vomiting, blood-stained stool, or abdominal distension were not present. Overall, enteral feeding was well tolerated and did not show serious adverse effects. In our experience, routine use of enteral feeding in critically ill neonates on veno-arterial ECMO is feasible.

Chapter 3 presents the effects of enteral nutrition on gut function during veno-arterial ECMO in newborns. The objective was to gain insight into the hormonal responses to enteral nutrition. We analyzed plasma gut hormone levels of gastrin, cholecystokinin and peptide-YY in relation to enteral nutrition in 24 consecutive newborns. Twelve received parenteral nutrition only. In 12 others, enteral nutrition was introduced later. The findings were compared with those of 16 measurements in eight non-ECMO treated age-matched controls. We found that concentrations of gastrin, cholecystokinin and peptide- YY were significantly higher in ECMO patients receiving enteral nutrition compared with ECMO patients who received parenteral nutrition only. The plasma hormone levels did not differ from those in age-matched controls. The findings from this study are consistent with intestinal hormone levels showing normal responses after introduction of enteral feeding.

The results do not provide an argument for withholding enteral nutrition even in the most severely ill neonates on venoarterial ECMO.

In **chapter 4** we retrospectively evaluated whether ECMO increased the risk of developing a chylothorax (CT) after congenital diaphragmatic hernia (CDH) repair. Eighty-nine patients with CDH - treated either with or without ECMO - were analyzed together with 114 patients treated with ECMO for other reasons and 100 patients who underwent thoracic surgery because of an esophageal atresia (EA). Postoperatively, 10% of the CDH infants developed a chylothorax—21% in CDH patients with ECMO treatment and 6% in CDH patients without ECMO treatment. This difference appeared to be significant. The presence of a patch as independent variable for the development of chylothorax also showed significance. In the group of patients treated with ECMO for other reasons, the incidence of chylothorax was 3.5% and in 4% it occurred after an esophageal atresia repair. Chylothorax in CDH patients mostly occurred on the herniated side and not on the side of the ECMO cannula. Apart from the finding that the presence of a patch to close the diaphragm increased the chance of developing a chylothorax, ECMO more likely seems to serve as a selection bias rather then a primary cause for the development of chylothorax.

In **chapter 5** we describe the plasma concentrations of midazolam and morphine in neonates undergoing veno-arterial ECMO treatment. This is a preliminary report of a larger study on the pharmacokinetic and pharmacodynamic properties of midazolam and morphine administered during ECMO. We analysed plasma concentrations of midazolam, 1-OH-midazolam, 1-OH-midazolamglucuronide, morphine, morpine-M3G and morphine-M6G at separate time points after discontinuation of morphine and midazolam just after cannulation and again after reintroduction of the medication. Plasma concentrations showed great variability. All but two infants needed both midazolam and morphine for adequate sedation. The median (IQR) time between discontinuation and reintroduction of medication was 10 (7.8 to 27) hours. Median dosage of morphine used during ECMO support was 11.5 (10.1 to 15.5) µg/kg/hr. Median dosage of midazolam used during ECMO support was 0.15 (0.1 to 0.2) mg/kg/hr. Future publications will report on the pharmacokinetic and pharmacodynamic analysis of morphine and midazolam using validated scales such as the COMFORT behaviour scale and VAS.

In the line of drug therapy during ECMO (**chapter 6**) we analysed over more than 2 years the effects of oral sildenafil in 15 consecutive neonates over more than two years with therapy resistant PPHN necessitating ECMO support. Seven neonates, all with congenital diaphragmatic hernia, died. We compared survivors and non-survivors. There was no significant difference in reduction of ECMO flow 24 hours after initiation of sildenafil nor in duration of ECMO support. The survivors had first received sildenafil significantly earlier after cannulation than the non-survivors; median (IQR) 41 (17 - 90) hours versus 200 (161 - 334) respectively. We also compared patients with or without concomitant iNO administration at the start of sildenafil. ECMO flow reduction over the next 24 hours was greater in patients with iNO and sildenafil than in patients who

received sildenafil only. In 12 patients a significant decline in systemic blood pressure in over the first 2 hours after initial sildenafil administration was observed, not related to dosage. These findings indicate that sildenafil therapy might be beneficial for individual cases of PPHN and that administration relatively early in the disease process with concomitant administration of iNO might be favorable. In contrast with earlier studies in animals and adults, we observed a significant decline in systemic arterial blood pressure.

In the long-term follow-up after ECMO (**chapter 7**) morbidity is reported in ECMO survivors at the age of 5 years when they start primary school and major decisions for their school careers must be made. Within the framework of an extensive follow-up program for neonatal veno-arterial ECMO survivors, ninety-eight 5-year-olds from the two designated ECMO centres in the Netherlands (Erasmus MC-Sophia Children's Hospital in Rotterdam, and University Medical Center Nijmegen) were assessed. The protocol included medical assessment, neuromotor assessment, and psychological assessment by means of parent and teacher questionnaires. We found neurological deficits in 17% of the 98 children included in the analysis. Six of those 17 (6% of total) showed major disability. Two of those six had a chromosomal abnormality. Three were mentally retarded and profoundly impaired. The sixth had a right-sided hemiplegia. These six children did not undergo neuromotor assessment. Motor difficulties were found in 26% of the remaining 92 patients. 15% actually had a motor problem and 11% were at risk for this. Cognitive delay was identified in 14%. The mean IQ score (100.5) was within the normal range. The study revealed that neonatal ECMO in the Netherlands is associated with considerable morbidity at 5 years of age. It appeared feasible to have as many as 87% of survivors participate in follow-up assessment, due to co-operation between two centers and small travelling distances. We believe that objective evaluation of the long-term morbidity associated with the application of this highly invasive technology in the immediate neonatal period requires an interdisciplinary follow-up program with nation-wide consensus on timing and actual testing protocol.

The extensive follow-up program mentioned before provides for lung function tests at different ages. In **chapter 8** we evaluated lung function longitudinally at 6 and/or 12 months of age in a group of ECMO survivors. Functional residual capacity (FRC_p) and forced expiratory flow at FRC ($V'max_{FRC}$) were measured and expressed as Z scores. We studied 45 infants, 35 were evaluated at 6 months and 35 at 12 months; 25 infants completed both measurements. We found normal lung volumes and normal expiratory flows with normal development at a level below average during that year. Furthermore we found higher lung volumes at both 6 and 12 months in infants receiving ECMO for CDH compared with infants receiving ECMO for MAS. This study does not only contribute to our understanding of the effects of ECMO in severe respiratory insufficiency, but also provides data on longitudinal growth of lung function in early infancy. Especially in the follow up of infants with CDH it is important to evaluate growth potential of the pulmonary blood vessels and airways.

In **chapter 9** we describe pulmonary sequelae in twenty-eight 5-year-old and fourteen 8-year-old ECMO survivors. Airway resistance was measured using the interrupter technique (R_{int}) during expiration and expressed as Z score at both 5 and 8 years. In addition we measured FVC, FEV_1, FEV_1/VC-ratio and MEF_{25} using a spirometer. In the 8–year-olds helium dilution was used to determine TLC_{he}, residual volume of helium (RV_{he}), $VC_{he,}$, FRC_{he} and RV/TLC-ratio. Airway resistance was within normal range for both age groups. After bronchodilatation airway resistance decreased significantly in both age groups. In 8 year olds FEV1/VC ratio and MEF_{25} before bronchodilatation showed mild airway obstruction. Values were significantly lower than those in the 5-year-olds. Diffusion capacity was within the normal range. The findings of this study confirm the presence of long-term pulmonary sequelae despite the use of lung rest during ECMO.

In **chapter 10** we discuss our findings and make recommendations for future studies.
The main conclusions obtained from the studies described in this thesis are the following:

- Introduction of enteral nutrition in critically ill newborns on ECMO was well tolerated and did not give rise to major complications (chapter 2).

- Together with the finding that gut hormone responses following the introduction of enteral nutrition in a theoretically compromised intestinal circulation were normal, these data do not provide arguments to withhold enteral nutrition in these newborns (chapter 3).

- More data on the pharmacokinetics and pharmacodynamics of sedatives and analgesia are needed to guide optimal treatment especially in case of combined therapy (chapter 5).

- Sildenafil in combination with iNO may be a promising adjuvant in the treatment for severe therapy resistant PPHN, also during ECMO (chapter 6).

- Follow-up of neonates treated with ECMO shows a considerable morbidity at age 5 years comparable to figures from the UK and the Unites States, consolidating the idea that structural follow-up of these infants remains important, preferably with involvement of representatives from different disciplines (chapter 7).

- Lung function in ECMO survivors during the first year of life revealed normal lung volume and normal expiratory flow at a level below average with normal growth and development during that year. Lower airway obstruction was only observed in the 8-year-olds, and not in the 5-year-olds (chapter 8 and 9).

Samenvatting

Extracorporele membraan oxygenatie (ECMO) is een techniek die wordt toegepast als levensondersteunende behandeling bij potentieel reversibele cardio-respiratoire insufficiëntie. Bij deze techniek wordt het bloed buiten het lichaam van zuurstof voorzien met behulp van een kunstlong. Op deze manier krijgen de longen van de patiënt de kans te herstellen omdat ze worden beademd met minimale beademingsvoorwaarden waarbij beschadiging door hoge zuurstofconcentraties en barotrauma zoveel mogelijk wordt voorkomen. ECMO wordt het meest gebruikt bij (bijna) voldragen pasgeborenen met ernstige ademhalingsproblemen en pulmonale hypertensie – hetzij primair (idiopathisch) of secundair optredend bij een meconium aspiratie syndroom (MAS) – met congenitale hernia diafragmatica of met sepsis. Dit proefschrift presenteert klinische studies naar bepaalde aspecten van de acute fase van ECMO-behandeling van pasgeborenen met respiratorische insufficiëntie evenals aspecten van de follow-up op de lange termijn.

Hoofdstuk 1 geeft een algemene inleiding over de ontwikkeling van ECMO door de tijd. Tevens worden de aspecten geïntroduceerd die zijn onderzocht, alsmede de doelstellingen van het proefschrift.

Hoofdstuk 2 beschrijft de resultaten van een retrospectieve studie over een periode van 5 jaar naar aspecten van haalbaarheid en tolerantie bij het routinematig geven van enterale voeding aan pasgeborenen tijdens ECMO. De haalbaarheid werd beoordeeld door de tijdsperiode te registreren voordat 40% van de totale vochtinname voor rekening kwam van enterale voeding. De tolerantie werd beoordeeld aan de hand van het optreden van ziekteverschijnselen die met de voeding te maken hadden. Zevenenzestig van de 77 kinderen kreeg enterale voeding tijdens ECMO. Zesendertig van deze (54%) bereikten de genoemde 40% enterale vochtinname binnen een mediane duur van 3 dagen (van 2 tot 4 dagen). Over de 5 jaar bleek een trend tot enterale voeding bij meer kinderen (71% tot 94%). Enterale voeding werd tijdelijk gestopt bij 16 patiënten, d.w.z. bij 14 vanwege maagretenties, bij 1 patiënt omdat deze oncomfortabel leek en bij 1 omdat deze wellicht had geaspireerd. Gallig braken, bloederige ontlasting of een bol gespannen buik werden niet waargenomen. Over het algemeen werd de enterale voeding goed verdragen en werden er geen ernstige complicaties waargenomen. Wij zijn daarom van mening dat het routinematig geven van enterale voeding aan ernstig zieke pasgeborenen tijdens ECMO haalbaar is.

In het vervolgonderzoek van enterale voeding voor pasgeboren tijdens ECMO wordt in **hoofdstuk 3** het effect op de darmfunctie beschreven. Het doel was om meer inzicht te krijgen in de hormonale respons op enterale voeding. Plasmaspiegels van de darmhormonen gastrine, cholecystokinine en peptide-YY werden bepaald na de introductie van enterale voeding. Twaalf van 24 pasgeborenen kregen alleen parenterale voeding. Bij de overige 12 werd enterale voeding na enkele dagen geïntroduceerd. De plasmaspiegels van deze 24 pasgeborenen werden vergeleken met 16 bloedmonsters van een controlegroep van 8 pasgeborenen die geopereerd waren voor een aangeboren

afwijking –bijvoorbeeld een oesophagusatresie – maar niet met ECMO werden behandeld. De plasmaspiegels van gastrine, cholecystokinine en peptide-YY gemeten bij pasgeborenen aan ECMO die enterale voeding kregen, waren significant hoger dan die van de pasgeborenen die alleen parenterale voeding kregen. Er bleken geen verschillen te zijn met de controlegroep. Concluderend kunnen we zeggen dat de plasmaspiegels van de onderzochte darmhormonen een normale respons laten zien na de introductie van enterale voeding. De resultaten van deze studie vormen geen ondersteunend argument voor het vigerende beleid om enterale voeding te onthouden aan zeer ernstig zieke pasgeborenen die ECMO-behandeling ondergaan.

In hoofdstuk 4 werd retrospectief geëvalueerd of ECMO de kans op het ontstaan van een chylothorax na operatieve correctie van een congenitale hernia diafragmatica vergroot. Bij 98 kinderen met een congenitale hernia diafragmatica, die al dan niet behandeld werden met ECMO, werd gekeken of ze na de operatie een chylothorax ontwikkelden. Dit werd ook gedaan voor 114 kinderen die behandeld werden met ECMO vanwege andere redenen. Als controlegroep fungeerden 100 kinderen die vanwege een oesophagusatresie werden geopereerd. Bij 10% van de patiënten met congenitale hernia diafragmatica bleek na operatie een chylothorax te zijn opgetreden; en uitgesplitst: bij 21% van hen die met ECMO werden behandeld en 6% van hen die niet met ECMO werden behandeld. Dit verschil bleek significant te zijn. Het gebruik van een patch voor het sluiten van het defect in het diafragma bleek als onafhankelijke variabele voor het ontstaan van een chylothorax eveneens significant te zijn. Bij kinderen die werden behandeld met ECMO voor andere redenen, en bij hen die geopereerd waren vanwege een oesophagusatresie bleek de incidentie van een chylothorax respectievelijk 3,5% en 4% te zijn. Een chylothorax trad meestal op aan de kant van het defect in het diafragma en niet aan de kant van de ECMO-canules. In samenhang met de bevinding dat de aanwezigheid van een patch een grotere kans geeft op het ontwikkelen van een chylothorax, lijkt het waarschijnlijker dat ECMO een selectiebias vormt dan dat het een primaire oorzaak is voor het ontstaan van een chylothorax.

In hoofdstuk 5 worden de plasmaconcentraties van midazolam en morfine beschreven bij 20 neonaten tijdens ECMO-behandeling. Het is een vooruitlopende beschrijving van een grotere studie naar de farmacokinetiek en farmacodynamiek van midazolam en morfine tijdens ECMO. Plasmaconcentraties van midazolam, 1-OH-midazolam, 1-OH-midazolam-glucuronide, morfine, morfine-M3G en morfine-M6G werden bepaald op verschillende tijdstippen na het staken van morfine en midazolam na cannulatie en tevens na herintroductie van deze middelen. De plasmaconcentraties van zowel morfine als midazolam lieten een grote variabiliteit zien. Achttien kinderen hadden zowel morfine als midazolam nodig voor toereikend sederen. De mediane (IQR) tijdsduur tussen het stoppen van de medicatie en de herintroductie hiervan was 10 (7,8 - 27) uur. De mediane dosering van morfine tijdens ECMO was 11,5 (10,1 - 15,5) µg/kg/hr. Van midazolam was dit 0,15 (0,1 - 0,2) mg/kg/hr. In nadere onderzoeken is het de bedoeling de farmacokinetische en –dynamische eigenschappen van morfine en midazolam te

evalueren, daarbij gebruik makend van gevalideerde pijnscores zoals de COMFORT en VAS.

In het kader van onderzoek naar medicijngebruik tijdens ECMO hebben we in **hoofdstuk 6** naar de effecten gekeken van orale toediening van sildenafil (Viagra®) bij 15 pasgeborenen die ECMO-behandeling kregen omdat ze pulmonale hypertensie hadden die niet met een conventionele therapie kon worden behandeld. Van deze 15 overleden er 7; allen met een congenitale hernia diafragmatica. De bevindingen bij de overlevenden werden vergeleken met die bij de overledenen. Er bleek geen verschil in de ECMO-duur en in het dalen van de ECMO-flow 24 uur na introductie van sildenafil. De overlevenden hadden sildenafil significant eerder na cannulatie gekregen dan de overledenen; respectievelijk 41 (17 - 90) uur en 200 (161 - 334) uur. Sommige kinderen kregen ook iNO toegediend gelijktijdig met sildenafil, en die werden vergeleken met de kinderen die geen iNO kregen. De kinderen die beide kregen vertoonden een grotere afname van de ECMO-flow in de eerste 24 uur na sildenafil-toediening dan de kinderen die alleen sildenafil kregen. Bij 12 kinderen werd een significante daling van de bloeddruk waargenomen in de eerste 2 uur na de eerste toediening van sildenafil. Deze daling hing niet samen met de dosis. De bevindingen van deze studie laten zien dat een behandeling met sildenafil gunstig kan zijn voor individuele gevallen van pulmonale hypertensie. Toediening van sildenafil relatief vroeg in het ziekteproces, en dan samen met iNO, geniet de voorkeur. In tegenstelling tot eerdere onderzoeken bij dieren en bij volwassenen werd in ons onderzoek een daling van de systemische arteriële bloeddruk waargenomen.

In het kader van de follow-up op de lange termijn wordt in **hoofdstuk 7** de morbiditeit beschreven bij 98 kinderen die nu 5 jaar oud zijn en als pasgeborenen ECMO-behandeling hadden ondergaan. Op deze leeftijd staan kinderen aan het begin van de basisschool en worden belangrijke beslissingen genomen voor de verdere schoolcarrière. Deze kinderen waren behandeld in de twee door de overheid aangewezen behandelcentra in Nederland; het Erasmus MC-Sophia kinderziekenhuis in Rotterdam en het Universitair Medisch Centrum st. Radboud in Nijmegen. Het follow-up programma bestond uit een medisch onderzoek, een neuro-motorische beoordeling en een psychologische evaluatie onder meer met behulp van vragenlijsten voor ouders en leerkracht. Bij 17% van de 98 kinderen werden neurologische afwijkingen gevonden. Bij 6 van deze 17 kinderen was sprake van een ernstige neurologische afwijking; 2 van de 6 hadden een chromosomale afwijking, 3 waren mentaal geretardeerd en motorisch gehandicapt. De zesde had een rechtszijdige hemiplegie. Deze 6 kinderen ondergingen niet het neuro-motorische onderdeel van het follow-up programma. Motorische problemen werden gevonden in 26% van de overgebleven 92 kinderen. Van deze had 15% daadwerkelijk een motorisch probleem, en 11% bevond zich in een risicogebied hiervoor. Bij 14% van de kinderen werd een cognitieve achterstand gevonden. De gemiddelde IQ score was normaal, d.w.z. 100,5. De resultaten tonen aan dat ECMO geassocieerd is met een aanzienlijke morbiditeit op de leeftijd van 5 jaar. Dankzij een goede samenwerking tussen de twee centra en een relatief korte reistijd voor kinderen in

Nederland was het mogelijk een groot aantal van 87% van de overlevende kinderen terug te zien in dit follow-up programma. Naar onze mening is er behoefte aan een multidisciplinair follow-up programma met nationale consensus over tijdstippen van meten en het te gebruiken testprotocol. Alleen dan kan de lange-termijn morbiditeit die voortvloeit uit de toepassing van een dergelijk invasieve technologie in de directe neonatale periode objectief worden geëvalueerd.

Als onderdeel van het eerder genoemde uitgebreide follow-up programma worden op verschillende leeftijden longfunctietesten verricht. In **hoofdstuk 8** worden de resultaten beschreven van longfunctietesten 6 en 12 maanden na neonatale ECMO-behandeling. De functionele restcapaciteit (FRC_p) en de geforceerde expiratoire flow op het moment van FRC ($V'max_{FRC}$) werden uitgedrukt in z scores. 35 kinderen ondergingen een longfunctieonderzoek op de leeftijd van 6 maanden en 35 op de leeftijd van 12 maanden; 25 kinderen werden zowel op 6 als op 12 maanden onderzocht. Er werden normale longvolumes en normale expiratoire flows gevonden bij een normale ontwikkeling op een benedengemiddeld niveau gedurende het eerste jaar. Daarnaast werden bij kinderen die met ECMO werden behandeld vanwege een congenitale hernia diafragmatica grotere longvolumes gevonden dan bij degenen die ECMO nodig hadden vanwege een meconium aspiratie syndroom. Dit was het geval zowel op de leeftijd van 6 als van 12 maanden. Dit onderdeel geeft ons niet alleen inzicht in de effecten van ECMO op ernstige respiratoire insufficiëntie, maar levert ook gegevens over longitudinale ontwikkeling van de longfunctie op jonge leeftijd. Met name voor de follow-up van kinderen met een congenitale hernia diafragmatica is het van belang de groeipotentie van luchtwegen en longvaten te blijven evalueren.

Hoofdstuk 9 beschrijft onderzoek naar de longfuncties van 28 vijf-jarigen en 14 acht-jarigen die als pasgeborenen ECMO-behandeling hadden ondergaan. De luchtwegweerstand werd gemeten op de leeftijd van 5 en 8 jaar met behulp van een interruptietechniek (R_{int}) tijdens de expiratie. De resultaten werden uitgedrukt in z scores. Tevens werd met behulp van de spirometer de FVC, FEV_1, FEV_1/VC-ratio en MEF_{25} gemeten. Op de leeftijd van 8 jaar werd met een heliumdilutiemeting de TLC_{he}, het restvolume helium (RV_{he}), VC_{he}, $FRC_{he,}$ en de RV/TLC ratio gemeten. De luchtwegweerstand lag voor beide leeftijden binnen normale grenzen. Na bronchodilatatie daalde de luchtwegweerstand in beide leeftijdsgroepen significant. Bij de 8-jarigen werd voor bronchodilatatie een lichte luchtwegobstructie geconstateerd n.a.v. een verlaagde FEV1/VC ratio en MEF_{25}. Deze waardes waren significant lager dan bij de 5-jarigen. De diffusiecapaciteit bij de 8-jarigen was normaal. De bevindingen van deze studie bevestigen de aanwezigheid van longschade ondanks de rust die de longen wordt gegund tijdens behandeling met ECMO.

Hoofdstuk 10 is een bespreking van de bevindingen van alle studies en bevat tevens aanbevelingen voor verder onderzoek. De belangrijkste conclusies zijn:

- Introductie van enterale voeding werd goed verdragen door ernstig zieke pasgeborenen tijdens ECMO-behandeling en had geen ernstige complicaties tot gevolg (hoofdstuk 2).

- Gezien het feit dat er normale darmhormoonwaarden in plasma werden gevonden na de introductie van enterale voeding bij neonaten met een in theorie verminderde intestinale doorbloeding, is dit geen reden om deze neonaten niet enteraal te voeden (hoofdstuk 3).

- Optimale sedatie en pijnstilling van pasgeborenen aan ECMO zijn in toenemende mate gebaat bij de beschikbaarheid van farmacokinetische en farmacodynamische gegevens.

- Sildenafil in combinatie met iNO zou een veelbelovende aanvulling kunnen zijn in de behandeling van ernstige therapieresistente PPHN, ook tijdens ECMO (hoofdstuk 6).

- Bij vijfjarigen die als pasgeborenen met ECMO zijn behandeld, blijkt er een aanzienlijke morbiditeit te bestaan, vergelijkbaar met soortgelijke patiënten in Engeland en de Verenigde Staten van Amerika. Dit bevestigt nogmaals dat structurele follow-up van deze kinderen belangrijk blijft, bij voorkeur in samenwerking met deskundigen van verschillende disciplines (hoofdstuk 7).

- Longfuncties gedurende het eerste levensjaar toonden een normaal longvolume en een normale expiratoire flow bij normale groei en ontwikkeling op een benedengemiddeld niveau. Tests op de leeftijd van 5 en 8 jaar lieten alleen in de oudste leeftijdsgroep een milde lagere luchtwegobstructie zien (hoofdstukken 8 en 9).

List of abbreviations

$AaDO_2$	Alveolar arterial oxygen gradient
ASD	Atrial septal defect
BIS	Bispectral Index Monitor
BPD	Bronchopulmonary dysplasia
CBCL	Child Behaviour Checklist
CCK	Cholecystokinin
CDH	Congenital Diaphragmatic Hernia
CMV	Conventional mechanical ventilation
CT	Chylothorax
D_{Lco}	Diffusion capacity
ECMO	Extracorporeal Membrany Oxygenation
ELSO	Extracorporeal Life Support Organisation
FEV_1	Forced expiratory volume in one second
FRC	Fucntional Resicual Capacity
FVC	Forced vital capacity
HFO	High frequency oscillation
iNO	Inhaled nitric oxide
IRDS	Respiratory distress syndrome of infancy
IQ	Intelligence quotient
M-ABC	Movement Assessment Battery for Children
MAS	Meconium aspiration syndrome
MEF_{25}	Maximal expiratory flow at 75% of expirated air.
NEC	Necrotising enterocolitis
OI	Oxygenation Index
PPHN	Persistent pulmonary hypertension of the newborn
PYY	Peptide-YY
RAKIT	Revised Amsterdam Intelligence Test
RTC	Thoracoabdominal compression technique
RV	Residual volume
SCV	Superior caval vein
TLC	Total lung capacity
TPN	Total parenteral nutrition
TRF	Teacher’s Report Form
VAS	Visual analogue scale
VC	Viral capacity
VSD	Ventricular septal defect

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Het lijkt nog zo onwerkelijk wanneer ik dit schrijf, maar het boekje is echt af. Het boekje zou er natuurlijk nooit gekomen zijn zonder de hulp van een heleboel mensen. Iedereen hartelijk bedankt! Een aantal mensen wil ik graag speciaal noemen.

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Curriculum Vitae

Manon Hanekamp was born on March 26th, 1972, in Apeldoorn, the Netherlands. She received secondary education at the Rijnlands Lyceum in Oegstgeest and passed her VWO exam in 1990. In the same year she started her medical training at the faculty of Medicine at the University of Leiden. During her studies she worked for Bio Implant Services in Leiden and did practical work in Groote Schuur Hospital, Cape Town, South Africa at the Department of Gynecology. She obtained her medical degree in September 1998. From November 1998 until March 1999 she worked as a company docter for Commit Arbo. From April 1999 until December 1999 she worked as a resident at the Department of Surgery of the Groene Hart Hospital, Gouda. From January 2000 until December 2001 she worked as a resident at the Department of Pediatric Surgery and at the Pediatric Surgical Intensive Care Unit of Erasmus MC-Sophia's Children Hospital, Rotterdam. In January 2002 she started working here as a research physician and performed short and long-term clinical studies in neonates treated with Extracorporeal Membrany Oxygenation (ECMO), which are presented in this thesis. Supervisors were Professor D. Tibboel and F.W.J. Hazebroek. In October 2004 she started her clinical pediatric residency in training (AGIO) at the Amphia Hospital, Breda (head Dr. A.A.P.H. Vaessen-Verberne) as part of her training at the Erasmus MC-Sophia Children's Hospital, Rotterdam (heads Professor A.J. van der Heijden and Dr. M. de Hoog). She is married to Harmen Hoek and has a daughter Noor.