Robert Jan Houmes

Pediatric Extracorporeal Membrane Oxygenation, **Why, When and How**

Pediatric Extracorporeal Membrane Oxygenation, Why, When and How

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**Pediatric Extracorporeal Membrane
Oxygenation, Why, When and How**

**Kunstlong behandeling bij kinderen,
waarom, wanneer en hoe**

Proefschrift

*ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus*

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Chapter 1

Introduction and outline of this thesis

Treatment of failing gas exchange in children.

And he [Elisha] went up, and lay upon the child, and put his mouth upon his mouth, … and the flesh of the child waxed warm.

(II Kings 4:34, King James version)

This is probably the first written example of successful treatment of failing gas exchange. In the present day, providing adequate gas exchange and oxygen delivery remains one of the cornerstones of intensive care medicine. Many things have been changed, improved and scientifically proven since ancient times but numerous questions and challenges remain to be explored and proven to be of benefit.

In 1929 Drinker and Shaw produced the first widely used external negative pressure mechanical ventilator, named the "Drinker respirator". The first patient treated with this 'iron lung' was an eight-year-old polio patient [1]. The Danish anesthesiologist Ibsen was one of the first to use positive pressure ventilation for diseased lungs outside the operating room, during the great poliomyelitis epidemic in Copenhagen in 1952 [2]. After that turning point in the history of intensive care permanent intensive care units were established and patients were ventilated with positive pressure ventilation. Today, ventilation worldwide is mostly performed with any form of positive pressure ventilation.

In the pediatric intensive care unit this type of ventilation is basically a form of time cycled variation of positive pressure levels, resulting in tidal volume changes in the lungs. Despite the benefits of positive pressure ventilation, many patients still die after initiation of mechanical ventilation either from therapy failure or from progressive deterioration of pulmonary functions. Moreover, mechanical ventilation might in itself be detrimental as since its beginning detrimental side effects of this therapy have been published. Multiple factors have been implicated for these effects such as oxygen toxicity, volume-trauma and barotrauma. Nowadays this negative effect of mechanical ventilation on the lung itself is referred to as ventilator-induced lung injury [3].

In 1992 Burkhard Lachmann published an editorial entitled *Open up the lung and keep the lung open* [4] in which he proposed a ventilator strategy aiming to protect the lung by reducing or even preventing therapy- or ventilator-induced lung injury. Since then many studies on ventilator-induced lung injury have been published, paying attention to issues such as pathogenesis, evaluation of ventilation strategies and alternatives to mechanical ventilation. Recently (2015) Amato et al. confirmed the original ideas of Burkhard Lachmann that ventilation of a diseased lung with high pressure differences can induce further damage to the lungs and can contribute to increased mortality and morbidity [5].

Ventilator settings are therefore important for adequate gas exchange with minimal secondary injury. Furthermore the underlying disease is of equal importance since mechanical ventilation can only provide sufficient gas exchange if enough well-perfused aeriated alveoli are present. In patients with severe respiratory failure with limited or insufficient alveoli even frantic efforts to maintain gas exchange, also with high ventilator pressures, will result in respiratory failure and death. Equally important is an adequate pulmonary blood flow. Severe pulmonary hypertension may reduce the pulmonary blood flow, increase ventilation and perfusion mismatch and thereby severely impede gas exchange even when alveoli are adequately ventilated.

An alternative approach to delivering sufficient gas exchange is that of gas exchange outside the body using artificial lungs and blood pumps. This is a technique developed in the early 1970s in which venous blood from the patient is pumped through an artificial lung where the blood is oxygenated and carbon dioxide is extracted before it is returned to the patient either via a vein or an artery. The variant in which the oxygenated blood is returned via a vein is called veno-venous (VV) extracorporeal membrane oxygenation (ECMO) and supports pulmonary functions; in the other variant – veno-arterial (VA) ECMO – the blood is returned in the arterial system and this technique functions as a cardiopulmonary bypass supporting both the respiration and circulation.

Since its introduction in the intensive care unit in 1972, this type of gas exchange in combination with mechanical ventilation has become an alternative treatment option in severe cardiorespiratory failure [6]. The use of ECMO was widely embraced in neonatal care as well. The first reported use in neonatal care dates from 1977 [7]. Since then over 36,000 neonates have been treated with ECMO. The use of ECMO for pediatric patients is increasing and more than 18,000 pediatric patients have been treated with ECMO until now. ECMO has become a reliable option *allowing* for intrinsic recovery of the lungs and potentially reducing secondary damage due to high pressure mechanical ventilation [8].

The Extracorporeal Life Support Organization (ELSO), Ann Arbor, Michigan, was formed in 1989 as a non-profit organization that aids centers using extracorporeal life support in the management of cardiopulmonary failure unresponsive to conventional medical and surgical therapies. The ELSO maintains a registry of extracorporeal life sup-

port cases and provides annual Extracorporeal Life Support (ECLS) survival information and center-based performance reports. Figure 1. shows a summary report of all patients in the registry up to January 2016.

Despite the many patients treated, many questions regarding the use of ECMO remain. Changes in ECMO materials such as devices and cannulas as well as other advances in the field have greatly altered ECMO indications and utility of ECMO in different populations. Changes in the underlying pathology in ECMO patients, the concept of minimal ventilation to prevent or reduce ventilator induced lung injury and the use of VV ECMO with double lumen single catheter cannulas have come with many challenges. With the shift from neonatal to pediatric and adult ECMO, clear insight from research is needed to reach consensus on contraindications for ECMO, the timing of ECMO initiation, optimal management strategies for subgroups of ECMO patients, diagnostic criteria and time estimates on recoverability of lung function.

ECLS Registry Report
International Summary
January, 2016

Extracorporeal Life Support Organization
2800 Plymouth Road
Building 300, Room 303
Ann Arbor, MI 48109

Overall Outcomes

	Total Patients	Survived ECLS		Survived to DC or Transfer	
Neonatal					
Respiratory	28,723	24,155	84%	21,274	74%
Cardiac	6,269	3,885	62%	2,599	41%
ECPR	1,254	806	64%	514	41%
Pediatric					
Respiratory	7,210	4,787	66%	4,155	58%
Cardiac	8,021	5,341	67%	4,067	51%
ECPR	2,788	1,532	55%	1,144	41%
Adult					
Respiratory	9,102	5,989	66%	5,254	58%
Cardiac	7,850	4,394	56%	3,233	41%
ECPR	2,379	948	40%	707	30%
Total	73,596	51,837	70%	42,947	58%

Centers

Centers by Year

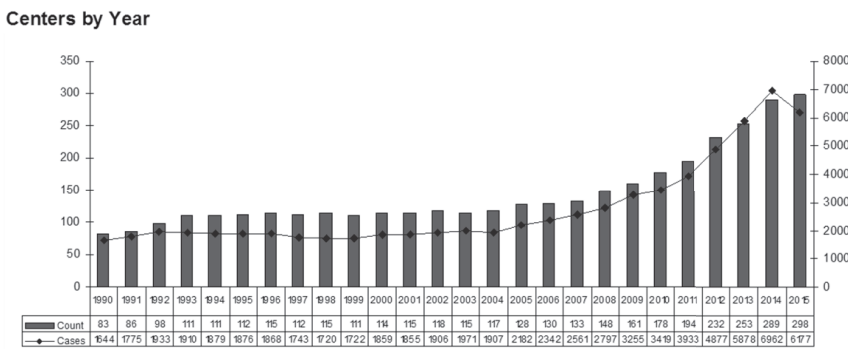|	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Count	83	86	98	111	111	112	115	112	115	111	114	115	118	115	117	128	130	133	148	161	178	194	232	253	289	298
Cases	1644	1775	1933	1910	1879	1876	1868	1743	1720	1722	1859	1855	1906	1971	1907	2182	2342	2561	2797	3255	3419	3933	4877	5878	6962	6177

Figure 1: International summary of extracorporeal life support cases in the ESLO registry.

OUTLINE OF THE THESIS

The general aim of this thesis is to provide scientifically valid data that will help to guide the treatment of failing gas exchange in pediatric patients. This thesis is in two parts.

Part 1. Mechanical ventilation for failing gas exchange in children

In **Chapter 2** we analyze the existing literature on ventilator modes in children aged from 28 days to 18 years, and we perform a search for articles comparing two different modes of ventilation. We discuss the reported differences between modes of ventilation with regard to length of ventilation, oxygenation, mortality, chronic lung disease and weaning.

After a search in the PubMed and EMBASE databases and the screening of 461 potentially relevant articles, nine full text articles were retrieved and assessed for eligibility. Four randomized controlled trials (RCTs) were excluded, however, for any of the following reasons: focus on triggering instead of ventilation; inclusion of infants below 37 weeks of gestational age; or not comparing two ventilation modes. **Chapter 2** contains the results of analysis of the pooled data of the remaining five RCTs [9].

With the knowledge obtained in chapter 2 we developed an invasive ventilation algorithm. The algorithm distinguishes between the presence of lung disease, in which pressure control is considered as the preferred mode, and the absence of lung disease, in which situation pressure-regulated volume control is preferred. In **chapter 3** we evaluate physician adherence to this new protocol [10].

In **chapter 4** we describe the use of extracorporeal membrane oxygenation (ECMO) in pediatric patients [11]. In this chapter we discuss the available evidence for the use of pediatric ECMO in respiratory and circulatory failure, focusing on indications and contra-indications and choice of ECMO mode.

Part 2. Aspects in the use of Extracorporeal Membrane Oxygenation to assist gas exchange in children

In **chapter 5** we present data on the use of arterial lactate for predicting mortality in children requiring ECMO [12]. We show that static arterial lactate measurements and, to a lesser extent, dynamic arterial lactate indices predict mortality in pediatric, but not in neonatal ECMO patients.

In **chapter 6** we present a retrospective analysis of the role of preoperative ECMO in neonates born with transposition of the great arteries with severe hypoxemia, despite conventional measures like balloon atrioseptostomy, ventilation, nitric oxide inhalation and inotropic support.

In **chapter 7** we describe prolonged use of ECMO defined as an ECMO run of more than 21 days in pediatric patients in particular. An analysis is performed on survival; the

occurrence and nature of complications; and the need for interventional and diagnostic procedures.

Chapter 8 reports on the benefits and drawbacks of open lung biopsy in neonatal and pediatric patients on ECMO. We describe all open lung biopsies performed during ECMO in the Netherlands in the period 1990-2014.

In **chapter 9** we investigated the feasibility of surgical correction of congenital diaphragmatic hernia while the patient is on ECMO and report on the surgical bleeding complications associated with this procedure [13].

We describe our findings on the pharmacological aspects during ECMO in **chapter 10**.

In **Chapter 11** we present a multicenter study on the use of a new diagonal pump for the use in ECMO. We pooled the patient data from seven European pediatric centers on a new miniaturized third generation diagonal centrifugal pump, to evaluate the feasibility, efficacy, complication-, and survival rate.

In **Chapter 12** we discuss the current status of the use of perfluorocarbons (PFC's) in respiratory failure.

Lastly, the implications of our findings are discussed and compared to the available literature in **chapter 13** [14].

Chapter 14 contains the summary of this thesis.

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Part 1

Mechanical ventilation for failing gas exchange in children

*Quality means doing it right
when no one is looking*

(Henry Ford 1863–1947)

Chapter 2

Invasive ventilation modes in children: a systematic review and meta-analysis

Anita Duyndam, Erwin Ista, Robert Jan Houmes, Bionda van Driel, Irwin Reiss, Dick Tibboel

ABSTRACT

Introduction

The purpose of this study was to critically review the existing body of evidence on ventilation modes for infants and children up to the age of 18 years.

Methods

The databases PubMed and EMBASE were searched using the search terms: 'artificial respiration', 'instrumentation', 'device', 'devices', 'mode', 'modes'. The review included only studies comparing two ventilation modes in a randomized controlled study (RCT) and reporting one of the following outcome measures: length of ventilation (LOV), oxygenation, mortality, chronic lung disease and weaning. We quantitatively pooled the results of trials where suitable.

Results

Five trials met the inclusion criteria. They addressed six different ventilation modes in 421 children: high frequency oscillation (HFO), pressure control (PC), pressure support (PS), volume support (VS), volume diffusive respirator (VDR) and biphasic positive airway pressure. Overall there were no significant differences in LOV and mortality or survival rate associated with the different ventilation modes. Two trials compared HFO versus conventional ventilation. In the pooled analysis, mortality rate did not differ between these modes (odds ratio (OR) 0.83, 95% confidence interval (CI) 0.30 to 1.91). High-frequency ventilation (HFO and VDR) was associated with a better oxygenation after 72 hours than was conventional ventilation. One study found a significantly higher PaO_2/FiO_2 ratio with the use of VDR versus PC ventilation in children with burns. Weaning was studied in 182 children assigned to either a PS protocol, VS protocol or no protocol. Most children could be weaned within two days and weaning time did not significantly differ between the groups.

Conclusion

The literature provides scarce data for the best ventilation mode in critically ill children beyond the newborn period. However, there is no evidence that high-frequency ventilation reduced mortality and LOV. Longer-term outcome measures such as pulmonary function, neurocognitive development, and cost-effectiveness should be considered in future studies.

INTRODUCTION

Ventilator-induced lung injury in critically ill children suffering from acute respiratory failure should be counteracted by adapting ventilation management to the cause of respiratory failure [1]. Ideally, management should be based on proven effective strategies. In a multicenter study bronchiolitis was the most frequent cause of respiratory failure in infants (43.6%); pneumonia that in older children (24.8%) [2]. Mortality in that study was rare (1.6%); the median duration of ventilation was 7 days. Randolph et al. [1] suggested that in pediatric clinical trials, long-term morbidity would be a more sensitive indicator of the effects of clinical ventilation interventions than mortality or duration of ventilation.

Pediatric intensive care units (PICUs) worldwide use a wide variety of ventilation modes: high frequency oscillation (HFO), pressure control (PC), synchronized intermittent mandatory ventilation (SIMV), pressure support (PS), pressure regulated volume control (PRVC) and, more recently, neurally adjusted ventilator assist (NAVA) [3, 4]. The ventilation mode is often not targeted specifically to the underlying disease but rather determined by the intensive care physician's experience, local PICU policy and protocols, or outcomes of studies in adults [1, 2, 5]. An unambiguous international guideline is still lacking [1, 5].

The objective of this article is to systematically review the randomized controlled trials (RCTs) comparing ventilation modes used in critically ill children (term born up to 18 years of age) on the following outcome measures: length of ventilation, oxygenation, mortality, chronic lung disease and weaning. We aimed to answer the question whether there is sufficient evidence to decide on the better mode.

METHODS

Search and selection

A systematic search was performed in PubMed and EMBASE in September 2010. MeSH terms and keywords searched for in the titles, abstracts and keywords areas were: 'artificial respiration', 'instrumentation', 'device', 'devices', 'mode', 'modes', combined with Boolean operators AND, OR. (Additional file 1 provides the complete search strategy). The search was limited to RCTs or quasi-experimental studies, with age limit > 28 days until 18 years. Only articles comparing at least two ventilation modes were selected for review. Articles on non-invasive ventilation, studies in premature neonates (< 37 weeks), and articles in other languages than English or Dutch were excluded. No limits were imposed on publication date.

Two authors (AvD, EI) independently reviewed abstracts and full-text articles to identify eligible studies. Reference lists of retrieved studies were hand searched for additional articles.

Quality assessment

Study quality and level of evidence were assessed on criteria established by the Dutch Institute for Healthcare Improvement CBO in collaboration with the Dutch Cochrane library (See Additional file 2 and Table 1) [6]. The major criteria were: 1) was assignment to study group randomized?; 2) were investigators blinded?; 3) was it an intention-to-treat analysis?; 4) were the study groups comparable?; and 5) was there appropriate report of outcome results for each group and the estimated effect size. Consensus between the authors on the interpretation of the extracted data was achieved.

Table 1: Level of Evidence

Level	Description of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort or studies High-quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant probability that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Data abstraction

Authors AvD and EI each independently recorded patient characteristics (sample size, age, respiratory failure), details of the ventilation mode and period over which outcome variables were measured. Outcome variables considered were the following: length of ventilation (LOV), oxygenation, chronic lung disease (CLD), mortality and weaning.

Statistical methods

We quantitatively pooled the results of individual trials, where suitable. We expressed the treatment effect as an odds ratio (OR) for dichotomous outcomes and as a weighted mean difference (WMD) for continuous outcomes with 95% confidence intervals. The pooled OR was estimated with the Mantel-Haenszel method which is generally the most robust model [7]. Differences were considered statistically significant if $p < 0.05$ or if the 95% confidence interval did not include the value 1. The analyses were performed with Microsoft ® Excel, Office 2007 for Windows.

RESULTS

Search and selection

After filtering out duplicate studies, titles and abstracts of 461 potentially relevant articles were screened (Figure 1). The reference lists yielded one other study that had been missed because the keywords were not in the title or abstract. Eventually, nine full-text articles were retrieved and assessed for eligibility. Four RCTs were excluded for any of the following reasons: focus on triggering instead of ventilation; inclusion of infants below 37 weeks of gestational age; not comparing two ventilation modes [8-11]. This review therefore includes five RCTs [12-16].

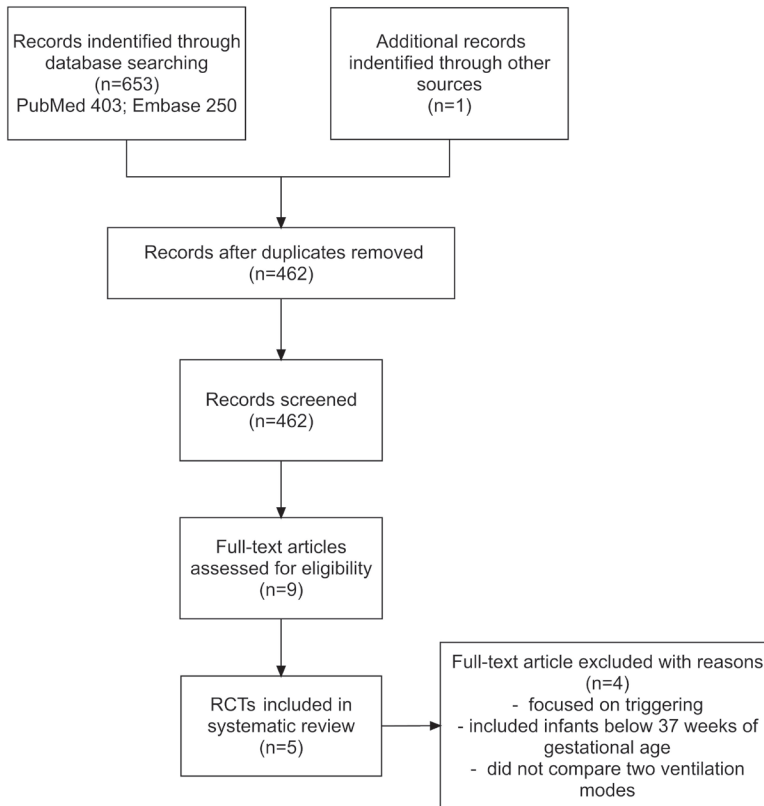Tabulated details of these five RCTs are presented in Tables 2 and 3.

Figure 1: Search results. RCT, randomized controlled trial.

Length of ventilation

Length of ventilation (LOV) served as outcome measure in four studies (Table 2). First, Arnold and colleagues [12] in a multi center trial compared HFO and conventional ven-

Table 2: Included randomized controlled trials - ventilation

Reference	Study population	Intervention/ mode	Mortality / survival	LOV (days)	Outcome measures Oxygenation	Outcome measures CLD	Level of evidence
Arnold et al, 1994 [12]	58 children (age HFO 2.5±2.5 vs 3.1 ± 3. 3 years) With diffuse alveolar disease and/or airleak syndrome	Multi-center study (five centers) — Comparison effectiveness of HFO (n=29) with CV (n=29) – crossover — Crossover: CV to HFO (n=19), HFO to CV (n=11)	Number of survivors at 30 days - CV: 17 of 29 (59%); HFO: 19 of 29 (66%); (NS); Death (Ranked)-CV: 40%, CV to HFO: 42% HFO: 6%, HFO to CV: 82% (p=<0.001)	Total-CV: 22 ± 17; HFO: 20 ± 27; Survivors (at 30 days)-CV: 29 ± 18; HFO: 27 ± 31. Non survivors (at 30 days)-CV: 11 ± 9; HFO: 8 ± 6 (NS)	Pao_2/Pao_2 increase over time (72hours) in HFO compared with CV ($p<0.001$); Pao_2,-HFO: 0.13 (0 hours) up to 0.26 (72hours); CV: 0.13 (0 hours) up to 0.22 (72hours). After crossover- Pao_2/Pao_2 increase over time (72hours) in CV to HFO group compared to HFO to CV group ($p=0.003$)	CV: n=10 (59%); HFO: n=4 (21%). (p=0.039; OR=5.4 95%CI 1.2-23.2) (O_2 at 30 days)	1+
Dobyns et al. [14]	99 children (age 0-23 years) with AHRF oxygenation index > 15	Multi-center study (seven centers) — Comparisons between patients treated with HFO + iNO (n=14), HFO alone (n=12), CV + iNO (n=35), and CV alone (n=38)	Trend of improved survival in the HFO + iNO- CV: 22 of 38 (58%); CV + iNO, 20 of 35 (53%); HFO, 7 of 12 (58%); HFO + iNO, 10 of 14 (71%) (p=0.994)	CV: 22 ±4; CV + iNO: 21 ± 3; HFO: 52 ± 28; HFO + NO: 17 ± 4; (p=0.098)	PaO2/FiO2 (PF) ratio - after 4 hours: HFO + iNO 136 ± 21 vs. CV 96 ± 6 (p = 0.2); after 12 hours: HFO + iNO 184 ± 45 vs. CV 107 ± 8 and CV + iNO 115 ± 9, HFO 136 ± 32 (p = 0.023); after 24 hours: treatment both HFO + iNO and HFO resulted in greater improvement in PF ratio than CV or CV + iNO (P = 0.005); after 72 hours: HFO 259 ± 60 vs. CV 148 ± 15 and CV + iNO 150 ± 19; HFO + iNO 213 ± 29 (p= 0.027)		1+
Jaarsma et al. [13]	18 children (age 0-10 years) with respiratory failure for ventilation	Single-center study — Compare BIPAP (n=11) with PS (n=7) determining which mode is effective, safe and easy	ND	BIPAP: 9.8 ± 9.2; PS: 6.4 ± 5.8; (p=0.27)	ND		1-
Carman et al. [16]	64 children (age 7.4±0.7 years) with inhalation injury	Single-center — Compare VDR (n=32) with PC (n=32)	VDR: 2/32 (6%); PC: 5/32 (16%); (NS)	VDR: 12±2; PCV: 11±2 (NS)	PF ratio- VDR: 563±16, PC: 507 ± 13; (p<0.05)		1-

Data presented as number/total (percentage) or mean ± standard deviation. AHRF, acute hypoxemic respiratory failure; BIPAP, biphasic positive airway pressure; CI, confidence interval; CLD, chronic lung disease; CV, conventional mechanical ventilation; HFO, high-frequency oscillation ventilation; iNO, inhaled nitric oxide; LOV, length of ventilation; ND, no data; NS, not significant; OR, odds ratio; VDR, volume diffusive respirator (high-frequency time-cycled pressure ventilator); PC, pressure-controlled ventilation; PS, pressure support ventilation.

tilation (CV) in 58 children with either diffuse alveolar disease and/or air leak syndrome; 29 had been randomized to HFO; 29 to CV. During the first 72 hours of study the mean airway pressure was significantly (p<0.001) higher in the HFO group. The HFO strategy entailed aggressive increases in mean airway pressure to attain the ideal lung volume and to achieve an arterial oxygen saturation of > 90% with FiO2 < 0.6. The CV strategy entailed stepping up the end-expiratory pressure and inspiratory time to increase mean airway pressure and to limit peak inspiratory pressure increases. Crossover to the alternate ventilator was required if the patient met defined criteria for treatment failure. LOV did not significantly differ between the CV and HFO groups (weighted mean difference (WMD) 2.0 days, 95% confidence interval (CI) -9.61 to 13.61).

Second, Dobyns et al. [14] in a multi center study compared HFO and CV in 99 children with acute hypoxemic respiratory failure. Seventy-three were treated with CV (38 without iNO, 35 with iNO); 26 with HFO (12 without iNO, 14 with iNO). Mechanical ventilation and FiO2 were adjusted to maintain SaO2 at 90% and pCO2 between 45 and 55 mmHg. Higher pCO2 values were tolerated as long as the arterial pH was 7.20. In the CV strategy the positive end-expiratory pressure was increased incrementally to improve oxygenation while avoiding clinical and radiographic signs of lung hyperinflation. The peak airway pressure was maintained at < 35–40 cm H2O by limiting the level of tidal volume and positive end-expiratory pressure. The initial HFO settings were: FiO2 of 1.0, 33% inspiratory time, frequency of 10 Hz, and mean airway pressure set at 2–4 cm H2O above that used on CV. Pressure amplitude was set to achieve perceptible chest wall motion and was adjusted if possible to optimize ventilation.

Table 3: Included randomized controlled trials- weaning

			Outcome measures			
Reference	Study population	Intervention/ mode	Duration of weaning (days)*	Extubation failure rate	Oxygenation	Level of evidence
Randolph et al. [15]	182 children (age 0-17 years) with weaning of ventilation support for more than 24 hours and who failed a test for extubation readiness on minimal PS	Multi-center study (10 centers) to evaluate weaning protocols comparing VS (continuous automated adjustment of PS by the ventilator) (n=59) - PS (adjustment by clinicians) (n=61) - to standard care (no protocol) (n=59)	PS: 1.6 (0.9-4.1); VS: 1.8 (1.0-3.2); no protocol: 2.0 (0.9-2.9), (p=0.75)	PS (15%), VS (24%); no protocol (17%) (p=0.44) Male children more frequently failed extubation (OR, 7.86 95% CI = 2.36-26.2; p<.001)	ND	1++

*Data presented as median (interquartile range). CI, confidence interval; ND, no data; OR, odds ratio; PS, pressure support; VS, volume support.

In this study HFO did not lead to a significantly shorter LOV (Table 2). However, for the two ventilation groups without iNO, LOV significantly differed between CV and HFO (WMD -30.0 days, 95%CI -45.89 to -14.11). Third, Carman et al. [16] compared the Volume Diffusive Respirator (VDR) with PC ventilation in burned children with inhalation injury. The VDR is a high-frequency, time cycled pressure ventilator that can ventilate, oxygenate and promote secretion removal. SaO2 was maintained at or above 90%; PaCO2 at <55 mmHg. Thirty-two children with a mean age of 5.5 years (SD±0.9) were treated with VDR; 32 children with a mean age of 9.4 years (SD±1.0) with PC ventilation (p=0.04 for mean age). LOV was significantly different between the study groups (WMD -1.0 days, 95%CI -1.98 to -0.02). Fourth, Jaarsma et al. [13] randomized 18 children with respiratory failure to either BIPAP (n=11) or PSV (n=7); their median age was 4 months (range 4 weeks to 10 years). Initial ventilator settings depended on age and the cause of respiratory failure and were adjusted according to thoracic excursions and measured tidal volume. Adjustments were made afterwards aiming at a pCO2 of 4–5 kPa and a pO2 of 8–11 kPa. LOV did not significantly differ between BIPAP (9.8 ± 9.2 days) and PS (6.4 ± 5.8 days).

Pooled analysis resulted in a significantly shorter LOV after CV in comparison with HFO (WMD -2.3 days, 95%CI= -3. 63, -1.04) (Table 4).

Table 4: Meta-analysis of trials comparing high-frequency ventilation with conventional ventilation: length of ventilation

Study	CV		HFOV		WMD (95%CI)	Z value (p-value)
	Mean (SD)	N	Mean (SD)	N		
Length of ventilation						
Arnold et al [12]	22 (17)	29	20 (27)	29	2 [-9.61, 13.61]	-0.338 (p=0.74)
Dobyns et al [14]	22 (4)	38	52 (28)	12	-30 [-45.89, -14.11]	3.699 (p=0.0002)
Subtotal		*67*		*41*	*-11.51 [-15.14, -7.88]*	*-6.221 (p<0.0001)*
Carman et al (VDR) [16]	11 (2)	32	12 (2)	32	-1 [-1.98, -0.02]	-2.0 (p=0.046)
Overall		*99*		*73*	*-2.34 [-3.63, -1.04]*	*-3.542 (p=0.0004)*

CI, confidence interval; CV, conventional ventilation; HFOV, High-frequency oscillation ventilation; SD, standard deviation; VDR, volume diffusive respirator (high-frequency time-cycled pressure ventilator); WMD, weight mean difference.

Oxygenation

Three studies addressed the effects of different ventilation modes on oxygenation.

In the study by Dobyns et al. [14] the PaO2/FiO2 (PF) ratio improved most in HFO mode with iNO after 4 hrs (136mmHg ±21 vs. CV 96±6; p=0.2)) and 12 hrs (HFOV+iNO 184mmHg ±45 vs. CV 107mmHg ±8 and CV+iNO 115mmHg ±9, p=0.023; HFOV 136mmHg ±32). After 24 hrs, HFO treatment both with and without iNO provided better oxygenation than CV both with and without iNO (p<0.05). After 72 hrs, HFO treatment was associated with the best improvement in PF ratio (HFO 259 mmHg ±60 vs. CV 148mmHg ±15 and

CV+iNO 150 mmHg ±19, p=0.027; HFOV+iNO 213 mmHg ±9). The two therapies did not differ in failure rate. Arnold et al. [12] reported a significant (p=0.001) relationship between time and a decreasing oxygenation index in the HFO group but not in the CV group. After crossover (19 patients crossed over from CV to HFO and 11 patients crossed over from HFO to CV) this relationship was significant in both crossover groups (p=0.03 crossover to CV; p=0.02 crossover to HFO).

Carman et al. [16] reported a significantly higher PF ratio in the VDR mode compared with PC (563 mmHg ± 15 vs. 507 mmHg ± 13, p<0.05) but did not specify the time point at which the best PF ratio was measured. As the oxygenation parameters in these three studies were not uniform it was not possible to pool the data.

Mortality, survival

Three studies focused on the outcome measure mortality or survival.

None found a significant difference in mortality between patients treated with HFO and those treated with CV. Arnold et al. [12] reported a mortality rate of 34% (10/29) for HFO versus 41% (12/29) for CV (OR 0.75, 95%CI 0.26 to 2.16). However, the mortality rate in patients not crossed over to CV from HFO or to HFO from CV was significantly better (p=0.003) than that in patients managed with CV only.

Dobyns et al. [14] showed that the survival rate for patients treated with HFO in combination with iNO was higher than that for patients treated with HFO only or with CV (71% vs. 58% in CV, 53% in CV +iNO and 58% in HFO). These differences did not achieve statistical significance. These authors speculated that the improved lung recruitment by HFO enhances the effects of low dose iNO on gas exchange. The mortality rate for HFO without iNO was 42% (5/12) versus 42% (16/38) for CV without iNO (OR 0.98, 95%CI 0.26 to 3.66) [14]. In the study of Carman et al. [16] five of 32 (16%) patients in the PCV group died versus two of 32 (6%) in the VDR group (OR 0.36, 95%CI 0.06 to 2.01).

In the pooled analysis, the mortality rates in HFO mode and CV did not differ (OR 0.70, 95%CI 0.33 to 1.47) (Table 5).

Table 5: Meta-analysis of trials comparing high frequency ventilation to conventional ventilation: Mortality

Study	Conventional ventilation	High-frequency oscillation ventilation	OR (95%CI)
Mortality			
Arnold et al [12]	12/29	10/29	0.75 (0.26, 2.16)
Dobyns et al [14]	6/38	5/12	0.98 (0.26, 3.66)
Subtotal Mantel-Haenszel	67	41	*0.83 (0.30,1.91)*
Carman et al (VDR)[16]	5/32	2/32	
Overall Mantel-Haenszel	99	73	0.70 (0.33, 1.47)

Data presented as number/total. VDR, volume diffusive respirator (high-frequency time-cycled pressure ventilator).

Chronic Lung Disease

Chronic lung disease was examined only in the study of Arnold et al. [12]. The proportion of patients treated with HFO and requiring supplemental oxygen at 30 days was lower than that of patients managed with CV (p=0.039; OR 5.4, 95% CI 1.2 to 23.2).

Weaning

Randolph et al. [15] randomized 182 children aged from 0 to 17 years to either a Pressure support (PS) protocol (n=62), Volume support (VS) protocol (n=60) or a no ventilation weaning protocol in which weaning was at the discretion of the physician (n=60) (Table 3). The VS and PS protocols dictated that FiO2 and PEEP be adjusted to maintain SpO2 at 95% or higher. In the PS protocol, the amount of pressure support was adjusted to achieve an exhaled tidal volume goal of 5 to 7 ml/kg. In the VS protocol, the ventilator automatically adjusted the level of pressure support to achieve an exhaled tidal volume of 5 to 7 ml/kg. Two outcome measures were assessed: weaning time and extubation failure (i.e. any invasive or non-invasive ventilator support within 48 hours of extubation). It was hypothesized that VS would result in shorter weaning time as the inspiratory pressures automatically decrease with improvement of lung compliance. Most children could be weaned within two days and weaning time did not significantly differ for the protocols used: PS (1.6 days), VS (1.8 days) and no protocol (2.0 days). Extubation failure rates were not significantly different for PS (15%), VS (24%) and no protocol (17%).

Quality of studies

These five studies compared six different ventilation modes in 421 children [12-14, 16]. Two studies, based on intention to treat analysis, met all CBO quality criteria [14, 15]. Blinding was not possible in any of these studies, because ventilator displays cannot be masked. In four studies patient characteristics and prognostic variables did not differ between the intervention groups. In the study of Carman et al. [16] the mean age differed significantly. Only one study calculated the estimated effect sizes (relative risk of odds ratio) for continuous outcome variables such as LOV, survival or weaning failure [15]. The study by Dobyns et al. [14] is of limited quality because it is a secondary analysis of data obtained from a previous multicenter, randomized trial on iNO treatment in pediatric acute hypoxemic respiratory failure [8]. The mode of ventilation was determined by the attending physician on the guidance of guidelines to maximize oxygenation. The patient was then randomized to treatment with or without iNO [14]. Levels of evidence for the different studies are presented in Tables 2 and 3.

DISCUSSION

This review aimed at identifying the various ventilation modes used in children over the last three decades and searching for any data that would favour a particular mode for pediatric ventilation. The five RCTs included in this review varied in the investigated modes of ventilations, in outcomes and in patient groups.

High-frequency ventilators may use different ventilation modes. Two studies included in this review concerned high-frequency oscillation ventilation [12, 14]; a third concerned the volume diffusive respirator (high-frequency time cycled pressure ventilator) [16]. The evidence from these studies does not allow making a recommendation on preferred type of high frequency ventilator. Two RCTs compared HFO with CV on the outcomes oxygenation, LOV and mortality. Neither study found significant differences in mortality and LOV. However, analysis of the pooled data revealed a significantly lower LOV for the conventional ventilation groups. A confounding factor for this finding is the threefold sample size of conventionally ventilated patients in the study of Dobyns et al. [14]. On the other hand, this analysis only concerned the patients treated with HFO and CV without iNO.

In all studies, oxygenation significantly improved over 72 hours for patients treated with high-frequency oscillators [12, 14, 16]. However, lack of uniform data on oxygenation prevented analysis of pooled data. This finding is in contrast with that reported for preterm neonates. The systematic reviews and meta analyses overall provide no evidence that HFO as the initial ventilation strategy offers important advantages over CV in terms of preventing chronic lung disease in preterm infants with acute pulmonary dysfunction [17-22].

The level of evidence proved moderate to good in three studies [12, 14, 15]. The study of Jaarsma et al. [13] was stopped halfway as both physicians and nurses preferred BIPAP. This, was assigned a 1- level of evidence because of the high risk of bias. Likewise, the study of Carman et al. [16] was assigned a 1- level of evidence because the randomization failed for the demographic variable age.

The strengths of the present review include a comprehensive search strategy, broad inclusion criteria (resulting in a representative, heterogeneous population), and assessment of clinically important outcomes. In addition, we have pooled the data. This statistical approach is also allowed for quasi-experimental, non-randomized studies, such as the study of Dobyns et al. [14] in which randomization of groups was not possible or failed [23]. Meta-analytic techniques in the analysis of nonrandomized studies have been criticized for their potential to perpetuate the individual biases of each study and give a false impression of cohesion in the literature thus discouraging further research [24]. The counter-argument is that statistical quantification and pooling of results from

many studies helps to identify reasons for variability, inconsistency or heterogeneity in the literature,

and thus may encourage further research [23, 25]. Nevertheless, the pooled results of this study should be interpreted cautiously in view of the diversity in patient groups, sample sizes, randomization methods, types of ventilators and ventilation strategies.

The reviewed RCTs cannot easily be compared owing to the heterogeneity in age, underlying disease and study outcomes. Therefore, we would recommend to set up studies investigating the best ventilation strategy for specific age categories or underlying pathology [1]. Furthermore, as mortality is rather low, longer-term outcome measures others than the short-term outcome measures studied in this review should be considered, such as pulmonary function, neurocognitive development and cost-effectiveness. Internationally consensus on the most appropriate outcome measures should be reached.

CONCLUSION

The available literature does not provide sufficient evidence on the best ventilation mode in critically ill children beyond the newborn period. High-frequency ventilation (HFO and VDR) provided better oxygenation after 72 hours than did conventional ventilation. There is no evidence that high-frequency ventilation would reduce mortality and LOV.

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ADDITIONAL FILE 1: SEARCH STRATEGY

PubMed
(artificial respiration[mesh] OR artificial respir*[tw] OR mechanical ventil*[tw] OR high frequency respirat*[tw] OR liquid ventilat*[tw] OR pressure respirat*[tw] OR positive airway pressure*[tw] OR pressure breath*[tw] OR pressure ventilat*[tw] OR ventilator wean*[tw] OR ventilation wean*[tw] OR ventilators, mechanical[mesh] OR pulmonary ventilat*[tw] OR respirator*[tw] OR ventilator*[tw]) AND (instrument*[tw] OR device*[tw] OR mode[tw] OR modes[tw]) AND (infan*[tw] OR child*[tw] OR adolescen*[tw] NOT adult[mesh]) AND (randomized controlled trial*[tw] OR randomized controlled trial*[pt] OR rct[tw])
Hits: n=403

EMBASE
(artificial AND 'ventilation'/exp OR (artificial OR mechanical OR 'high frequency' OR 'liquid ventilation' OR 'liquid ventilator' OR pressure OR 'positive airway pressure' OR wean* OR pulmonary) NEAR/3 (breath* OR ventilat* OR respirat*) OR respirator*:de,ab,ti OR ventilator*:de,ab,ti) AND (instrument*:de,ab,ti OR device*:de,ab,ti OR mode:de,ab,ti OR modes:de,ab,ti) AND ([randomized controlled trial]/lim OR 'randomized controlled trial':ti,ab,de OR rct:ti,ab,de) AND ([newborn]/lim OR [infant]/lim OR [preschool]/lim OR [school]/lim OR [child]/lim OR [adolescent]/lim) NOT [adult]/lim NOT [aged]/lim AND [humans]/lim
Hits: n=250

ADDITIONAL FILE 2: EVALUATION FORM OF RCTS

Assessment of the quality of a randomized controlled trial (RCT)

1. Was the intervention assignment truly random?
2. The person who includes subjects in the study should be unaware of the randomization order; was that the case?
3. Were patients blinded to treatment allocation?
4. Were caregivers blinded to treatment allocation?
5. Were persons measuring the outcomes blinded?
6. Were the groups comparable at baseline?
7. Was complete follow-up available for a sufficient proportion of all included patients? (loss-to-follow-up)
8. Were all included patients analyzed in the group to which they were randomized? Intention to treat analysis
9. Other than the intervention, was all care that patients received the same?

Intermediate conclusion

10. Are the results of the study valid and relevant?
11. Results. For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g. 95% CI)
- Dichotomous outcomes
- Continuous outcomes

Applicability in healthcare

12. Is the result found applicable to the situation in the Netherlands?
13. To which echelon(s) can the result be applied?
14. Conclusion

Chapter 3

How to achieve adherence to a ventilation algorithm for critically ill children?

Anita Duyndam, Robert Jan Houmes, Monique van Dijk, Dick Tibboel, Erwin Ista

ABSTRACT

Background

PICUs worldwide use different ventilators with a wide variety of ventilation modes. We developed an algorithm, as part of a larger protocol, for choice of ventilation mode at time of admission.

Aims and objectives

To evaluate to what extent physicians on a paediatric intensive care unit (PICU) adhered to a newly implemented ventilation algorithm.

Design

This study was performed in a level III PICU of a university children's hospital and had an uncontrolled, pre-post test design with a period before implementation (T0) and two periods after implementation (T1 and T2).

Methods

An invasive ventilation algorithm targeted at two patient groups was implemented in October 2008. The algorithm distinguished between lung disease, in which pressure control was considered as the preferred mode, and no lung disease, in which pressure-regulated volume control was preferred. Nurses and physicians were instructed in the use of the algorithm before implementation.

Results

During three test periods, a total of 507 children with a median age of 5 months [interquartile range (IQR) 0–50] on conventional invasive mechanical ventilation were included. In patients with lung disease, pre-implementation adherence rate was 79% (67/85). At T1 it was 71% (51/72); at T2 84% (46/55). The slight improvement from T1 to T2 was statistically not significant (p=0.092). In patients with no lung disease, the adherence rate rose statistically significantly from 66% at T0 (62/93) to 78% (79/101) at T1, and 84% at T2 (85/101) (p=0.015).

Conclusion

Implementation of a new ventilation algorithm increased physicians' adherence to this ventilation algorithm and the effect was sustained over time. This was achieved by education, reminders and organizational changes such as admission of postcardiac surgery patients with protocolized nursing care including preset ventilator settings.

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INTRODUCTION

Pediatric intensive care units (PICUs) worldwide use different ventilators with a wide variety of ventilation modes: high frequency oscillation (HFO), pressure control (PC), synchronized intermittent mandatory ventilation (SIMV), pressure support (PS), pressure regulated volume control (PRVC) and, more recently, neurally adjusted ventilator assist (NAVA) [1, 2]. An unambiguous international guideline is lacking; ventilator type and ventilation mode are often chosen based on the intensive care physician's experience and preference, financial concerns, or local PICU policy, independent of the underlying disease [3-5].

The literature is scarce on the best ventilation mode in critically ill children beyond the newborn period [6]. One study found that high-frequency ventilation was associated with better oxygenation after 72 hours than was conventional ventilation [7]. However, there was no evidence of reduced mortality and duration of ventilation. Furthermore, most trials were significantly underpowered as they included small numbers of children [6].

Because of a lack of a ventilation protocol for clinical practice, we developed an algorithm guiding the choice of the most appropriate mode of ventilation upon admission of a child to our ICU, either PC or PRVC. A different protocol applies in case of need of HFO at admission. HFO is not included in this algorithm because it is not often used.

Separate protocols are in place for HFO and non-invasive ventilation.

This algorithm is based on evidence in the adult literature [8-11] and outcome of consensus meetings of all consultants of our unit. However, adherence to protocols and guidelines remains a difficult issue and successful implementation is time consuming [12-16]. In this study we evaluated to what extent the physicians adhered to the ventilation algorithm.

METHODS

Design
The study had an uncontrolled, pre-post test design with a pre-test (T0) from January 2008 - July 2008, and two post-tests: from May-November 2009 (T1); and from May-November 2010 (T2). The test periods were chosen to cover seasonal diseases. The T2 measurement served to evaluate the long-term sustainability of the implementation. The Erasmus MC Medical Ethics Review Board approved the study and due to the non-invasive nature of the study waived the need for informed parental consent.

Setting and patients

The study was performed in the 28-beds ICU of the Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands, a level III referral academic hospital. This ICU consists of four 7-beds units, each with a specific focus: neurology, cardiology, (neonatal) surgery and high dependency care. The ICU also serves as one of the two national ECMO centers and provides all forms of mechanical cardiac support. It is the only one in the Netherlands to provide care to pediatric cardiac transplant recipients.

The annual number of admissions is around 1800, and 30% of patients are ventilated mainly with the Servo-i ventilator of Maquet (Solna, Sweden). Overall, 50% of admitted patients are postoperative patients of all surgical subspecialties. The main reasons for admission are: respiratory insufficiency (20%), general pediatric surgery (20%), cardiac surgery and cardiovascular problems (20%), neurosurgery and neurological problems (10%), injuries and intensive care monitoring (20%), and major congenital anomalies, gastrointestinal and kidney problems (10%). (data retrieved from the electronic patient data management system and the local Quality and Safety Registry)

During the study periods the medical staff included twelve pediatric intensivists, of whom one had a basic training in anesthesiology; four fellows in training for pediatric intensivist; and six physicians in training (pediatrics (n=4) or anesthesiology (n=2).

Development of ventilation algorithm

A multidisciplinary team consisting of a pediatric intensivist-anesthesiologist (R.J.H.) and four ventilation practitioners (whose role is similar to that of a respiration therapist) developed a ventilation algorithm for the target population aged from 0 to 18 years. The algorithm is based on lung protective ventilation strategies which are likely to be of benefit to acute lung injury and acute respiratory distress syndrome: open-lung strategy; low tidal volumes (5-8 ml); and a recruitment maneuver in case of increased oxygen need [8-11, 17, 18]. Furthermore, permissive hypercapnia will avoid high ventilation pressure and thus prevent further lung damage [8, 11, 19].

The general purpose of our local ventilation strategy, as far as possible based on evidence, is to achieve the following conditions:

· pH: > 7.30 and < 7.48
· PCO_2: 5-8 kPa;
· PC above above Positive end expiratory pressure (Peep) ≤ 15cm H_2O;
· Tidal volume: 6 ml/kg (this was set in PRVC and pursued in PC);
· SpO_2 > 95%; or a lower saturation in case of a cardiac disease with mixed circulation
· Inspiration time: 0.3-0.6 seconds for neonates and I:E ratio 1:2 for children aged above 6 months with an age-dependent frequency.

The algorithm was primarily designed to guide physicians in the choice of ventilation mode upon admission of a patient requiring invasive mechanical ventilation. Also, it accounted

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for conversion of ventilation mode in case a patient's condition deteriorated. In addition, if ventilation with high pressures was needed (ARDS) some of the above-mentioned conditions were to be modified: pH ≥ 7.20 <7.48; pCO2 ≤ 9 kPa; and SpO$_2$ ≥ 85%.

In specific diseases such as pulmonary hypertension and traumatic brain injury (TBI) other target values for pH and PCO2 are applied, described in different protocols (TBI: pCO2 values between 4.5 and 5.0 kPa; for pulmonary hypertension initial normocapnia is the aim, provided that the needed inspiratory pressure is not too high. Otherwise permissive hypercapnia is accepted till values of ≥ pH 7.20). I:E ratio is also modified when lung condition deteriorates, dependent on the underlying disease. Extracorporeal membrane oxygenation (ECMO) is indicated at oxygenation index around 40.

The algorithm was developed with two patient groups in mind: 1) those with lung disease, such as acute respiratory distress syndrome, pneumonia, or bronchiolitis; and 2) without lung disease but receiving ventilation for epilepsy, postoperative care or traumatic brain injury (Figure 1). The PC mode was assumed to be the most appropriate for group 1 because it maintains constant pressure not exceeding 15 cmH$_2$O above PEEP. Thus, volutrauma is potentially avoided and a tidal volume of 6 ml/kg is achieved [10, 20]. PC is also suited in children at risk of compression atelectasis, in children with pulmonary hypertension [9], and to compensate for leakage around the tube.

The PRVC mode was considered the most appropriate for group 2 because it provides the lowest possible pressure at a constant tidal volume and achieves a more stable EtCO$_2$ and pCO$_2$. It has a decelerating inspiratory flow pattern with automatic adjustment of the inspiratory pressure for changes in compliance and resistance, resulting in a guaranteed constant tidal volume. However, volutrauma may occur when the pressure rises in case of deteriorating lungs with different dependent lung regions. Then the aerated lung regions will receive all the volume (higher than 6 ml/kg). There is no evidence for the use of PRVC in case of neurotrauma, although CO$_2$ has a direct influence on the diameter of the vessels of the brain and the blood volume and therefore influences the intracranial pressure. Since ICP and CO$_2$ are inter-related, maintaining a constant CO$_2$ is indicated in case of brain injury. ICUs worldwide mostly use Volume Controlled Ventilation for this purpose, but as PRVC provides constant tidal volume, we opted for this mode in traumatic brain injury [21].

In the PC mode, ventilation is adjusted to pressure support as soon as the patient is breathing spontaneously (triggering in the figure); in the PRVC mode, ventilation is adjusted to volume support. Sedation provided at the start of ventilation is reduced stepwise on the guidance of scores on the COMFORT behavior scale [22].

A protocol for extubation readiness is not in place at our ICU, and a spontaneous breathing trial (SBT) is not used. The following extubation criteria are commonly used: cough/swallowing reflex present, respiration indication solved, FiO2 < 0.4, hemodynamically stable with little inotropic support, sufficient muscle strength, no excessive

Ventilation Algorithm

Lung diseases

- ARDS, pneumonia, bronchiolitis
- Leakage along the tube
- Stomach problems, fat belly with compression atelectasis
- Pulmonal hypertension: with or without NO

No lung diseases

- Ventilation because of other reasons than lung disease
- Traumatic brain injury, where PCO_2 has to be stable

Pressure Control

Purpose Conventional ventilation:

- pH > 7.30 < 7.48
- pCO_2 5-8 kPa
- PC above PEEP ≤ 15cmH2O
- Vt 6 ml/kg (ideal weight)
- SpO_2> 95%
- Ti: 0.3-0.6 sec. neonates
- I:E ratio 1:2 > 6 months

Pressure Regulated Volume Controlled

Weaningcriteria reached?*

Weaningcriteria reached?*

*Weaningcriteria
- Cough/swallowing reflex present
- Respiration indication solved
- PaO2/FiO2 > 200mmHg/26.7kPa
- Hemodynamical stable/ little inotropic support
- Sufficient muscle strength
- No excessive mucus
- PEEP < 8 cmH2O
- Proper fluid balance/ no signs of edema
- GCS > 8
- No sedative or low dose
- pH > 7.35 < 7.48
- No signs of infection
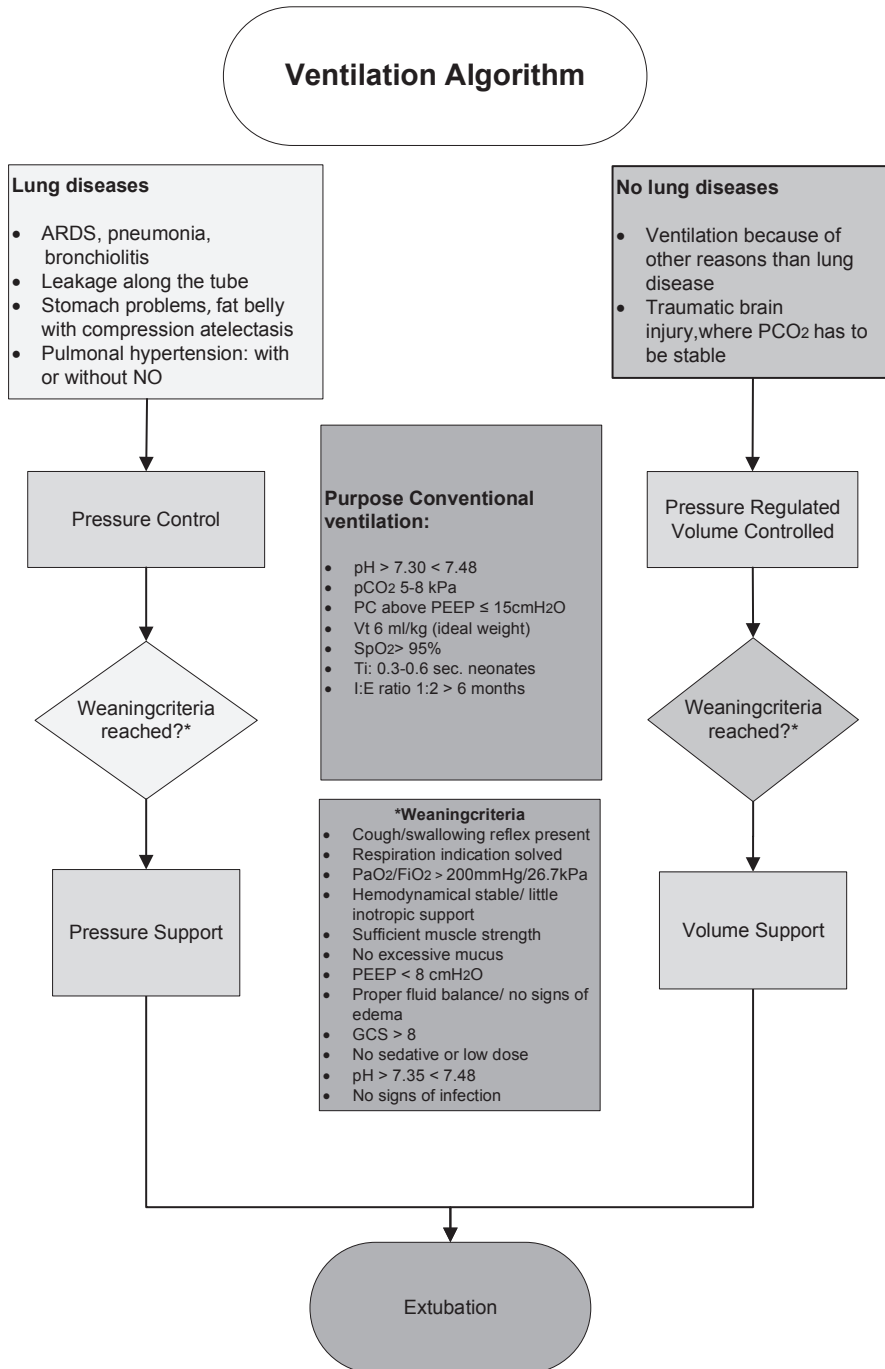
Pressure Support

Volume Support

Extubation

Figure 1: Ventilation protocol. PC, pressure control; PRVC, pressure-regulated volume control; PS, pressure support; VS, volume support; Ti, inspiration time; SpO2, oxygen saturation; Vt, tidal volume; NO, nitric oxygen; pCO2, carbon dioxide partial pressure; ARDS, acute respiratory distress syndrome.

sputum, PEEP < 8 cmH$_2$O, proper fluid balance, no edema, Glasgow coma score > 8, no or low-dose sedatives, pH between 7.35 and 7.45, no signs of infection [23-25]. Separate protocols are in place for HFO and non-invasive ventilation.

Implementation

To enhance adherence, approval of the ventilation algorithm was sought from all medical staff before implementation. In July 2008 the ventilation practitioners instructed all physicians and critical care nurses how to use it. Newly recruited residents after July 2008 also received instruction and in addition were familiarized with the theory of ventilation and the ventilator software. All information was also made available in print and by email. The algorithm was made available on each unit. A laminated version of the algorithm was placed at each ICU-bed.

The algorithm was put into use in October 2008 after the ventilation practitioners had presented it to all physicians. Since 2010 all ICU staff are provided with a pocket manual that contains all PICU protocols including the ventilation algorithm. Furthermore, in 2010 the protocol for admission of traumatic brain injury patients was changed to the effect that the PRVC mode became the preferred one for these patients. To ensure that this policy was adhered to, a sticker reminding of this ventilation mode was placed on a crash cart for patients with brain injury. For organizational and logistical reasons, from January 2010 cardiac surgery patients were directly admitted to our ICU for postoperative care. The protocol introduced since then prescribed PRVC as the preferred mode for these patients, unless they had serious pulmonary edema. Extubation was attempted in these patients as soon as possible upon arrival at the ICU, usually within 6-12 hours after admission. As such the postoperative cardiac surgery protocol included an algorithm for weaning off the ventilator. Before admission of these patients, nurses prepare the ventilator settings based on the cardiac weaning procedure described in the ventilation algorithm. The nurses are responsible for weaning but need to ask permission from the physician in charge for actual extubation.

Study procedure

All patients on conventional invasive mechanical ventilation during the three study periods were included. The initial ventilation mode was chosen by the physicians. In all three periods we recorded the initial ventilation mode set for newly admitted patients and recorded the reason for ventilation as an indication to what mode this patient should have been assigned. Patients on HFO and non-invasive ventilation were excluded. During the course of the study times there was no change in ventilation strategy. Patients were not excluded due to the their condition. Data were retrieved from the electronic patient data management system that prospectively stores data of all physiological parameters, laboratory results, medication, procedures, assessments and care plans.

Outcome measure

Adherence to the ventilation algorithm was measured as: number of patients with correct ventilation mode according the algorithm divided by the total number of ventilated patients during the study period in question.

Statistical analysis

Patients' characteristics, reason for admission, and initial mode of ventilation are summarized by descriptive statistics. Data are presented as percentages: mean (SD) for normally distributed data; median and IQR (interquartile range) for non-normally distributed data. Background characteristics for the pre- and posttest groups were compared using Chi-Square (categorical variables) and Kruskal-Wallis test for continuous variables. In all three test periods, the difference in adherence to the protocol was compared and tested for the two groups (lung disease versus no lung disease) with the Chi-square test. A *p* value of 0.05 (two-sided) was considered statistically significant. Data were analyzed with IBM SPSS® version 18.

RESULTS

During the three study periods 615 patients received ventilator support. In total 108 patients were excluded for analysis (HFO, n=31; non-invasive (home) ventilation, n=87). Thus, analysis was based on 507 patients, with a median age of 5 months (IQR 0-50) (T0: N=178; T1: N=173; T2: N=156). Age and gender were not significantly different between the three periods. However, the reason for ventilation significantly differed between the periods, due to the admission of direct postoperative cardiac patients during T2 (Table1).

Lung disease

Before implementation of the ventilation algorithm (T0), 67 of the 85 patients (79%) with lung disease were ventilated according to the algorithm (PC). After implementation, this held true for 51 of 72 patients (71%) in period T1, and 46 of 55 patients (84%) in period T2 (p=0.215). Adherence to the algorithm slightly improved from T1 to T2 (p=0.092) (Table 2).

No lung disease

At T0, 62 of the 93 patients (66%) with lung disease or no lung disease were ventilated according to the algorithm (PRVC). After implementation this held true for 79 of 101 patients (78%) in period T1, and 85 of 101 patients (84%) in period T2 (Table 2). This means that adherence statistically significantly improved from 66% at T0 to 78% at T1 to 84% at T2 (p=0.015).

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Table 1: Demographic characteristics

	T0 n =178 n (%)	T1 n =173 n (%)	T2 n =156 n (%)	p-value
Gender (male/female)	91/87 (51.1/ 48.9%)	94/79 (54.3/ 45.7%)	86/70 (55.1/ 45.7%)	0.73 [a]
Age				0.66 [a]
0 – 12 months	105 (59%)	97(56.1%)	95(60.9%)	
1 – 3 years	33 (18.5%)	27 (15.6%)	19(12.2%)	
4- 12 years	26 (14.6%)	32 (18.5%)	25(16%)	
> 12 years	14 (7.9%)	17 (9.8%)	17(10.9%)	
Median age in months (IQR)	4 (0-211)	8 (0-233)	4.5 (0-218)	0.60 [b]
Reason for ventilation				<0.001
Cardiac	14	9	13	
Cardiac - postoperative surgery	22	31	50	
Respiratory failure - acute Pulmonology (e.g. bronchiolitis, pneumonia)	36	34	16	
Respiratory failure - upper airway	2	8	4	
Respiratory failure - others	6	7	0	
Neurologic – e.g. trauma injury, epilepsy	16	15	19	
Hypo plastic lung		1	2	
Shock/sepsis/ECMO/Resuscitation	18	15	18	
Trauma	5	7	1	
Post operative	23	25	12	
Post operative - abdominal	28	20	17	
Others ([c])	8	1	4	

[a]Chi-squared test. [b]Kruskal-Wallis test. [c]Congenital diseases such as oesophageal atresia, pulmonary hypertension, meconium aspiration, metabolic diseases and neuromuscular diseases.

Table 2: Adherence rates

	T0 Jan – July 2008 (n=178)	T1 May – Nov 2009 (n=173)	T2 May - Nov 2010 (n=156)	p-value
Lung disease (PC)				
Ventilated according to the algorithm*:	67 (79%)	51 (71%)	46 (84%)	p=0.215
No lung disease (PRVC)				
Ventilated according to the algorithm**:	62 (66%)	79 (78%)	85 (84%)	*p=0.015[#]*

* p=0.092 (between T1-T2); ** Between T0 and T1: p = 0.072 and between T0 and T2: p=0.005. [#]p-value of 0.05 was considered statistically significant.

Related factors for (non) adherence

Adherence to the algorithm (correct choice of ventilation mode) was not statistically significant associated with patient's age, shift (day versus evening/night), reason for ventilation (lung disease vs. no lung disease) and unit (p=0.52, p=0.16, p=0.84 and p=0.06 respectively). In the cardiology unit, however, adherence to the algorithm increased significantly from 74% at T0 to 91% at T2 (p=0.018). Adherence to the algorithm in cardiac and postoperative cardiac surgery patients increased significantly from 68% at T0 to 90% at T2 (p=0.027).

Adherence to the algorithm in traumatic brain injury patients seems to have increased. In 2010 only one patient was ventilated with PC rather than the prescribed PRVC. This also applies to patients with acute respiratory failure during period T2 who were then mostly ventilated with the prescribed PC.

DISCUSSION

Implementation of a ventilation algorithm for PICU patients resulted in higher adherence to the ventilation algorithm in comparison to the pretest periods, especially for patients without lung disease. Adherence was not associated with patient factors (e.g. age), shift or reason for ventilation (lung disease vs. no lung disease). Adherence to the ventilation algorithm tended to be best among post cardiac surgery patients, who receive protocolized nursing care including pre-set ventilator settings. The improvement in adherence regarding patients with lung disease is less marked. Before implementation adherence was even better (79%) than during the first post-test period (71%). It would seem that even after education and approval of the algorithm, physicians need time to put personal preferences aside. Still, adherence had increased during the second post-test (84%). Regrettably, still too many postoperative patients with abdominal problems were not ventilated as the algorithm dictated. This violation is perhaps easily overlooked; it would be more easy to remember that the first choice of ventilation for postoperative patients is PRVC, except for those who have undergone abdominal surgery. A reminder sticker on the ventilator, in combination with feedback in case of violations, could perhaps optimize adherence for this patient group. The use of cuffed tubes vs. uncuffed tubes might have played a role as well. The data do not indicate, however, if PC in case of no lung disease was chosen on the grounds of leakage along the tube. If so, the choice was right. Any leakage usually occurs later than in the first hour of ventilation, and therefore we assume that leakage will not have greatly influenced the choice of initial ventilation.

We speculate that the relatively high adherence rates (>80%) in the final post-test period can be ascribed to the fact that all newly appointed physicians and residents were

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well instructed. Furthermore, nurses – provided with a pocket manual of the ventilation algorithm – reminded physicians of the correct ventilation mode in cardiac surgery patients. We also assume that the use of reminders, such as a sticker on the crash car for traumatic brain injury patients, increased adherence to the ventilation algorithm. This is consistent with the literature in the ICU and other healthcare settings [26, 27].

Research has shown that consistent use of evidence based guidelines can significantly increase the extent to which patients receive recommended therapies [12, 13]. However, it is a great challenge to stimulate consistent use of these guidelines and protocols. Apart from attempts to change behavior, this requires insight in all influencing factors (e.g. human behavioral, organizational, provider characteristics). Therefore, identifying potential influencing factors, e.g. with the barrier identification and mitigation tool [13], can improve adherence to new protocols. Unfortunately, scarce data are available to guide decisions on optimal strategies to implement guidelines and protocols in the intensive care unit [12, 14, 28]. On the one hand, it has been suggested that guideline implementation strategies tailored to overcome barriers to change might be more effective than the multifaceted "one size fits all" strategy. On the other hand, multi-faceted implementation strategies were considered important enablers of protocol and guideline adherence [16, 29]. One example is education tailored to the specific learning needs of the ICU team combined with bedside reminders, audit, and visual feedback [15, 29, 30]. Also, we believe – and previous studies have demonstrated this – that ICU culture qualities such as interdisciplinary collaboration, effective communication, and leadership support are associated with better quality of care [31, 32]. This is also confirmed in two recent studies about interdisciplinary collaborative decision making regarding ventilation and weaning [33, 34]. Enhanced communication and collaboration between professionals could probably avoid unnecessary prolonged ventilation and weaning [33, 34]. We speculate that manipulating these specific organizational characteristics (interdisciplinary collaboration, effective communication, leadership support and organizational aspects like nurse-to-patient ratio and ongoing education) may be an effective strategy to improve adherence to protocols, which deserves to be explored and evaluated in further implementation projects [27]. However, ICU culture qualities on our unit also need to be further studied.

Regarding strengths and limitations, a strength of this study is the prospective data collection. A limitation is the lack of a control group or randomization. However, it would have been difficult to blind physicians or other ICU staff to the study. Second, reasons for non-adherence with the algorithm were not documented in the patient data management system.

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Implications for nurses in the implementation of new algorithms

Care for ICU patients will benefit from interdisciplinary collaboration, also when new algorithms or protocols are implemented, related to either nursing care or medical care. To improve physicians' adherence to a medical algorithm, nurses should remind physicians of the steps to take. Nurses are always present at the bedside and as such represent the patient. In summary, the following measures may successfully improve adherence:

·   A well thought-out implementation plan, with attention to potential barriers and facilitators is a crucial first step.
·   Use reminders as pocket manuals and stickers.
·   Provide repeated education about the algorithm and the results of its use (performance feedback).
·   Provide leadership support at doctor's and nursing level.
·   Report non-adherence through safety first reports and feedback when protocol violations occur.

CONCLUSION

Implementation of a new ventilation algorithm increased physicians' adherence to this ventilation algorithm and the effect was sustained over time. This result was achieved by education, reminders and organizational changes such as protocolized admission of post cardiac surgery patients with protocolized nursing care including pre-set ventilator settings.

Interdisciplinary collaboration between physicians and nurses, effective communication, leadership support and organizational aspects like nurse-to-patient ratio and ongoing education may be effective strategies to improve adherence to protocols.

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Chapter 4

Challenges in non-neonatal Extracorporeal Membrane Oxygenation

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ABSTRACT

This review will address the different challenges for the use of non-neonatal Extracorporeal Membrane Oxygenation (ECMO) will be discussed. It will discuss the available evidence for the use of pediatric ECMO in respiratory and circulatory failure, focusing on indications and contra-indications and choice of ECMO mode. Furthermore we will try to define optimal treatment goals, identify primary outcome parameters and calculate the expected need for non-neonatal ECMO per 1.000.000 inhabitants.

In the past 30 years over 46.000 patients have been admitted to dedicated ECMO-centers; the overall survival rate was 62% (Extracorporeal Life Support Organization (ELSO) registry July 2011). Most of these were newborns (30.000) and the number of older children amounts to over 11.000; the respective survival rates were 75% and 50%.

One of the striking trends in the last decade is the decreasing need for neonatal ECMO. This is partly due to new technologies such as high frequency oscillation with or without inhaled nitric oxide, therapeutic modalities for treatment of pulmonary hypertension such as Phosphodiesterase inhibitors (Sildenafil) and endothelial receptor blockers (such as Bosentan) and gentle ventilation strategies with permissive hypercapnia and low tidal volumes More specifically, improvement in perinatal care has also resulted in a much lesser need for ECMO in term infants with respiratory failure like meconium aspiration syndrome and GBS sepsis. Moreover, therapies such as surfactant administration and surfactant lavage have also contributed to reducing the inflammatory response and thus decreasing the need for ECMO in neonates with acute respiratory failure [1].

While indications for neonatal ECMO have been clearly defined, this is not the case for non-neonatal ECMO. In many instances, even today, non-neonatal ECMO is considered as rescue therapy that brings relief in individual cases. Different concepts on how and when to use non-neonatal ECMO have emerged, partly due to the lack of experience owing to the relatively few cases in individual centers. Due the variety in etiology and recent improvements in the treatment of respiratory failure, it is difficult for the clinician to know when to consider ECMO in each individual case. Unlike neonatal indications, solid entry criteria are still not available. Each ECMO center has its own set of treatment protocol and indication for ECMO. Over the years case series have been reported with patients with burns or malignancies and with trauma patients. Therefore when an ECMO treatment is considered, each patient must be discussed with the ECMO center, keeping in mind that the chance of successful weaning of ECMO is improved when the patient is ventilated less than 10 days [2, 3]. Over the past 10 years a steady increase in numbers of non-neonatal ECMO cases reported to ELSO have been seen, especially in cardiac patients. More and more cardiac surgeons realize that postoperative continuation of

cardiopulmonary bypass in the form of ECMO is effective and lifesaving as ECMO decreases the workload of the heart and so, supporting recovery of the myocardium [4].

In this review the different challenges for the use of non-neonatal ECMO will be discussed such as:

1) Indications / contra-indications.
2) Definition of optimal therapy.
3) Primary outcome parameters.
4) Calculated need per 1.000.000 inhabitants.

In all circumstances the application of ECMO for pediatric respiratory and cardiac failure should be weighed against the other available treatment modalities, such as small tidal volume ventilation, recruitment maneuvers, high frequency oscillation, surfactant therapy, inhaled nitric oxide, prone position, kinetic therapy, and corticosteroid administration [5]. The most difficult decision is when to consider ECMO and when to transfer patients to an ECMO center. Performing ECMO in non-neonatal patients requires an individualized approach.

In principle, non-neonatal ECMO is used as adjuvant therapy for which a venovenous mode is used. The main differences between the venoarterial mode and the venovenous mode are shown in Table 1.

Approximately half of the pediatric respiratory ECMO cases used venovenous (VV)-ECMO, whereas traditionally venoarterial (VA)-ECMO has been predominant. Improved myocardial oxygen delivery, as provided by direct delivery of highly oxygenated coronary blood with VV-ECMO is expected to improve myocardial performance [6].

Table 1: Difference between venoarterial- and venovenous ECMO

Venoarterial ECMO	Venovenous ECMO
Higher PaO2 is achieved	Lower PaO2 is achieved
Lower perfusion rates are needed	Higher perfusion rates are needed
Bypasses pulmonary circulation	Maintains pulmonary blood flow
Decreases pulmonary artery pressures	Elevates mixed venous PO2
Provides cardiac support to assist systemic circulation	Does **not provide cardiac support** to assist systemic circulation
Physiologic blood flow **NOT** maintained	Physiologic blood flow maintained
Requires arterial cannulation	Requires only venous cannulation

Indications / contra-indications.

Unfortunately the indications to start ECMO in a non-neonatal respiratory and cardiac failure differ between institutions and individual physicians. The shortage of randomized controlled trials to prove a positive effect of ECMO has hampered the development of internationally broadly accepted guidelines.

Following the United Kingdom collaborative trial that showed the positive effect of ECMO in neonatal respiratory failure, it took 15 years before the Cesar trial showed a positive effect of ECMO in adult respiratory failure [7]. More specifically the Cesar trial showed that referral of adult Acute Respiratory Distress Syndrome (ARDS) patients with a Murray score of three and a pH below 7.2 (managed with optimal conventional management) resulted in improved survival rates compared to lung protective ventilation in non ECMO centers.

With death or severe disability six months after randomization as a primary outcome measure, allocation to an ECMO center proved beneficial in 63% of patients versus 47% of patients treated by conventional therapy. Relative risk: 0.69 in favor of the ECMO group (95%-confidance interval: 0.05 – 0.97; P = 0.03). Although the restrictions for ECMO (ventilation < 7 days) can be debated as well as the number of patients and the duration of the trial (5 years), no other data are available to support the use of ECMO in the non-neonatal group. The Cesar trial provides some general guidelines for referral to ECMO centers although it remains unclear if these results can be extrapolated to the pediatric population. Ideally the Cesar trial should be repeated in the pediatric age group.

A multicenter trial is warranted because only very few centers perform more than 5 non-neonatal ECMO-runs a year. Experience in Europe is therefore diluted and widely ranging survival rates have been reported. Clear-cut primary endpoints should be defined for such a clinical trial, as well as diagnostic groups and technical modalities such as the tubing oxygenators and the ECMO mode: VV-ECMO, VA-ECMO, or other variants. Zabrocki et al. clearly showed considerable co-morbidity in pediatric patients on ECMO (i.e. in 34% of patients) with a primary diagnosis of acute respiratory failure [5]. Renal failure and chronic lung disease were the most common co-morbidities in the ELSO registry. One of the main outcome determinants is the pre-ECMO ventilation period. Survival was 38% when this was > 14 days versus 56-61% when this was shorter [5]. These authors concluded that despite ECMO, the mortality for acute respiratory failure due to acute lung injury or ARDS in pediatric patients remains high (18-35%) [5].

Overall survival rates of around 50-60% have been reported for "classic indications" such as viral and bacterial pneumonia, aspiration pneumonia, ARDS, and non-ARDS-related acute respiratory failure. From time to time new diseases emerge such as the recent worldwide spread of H1N1 influenza. Physicians in New Zealand and Australia predicted a significant need of ECMO for H1N1 related lung disease in the northern hemisphere, which forced governments and medical societies to set up systems for optimal distribution of ECMO facilities and infrastructure (Italian ECMO network) [8]. The Italian ECMO network, established to cope with the predicted increase in ECMO patients, treated 153 adult H1N1 ARDS patients in dedicated ECMO centers with an overall survival of 68% [9]. Sixty patients (39%) of all patients were treated with ECMO support. Noah et al. showed a reduced mortality in patients referred and treated in

dedicated ECMO centers in the UK. Using propensity score and Genmatch matching the authors compared adults suffering from severe H1N1 influenza related ARDS treated in ECMO centers vs. those treated in non-ECMO centers. They found a reduced mortality patients treated in ECMO centers. (23.7% vs. 52.5%, RR 0.45 [95% CI, 0.26-0.79]; P = .006) [10]. These results are comparable to the Cesar Trial result published by the same group. Although the cohort study does not lend itself to identifying individual risk factors, the Italian experience clearly showed prolonged mechanical ventilation (e.g. >7 days) was associated with higher mortality [9].

In most countries, however, relatively few pediatric patients received ECMO. The number in our institution was six, of whom four survived. Again it remains unclear whether these results can be extrapolated to the pediatric population. However these studies suggest that early referral to dedicated ECMO centers may improve overall survival in patients with severe respiratory failure.

Another group of patients who might benefit from ECMO are those who need a form of mechanical support of the systemic and pulmonary circulation and in which optimal use of inotropic drugs as well as mechanical ventilation with or without inhaled nitric oxide fails.

Mclaren et al. showed improved survival using transthoracic cannulation in pediatric VA-ECMO for refractory septic shock. Survival significantly increased from 47% to 73% in the Children's Hospital in Melbourne, which has a major cardiac program supporting their ECMO facility [11]. Whereas double lumen venous catheters are the preferred choice for VV-ECMO, Mclaren et al. showed that for cardiovascular support arterial access via the carotid artery may not always be the most beneficial. Whether transthoracic access is possible depends on the logistics and available expertise in the local ECMO centers. Rapid cannulation may also be achieved using the femoral artery. In adults with circulatory failure peripheral cannulation was as effective as transthoracic cannulation with significantly reduced bleeding complications compared to open chest ECMO [12]. Although this technique seems established in the adult setting but data on efficacy and safety are lacking in the pediatric population.

Another patient category that may benefit from early institution of VA-ECMO are patients with myocarditis, notably those with enterovirus 71 (EV71) infection) as their cardiac failure is considered to be temporary [13]. When patients do not recover within a "certain" timeframe, ECMO may serve as a bridge to ventricular assist devices [14-16]. Early institution of ECMO is important: a 2010 review of the ELSO data by Rajagopal et al. concluded that 61% of patients with myocarditis survived to discharge. However, ECMO treatment had been withdrawn after multiple organ failure in an alarmingly high 70% of non-survivors [17].

Early identification of patients at threat for therapy resistant cardiac failure is of great importance in this particular age group to avoid these complications.

Apart from infection or cardiac failure, ECMO may also have potential benefits in cardiac surgery as a bridge to transplant or as back up in high risk patients for cardiac and pulmonary vasculature failure after cardiac surgery. The inability to come off Cardio Pulmonary Bypass (CPB) despite inotropic support or nitric oxide to reduce pulmonary vascular resistance in the presence of left or right ventricular dysfunction may necessitate ECMO support in the direct postoperative phase. The final outcome of ECMO as a form of prolonged CPB is highly dependent on the attitude of the cardiac surgery team and the possibility in individual hospitals to provide fast response ECMO around the clock. According to European and American recommendations, centers of congenital heart surgery should have ECMO available [18]. The conversion from CPB intra-operative to an ECMO procedure is relatively simple although significant hemorrhages may occur after open chest surgery. Then, ECMO is primarily used as a way to relieve the heart and in most instances this will resolve in a successful ECMO-run in 48-72 hours.

ECMO can be used as a form of "very advanced life support" in resuscitation for cardiac arrest. Although many remain guarded about the outcomes for patients who receive ECMO in the setting of cardiopulmonary resuscitation (CPR), there are now a number of case series describing promising outcomes if emergency cardiac life support is initiated with sufficient rapidity [19-21].

Rapid deployment of extracorporeal cardiopulmonary resuscitation (ECPR) will most likely produce the best results in terms of minimizing the duration as will optimizing the technique of conventional CPR [22]. Survival without significant neurologic impairment following a witnessed cardiac arrest is approximately 20-30% in children, and early implementation of ECMO can improve the percentage of survivors to 50% [20, 23].

Patients with immune compromised conditions comprise a very special group. A relatively recent review of ELSO registry data identified six subgroups: immune deficiency, leukemia lymphoma, other forms of cancer, opportunistic infection, solid organ transplant and bone marrow transplant [24, 25]. In each of these subgroups a reduced hospital survival was documented varying from 35.6% (solid organ transplant) to 0% (bone marrow transplant).

In these particular patients the main determinants of outcome are the attitude of the oncology team related to the therapy phase and the possibility to perform ECMO in isolation. As a consequence a number of ECMO centers refrained from treating these patients and the real significance or contribution of ECMO for individual diagnosis should be based on ongoing ELSO data acquisition.

Different ECMO indications bring different challenges. Post-operative cardiac ECMO support requires strict control of coagulation. "Traditional" neonatal coagulation protocols may be insufficient in these patients. Alternatives to heparin based coagulation strategies may have benefits that need to be explored [26]. The use of smaller, coated

ECMO circuits may reduce the need for anticoagulation therapy thereby reducing the risk of bleeding complications.

Cardiovascular drugs will be frequently used in these patients during ECMO. There is almost no pharmacokinetic data guiding clinicians in dosing these drugs, whereas adequate treatment is essential to wean these patients from mechanical support [27].

In prolonged ECMO runs for cardiomyopathy or respiratory failure there is a high risk for nosocomial infections [28]. Almost 20% of all non-neonatal respiratory ECMO patients have an infection. (ELSO registry 2011 international summary) Pharmacokinetic data for most antibacterial, antifungal and antiviral drugs are lacking for the pediatric age group [29]. From in vitro studies it is clear that there is a significant loss of lipophilic drugs in ECMO systems [30]. There are considerable differences in drug absorption between different circuit components which makes it difficult to predict the Pharmacokinetics of newer drugs [30].

The ability to control or treat complications during ECMO therapy as well as the development of clear ECMO criteria may determine whether ECMO remains an individual rescue therapy or a standard treatment modality for selected patients.

Definition of optimal therapy.

In contrast to neonatal ECMO, for which respiratory parameters such as oxygenation index (OI) and alveolar-arterial oxygen tension difference (AaDO2) have been defined, there is virtually no generally accepted respiratory parameter to start ECMO in the non-neonatal group. The standard of care is highly institution–dependent, based on level of experience of the (Pediatric) Intensive Care Unit ((P)ICU) teams, logistics around the start of ECMO in individual patients, and ethical considerations. From respiratory insufficiency mortality statistics in two designated PICUs in the Netherlands over a three-year period we calculated that 1 patient per 1.000.000 inhabitants/year would need non-neonatal ECMO. This figure can be used as a rough estimate for the institution of a non-neonatal ECMO program in any given country. Over the last couple of years this figure fits the actual performance of ECMO in our institutions; it has been increasing slowly over the past 5 years.

As failure of optimal therapy is defined as; the best inclusion criteria for non-neonatal ECMO, the percentages of patients referred for ECMO and those actually treated with ECMO, have been evaluated.. Due to adjustments in the management of the patient in the ECMO center or the identification of "hidden" contra-indications upon arrival in the ECMO center only 30-40% of all referred pediatric patients were treated with ECMO.

For patients in a cardiac center the calculated need depends on post-operative mortality (usually 3-5%) and number of deaths within 24 hours post-surgery. Thus, we calculated the potential need for post-cardiac ECMO support at between 2-5 patients/ year (based on 200 CPB yearly). Morris and others advocate a greater use of ECMO,

considering improvements of the results in terms of survival [31]. According to European and American recommendations, centers of congenital heart surgery should have ECMO available [32].

Taking into account post-cardiac cases, the overall need for non-neonatal ECMO is around one patient/1.000.000 inhabitants/year. Non-neonatal ECMO therefore should be concentrated in large regional centers rather than performing "occasional" ECMO in centers with little experience.

Primary outcome parameters.

Mortality is usually considered as a primary outcome parameter, but data should be evaluated very carefully. All reports document a significant discrepancy between a successful ECMO run and survival till discharge or transfer. Moreover, a number of patients will die even after transfer elsewhere. Post-transfer mortality should also be taken into account as to ECMO-related death. Fair reporting including survival after six and twelve months is important to identify the real contribution of ECMO to survival rates in certain disease states.

Equally important is careful evaluation of long term outcome, including not only somatic aspects but also psychosocial and motor development. Assessed with validated scales, in contrast to neonatal ECMO, underlying morbidity or persistent co-morbidity determines outcome in many of these children. The risk of neurological damage as a result of the ECMO procedure in itself is significantly lower in non-neonatal ECMO because the primary ECMO mode is mainly venovenous using either the neck (double lumen venovenous) or two sides (neck and groin). Apart from myocarditis and cardiac surgery, ECMO is typically used improve CO_2 removal and should be considered as an adjuvant therapy diminishing the need for ventilatory support (peak pressures, FiO_2); in other words, really buying time and preventing ongoing damage.

Previously ECMO was believed to be too complex to be used during patient transport. At present, however, numerous patients have been transported worldwide [33, 34]. These experiences included both adult and pediatric patients and involved patients who require support for pulmonary as well as cardiac failure. Further improvement of transport systems can lead to a reduction in the number of ECMO centers, resulting in a higher number of patients per individual center, which could benefit outcome.

In conclusion

Non-neonatal ECMO is a high resource demanding treatment modality that should be restricted to large regional centers which perform at least one ECMO procedure per month and in which the indications for the individual patient are solidly discussed in an interdisciplinary team.

We have to realize that non-neonatal ECMO is not yet supported by properly designed randomized controlled trials, so that it should be reluctantly included among the treatment modalities available for pediatric respiratory and cardiac failure. ECMO should be performed in specialized centers with an adequate infrastructure. In our opinion this includes an interdisciplinary long term follow up which integrates short (survival at discharge six months and one year) as well as long term morbidity as outcome measurements.

The short and long term morbidity figures may shed a light on the value of ECMO in the health care system and its costs effectiveness and may support the planning of high resource facilities within countries and institutions.

4

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Part 2

Aspects in the use of Extracorporeal Membrane Oxygenation to assist gas exchange in children

Learn from yesterday, live for today, hope for tomorrow. The important thing is not to stop questioning
(Albert Einstein 1879 – 1955)

Chapter 5

Arterial lactate for predicting mortality in children requiring extracorporeal membrane oxygenation

Erik Buijs, Robert Jan Houmes, Dimitris Rizopoulos, Enno Wildschut, Irwin Reiss, Can Ince, Dick Tibboel

ABSTRACT

Background

Dynamic arterial lactate indices predict mortality more accurately than static arterial lactate measurements in children with septic shock or congenital cardiac defects. The current study evaluates whether this also applies to children with primary respiratory disease requiring extracorporeal membrane oxygenation (ECMO).

Methods

Static arterial lactate levels (LACabs) were prospectively collected before and during ECMO support for this single center, observational cohort study. Also, time-weighted arterial lactate (LACtw) and lactate change over time (LACdelta) were calculated as dynamic indices for, respectively, the duration and the trend over time of lactate derangement. Intensive Care mortality was the primary endpoint. Analyses were performed for neonatal and pediatric patients separately.

Results

Fifty-six neonatal and 39 pediatric patients were included. Eighteen (32%) neonatal and 12 (31%) pediatric patients died. The evolution of LACabs and LACdelta differed between the pediatric survivors and the pediatric non-survivors (p<0.001, p=0.025). The hazard ratio was 1.23 (CI$_{95}$=1.06-1.43, p=0.007) for LACabs and 20.64 (CI$_{95}$=1.99-214.20, p=0.011) for LACdelta, indicating that higher lactate levels increase the risk for mortality. The predictive value for LACabs was 0.75 (CI$_{95}$=0.57-0.93) and for LACdelta 0.69 (CI$_{95}$=0.51-0.87), respectively. There were neither consistent differences for LACtw in the pediatric patients, nor for any of the static or dynamic lactate indices in the neonatal patients.

Conclusion

Static arterial lactate measurements and, to a lesser extent, dynamic arterial lactate indices predict mortality in pediatric, but not neonatal ECMO patients. The magnitude and trend over time rather than the duration of lactate derangement are associated with mortality.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) can serve as rescue treatment for children with therapy-resistant, primary respiratory failure [1]. From the year 2000 to 2012, over 10,750 neonatal and 3,800 pediatric patients received ECMO worldwide [2]. Mortality rate is high and differs between neonatal (32%) and pediatric patients (44%) despite ECMO support [2].

Lactate –an end product of carbohydrate metabolism– is constantly produced during glycolysis and, thereafter, metabolized [3]. Unlike pH, pO2, or pCO2, the lactate concentration can increase during both anaerobic and aerobic conditions. The latter include: a) liver dysfunction resulting in reduced lactate clearance; b) enhanced glycolysis –e.g. in cytokines or due to hyperglycemia; c) increased catecholamine levels affect cellular glucose uptake; d) alkalosis causing increased cellular efflux of lactate; e) mitochondrial dysfunction; and f) drug infusion / intoxication –e.g. epinephrine, nucleosidic reverse transcriptase inhibitors, methanol–[3, 4]. Lactate concentration correlates to both severity of illness and mortality [3-5]. However, lactate concentration can also be false negatively low –e.g. sepsis-induced decrease of peripheral perfusion or necrosis-induced absence of carbohydrate metabolism–[3]. Also, age-related differences in lactate production and lactate metabolism have been described between adults and children and between newborns and older children[6-11]. Therefore, the value of lactate for predicting mortality might dependent on age, disease type, co-morbidity, and disease severity or –in other words– time [5]. It was demonstrated recently that dynamic measures of lactate derangement –i.e. incorporating duration or trend over time next to magnitude– are better predictors for survival than static lactate measurements in septic children and children with congenital cardiac defects [12-15].

Neonatal and pediatric ECMO candidates are amongst the most critically ill children conceivable. Static lactate measurements are established predictors for mortality in ECMO children with primary cardiac disease [16-20]. The few studies that focused on children with primary respiratory failure included both neonatal and pediatric patients, still included some children with primary cardiac disease, recruited patient cohorts from before the year 1997, and included patients suffering from prolonged hypoxia [21-24]. Today, however, ECMO is generally started early in order to prevent ventilator-induced lung injury whilst the ECMO population is has more co-morbidity, amongst other differences [25]. Moreover, none of the reports described dynamic lactate indices [21-24]. Therefore, this study aimed to evaluate the predictive value of both static and dynamic arterial lactate indices obtained before and during ECMO in a general population of children with primary respiratory disease. In line with the registry maintained by the Extracorporeal Life Support Organization and the majority of scientific literature [26], and given that lactate kinetics, patient characteristics, and the crude mortality rate differ

between newborns and older ECMO children, data will be presented for neonatal and pediatric patients separately.

MATERIALS AND METHODS

Study design and Setting

This observational cohort study entails data collected prospectively in patients admitted to the intensive care (IC) of a level III university children's hospital. The local medical ethical review board approved the study and waived the need for informed consent.

Patients

Consecutive neonatal –age at admission below 28 days– and pediatric patients –age at admission 29 days to 18 years– with primary respiratory disease receiving ECMO between 2008 and 2011 were included. This inclusion period was chosen for two reasons: 1) at the end of 2007 a new protocol was implemented for CDH patients – who form a major part of the patients in the neonatal ECMO group; and 2) in 2011 our department switched to another ECMO system [27, 28]. Both factors were anticipated to lower mortality rate, which is the primary endpoint of the current study [29].

Patients with primary cardiac disease and patients with less than two lactate measurements were excluded. Only the first ECMO run was included in case patients (n=3) received multiple ECMO runs.

Data collection

The primary endpoint was IC mortality, the primary study parameters were static arterial lactate (LACabs) and the dynamic arterial lactate indices time-weighted arterial lactate (LACtw) and lactate change over time (LACdelta). LACabs was included as it is used in most of the previous studies. The rationale for including dynamic lactate indices is threefold: 1) dynamic indices describe duration and trend over time next to magnitude and can account disease-severity-induced adjustments over time; 2) results are promising in non-ECMO children with septic shock or cardiac defects [12-15]; 3) a study in post-cardiac surgery children showed that mortality lowered after introducing lactate-guided therapy [29]. LACabs levels were determined using an ABL-800 flex blood gas analyzer (Radiometer Medical Aps, Copenhagen, Denmark) and stored unit's electronic system. From this system we retrieved all LACabs measurements before and during ECMO support. Thereafter LACtw and LACdelta were calculated [30]. LACtw –incorporating magnitude and duration of lactate derangement– was determined by summing the mean value of LACabs between consecutive time points multiplied by the time period in between and then dividing by the total time [30]. For LACdelta –incorpo-

rating magnitude and trend over time– LASabs values were regressed against time for each individual patient, with the regression slope representing the projected change of consecutive measurements over time [30].

We also obtained patient demographics and disease severity indices –i.e. pediatric risk of mortality II (PRISM II), pediatric index of mortality II (PIM II), pediatric logistic organ dysfunction (PELOD), oxygenation index (OI), and the level of vasopressor support (VP-score) [29-33]. Co-morbidity was registered using definitions described earlier [25, 36]. Renal failure was assessed only prior to cannulation because after cannulation all patients received hemofiltration. Pulmonary hypertension was assumed present in case of inhaled nitric oxide therapy combined with either echocardiographic reporting or with consistent pre-ductal to post-ductal saturation differences greater than 20%. The mode of ECMO support was scored as either venoarterial ECMO (VA-ECMO) or venovenous ECMO (VV-ECMO). If the ECMO mode was converted, the ECMO mode with the longest duration was scored.

Hospital treatment protocol

After initial stabilization and IC admission, patients were treated according to institutional policy. Respiratory and circulatory management have been described previously, as have the ECMO inclusion and exclusion criteria, the sedative and analgesic management, the cannulation procedure, and the ECMO weaning procedure [37, 38]. In short, the ECMO criteria were: prolonged OI>25 or cardiorespiratory failure for more than three hours with pH<7.15 and PaO2<5.3 kPa. VV-ECMO was preferred for patients with isolated primary respiratory failure –i.e., good myocardial function as assessed by cardiac echo and no severe circulatory failure as assessed by conventional hemodynamic parameters. VA-ECMO was preferred in patients with congenital diaphragmatic hernia (CDH) or isolated septic shock, and in patients with primary respiratory failure that was accompanied by poor myocardial function and/or circulatory failure. Both the timing of ECMO and type of ECMO modality were decided by the attending intensivist. The ECMO membrane and tubing were supplied by Medtronic (Medtronic Inc., Minneapolis, MN, USA); the ECMO roller pumps were provided by Stöckert Instrumente GmbH (Stöckert Instrumente GmbH, Munchen, Germany). The normal range for arterial lactate was: 0.5 to 2.0 mmol/L.

Statistical analysis

Data are presented and analyzed separately for neonatal and pediatric patients (see introduction). LACabs, LACtw, and LACdelta are expressed as means with 95%-confidence interval (CI_{95}). Statistical analysis was done in three steps. Firstly, to assess evolutional differences, a repeated measurements analysis was performed using linear mixed effects models thereby accounting for correlating measurements within each patient. For

the linear mixed effects model specification, we used regression splines –i.e. natural cubic splines– for both the fixed and the random-effects parts to account for potential non-linearity. The models' assumptions were validated using residuals plots. Secondly, as a summary measure of the static and dynamic lactate indices, we calculated per patient the area under the longitudinal curve corrected for days of follow-up. Using Cox proportional hazards modeling, these were subsequently used to determine the hazard ratios (HR) with CI_{95} and the concordance index (concindex) with CI95, the latter representing the predictive value. Finally, the area (AUC) under ROC curve was calculated together with the best cut-off value and its sensitivity, specificity, positive predictive value, and negative predictive value in case relevant. All other data are described as medians (IQR). The correlation between vasopressor score and the respective lactate indices was calculated using the spearman rank correlation coefficient. Descriptive statistics and non-parametric inferential testing were done using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The advanced statistical testing for the lactate indices was done using R2.15.2. A p-value below 0.050 was considered statistically significant.
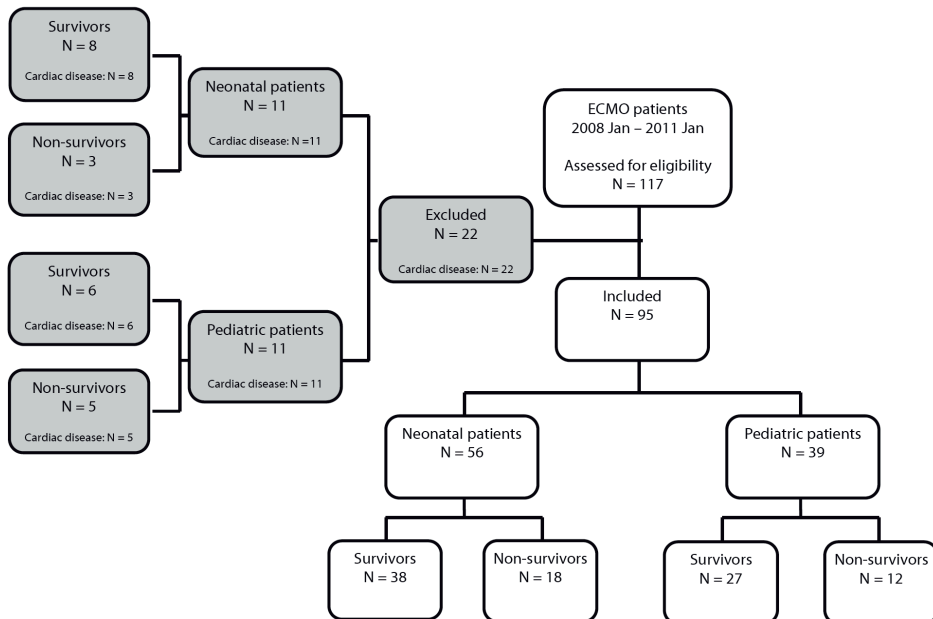

Figure 1: Flowchart for the patients with primary respiratory disease requiring extracorporeal membrane oxygenation who were assessed for inclusion in the study.

RESULTS

We enrolled 56 neonatal and 39 pediatric patients. Seventeen patients with primary cardiac disease were excluded (Figure 1). Of those included, 18 (32%) neonatal and 12 (31%) pediatric patients died. Table 1 shows the baseline and ECMO-related patient characteristics.

VA-ECMO was used more often in the neonatal non-survivors than in the neonatal survivors while fewer non-survivors were transferred from another hospital to the study site. The time between admission and ECMO start did not differ. Vasopressor support at admission was lower in the non-survivors. The other disease indices differed neither before nor or during ECMO. The non-survivors received ECMO support longer than the survivors. In one survivor, the ECMO mode was converted from VV-ECMO to VA-ECMO because the maximum VV-ECMO blood flow was insufficient to restore cardiorespiratory parameters. Eighteen (32%) neonates died. In four patients ECMO could not be weaned due to: irreversible primary pathology (n=2; alveolar capillary dysplasia and persistent pulmonary hypertension [PPH]), hemorrhagic complication, thromboembolic complication. The 14 other non-survivors were successfully weaned off of ECMO, but died prior to IC discharge –median (IQR) time after ECMO stop: 17 (3-21) days–. Here the causes of death were PPH in CDH (n=11), septic shock (n=2), and chronic pneumonitis of infancy.

In the pediatric patients, VA-ECMO was started as often in survivors as in non-survivors. In five pediatric patients (four survivors) the ECMO mode was converted from VV-ECMO to VA-ECMO while in one pediatric patient VA-ECMO was switched to VV-ECMO. Before or during ECMO there were no differences in any of the disease severity indices, apart from a clinically irrelevant difference in vasopressor support at admission. Neither the time between admission and ECMO start, nor the duration of ECMO support differed between the survivors and the non-survivors. In nine (75%) non-survivors, ECMO could not be weaned. The causes of death included: pulmonary consolidation (n=2), PPH, septic shock, cerebral haemorrhage, ischaemic-hypoxic encephalopathy, cardiac tamponade, Waterhouse-Friderichsen syndrome, and auto-immune-induced interstitial lung disease. Three pediatric non-survivors were successfully weaned, but died before IC discharge –median (IQR) time after ECMO stop: 7 (6-11) days. The causes of death were septic shock, idiopathic PPH, and ischaemic-hypoxic encephalopathy.

Arterial lactate before & during ECMO

Neonatal patients
Fifty-six neonates were included in whom in total 3,430 arterial lactate measurements were performed (median [IQR] number per patient: 37 [17-97]). The number of lactate measurements on day 1 and day 2 of IC admission was higher in the non-survivors than

Table 1: The baseline patient characteristics for the neonatal- and pediatric extracorporeal membrane oxygenation patients who did survive and those who did not survive.

	Neonatal ECMO patients			Pediatric ECMO patients		
	Survivors n = 38	Non-survivors n = 18	p-value	Survivors n = 27	Non-survivors n = 12	p-value
Male gender n (%)	21 (55)	6 (33)	NA	19 (70)	7 (58)	NA
Age at admission in days Median (IQR)	1 (1 to 1)	1 (0 to 1)	0.120	-	-	NA
Age at admission in months Median (IQR)	-	-	NA	19 (5 to 64)	94 (43 to 164)	0.028
Weight at admission in kilograms Median (IQR)	3.5 (3.0 to 4.1)	3.0 (2.2 to 3.3)	0.019	11.0 (4.2 to 17.0)	24.7 (15.0 to 51.5)	0.008
Transferred from another hospital n (%)	25 (66%)	4 (22%)	0.004	27 (100)	12 (100)	NA
Length of IC stay in days Median (IQR)	21 (8 to 79)	26 (15 to 40)	0.875	19 (11 to 24)	19 (5 to 34)	0.692
PRISM II Median (IQR)	28 (22 to 33)	25 (19 to 29)	0.147	22 (15 to 27)	21 (10 to 30)	0.776
PIM II Median (IQR)	-1.7 (-2.6 to -1.3)	-1.7 (-2.3 to -1.1)	0.757	-2.8 (-3.4 to -2.2)	-2.6 (-4.1 to -1.6)	0.776
ECMO mode n (% VA)	25 (66)	17 (94)	0.023	13 (48)	9 (75)	0.168
Conversions n (% conversions VV to VA)	1 (3)	0 (0)	1.000	4 (15)	2 (17)	1.000
IC admission to ECMO start in days Median (IQR)	1 (0 to 2)	3 (0 to 9)	0.114	1 (0 to 2)	1 (0 to 7)	0.819
Length of ECMO support in days n (%)	4 (3 to 7)	11 (6 to 15)	0.000	8 (4 to 9)	10 (3 to 21)	0.260
ECMO stop to discharge / death in days Median (IQR)	15 (4 to 58)	9 (1 to 19)	0.060	7 (2 to 18)	0 (0 to 3)	0.000
OI at admission Median (IQR)	23 (12 to 42)	18 (11 to 24)	0.368	28 (8 to 37)	18 (5 to 35)	0.548
OI after cannulation Median (IQR)	7 (4 to 14)	7 (4 to 11)	0.744	16 (9 to 29)	10 (5 to 23)	0.207
VP-score at admission Median (IQR)	6 (0 to 35)	0 (0 to 3)	0.019	0 (0 to 6)	0 (0 to 0)	0.034
VP-score after cannulation Median (IQR)	20 (4 to 47)	30 (18 to 62)	0.116	0 (0 to 17)	11 (0 to 44)	0.169
PELOD at admission Median (IQR)	21 (20 to 31)	30 (21 to 31)	0.254	22 (17 to 37)	21 (21 to 50)	0.971
PELOD after cannulation Median (IQR)	21 (13 to 22)	20 (12 to 22)	0.754	21 (17 to 31)	30 (21 to 42)	0.185
Primary COD n (%)						
- Irreversible respiratory disease	-	14 (78)		-	5 (42)	
- Septic shock	-	2 (11)	NA	-	2 (17)	NA
- Irreversible neurological damage	-	1 (6)		-	3 (25)	

Table 1: The baseline patient characteristics for the neonatal- and pediatric extracorporeal membrane oxygenation patients who did survive and those who did not survive. (continued)

	Neonatal ECMO patients			Pediatric ECMO patients		
	Survivors n = 38	Non-survivors n = 18	p-value	Survivors n = 27	Non-survivors n = 12	p-value
- Irreversible cardiac disease	-	1 (6)		-	2 (17)	
Diagnosis at the time of cannulation n (%)						
- MAS	13 (30)	1 (6)		0 (0)	0 (0)	
- CDH	10 (23)	13 (72)		0 (0)	0 (0)	
- Idiopathic PH	5 (12)	0 (0)		1 (4)	1 (8)	
- Respiratory disease infectious	1 (2)	0 (0)	NA	17 (63)	3 (25)	NA
- Respiratory disease non-infections	4 (9)	2 (11)		6 (22)	3 (25)	
- Septic shock	5 (12)	2 (11)		3 (11)	5 (42)	
Comorbidity n (%)						
- Pulmonary hypertension	35 (92)	16 (89)		9 (33)	3 (25)	
- Neurologic disease	4 (11)	3 (17)		4 (15)	6 (50)	
- Renal failure	6 (16)	3 (17)		7 (26)	3 (27)	
- Cardiac disease	1 (3)	2 (11)		6 (22)	3 (25)	
- Cardiac arrest (yes/no)	8 (21)	3 (17)		9 (33)	7 (58)	
- Hemorrhagic/coagulation disorder	22 (58)	16 (89)	NA	5 (19)	4 (33)	NA
- Liver failure	4 (11)	2 (11)		9 (33)	9 (75)	
- Malignancy	0 (0)	0 (0)		0 (0)	0 (0)	
- Organ transplantation	0 (0)	0 (0)		1 (4)	0 (0)	
- Primary immunodeficiency	0 (0)	1 (6)		0 (0)	0 (0)	

Continuous data are presented as medians and interquartile range, discrete data as number and percentage. Differences vs. survivors at p<0.05 using non-parametric tests. CDH: congenital diaphragmatic hernia, COD: cause of death, ECMO: extracorporeal membrane oxygenation, IC: intensive care, MAS: meconium aspiration syndrome, NA: differences not assessed, OI: oxygenation index, PELOD: pediatric logistic organ dysfunction, PH: pulmonary hypertension, PIM II: absolute pediatric index of mortality II, PRISM II: absolute pediatric risk of mortality II, VA: venoarterial extracorporeal membrane oxygenation, VP-score: vasopressor score, VV: venovenous extracorporeal membrane oxygenation.

in the survivors: median (IQR) number= 15 (5-18) vs. 7 (4-13). For the other days, there were no differences.

In the neonatal patients, the mean (CI95) LACabs, LACtw, and LACdelta before and during ECMO in relation to outcome are presented in Table 2. The evolution of LACabs, LACtw, and LACdelta from admission to ECMO stop is shown in Figure 2. Linear mixed effects modeling showed that, based upon the likelihood ratio, the evolution of LACabs did not differ between the survivors and the non-survivors (Table 3). Cox regression modeling showed that the hazard ratio of LACabs was not significant and that its predictive value, estimated by the concordance index, was poor (Table 3). The evolution of the dynamic lactate index LACtw in the non-survivors differed from that of the survivors. However, the hazard ratio of LACtw was not significant and its predictive value was poor. LACdelta's hazard ratio was statically different, but the predictive value was poor.

The supplemental table 1 shows the vasopressor score in relation to LACabs, LACtw, and LACdelta for the neonatal (and the pediatric) VA-ECMO and VV-ECMO patients.

Table 2: The levels of static, absolute arterial lactate level (LACabs), time-weighted arterial lactate (LACtw), and lactate change over time (LACdelta) for the neonatal- and pediatric extracorporeal membrane oxygenation patients.

		Neonatal patients		Pediatric patients	
		Survivors n = 38	Non-survivors n = 18	Survivors n = 38	Non-survivors n = 18
Lactate levels total follow- up	LACabs in mmol.L⁻¹	1.9 (1.8 to 2.0)	1.8 (1.8 to 1.9)	2.0 (2.0 to 2.1)	2.5 (2.4 to 2.6)
	LACtw in mmol.L⁻¹	2.3 (2.2 to 2.4)	1.9 (1.9 to 2.0)	2.2 (2.1 to 2.3)	2.9 (2.8 to 3.0)
	LACdelta in mmol.L⁻¹	-0.02 (-0.06 to 0.03)	-0.04 (-0.16 to 0.07)	-0.02 (-0.06 to 0.01)	0.06 (-0.02 to 0.15)
Lactate levels pre-ECMO start	LACabs in mmol.L⁻¹	2.4 (2.2 to 2.6)	2.2 (2.1 to 2.4)	2.1 (1.7 to 2.5)	2.8 (2.4 to 3.2)
	LACtw in mmol.L⁻¹	2.4 (2.2 to 2.6)	2.2 (2.2 to 2.3)	2.1 (1.7 to 2.4)	2.5 (2.2 to 2.9)
	LACdelta in mmol.L⁻¹	0.02 (-0.08 to 0.12)	0.07 (-0.02 to 0.15)	-0.03 (-0.19 to 0.13)	0.19 (-0.08 to 0.45)
Lactate levels post-ECMO start	LACabs in mmol.L⁻¹	1.7 (1.6 to 1.8)	1.6 (1.5 to 1.7)	2.0 (1.9 to 2.1)	2.4 (2.3 to 2.6)
	LACtw in mmol.L⁻¹	2.2 (2.1 to 2.3)	1.8 (1.8 to 1.8)	2.2 (2.1 to 2.3)	3.0 (2.8 to 3.1)
	LACdelta in mmol.L⁻¹	-0.03 (-0.08 to 0.02)	-0.09 (-0.26 to 0.07)	-0.02 (-0.04 to 0.00)	0.03 (-0.05 to 0.12)

Data are presented in mean (CI₉₅) for the total study period, for the measurements before the start of extracorporeal membrane oxygenation (ECMO), and for the measurements during the course of ECMO. Intergroup differences were no assessed. Mmol.L⁻¹ millimoles per liter.

Table 3: The evolution (expressed by the likelihood ratio), the hazard (expressed by the hazard ratio), and the predictive value (expressed by the concordance index) of static, absolute arterial lactate level (LACabs), the dynamic measure time-weighted arterial lactate (LACtw), and the dynamic measure lactate change over time (LACdelta) in the neonatal and the pediatric patients requiring extracorporeal membrane oxygenation.

		Longitudinal evolution		Hazard			Predictive value	
		Likelihood ratio	p-value	Hazard ratio	CI_{95}	p-value	Concordance index	CI_{95}
Neonatal patients	LACabs	6.78	0.237	0.94	0.66 to 1.34	0.716	0.47	0.32 to 0.62
	LACtw	12.24	0.032	0.85	0.59 to 1.22	0.381	0.46	0.31 to 0.61
	LACdelta	2.52	0.77	0.73	0.56 to 0.97	0.028	0.39	0.24 to 0.54
Pediatric patients	LACabs	30.24	< 0.001	1.23	1.06 to 1.43	0.007	0.75	0.57 to 0.93
	LACtw	6.54	0.257	1.13	1.00 to 1.27	0.056	0.63	0.47 to 0.79
	LACdelta	11.11	0.025	20.64	1.99 to 214.20	0.011	0.69	0.51 to 0.87

Pediatric patients

Thirty-nine pediatric were included in whom in total 3,045 arterial lactate measurements were performed (median (IQR) number per patient: 57 (29-87)). In the pediatric non-survivors, the number of lactate measurements was higher only on day 2 of IC admission when compared to the survivors: median (IQR) number=6 (9-13) vs. 4 (6-8).

For the pediatric ECMO patients, mean (CI95) LACabs, LACtw, and LACdelta before and during ECMO are presented in Table 2 and the evolution is presented in Figure 3. The evolution of LACabs and LACdelta differed significantly between the survivors and the non-survivors (Table 3). In the pediatric non-survivors, LACabs was constantly higher before and during ECMO. Its hazard ratio was 1.23 (CI95= 1.06-1.43, p= 0.007) and the predictive value was good (concindex= 0.75, CI95= 0.57-0.93). The overall hazard ratio of LACdelta was 20.64 (CI95= 1.99-214.20, p= 0.011) and the predictive value was 0.69 (CI95= 0.51-0.87). The hazard ratio of LACtw failed to reach statistical significance. Its predictive value was 0.63 (CI95= 0.47-0.79).

Figure 3 shows that the most prominent differences for LACabs and LACdelta occurred from IC admission up to day 4. These LACabs and LACdelta measurements were used subsequently to determine the AUC of the ROC together with the best cut-off value in case relevant. For LACabs, the AUC was 0.73 (p-value <0.001) and the best cut-off value was 2.5 mmol/L –sensitivity: 62% (CI95:57-67), specificity: 75% (CI95:72-79), positive predictive value: 58% (CI95:53-63), and negative predictive value: 79% (CI95:75-82). For LACdelta the AUC failed to differ significantly. Hence, a cut-off value was not determined.
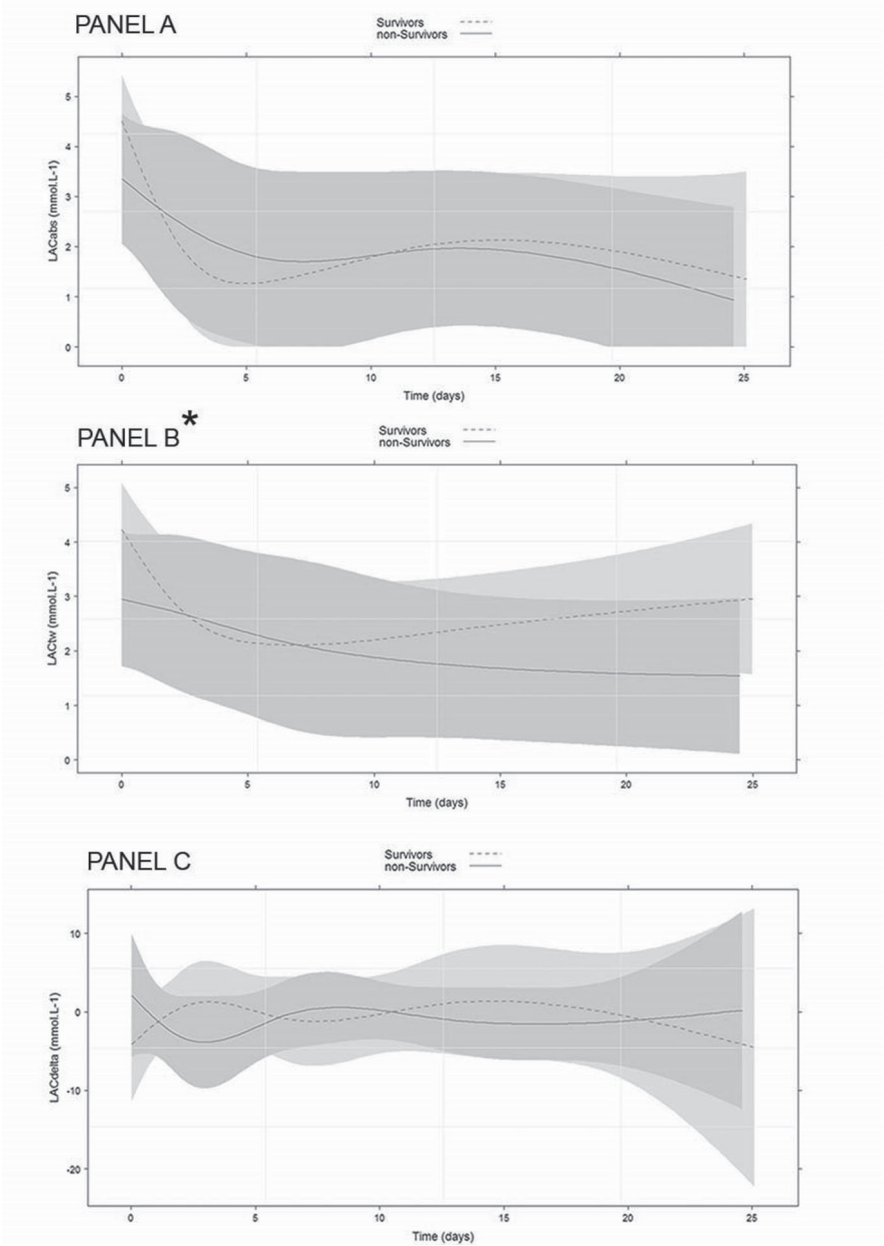
Figure 2: The evolution of static, absolute arterial lactate level (LACabs; panel A), time-weighted arterial lactate (LACtw; panel B), and lactate change over time (LACdelta; panel C) in relation to mortality in neonates with primary respiratory disease requiring extracorporeal membrane oxygenation. LACtw differed between the neonatal survivors and the neonatal non-survivors, in contrast to LACabs and LACdelta. Data are presented as mean (lines) with CI_{95} (gray areas), * $p<0.050$ vs. survivors using mixed effects models.
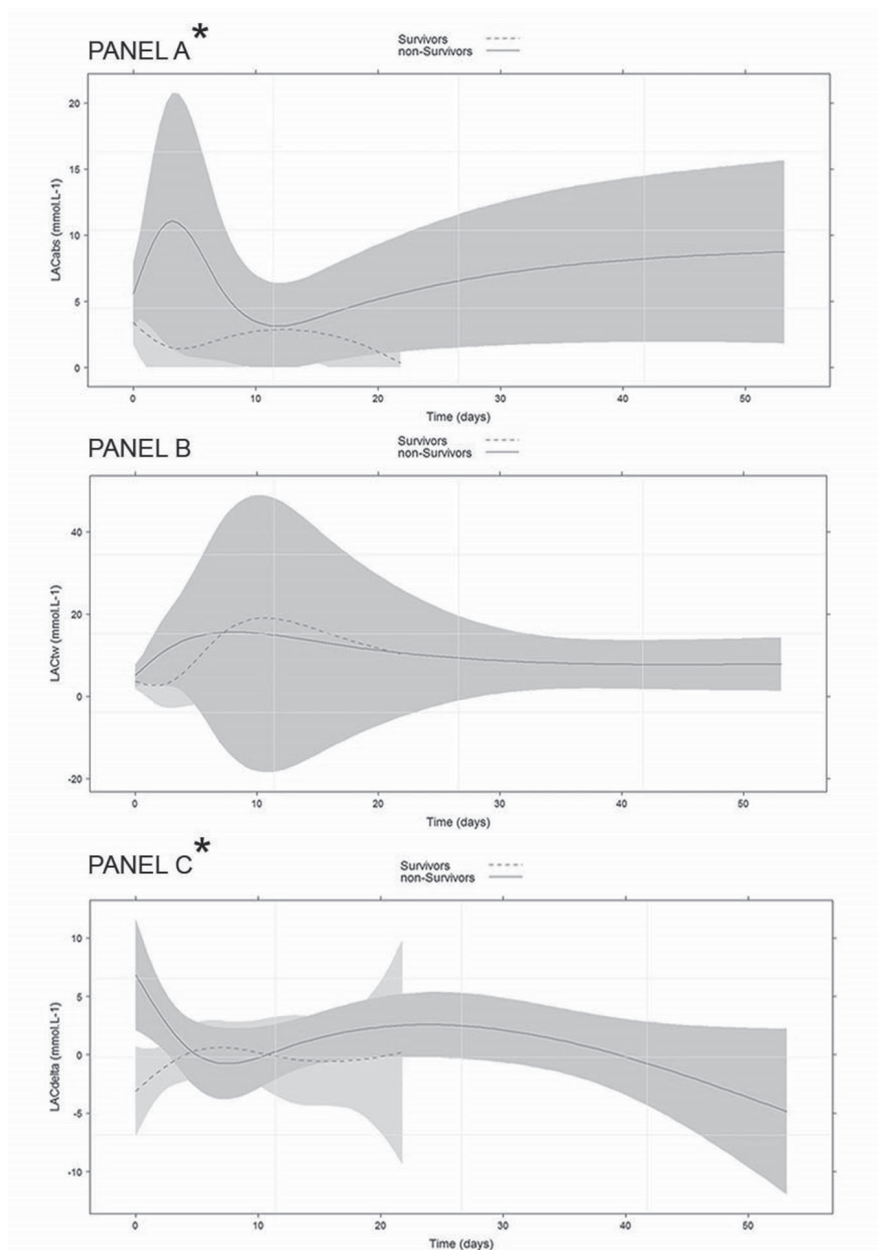
Figure 3. The evolution of static, absolute arterial lactate level (LACabs; panel A), time-weighted arterial lactate (LACtw; panel B), and lactate change over time (LACdelta; panel C) in relation to mortality in pediatric patients with primary respiratory disease requiring extracorporeal membrane oxygenation. Both LACabs and LACdelta, but not LACtw, differed between the pediatric survivors and the pediatric non-survivors. Data are presented as mean (lines) with CI$_{95}$ (gray areas), * p<0.050 vs. survivors using mixed effects models.

DISCUSSION

Our study shows that neither LACabs nor LACdelta or LACtw predicted mortality in neonatal ECMO patients. In contrast, LACabs was a good predictor in the pediatric ECMO patients. Its hazard ratio indicated that for every one unit increase, the risk for non-survival increased by 23%. Moreover, albeit less predictive than LACabs, LACdelta's hazard ratio was very high whilst LACtw did not differ significantly. So, not the duration of lactate derangement, but the magnitude and trend over time of lactate derangement are in particular associated with mortality in pediatric ECMO patients with respiratory disease.

Multiple studies have reported that static hyperlactatemia is associated with higher mortality in ECMO patients with primary cardiac disease [16-20]. For children with primary respiratory disease, there is one study that focused on a cohort of both neonatal and pediatric patients and three studies that focused on neonates exclusively [21-24]. The neonatal studies showed that, in contrast to our results, higher static lactate was associated with higher mortality [22-24]. The reported mean or median lactate levels were, however, markedly higher than ours, as was the oxygenation index and VP-score. Catecholaminergic support in itself can increase arterial lactate levels, as has been reported previously by others and as can be deduced from some of our results that are presented in the Supplemental table 1 [3, 4]. Therefore, the discrepancy in results is most likely attributable to differences in treatment, disease severity, and, possibly, to differences in ECMO population characteristics.

The question as to why arterial lactate is associated with poor outcome in pediatric patients, but not in neonatal patients, is intriguing. In contrast to the neonatal non-survivors, relatively many pediatric non-survivors were diagnosed septic shock. Sepsis is a microcirculatory disease and lactate is more likely to increase. Moreover, when compared to the neonates, more pediatric patients were referred to our center and more pediatric non-survivors had co-morbidity –most notably liver dysfunction. Additionally, less pediatric patients suffered pulmonary hypertension while a higher proportion of neonatal survivors was treated with VV-ECMO. Right-to-left shunting through persistent fetal pathways and mixing of deoxygenated and oxygenated venous blood in the case of VV-ECMO might increase the amount of "venous" blood in the arterial circulation. Given that venous blood is associated with higher lactate than arterial blood, both phenomena could act as confounders in the neonatal population. Thus, differences in disease type, co-morbidity, timing of treatment, and type of treatment might explain why lactate predicts outcome only in the pediatric patients [5]. The observed differences are unlikely to be of procedural nature as the measurement error of the blood gas analyzers was small, the ECMO entry criteria remained unaltered during the study, the cannulation procedure was standardized, and the primed ECMO circuit was checked and adjusted to

normal values pre-cannulation. Furthermore, the number of conversions did not differ and there were no indications that ECMO support was more often insufficient in the pediatric non-survivors.

This is the first study to focus on the predictive value of static and dynamic lactate measures in pediatric ECMO patients with primary respiratory disease. Lactate derangement has been associated with mortality in various groups of pediatric, critically ill non-ECMO patients[3, 13, 39]. Particularly interesting is the report by Rossi et al. that describes a marked decrease in mortality in post-cardiac surgery children after implementation of lactate-guided therapy[29]. Others observed that dynamic lactate indices predicted mortality better in critically ill, pediatric non-ECMO patients[12,13]. We observed the reverse: static lactate measurements are a better predictor than dynamic indices. In our study, the arterial lactate levels wererelatively low upon admission and after three or more days of ECMO support. Likewise, the oxygenation index and the VP-score were relatively low. Furthermore, all pediatric patients and approximately 50% of the neonatal patients were referred to our center. Therefore, our data are most likely attributable to the early referral of patients to our center, which is regarded good practice in our country. Moreover, estimating LACdelta and LACtw in only the first few days before and after ECMO support will result in other, probably more convincing, differences and in higher predictive value.

Interestingly, relative hyperlactatemia –i.e. higher lactate concentrations within the normal reference range–is associated with increased mortality in critically ill adults [40, 41]. While relative hyperlactatemia is not truly applicable to our study and the topic is beyond our scope, it might be interesting for future researchers to investigate whether relative hyperlactatemia is also clinically relevant in critically ill children.

The most important limitation of the current study is the modest number of included patients. This limited the possibility to correct for hypothetic confounders such as disease type at admission, co-morbidity, level of catecholaminergic support, ECMO mode, and age during statistical analysis. Results should thus be interpreted with caution. However, statistically significant results were still obtained in spite of the small sample and effect size. Moreover, in accordance with a review by Allen we do not believe that a single biomarker should be used to amend or stop therapy and that, for correct interpretation, the cause –i.e. anaerobic or aerobic (co-) morbidity– of lactate increments should ideally be identified[3]. The clinical relevance of the current study should be sought in the fact that, for pediatric patients, mild lactate derangements that fail to normalize over time can serve as warning sign. The high hazard ratio of LACdelta shows that dynamic lactate indices –which account for disease-severity-induced adjustments over time– could be a valuable addition to clinical practice. Therefore, future prospective studies should substantiate the value of absolute and dynamic arterial lactate levels, preferably in homogeneous ECMO patient groups, and with respect to type, timing, and level of therapy

delivered. Ideally, arterial lactate should then be evaluated together with other biomarkers such as microcirculatory perfusion [39]. In septic shock children, microcirculatory perfusion has been associated with mortality [42]. For neonatal ECMO patients with primary respiratory disease, future research should elucidate whether arterial lactate monitoring in neonates may be used for other clinically relevant purposes.

CONCLUSION

Static arterial lactate measurements and, to a lesser extent, dynamic arterial lactate indices predict mortality in pediatric ECMO patients with primary respiratory disease. The magnitude and trend over time of arterial lactate levels, but not the duration of lactate derangement predict mortality. In contrast, the value of arterial lactate for predicting outcome in neonatal ECMO patients is limited. A prospective multicenter study should substantiate the findings presented here in relation to intervention and a panel of biomarkers.

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Chapter 6

Preoperative ECMO in neonates with transposition of the great arteries and preoperative cardio-pulmonary instability

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ABSTRACT

Background

Pulmonary hypertension (PHT) in neonates with transposition of the great arteries (d-TGA) can be difficult to treat. Next to the use of prostaglandin E1 and balloon atrial septostomy, pharmacological pulmonary vasodilator therapy including inhaled nitric oxide cannot prevent preoperative mortality. ECMO support, however, may help reduce pulmonary hypoxic vasoconstriction and improve pulmonary vascular resistance (PVR).

Design

Retrospective, cohort study.

Setting

Single, tertiary-care center PICU

Methods

The local ethics review board approved the retrospective review of all neonatal d-TGA patients in our hospital in the period 2002-2012 and those in the ELSO database to describe the incidence of PHT and the use of ECMO in these patients.

Measurements and Main Results

Our hospital admitted 92 d-TGA patients in this period, 17 of whom had preoperative PHT receiving conventional treatment (18%). Conservative treatment failed in eight of these 17 patients (47%). Six of these eight patients were cannulated for ECMO. All six were term neonates and survived to surgery and survived ECMO. As one infant died three months after surgery, one-year survival in the ECMO-treated group was 83%. All other five patients had favorable neurologic outcome at one year.

Conclusion

If conservative treatment of PHT does not sufficiently reduce PVR in d-TGA patients and results in profound hypoxia, pre-operative ECMO can safely be used as therapy for PHT and to bridge the period to surgery.

INTRODUCTION

Patients with a transposition of the great arteries (TGA) account for 5% to 7% of the congenital heart defects [1]. When d-transposition (D-TGA) is present and the parallel circulations do not mix sufficiently severe hypoxemia can result [2].

This is a challenging combination for clinicians especially when the ventricular septum is intact. The usually effective pre-operative interventions to increase mixing of the blood are prostaglandin E1 and balloon atrial septostomy (BAS). However some of these patients respond poorly and hypoxemia persists. In addition to mixing problems pulmonary hypertension (PH) aggravated by hypoxemia leads to impaired pulmonary flow and decreased left sided atrial filling. PH is present in 1-3% of D-TGA patients [3] In these persistent hypoxemic cases an immediate primary repair by performing an arterial switch operation (ASO) could benefit the patient. However in cases of severe PH midterm survival is poor. [4] Another option is to treat PH pharmacologically or to start extracorporeal membrane oxygenation (ECMO) [5].

ECMO in the pre-operative TGA setting can be used to improve gas exchange and the resulting increase in oxygenation can help to reduce pulmonary vascular resistance (PVR) thus stabilizing the patient before corrective surgery.

Several papers, mainly case reports, show successful treatment with ECMO in the pre-operative period [6-9]. Despite these reports, there is still a paucity of data on the indications, choice of ECMO mode and short term effects of preoperative ECMO in these cases. In TGA patients the ECMO-mode itself does not influence pulmonary blood flow. Both VV ECMO as well as VA ECMO circulate oxygenated blood into the systemic circulation either by returning saturated blood in the right atrium or in the aorta which originates from the right ventricle.

It remains uncertain if preoperative ECMO improves mortality and long term outcome in these patients. Furthermore it is unclear which ECMO-mode should be preferred. We describe the short and long-term outcomes of six patients successfully bridged to surgery using ECMO in the pre-operative phase.

MATERIALS AND METHODS

We performed a single-center retrospective observational study in the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands, which serves as a level III referral center. It is one of four designated pediatric cardiac surgery centers and one of two designated ECMO centers in the Netherlands with on average 30 ECMO runs per year. The institutional medical ethics review board approved the study, and waived the need for informed consent. All neonates admitted between January 1st 2002 and December

31st 2012 with the diagnosis of d-TGA with or without VSD were identified. Clinical medical records and databases were retrospectively reviewed for details on ECMO support.

Inclusion and exclusion criteria for ECMO support were conform the ELSO criteria for neonatal ECMO treatment at that time: Gestational age > 34 weeks, birth weight > 2.0 kg, mechanical ventilation < 14 days. Contraindications for ECMO were: Lethal chromosomal disorder or lethal anomaly, irreversible brain damage, uncontrolled bleeding or grade III or greater intraventricular hemorrhage. The in- and exclusion criteria for ECMO had not changed over the studied period.

Prospectively collected physiological parameters were derived from the hospital's computerized patient data management system. The following data were retrieved from the medical records: mortality, primary diagnosis, timing of BAS, inotropic support, NO, saturation, use of PHT medication, blood lactate, pH, ECMO mode and timing of ECMO. Pre-ECMO circulatory inotropic or vasopressor support was expressed as the converted to vasoactive inotrope score: Dopamine dose (µg/kg/min) + Dobutamine dose (µg/kg/min) +100 × epinephrine dose (µg/kg/min) + 10 X Milrinone dose (µg/kg/min) + 100 × Norepinephrine dose (µg/kg/min) [10].

The ECMO patients reported in this study participated in a structural follow-up program – initiated in 2001 – in which lung function, growth and developmental parameters are regularly assessed until 18 years of age [11]. Based on the national consensus on neonatal follow-up and the Dutch Ministry of Health's requirement to provide relevant data, the assessment protocol is the standard of care following ECMO treatment in the Netherlands. At 12 months after ECMO treatment the Bailey Scales of Infant Development – Second Edition – Dutch version (BSID-II-NL) was administered [12]. This standardized instrument assesses motor and mental development of 2 to 30-month-old children.

RESULTS

In the period 2002-2012, 92 d-TGA patients, including 19 patients with associated VSD, were admitted to the Erasmus MC-Sophia Children's Hospital. Six of 92 patients were cannulated for ECMO (6/92; 6,5%): four within 48 hours after birth due to severe pulmonary hypertension, one after 10 days because of recurrent PHT and suspicion of sepsis, and one, three weeks after birth because of low saturations and multi organ failure due to closure of the PDA. In all cases the patient was considered too unstable to undergo an arterial switch operation (ASO) and the decision to start ECMO was made by a multidisciplinary team including neonatologists, ECMO specialists, pediatric cardiologists and pediatric cardiothoracic surgeons. Table 1 shows characteristics and pre ECMO therapies of these six patients, as well as the vasoactive inotrope score reflecting pre-ECMO circulatory inotropic or vasopressor support. Four patients were supported with VV- ECMO via

a 12 or 13 Fr (OriGen Biomedical, Austin, TX) double lumen catheter inserted in the right jugular vein. Two patients were cannulated for VA-ECMO using the right jugular vein and the right carotid artery. Median time on ECMO was 10,5 days (IQR 1-22). Four patients were weaned from ECMO before the ASO, one patient was decannulated immediately post-surgery, and one patient was decannulated 96 hours after the operation. Figure 1 shows the CONSORT patient flow diagram.
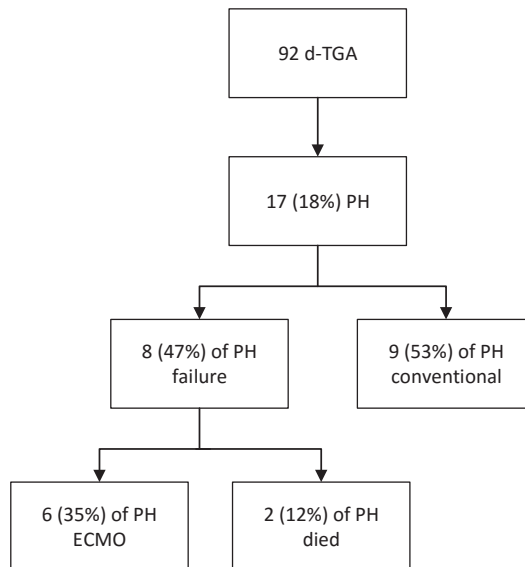
All six neonates who received ECMO support survived to surgery.

Figure 1: Consort patient flow diagram.

All patients are still alive except for one patient who died in the ICU three months after the ASO due to an ongoing sepsis with capillary leakage syndrome, chylothorax and recurrent pulmonary hypertension. Thus, one-year survival in the ECMO-treated group was 83%.

Table 1: Pre-ECMO data of six consecutive patients with transposition of the great arteries (d-TGA) and preoperative cardio-pulmonary instability in the period 2002-2012.

Patient No:	1	2	3	4	5	6
Diagnosis	d-TGA-IVS	TGA-VSD-ASD	d-TGA-IVS	d-TGA-IVS	d-TGA-IVS	d-TGA-IVS
Body weight (gram)	4800	3200	4020	3900	3860	3350
Age at admission (days)	0	0	0	27	0	25
NO (ppm)	20	20	20	20	20	20
Prostaglandin E1	+	+	+	+	+	+
Vasoactive Inotrope Score	42	70	90	50	98	30
BAS days after admission	0	0	0	0	0	1
Oral sildenafil (mg/kg/day)	3	2	4	0	0	0
Bosentan (mg/kg/day)	0	0	2	0	0	0
Saturation preductal (%)	32	48	37	38	48	52
Saturation postductal (%)	45	65	45	44	76	53
Lactate (mmol/l)	6.3	2	1.6	3.1	5.5	3.9

NO = nitric oxide; BAS balloon atrial septostomy; PH = pulmonary hypertension; IVS = intact ventricular septum; ASD = atrial septal defect; VSD ventricular septal defect; ppm = parts per million.

Table 2: ECMO and post-ECMO data of 6 consecutive d-TGA patients with PHT in the period 2002-2012.

Patient No:	1	2	3	4	5	6
ECMO data						
ECMO mode	VVDL	V-A	V-A	VVDL	VVDL	VVDL
ECMO after admission (days)	1	1	10	5	1	1
Start ECMO (days post-partum)	1	1	10	32	1	26
ECMO duration (days)	8	5	7	3	3	5
ASO after start ECMO (days)	10	26	2	3	19	11
Extubation after admission (days)	-	28	47	14	16	17
Discharge to home (days post-partum)	-	36	101	37	28	26
ECMO follow-up data						
Bayley Scales of Infant Development-II						
Mental at 1 year	Deceased at	Normal	Normal	Normal	Normal	Above normal
Motor at 1 year	3 months	Normal	Below average	Normal	Normal	Normal

ASO = arterial switch operation; VVDL = venovenous double lumen; VA = venoarterial.

All five surviving ECMO patients were included in the structural follow-up program. Motor and mental development were tested with the BSID-II-NL at age 12 months. Scores were normal or above average, except for patient No. 3 on the motor scale (Table 2).

DISCUSSION

To our knowledge the present study reports the largest cohort of d-TGA patients with ECMO before ASO. Six percent (6.5%) of all d-TGA patients were supported with ECMO prior to surgery with only one patient needing ECMO postoperatively. All 6 survived to surgery or discharge from the ICU. Overall one year survival was 83% with all five surviving ECMO patients demonstrating favorable neurological outcome at one year.

Despite apparent adequate options for mixture of oxygenated and deoxygenated blood patients with TGA sometimes present with persistent hypoxemia. Alone or in combination with PH, TGA patients can become extremely difficult to manage preoperatively.

Oxygenation depends on adequate mixture of oxygenated and deoxygenated blood across the patent foramen ovale. Decreased pulmonary flow due to a pulmonary artery-aortal-right-to-left shunt across the ductus arteriosus in PH will result decreased oxygenation and left atrial filling. The resulting right to left shunt over the oval foramen, by admixture, will further reduce the saturation of the pulmonary arterial blood. Thus, both PVR and pulmonary artery blood pressure are further increased, resulting in even

lower pulmonary flow. Although iNO therapy has been shown to improve oxygenation in neonates with PHT and has improved survival in TGA patients mortality remains high in d-TGA patients with severe pulmonary hypertension [3]. Alternative interventions include sildenafil and bosentan, but the role of these drugs in the acute phase remain unclear.

In these unstable patients one option is to go for acute ASO with an option to use ECMO in the postoperative setting to stabilize these patients via transthoracic or carotid cannulation [5].

However, high overall mortality has been reported in patients needing ECMO directly post-surgery in congenital cardiac defects [13]. Conversion from cardiopulmonary by-pass to ECMO, difficulties in coagulation management and high risk of infection in open chest cannulation might all contribute to a high mortality in these patients [14, 15].

Overall pre-operative ECMO in pediatric cardiac patients was shown to have a sig-nificant lower mortality compared to postoperative ECMO in heart surgery [16]. This therefore bears the question whether pre-operative ECMO in TGA patients might be beneficial compared to a risk of post-operative ECMO. Besides potential easier coagula-tion management it opens op the opportunity for VV ECMO to improve oxygenation.

A search in the ELSO-ECMO database identified 217 patients with ECMO in combina-tion with d-TGA. However pre- and post-ASO patients could not be differentiated due to the set-up of the ELSO database. The overall survival to discharge rate for VV-ECMO patients was 67% vs. 55% for VA-ECMO patients. PHT (ICD-9 747.83) was recorded as a secondary diagnosis for 25 ELSO-ECMO patients and survival to discharge in this sub-group was 52%. The ELSO data show a predominant use of VA-ECMO, although a clearly improved outcome has been demonstrated from the use of VV-ECMO as primary mode in the general ECMO population [13, 17]. Even in non-cardiac sepsis patients VV-ECMO was associated with a better survival rate [17]. Reasons for this improved outcome are unclear but the decreased risk for neurological sequelae has been suggested. VA-ECMO compared to VV-ECMO is reported to result in a higher rate of neonatal neurologic com-plications [18, 19]. In a group of CDH patients with mostly severe PHT, the incidences of seizure disorders and infarction were highest in those on VA-ECMO [18].

However in TGA patients VV-ECMO oxygenates the same blood compartment as in VA-ECMO due to the unique configuration of TGA. ECMO-related emboli will have the same systemic and neurologic effects. VA-ECMO in these patients only differs from VV-ECMO in that it requires carotid cannulation, an (artificial) atrial septal defect and left atrial venous drainage, which can result in decreased pulmonary blood flow. Other factors including reduction of complication risks which are associated with VA ECMO post operatively might play an important role [14].

We found a 83% survival at one year with only one patient needing extended post-operative ECMO support. Importantly four out of six of our patients were cannulated

using a double lumen catheter and supported with VV ECMO despite high inotropic support, whereas post operatively almost all patients would have been supported with VA-ECMO. Furthermore four patients could be weaned from ECMO before surgery with only one patient on ECMO support after surgery, thereby avoiding potential bleeding complications associated with post-operative ECMO [20]. These factors might have contributed to the positive results of our study [21].

It is not yet clear whether either pre-operative VV-ECMO or immediate ASO, with post-operative ECMO as a backup in case of postoperative LV failure – with the inherent risks of postoperative bleeding and arterial cannulation – is the best option for TGA patients with severe PHT. Still both our short and long term one-year outcome data on the use of ECMO in the pre-operative setting in this small sample are promising. The search in the ELSO registry for d-TGA in combination with ECMO and PHT resulted in too few results to make definite conclusions, but closer evaluation of ECMO in TGA might be warranted.

Based on our findings and the ELSO database, we feel that preoperative ECMO is a viable option in neonates with severe therapy resistant hypoxemia not responsive to BAL, iNO and inotropic support. Furthermore VV-ECMO could be considered the first choice of ECMO mode in pre-operative TGA patients.

Timing of decannulation or surgery depends on reversibility of PPHN. Daily echographic estimates of pulmonary artery pressure can be made while the patient is on ECMO, in order to prevent left ventricular deconditioning and to guide timing of ASO. The presence of unidirectional left-to-right ductal shunting could indicate optimal AOS timing [8].

LIMITATIONS

This is a retrospective case series of pre-operative ECMO use in d-TGA patients. With 6,5 % need of ECMO support there seem to be a high number of patients who do not respond to conventional therapies. Several authors have shown that a postnatal diagnosis of cardiac defects instead of an antenatal diagnosis may adversely influence outcome [22, 23]. Delaying therapies in situations with severe hypoxemia may only aggravate the situation resulting in therapy resistant PPHN in these patients. In our study all but one of the ECMO patients were not diagnosed antenatally which might have resulted in delayed therapy and ultimately therapy failure. Table 2 shows all patients were severely hypoxic with all but one having lactate acidosis showing signs of severe hypoxemia necessitating ECMO support. Whether these patients would have required post-operative ECMO if they were operated early remains uncertain but with a 83% survival at one year with favorable outcome it is at least a viable alternative to acute ASO in these patients.

As PHT in d-TGA patients is relatively rare, randomized controlled trials are unavailable and international data reports are sparse on both pre-operative mortality, utility of ECMO pre or postoperatively and effects of conventional therapies. Case series as well as large cohort data from registries such as the ELSO registry can therefore be of great value when adapted or expanded to include extra data for specific patient categories. Furthermore, long-term follow-up programs are essential to guide decisions concerning which short-term solutions are the best for future outcome.

CONCLUSION

When in d-TGA patients conservative treatment of PHT does not sufficiently reduce PVR and results in profound hypoxia, VV-ECMO can be considered as a bridge to surgery.

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Chapter 7

Diagnostic and interventional procedures during prolonged ECMO therapy in pediatric patients.

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ABSTRACT

Introduction

Extracorporeal membrane oxygenation (ECMO) is a means of gas exchange in cases of acute severe but temporary cardiorespiratory failure. We determined the frequency of pediatric ECMO treatment for longer than 20 days in our tertiary referral center as well as related interventions.

Method

We searched our institutional database for neonatal and pediatric patients on ECMO for 21 days of longer and evaluated overall survival, possible causes of death and ECMO-related complications and subsequent management.

Results

Three cardiac and nine respiratory failure patients in the period 2009 till August 2015 received ECMO for 21 days or longer. The median age was 3.3 (IQR 0.3-13.4) years; the median duration of ECMO support 25.2 (22.6-35.2) days. The overall survival was 33%; survival in the patients with primary respiratory disease was 44% (4/9). For most non-survivors continuation of ECMO therapy was considered futile. Switching the ECMO system was needed at least once in all patients. Bronchoscopy (N=35 in total) was the most frequent diagnostic procedure, without major sequelae. A thoracotomy was performed in two patients during ECMO without significant bleeding complications. Seven patients underwent diagnostic CT scans to assess the potential reversibility of pulmonary damage/underlying pathology at a median of 19 days of ECMO therapy.

Conclusion

Prolonged ECMO is feasible in view of the 44% survival to discharge in respiratory patients. Still many diagnostic and intensive therapeutic interventions were needed. These data can help to formulate clear guidelines on management and maximum duration of prolonged ECMO, which are currently lacking.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a technique to support cardiac and pulmonary functions in patients with severe reversible cardiopulmonary failure. It enables gas exchange or oxygen delivery if conventional treatment modalities fail. In the first decades after its introduction in the late 1980s ECMO was primarily used to support acute respiratory failure in newborns with persistent pulmonary hypertension for no longer than two weeks. This period was rather arbitrarily set internationally as a cut-off period and prolongation was long considered futile. Runs longer than two to three weeks were found to carry a high risk of complications and were associated with high mortality [1, 2]. Since then, however, indications for ECMO support have broadened to include primary cardiac failure, post cardiac surgery patients and primary respiratory failure in older patients. Especially since the 2009 influenza H1N1 pandemic, ECMO is being applied more and more in the older pediatric and adult populations with conditions that may require longer ECMO runs as a bridge to either recovery or transplantation [3].

Apart from the introduction of alternative ECMO-modes, smaller systems and centrifugal pumps combined with changes in the overall management of patients have increased the feasibility of prolonged ECMO runs. Recently a 265-days ECMO run in an adult with cryptogenic organizing pneumonia proceeded without major problems [4]. Even longer ECMO runs are imaginable if complications such as bleeding, thrombosis and infections can be prevented. The question remains how to achieve this. Other questions concern the issue of when to decide that treatment is futile or that normal organ function can be regained [5].

To provide more data on both outcome and management of patients on prolonged ECMO we evaluated data of all patients supported with either venovenous or venoarterial ECMO in our institution for more than 20 days with special focus on respiratory management and complications.

METHODS

Setting

We performed a single-center retrospective observational study in the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands, which serves as a level III referral center. It is one of two designated ECMO centers in the Netherlands with on average 30 ECMO runs per year. The Erasmus MC institutional medical ethics review board approved the study, and waived the need for informed consent.

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Patients

We searched records and databases for patients treated with ECMO in our institution between January 1990 and August 2015 and retrieved data of those patients who had been on ECMO for ≥ 21 days. This cutoff period was based on previous reports on prolonged ECMO [1, 6]. If a patient had received more than one course of ECMO ≥ 21, only data on the longest course were included.

ECMO procedure

Decisions to start or stop ECMO treatment were made by the attending pediatric ECMO-intensivist and regarding cardiac patients in collaboration with the pediatric cardiologist and cardiothoracic surgeon. Cardiac patients who were eligible for cardiac transplantation were switched from ECMO to a Berlin Heart ventricular assist device.

Open or semi-percutaneous cannulation was performed by a pediatric surgeons in the right jugular vein and if needed the carotid artery in children ≤ 15 kg or the femoral vessels in children >15 kg. The preferred mode of venovenous (VV-) ECMO was by double lumen cannula, with either an Origen ™ (VR13, OriGen Biomedical, Austin, TX) or Avalon elite ™ (Maquet, Rastatt, Germany) cannula.

Up to 2011 we used a roller pump (Stockert-Shiley SIII) with a Medtronic silicone membrane ECMO oxygenator (Medtronic, Minneapolis, MN, USA) in all cases, which was then replaced with the Novalung iLA active system centrifugal system (iLA active®, Novalung, Germany) with an appropriately sized polymethylpentene diffusion membrane oxygenator. Hemofiltration, incorporated into the ECMO circuit, can be started by the attending ECMO physician if the child has a low urine output or kidney failure.

Data collection

We collected patient characteristics and data on diagnostics and interventions to improve lung function, including the frequency and timing of extubation, chest CT, bronchoscopy, high dose corticosteroid administration and surgical interventions. In addition we collected data on ECMO-related complications. The data were retrieved from medical records and from our patient data management system, i.e. prospectively collected physiological data, and data on medication use and support modalities. Additionally, the institutional part of the Extracorporeal Life Support Organization registry (ELSO) (Ann Arbor, MI) registry was accessed to retrieve data on reported complications during the individual prolonged ECMO runs.

Statistical analysis

Data are presented as median values and interquartile range. When applicable a chi-square test was used to test for significance.

RESULTS

Between 1990 and August 2015, 618 patients had been treated with ECMO. The first ECMO run longer than 20 days (38 days) was in 2009. Between 2009 and 2015, 196 patients had been treated with ECMO, of whom 12 (6%) for ≥ 21 days, i.e. three cardiac patients and nine respiratory failure patients. The median age of all 196 patients was 2.2 (interquartile range (IQR)0.1-48.5) months versus 3.3 (0.3-13.4) years for the group receiving prolonged treatment. The median duration of ECMO support was 5.9 (3.1-11.1) days and 25.2 (22.6-35.2) days, respectively. The median number of days of ventilation before prolonged ECMO initiation was 5.5 (IQR 1.8-8.0). The survivors had been ventilated for a median of 45 (IQR 34.5 50.3) days after cessation of ECMO. Seven of the patients receiving prolonged treatment were boys (58%). All 12 were sedated and received pressure controlled ventilation or pressure support. Eight were supported using any form of VV-ECMO (7 respiratory, 1 cardiac). Four patients (Nos 1, 2, 9, 10) were supported on venoarterial (VA)-ECMO. Two of the three cardiac patients and three of the nine respiratory patients were initially supported with VA-ECMO mode (see table 1). A switch from VV-ECMO to VA-ECMO was needed in two patients with cardiac failure.

Two patients were paralyzed for more than 48 hours to reduce respiratory drive and to improve oxygenation. Attempts to extubate and mobilize were successful in two patients only. Further demographics are presented in Table 1.

Survival

Overall survival to decannulation and discharge from the ICU was 33% (4/12). None of the three cardiac patients survived; they were taken off ECMO because continuation of treatment was considered futile. All three patients had contra-indications for cardiac transplantation unrelated to any ECMO complications. Four out of the nine patients (44%) with respiratory failure survived to discharge home (Figure 1).

Two respiratory failure patients (Nos 1 and 2) had died due to septic shock and multiple organ dysfunction. Treatment of one of them (No. 2) had been stopped on parental request. One other patient (No. 7) had died due to persistent inoperable pericardial tamponade. ECMO treatment was withdrawn in the case of two other patients whose lung function was not expected to recover at that time. These two patients had not been perceived as candidates for lung transplantation and died. Interestingly, the survivors represented the most recent cases. Figure 2 shows the increase in survival over time.

All five patients receiving VA-ECMO as initial mode died and one (No. 7) of the two patients (Nos 3 and 7) who had been switched from VV-double lumen to venoarterial-venous ECMO to treat hemodynamic instability died.

Table 1: Patient, Disease, and ECMO Characteristics.

Patient No.	Age	Weight (kg)	Diagnosis	Comorbidities	Ventilator days before ECMO (days)	Type ECMO	Pump type	Switch type after start ECMO (days)	Days on ECMO	Extubated days after start ECMO	CVVH	Survival
1	15 Yr	62	Influenza + Staph Aur	None	1	VA	Roller		38		Y	Deceased Stop treatment no LTX candidate
2	3 Yr	17	ARDS	Thalassaemia hematopoetic stem cell transplant	8	VA	Roller		27		Y	Deceased Stop treatment no therapeutic options
3	4 Yr	17	Pulmonary hypertension	Coronary heart disease single ventricle	1	VA to VV	Roller	8	23	10	Y	Deceased Stop treatment no therapeutic options
4	4 M	5.5	Drug induced pneumonitis	Hemangio-endothelioma	5	VVDL	Centrifugal		23		Y	Deceased Septic shock
5	1 M	6.1	RSV + Staph Aur	None	8	VVDL	Centrifugal		24		N	Survived
6	13 Yr	50	ARDS post trauma	None	12	VVDL	Centrifugal		35	3	Y	Survived
7	3 Yr	15	Necrotising pneumonia	None	9	VVDL to VVA	Centrifugal	20	23		N	Deceased Persistent pericardial tamponade
8	13 Yr	46	Parainfluenza + Staph Aur	None	2	VVDL	Centrifugal		44		N	Survived
9	24 D	4	Cardiomyopathy ECPR	None	7	VA	Centrifugal		28		Y	Deceased Stop treatment no HTX candidate

Table 1: Patient, Disease, and ECMO Characteristics. (continued)

Patient No.	Age	Weight (kg)	Diagnosis	Comorbidities	Ventilator days before ECMO (days)	Type ECMO	Pump type	Switch type after start ECMO (days)	Days on ECMO	Extubated days after start ECMO	CVVH	Survival
10	8 D	3.2	Cardiomyositis ECPR	None	0	VA	Centrifugal		35		Y	Deceased Stop treatment no HTX candidate
11	16 Yr	55	Influenza + Staph Aur	None	4	VV	Centrifugal		22		Y	Deceased Septic shock
12	2 Yr	15	Auto-immune disease	None	6	VVDL to VVA	Centrifugal		21		Y	Survived

Yr, year(s); M, month(s); D, day(s); Staph Aur, staphylococcus aureus; ecpr, extra-corporeal cardiopulmonary resuscitation; ARDS, acute respiratory distress syndrome; VA, venoarterial; VV venovenous; VVDL, venovenous double lumen; VVA venovenous-arterial; Y, yes; N, no; ECPR, Patients are listed in chronological order.

Table 2: Diagnostic and therapeutic interventions.

Patient No.	CT chest (days from start ECMO)	Utility of CT chest	Lung biopsy (days after start ECMO)	Utility of lung biopsy	Bronchoscopy (days after start ECMO)	Utility of bronchoscopy	Therapy changes & (days after start ECMO)	M-pred. pulse (days after start ECMO)	Beta blocker
1	9	Probably no irreversible damage	12	Additional unsuspected severe aspiration	2, 5, 7, 10, 11, 13	Mucus/aspirate clearance		26, 27, 28	No (VA)
2	5, 20	Probably no irreversible damage (5, 20)	no		21	Surfactant deposition	Surfactant (21)	15, 16, 17	No (VA)
3	(-17), 20	Helped in grading pulmonary vasculature (20)	no		21	Cultures			No (Cardiac)
4	no CT		no		4	Cultures & microscopy	Partial liquid ventilation (18)	0, 1, 2	Yes
5	19	Probably no irreversible damage	no		6, 9, 19, 22	Mucus clearance Surfactant deposition	Surfactant (16, 17)		No
6	(-13), 8	Probably no irreversible damage (8)	no		24 - 29	Tracheal-bronchial desobstruction (clots after bleeding)		10, 11, 12	Yes
7	(-4)	Probably no irreversible damage	no		5, 12, 13, 17	Broncheal blocker placement mucus clearance, surfactant	Surfactant (12)	14, 15, 16	Yes
8	29, 37	Evaluation VATS (29) Indication for surgery (37)	20	Indeterminate sample	9, 13, 15, 17, 18, 19, 23, 35	Clots, deposition of fibrinolytics, mucus clearance, cultures		24, 25, 26	Yes
9	(-6)	Normal coronairy arteries	no						No (cardiac)
10	no CT		no						No (cardiac)
11	19	Severe destruction of parenchym	no		3, 10, 16	Mucus clearance, cultures		15 - 20	Yes
12	(-5)	Probably no irreversible damage	No		6	Exclusion several potential diagnoses (no alveolar proteinosis)		(-4,-3,-2)	Yes

M-pred, Methylprednisolone; VA, venoarterial; VATS, video assisted thoracic surgery
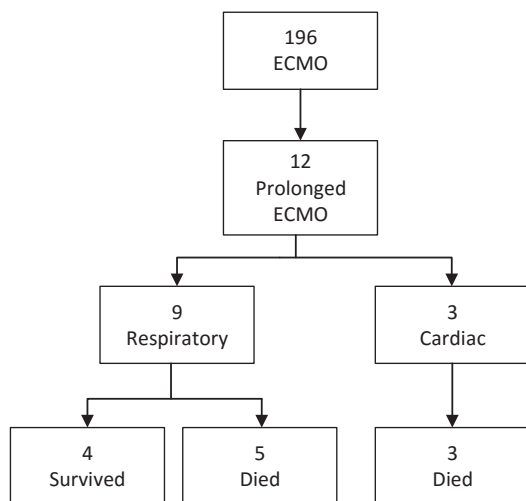
Figure 1: The Consort diagram showing the flow of patients

ECMO related complications

A median of 7 complications during the ECMO run had been reported for the survivors versus a median of 4.5 for the non-survivors. Table 2 shows the type and number of complications reported. There was no significant difference in the complications rate between survivors and non-survivors (table 3). ECMO system switches were done at a median of 13, 17, 22 and 32 days in 11, 5, 4, 2 patients, respectively.

Table 3: Types and numbers of complications.

complication	Nonsurvivors (n=8)	Survivors (n=4)	Combined (n=12)
Pulmonary	1	6	7
Mechanical	17	12	29
Hemorrhagic	3	6	9
Cardiovascular	10	3	13
Infectious	2	4	6
Renal	5	3	8
Metabolic	1	0	1
Total	39	34	73

Airway-related problems

During ECMO treatment, flexible or rigid bronchoscopy (N=35) was performed for diagnostic purposes in the nine respiratory failure patients and one cardiac patient (table 2). Indications for bronchoscopy were a sudden reduction of tidal volume or a persistent white out of the lungs. Median day for first bronchoscopy was after 6 (IQR 4.3-18) days on
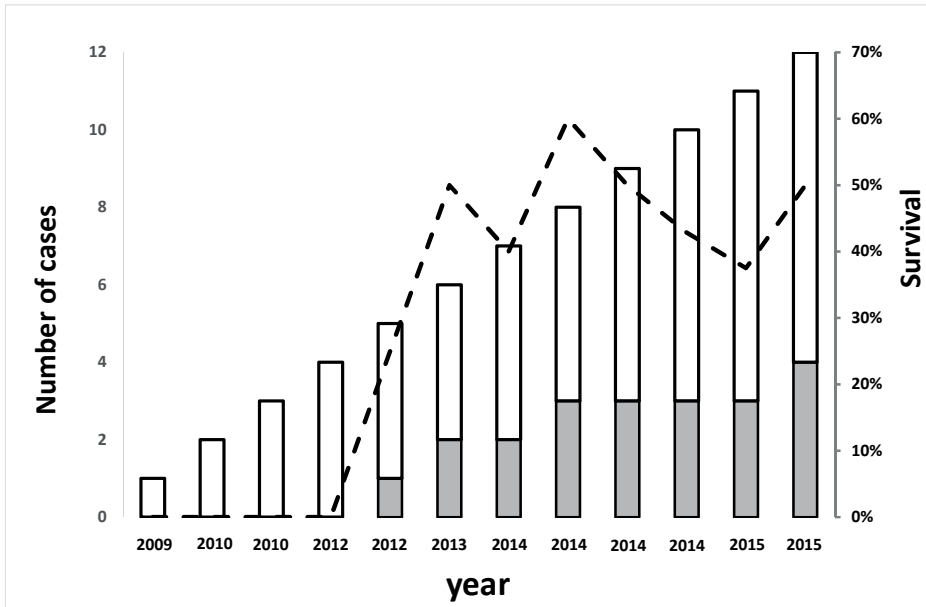
Diagnostic and interventional procedures during prolonged ECMO therapy in pediatric patients.

Figure 2: Cumulative survival in patients on prolonged ECMO.
The shaded bars represent the cumulative number of patients surviving ECMO (≥21 days). The open bars represent the non-survivors. The dotted line shows the cumulative survival.

ECMO. Three out of the 10 patients had severe bronchial obstruction. One patient (No. 7) had severe thick mucoid secretions and two patients had extensive trachea-bronchial obstruction with clots either due to bleeding following tracheotomy (patient No. 6) or lesions following duodenal feeding tube placement (patient No. 8).

One patient (No. 11) suffered from bronchoscopy-related bleeding, which had been treated with a topical vasoconstrictor. All other bronchoscopies were not associated with significant bleeding or other complications. The anticoagulation management complied with the standard departmental ECMO protocol and was not adjusted in preparation for bronchoscopy.

Diagnostic procedures
A total of nine chest CTs were made during prolonged ECMO, i.e. in 7 patients (6 with respiratory failure). In five patients a chest CT was also made prior to ECMO initiation (table 2). No major incidents were reported during transfer to the CT room and back. Timing of CT scans during ECMO varied widely with a median of 19 (IQR 9-20) days after initiation. The primary reason for a CT-scan was evaluation of reversibility of pulmonary damage. The details of utility and consequences of chest CT-scans are shown in table 2. In six respiratory patients, VV-ECMO provided only marginal sufficient oxygenation due to limitations of ECMO flow. These patients received a β blocker to reduce cardiac output

and in all patients oxygenation improved sufficiently so that additional interventions were not necessary.

Surgical procedures

Patient No. 2 underwent left thoracotomies on days 5 and 11 of ECMO for persistent blood loss and clots after placement of a chest drain for pneumothorax.

One patient (No. 8) underwent a Video-assisted thoracic surgery procedure, a phased bilateral thoracotomy for pleural empyema removal and for the resection of restrictive sub pleural thickening, and removal of organizing pleural exudates. All three operations were performed without any complications.

DISCUSSION

We show that prolonged ECMO in 12 pediatric patients is feasible and was associated with an overall survival of 33% and a 44% survival in patients with primary respiratory disease. Cessation of therapy was the major cause of death.

A survey of the ELSO registry learned that none of the neonates with acute respiratory failure on ECMO support for >43 days survived [1].

In a review of respiratory disease patients in the ELSO registry, the overall survival of these patients receiving prolonged ECMO was 38%. In this review, the highest survival (41%) was found in the patient group one month to one year of age [6]. Both our and previously published data indicate that prolonged ECMO treatment for respiratory failure patients is associated with acceptable survival. Still little is known neither about the time to recovery for specific diagnoses nor the moment to decide that further treatment is futile. Although useful and important for benchmarking, large data bases such as the ELSO registry unfortunately lack sufficient details to develop treatment guidelines.

A single center study on 22 pediatric patients supported with VA-ECMO for 28 days or more reported that ten (45%) patients were successfully decannulated. In 15 out of all 22 patients the primary indication for ECMO was cardiac failure, either post-operative low cardiac output syndrome (n=8) or cardiomyopathy/myocarditis (n=7) [5]. For six of them ECMO served as a bridge to transplantation and for one as a bridge to recovery.

In the above-mentioned study only four patients (19%) survived to discharge. It is a disturbing thought that none of the patients with respiratory failure survived. The authors suggest that "prolonged ECMO while waiting for healing of potentially recoverable lesions may lead to life-threatening complications and may even increase the risk of death" [5].

Management during prolonged ECMO

Attempts to extubate and mobilize patients were successful in only two patients. This issue is often raised at ECMO congresses, but the pediatric literature on this subject is still scarce [7, 8]. Deciding on extubation or allowing for spontaneous breathing during prolonged ECMO can be difficult if the patient shows rapid breathing and apparent dyspnea despite adequate gas exchange. We speculate that the Hering-Breuer reflex could play an important role in the disturbed breathing and success of extubation. Unsuccessful attempts at extubation could be due to near total collapsed lungs either as a result of infections or interstitial lung disease [9, 10]. Tracheostomy has been suggested to reduce duration of sedation on ECMO, but little is known about indications and the optimal timing of tracheostomy in pediatric ECMO patients [11, 12].

Testing the recruitability

Little data is available on the time to recovery in prolonged ECMO. To test the recruitability of the lungs after the first signs of improvement on plain chest films we instilled surfactant by bronchoscopy or perfluorocarbon via the tracheal instillation of in combination with recruitment maneuvers on the ventilator to open up the lung. The use of surfactant therapy during ECMO was recently described to be safe and to improve the respiratory system compliance [19]. Our standard ventilator resting settings during ECMO therapy are: peak 20 cm H2O and PEEP 10 cm H2O. After successful recruitment of the lungs PEEP was increased on the guidance of the attending intensivist. We do not know if this strategy will reduce days on ECMO and further studies on this procedure are warranted.

Deterioration of oxygenation due to increased cardiac output can be treated with beta-blockers [13, 14]. We used beta-blockers to prevent critical hypoxemia during prolonged VV-ECMO. Our policy is to start with esmolol to test the patient's response. To achieve prolonged β blockade we then switch to enterally administered propranolol to avoid propylene glycol related toxicity [15]. We try this strategy first before embarking on more invasive, potentially higher risk procedures like multiple cannulations or VA-ECMO.

Diagnostic and therapeutic interventions

Bronchoscopy
Diagnostic tests to determine the likelihood of native lung recovery are not yet available [16]. To confirm the diagnosis or to diagnose concurrent disease in our study population we made use of flexible and rigid bronchoscopies. A low threshold for bronchoscopy helped to diagnose the buildup of clots, which had gone unnoticed after tracheotomy in one patient and continuing nasopharyngeal bleeding after feeding tube placement

in another patient. Due to the absence of tidal volume in severe respiratory failure the ventilator volumes were not changed and clots could accumulate over time. Multiple prolonged bronchoscopy sessions, in combination with endotracheal administration of alteplase to induce thrombolysis of the clots, were necessary to clear the airways. With only one bleeding due to bronchoscopy the rate of complications was low and comparable to a case series on flexible bronchoscopy on ECMO [17].

CT scanning

In case of complete opacity of the plain film chest exam in patients with severe respiratory failure, chest CT can help to identify complications or underlying pathology. In a separate study, a chest CT was performed in 4.2% of the ECMO patients with respiratory disease, at a median 18 days after initiation of ECMO [18].

In our study, chest CTs helped in the decision to start surgical interventions (video assisted thoracic surgery or thoracotomy) or guided the application of regional surfactant instillation to assess the recruitability of the collapsed lung. Some scans had to be delayed due to instability of the patient, especially when ECMO flow was at maximal capacity due to the size of the cannulas and oxygenation was only marginal. If contrast CT scanning was performed, the ECMO flow was temporally minimized and contrast dose was optimized for adequate dose [18].

This is a retrospective case series covering a 7-year period during which several changes in ECMO management had been implemented that make it difficult to generalize the results. For example, we switched from roller pumps with silicone membranes to centrifugal pumps with PMP membranes. In respiratory failure patients we now preferably start with VV-ECMO and try to minimize the amount of additional cannulas. Still, this case series describes several steps in a single high volume pediatric ECMO center that might influence outcome in these patients.

CONCLUSIONS

Although guidelines on prolonged ECMO treatment are lacking and no clear-cut points of futility have been published, combinations of interventions and to the application of prolonged ECMO may improve outcomes of these patients over time. This may especially be true for respiratory patients, for whom we showed a 44% survival to discharge. No single item will dramatically improve outcome, but sharing of experiences and centralization of prolonged ECMO cases will potentially improve quality.

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Chapter 8

Risk and relevance of open lung biopsy in pediatric ECMO patients: the Dutch experience

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ABSTRACT

Background

Open lung biopsy can help differentiate between reversible and irreversible lung disease and may guide therapy. To assess the risk-benefit ratio of this procedure in pediatric extracorporeal membrane oxygenation (ECMO) patients we reviewed all open lung biopsies performed in the Netherlands in the period 1990-2014.

Results

In nineteen neonatal and six pediatric patients (0-15 years), twenty-five open lung biopsies were performed during the study period. In 13 patients (52%) a classifying diagnosis of underlying lung disease could be made. In another nine patients (36%) specific pathological abnormalities were described. In three patients (12%) only non-specific abnormalities were described. The histological results led to withdrawal of ECMO treatment in 6 neonates with alveolar capillary dysplasia/misalignment of pulmonary veins (24%) and in another 6 patients corticosteroids were started (24%) All patients survived the biopsy procedure. Hemorrhagic complications were rare.

Conclusion

An open lung biopsy during an ECMO run in neonates and children is a safe procedure with a minimum risk for blood loss and biopsy-related death. It can be very useful in diagnosing the underlying pathology and can guide cessation of ECMO treatment and thereby avoid continuation of futile treatment, especially in neonatal patients.

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BACKGROUND

In cases of severe respiratory failure in neonates and children, clinicians may be facing uncertainty about the underlying diagnosis, different forms of interstitial lung disease and thoracic X-rays not explaining underlying disease. An open lung biopsy procedure is potentially helpful to determine the cause of respiratory failure [1]. When on clinical grounds a diagnosis incompatible with life is expected, this procedure ideally should be performed before ECMO is initiated. Still, these patients' clinical condition seldom allows postponing the initiation of ECMO. Histological findings following an open lung biopsy may help clarify the underlying disease and deciding between continuation and withdrawal of ECMO or help in changing other aspects of the treatment. This important role in decision-making justifies performing the procedure during ECMO despite its potential drawbacks, such as bleeding and infection [2-4].

Surgical interventions during ECMO, such as repair of congenital diaphragmatic hernia, laparotomy and thoracotomy are possible without a high incidence of major complications [5, 6]. A few reports have already shown the usefulness and safety of an open lung biopsy in neonatal and pediatric ECMO patients, although study populations were small, ranging from 1-9 patients [3, 5, 7, 8]. Many questions pertaining to indications, timing and implications of biopsies remain. We reviewed data of all patients who underwent an open lung biopsy during ECMO in one of the two pediatric ECMO centers in a nationwide study in the Netherlands. The aim of the study was to describe the results of the biopsies and to evaluate the effect on the patient's treatment. Furthermore to describe complications (i.e. safety) of this surgical procedure performed on ECMO.

METHODS

The Erasmus MC institutional medical ethics review board approved the study, and waived the need for informed consent as only data from our patient data management system, i.e. prospectively collected physiological data and information on medication and support modalities, were used. Data of pediatric patients requiring ECMO in the period 1990-2014 were reviewed retrospectively. These patients have been treated either in the Erasmus MC-Sophia Children's Hospital Rotterdam (EMC) or the Radboudumc Amalia Children's Hospital Nijmegen (RAD). All patients <18 years undergoing an open lung biopsy during ECMO were included. Patients undergoing a biopsy before or after ECMO or post-mortem were excluded. Information was obtained about age at admission, gender, days of ECMO treatment when biopsy was taken, heparin administration, anticoagulation parameters, and blood loss in the first 24 hours after biopsy, histological findings and possible change in treatment.

We studied the effect of timing of the biopsy on treatment change by comparing data. Furthermore we studied the effect of heparin dosage, activated clotting time (ACT) and patient's age on the amount of blood loss (Pearson correlation). P-values <0.05 were considered statistically significant.

Coagulation management

Anticoagulation was adjusted according to the hospital protocols. All patients received unfractionated heparin as anticoagulation. One hour prior to a surgical intervention a loading dose (4 mg/kg) tranexamic acid was administered followed by a continuous infusion of 1 mg.kg^{-1}.h^{-1} during 24 hours postoperatively. Heparin infusion was adjusted to decrease actual ACT levels by 20 s. Platelet level was maintained greater than 100,000/mm^3; fibrinogen level was corrected when fibrinogen was < 1 g/l. These values were maintained for 24 hours and controlled directly postoperatively and at 6-8 hour intervals.

Surgery

Open lung biopsy was performed at the hospital's intensive care unit. Under general anesthesia, preferably a left lateral or ventral thoracotomy was performed. When a solitary right-sided lesion was present, the procedure was performed on the right side. A chest tube was placed at the discretion of the surgeon.

RESULTS

Between 1990 and 2014, 1008 pediatric patients were treated with ECMO (EMC n=602, RAD n=406). The majority of these patients were neonates (EMC n=440, RAD n=353). In total 25 patients (2.5%) underwent open lung biopsies during ECMO and were included in this study (EMC n=16, RAD n=9), of whom 11 were boys (44.0%) and 14 were girls (56%). None of these patients were diagnosed with congenital diaphragmatic hernia. Details of this group are shown in table 1. Nineteen of them were neonates (76%). Three patients had been born preterm (<37 weeks of gestational age); four with a low birth weight (<2500 grams). The lowest bodyweight at initiation of ECMO was 2200 grams. Other parameters of these preterm and low birth weight patients did not differ from those of the other patients who underwent lung biopsy. In all patients the indication for the biopsy was unexplained pulmonary hypertension and/or respiratory failure.

Biopsies and their relevance

A classifying diagnosis was provided by the biopsy in thirteen (52%) patients. Six patients were diagnosed with alveolar capillary dysplasia/misalignment of pulmonary veins (ACD/MPV), three with meconium aspiration syndrome (MAS), two with pulmo-

nary interstitial glycogenosis (PIG), one with chronic pneumonitis of infancy (CPI) and one with miliary tuberculosis (table 1).

Regarding the patients without a definite diagnosis, inflammation with or without fibrosis was reported for three of them and pulmonary hypertensive vascular changes for six - in two cases together with sepsis. Specific abnormalities were not reported for the remaining three patients.

Table 1: Individual patient data.

No	Age at admission (days)	Length of ECMO run (days)	ECMO day biopsy performed	Heparin dosage (EH/kg/h)	Blood loss (ml/kg)	Histological Diagnosis	Change in treatment?	Outcome	Deceased after biopsy (days)
1	0	13	7	13.3	10	ACD/MPV[#]	Stopped*	Died	6
2	0	7	6	35	245	ACD/MPV[#]	Stopped*	Died	1
3	1	5	3	6.7	4	Idiopathic PH	no	Survived	-
4	1	8	3	30	no drain	Non-specific[+]	no	Survived	-
5	1	16	9	32.5	11.6	Non-specific[+]	no	Survived	-
6	1	14	11	42.5	6.3	ACD/MPV[#]	Stopped*	Died	3
7	2	13	8	20	5.3	ACD/MPV[#]	Stopped*	Died	5
8	2	9	8	40	no drain	ACD/MPV[#]	Stopped*	Died	1
9	3	7	4	30	15.3	Undefined[+]	No	Survived	-
10	5	7	3	28.7	2.6	MAS[#]	No	Survived	-
11	6	17	11	22.2	1.7	MAS[#]	No	Survived	-
12	7	7	1	2.8	12.3	PH with sepsis	No	Died	6
13	7	9	8	52.5	4.4	ACD/MPV[#]	Stopped*	Died	1
14	9	15	6	20.6	14.5	MAS[#]	No	Died	37
15	10	15	3	18.5	1.5	PIG[#]	Cortico-steroids*	Died	86
16	10	11	10	32.5	4.6	PIG[#]	Cortico-steroids*	Died	1
17	13	8	1	37.5	0.5	CPI[#]	Cortico-steroids*	Survived	-
18	21	13	2	51	1.9	Idiopathic PH	No	Died	14
19	21	11	6	63.6	34.1	Idiopathic PH	No	Died	9
20	190	15	6	40	120	PH with sepsis	No	Died	9
21	196	14	7	44.6	no drain	Idiopathic PH	No	Died	19
22	480	18	8	40	0.6	Fibrosis and inflammation[$]	Cortico-steroids*	Died	15
23	1207	24	11	15	47.3	Miliary tuberculosis[#]	No	Died	64
24	1839	17	9	30	13.7	Fibrosis and inflammation[$]	Cortico-steroids*	Survived	-
25	5649	38	13	15	3.4	Inflammatory pneumonia[$]	Cortico-steroids*	Died	25

*PH = pulmonary hypertension, MAS = meconium aspiration syndrome, ACD/MPV = alveolar capillary dysplasia with misalignment of pulmonary veins, PIG = pulmonary interstitial glycogenosis, CPI = chronic pneumonitis of infancy. * = Biopsy result with consequences for treatment, # = classifying diagnosis, $= Descriptive diagnosis with consequences for treatment, + = Descriptive diagnosis without consequences for treatment.*

A post mortem examination was performed in four patients. In one patient the biopsy during ECMO showed minor alveolar damage without clear evidence for ACD/MPV. ECMO was withdrawn because of lack of clinical improvement and the patient subsequently died. In this patient suspicion of ACD/MPV remained high and therefore post mortem examination was performed and showed ACD/MPV. In one patient the post mortem examination confirmed the diagnosis ACD/MPV, in one the diagnosis fibrosis and inflammation was reported as "end stage fibrosis", and in one patient pulmonary interstitial glycogenosis in the biopsy was revised to pulmonary capillary hemangiomatosis post mortem.

In twelve patients (48.0%) the result of the biopsy had an effect on the therapy. In six of these patients (24.0%), all diagnosed with ACD/MPV, the results of the biopsy led to cessation of treatment and six other patients (24.0%) were given corticosteroids. In thirteen patients (52.0%) the treatment did not change.

Eight patients survived to discharge (32.0%) and 17 died (68%). Death was caused by the lethal disease ACD/MPV in six cases (35.3%). The other deaths could not be attributed to a fatal prognosis. The pathology contributing to death in this group was pulmonary hypertension (PH) in five, PIG in two and MAS in one patient. Three patients (all non-neonates) died of pneumonia or tuberculosis. The reason to perform an open biopsy in the three patients with a clinical diagnosis of MAS was uncertainty whether other underlying pathology was also present.

Timing of biopsy

The median length of the ECMO run was 13 (IQR 85 to 16) days. In the neonatal patients biopsy was performed at a median of 6 (IQR 3-8) days on ECMO and in the non-neonatal patients at a median of 8 (IQR 7 – 10) days. In all non-neonatal patients ECMO treatment was continued for at least a week after the biopsy.

In total, fourteen patients (56.0%) were on ECMO for less than a week when the biopsy was performed. In three neonates suspected of ACD/MPV the procedure was performed within two days after initiation of ECMO. Four neonates were taken off ECMO within two days after the biopsy. Three of them were diagnosed with ACD/MPV; the other was respiratory stable enough to be weaned from ECMO and survived.

Regarding the eleven patients (44.0%) in whom the biopsy was performed one week or later after initiation of ECMO, treatment was not changed in three, treatment was stopped in four (all diagnosed with ACD/MPV) and four were given corticosteroids. In the group of patients who were biopsied after a week of ECMO, the percentage of patients without a change of treatment was less compared to the early biopsy group (72% vs 28%), while the percentage of patients who were given corticosteroids was higher (14% vs. 36%) (table 2).

Table 2: Treatment policy after open lung biopsy performed either in the first week of ECMO or later

	Biopsy in first week of ECMO (n=14)	Biopsy after first week of ECMO (n=11)
No change in treatment	10 (72%)	3 (28%)
Stop treatment	2 (14%)	4 (36%)
Give corticosteroids	2 (14%)	4 (36%)

Safety of the procedure

The heparin dosage during the start of the lung biopsy varied from 2.8 to 63.6 IU/kg/h (mean 30.0); the ACT at time of biopsy varied from 154 to 247 seconds (mean 198). Median blood loss in the first 24 hours was 5.2 ml/kg (range 0.6-244.8). In five patients (20.0%) the blood loss was more than 15 ml/kg in the first 24 hours. When no drain was placed (n=3), we assumed that the blood loss would have been minimal.

There was no significant correlation between the heparin dosage or ACT and the amount of blood loss. Patient age did not correlate significantly with the total amount of blood loss or the blood loss per kilogram body weight (data not shown). Unfortunately in one patient biopsy was complicated by a sampling error showing thymus tissue, whereupon another open lung biopsy was performed the next day.
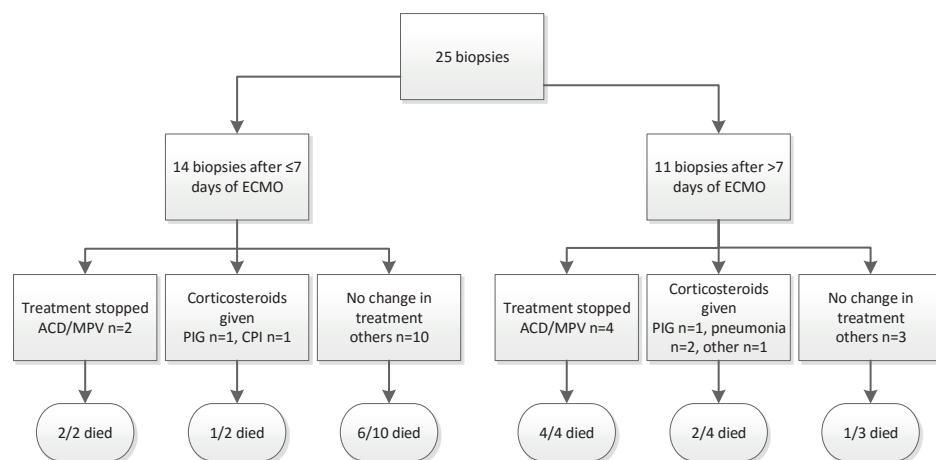
Figure 1: Consort of lung biopsies

DISCUSSION

We found that an open lung biopsy had been performed in 25 of all 1008 ECMO patients (2.5%) in the two pediatric ECMO centers in the Netherlands. In 22 cases (88.0%) the biopsy contributed to understanding of the pulmonary pathology, i.e. either a classifying diagnosis or specific pathological findings. In almost half of the cases the biopsy

result led to a change in therapy or cessation of ECMO. Biopsy within the first week resulted in a therapy change in four (28.6%) patients; a later biopsy resulted in a therapy change in eight (72.7%) patients. No significant complications of the procedure were reported. In the literature most reports deal with the issue of a solid pathology diagnosis to determine whether treatment should be continued or considered futile [5, 7].

As the majority of the biopsies were performed in neonates with therapy-resistant atypical PH, the subsequent requests to the pathologist involved primarily ACD/MPV. The longest reported survival in ACD/MPV is about 8 months with severe morbidity [9, 10]. The definitive diagnosis of ACD/MPV in our population resulted in withdrawal of life support therapy in all patients diagnosed as such. In rare cases ACD/MPV can also present beyond the neonatal age [11]. If ACD/MPV is considered, an open lung biopsy should ideally be performed before ECMO is initiated, thereby preventing possibly futile ECMO therapy [5, 12]. In this regard, a clinical algorithm has been proposed for infants with atypical PH who are suspected of ACD/MPV, defined as a near term born infant with a normal Apgar score, severe respiratory/circulatory failure ≤48 hours or a positive family history and having associated anomalies [12]. If ECMO has been started already, biopsy is recommended when no clinical improvement is seen after 7-10 days. Some patients can still be taken of ECMO successfully but then a biopsy is recommended in case of cardiopulmonary deterioration [12].

Our neonatal ECMO patients were found not clinically stable enough to undergo an open lung biopsy before ECMO initiation. In this situation when ACD/MPV or another lethal congenital pulmonary abnormality was highly suspected, the procedure was performed within the first seven days of the ECMO-run.

In eight of the twelve cases biopsied in the first seven days of ECMO, treatment had not been adjusted. In two of these patients life support was withdrawn after ACD/MPV was confirmed. One patient was diagnosed with CPI, for which corticosteroids were given and ECMO could be successfully stopped after eight days of ECMO. One patient with PIG was successfully decannulated before the results of the biopsy were known because respiratory support was hardly needed. However he died due to severe rebound PPHN shortly after decannulation.

The biopsy results were often clinically helpful, although a definite classifying diagnosis could be made in only 13 of the 25 cases. This is in line with prior findings [2, 3]. In twelve of the cases (48%) the biopsy result lead to a goal directed change of treatment. Of the patients without a change of treatment 7 of 13 (54%) died. On the other hand, in six patients the biopsy led to the diagnosis ACD/MPV. Consequently ECMO was stopped and therefore prolongation of futile treatment was avoided.

Safety of the procedure

Given our results, open lung biopsy during ECMO can be considered a safe procedure with no biopsy-related mortality and minimal morbidity.

Several studies reported about biopsies during ECMO [3, 5, 12]. None reported severe complications including biopsy-related deaths. Biopsy-related hemorrhagic complications occurred in respectively 2/5 and 1/9 patients [5, 12]. Jaklitsch et al. specifically reported about four patients who developed sepsis syndrome post-operatively, all of whom had an underlying infectious lung disease [3]. In our patient group we did not see any infectious complications.

CONCLUSIONS

An open lung biopsy during an ECMO run can be very useful in diagnosing the underlying reason for PH, especially in neonatal patients. In case of a fatal prognosis, ECMO can be stopped to avoid futile treatment. The histological diagnosis can lead to the prescription of corticosteroids, whereby treatment can be started earlier. In older patients, the chance of a fatal prognosis is minimal, but biopsy can guide therapy or diagnostic workup. Biopsy is recommended after seven days of ECMO, except when ACD/MPV or another lethal congenital pulmonary abnormality is highly suspected. In that case biopsy is recommended within the first week of ECMO. Performing an open lung biopsy during an ECMO run is a safe procedure with a minimum risk for blood loss and biopsy-related death.

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Chapter 9

Congenital diaphragmatic hernia; to repair on or off ECMO: that is the question

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ABSTRACT

Background:

Congenital diaphragmatic hernia (CDH) can be repaired on or off ECMO (extracorporeal membrane oxygenation). In many centers, operating off ECMO is advocated to prevent bleeding complications. We aimed to compare surgery-related bleeding complications between repair on or off ECMO.

Methods

All patients with CDH repair and ECMO treatment between January 1st 1995 and May 31st 2008 were retrospectively reviewed. Tranexamic acid was routinely given to all patients repaired on ECMO for 24 hours peri-operatively after 2003. Extra fluid expansion, transfusion or relaparotomy due to post-operative bleeding were scored as surgery-related bleeding complications and were related to the Extracorporeal Life Support Organization (ELSO) registry. We used Chi square test and t-test for statistics.

Results

Demographic data and surgery-related bleeding complications in the on ECMO group were not significantly different compared to the off ECMO group (p= 0.331) in our institute. In contrast, more surgery-related bleeding complications were reported by ELSO in their on ECMO group (p<0.0001).

Conclusion

In contrast to data from the ELSO registry, we did not observe significantly more surgery-related bleeding complications after CDH repair on ECMO. Using a specific peri-operative hemostatic treatment enabled us to perform CDH repair on ECMO with a low frequency of bleeding complications, thereby taking advantage of having the physiologic benefits of ECMO available peri-operatively.

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INTRODUCTION

Congenital Diaphragmatic Hernia (CDH) is a developmental defect in the diaphragm resulting in herniation of the abdominal viscera into the thorax. The incidence of CDH is approximately 1 in 2200 live births. The primary determinants of mortality in CDH patients are the amount of associated pulmonary hypoplasia (PH) and persistent pulmonary hypertension (PPH) (reviewed in Sluiter et al.) [1]. The treatment of CDH consists of preoperative stabilization directed towards optimal management of PH and PPH, followed by surgical repair of the diaphragmatic defect either with a patch or primarily [2].

Treatment of CDH remains a challenge for both pediatric surgeons and pediatric intensive care specialists. Survival of these children has improved substantially during the past decades. Better antenatal diagnosis and improvement of neonatal intensive care following the introduction of gentle ventilation strategies are responsible for this [3].

One of the treatment modalities for CDH in the neonatal intensive care is extracorporeal membrane oxygenation (ECMO). ECMO provides a temporary cardiopulmonary bypass system to overcome reversible lung failure. This respiratory failure can be attributed to the PPH and/or PH that are associated with CDH. [3,4,5]. Survival rates for CDH patients undergoing ECMO treatment currently range from 44-86% [6]. ECMO has been available in our institution since 1993. Indication for ECMO treatment of CDH babies in our institution is failure of maximal conventional therapy together with the fulfillment of strict ECMO criteria predicting an 80% mortality as published before by us [7]. Different criteria exist between institutions with respect to the moment to initiate ECMO treatment [8,9].

In 2002, the CDH study group reported that 54 % of CDH infants placed on ECMO underwent repair of the diaphragmatic defect while on ECMO [8]. Timing of CDH repair in patients requiring ECMO remains controversial and is dependent on local protocols [6]. One of the reasons to operate subsequent to ECMO treatment is the concern of surgery related bleeding complications. Hemorrhage in general is a major complication in neonates on ECMO [8].

The aim of our study was to determine the number of surgery-related bleeding complications in patients undergoing CDH repair on ECMO and to compare this number to those undergoing CDH repair off ECMO in our institution. We were able to perform this study because we started CDH repair after ECMO treatment, but switched to CDH repair while on ECMO after the institution of a new protocol to prevent bleeding complications in 2003. We observed no significant differences in surgery-related bleeding complications between the on ECMO and off ECMO CDH repair group in our institution. Subsequently we related these results to the results of the Extracorporeal Life Support Organization registry (ELSO registry) and found that there were a significantly higher

number of surgery-related bleeding complications in the on ECMO CDH repair group in the ELSO registry.

MATERIALS AND METHODS

Eligibility criteria

We retrospectively reviewed all charts of patients undergoing open abdominal CDH repair while on ECMO or after ECMO treatment in our institution between January 1st 1995 and May 31st 2008.

Surgery

During this study all patients were operated using an open CDH repair and all surgeons used a subcostal incision. Diaphragmatic defects were closed using either non-absorbable interrupted sutures or a Goretex® patch, upon the discretion of the attending surgeon. All patients undergoing repair on ECMO were operated in the ICU, whereas patients repaired off ECMO were operated in the operating room.

ECMO protocol in our institute

During the study period the same circuit, type of tubing and roller pump was used in all patients. Hemolysis was evaluated on a daily basis as discussed below in more detail. All patients in our institute are treated with tranexamic acid (Cyklokapron, Pfizer, The Netherlands) peri-operatively until 24 hours postoperatively since 2003. In detail, a loading dose (4 mg/kg) is given 1 hour prior to surgery and continued for 24 hours postoperative as a drip at 1 mg/kg/hr. Platelets are kept higher than 100.000, fibrinogen levels above 1 and ACT (activated clotting times) levels are decreased by 20% (normal 200-230 sec) for 24 hours. Clotting analysis following surgery includes platelets, hemoglobin, fibrinogen, APTT (activated partial tromboplastin time) and factor V Leiden and levels are corrected if necessary. In case fibrinogen levels are lower than 1, fibrinogen (Haemocomplettan, CSL Behring, The Netherlands) is given in doses of 0.5-1 g as a drip for 30 minutes.

Variables

The following demographic data were collected for all patients treated in our institution: gender, gestational age in weeks, birth weight in kilograms, APGAR score at 1 minute, side of the diaphragmatic defect (left/right), type of CDH repair (primary or patch), ECMO mode (venous-arterial or veno-venous) and age at repair in days.

The group of patients undergoing CDH repair on ECMO was compared to the group undergoing repair following ECMO. The primary outcome measure was the occurrence of surgery-related bleeding complications. Surgical site bleeding was scored positive if

extra fluid expansion, transfusion or relaparotomy due to postoperative bleeding were reported in the charts and data derived from our data management system (PDMS). This is a computer based prospective collection of all physiological parameters including amount of fluid, ventilation settings and eventually ECMO settings. Due to the change in timing of CDH repair over time in our institution, analysis was performed in 3 sub-groups, indicative of three different time periods, to try to eliminate other confounding treatment factors that might influence the primary outcome. The entire population was thus subdivided into three groups to indicate the number of patients operated on or off ECMO. During the study period the entry criteria for ECMO in CDH did not change.

Secondary outcome measures were length of stay in ICU in days, duration of mechanical ventilation in days, ECMO runtime in days, and duration of CDH repair in minutes.

Comparison to the ELSO registry

Data derived from the ELSO registry were used to correlate our data to a large international patient cohort. All patients in this registry from 1984 until 2008 that had ECMO treatment together with CDH repair were included and surgery-related bleeding complications were compared to those in our institution. Surgical site bleeding was scored positive according to the supplied data from the ELSO registry database.

Statistics

Three investigators collected data from patient charts and existing databases in an Excel-spreadsheet. Subsequently, all data were exported to SPSS for statistical analysis. Normally distributed continuous variables were compared using a Student's t-test, while non-normally distributed variables were analyzed using the Mann-Whitney-U non-parametric test. To compare categorical variables a Chi square test and Fisher's exact test were performed. A p-value < 0.05 was considered statistically significant.

The Institutional Review Board of ErasmusMC-Sophia, Rotterdam, The Netherlands, approved the study.

RESULTS

Results ErasmusMC-Sophia

Between January 1995 and May 2008, 195 CDH patients were admitted to our institution. Of this group, 129 (66,2%) underwent repair of the diaphragmatic defect. Initially, survival was 50% and has increased over the years to 85% during the last three years [10]. Of all the patients undergoing CDH repair, 51 (39.5%) required ECMO treatment. Three patients underwent CDH repair and required ECMO treatment afterwards; these

patients were excluded from this study. All patients underwent venous-arterial ECMO. Demographic data are summarized in Table 1. Sex, mean gestational age at birth, mean birth weight, side of the hernia and median APGAR score after 1 minute were not significantly different.

Table 1: Demographic data ErasmusMC-Sophia

	Repair on ECMO	Repair off ECMO	p-value
n	32	16	
Birth weight in kilograms (mean±SD)	3,04 (±0,65)	3,21 (±0,43)	0,714[a]
Gestational age in weeks (mean ±SD)	38,63 (± 1,76)	39,0 (±1,15)	0,121[a]
Gender (M/F) (number)	21/11	8/8	0,297[b]
Side Hernia (left/right)	15/1	29/3	0,348 [b]
Median APGAR score at 1 minute (IQR)	5 (2)	7(4)	0,124[c]

a: T-test, b: Chi square, c: Mann- Whitney-U non parametric test

In our institution, surgery-related bleeding complications following CDH repair on ECMO (4 out of 32 patients (12.5%)) were higher, but not significantly different from surgery-related bleeding complications following repair off ECMO (1 out of 16 patients (6.25%)) (p=0.652, see Table 2). Changes in management over time could result in potential bias and therefore a subgroup analysis was performed for three different time periods: 1995-1999, 2000-2004 and 2005-2008.

Since 2005, CDH repair in patients requiring ECMO was only performed on ECMO (Figure 1). In contrast, during the first study period when ECMO was instituted (1995-1999), half of the patients had CDH repair off ECMO.

Results surgical site bleeding ELSO registry

The group of patients undergoing CDH repair on ECMO was bigger than that off ECMO in the ELSO registry during all periods. The ELSO registry registered surgical site bleeding in their database for all patients that had repair of their CDH. Table 2.2 demonstrates that 616 out of 2230 patients (27.6%) undergoing CDH repair on ECMO were reported to have surgical site bleeding, compared to 34 out of 1109 patients (3.07%) undergoing CDH repair off ECMO in the ELSO registry between 1984 and 2008 (p<0.0001).

Secondary outcome measures ErasmusMC-Sophia

Surgical data

Surgical data are summarized in Table 3. The number of patients undergoing CDH repair using a patch was 42 (87.5%) and was not significantly different in both groups. In the repair on ECMO group, 6.6 % (2 out of 30) had a primary repair compared to 12.5% (2 out of 16) in the repair off ECMO group (p= 0.602). For two patients it was not known

Table 2: Bleeding complications ErasmusMC-Sophia versus ELSO registry

2.1: ErasmusMC-Sophia

	Surgery related bleeding complications ErasmusMC-Sophia		Total
	Yes	No	
On ECMO	4	28	32
Off ECMO	1	15	16

2.2 ELSO registry

	Surgery related bleeding complications ELSO registry		Total
	Yes	No	
On ECMO	616	1614	2230
Off ECMO	34	1075	1109

Table 3: Surgical data

	Repair on ECMO	Repair off ECMO	P -value
Primary/patch closure*	2/28	2/14	0,602[a]
Median time of repair in hours (IQR)	2,00 (0,65)	1,9 (1,07)	0,188[b]
Median age at repair in days (IQR)	5,0 (5,0)	20,5 (22,50)	0,000[b]

*: missing values: for two patients information on whether a patch was used for the repair could not be retrieved, a: chi square, b: Mann-Whitney *U* non-parametric test

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whether repair was done by using a patch or by primary closure of the diaphragmatic defect. Operating time between the two groups was also not different. Median operating time was 2.0 hours in the repair on ECMO group compared to 1.9 hours in the repair off ECMO group (p=0.188). Patients undergoing CDH repair on ECMO were significantly younger compared to those repaired off ECMO. Median age at repair in the repair on ECMO group was 5.0 days (IQR 5) compared to 20.5 days (IQR 23) in the repair off ECMO group (p< 0.0001)

ECMO / ventilation data

There was no difference in days of admission to the ICU and duration of mechanical ventilation between the two groups (Table 4). Patients undergoing repair on ECMO had a median ICU stay of 37 days (IQR 59) compared to 57 days (IQR 62) in the group that had repair after ECMO (p=0.404). The median number of days requiring mechanical ventilation was 21 days (IQR 28) in patients undergoing repair on ECMO compared to 28 days (IQR 34) in those undergoing repair off ECMO. However, ECMO runtime was significantly less in the repair off ECMO group. Median ECMO runtime in the group that had repair on ECMO was 9.77 days (IQR 8) compared to 7.11 days (IQR 5) in the off ECMO group (p=0.041).

Congenital diaphragmatic hernia; to repair on or off ECMO: that is the question.

Table 4: ECMO/ventilation data

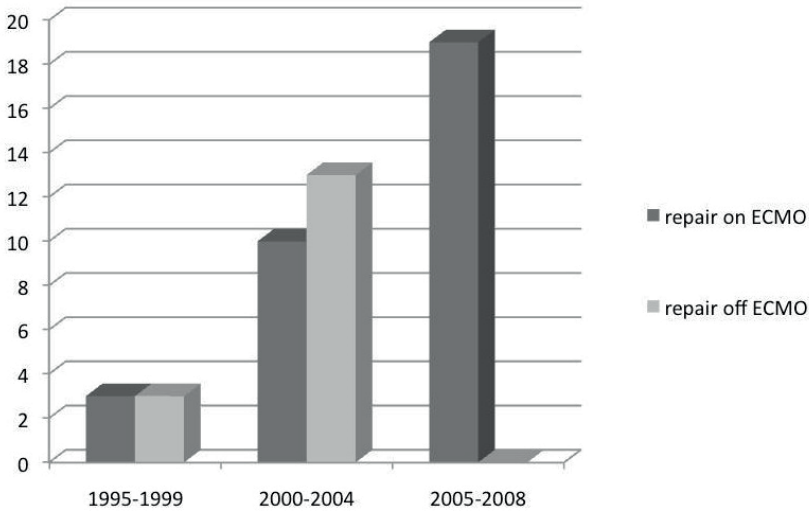|	Repair on ECMO	Repair off ECMO	p-value
Median ECMO runtime in days (IQR)	9,77 (8)	7,11 (5)	0,041[a]
Median time on mechanical ventilator in days (IQR)	21 (28)	27,67 (33,63)	0,552[a]
Median time on ICU in days (IQR)	37 (59,23)	57 (62)	0,404[a]

Figure 1: The number of patients operated on or off ECMO during three different time periods. After 2005 all patients were operated on ECMO
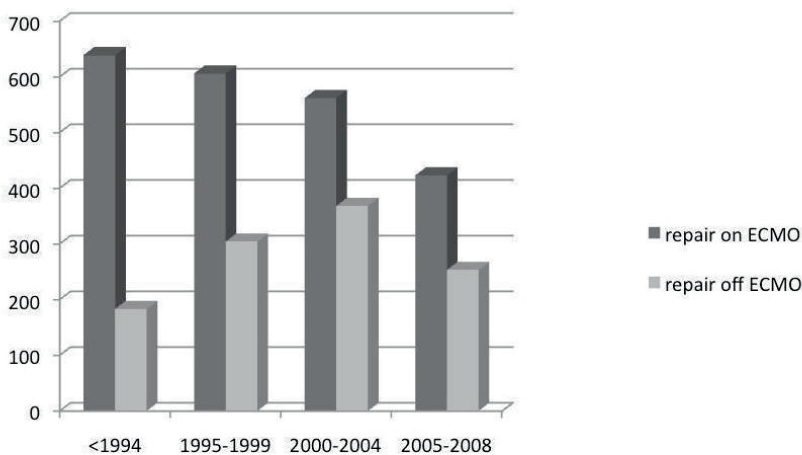

Figure 2: The number of patients operated on or off ECMO during four different time periods, as registered in the ELSO registry database

DISCUSSION

To our knowledge this is the first study to demonstrate the feasibility of neonatal CDH repair on ECMO using a specific anticoagulant protocol. Although we found a higher bleeding complication rate in the group repaired on ECMO, this percentage was not statistically significant and lower than the number reported in the ELSO registry. This is despite the fact that the definition of surgery-related bleeding complications was less well defined in the ELSO registry as compared to our group. This corroborates with previous reports, which observed more surgery-related bleeding complications when repair was done on ECMO [11,12, 13]. In addition, we observed a trend towards a shorter length of stay in the ICU in the repair-on ECMO group as well as a trend towards a shorter duration of mechanical ventilation in the repair-on–ECMO-group compared to the repair off ECMO group. However, changes in management over time have certainly contributed [10, 14].

Results from the ELSO registry indicate that nowadays more CDH patients treated with ECMO are operated on ECMO than off ECMO internationally. Van der Staak et al. reported already in 1997 that repair on ECMO may increase the risk of bleeding complications and that these complications can be a hallmark of poor outcome. The administration of Tranexamic acid (TEA) is effective in reducing hemorrhagic complications, but might increase the risk of thrombotic complications [11]. However, after introducing our specific peri-operative bleeding prevention protocol, we did not observe more clotting problems in the ECMO circuit and/or oxygenator. Since the institution of a protocol to prevent complications from bleeding in 2003 we used TEA during all our repairs on ECMO, and data from the ELSO registry database did not indicate the use of TEA. In addition to the importance of antifibrinolytic agents in a specific peri-operative bleeding prevention protocol like ours, the importance of a delicate and meticulous surgical technique should not be underestimated.

Vasques and Cheu report that surgery-related site bleeding complications as well as overall hemorrhagic complications were significantly higher in patients undergoing CDH repair on ECMO. These data included also data from the ELSO registry and were derived from 88 ECMO centers during the period of January 1989 until December 1991. In addition, they report that patients repaired on ECMO are more prone to have acidosis and hypoxia compared to those that had repair off ECMO [12]. However, both acidosis and hypoxia were associated with hemorrhage and the authors did not report significant differences in these parameters between both groups. Another retrospective study performed by Sigalet et al. in 1995 demonstrated that in a group of 60 CDH patients, the 9 patients that had repair on ECMO required a significantly higher transfusion volume and they advice against repair of CDH on ECMO [13].

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One of the limitations of our study is the small number of patients (N=48). The low observed frequencies of bleeding complications in both groups of our series makes it difficult to draw firm conclusions about significant differences. However, a more relevant finding from our study is that we observed only 12.5% bleeding complications in the group repaired on ECMO, despite the fact that we used a broader definition of bleeding complications than the ELSO registry.

Another limitation is the retrospective character of our study. At ErasmusMC-Sophia surgery-related bleeding complications were scored positive if extra fluid expansion, transfusion or relaparotomy due to post-operative bleeding were specifically reported in our prospective computerized patient data management system (PDMS). Although till 2003 information was retrieved from the patient charts, our data were very reliable from that time point onwards as patients were operated in the ICU and therefore all data including extra fluids are integrated prospectively in PDMS.

The data from the ELSO registry was lacking any demographic data and potentially very different among centers. Moreover, the ECMO and anti-coagulant protocol used in these patients was not reported. Differences in anti-coagulant protocols could therefore result in substantial bias in this analysis, because this was found to be a major determinant of hemorrhagic complications in our series at ErasmusMC-Sophia. Surgery-related site bleeding complications reported in the ELSO registry were not well defined, and data in this registry originate from different hospitals, so correcting for these data was not possible. Because we used a broader definition of surgery-related site bleeding complications, our bleeding complications are probably overestimated as compared to the norm of the ELSO registry. At a glance, our bleeding complications in the on-ECMO group were lower than reported in the ELSO registry: 12.5% versus 27.6%. We choose not to compare our numbers statistically to the numbers of the ELSO registry due to a lack of a clear definition of surgery-related bleeding complications in the latter group.

Days on ICU together with duration of mechanical ventilation were reviewed as secondary outcome measures in our series. We observed a trend towards a shorter ICU stay and a shorter period of mechanical ventilation in the patients repaired while on ECMO. This trend was not statistically significant and is probably more related to modernized ICU management than to the actual repair on ECMO. Due to the small sample size, matching of patients was not possible. These parameters were not measured in the population from the ELSO registry.

Although this is a retrospective study which has its limitations as stated above, conclusion remains that in a single center in a 13 years experience period no major surgery related bleeding complications are seen in our institution while performing repair of CDH on ECMO. In addition, we see a trend towards shorter ICU stay and a shorter period of requiring mechanical ventilation. In the past 5 years all patients requiring ECMO were operated on ECMO for their CDH in our institute, without major bleeding complications.

In conclusion, CDH repair on ECMO is feasible and using a specific anticoagulation protocol with tranexamic acid resulted in a low complication rate. A large prospective study should be performed to evaluate whether there are indeed differences in surgery-related bleeding complications and which coagulant protocol should be used to perform repair on ECMO as safely as possible.

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Chapter 10

Pharmacotherapy in neonatal and pediatric extracorporeal membrane oxygenation (ECMO)

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ABSTRACT

ECMO support is an established lifesaving therapy for potentially reversible respiratory and/or cardiac failure. Improvement of outcome depends on effective treatment of the primary diagnosis and complications. Adequate drug therapy is important in reaching these goals. Pharmacokinetic and pharmacodynamic data in neonates and older children on ECMO are sparse. Most studies show altered volume of distribution and clearance for the drugs studied. This article gives an overview of the available PK and PD studies in neonates and children on ECMO, suggests possible mechanisms of altered PK and PD and identifies areas of interest for further research.

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INTRODUCTION

Pharmacological data in the pediatric population is sparse, especially within the pediatric ICU [1]. Dosing of frequently used drugs in the intensive care unit such as sedatives, analgesics, antibiotics and inotropes are partly based on non ICU pediatric or adult patients. A special category of patients are those receiving prolonged cardiopulmonary support where pulmonary and/or cardiac functions are mechanically supported using extracorporeal circuits.

Extracorporeal life support or extra corporeal membrane oxygenation (ECMO) is a technique for providing life support in severe but potentially reversible cardio-respiratory failure in patients with an expected mortality greater than 80% [2].

First pioneered in cardiopulmonary bypass during cardiac surgery, extracorporeal life support has been used as prolonged cardiopulmonary support in neonates since 1976 [3] with a proven survival benefit in neonates and adults [4, 5]. New diseases, such as the recent H1N1 influenza pandemic, results in an increased need for ECMO support in young adults as well as children with severe pulmonary failure [6].

ECMO provides extracorporeal gas exchange and circulatory support by pumping blood from the patient through an artificial circuit comprising of tubing, a pump, an oxygenator and a heater. The oxygenator is used to oxygenate the blood and extract carbon dioxide. Blood is drawn from a venous access site, preferably a central catheter positioned in the right atrium, and returned either into the right atrium via a double lumen catheter (venovenous ECMO) for respiratory support, or via the carotid artery (venoarterial ECMO) for cardiopulmonary support. Alternatively venous or arterial access can be achieved via the femoral vein or artery.

ECMO support is used in a variety of diagnoses. Neonatal indications include congenital diaphragmatic hernia, meconium aspiration syndrome, persistent pulmonary hypertension of the newborn, congenital heart defects and sepsis. Pediatric and adult diagnoses include cardiomyopathy, cardiomyositis, sepsis, viral and bacterial pneumonia and acute respiratory distress syndrome. ECMO support can also be used as a bridge to recovery or organ transplant. Although it may be life-saving in critically ill patients, ECMO treatment is associated with several complications and co-morbidity. Up until July 2011 ECMO support has been initiated in a total of 46.509 patients worldwide, including 29.839 neonates, 11.779 pediatric patients and 4891 adult patients, with an overall survival of 62 %. (Extracorporeal Life Support Organization (ELSO) registry report July 2011)

Overall survival after ECMO support is 62%, and mortality is primarily associated with the underlying disease and complications on ECMO such as bleeding, renal failure and infections. [7-11] Prolonged ECMO support (eg > 10 days) is associated with increased complications (such as nosocomial infections [12-21]) and poor outcome [11, 22].

Surgical and pharmacological treatment of the underlying disease and occurring complications remains pivotal in the overall management of ECMO patients. Effectiveness and

complications of these treatment modalities are main determinants of outcome, apart from the ECMO procedure itself. ECMO indications may be expanded to include new diseases that necessitate specific medication. The H1N1 pandemic emphasized the lack of knowledge of pharmacokinetic (PK) and pharmacodynamic (PD) properties of antiviral drugs in these patients. It was unclear if therapeutic levels could be achieved and if so if any dose adjustment was necessary. The same holds true for a myriad of other regularly used drugs.

This article gives an overview of the available PK and PD studies in neonates and children on ECMO, suggests possible mechanisms of altered PK and PD and identifies areas of interest for further research.

PHARMACOKINETIC STUDIES IN NEONATAL AND PEDIATRIC ECMO

Patients on ECMO generally receive more than ten different drugs per day [23]. These patients are heparinized to prevent clotting of the ECMO circuit, most often receive sedatives and analgesics to alleviate pain and discomfort, diuretics to manage fluid overload and antibiotics or antiviral medication to treat infections [23]. PK and PD data of widely used drugs on ECMO are sparse; concentration versus time profiles and concentration effect relationships have not systematically been evaluated.

There are several factors that may influence PK and PD. By connecting patients to an extracorporeal life support system the circulating volume of the patient is increased due to the added blood volume necessary to fill the circuit. There are different ECMO circuit components available with varying materials, priming volumes and total surface area. The total volume of an ECMO circuit may increase the total circulating volume of a patient by between 5 and 100%, which influences blood composition, coagulation, circulation and pharmacokinetics. ECMO may influence organ perfusion and organ function, with a potential influence on drug absorption, distribution, metabolism and elimination. Patients on ECMO are critically ill, which in itself changes PK and PD [24-26]. Whether ECMO patients differ from critically ill non ECMO patients in this regard remains to be determined. Profound changes in drug metabolizing enzymes, organ function and body composition take place in early infancy. This results in age and drug specific PK changes [27, 28]. These changes should be taken into account when evaluating PK changes during ECMO treatment.

Since the use of extracorporeal life support there have been reports showing altered pharmacokinetics for a variety of drugs. Most available studies have demonstrated altered pharmacokinetics with changes in volume of distribution as well as clearance [29-43]. These studies have been summarized in a review article in 2003 [23]. The number of drugs studied has increased since then, shedding more light on possible mechanisms underlying PK changes in ECMO patients. Table 1 gives an overview of all the PK studies

in children on ECMO. Antibiotics, especially gentamicin and vancomycin, and sedatives and analgesics are the most studied drugs and will be discussed in the next section.

Table 1: PK and PD studies in ECMO patients

Drugs	No.	studies	Effect on PK-PD
amiodarone	1/n	[117]	Yes
bumetanide	11/n	[43]	Yes
caspofungin	2/a	[74]	No
caspofungin	1/a	[73]	Yes
cefotaxime	37n/i	[65]	Yes
esmolol	1/i	[118]	Yes
fentanyl	12/i	[83]	Yes
furosemide	7/n	[105]	No
gentamicin	29/n	[32]	Yes
gentamicin	18/i	[33]	Yes
gentamicin	17n/i	[34]	Yes
gentamicin	15/n	[35]	Yes
gentamicin	10/n	[36]	Yes
midazolam	20/n	[29, 82]	Yes
midazolam	20/n	[57, 85]	Yes
morphine	11n/i	[31]	No
morphine	7/n/i	[47]	Yes
morphine	14/n	[30, 101]	Yes
nesiritide		[119]	Yes
nicardipine		[120, 121]	No
oseltamivir	3/ch	[71]	No
phenobarbital	1/n	[111]	Yes
prostaglandin E1		[122]	Yes
ranitidine	13/n	[41]	Yes
ribavirin	1/n	[75]	yes
sildenafil	23/n	[110]	Yes
theophyline	75n/ch	[42]	Yes
ticarcillin-clavulanic acid	2/ch	[76]	No
vancomycin	12/i	[39]	Yes
vancomycin	15/n	[37]	No
vancomycin	45n/i/ch	[38]	Yes
voriconazole	2/a	[74]	Yes
voriconazole	1/ch	[72]	Yes
voriconazole	1/a	[83]	Yes

No= number of patients included in study /n neonates, i=infants, ch=child >2years, a=adult

Table 2a: Differences between in-vitro studies

Studies		Pump	No. of circuits	priming	tubing	Additional material	oxygenator	duration of study (h)
1 [49]	a	Roller pump	3	blood	Medtronic ¼ In superTygon®	Medtronic® Heat Exchanger bladder, hemofilter	Medtronic® 1,5 m2 silicone membrane	3
	b	Centrifugal pump	2	blood	Intercept® CLASS VI ¼ in	Medtronic® Heat Exchanger bladder, hemofilter	MEDOS HILITE® 800LT RHEOPARIN®	3
	c	Roller pump	2	blood	Medtronic 3/8 in superTygon®	Medtronic® Heat Exchanger bladder, hemofilter	Medtronic® I-2500-2A 2,5m2 silicone membrane	3
	d	Roller pump	2	blood	Medtronic ¼ In superTygon®	Medtronic® Heat Exchanger bladder, hemofilter	Medtronic® 1,5 m2 silicone membrane	3
2 [45]	a	Roller pump	?	cristalloid	Medtronic ¼ In superTygon®		Medtronic® 1,5 m2 silicone membrane	24
	b	Roller pump	2	blood	Medtronic ¼ In superTygon®		Medtronic® 1,5 m2 silicone membrane	24
3 [48]	a	Roller pump	1	blood	?		?	4
	b	Roller pump	1		?		?	
4 [44]	a	Roller pump	3		Medtronic ¼ In superTygon®		Medtronic® 0,8 m2 silicone membrane	6
	b	Roller pump	3		Medtronic ¼ In superTygon®		Medtronic® 0,8 m2 silicone membrane	
5 [50]		Roller pump	1	cristalloid	Norton S-65-HL PVC superTygon®	ECMOTherm II Avecor, bladder, Heat exchanger	ECMO 0800 Avecor	0,5

In Vitro studies

Absorption of drugs to the material of the ECMO systems may contribute to the reported altered pharmacokinetics. Absorption rates have been tested for several drugs [29, 44-47]. In vitro tests show significant absorption, especially of lipophilic drugs, to different ECMO circuits. Dagan et al. described significant drug loss in two blood primed closed looped systems [48]. Later studies confirmed significant drug loss in ECMO systems [45, 49, 50].

Our own group demonstrated that absorption was correlated with lipophilicity, where higher Log P values resulted in increased drug loss [49].

Several authors tried to identify the major absorption point of drugs within the ECMO circuit. Midazolam and fentanyl seem to be mostly absorbed in the membrane, especially silicone based membranes [50, 51]. Silicone membranes have been shown to highly increase drug loss of these drugs compared to the newer microporous polypropylene membranes [49, 52]. Intriguingly Preston et al. found significant fentanyl absorption in the PVC tubing of an ECMO circuit, with only a 6% increase in drug loss after addition of a microporous polypropylene membrane [53]. There is also evidence that different coatings may influence absorption rates and therefore PK of certain drugs [54], although others report no clear effect on drug absorption [55].

There are ma.ked differences in drug absorption between the different in vitro studies. (Table 2) Some studies show a rapid decrease of drugs within minutes of injection [48, 49, 56], whereas others find a slowed decrease over time [45, 50].

Study design differs significantly between studies from single component testing to full blood primed ECMO circuits. All set-ups have their advantages and disadvantages. Single component testing gives us information concerning saturation of binding sites and enables calculation of a theoretical maximum drug loss for an ECMO circuit, whereas blood primed circuits reflect daily clinical practice and enable comparison of new and used ECMO circuits.

There are some conflicting data concerning saturation effects of binding sites in used ECMO systems. There is a clear saturation effect of binding sites of PVC tubing and silicone membranes when tested separately [50]. Furthermore Dagan et al. showed decreased drug loss in clinically used ECMO circuits compared to newly primed circuits. [48] This could however not be confirmed by others [44, 49]..

Translating in vitro results to clinical practice remains difficult. There is a large discrepancy between drug absorption observed in *in-vitro* tests and the increased volume of distribution observed in the pharmacokinetic studies in neonates on ECMO [57]. Whether this is due to rapid distribution in body fat tissues or whether continuous infusion rates are higher than absorption rates in ECMO circuits remains uncertain.

In conclusion, ECMO circuits affect drug availability by absorption to components of the ECMO circuit. Circuit material, size and priming fluid composition could affect the

Table 2b: In vitro studies performed with ECMO circuits

Study No.	1a	1b	1c	1d	2a	2b	3a	3b	4a	4b	5
Drugs*	*	*	*	*	*	*	*	*	*	*	*
Ampicillin					72%	15%					
Cefazolin					21%						
Cefotaxime	16%	2%	51%	22%							
Dopamine						30%					
Diazepam											50%
Epinephrine					97%						
Fentanyl	100%	66%	100%	99%	87%	100%					
Fosphenytoin					18%	31%	43%	0%			
Gentamicin							10%	0%			
Heparin					33%	53%					
Lorazepam									30%	50%	25%
Meropenem	17%	11%	42%	27%							
Midazolam	99%	36%	99%	0							75%
Morphine	76%	68%	69%	70%	18%		36%	16%	20%	40%	
Paracetamol	66%	56%	55%	53%							
phenobarbital							17%	6%			
Propofol											100%
Vancomycin	32%	33%	46%	46%			36%	11%			
Voriconazole						71%					

* percentage of drug loss

increase in volume of distribution upon cannulation [50, 56, 58-60]. Silicone membranes have a higher capacity for drug absorption compared to the newer microporous membranes. Given that most pk studies used silicone based membranes, extrapolation of these data to the newer circuits and oxygenators should be done with caution. The in vitro results with rapid absorption within minutes after injection indicate that highly lipophilic drugs should not be administered via the ECMO circuit. The relationship between log P values and absorption will enable clinicians to predict the extent of absorption of different drugs, based on their chemical properties. Future studies need to address maximum absorption rates and need to try to incorporate in vitro data into pharmacokinetic models. The development of new ECMO circuits or ECMO circuit components may influence PK and drug absorption should be evaluated for these components.

Antimicrobial drugs

Infections remain a significant problem in neonates and children on ECMO, with 37% of patients with a proven infection prior to, or during ECMO support. Nosocomial blood stream infection (BSI) rates in ECMO patients range from 14% or 23 BSI/1000 ECMO

days to 9% or 13 BSI/1000 ECMO days depending on definitions [12]. Even using Center of Disease Control (CDC) criteria for nosocomial BSI, infection rates are still 5-10 times higher than the central line related BSI in non ECMO critically ill children [14, 61]. Nosocomial infections are associated with higher mortality, although most patients die due to the underlying disease [62].

Besides the use of preventive measurements there is an urgent need for PK data on antibiotics.

Efficacy of antibiotics whose effectiveness depends on peak concentrations (such as aminoglycosides) may be reduced by increased volume of distribution. At the same time, the risk of adverse events related to trough levels may be increased due to reduced clearance. Antibiotics whose effectiveness depends on time above minimal inhibitory concentration (such as cefalosporins and vancomycin) may be affected by differences in drug clearance as well as volume of distribution. Both undertreatment and toxicity need to be considered when dosing antibiotics on ECMO. To guide antibiotic dosing regimens in ECMO patients, PK models that take into account ECMO-related PK-changes need to be developed.

Gentamicin

Several studies describe gentamicin PK in neonates and infants on ECMO. The five studies published so far show an increased volume of distribution ranging from 0.51 L/kg [36] to 0.748 L/kg [32-35] compared to 0.45 L/kg in post ECMO patients and critically non ECMO patients. [34, 35] Clearance on ECMO was decreased compared to the clearance in the post ECMO period: +/- 45 ml/kg/hour vs. of +/- 60 ml/kg/hour [34, 35]. Choosing suitable control patients may be difficult since gentamicin PK varies, especially in the new-born period. Compared to term septic neonates gentamicin clearance on ECMO seems to be comparable or slightly increased [32-36, 63]. All studies showed an increased elimination half-life of 10h compared to 5-6 hours in non ECMO patients.

Dosing regimens from literature do not reflect current insights into aminoglycoside dosing in neonates and infants [64]. The altered PK with decreased volume of distribution and increased elimination half-life make aminoglycoside dosing a challenge in ECMO patients.

Vancomycin

In 1990 Hoie and colleagues were the first to describe vancomycin PK in six neonates on ECMO. They found a volume of distribution of 0.68 l/kg and a clearance of 1.1 ml/kg/min, resulting in an elimination half-life of 7.71 h [40]. All patients had a normal creatinine level. Amaker et al. used a two compartment model to describe the data of 12 neonates on ECMO with a volume of distribution of 1.1 l/kg and a mean vancomycin clearance of 0.78 ml/ kg/ min, resulting in an elimination half-life of 16.9 hour. They found that

vancomycin clearance was strongly correlated with renal function [39]. These findings were confirmed by Mulla et al. who improved model fit by modelling clearance as a nonlinear function of serum creatinine. [38] They developed a dosing regime based on age and renal clearance as described by serum creatinine.

A retrospective study of 15 neonates on ECMO found a prolonged elimination half-life in the ECMO group compared to non ECMO controls (8.3h vs. 6.5h). However volume of distribution and clearance alone did not show significant differences [37]. Based on the available literature vancomycin dosing intervals should be based on age and renal function. Drug monitoring should be used to adjust dosing.

Cefotaxime

Cephalosporins are widely used in pediatric patients including those on ECMO. Using NONMEM and sparse sampling, our group was able to describe cefotaxime PK in neonates and young children. [65] The cefotaxime clearance estimate found in ECMO patients (0.36 L/h) was similar to those for non-ECMO treated full-term neonates, which vary from 0.20-0.55 L/h. [66-68] The distribution volume however was larger than in non-ECMO patients (1.82 L vs. 0.68-1.14 L) [67, 68]. These differences could be caused by hemodilution due to the additional blood volume or capillary leakage of protein-bound drug into the extravascular compartment, especially in the early phase of ECMO (24h-36 h after cannulation).

Despite the increased distribution volume, the percentage of time above the minimal inhibition concentration was at an effective level for all patients. Dose adjustments therefore do not seem to be necessary in ECMO patients. There was considerable variability in plasma concentrations of both cefotaxime and the metabolite. The altered PK found in patients on ECMO as well as the inter-patient variability did not influence dose requirements; probably due to the large therapeutic window of cefotaxime, which has allowed relatively high dosing in non-ECMO patients without adverse effects. The only covariates with a statistically significant correlation were body weight and time after decannulation (cefotaxime clearance post ECMO), and hemofiltration flow and time after decannulation (desacetylcefotaxime clearance post ECMO). [65] Although the article identified several variables with a statistically significant effect on cefotaxime and desacetylcefotaxime PK, the percentage of variability explained is max. 8.1%.

Oseltamivir

In the recent H1N1 influenza pandemic ECMO support was successfully instigated in children and adults with survival rates of 70% [6, 69, 70]. Oseltamivir is the drug of choice in H1N1 new influenza, where alternatives such as inhaled zanamivir or intravenous zanamivir have not been evaluated in critically ill children. A case report describing three patients with H1N1 new influenza supported with ECMO showed that adequate

plasma levels were achieved in two out of three patients. More specifically a two fold dose increase of 4mg/kg/d (vs. 2mg/kg/d) resulted in a two fold increase in plasma levels. The influence of the ECMO circuit seems to be limited in this small case series. One patient with profuse gastric retentions and hematemesis failed to achieve adequate plasma concentrations of oseltamivir and oseltamivir carboxylate probably reflecting insufficient oral absorption of the parent drug [71].

Voriconazole
There is one case report of voriconazole PK in a 5 year old pediatric patient on ECMO. Using therapeutic drug monitoring the authors increased the voriconazole dosing two fold to achieve adequate plasma levels. They found a decreased clearance compared to non ECMO pediatric patients [72]. Similar findings are reported in the adult population [73, 74].

Caspofungin
There are no pediatric data concerning caspofungin in pediatric ECMO patients. Spriet et al. report no altered PK in two adult ECMO patients, whereas Ruiz et al. found inadequate or undetectable caspofungin levels in one patient [73, 74].

Ribavirin
Ribavirin PK may be altered during ECMO treatment. In a 21 day old neonate treated with ribavirin intravenously volume of distribution was markedly increased compared to non ECMO children although neonatal data in non ECMO patients is lacking. Clearance during hemofiltration seemed to be unaltered. The authors concluded that no dose adjustments are necessary [75].

Ticarcillin-clavunate acid
A case series of reporting the use of ticarcillin-clavunate acid in three children including two patients on ECMO and hemofiltration showed no clear effect on volume of distribution or clearance due to ECMO. Both volume of distribution and clearance varied widely between the three subjects. Based on these data dose adjustment do not seem necessary [76].

Fluoroquinolones
Fluoroquinolones are broad spectrum antibiotics. Although PK and PD data in neonates and children is limited both ciprofloxacin and levofloxacin have been used in severely ill neonates and children [77, 78]. There are case reports mentioning the use of fluoroquinolones in pediatric ECMO patients [79]. However there is no data available on fluoroquinolones PK during ECMO. In adults during cardiopulmonary bypass Volume of

Distribution does not seem to be affected, whereas clearance decreases during surgery [80] Concerns of toxicity as well as increased risk of multiresistent pathogens with these drugs necessitate evaluation of PK parameters during ECMO in all age groups essential.

Sedatives and analgesic drugs
Children on ECMO receive multiple sedative and analgesic drugs to provide comfort and pain relief. A survey among different ECMO centers in the United States showed a wide variety of sedatives and analgesics used in children on ECMO, with a preference for fentanyl and midazolam. [81] Reported sedation goals differ from no motor movement and deep sedation, to spontaneous movement and conscious sedation [81].

Data on sedation and analgesia in ECMO patients are only available from newborn studies. Higher sedative needs have been reported for these patients [47, 82, 83, 84.]. In an unpublished cohort study including 78 neonates, infants and older children we found that 50% of all ECMO patients required three or more drugs to achieve adequate sedation evaluated by COMFORT-B and Numerical Rating Scale (NRS) pain scores. Medication included morphine, midazolam, fentanyl, clonidine, ketamine-S and continuous pentobarbital infusions. Furthermore 65% of all patients received morphine despite low NRS pain scores. This suggests that morphine was predominantly used as a sedative in the study population, not as an analgesic. Since cannulation for ECMO is considered a minor surgical procedure non-opioid analgesics such as paracetamol might suffice to achieve adequate pain relief. This approach may reduce opioid use and its related adverse events [85].

Prolonged and high cumulative dosages of opioids and benzodiazepines in neonates and children are associated with serious adverse effects such as tolerance, physical dependency and subsequent withdrawal syndrome in neonates and children [86-93]. This may necessitate strict weaning protocols in individual patients, even up to six months after hospital discharge. [94].

Developing standardized PD parameters and endpoints is invaluable in interpreting PK data. A myriad of co-variables influence PK and PD in ECMO patients. Difference in desired levels of sedation, the use of multiple drugs and poor correlation between sedation scores and plasma concentrations make it difficult to use PK data to create dosing guidelines for sedatives and analgesics.

In a cohort study of 20 neonates on ECMO, our group evaluated the safety and efficacy of sedation interruption in this population [85]. Interruption of all sedatives and analgesics was feasible and safe in these patients and resulted in a median (interquartile range) time without any sedatives of 10.3 hours (5.0-24.1 h). Median plasma levels of midazolam were significantly lower compared to the plasma levels reported by Mulla et al.: median (interquartile range) 107ng/ml (48-184 ng/ml) vs. 1400-2600ng/ml. In previous studies the correlation between plasma concentrations of midazolam and

level of sedation has been poor, with large inter and intra-patient variability [95-98]. The study outcomes support the hypothesis that daily sedation interruption may result in reduced cumulative dose requirements of sedatives and analgesics for ECMO patients. Furthermore they show that, PK data alone are not enough to come to evidence based dosing regimens. To our knowledge only morphine, midazolam and fentanyl PK have been studied in neonatal and pediatric ECMO patients.

Midazolam

There are two PK studies evaluating midazolam in neonates on ECMO. Mulla et al. described a one-compartment model with time-dependent change in volume of distribution. The volume of distribution expanded monoexponentially from the onset of ECMO from 0.8 L/kg to a maximum value of 4.1 L/kg. Consequently, plasma half-life was substantially prolonged: 33.3 h. Total body clearance was constant at 1.4 +/- 0.15 ml/kg/min. Due to a prolonged elimination half-life there was accumulation of midazolam after 48 hours on ECMO. Adequate sedation levels were achieved with plasma levels of 1400-2600 ng/ml [46].

Furthermore they showed that patients receiving midazolam via the circuit required higher doses within the first 24h compared to those who were given midazolam via an indwelling venous line [29]. In a similar cohort of neonates Ahsman et al. reported a comparable threefold increase of volume of distribution immediately after cannulation [57]. Contrary to the report by Mulla et al. there was an increase of midazolam clearance over time on ECMO from 2.6ml/kg/min to 7.6 ml/kg/min. Interpatient variability estimates of midazolam and the two metabolites for clearance and volume of distribution between 87% and 129%. The clearance of hydroxymidazolamgluruonide seems to lag behind midazolam clearance [57]. This could lead to active concentrations even after just a couple of days on ECMO, causing prolonged sedation [99]. Most variability remains unexplained, which exemplifies our limited understanding of physiology, organ function and their effects on pediatric PK during critical illness and ECMO.

The only apparent differences between the two datasets are the type of ECMO applied (venovenous vs. venoarterial), and possibly the composition of circuits and membranes. Midazolam drug loss reported by Mulla et al. in an in vitro study were lower compared to the absorption rates in the ECMO circuit used by Ahsman et al. [49, 50].

In conclusion, volume of distribution and clearance of midazolam are higher during ECMO, adsorptive drug loss could be a cause of higher dose requirements. Although PK data suggests a dose increase following cannulation, alterations in PD and sedation goals may instead allow the physician to decrease or stop sedation following cannulation and titrate sedation based on validated sedation scores. Future studies need to focus on both PK and PD data using validated scores such as COMFORT-B and NRS-pain scores as PD outcome measures [85].

Fentanyl
Koren et al. reported drug sequestration of fentanyl in extracorporeal circuits [51] with a subsequent need for high fentanyl infusion rates. High fentanyl infusion rates have been reported by others as well indicating altered PK or PD in these patients [83, 100].

Morphine
Morphine is widely used in neonatal intensive care as an analgesic and as a sedative during mechanical ventilation and ECMO. In 1994 Dagan et al. reported decreased morphine clearance in neonates on ECMO of 0.574 L/kg/h during ECMO with a concomitant two fold increase following decannulation. [47] Geiduschek et al. found a similar clearance of morphine in eleven newborns on ECMO. Almost half of the patients showed increased clearance over time possibly reflecting age related maturation of drug metabolizing enzyme activity. Furthermore they found no significant decrease of morphine levels directly following cannulation. They concluded therefore that PK of morphine was not significantly altered during ECMO [31].

In 2006 Peters et al. reported a two fold increase of volume of distribution for morphine in neonates on ECMO compared to postoperative non ECMO patients. Furthermore clearance was decreased at start of ECMO but increased over time, equalling age normalized clearance by day 14. The clearance of morphine-3-glucoronide and morphine-6-glucoronide is related to creatinine clearance [30, 101].

Krekels et al. developed a new model for morphine PK in neonates, infants and children resulting in an alternative dosing advice for neonates and children below the age of two years. In validating this model in different data sets they found that it was also predictive for neonates on ECMO, indicating no significant difference in PK. There was however an underestimation of metabolites in neonates without hemofiltration support indicating diminished renal clearance in these patients, which was corrected by introducing hemofiltration [102].

All studies reported high interpatient variability. Although morphine PK is altered in neonates on ECMO clear dose adjustments cannot be made based on the available literature and should be based on effect using validated scores. The data suggests that morphine PK is less affected than fentanyl and should be the preferred choice of opioids in ECMO patients.

Although there are limited pharmacokinetic data on morphine and midazolam in neonates on ECMO, no data are available in older children on ECMO. Also there are no pharmacokinetic data on clonidine or ketamine-S in ECMO patients of any age. Dosing of these drugs is titrated to effect, but the therapeutic window in ECMO patients is unknown.

Cardiovascular drugs

There are case reports describing the PD of amiodarone, esmolol, prostaglandin E1, nesiritide, and nicardipine in pediatric ECMO patients. These studies have been evaluated in a recent review by Watt et al., in which they conclude that there is either no effect (nicardipine) or increased dose requirements (amiodarone, esmolol, prostaglandin E1, nesiritide) [103]. Although helpful these reports do not provide combined PK and PD data necessary to develop an evidence based dosing regimen. A case series of 23 neonates treated with hydralazine did not show any clinical benefit on cardiac performance during ECMO. Whether this is caused by altered PK, with subtherapeutic drug concentrations, remains unclear since PK data is lacking [104].

Furosemide

There are two studies on furosemide use in ECMO patients. Van der Vorst et al. showed that continuous furosemide administration is well tolerated in ECMO patients and leads to stable and adequate diuresis. In a follow up study continuous infusions furosemide of 4mg/kg/d resulted in plasma concentrations below toxic levels [105] [106].

Bumetanide

Bumetanide PK was evaluated in eleven neonates treated with ECMO. Wells et al. found an increased volume of distribution and elimination half-life for bumetanide with high non renal bumetanide clearance. Although effective diuresis was achieved, the effects were less than expected due to possible sequestration of drug within the ECMO circuit [43].

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Sildenafil

Sildenafil has been used off-label to treat pulmonary hypertension in the neonatal and pediatric setting, with dose regimens based on titration and a few case reports [107, 108]. Mukherjee et al. showed in their PK analysis of intravenously administered sildenafil that sildenafil clearance increases over time from 0.7 L/h at a postnatal age of 1 day up to 3.3 L/h at 10 days, which suggests a clearance maturation that may require dose adjustments over time [109]. Our group examined sildenafil PK after nasogastric administration of extemporaneously prepared capsules during ECMO and in the post-ECMO period [110]. There was a gradual non-linear increase of sildenafil PK parameters over the course of an ECMO-run, with a return to pre-ECMO levels upon decannulation. For a 6 day-ECMO run, sildenafil clearance increased from 1.0 to 6.7 L/h, The distribution volume also increased: from 50 to 116 L. Simulations showed that a dose of 3 - 5 mg/kg/24h leads to a combined sildenafil and desmethylsildenafil exposure equivalent to that of an adult treated with 3 dd 20 mg p.o. During ECMO, a dose of between 5 and 7 mg/kg/24h provides the same exposure. As a result of the return of PK parameters to

non-ECMO values, the total exposure would increases at decannulation, unless the dose is reduced by approximately 50%.Clinicians should therefore be aware of a potential increase in efficacy or side effects after the end of ECMO therapy [110].

Miscellaneous

Ranitidine
Wells et al. described both PK and PD of ranitidine in term neonates on ECMO. A single intravenous dose of ranitidine resulted in an intragastric pH to rise above 5 in all patients. Volume of distribution (1.8L/kg) is slightly higher and clearance (0.25L/kg/h) is slightly lower compared to non ECMO neonates, but this difference does not seem to be clinically relevant [41]. The authors advised that dose adjustments should be made based on intragastric pH measurements.

Theophylline
In 2003 Mulla et al. described a one-compartment model with first order elimination for theophylline in 75 neonates on ECMO. Bodyweight and age were predictors for volume of distribution and clearance respectively. The results showed the familiar pattern of an increased volume of distribution and decreased clearance compared to non ECMO patients. Again the authors reported large unexplained interpatient variability [42].

Phenobarbital
Phenobarbital PK data is limited to a single case report. A slightly higher volume of distribution (1.2L/kg) with normal elimination half-life (92hours) resulted in low but therapeutic serum concentrations. Dose recommendations cannot be made based on this single case reports, but clinicians should be aware that higher loading doses may be required [111].

Heparin
Green et al. described heparin PK in 5 patients on ECMO. Heparin clearance was markedly influenced by the ECMO circuit, accounting for approximately 50% of total Clearance [112]. Reported heparin doses range between 20 and 70E/kg/h in ECMO patients [113]. Higher than normal heparin requirements on ECMO may be expected.

FUTURE PERSPECTIVES

Evidence based dose regimens are still lacking for many regularly used drugs in neonates and older children on ECMO. PK-PD studies could help us construct dose regimens, but

they require sufficiently large datasets with clinical records, dose information, plasma concentrations and relevant clinical outcome parameters. extracorporeal circulation can help our understanding of the behavior of individual drugs. Several recent pharmacokinetic studies NONMEM population modeling. This enables the construction of PK models with limited and random patient samples. Using these techniques routine collection of blood samples in combination with registration of clinical and dose information in a patient data management system (PDMS) would improve the availability of data for these analyses. By analyzing samples in such a biobank, it might be possible to get enough samples to model these drugs and their metabolites as well, so that proper dose regimens can be constructed [114]. Perhaps the number of samples might be increased in future by using leftover material from routine clinical chemistry measurements using LC-MS. Finally the PK models need to be validated in a prospective study. Combining PK sparse sampling with randomized controlled trials including clear PD outcome measurements will help us to construct evidence based dosing guidelines, evaluate toxicity and establish efficacy of drugs. Rayyan et al. suggested a similar strategy. They also emphasized the need for randomized controlled trials and well defined PD outcome [115].

The power of PK studies in these patients could be enhanced by incorporating data from critically ill and relatively healthy non-ECMO patients, but only for drugs that are used in different patient categories. For drugs like midazolam (for which the influence of illness and maturation are being studied by combining different datasets in non-ECMO patients [116] the ECMO data might be included in the model. Studies into the mechanisms of PK changes due to maturation, disease progression or the extracorporeal circulation can help our understanding of the behavior of individual drugs. To help identify factors that underlie PK changes, studies into fluid dynamics, organ perfusion, organ function, capillary function and microcirculation might be useful, but it is still a long way before they might be used in (mechanistic) population PK analyses. Developing accurate mechanistic population models will enable us to predict PK and possibly PD for new drugs used in these patients, thereby avoiding toxicity and increase efficacy of drugs.

CONCLUSION

PK for several drugs is altered in neonates and children on ECMO. Our understanding of ECMO-induced PK-altering mechanisms is insufficient to prepare a predictive model, reflected by the large interpatient variability found in almost all studies. This variability as well as the lack of clear PD endpoints makes it difficult to construct ECMO specific dosing regimens for most drugs. Changes in PK are drug and circuit dependent with more dramatic changes found in lipophilic drugs and silicone oxygenators. Differences

in ECMO circuits, patient populations and diseases may influence PK and PD further. The combination of routine sparse sampling, drug assay via LC-MS and a PK analysis using NONMEM in combination with validated PD endpoints such as the COMFORT-B will allow the study of drug behaviour in these vulnerable patients without harm to the individual subject. Combining data sets and a biobank may enable researchers to fine-tune PK models and hopefully this, in combination with a good cooperation between pediatricians, pharmacists and clinical pharmacologists, leads to more evidence-based dose regimens for neonatal and pediatric ECMO patients. Finally PK models need to be validated in prospective randomized controlled trials to proof efficacy and accuracy.

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Chapter 11

Multicenter experience with mechanical extracorporeal assist using a new diagonal pump in 241 pediatric patients

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ABSTRACT

Objective

Mechanical circulatory support for heart and/or lung failure has become routine in specialized pediatric centers. We report on the first multicenter results with a new miniaturized third generation diagonal centrifugal pump.

Methods and Results

241 neonates and older children, age median 2.2 (range 0-201) months, from 7 centers were treated with the pump system (16 ml priming volume), able to generate a flow of below 0.5 up to 8 liters. A fully preconnected set and quick pump-driven priming allows transportation.

Veno-arterial ECMO was used in 163 and veno-venous ECMO in 70 patients. In 8 the pump was used as ventricular assist device. Supporting time was median 5.5 (range 0.2-69) days. 116 infants presented with primary cardiac and 125 with pulmonary indications, including 8 oncologic patients. In 24 children veno-arterial ECMO was installed under ongoing cardiopulmonary resuscitation.

All 8 oncologic patients died of pulmonary failure after a median support time of 15 days. The overall weaning rate from bypass of the 233 other patients was 72.5% with a discharge home rate of 59%. 127 (55 %) children were without severe complications. Bleeding occurred in 75 and technical failure in 5 patients. Three children suffered a fatal cerebral event. Renal replacement therapy was performed in 28% and pump exchange in 24%. Multivariable analysis identified pump exchange (OR 1.94), kidney failure (OR 3.43) and complications on support (OR 2.56) as risk factors for dismal outcome.

Conclusion

The pump's use proved to be feasible, efficient, and was associated with a low complication rate. It is multifunctional, useful in different kinds of support and can be initiated outside an intensive care unit or operating room.

INTRODUCTION

After the first report in 1974 on its use in children, extracorporeal membrane oxygenation (ECMO) became a lifesaving tool for patients with pulmonary failure and children suffering from cardiac failure [1, 2]. The goal of veno-venous (VV) and veno-arterial (VA) ECMO is to serve as a bridge to recovery or transplantation, or to medical-, interventional- or surgical therapies once a diagnosis is made [3-5]. Cannulation sites now include the neck, groin, direct intracardiac access, or a combination thereof. Since the circuits have become smaller, rapidly employed, and easier to handle, VA-ECMO-supported cardiopulmonary resuscitation (E-CPR) is being increasingly administered in specialized pediatric centers [6].

The past decade has seen a shift from roller pumps towards miniaturized centrifugal pump technology [6-8]. Nevertheless, ECMO runs worldwide are still often carried out with first generation centrifugal pumps or even traditional roller pumps, a decade-old technology [5].

With this multicenter study we aimed to evaluate the feasibility, efficacy, complication-, and survival rate associated with a new miniaturized third generation diagonal centrifugal pump used in Europe in 241 consecutive neonatal and pediatric patients.

PATIENTS AND METHODS

After having obtained institutional Review Board approval from all seven centers, we enrolled 241 consecutive neonates, infants and children (53% male) supported with this new pump between 1st January 2012 until 31 March 2015 in this retrospective study. All centers included their consecutive patients treated with a Xenios Deltastream® DP-3 diagonal pump without exception, with number per center ranging from 12 to 94 (median 32). Patients' demographics and supporting times are shown in table 1. Forty of the patients have previously been reported in a study focusing on different aspects [9].

The indication of almost half of the patients (n = 116) was of cardiac origin, e.g., weaning failure from cardiopulmonary bypass or later circulatory collapse after cardiac surgery; chronic cardiac disease like cardiomyopathy or myocarditis; and sudden cardiac arrest with E-CPR. In the other 125), the indication was of primary pulmonary origin like ARDS, pneumonia, lung hypoplasia in congenital diaphragmatic hernia, or meconium aspiration syndrome (Table 2).

Weaning success was defined as survival longer than 24 hours without mechanical support.

Table 1: Patient demographics and supporting time

	All patients, n=241 Median Quartiles Range	Oncology pt, n=8 Median Quartiles Range	NOP, n=233 Median Quartiles Range
Age (months)	2.2	57.5	1.9
	0.1/28.8	6.1/85.2	0.1/24.9
	0-201	5.1-128	0.1-201
Bodyweight (kg BW)	4.1	10.7	4.1
	3.1/11.8	6.1/17.5	3.0/11
	1.7-72	3.6-33	1.7-72
Days on support (d)	5.5	15.0	5.5
	3.1/10.6	4.0/17	3.1/10
	0.2-69	2.0-26	0.2-69

Table 2: Diagnosis of the DP3-patients

Indication (all)	n = 241 (%)
Cardiac indication n = 116 (48.1%)	
Cardiac arrest, ECLS under CPR	24 (10%)
Post-cardiac surgery #	73 (30.2%)
Cardiac disease, chronic *	19 (7.9%)
Pulmonary failure n = 125 (51.9%)	
PPHN	4 (1.7%)
CDH	35 (14.5%)
MAS	15 (6.2%)
Pneumonia/sepsis	25 (10.4%)
ARDS	45 (18.7%)
Chronic lung failure	1 (0.4%)

*myocarditis n=4; cardiomyopathy n=11; others n=4
#weaning failure n=51, LCOS at ICU n=5, CPR n=14, unknown n=3
ARDS, acute respiratory distress syndrome; CDH, congenital diaphragmatic hernia;
 CPR, cardiopulmonary resuscitation; ECLS, extracorporeal life support; MAS, meconium aspiration syndrome; LCOS, low cardiac output state

MATERIALS

The Deltastream® DP-3 (Xenios, Deltastream, Aachen, Germany) is a rotational pump (Fig 1). This diagonal pump system unifies the advantages of a radial pump with high hydraulic capacity and low inertia and the small size of an axial pump system. The DP-3 pump system with 16 ml priming volume can generate a flow of up to 8 liters per minute and a pressure up to 600 mmHg. Maximum rotational speed is 10,000 revolutions per

minute. The flow can be adjusted even at ranges under 0.5 l/min, essential for its use in babies. Thus the system is applicable in a broad age range from neonates up to adults. The entire pump circuit has obtained its seven days CE Mark and is composed of a single-use diagonal blood pump, motor, driving console, and flow probe. Safety functions are ensured by several control systems: cannula aspiration is prevented by preload control; brief interruption of the flow can be managed with the zero-flow mode without risking back- flow. The pump can be driven in pulsatile mode by varying the pump speed under different frequencies [10]. The system is multifunctional and applicable in all kinds of mechanical cardiac support (MCS) like ECMO, ECLS or as a ventricular assist device (VAD) for the right (RVAD) or left (LVAD) ventricle, and as uni- or biventricular support.
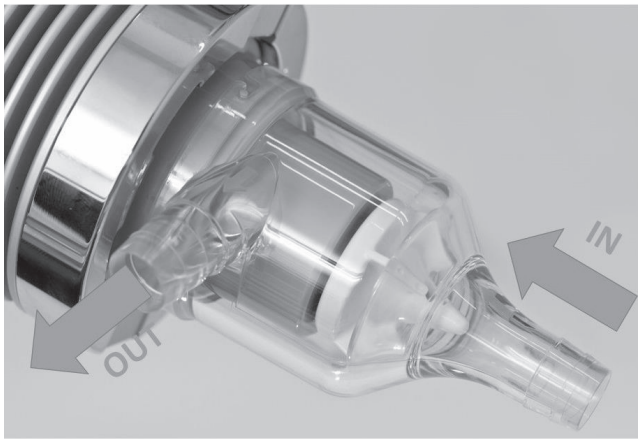

Figure 1: DP-3 diagonal centrifugal pump.

STATISTICAL ANALYSIS

Patient and procedure characteristics were analyzed descriptively. Categorical data are presented as absolute and relative frequencies. Continuous data are presented as median, quartiles, and range. The incidences of successful weaning, death on device, and change to other device over time were estimated with cumulative incidence rates.

The effects of patient and procedure characteristics on the outcome parameter death on device and death before discharge were analyzed using logistic regression models. Effects were estimated as odds ratios (OR) with 95%-confidence intervals (CI) and tested at a two-sided significance level of 0.05. First, all variables were analyzed in univariate models. In a second step, variables with $p<0.05$ in the univariate analysis were simultaneously analyzed in a multivariate model.

Since the statistical analyses were not planned prospectively in a confirmative manner, all p-values have to be interpreted in a descriptive sense.

RESULTS

1. The total group (n = 241)

Cannulation
Mechanical circulatory support implantation was performed in the NICU/PICU in 59.0%, in the OR in 33.2%, within the hospital but outside an OR/ICU in 3.5%, and at an external clinic followed by transport under ongoing MCS in 4.4%. (Fig. 2). Intracardiac access by open chest was made in 85 patients (77 VA-ECMO and 8 VAD), and 75 patients underwent VA-ECMO with cervical cannulation. Of the 85 patients with intracardiac cannulation, 77 were supported with VA-ECMO and 8 with VAD without an oxygenator. Details on cannulation are given in table 3. Cannulation access had no significant influence on weaning rate (p = 0.24) or discharge home rate (p = 0.81). 69% of the femorally-cannulated patients were weaned successfully and 54% were discharged home. The corresponding figures for the cervically-cannulated patients are 73% 60%, respectively and for the patients with intracardiac cannulation 83% and 57%, respectively.
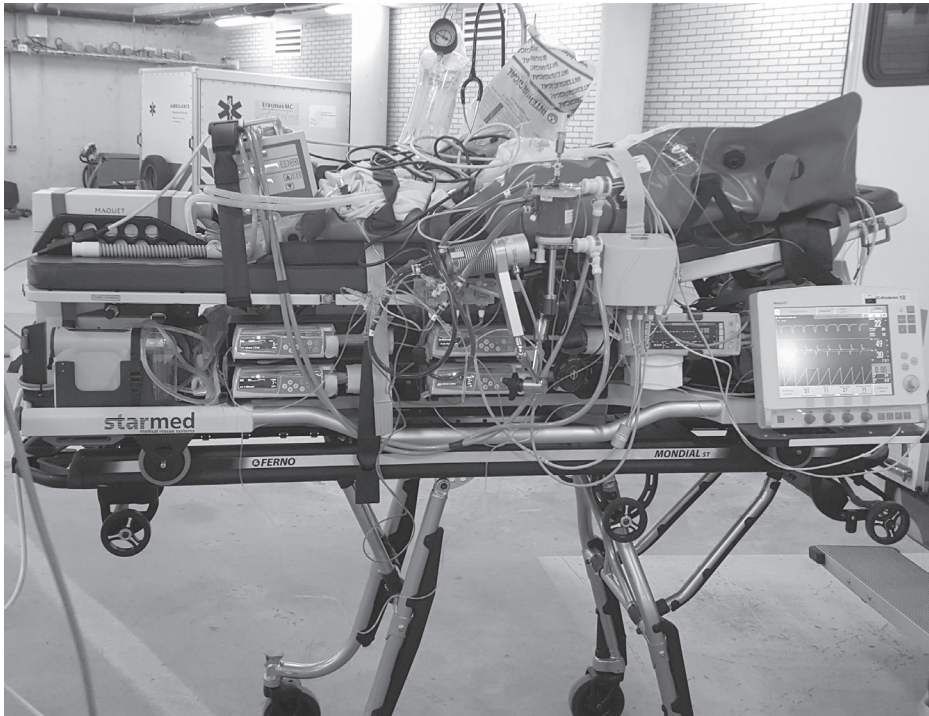
Figure 2: DP-3 system for interhospital ECMO transport.

Table 3: Cannulation details

	n	Cannulation site	n	Comments
VA-ECMO	163	Intra-cardiac	77	9 with LA vent
		Cervical	62	1 with septostomy, 1 LA vent
		Femoral	11	2 with septostomy
		Cervical + femoral	13	
VV-ECMO	70	Cervical, dual lumen	52	
		Cervical, single lumen	9	
		Femoral	2	
		Cervical + femoral	7	
VAD	8	LVAD (LV-Ao)	2	
		RVAD (RA-PA)	2	
		Univentricular VAD (V-Ao)	4	

Abbrev.: Ao, aorta ascendens; LA, left atrium; RA, right atrium; PA, pulmonary artery; VAD, ventricular assist device;

VV- vs. VA-ECMO

The DP-3 was used in 70 children as VV-ECMO, in 163 as VA-ECMO; and as a VAD without oxygenator in eight patients with cardiac failure and restored lung function solely for left- or right or univentricular heart support (Table 3).

Survival

Weaning was successful in 169 (70.1%) patients, 63 (26.1%) patients died while on the device or failed to survive 24 hours after weaning, nine (3.7%) were switched to another device, and 137 (56.9%) patients were ultimately discharged home (Table 4).

Table 4: Total outcome:

	n=241	%
Weaning successful	169	70.1
Death on device	63	26.1
Switched to another device	9	3.7
Discharged home	137	56.9

Bridging to another device

Nine children needing long-term cardiac support were switched to other devices after a median DP-3 pumping time of 10.0 days (range 2 – 40 days). Six were older than one year of age, five had a bodyweight of > 10 kg. Eight out of nine underwent VA-ECMO because of a cardiac indication, four because of weaning failure after cardiac surgery, three with acute decompensation of chronic cardiac disease, and one after sudden cardiac arrest and e-CPR. Five were discharged home.

Complication rates

Overall complication rate was 45%; the most frequent complication was bleeding in 32%, followed by thromboembolism in10 % and blood culture-positive sepsis in 9% (Table 5). Of the five patients (2.1%) with technical failure, two were successfully weaned and three died on support. 55 % of the patients were without major complications. Renal replacement therapy (RRT) was reported in 67 children (28.4 %, in five patients data on RRT were missing). Hemolysis was reported in 22 patients (12%).

Table 5: Complications

	n	%
None	127	54.5
Bleeding	75	32.2
Thromboembolism	23	9.9
Seizures	3	1.3
Sepsis (blood culture Positive)	21	9.0
Others	10	4.3
Technical failure	5	2.1

Missing 8, multiple answers possible
-severe cerebral events in 3 children: 2 cerebral bleeding and 1 thromboembolism
-renal replacement therapy in 67 patients (28.4%), 5 missing
-hemolysis in 22 patients (11.6%), 52 missing

2. Children with oncologic disease and pulmonary failure (n = 8)

A total of 8 children on long-term immunosuppression due to malignant disease were treated with ECMO in three centers (Table 1, fig. 3). The mean age of these children was higher than that of the other children (57.5 vs. 1.9 months) and their ECMO support lasted longer (median 15.0 vs. 5.5 days). Indications in this patient group were: pulmonary failure due to ARDS (n = 6), pneumonia/sepsis (n = 1) and chronic lung disease (n = 1). Seven children underwent ECMO implantation in a PICU, 1 in the operating room. VV-ECMO was performed in 5 with double lumen cervical cannulation, two had VV single lumen ECMO, and in one case VA-ECMO was implanted. No technical device failure was reported; nevertheless all patients died without successful weaning. The complications were: bleeding in 2 (one cerebral); new blood culture positive sepsis in 1; kidney failure requiring dialysis in 3; signs of hemolysis in 2.

3. Non-oncology patients

Characteristics of the 233 non-oncology patients are given in Table 1. The overall successful weaning rate was 72.5 %, and 58.8 % survived until discharge home. The discharge home rate was 62% in the pulmonary indication group as compared to 55% in the cardiac group. Best reported results were in the subgroup of 15 MAS patients, of whom 14 (93%)
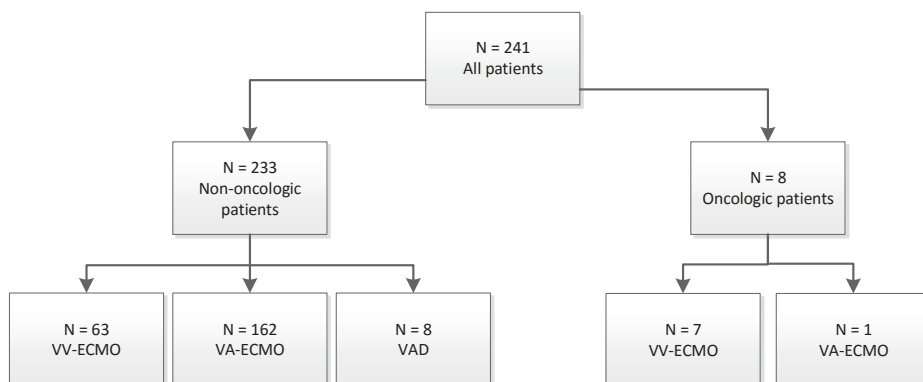
Figure 3: Flowchart of the patients

survived to discharge home. Further details are given in table 6. During hospital stay 37 children died although weaning was successful. Time interval between weaning and death was a median 12.0 days (quartiles 3.3 – 27.3 days). Twenty-four of these patients had a cardiac indication as compared to 13 patients with a pulmonary indication; 81% were in their first year of life. Most of these children received VA-ECMO (92%).

The rate of change of pump head, oxygenator or the entire system ranged from 0 - 85% of the patients per center. At least one change was applied to 61 (26%) of all systems had. There was no difference in this regard between pulmonary or cardiac indication or between VV- and VA-ECMO. In 8 VAD patients whose system had no oxygenator, the change rate was 50%.

Table 6: Indication for DP-3 implantation and outcome of all non-oncologic patients (NOP)

Indication (NOP)	n (%)	Weaning successful	Discharge home
All non-oncologic patients	233 (100%)	169 (72.5%)	137 (58.8%)
Cardiac indication	116 (49.8%)	83 (71.6%)	64 (55.2%)
Cardiac arrest, E-CPR	24 (10.3%)	13 (54.2%)	9 (37.5%)
Post-cardiac surgery #	73 (31.3%)	57 (78.1%)	43 (58.9%)
Cardiac disease, chronic*	19 (8.2%)	13 (68.4%)	12 (63.2%)
Pulmonary failure	117 (50.2%)	86 (73.5%)	73 (62.4%)
PPHN	4 (1.7%)	3 (75.0%)	1 (25.0%)
CDH	35 (15.0%)	28 (80.0%)	21 (60.0)
MAS	15 (6.4%)	14 (93.3%)	14 (93.3%)
Pneumonia/sepsis	24 (10.3%)	18 (75.0%)	15 (62.5%)
ARDS	39 (16.7%)	23 (59.0%)	22 (56.4%)

*myocarditis n=4; cardiomyopathy n=11; others n=4
weaning failure n=51, LCOS at ICU n=5, CPR n=14, unknown n=3

Table 7: Univariate analysis of effects of patient and procedure characteristics on death on device or before discharge home.

All patients (non-oncology) n = 233	n	Weaning failure Death on device			Death before discharge home		
		n (%)	OR (95% CI)	p	n (%)	OR (95% CI)	p
Male	122	28 (23)	1.00	0.84	44 (36)	1.00	0.12
Female	108	26 (24)	1.06 (0.58 – 1.96)		50 (46)	1.53 (0.90 – 2.59)	
Age ≥ 1 year	76	21 (28)	1.00	0.32	30 (39)	1.00	0.71
Age < 1 year	157	34 (22)	0.72 (0.39 - 1.36)		66 (42)	1.11 (0.64 – 1.94)	
Bodyweight ≥ 10 kg	62	16 (26)	1.00	0.63	24 (39)	1.00	0.64
Bodyweight < 10 kg	171	39 (23)	0.85 (0.43 – 1.66)		72 (42)	1.15 (0.64 – 2.09)	
Indication							
Pulmonary	117	30 (26)	1.00	0.073	44 (38)	1.00	0.17
Cardiac with surgery	73	12 (16)	0.57 (0.27 – 1.20)		30 (41)	1.16 (0.64 – 2.10)	
Cardiac without surgery	19	3 (16)	0.54 (0.15 – 2.00)		7 (37)	0.97 (0.35 – 2.64)	
E-CPR	24	10 (42)	2.07 (0.83 – 5.15)		15 (63)	2.77 (1.12 – 6.85)	
Previous CPR							
No	171	37 (22)	1.00	0.24	64 (37)	1.00	0.053
Yes	62	18 (29)	1.48 (0.77 – 2.86)		32 (52)	1.78 (0.99 – 3.21)	
1 – 15 min	11	4 (36)			5 (45)		
16 – 30 min	16	3 (19)			9 (56)		
31 – 45 min	14	5 (36)			9 (64)		
>45 min	19	6 (32)			9 (47)		
Cannulation							
Intra-cardiac	81	14 (17)	1.00	0.24	35 (43)	1.00	0.81
Cervical	134	36 (27)	1.76 (0.88 – 3.51)		53 (40)	0.86 (0.49 – 1.51)	
Femoral	13	4 (31)	2.13 (0.57 – 7.89)		6 (46)	1.13 (0.35 – 3.65)	
VA-ECMO	165	36 (22)	1.00	0.21	73 (44)	1.00	0.18
VV-ECMO	64	19 (30)	1.51 (0.79 – 2.90)		22 (34)	0.66 (0.36 – 1.20)	
Pump exchange							
No	172	38 (22)	1.00	0.36	62 (36)	1.00	0.008
Yes	61	17 (31)	1.36 (0.70 – 2.65)		34 (35)	1.94 (1.00 – 3.72)	
Complications							
No	123	18 (15)	1.00	0.0005	37 (30)	1.00	
Any	103	35 (34)	3.13 (1.65 – 5.97)		56 (54)	2.77 (1.60 – 4.78)	0.0003
No bleeding	153	28 (18)	1.00	0.005	54 (35)	1.00	0.010
Bleeding	72	26 (36)	2.47 (1.32 – 4.64)		39 (53)	2.00 (1.13 – 3.52)	
No Thrombosis	203	46 (23)	1.00	0.20	80 (39)	1.00	0.12
Thrombosis	23	8 (35)	1.82 (0.73 – 4.56)		13 (57)	2.00 (0.84 – 4.78)	
No technical failure	226	53 (23)	1.00	0.082	91 (40)	1.00	0.11
Technical failure	5	3 (60)	5.02 (0.82 – 30.8)		4 (80)	5.93 (0.65 – 54.0)	
No renal support	164	30 (18)	1.00	0.003	51 (31)	1.00	< 0.0001
Renal support	64	24 (38)	2.68 (1.41 – 5.10)		42 (66)	4.23 (2.29 – 7.81)	

OR = Odd ratio; CI = 95%-confidence interval.

A pump change had no effect on the complication rate (48.3% of patients with pump change versus 44.6% of patients without pump change). On the other hand, kidney failure occurred more often in the former group (43% vs. 23%), and also the death rate before discharge home rate was higher in in patients with pump change (56% vs. 36%, see tables 7 and 8).

Cardiopulmonary resuscitation occurred in 62 of these 233 non-oncology patients but this had no effect on later outcome even in the group resuscitated longest (> 45 min) (Table 7).

E-CPR involving emergency cannulation under ongoing chest massage was performed in 24 patients (10%) with a successful weaning rate of 54% and survival to discharge rate of 38%.

Pump change, complications, and renal support were related with outcomes (death on device and death before discharge home) in univariate and multivariate analyses (for details see tables 7 and 8). Patients with pump exchange had a death before discharge rate of 56% as compared to 36% for patients without pump exchange (odds ratio (OR) with 95%-confidence interval from multivariate analysis 1.94 (1.00-3.75), p=0.049). Patients with complications had a death before discharge rate of 54% as compared to 30% in patients without complications (OR=2.56, 95%-CI (1.43-4.60), p=0.002). Patients with renal support had a death before discharge rate of 66% as compared to 31% in patients with- out renal support (OR=3.43, 95%-CI (1.80-6.53), p=0.0002.

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Table 8: Multivariate analyses of effects of patient and procedure characteristics on death on device or before discharge home) in non-oncologic patients

	Weaning failure Death on device		Death before discharge home	
	OR (95% CI)	p	OR (95% CI)	p
Pump exchange		0.64		0 049
No	1.00		1.00	
Yes	1.19 (0.58 – 2.45)		1.94 (1.00 – 3.75)	
Complications		0.002		0 002
No	1.00		1.00	
Yes	2.91 (1.50 – 5.68)		2.65 (1.43 – 4.60)	
Renal support		0.024		0.0002
No	1.00		1.00	
Yes	2.20 (1.11 – 4.36)		3.43 (1.80 – 6.53)	

OR = Odd ratio; CI = 95%-confidence interval.

DISCUSSION

In this multicenter study of 241 children with life threatening organ failure, treatment with the new miniaturized third generation diagonal centrifugal pump (DP-3) proved to be feasible, efficacious and was associated with a low complication rate and with 70% a quite good weaning rate. The DP-3 proved suitable not only for VV- or VA-ECMO in case of pulmonary or combined cardiopulmonary support in children but also as a ventricular assist device, without oxygenator, in patients with cardiac failure only.

In our main data analysis we excluded the severely immunodeficient oncologic patients. Although in all cases technical failure was not encountered and the time courses were even much longer (median 5 times longer, 15 vs. 3 days) compared to the non-oncologic group, all eight died on the system without any weaning chance or even a short glance on the ECMO horizon. In many centers children with severe chemotherapy-induced cytopenia and respiratory failure combined with bacterial or fungal infections are excluded from ECMO programs. Although they have a poor prognosis, there are some case reports of successful support [11]. Our retrospective analysis suggests a restraint decision making process is needed for this population.

Indications for ECMO play a significant role in predicting the outcome. The Kids' Inpatient Database found congenital heart disease to be an independent predictor of increased mortality, followed by respiratory distress syndrome and persistent pulmonary hypertension of the newborn (PPHN) [12]. In our patients the type of indication had no effect on the weaning rate. Nevertheless we confirm poor outcome in oncologic patients, followed by PPHN, whereas the discharge home rate of children with ECMO due to meconium aspiration syndrome was 93 %.

The ELSO registry documents a neonatal / pediatric survival-to-discharge-or- transfer rate of 74% / 58% in pulmonary indications and 41% / 51 % in cardiac indications, which compares well with our discharge home rate of non-oncologic patients of 59 % (62 % pulmonary and 55% cardiac indications). A comparative analysis of the results is not effective since the ELSO data are mixed data without detailed knowledge of the devices used or the reporting quality of the centers. (ECLS Registry Report, International Summary, January 2016). Moreover our study was not set up as a comparative analysis between different devices using a randomized trial design because the individual centers have not yet passed their learning curves and aspects such as the anticoagulant strategy, ventilator management etc. have not yet been harmonized.

Since the pumps have become smaller and smaller and more mobile, E-CPR has become focus of attention [13, 14]. Ten percent of our patients were temporarily rescued with E-CPR and otherwise would have died. The successful weaning rate of these patients was 54 %. Survival to discharge was reduced to 35.5 %, however, mainly because of cerebral dysfunction. In the ELSO registry 2.6% of all cases were cannulated under E-CPR with a

discharge rate of 38% [15]. In this group the indication and length of cardiac arrest and quality of previous CPR determines the result. Nevertheless, in contrast to roller pumps, this diagonal pump with its small size, the fully preconnected set, short tubings and the high speed of pump priming makes this pump eligible for e-CPR either in the OR, the ICU or other wards in the hospital and allows stable transport under ongoing support.

Zamora et al. [16] using data from the ELSO registry concluded that single-vessel double lumen cannulation has become the preferred modality for ECMO therapy in younger children with respiratory failure. In our study, 74 % of all VV-ECMO runs were performed with the double lumen cannula and this had no effect on outcome. It is advantageous to implant the double lumen catheter in Seldinger technique through the internal jugular vein in infants, where femoral access is limited due to the small vessel dimensions [17].

The thromboembolism rate of 9.9% that we found is lower than that of the ELSO registry, that is a 12% stroke rate while receiving ECMO for cardiac indication, and those with stroke had greater in-hospital mortality (72% versus 51%) [18].

Regarding eight cardiac patients after the rescue application of ECLS for short-term support, we used the given „time-to-decision" to communicate with the care givers. For ethical reasons it is important to prove neurology before switching to a suitable long term device such as the HeartWare device (HeartWare Systems, Framingham, MA) or for smaller children the Berlin Heart EXCOR (Berlin Heart, Berlin, Germany) as a bridge to recovery or to wait for a suitable donor 19. The BerlinHeart US trial showed that ECMO before implantation of the BerlinHeart for longer term support was not associated with mortality [19].

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LIMITATIONS

One of the main limitations of this study is its retrospective character, with a trend of underestimating minor complication events. On the other hand, all centers reported their cases serially, without exception, and thus there is no selective reporting. Centre practice variability, which is expressed in the different diagnosis, in the practice of pump exchange, anticoagulation, use of renal support, length of DP-3 support etc. makes it difficult to compare the cases, but on the other hand testifies to the wide spectrum of the DP-3 application. Another limitation is the lack of mid- or long-term follow-up and resilient neuro-imaging like CCT or CMRI.

CONCLUSION

The new miniaturized third generation diagonal centrifugal pump DP-3 proved to be feasible, efficacious and was associated with a low complication rate, and thus makes e-CPR and transport und ongoing support feasible.

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Chapter 12

Liquid ventilation in congenital diaphragmatic hernia - back on stage?!

Kitty G. Snoek; Robert Jan Houmes Dick Tibboel

In congenital diaphragmatic hernia (CDH), lung hypoplasia and pulmonary hypertension are the main causes of neonatal mortality [1]. Mortality significantly decreased over the last 10 years, after the introduction of the gentle ventilation strategy and the development of international standards for postnatal therapy [2]. Still, ventilator induced lung injury is largely responsible for the development of chronic lung disease in children with CDH [3].

In this issue of *Pediatric Critical Care Medicine*, Herber-Jonat and colleagues present the results of a well performed laboratory study in rabbits with induced CDH [4]. CDH was induced by fetal surgery and five days later perfluorooctylbromide (PFOB), a perfluoro-carbon, was instilled into the lungs of randomly selected fetal rabbits; other fetal rabbits received saline. A third group were non-operated fetuses who served as controls. Fetal instillation of PFOB was associated with improvement of lung to body weight ratio, total lung capacity and lung compliance as compared to fetal instillation of saline. Secondly, at mRNA level only, expression of genes involved in extracellular matrix formation and remodeling in the hypoplastic lung was increased. However, surfactant protein expression, distal airway size, mean linear intercept and airspace and tissue fractions were similar between the two groups and also similar to fetuses who were not operated upon. The authors concluded that fetal PFOB treatment resulted in improved lung growth, lung mechanics and extracellular matrix remodeling. Extra-pulmonary effects of PFOB, such as effects on neuronal cell alteration and effects in the brain should be determined in future studies before this therapy can be studied in human prenatal studies.

A ventilation technique known as liquid ventilation stems from the year 1929, when Von Neergard incidentally found that filling the lungs with saline solution dramatically improved the static pulmonary compliance in cats [5]. After further investigation of different types of liquids, Clark and Gollan received fame for their experiments of liquid ventilation by using perfluorocarbon in mice for the first time [6]. In 1989, liquid ventilation showed its potential in a first trial in prematurely born neonates [7]. In CDH Hirschl and colleagues conducted a randomized trial in sheep [8] and concluded that partial liquid ventilation (PLV) during extracorporeal membrane oxygenation may have beneficial effects on pulmonary function and gas exchange. Pranikoff and coworkers applied partial liquid ventilation with the use of perflubron in four CDH patients who required extracorporeal life support postnatally [9]. They concluded that this therapy was possibly associated with improvement in gas exchange and lung compliance. Later on Hirschl and colleagues conducted a randomized trial in 13 CDH infants who were randomized to either PLV perfluorocarbon-induced lung growth or conventional mechanical ventilation [10]. They found that perfluorocarbon-induced lung growth can be performed safely. However, when this trial was still ongoing, in 2001 the FDA decided that all clinical trials with perflubron had to be discontinued until safely data were available. That decision was based on findings that adults with acute respiratory distress

syndrome randomized to PLV had no improved outcome and experienced more adverse events such as more pneumothoraces, hypoxic episodes and hypotensive episodes [11]. Nevertheless in China adults with acute respiratory distress syndrome are currently recruited in a randomized controlled trial of perfluorocarbon instillation (NCT01391481).

In normal fetal lung development, the lungs are liquid-filled and fluid secretion and fetal breathing movements are necessary for lung maturation [12]. In abnormal situations such as in prematurely born neonates in which transition from liquid-breathing to an air-breathing situation takes place prematurely, and in fetuses with an amniotic fluid-deficient environment, lung development is likely to be immature resulting in lung related problems postnatally. Instillation of PFOB in the trachea approximately to functional residual capacity can simulate the antenatal situation of liquid-filled airway branches. Thereafter, gas tidal volumes are delivered by using a mechanical conventional ventilator. This is called partial liquid ventilation. In total liquid ventilation the lungs are completely filled with a liquid whereas in partial liquid ventilation the lungs are filled until functional residual capacity. Perfluorocarbons have a high solubility for respiratory gases [6]. By eliminating the air-liquid interface, lung compliance can be improved [13]. Due to their dense characteristics, PFOB gravitate to dependent part of the lungs, and collapsed regions can be re-opened and ventilation/ perfusion ratio may improve [13]. Next to these advantages, pulmonary inflammation and injury may be reduced as a result of decreased cytokine production. Moreover, in pigs receiving PLV a redistribution of pulmonary blood flow away from the dependent region of the lung was found, as well as increased vascular resistance and pulmonary artery pressure [14].

In line with the experiments of the article from Herber-Jonat and colleagues, we know that a complete obstruction of the fetal airways results in massive lung distension and a poly-alveolar lung the so called congenital high airway obstruction syndrome (CHAOS) [15]. Taking this concept, the TOTAL trial (NCT01240057) is an ongoing trial of tracheal occlusion to accelerate lung growth in prenatally diagnosed high-risk CDH infants stratified according to observed to expected lung-to-head ratio. Another study is planning to include patients for early tracheal occlusion (NCT01731509). Moreover, a trial known as the VICI-trial (NTR 1310) was performed in nine European centers to identify the optimal ventilation strategy in antenatally diagnosed CDH infants. These studies might solve some of the challenges that stand in the way of further improvement in the treatment of CDH infants. Herber-Jonat and colleagues conducted a randomized laboratory study in animals with a unique study design. Instead of only obstructing the fetal airway, they antenatally filled the lungs with PFOB, thus simulating the situation in normal lung development. However, the authors focused on mRNA expression and protein analyses were not performed which should be a serious limitation for the interpretation of the results. Secondly, in this study diaphragmatic hernia was induced by fetal surgery of normal programmed lungs which makes the pathophysiology of developing CDH

potentially different as compared to humans. Moreover, in rabbits term birth occurs in the early saccular stage of lung development whereas in humans the alveolarization process has taken place already during gestation. Therefore a different respons on PFOB may be found in humans.

Although the prognosis of CDH has improved over the last years, it is still a life-threatening disease and ventilator induced lung injury remains a significant problem. Conclusive findings from randomized clinical trials may enable us to further improve the outcome of CDH. Once adverse long term effects of PLV have been excluded, setting up a randomized clinical trial of antenatal or postnatal instillation of PFOB in carefully selected patients might be a promising tool to further investigate alternative ways of supporting the vulnerable lungs in high risk newborns with CDH.

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Chapter 13

General discussion

Artificial ventilation of the lungs has been used to provide gas exchange both in healthy lungs and in diseased lungs due to a variety of congenital and acquired abnormalities. During the course of time the mode of ventilation has varied from negative pressure ventilation to positive pressure ventilation either in low or high frequency. The best way to ventilate children with acute respiratory failure has not yet been defined however. One of the problems is that these children have different underlying pathology and that we also have to take into account age-related factors such as lung growth and responses from the innate and adaptive immune systems [1]. In **chapter 2** we systematically reviewed randomized controlled trials comparing different ventilation modes used in critically ill children (term born up to 18 years of age) to find evidence for the best mode of ventilation. It is obvious that a "one size fits all" approach would be an overt oversimplification of the underlying problem as there is no standard method for measuring the effect of the mode of ventilation. In this regard, Randolph et al., suggested that long-term morbidity would be a more sensitive indicator than mortality or duration of ventilation [2, 3]. As long-term morbidity data were not available we pooled the results of five randomized clinical trials assessing the following outcomes: length of ventilation, oxygenation, chronic lung disease (CLD), mortality and weaning. Still we failed to find sufficient evidence for the best ventilation mode in critically ill children beyond the newborn period.

Therefore future clinical studies should be designed in such a way that modes of ventilation can be related to outcome [4, 5]. This strong recommendation from the pediatric acute lung injury consensus conference for mechanical ventilation of pediatric patients with acute respiratory distress syndrome is in line with our conclusions as formulated in **chapter 2** [1]. The Pediatric Acute Lung Injury Ventilation (PALIVE) study concluded that a robust study with reduction in mortality as an endpoint would take four years and 60 PICUs to enroll 800 patients, which is only possible by international collaboration [6]. If nevertheless a mode of ventilation could be selected for a certain group of patients, target ventilator settings with concomitant adjustment of ventilation need to be determined.

In **chapter 3** we described the implementation of such an algorithm for use in our PICU. Implementation of the algorithm improved physician adherence and this was sustained over time. However the maximum adherence was only 84% and was mainly achieved in the so-called "no-lung-disease" group. This result was obtained by intensive education and training indicating that implementation strategies tailored to specific circumstances are needed to increase adherence to protocols and guidelines. In healthcare in general and in particular in the intensive care setting it is still a challenge, however, to successfully implement evidence based strategies or therapies into daily clinical practice [7-10]. Apart from attempts to change healthcare professionals' behavior, organizational and structural (non-behavioral) implementation strategies need to be combined with

education and training. Therefore, getting insight in all influencing factors (e.g. human behavior, organization, provider characteristics) is a crucial first step to a tailored and multifaceted implementation strategy which could be more effective than the earlier mentioned "one size fits all" strategy. I agree with the authors [4], that international collaboration is imperative to design and perform large multicenter studies. **Chapter 3** also illustrates that protocols guiding daily care are a prerequisite for collaborative studies. Scientific societies like the European Society of Pediatric and Neonatal intensive Care (ESPNIC) or the Society of Critical Care Medicine (SCCM) should take the lead in organizing these studies.

Protective ventilation of the lungs

Despite optimal ventilator settings, gas exchange nay still be insufficient. Researchers have therefore explored alternative ways to recruit lung volume to participate in gas exchange. In 1992 an editorial by Burkhard Lachmann entitled "Open up the lung and keep the lung open" introduced the concept of recruiting atelectatic lung volume and ventilating the lung in the least harmful way [11]. This basic concept is still valid and just recently Amato nicely described the importance of the second part of the concept: Ventilate the lung in the least harmful way [12]. The focus on reducing tidal volume, initiated by the ARDS Network trial, means a shift away from Lachmann's original ideas [13]. Amato clearly demonstrated in adults that decreases in pressure amplitudes were significantly associated with increased survival [12]. Although the same physiological paradigms underlying the low tidal volume approach seem to apply to children, there are currently no pediatric studies showing any changes in outcome. Several reasons could be suggested. First of all the incidence, prevalence and mortality of pediatric ARDS are much lower than those of adult ARDS, so that mortality seems an inappropriate endpoint for prospective studies [14-16]. As stated earlier, long term morbidity might a better outcome parameter but clear definitions and data are lacking. Secondly, both the etiology of pediatric ARDS and the associated comorbidity might be different from adult ARDS. Lastly, recoverability of the lung might be different between adults and children, with inherent differences in the long term outcome of mechanical ventilation. Future research will need to focus on alternative outcome parameters including long term changes of lung function. Currently only adult data and animal data support the use of low tidal volume strategies in children on mechanical ventilation.

Several therapeutic strategies to increase recruitment of the lung and to improve gas exchange without increasing plateau pressures have been studied. Prone positioning is a method to recruit lung tissue; the patient is turned from supine to prone position thus allowing gravity to achieve changes in ventilation and perfusion of the lung. After several failed studies Gattinoni et al. finally showed improved survival in prone positioned patients, supporting the idea of "opening" up the lung [17].

Endotracheal application of surfactant is another of these therapies, and this has proven to be of benefit to premature neonates, both in randomized controlled trials as well as in meta-analyses and Cochrane reviews [18, 19]. The use of surfactant in the pediatric population beyond the neonatal period has shown mixed results in trials. It usually improved the oxygenation but without a beneficial effect on outcome and ventilator free days [20, 21]. Therefore the routine use of surfactant cannot be recommended [22]. In selected cases it may be feasible however, and we used surfactant as diagnostic/therapeutic tool (**chapter 7)** to test recruitability in individual patients during prolonged (i.e. 21 days or longer) extracorporeal membrane oxygenation (ECMO).

Another therapeutic approach to improve gas exchange is the use of perfluorocarbons (PFCs). Despite promising pre-clinical studies [23, 24] and initial enthusiasm in early clinical trials [25, 26] a larger randomized study showed no difference in mortality and patients ventilated with PFCs had fewer ventilator-free days [27]. Those patients also experienced more adverse events such as pneumothorax and hypoxic- and hypotensive episodes. These negative effects meant the end of the pharmaceutical company that supported these trials. The use of PFCs can still be attractive, however, for their anti-inflammatory effects and their potent to clear the airway from debris and stabilize the lung [28]. However currently the routine use of perfluorocarbons cannot be recommended, but its use in very special circumstances, for example to stimulate lung growth in neonates with congenital diaphragmatic hernia, might prove to be of benefit [29, 30]. We used PFCs to recruit lung volume in one case during prolonged ECMO (**chapter 7)**. To prevent ongoing lung injury other strategies can include the acceptance of mild hypoxia and hypercapnia in these patients. Ultimately the least harmful way to ventilate a lung is obviously to refrain from artificial ventilation, and to use other means of gas exchange to sustain life whereby hypercarbia and/or acidosis is avoided.

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Extra corporeal membrane oxygenation (ECMO)

The Pediatric Acute Lung Injury Consensus Conference Group strongly recommends the use of ECMO when respiratory failure is believed to be reversible and lung protective strategies result in inadequate gas exchange [31]. For children older than 4 weeks the type of ECMO to be used, the optimal way of vascular access and the optimal duration of ECMO are not yet well defined.

The first reported use of ECMO in the neonatal population dates from 1977 [32]. Since then over 36,000 neonates have been treated with ECMO [33]. In 2008 a Cochrane review of four randomized neonatal ECMO trials demonstrated strong benefit of ECMO on mortality compared to conventional ventilation, in that one death could be prevented with a number needed to treat of only three [34]. Over the last five years the number of neonates treated with ECMO for non-CDH respiratory failure has been slowly declining [35]. ECMO treatment for meconium aspiration syndrome (MAS) has decreased since the

end of the last century due to improvements in obstetric and neonatal intensive care [36, 37]. For a long time MAS was the most frequent non-CDH indication for ECMO resulting in the highest survival rate of all neonatal ECMO indications. To prevent reperfusion injury the care for children with MAS with an oxygenation index of 25 or higher is best discussed with or undertaken in an ECMO center [37]. Regarding CDH the role of ECMO is still not completely clear as many centers use ECMO either according to strict criteria or as a last attempt to save an individual newborn's life. In the VICI trial no definitive advantage of ECMO could be identified but survival was statistically better in patients treated in the ECMO centers without the actual use of ECMO [38].

In **chapter 4** we describe the current indications and contraindications of non-neonatal ECMO. In the case of children older than 4 weeks a tailored ECMO approach is needed to account for the wider diversity of disease. Furthermore, care for these patients needs to be centralized. The 2014 version 1.8 ELSO guidelines for ECMO centers states that a minimum of six ECMO cases per year is a criterion for quality of care. The arguments used are strong and self-explanatory arguments: Both the cost effectiveness and the clinical expertise are endangered with fewer than six cases per year. Recently a minimum of 20 cases per year was suggested for centers that offer ECMO for adult patients with adult acute respiratory failure [39]. Pediatric ECMO centers with a caseload of 22 or more show improved survival [40].

Due to the diverse nature of cardio-pulmonary failure it is difficult to define when ECMO is indicated. Evidence based criteria are even lacking for the initiation of ECMO in the case of pediatric acute respiratory distress syndrome (PARDS), which is a common indication for ECMO. The best indices for defining the severity of PARDS are the oxygenation index and PaO_2/FiO_2, although their ability to predict poor outcome for individual patients is poor [31].

Lactate as a biomarker
Increased arterial lactate, one of the end products of carbohydrate metabolism, was shown to be related to increased risk for mortality in critically ill adult patients [41, 42]. A study of goal-directed therapy in adult septic shock patients used lactate as a primary endpoint and showed improved outcome [43]. Reperfusion of tissue can result in a rise in arterial lactate because energy is needed for lactate formation [44]. Differences in lactate level can also be related, however, to age, time or other non-disease related situations [45, 46]. To account for these confounding factors, dynamic lactate indices have been developed that take into account duration of elevated lactate level and trend over time [47, 48]. A study presented in **chapter 5** evaluated the predictive value for mortality of static lactate and dynamic lactate indices in the prediction of. We found that in neonatal ECMO lactate did not predict mortality and that in pediatric ECMO static arterial lactate was the better predictor for mortality in patients with primary respiratory disease. In this

study, however, repeat measurements were not performed on the guidance of changes in clinical parameters, which should be done in future investigations. The same holds true for the concept of lactate-based therapy, which was successful in adult patients with sepsis who did not receive ECMO treatment. Apart from changes in lactate there are many descriptive studies about the latest and most predictive biomarkers for individual diseases and age groups. For example, more than 20 different biomarkers have been suggested to predict the development of bronchopulmonary dysplasia in prematurely born neonates, without finding the Holy Grail so far.

ECMO and Transposition of the great arteries (TGA)
Of all congenital heart defects, 5 to 9% are diagnosed as "simple" D-transposition of the great arteries (TGA) and this is the most frequent type of congenital cyanotic heart lesions. In this situation two parallel circulations exist: deoxygenated blood is re-circulated through the systemic circulation and oxygenated blood keeps circulating in the pulmonary circulation [49]. Profound hypoxemia may occur when the two circulations are inadequately mixed, resulting in death. Under these circumstances intra-cardiac, atrial or ventricular connections and a patent ductus arteriosus facilitate mixing of both circulations. If inadequate mixing occurs in the pre-operative postnatal period, urgent pharmacologic or interventional therapy, such as a balloon septostomy (Rashkind procedure), may be needed to provide adequate tissue oxygenation. When these measures fail to achieve adequate oxygenation two options remain. The first option is a so-called emergency arterial switch operation (ASO), which carries increased risks. The second option is to oxygenate the blood by using an extra corporeal circuit. In **chapter 6** we report six pre-operative ECMO patients with TGA. Five of those had pulmonary hypertension and one had persistent inadequate mixing of both circulations. These patients are not the first reported cases to receive pre-operative ECMO in TGA [50] but we provided additional information and were the first to show one year follow-up results of these patients. We discussed the difference between venovenous and venoarterial ECMO in this condition and argued that venovenous ECMO might be a good alternative to urgent ASO. To demonstrate a benefit of either treatment option in a prospective randomized clinical trial will be difficult as the reported incidence of severe pulmonary hypertension in TGA is only 5.3% [51]. Therefore a large number of pediatric cardiac centers would be needed to statistically prove differences in outcome between both treatment options.

Prolonged ECMO
Despite the enormous amount of patient data in the ELSO database this database has its limitations.
   Although outcome is registered no detailed information is available on how this was achieved. Moreover, data on diagnostic and therapeutic interventions are not consis-

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tently registered and no internal control of the data is provided or obligatory. It is therefore difficult to evaluate individual therapies during ECMO, especially during long ECMO runs where timing of interventions might be crucial to their success or failure. In **chapter 7** we report our case series of patients treated with ECMO for 21 days or longer, which occurs increasingly nowadays. Special attention was paid to the diagnostic procedures to assess reversibility of disease and to interventions needed, as the management and prognostication of these patients remains a challenge.

Most of these patients are so-called respiratory ECMO patients. The initial diagnosis may vary widely but for most patients ECMO is initiated to reduce the risk of ventilator-induced lung injury (VILI) or to maintain oxygenation or decarboxylation with failing mechanical ventilation. In practice it appears that most patients experience a period of extremely low or even no tidal volumes. There is currently no clear guideline on how to ventilate these patients.

CT scanning of the chest either in combination with abdominal scanning can provide quick and reliable information and can guide surgical or other interventions during ECMO [52]. When contrast is used during CT scanning, attention should be paid to the additional circulating blood volume and in case of venoarterial ECMO, to the amount of blood bypassing the lung through the ECMO system [53, 54].

Like in ARDS patients, for patients treated with ECMO interventions can be initiated to recruit lung volume or to improve oxygenation [55]. Few of those have been proven beneficial and some, like prone positioning, are inherently more dangerous for patients on ECMO. To date no good data exist about the usefulness of these interventions in extreme respiratory failure patients on ECMO, in which standard lung protective settings even after prolonged therapy do not seem to improve the patients' condition. In a prolonged ECMO setting these attempts to improve gas exchange might prove to be beneficial as the risks and costs of ECMO could be reduced by reducing time on ECMO. However it is as yet unclear whether this is beneficial and if so, what would be the appropriate timing of these procedures.

The reduction in sedatives consumption can lead to more interactive patients. Some patients can thus become eligible for extubation. This so-called awake type of ECMO in combination with minimal sedation is one of the newest insights in ECMO treatment, which can possibly help to prevent critical illness myopathy and neuropathy (CRIMYNE) [56-58]. In some cases, however, efforts to minimize sedation and to extubate the patient do not seem to be successful. Despite adequate gas exchange and reducing hypercarbic breathing drive some patients seem to be in respiratory distress. They show signs of dyspneic breathing or nasal flaring although when asked they report to feel fine. This situation requires a different mindset of the healthcare team and the parents [59].

Most patients experience a period with very low to no tidal volumes. In our cohort of patients on prolonged ECMO, tracheal occlusion or bronchial occlusion occurred fre-

quently as a complication and routine bronchoscopy in these patients seems indicated to optimize ventilation. Other restricting factors to lung recruitment should be evaluated. Timing of these interventions remains controversial, especially since recoverability of the primary disease as well as the potential to add secondary damage need to be balanced.

When ECMO has been started but there are still uncertainties about the nature or reversibility of disease, both a CT scan and an open lung biopsy can help to classify the disease and guide therapy.

Based on our experience described in **chapter 7** we propose that in patients on ECMO high ventilator settings leading to increased risk of VILI should be avoided. In the early phase peak pressures as well as tidal volumes should be kept low. Appropriate PEEP levels to keep the lung open should be chosen but in many patients no ventilation will be possible for several days or even weeks. All patients should be evaluated for potential airway obstruction and restrictive pleural, thoracic or abdominal abnormalities that might be treated. Future research should focus on long-term recoverability of lung function. Evaluating lungs function by standardized recruitment maneuvers once every week and supplemented by standardized CT scans on days 14 and 28 in all ELSO ECMO centers could provide a better categorization of lung pathology and potential lung recoverability, especially if this data is consistently added to the ELSO registry.

Surgery and ECMO
In **chapter 8** we show the potential benefit and feasibility of open lung biopsy on ECMO. All open lung biopsies during ECMO from the two designated Dutch neonatal ECMO centers were analyzed as well as the clinical impact of the biopsy results. There is a major difference in this regard between newborns and older children. In the newborn the main diagnosis to be ruled out is alveolar capillary dysplasia/misalignment of pulmonary veins (ACD/MPV), which is a reason to consider continuation of ECMO as futile. For obvious reasons this diagnosis should ideally be made prior to the institution of ECMO but unfortunately in many cases the clinical condition of the individual child is not stable enough to justify such an approach. Genetic evaluation predominantly focusing on the FOXF1 gene mutation can support the diagnosis but as approximately only 50% of patients carry this mutation, false negative cases do occur. Other diagnoses leading to reconsidering the continuation of ECMO are lymphangiomatosis of the lung and the very rare cases of interstitial glycogenosis. In most reports from high volume ECMO centers we can find cases of withdrawal of therapy. Another diagnosis that should be proven or ruled out is a surfactant-B deficiency as the cause of the respiratory failure, preferably before starting ECMO treatment by DNA analysis of blood and/or tracheal aspirates. Deciding on futility of treatment in non-neonatal ECMO can be very difficult or even impossible [60] Biopsy of the lung could guide therapy, however, seeing that the

result was a reason for a change in therapy in most adult patients, but not in all pediatric patients. It may be the only option to obtain a diagnosis while the patient is alive [61, 62]. In case no biopsy result is available before death of the patient it is essential to obtain a postmortem tissue specimen in the first hours after death by open biopsy. When postmortem lung biopsy is performed, it preserves the opportunity for the parents to take their child home, as is done frequently in the Netherlands.

In **chapter 9** we analyzed the surgical pitfalls of the correction of CDH on ECMO, notably the risk of bleeding, and found that despite anticoagulation this practice is safe and feasible.

There is no consensus on the optimal timing of surgical correction of a diaphragmatic defect although in general the risk of bleeding is higher during ECMO then after ECMO [63]. In our institution over the years we shifted from late repair to repair 48-72 hours after the initiation of ECMO so as to profit from ECMO support in case of surgical complications, decreased lung volume and possible pulmonary hypertension. There are no RCTs evaluating the best timing of the procedure and many clinics are probably not willing to participate in such a trial against the background of their best practice "gut feeling" on this subject. Besides timing of repair, also expertise in repairing such as the optimal patch material and the determination of the size of the patch are points to investigate systematically. In principle a classic laparotomy provides the best view on the defect. The treatment of bleeding sites during and after repair is a fundamental part of the success rate and no guidelines are at present available to determine best practice. Newer ECMO systems may provide for absence of systemic anticoagulation during the surgical correction of the diaphragmatic defect.

Pharmacotherapy and ECMO

ECMO in itself is not a cure, it is merely a life-sustaining therapy on the way to recovery. Pharmacotherapy plays an important role in both the management and treatment of ECMO patients. Analgesics and sedatives, inotropes, anticoagulants and antibiotics are routinely given to almost all patients. Furthermore antivirals, anticonvulsants and anti-inflammatory drugs may be administered during the course of ECMO. Although by now we have a fair amount of knowledge on the changes of pharmacokinetics (PK) in children, clear pediatric data are still lacking for most drugs [64]. Dosing is mostly based on adult healthy volunteer data and extrapolated to children. Ontogeny plays an important role in the changes of PK and pharmacodynamics (PD) in children [65]. With maturation of organ and enzyme functions the PK and PD change rapidly over time from the newborn to the adolescent age [65, 66]. Besides ontogeny critical illness and multiple organ dysfunction will change PK and thereby total drug exposure. Fluid loss, fluid overload and changes in protein content can influence volume of distribution, e.g. how the drug disperses in the body. While organ perfusion will change in accordance

with cardiac function, renally cleared drugs will be influenced by renal function. For hepatically cleared drugs it is more difficult to estimate clearance. The most important mechanism of liver clearance is via the cytochrome P450 enzyme system. Several authors have shown that this system is inhibited during critical illness [67-70]. Vet et al. recently showed a clear correlation of midazolam clearance and CRP in that high CRP levels were associated with a reduced midazolam clearance [69, 71]. Adding ECMO to this already complex system complicates the situation further. The earliest reports of altered PK during ECMO date from the 1980s and 1990s, showing altered PK for fentanyl and morphine [72, 73]. The ECMO system itself was shown to adsorp considerable amounts of drugs in either the membrane or tubing [72-74]. There seems to be a clear relationship between lipophilicity and adsorption rates where highly lipophilic drugs such as midazolam and midazolam are almost completely adsorped in silicone based membranes [75]. Still, the new smaller ECMO circuits with hollow fiber membranes considerably reduced the amount of loss of the more lipophilic drugs [75]. Thus, changes in ECMO system design may have profound effects on drug availability indicating the need to study drug adsorption in newly designed circuits. Changes in coating may also affect drug adsorption and should be taken into account when changing ECMO circuits [76, 77].

Recently Shekar et al. performed a series of in vitro studies showing variable adsorption rates of antibiotic and antimycotic drugs [78]. Furthermore both lipophilicity and the amount of protein binding were associated with the amount of drug loss [78]. Mulla et al. showed that both the membrane and the tubing can be saturated with drugs although in vitro studies contradict each other on differences in drug adsorption between used and new ECMO circuits [74, 75].

In **chapter 10** we give an overview of the different aspects of PK and PD in ECMO patients by reviewing the literature.

Initial reports show increased volume of distribution with decreased clearance, suggesting increased loading doses and reduced maintenance doses. Increasingly there are reports on increased clearance on ECMO [79, 80]. Several mechanisms may play a role here. Compared to pre ECMO conditions patients rapidly improve on ECMO with both hemodynamics and oxygenation being restored. Improvements in organ perfusion may result in improved drug clearance over time. Secondly, some drugs such as meropenem are sensitive to light if exposed for more than three hours [81]. In the normal clinical setting this may be irrelevant but it may have played a role in a study by Shekar et al. who found increased clearance of meropenem in ECMO patients [79]. In vivo case reports and cohort studies are increasingly showing PK in individual drugs. For some drugs such as oseltamivir or cefotaxim no change in dosing seems to be necessary, which is valuable information [80, 82]. For other drugs the clearance is significantly altered necessitating dose changes, but more often data is conflicting as both decreased and increased clearance over time is reported [79, 83-85].

For sedatives and analgesics it is clear that lipophilic drugs such as fentanyl, propofol and midazolam are adsorped to a large extent and several studies show increased dosing requirements for these drugs. Initial drop in sedatives will result in high doses. Changes in clearance over time may subsequently result in overdosing and drug dependency with severe withdrawal syndrome as a result. Efforts to wake our ECMO patients and have them extubated are sometimes frustrated by this problem necessitating prolonged intubation during weaning of sedatives.

Especially with prolonged ECMO treatment it is difficult to predict the changes in PK over time. Changing ECMO systems, changes in fluid overload, organ function and inflammation all influence PK and may result in either under or oversedation. The current efforts to identify specific drug characteristics that predict PK changes in ECMO patients should be continued supplemented by case reports on rare drugs. Ultimately larger cohorts such as the ASAPECMO initiative are needed to identify covariates that predict changes over time. To increase the accuracy of these models this should be evaluated in conjunction with non- ECMO data. By combining non-ECMO and ECMO data Krekels et al. demonstrated that a non-ECMO model would predict ECMO drug levels accurately showing that for morphine ECMO itself is not a relevant covariate [86].

In vitro testing should be done on all new ECMO circuits and coatings to predict drug adsorption with an added focus on saturation and potential reversal of adsorption during prolonged ECMO. Then possible routine measurement of frequently used drugs will enable accurate dosing in these patients.

A new mini pump for ECMO

In **chapter 11** we describe a case series of 241 consecutive ECMO patients treated with a newly developed mini pump with a very small priming volume. In comparison with the classic ECMO therapy using a roller pump, a significant priming volume of the ECMO circuit and a different material of the membranes, the results of the use of the mini pump system are at least comparable with the "old" system. It would have been ideal to have had a different design of our study such as a comparative effectiveness design of our prospective data collection. However the use of a new system places treatment teams for other challenges and the effect of a learning curve should not be underestimated before a real comparative approach could be tested. Our study describes the largest international data collection within a reasonable time frame and forms as such a reference for future studies regarding the feasibility, efficacy and complications during the use of this mini pump system. An additional advantage given the size of the system is the opportunity for transport of patients on ECMO and its ease of use in emergency situations such as rescue therapy during resuscitation either inside or outside the hospital.

In **chapter 12** we discuss the current status of the use of perfluorocarbons (PFCs) in respiratory failure. Our editorial comments on the paper by Herber-Jonat, which describes the prenatal Intrapulmonary instillation of PFCs in rabbits with induced congenital diaphragmatic hernia and shows that the use of PFCs resulted in an improvement of lung-to-body weight ratio of these lungs.

Considerations and perspectives

Primum non nocere, meaning "first do no harm" and often attributed to Hippocrates but traceable to Thomas Inman (1820-1876), is in itself the guidance for medical care [87]. In the treatment of patients with failure of gas exchange, the stakes are high and "harm" lurks around the corner. Too little is known about the "harm" inflicted by mechanical ventilation, ECMO, or both in synergy. As ECMO is a high-tech treatment modality, there is considerable risk of "iatrogenesis" on top of the potential unwanted effects for the individual patient. Focus on survival as outcome parameter still drives the current literature although ECMO seems to have evolved from a rescue therapy to a means of chronic support for failing gas exchange and even as a means to prevent secondary lung damage. Super acute ECMO resuscitation or ECPR represents the other end of the spectrum where the primary focus still lies on increasing survival. Management of ECMO patients is still highly experience based. Large databases like the ELSO registry report on worldwide averages in outcome of different patient groups, but cannot explain differences in outcome between different centers. Moreover there is no adequate system of quality control of the data provided by the centers. The offered possibility to benchmark the individual results of the participating centers does not benefit the group as a whole. Data on diagnostics and therapeutic interventions are not consistently registered in the ELSO registry. Individual centers have to focus on all items and must draw conclusions from the available information. This approach therefore cannot lead to a universal set of treatment guidelines. More detailed data collection might make it possible to conduct larger comparative effectiveness trials to identify effective treatment modalities or care bundles associated with better outcome, as is currently done in the field of traumatic brain injury [88-90].

Another option is to reduce the number of centers treating these "difficult" cases. In the Netherlands the balance between centralization and individual freedom to treat is changing. Over the last decade ECMO patients on adult ICUs have been centralized, whereas PICUs more and more start their own ECMO programs and individual patients are consequently subject to the learning curve effects of these centers. At present ECMO is offered in the four pediatric cardiac centers in the Netherlands as a way of postoperative cardiac support in direct relation to cardio pulmonary bypass. However, patient with other indications should all be treated in the two designated ECMO centers in the

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Netherlands as approved by the Dutch Healthcare Authority NZA. Before widespread use can be deployed several issues need to be clarified.

Device technology
Despite progress in design, reliability and costs, the manufacturers of ECMO related equipment should take their responsibility to manufacture state of the art equipment specialized for neonatal and pediatric use. One of the "big three" issues in ECMO care is cannula technology and availability of these cannulas. Recently many types of ECMO cannula have been withdrawn from the market and especially the availability of heparin coated types has become minimal. As with other medical products, the vulnerability of production processes frequently results in shortages in cannulas. Whether surgical or echo-guided percutaneous cannulation is preferable needs to be investigated. Innovations such as a Dacron cuff might help to stabilize ECMO cannula position in prolonged ECMO runs and possibly prevent infection.

Anticoagulation technology
The traditional use of heparin as the major drug for anticoagulation will remain. However the amount of anticoagulation will need to be targeted to age, disease severity and type of equipment. The way of testing the level of anticoagulation needs to become universal, as only then international comparisons become valid. Unfortunately, structured collaboration between ECMO treatment teams and hematologists is still minimal in many institutions. Multicenter approaches are essential to tackle this problem [91].

Patient selection
In analogy to the results of the CESAR trial in adults, where referral to an ECMO center resulted in improved survival, it would be worthwhile to know which pediatric patients with what diagnoses will benefit from referral to an ECMO center [92]. Compiling a list of diagnoses with dismal outcome is equally important. Alternatively the conclusion could be that contraindications are disappearing [93]. Up to then liberal communication about early referral between centers is desired. This will for the individual patient not result in automatically start of ECMO in the centers upon arrival. In our experience, ECMO was not started in about 40% of the non-neonatal patients transferred for ECMO. A change in supportive therapy and/or reevaluation of the indication or contraindication determined whether ECMO was started. Even today no international consensus exists on the indications for non-neonatal ECMO candidates and many centers are not aware of the relative contribution in the mortality rates of patients with isolated respiratory failure in their respective units over the last five years. These data could determine the role of ECMO in the prevention of mortality.

With the increasing complexity of ECMO patients, a multidisciplinary approach is essential to manage these patients successfully [94]. The entire ECMO process starts with the indication for ECMO, but continues far longer than the eventual decannulation. Long-term follow up care must form an integral part of an ECMO program. The risks and benefits for the individual patients of diagnostic or therapeutic interventions during ECMO need to be weighed by an experienced team with members from a wide range of disciplines and obviously the infrastructure should allow for performing these interventions as safely as possible. Concentration of ECMO patients does therefore not only pertain to the ECMO physicians, perfusionists and ECMO nurses but should involve the whole range of pediatric specialists, rehabilitation and physiotherapists.

In conclusion: ECMO has found a place in the contemporary arsenal to treat the individual pediatric patient but is still a modality with inherent high risk factors. ECMO should therefore be applied only in designated centers with experienced teams. Furthermore, survivors should be included in a long-term follow-up program to establish any long term morbidity. It is the responsibility of the ECMO teams to share the information obtained with the medical and layman communities.

ECMO is a fascinating relatively new technology to which the words of Spinoza may still apply:

"Be not astonished at new ideas; for it is well known to you that a thing does not therefore cease to be true because it is not accepted by many." - Spinoza (1632-1677)

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Chapter 14

Summary, Samenvatting, List of abbreviations.

SUMMARY

The overall aim of this thesis is to provide scientific data that will help to guide the treatment of failing gas exchange in pediatric patients.

Part 1. Mechanical ventilation for failing gas exchange in children

In **chapter 2** we search the literature for evidence to provide the optimal ventilatory modes for artificial ventilation of pediatric patients. We show that the available literature does not provide sufficient evidence on the best ventilation mode in critically ill children beyond the newborn period. With regards to high-frequency ventilation we found that it provided better oxygenation after 72 hours than conventional ventilation. However, there is no evidence that high-frequency ventilation would reduce mortality and length of ventilation. With this knowledge we defined our institutional algorithm for ventilation of critically ill children. In **chapter 3** we describe the implementation of such an algorithm for use at our PICU. This algorithm improves physician's adherence to the ventilation algorithm and the effect was shown to be sustainable over time.

When lung protective ventilation does not provide sufficient gas exchange an alternative way to supply oxygen and to remove carbon dioxide is Extracorporeal Membrane Oxygenation (ECMO). In **chapter 4** we describe the available evidence for the use of pediatric ECMO in respiratory and circulatory failure. With this evidence at hand we propose indications and contraindications for non-neonatal ECMO that can for the base for international collaboration.

Part 2. Extracorporeal Membrane Oxygenation to assist gas exchange in children

In **chapter 5** we focus on the predictive value of lactate measurements. Lactate, is an end product of carbohydrate metabolism and correlates to both severity of illness and mortality. We evaluated the significance of static lactate and dynamic lactate indices in the prediction of mortality. The outcome of this study illustrated that in neonatal ECMO lactate did not predict mortality and in pediatric ECMO static arterial lactate was the better predictor for mortality in patients with primary respiratory disease.

In **chapter 6** we present a retrospective analysis of the potential role of preoperative ECMO in neonates born with transposition of the great arteries with severe hypoxemia despite conventional measures. We show that despite interventions to improve oxygenation, critical hypoxemia does occur and that preoperative ECMO can help to stabilize the patient and allows for subsequent surgical correction of the defect.

With more and more patients on ECMO for increasing periods of time, well defined guidelines in the literature how to manage these patients are missing. We reported

in **chapter 7** our patients on ECMO for 21 days or longer. We show that especially in respiratory ECMO cases survival to discharge can be 44%. We show that both medication and interventions play an important role in the management of these prolonged ECMO cases.

One of those interventions during ECMO is open lung biopsy. This technique is used to determine the origin of the disease and sometimes can be used to guide therapy of to determine futility. In **chapter 8** we report on the feasibility and safety and results of open lung biopsy during ECMO. We show that biopsy is recommended after seven days of ECMO, except when ACD/MPV or another lethal congenital pulmonary abnormality is highly suspected. In that case biopsy is recommended within the first week of ECMO or ideally before ECMO is initiated. Another intervention during ECMO is surgery. Surgery during a status of anticoagulation can be troublesome. In **chapter 9** we show that with slight adjustments in the level of anticoagulation surgical correction of congenital diaphragmatic hernia can safely be performed during ECMO.

Chapter 10 gives an overview of the available pharmacokinetic (PK) and pharmacodynamics (PD) studies in neonates and children on ECMO, suggesting a number of possible mechanisms of altered PK. PK of several drugs is altered in neonates and children on ECMO. Changes in PK are drug and circuit dependent with more dramatic changes found for lipophilic drugs and in case the circuit contains silicone oxygenators. But basically this chapter shows that evidence based dose regimens are still largely lacking for many regularly used drugs in neonates and older children on ECMO.

In **chapter 11** we describe a case series of 241 consecutive ECMO patients, treated with a new diagonal centrifugal mini pump with a very small priming volume. The results of this study are at least comparable with the" old" system and shows the largest international data collection within a reasonable time frame. As such it can form a reference for future studies

Chapter 12 contains amongst others an editorial paper based on a laboratory study in rabbits with induced congenital diaphragmatic hernia (CDH), in which we discuss the future perspectives of the use of perfluorocarbons in CDH.

In **chapter 13** the main results of our studies are discussed within the context of the international literature and considerations and perspectives are defined for the future management of pediatric ECMO patients including a plea for international evidence based guidelines and collaboration. **Chapter 14** contains the summary.

SAMENVATTING

Het doel van dit proefschrift is om wetenschappelijke gegevens te genereren die helpen om de behandeling van falende gasuitwisseling bij kinderen te verbeteren.

Deel 1. Mechanische beademing voor falende gasuitwisseling bij kinderen

In **hoofdstuk 2** zoeken we in de literatuur naar bewijzen voor optimale beademingsinstellingen tijdens kunstmatige beademing bij kinderen. De beschikbare literatuur voorziet niet in voldoende bewijs voor de beste ventilatiemodus bij ernstig zieke kinderen buiten de pasgeboren periode. Met betrekking tot hoogfrequente beademing vonden we dat dit een betere oxygenatie geeft na 72 uur dan conventionele beademing. Er is echter geen bewijs dat hoogfrequente beademing de mortaliteit en beademingsduur zou verminderen. Met deze kennis werd op onze afdeling een algoritme voor beademingsinstellingen van ernstig zieke kinderen vastgesteld. In **hoofdstuk 3** beschrijven we de implementatie van een dergelijk algoritme voor het gebruik op onze kinderIC. Dit algoritme verbetert de uitvoering door artsen van het beademingsalgoritme en dit effect bleek duurzaam te zijn.

Wanneer long beschermende beademing niet voldoende gasuitwisseling geeft, is een alternatieve manier om zuurstof to te dienen en kooldioxide te verwijderen, Extracorporele Membraanoxygenatie (ECMO). In **hoofdstuk 4** beschrijven we het beschikbare bewijs voor het gebruik van ECMO buiten de pasgeboren leeftijdsperiode voor respiratoir en circulatoir falen. Met dit bewijs stellen wij indicaties en contra-indicaties op voor niet-neonatale ECMO, die de basis kunnen vormen voor internationale samenwerking.

Deel 2. Extracorporele membraanoxygenatie om gasuitwisseling bij kinderen te ondersteunen

In **hoofdstuk 5** richten we ons op de voorspellende waarde van lactaat metingen. Lactaat is een eindproduct van koolhydraatmetabolisme en correleert met zowel de ernst van ziekte als de sterfte. We evalueerden de betekenis van lactaat; statische en dynamische lactaat indices in de voorspelling van mortaliteit. De resultaten van deze studie hebben aangetoond dat bij pasgeborenen tijdens ECMO lactaat niet voorspellend was voor de kans op overlijden en bij oudere ECMO patiënten statische arteriële lactaat meting een hogere voorspellende waarde heeft voor het overlijden bij patiënten met primair falen van de longen.

In **hoofdstuk 6** presenteren we een retrospectieve analyse naar de mogelijke rol van preoperatieve ECMO bij neonaten, geboren met een transpositie van de grote vaten, met een ernstige hypoxemie ondanks conventionele maatregelen. We laten zien dat ondanks interventies om de oxygenatie te verbeteren, kritische hypoxemie optreedt en

dat preoperatieve ECMO kan helpen de patiënt te stabiliseren en zo de mogelijkheid biedt voor verdere chirurgische correctie van het hart.

Met meer en meer patiënten aan ECMO, voor steeds langere perioden, ontbreken in de literatuur goed gedefinieerde richtlijnen voor de behandeling van deze patiënten. We beschrijven in **hoofdstuk 7** onze patiënten, die gedurende 21 dagen of langer ECMO-behandeling kregen. We laten zien dat met name bij patiënten met respiratoire ECMO , overleving tot ontslag 44% kan zijn. We tonen aan dat zowel medicatie als interventies een belangrijke rol spelen bij de behandeling van deze langdurige ECMO patiënten.

Een van de interventies tijdens ECMO is "open longbiopsie". Deze techniek wordt gebruikt om de oorsprong van de ziekte te bepalen en soms wordt de uitkomst gebruikt om de therapie aan te passen of om vast te stellen dat de behandeling uitzichtloos is. In **hoofdstuk 8** beschrijven we de haalbaarheid en de veiligheid en de resultaten van de "open longbiopsie" tijdens ECMO. We laten zien dat biopsie wordt aanbevolen na zeven dagen ECMO, tenzij Alveolaire Capillaire Dysplasie (ACD / MPV) of een andere dodelijke aangeboren longafwijking sterk wordt vermoed. In dat geval wordt biopsie aanbevolen binnen de eerste week van ECMO of idealiter voor de start van ECMO. Een andere interventie tijdens ECMO is een operatie. Chirurgie tijdens het gebruik van ontstolling kan lastig zijn.

In **hoofdstuk 9** laten we zien dat met kleine aanpassingen in het antistollingsniveau, chirurgische correctie van een congenitale hernia diafragmatica veilig kan worden uitgevoerd tijdens ECMO.

Hoofdstuk 10 geeft een overzicht van de beschikbare farmacokinetische (PK) en farmacodynamische (PD) studies bij pasgeborenen en kinderen aan ECMO en beschrijft een aantal mogelijke mechanismen voor veranderingen in de farmacokinetiek De PK van verschillende geneesmiddelen verandert bij pasgeborenen en kinderen aan ECMO. Veranderingen in de PK zijn medicatie en circuit afhankelijk, waarbij grotere veranderingen gevonden worden bij zogenaamde lipofiele geneesmiddelen en bij het gebruik van systemen met siliconen membraanlongen. Maar vooral laat dit hoofdstuk zien dat evidence-based doseringsschema's nog grotendeels ontbreken voor veel van de regelmatig gebruikte medicijnen bij pasgeborenen en oudere kinderen aan ECMO.

In **hoofdstuk 11** beschrijven we een serie van 241 opeenvolgende ECMO patiënten, behandeld met een nieuwe diagonale mini centrifugaalpomp met een zeer klein volume. De resultaten van deze studie zijn ten minste vergelijkbaar met de "oude" systemen en tonen aan dat een grote verzameling internationale gegevens binnen een redelijke termijn te verkrijgen is. Als zodanig kan dit een referentie voor toekomstige studies vormen.

Hoofdstuk 12 bevat een editorial naar aanleiding van een experimentele studie bij konijnen met geïnduceerde congenitale hernia diafragmatica, waarin we het gebruik van perfluorocarbons bij congenitale hernia diafragmatica evalueren.

In **hoofdstuk 13** worden de belangrijkste resultaten van onze onderzoeken besproken in de context van de internationale literatuur. Overwegingen en perspectieven worden gedefinieerd voor de toekomstige behandeling van kinderen met ECMO, waaronder een pleidooi voor internationale evidence-based richtlijnen en samenwerking.

Hoofdstuk 14 bevat de samenvatting.

14

LIST OF ABBREVIATIONS

AaDO2	Alveolar-arterial oxygen tension difference
ACD/MPV	Alveolar capillary dysplasia/misalignment of pulmonary veins
ACT	Activated clotting time
ARDS	Acute respiratory distress syndrome
ASO	Arterial switch operation
BAS	Balloon atrial septostomy
BSI	Blood stream infections
CDC	Centre for disease control
CLD	Chronic lung disease
CPB	Cardio pulmonary bypass
CPR	Cardio pulmonary resuscitation
ECMO	Extracorporeal Membrane Oxygenation
ECLS	Extracorporeal life Support
ELSO	Extracorporeal life support organization
FiO2	Fraction of inspired oxygen
ICU	Intensive care unit
IQR	Inter quartile range
LCOS	Low cardiac output state
LC-MS	Liquid chromatography-mass spectrometry
LOV	Length of ventilation
MCS	Mechanical cardiac support
NO	Nitric oxide
NONMEM	Nonlinear mixed effect modelling
NRS	Numeric rating scale
O.I.	Oxygenation index
pCO2	Partial arterial pressure of carbondioxide
PD	Pharmacodynamics
PDMS	Patient data management system
PF	Pao2/Fio2 ratio
PFC	Perfluorocarbon
PH	Pulmonary hypertension.
(P)ICU	(Pediatric) intensive care unit
PK	Pharmacokinetics
pO2	Partial pressure of oxygen
RRT	Renal replacement therapy
SaO2	Saturation of oxygen
VA	Venoarterial
VAD (R)(L)	Ventricular assist device (R)ight, (L)eft
VA-ECMO	Venoarterial extracorporeal membrane oxygenation
VV	Venovenous
VV- ECMO	Venovenous extracorporeal membrane oxygenation
VVDL	Venovenous double lumen

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CURRICULUM VITAE

Robert Jan Houmes was born on the 10 of August 1963 in Middelburg. He finished is high school at the Stedelijke Scholengemeenschap Middelburg (SSGM) in 1983 and in 1992 he obtained his medical degree at the Erasmus University Rotterdam. After his medical degree he started medical research at the department of experimental anesthesiology at the Erasmus University at the department of professor Lachmann. In 1994 he started clinical work as a resident in anesthesiology at the Erasmus MC Hospital in Rotterdam. In 1998 he started working as a helicopter emergency physician (HEMS) at the Mobile medical team (MMT) of the trauma center at the ErasmusMC Hospital. In 2001 he became the medical coordinator of the MMT. In 2001 after he finished his training as an anesthesiologist he continued working in the same department as pediatric anesthesiologist (prof W. Erdmann). In 2001 he started working part-time as pediatric intensivist at the Pediatric Surgical ICU of the Department of Pediatric Surgery of the Erasmus MC Sophia Children's Hospital (head prof D. Tibboel). In 2004 he was appointed as medical coordinator of the Pediatric Surgical ICU of the Department of Pediatric Surgery of the Erasmus MC Sophia Children's Hospital. In 2007 he became medical coordinator of the ECMO program of the Erasmus MC Sophia Children's Hospital. In 2008 after the merging the two specialized ICU's in the Erasmus MC Sophia Children's Hospital he became medical coordinator of the ICU. Robert Jan lives in Dordrecht with his wife Judith and their children Maurits and Hannah and their dog Maggie.

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PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Robert Jan Houmes
Erasmus MC Department: Intensive Care and Department of Pediatrics
PhD period: 2011-2016
Promotors: Prof.dr. D. Tibboel
                        Prof.dr. R Wijnen
Copromotor: Dr. E.D. Wildschut

	Year	Workload (ECTS)
General courses		
BROK (Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers)	2016	1
Research Integrity	2016	0.3
Specific courses		
Advanced Life Support	2014	0.4
Symposia and workshops		
Erasmus Airway Management day, Rotterdam The Netherlands (oral presentation)	2011	1
Erasmus Critical Care Days, Rotterdam The Netherlands (oral presentation)	2011	1
Post Academisch Onderwijs Sophia Fellowdag Kinder-IC/Kindercardiologie (oral presentation)	2012	1
2e Erasmus Critical Care Day Rotterdam, The Netherlands (oral presentation)	2013	1
ECMO, Extra Corporele Membraan Oxygenatie, opereren op de IC", Rotterdam, The Netherlands. (oral presentation)	2013	1
Nederland Waterland: De Traumazorg op Koers, Leiden, The Netherland, (oral presentation)	2014	1
Erasmus Airway Management day (oral presentation)	2015	1
Werkgroep educatieve symposia (WES) symposium: (oral presentation)	2015	1
Workshop Xenios ECMO, Freiburg, Germany	2015	0.3
Ontwikkelingen in de acute zorg, Rotterdam, The Netherlands (oral presentation)	2016	1
(Inter)national Conferences		
37.Jahrestagung der Gesellschaft fur Neonatologie und PadiatrischeIntensivmedizin, Mannheim Germany	2011	1
International Course on ECMO and Short Term Circulatory Respiratory System, Paris, France	2011	1
The 27th CNMC Symposium ECMO and Advanced Therapies for Respiratory Failure, Keystone, USA	2011	1

International Course on ECMO and Short Term Circulatory Respiratory System, Paris, France	2012	1
24th Annual Meeting of the European Society of Pediatric and Neonatal	2013	1
Intensive Care, Rotterdam, The Netherland BAPA Annual Scientific Meeting, Airway and trauma management in Children, Leuven, Belgium oral presentation)	2013	1
5th International Pediatric Simulation Symposia and Workshops,	2013	0.9
New York, USA ECMO and Advanced Intensive Care, The 2nd ECMO EuroELSO Meeting, Stockholm.Sweden (oral presentation)	2013	1
International Course on ECMO Short Term Circulatory Respiratory support, Paris, France	2013	1
symposium Kinder orgaan donatie, Rotterdam, The Netherlands, (oral presentation)	2013	0.2
3rd European Conference on Pediatric and Neonatal Cardiac Intensive Care. Luzern, Switserland. (oral presentation)	2013	1
6th International Pediatric Simulation Symposia and Workshops, Vienna, Austria	2014	0.4
3th International Course on ECMO and Euro-ELSO.Paris, France oral presentation	2014	1
36th Congres Kindergeneeskunde,Veldhoven, The Netherlands (oral presentation)	2014	1
EuroELSO 2015,4th International Congress, Regensburg, Germany	2015	1
Teaching activities		
ECMO training Florence, Italy	2015	0.5
ECMO training. Rotterdam, The Netherlands	2011	1.2
	2012	0.4
	2013	0.7
	2014	0.2
	2015	0.9
Crew resource management, Rotterdam, The Netherlands	2011	0.5
	2012	5.4
	2013	3.4
	2014	3.4
	2015	0.3
Scenario based team training, Rotterdam, The Netherlands	2011	0.3
	2012	0.5
	2013	0.2
	2014	0.1
	2015	0.1

ECTS = European Credit Transfer and Accumulation System
1 ECTS credit represents 28 hours

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