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Retinal findings in neonates with congenital diaphragmatic hernia and extracorporeal membrane oxygenation☆,☆☆

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ABSTRACT

Purpose: To evaluate the prevalence of retinal pathologies in neonates with congenital diaphragmatic hernia (CDH) receiving extracorporeal membrane oxygenation (ECMO) therapy.
Methods: This retrospective study included consecutive infants that received ECMO therapy for CDH at our hospital between 2012 and 2018. Retinal changes were assessed by mydriatic indirect funduscopy. Recorded patient parameters include gestational age (GA), type of delivery, duration of ECMO therapy, duration of inhalative oxygen supplementation, and postmenstrual age at fundus examination.
Results: Of 54 infants that were treated by ECMO therapy for CDH during the study period, 27 were medically stable enough to receive funduscopic examination and were thus included in the study. Mean GA of these 27 children was 37.3 weeks (range 33.1–40.6) and mean duration of inhalative oxygen supplementation was 12.8 weeks (range 2.7–56.4). Retinal changes were observed in 3 neonates (11.1%). These included multiple midperipheral blot intraretinal hemorrhages in 5 eyes of 3 children and retinopathy of prematurity (ROP) in 2 eyes (stage 3 and stage 2, respectively, without plus disease) of 1 child (GA 35.0 weeks; duration of inhalative oxygen supplementation, 11.9 weeks). In all infants, retinal changes regressed without therapeutic intervention.
Conclusions: Neonates treated with ECMO due to CDH may exhibit retinal hemorrhages, however usually without need for intervention. Prematurely born infants receiving ECMO may develop ROP and thus require ROP screening examinations.
Type of study: Prognosis study.
Level of evidence: Level III.

Congenital diaphragmatic hernia (CDH) is a malformation of the diaphragm that occurs in about 1:4000 live births [1,2]. Incomplete formation of the diaphragm during embryogenesis leads to a lack of separation of the abdominal and thoracic cavities allowing the abdominal viscera to protrude into the chest cavity which impairs normal growth and development of the fetal lung [3]. Subsequently, distinct anatomic changes may entail, consisting of pulmonary hypoplasia, abnormal bronchial and vascular branching pattern, and an impaired pulmonary vasoreactivity [4]. Usually, these patients present with severe respiratory failure and pulmonary hypertension at birth.

Extracorporeal membrane oxygenation (ECMO) functions as a circulatory and respiratory support to prevent irreversible organ dysfunction caused by severe hypoxemia. This may allow recovery of lungs or decline of elevated pulmonary vascular resistance. However, ECMO potentially bears significant system-related complications that influence survival and long-term outcome. ECMO involves systemic anticoagulation placing infants at risk for life threatening hemorrhages and thrombosis due to an increased activation of the coagulative system after contact with foreign material of the ECMO system [5,6]. Despite improvements in technology, these hemostatic complications remain relevant causes of morbidity and mortality in neonates on ECMO [7].

ECMO-associated retinal changes have already been described in the 1980s and 1990s [8–11]. Since then, however, significant advances in neonatal and surgical care of CDH newborns and improvement in the ECMO technique itself (e.g. ECMO circuit, pumps, oxygenator) have

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been achieved which may affect the development of associated retinal changes. Therefore, this study evaluated the prevalence of retinal pathologic alterations in neonates receiving state-of-the art ECMO therapy.

1. Patients and methods

1.1. Data collection and ethical approval

We retrospectively reviewed consecutive infants receiving ECMO treatment for CDH at the University Hospital Bonn between August 2012 and December 2018. This study followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of the University Hospital Bonn (approval no. 282/15). Due to the retrospective design of the study, the committee waived the need for patient informed consent.

1.2. Patient data

Patient parameters including gestational age (GA), birth weight, duration of hospitalization, duration of ECMO treatment, duration of inhalative oxygen supplementation, and postmenstrual age (PMA) at the time of examination were collected and analyzed anonymously. During prenatal ultrasound assessment, the severity of CDH was evaluated by means of lung size, using the observed-to-expected lung-to-head ratio (o/e LHR), and intrathoracic liver herniation ("liver-up") as previously described [12].

1.3. Standard treatment protocol

All patients were treated as described before and according to published guidelines [13–15]. CDH newborns were intubated after birth and permissive hypercapnia ($PaCO_2$ 45–65 mmHg) was used as protective ventilation strategy whenever applicable. During initial delivery room management, the inspired oxygen fraction (FiO_2) was set at 1.0 and was titrated to achieve a postductal PaO2 of 80–150 mmHg.

ECMO was initiated according to at least one of the following criteria as recommended by the CDH Euro Consortium [13]: A preductal oxygen saturation < 85% or postductal saturation < 70%; oxygenation index (OI) ≥40 consistently present; PaCO2 > 70 mmHg with pH < 7.15; peak inspiratory pressure ≥ 28 cm H2O or mean airway pressure ≥ 17 cm H2O; or systemic hypotension (mean arterial pressure < 40 mmHg) resistant to fluid and inotropic therapy. During the study period, veno-venous ECMO (vv-ECMO) with a 13-French double-lumen cannula was preferentially used and veno-arterial ECMO (va-ECMO) was used in infants with vessels being too small to fit a 13-French cannula. In infants receiving va-ECMO, a 10-French venous cannula and an 8-French arterial cannula were employed. Additionally, infants with severe biventricular cardiac dysfunction were supported with va-ECMO according to the appreciation of the treating team. In all infants, echocardiography was performed after admission to our neonatal intensive care unit to assess the severity of concomitant pulmonary hypertension, and inhaled nitric oxide was started in infants with a pulmonary artery pressure of at least 2/3 systemic pressure. Infants responding insufficiently to inhaled nitric oxide were started on intravenous sildenafil.

Although no formal criteria to undergo surgical repair were established, surgery was performed with a delayed repair strategy allowing for cardiorespiratory stability before surgery. In general, surgical repair was performed within 24 h after discontinuation from ECMO treatment.

1.4. Ophthalmological examination

The critical condition of these neonates precluded any ophthalmological examination prior to ECMO therapy. After completion of ECMO treatment, children were examined for retinal changes by mydriatic indirect funduscopy in the dark using topical anesthesia, scleral indentation, and external bulb rotation.

2. Results

Of 54 neonates with CDH that were treated by ECMO at the University Hospital Bonn between August 2012 and December 2018, 36 (66.7%) survived ECMO treatment and 27 were sufficiently medically stable to allow for funduscopic examination. Of the 27 examined infants, 24 further survived until discharge from hospital. We included all 27 examined children in our study analysis.

In the study cohort of 27 examined infants, 23 children (85.2%) were male, mean GA was 37.3 weeks (range 33.1–40.6), mean birth weight was 2969.6 g (range 1990–3930) and mean interval between birth and initiation of ECMO was 17.6 h (range 4.3–70.1; Table 1). For those 24 neonates that survived until discharge, mean duration of hospitalization was 16.1 weeks (range 5.5–56.4), and mean duration of inhalative oxygen supplementation was 12.8 weeks (range 2.7–56.4).

Ophthalmological examination was performed at a mean PMA of 45.2 weeks (range 35.9–71.4), and the mean interval between ECMO decannulation and ophthalmological examination was 45.8 days (range 6.3–220.5). Three children (11.1%) exhibited retinal changes (Table 2), including multiple midperipheral blot intraretinal hemorrhages in five eyes of three children (11.1% of children) and retinopathy of prematurity (ROP) in two eyes of one child.

In the infant with ROP, GA was 35.0 weeks, birth weight was 1990 g, and duration of inhalative oxygen supplementation was 11.9 weeks. According to German guidelines, the child was included into the ROP screening program as GA was below 36 weeks and duration of oxygen supplementation was more than 3 days. The first ophthalmological examination was performed 28.5 days after ECMO decannulation at a PMA of 40.2 weeks and a PNA of 5.2 weeks and revealed intraretinal hemorrhages in both eyes, i.e. stage 3 ROP in zone II without plus disease in the right eye and stage 2 ROP in zone II without plus disease in the left eye. ROP regressed over the following weeks and no treatment was required.

During the course of hospitalization, three neonates died due to complications of laparotomy, severe cardiac dysfunction and arrhythmia, and pulmonary hypoplasia with refractory pneumothoraces, respectively. None of those infants exhibited retinal changes.

Table 1
Patient characteristics of the 27 neonates included in the study.

	Mean / %	Range
Gestational age and range [weeks]	37.3	33.1–40.6
Male	85.2%	-
Birth weight	2969.6	1990–3930
Prenatal diagnosis	96.3%	-
Observed-to-expected lung to head ratio (o/e LHR)	35.1	17.6–69.0
Intrathoracic liver herniation (liver-up)	70.4%	-
Left-sided defect	81.5%	-
Fetal endoscopic tracheal occlusion (FETO)	25.9%	-
Sildenafil treatment	100%	-
Age at initiation of ECMO treatment [h]	17.6	4.3–70.1
Duration of ECMO treatment [days]	8.1	2.4–34.5
Age at day of surgery [days]	11.0	4.3–36.0
Diaphragmal patch repair	92.6%	-
Length of oxygen support [days][a]	89.9	18.6–394.8
Length of hospital stay [days][a]	112.9	38.5–394.8
Proportion of veno-venous ECMO	81.5%	-
PNA at eye examination [weeks]	7.9	2.8–32.7
PMA at eye examination [weeks]	45.2	35.9–71.4
Interval between ECMO decannulation and ocular examination [days]	45.8	6.3–220.5

[a] Those values were only calculated for the 24 of the 27 included children that survived to discharge.

Table 2
Patient characteristics and ocular findings of infants with observed retinal changes.

Patient no.	GA	Birth Weight	Mode of delivery	Duration of ECMO [days]	Type of ECMO	PNA at examination [weeks]	PMA at examination [weeks]	Interval between ECMO decannulation and ocular examination [days]	Ocular findings
1	33.1	2200 g	Cesarean section	11.8	Veno-arterial	2.8	35.9	7.3	Both eyes: intraretinal hemorrhages
2	35.0	1990 g	Cesarean section	7.6	Veno-venous	5.2	40.2	28.5	Right eye: ROP stage 3 in zone II without plus disease, left eye: ROP stage 2 zone II without plus disease, both eyes: intraretinal hemorrhages
3	38.6	3100 g	Vaginal delivery	16.0	Veno-venous	4.0	42.5	11.4	Right eye: intraretinal hemorrhages

3. Discussion

Previous studies describing the prevalence of retinal changes associated with ECMO and CDH were conducted several decades ago [8–11], and significant advances have since been made in both neonatal and surgical care of CDH newborns and in the ECMO technique that may also impact the development of ECMO-associated retinal changes. E.g., the veno-venous ECMO perfusion technique is nowadays preferentially used in children with CDH in our department whereas veno-arterial ECMO is mostly reserved for severe cardiac dysfunction [13]. Indeed, most children in our cohort had received veno-venous ECMO. In contrast, all previous reports on retinal findings examined patients who underwent veno-arterial ECMO [8–11,16].

In this study, we evaluated the prevalence of retinal pathologic alterations in neonates receiving state-of-the-art ECMO therapy and, to the best of our knowledge, for the first time describe retinal findings in veno-venous ECMO.

3.1. Prevalence of retinal hemorrhages

ECMO is believed to increase the likelihood of bleeding complications mainly due to extensive anticoagulation (usually by unfractionated heparin) that is needed to prevent thrombotic complications. Particularly in neonates, the management of anticoagulation is challenging owing to the developing hemostatic system [5,9].

Previous studies have described the likelihood of retinal hemorrhages following ECMO [8,10]. In these studies, funduscopic examination was performed at an average of less than 23 days after decannulation, and a total of 12 (5.3%) neonates were observed to have retinal hemorrhages [8–11]. In our study, three out of 27 infants receiving ECMO (11.1%) exhibited retinal hemorrhages. These retinal hemorrhages regressed without treatment and were not considered to be of amblyogenic relevance. On average the examination took place 45.8 days after decannulation as critical condition of the neonates precluded earlier examinations. Despite the later time point of examination, we observed a higher percentage of retinal hemorrhages. Pooling of the results of the four previous studies and our own data results in a prevalence of 6.0% for retinal hemorrhages in neonates with ECMO therapy. Table 3 compares our results to previous studies on ocular hemorrhages after ECMO in neonates.

3.2. ECMO-related and perinatal hemorrhages

As our cohort received retinal examinations only after completion of ECMO treatment, we do not know whether the observed retinal hemorrhages were already present before treatment. A previous study observed retinal hemorrhages in 34% of healthy newborns [17]. The incidence was highest for vacuum assisted deliveries (75%) and lowest for cesarean section deliveries (7%), and the hemorrhages usually resolved within 4 weeks [17]. Similarly, a meta-analysis based on 1.777 infants concluded that birth-related retinal hemorrhages occur in 25.6% of healthy newborns, are less likely in cesarean section compared to vaginal deliveries, and very rarely persist longer than 6 weeks [18]. Against this background, some of the retinal hemorrhages observed early in ECMO-treated infants in our and previous studies may be birth-associated rather than ECMO-related. In our study, the three children with retinal hemorrhages were examined at a postnatal age of 2.8, 4.0, and 5.2 weeks, respectively, and thus fall well within the age range in which perinatal hemorrhages may still be visible. However, two of these three children were delivered by cesarean section, which is less likely to result in birth-related retinal hemorrhages. In summary, the questions whether the retinal hemorrhages observed in our study are a result of birth trauma or ECMO-related remains unsolved.

Table 3
Literature review of studies describing retinal changes following ECMO.

	No. of infants examined	No. of infants with CDH	Mean GA [weeks]	Mean PNA at initiation of ECMO [days]	Mean duration of ECMO [days]	Mean time of examination after ECMO [days]	Mean PNA at examination [days]	No. of infants with retinal hemorrhages	No. of infants with retinal vasculopathy[a]	No. of infants with CDH and retinal hemorrhages	No. of infants with CDH and retinal vasculopathy
Patrias (1988)	11	3 (27.3%)	39.3	49.7	5.8	1.2	56.7	2 (18.2%)	6 (55.0%)	0	2 (66.7%)
Gonzalez (1993)	86	9 (10.5%)	39	2.1	5.5	23.3	30.9	0	4	0	n/a
Pollack (1996)	37	1 (2.7%)	38.1	2	6.2	16	24.2	5 (14.0%)	0	1 (100.0%)	0
Young (1997)	91	9 (9.9%)	39.1	1.5	6.5	11.1	20.0	5 (5.5%)	7 (7.7%)	3 (33.3%)	6 (66.7%)
Present study (2019)	27	27 (100%)	37.3	<1	8.1	45.8	55.0	3 (11.1%)	1 (3.7%)	3 (11.1%)	1 (3.7%)
Total	252	49 (19.4%)						15 (6.0%)	18 (7.1%)	7 (14.3%)	9 (18.4%)

[a] Including retinopathy of prematurity, retinal congestion and retinal tortuosity.

3.3. ECMO due to CDH and other diseases

In contrast to previous studies on retinal findings in neonates with ECMO treatment, our cohort consisted entirely of children treated for CDH, and retinal changes in patients receiving ECMO for CDH may differ from those treated by ECMO for other diseases. Young et al. hypothesized a distinct vasculopathy related to CDH and ECMO. In a cohort of 91 neonates, they reported that 6 of 9 (66.7%) neonates with CDH and ECMO exhibited retinal vascular changes, including ROP-like pathology, retinal congestion and retinal tortuosity. They also observed that patients with CDH required more time on ECMO therapy compared to other diagnoses and had a reduced overall survival rate after ECMO therapy. Average ECMO treatment time across all ECMO indications was 6.5 days, increasing to 11.5 days for the 6 neonates with CDH and retinal changes. Moreover, survival rate of ECMO therapy was 60% in patients with CDH compared to an overall survival rate in this study of 84–96% [8].

Our data regarding ECMO treatment are consistent with the results of Young et al. [8], as average ECMO treatment time in our CDH cohort was 8.1 days and ECMO survival rate in our cohort was 66.7%. With 6 of 9 children (66.7%), however, their observed rate of retinal changes was significantly higher than in our cohort (11.1%). Likewise, when pooling the results of four previous studies [8–11], 9 of 22 (40.9%) neonates with ECMO due to CDH exhibited retinal changes, which still is a larger proportion than in our cohort. The lower prevalence in our cohort may be the result of improvements in neonatal care and ECMO technique, compared to these studies from several decades ago.

A higher vulnerability for retinal changes of the left eye as compared to the right eye has been suggested by some authors due to the asymmetry of CDH [8]. Even though CDHs in our cohort were also predominantly left-sided, we did not see any predominantly left-sided asymmetric retinal findings. In contrast, one child with a left-sided CDH exhibited retinal hemorrhages only in the right eye, but not in the left eye. Thus, our results do not support the hypothesis of increased vulnerability of the left eye in CDH.

3.4. ECMO and ROP

Oxygen supplementation is a known risk factor for the development of ROP in prematurely born infants [19]. One previous study reported retinal changes in a child under ECMO treatment that was described as similar to stage 2 ROP [8]. However, this patient was born at term and was examined 17 days after ECMO decannulation. The retinal changes were described as unilateral (left eye) fundus changes with marked venous tortuosity, peripheral retinal edema and exudation, and immature retinal development temporally separated by a ridge. Regular follow-up was performed until complete resolution, and no treatment was required. The causes for the ROP-like retinal changes in this term-born child remain unclear.

Interestingly, our cohort included one premature infant with ROP which, to the best of our knowledge, represents the first report of ROP development under ECMO. This child was born with a GA of 35.0 weeks and received inhalative oxygen supply for a total of 83.1 days. Maximal severity of ROP was of stage 3 (neovascularizations) in one eye and stage 2 (ridge) in the other eye, both eyes without plus disease. Subsequently, the disease resolved without treatment. This case demonstrates that ROP may develop in prematurely born infants receiving ECMO, and thus ROP screening seems prudent in this subgroup of children.

4. Conclusion

In conclusion, we report that a significant percentage of infants undergoing ECMO therapy due to CDH exhibits retinal changes including retinal hemorrhages and ROP. While retinal hemorrhages usually do not require treatment and resolve without sequelae, ROP may progress towards blindness if not treated sufficiently. Therefore, ROP screening examination should be considered in prematurely born children receiving ECMO to allow for timely detection and treatment of ROP.

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