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Reconsidering ECMO in Premature Neonates

K. Taylor Wild[a] Holly L. Hedrick[b, c, d] Natalie E. Rintoul[a, b, c]

[a]Division of Neonatology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [b]The Center for Fetal Diagnosis and Treatment, The Children's Hospital of Philadelphia, Philadelphia, PA, USA; [c]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [d]Department of Pediatric General, Thoracic, and Fetal Surgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA

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Abstract
Extracorporeal membrane oxygenation (ECMO) is a life-saving intervention for neonates with respiratory failure or congenital cardiac disease refractory to maximal medical management. Early studies showed high rates of mortality and morbidities among preterm and low birthweight (BW) neonates, leading to widely accepted ECMO inclusion criteria of gestational age (GA) ≥34 weeks and BW >2 kg. In recent years, publications involving neonates of 32–34 weeks GA have reported improved survival and decreased intracranial hemorrhage. As such, ECMO should be considered on a case-by-case basis in premature neonates as long as the risks are understood.

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a universally accepted and life-saving intervention for neonates with respiratory failure or congenital cardiac disease refractory to maximal medical management. Intracranial hemorrhage (ICH) is a known complication of both ECMO and prematurity that may be related to physiologic instability of the germinal matrix during the first few days of life. The risk of ICH is thought to be higher for premature neonates requiring ECMO given the need for continuous anticoagulation [1]. Early studies found an unacceptable risk of mortality and morbidities such as ICH among preterm and low birthweight (BW) neonates, leading to widely accepted ECMO inclusion criteria of gestational age (GA) ≥34 weeks and BW >2 kg (kg) [2, 3].

Historical Perspective

In 1986, a retrospective review of 35 neonates treated with ECMO found that 8/8 (100%) neonates <35 weeks GA suffered an ICH compared to only 2/27 (7%) neonates ≥35 weeks GA. Thus, the authors concluded that

karger@karger.com
www.karger.com/fdt

K. Taylor Wild
Division of Neonatology, Children's Hospital of Philadelphia
3401 Civic Center Blvd.
Philadelphia 19104 (USA)
wildk@email.chop.edu

ECMO should be contraindicated in neonates <35 weeks GA [2]. Similarly, in one of the first large cohorts of patients on ECMO, Bartlett et al. [3] found that 89% of neonates <35 weeks GA suffered ICH. In 1992, Revenis et al. [4] compared neonates with a BW between 2 and 2.5 kg with neonates >2.5 kg and found that mortality was 3 times greater for lower BW neonates. This study also found ICH to be highly correlated with mortality [4].

Recent Studies

However, since these early landmark studies, many technological advancements have occurred in the management of both prematurity and neonatal ECMO. In 2018, a survey among the members of the American Pediatric Surgical Association-Critical Care Committee found that only 62.5% of respondents agreed with BW <2 kg as a contraindication to ECMO. Moreover, only 43.8% agreed that GA <34 weeks should be a contraindication. When asked about neonates at 32 weeks GA, only 33.3% of respondents agreed that GA <32 weeks should be a contraindication to ECMO [5].

In 1993, Hirschl et al. [6] compared neonates ≥35 weeks GA with neonates ≤34 weeks GA, as well as neonates ≥2 kg with neonates <2 kg in the Extracorporeal Life Support Organization (ELSO) Registry between 1988 and 1991. While survival was significantly lower in the neonates ≤34 weeks GA with 63% survival compared to 84% in those ≥35 weeks GA, survival was still likely greater than if ECMO had not been offered. Similarly, survival in neonates <2 kg was 65% compared to 83% in neonates ≥2 kg. Rates of ICH were also increased in the group ≤34 weeks GA at 37% compared to 14% in those ≥35 weeks GA. There was a linear correlation between postconceptional age and ICH with 26% of patients at 32 weeks GA suffering an ICH versus only 6% of patients at 38 weeks GA (p = 0.004). There was no significant difference in ICH based on BW. The acceptable survival rates shown in neonates between 32 and 34 weeks GA suggest a possible revision of the current ECMO inclusion criteria [6].

When using criteria of GA or BW to determine ECMO candidacy, there has been debate about which is more important to survival and risk of ICH. Measures such as GA, postnatal age (PNA), postconceptional age (PCA), defined as the sum of GA and PNA, and BW have all been studied. When comparing GA and BW, Revenis et al. [4] found that BW, but not GA was significantly related to survival and risk of ICH. Hirschl et al. [6] found decreased survival based on both BW and GA, but no significant difference in ICH based on BW. In 2004, Hardart et al. [1] evaluated the rates of ICH and survival among 1,398 neonates <37 weeks in the ELSO Registry, including 327 neonates ≤34 weeks GA. They found that PCA predicted the development of ICH, as did a primary diagnosis of sepsis, acidosis, and treatment with bicarbonate prior to ECMO initiation. GA alone did not predict ICH. There was also not a dramatic reduction in ICH risk for premature neonates after the first few days of postnatal life, as is seen with spontaneous ICH. They concluded that this might suggest that the "underlying cause and pathophysiology of spontaneous ICH is different from that of ICH in neonates treated with ECMO and that premature neonates cannulated for ECMO after the first 3–4 days of postnatal life do not have a dramatically reduced risk of development of ICH" [1].

Using the ELSO Registry from 1976 to 2008, Church et al. [7] studied 752 neonates 29–34 weeks GA. When compared to survival rates of 34 weeks GA neonates (58%), survival was statistically different for 29–33 weeks GA neonates (48%, p = 0.05); however, there was not a significant difference in ICH (17 vs. 21%, respectively, p = 0.195). There was, however, a significant difference in the incidence of cerebral infarct between groups (16% for 34 weeks vs. 22% for 29–33 weeks; p = 0.03). Although survival was lower in the 29–33 weeks GA group, the difference was relatively modest, leading these authors to conclude that GA <34 weeks may not be an absolute contraindication to ECMO [7]. One limitation of this study is that the PNA, and therefore the PCA, of the 29–33 weeks GA neonates is not known. It is possible that some of these neonates may have been several days to months old when cannulated onto ECMO.

While some of these more recent studies have suggested decreased, but acceptable, survival of neonates <34 weeks GA and BW <2 kg, these neonates are still at higher risk of mortality and morbidities such as ICH, compared to their full-term counterparts. In 2011, in a study of 21,218 neonates in the ELSO Registry from 1986 to 2006, Ramachandrappa et al. [8] divided neonates into 3 groups: late preterm (34 0/7 to 36 6/7), early-term (37 0/7 to 38 6/7), and full-term (39 0/7 to 42 6/7). Survival was lowest in the late preterm neonates at 74% compared to 82% in the early-term neonates and 89% in the full-term neonates [8].

In 2004, Rozmiarek et al. [9] divided all neonates (14,305) less than 30 days in the ELSO Registry from 1991 to 2002 into 2 groups, neonates with BW >2 kg (13,642) and neonates with BW ≤2 kg (663). They found a survival rate of 53% in the low BW neonates compared to

77% in the higher BW neonates with no significant difference year to year over the course of the study. Using a regression analysis to determine the lowest BW at which a 40% survival probability could be achieved, they found a threshold weight of 1.6 kg [9].

Special Populations

Congenital diaphragmatic hernia (CDH) is known to predict higher mortality among neonates on ECMO; thus, it deserves special consideration when discussing the feasibility of ECMO in premature or low BW neonates [7, 10]. Among the articles discussed in this review, many excluded neonates with CDH [4, 8]. Rozmiarek et al. [9] included neonates with CDH and found that among neonates with BW >2 kg, the survival rate was 55% for patients with CDH compared to 82% in neonates without CDH ($p < 0.0001$). By contrast, in low BW neonates, the survival rate was only 38% in patients with CDH compared to 60% in neonates without CDH ($p < 0.005$). These data indicate that factors including CDH significantly impact survival and distinguish low BW neonates from higher BW neonates [9].

A large study of the ELSO Registry from 1988 to 2015 included 7,564 neonates with CDH, including 100 with BW <2 kg and 109 with GA <34 weeks. The overall mortality was 50%, with an unadjusted odds ratio of 2.39 (95% confidence interval: 1.53–3.74; $p < 0.01$) for neonates with a BW <2 kg. Even when adjusting for potential confounding variables, the odds ratio remained high at 2.11 (95% confidence interval: 1.30–3.43; $p < 0.01$). However, importantly, there was no difference in mortality observed in neonates with GA <34 weeks after adjusting for weight [11]. Although this study found that survival is possible in neonates with CDH with BW <2 kg, this population is already at high risk of death and intellectual disability [12–14].

That being said, in a case series of 3 neonates born prematurely with CDH and BW <2 kg from 2010 to 2015, all 3 survived with only mild developmental delay. The 3 patients were 31 4/7 weeks GA and 1.8 kg, 31 5/7 weeks GA and 1.5 kg, and 36 3/7 weeks GA and 1.64 kg. The first patient had several dysmorphic features including unilateral cleft lip/palate. Although this patient did not meet traditional ECMO inclusion criteria, she was cannulated onto ECMO following an interdisciplinary discussion that included her family. She was later diagnosed with Fryns syndrome. The second patient had FETO (Fetoscopic Endotracheal Occlusion) attempted at 29 weeks; however, the fetal trachea could not be accessed in utero. The mother then presented in labor at 31 5/7 weeks, and the neonate was emergently cannulated on ECMO. Finally, the third patient had intrauterine growth restriction and was postnatally diagnosed with Russell-Silver syndrome following 7 days of ECMO with ECMO repair on day of life 3. All 3 patients had 8-Fr venous and arterial cannulas.

These nontraditional ECMO candidates illustrate that ECMO can be performed with success and without complications in some patients <34 weeks GA and <2 kg BW [15]. However, lethal chromosomal abnormalities and severe/uncorrectable congenital heart disease must still be considered contraindications to ECMO independent of GA.

Venoarterial versus Venovenous

There is an ongoing debate in the literature about the merits of venoarterial (VA) versus venovenous (VV) ECMO in the neonatal population. In the studies discussed here that specified VA versus VV ECMO, the majority of premature neonates were placed on VA ECMO. Vessel size is the greatest limiting factor in the use of VV ECMO in premature neonates since the smallest VV double lumen cannula currently available is a 13-Fr cannula. In VA ECMO, the neonate's carotid artery must be able to accommodate an 8-Fr arterial cannula with adequate flow. In studies comparing VA versus VV ECMO, mortality is not significantly different. Renal complications and on-ECMO inotrope use are common in VV, whereas neurologic complications, including seizures and central nervous system infarcts occur more frequently in VA. Further, in a study comparing VA and VV ECMO in CDH patients, 18% of VV patients required conversion to VA, which was associated with a significantly higher rate of mortality [16]. Because neurologic complications, including seizures and infarcts, are more common in VA ECMO [16], these risks must be carefully weighed when cannulating premature neonates onto ECMO since VA ECMO may be the only option given the vessel size.

Limitations

Some limitations in reviewing these data include that many of these studies did not provide differentiation of ICH by grade. Given that many of these studies utilized

Table 1. Summary of studies discussed

Citation	Patients, *n*	Mode	Study comparisons	Summarized findings	Years studied	CDH included (Y/N)
Hardart et al. [1]	1,398 neonates <37 weeks GA in ELSO Registry	83% VA, 14% VV, and 3% VV-VA	327 neonates ≤34 weeks GA and 132 PCA ≤34 weeks	61% overall survival <37 weeks GA and 26% of neonates ≤32 weeks GA suffered ICH	1992–2000	Y
Cilley et al. [2]	35 neonates, single center	ns	8 neonates <35 weeks GA versus 27 neonates ≥35 weeks GA	8/8 (100%) neonates <35 weeks GA suffered ICH versus 2/27 (7%) neonates ≥35 weeks GA	1981–1984	Y
Bartlett et al. [3]	100 neonates, 3 centers	ns	19 neonates <35 weeks GA versus 81 neonates ≥35 weeks GA	72% overall survival and 89% of neonates <35 weeks GA suffered ICH	1973–1986	Y
Revenis et al. [4]	264 neonates, single center	100% VA	29 neonates 2–2.5 kg versus 235 ≥2.5 kg	Mortality 3× greater for 2–2.5 kg neonates	1984–1990	N
Hirschl et al. [6]	4,359 neonates in ELSO Registry	ns	158 neonates ≤34 weeks GA versus 4,128 ≥35 weeks GA and 26 neonates <2 kg versus 4,333 neonates ≥2 kg	63% survival ≤34 weeks GA compared to 84% in those ≥35 weeks GA, 65% survival <2 kg versus 83% ≥2 kg. 37% ICH ≤34 weeks GA versus 14% in those ≥35 weeks GA	1988–1991	Y
Church et al. [7]	752 neonates 29–34 weeks GA in ELSO Registry	92% VA 29–33 weeks and 91% VA 34 weeks	509 neonates 34 weeks GA versus 243 neonates 29–33 weeks GA	58% survival 34 weeks GA neonates versus 48% 29–33 weeks GA and no significant difference in ICH (17 vs. 21%, respectively)	1976–2008	Y
Ramachandrappa et al. [8]	14,528 neonates in ELSO Registry	ns	2,135 late preterm (34 0/7 to 36 6/7) versus 3,119 early-term (37 0/7 to 38 6/7) versus 9,274 full-term (39 0/7 to 42 6/7)	74% survival in late preterm versus 82% in early-term versus 89% in full-term neonates	1986–2006	N
Rozmiarek et al. [9]	14,305 neonates in ELSO Registry	ns	13,642 neonates >2 kg and 663 ≤2 kg	53% survival in ≤2 kg versus 77% in >2 kg	1991–2002	Y
Delaplain et al. [11]	7,564 neonates with CDH in ELSO Registry	95% VA, 5% VV <2 kg, 84% VA, and 16% VV ≥2 kg	100 neonates with BW <2 kg and 109 with GA <34 weeks	50% overall mortality, >2× greater mortality if BW <2 kg. No difference in mortality in neonates <34 weeks GA after adjusting for weight	1988–2015	Y

ICH, intracranial hemorrhage; BW, birthweight; GA, gestational age; ELSO, Extracorporeal Life Support Organization; PCA, postconceptional age; CDH, congenital diaphragmatic hernia; VA, venoarterial; VV, venovenous; ns, not specified.

the ELSO Registry, there may also be a selection bias among which low BW or early GA neonates were cannulated onto ECMO that is not explained in the registry. Another major limitation of this review is that all of the included studies are either small series or registry studies that either have limited, biased data, or large subsets of data with limited granularity, respectively.

Finally, to our knowledge, there are no data on the neurologic outcomes of premature neonates who survive ECMO. Follow-up studies of neonates >34 weeks GA who survive ECMO demonstrate intelligence within the normal range at school age; however, survivors demonstrate more behavioral concerns relative to their counterparts [17, 18]. As premature neonates are at a higher risk of adverse neurodevelopmental outcomes than their full-term counterparts, premature neonates who survive an ECMO course may be at an even higher risk for some of these complications. However, in recent years, adverse neurodevelopmental outcomes are occurring in rates lower than historically noted in formerly premature neonates [19]. Thus, the outcomes of premature neonates who survive ECMO may be promising, but this will be an important area of research as an ECMO community as more premature neonates are treated with ECMO.

Future Directions

Neonates who have undergone fetal interventions, including FETO and RAFT (Renal Anhydramnios Fetal Therapy), are at risk for premature delivery with critical physiology [12]. Thus, it is important to consider ECMO in patients less than the traditional 34 weeks GA.

Evolving technology such as an artificial placenta or pumpless ECMO without anticoagulation may allow us to continue to re-evaluate the boundaries of neonatal ECMO. The purpose of developing an artificial placenta is to utilize ECMO to avoid the harm of mechanical ventilation while allowing premature lungs to develop to the point where they can provide adequate gas exchange. This technology maintains fluid-filled lungs that are protected from gas exchange and preserves fetal circulation. Fetal lambs that are developmentally equivalent to extremely premature neonates of 24 weeks GA have survived for up to 4 weeks using artificial placenta technology with stable hemodynamics, growth, and development [20, 21]. As this innovative model continues to achieve success, there may be an expanded use for ECMO in premature neonates.

To address the potential complications of anticoagulation in these extremely premature neonates, researchers have developed pumpless ECMO circuits that have supported CDH model lambs for up to 3 weeks without systemic heparinization [22]. Pumpless ECMO circuits may offer the potential to support premature neonates with CDH, as well as other causes of respiratory failure or pulmonary hypertension without systemic anticoagulation. Thus, this technology has the potential to reduce rates of ICH on ECMO.

Conclusion

The studies discussed here are summarized in Table 1. Our institution has primarily followed the ELSO inclusion criteria guidelines of ≥34 weeks GA and BW >2 kg. Our prior experience in cannulating infants with a GA <34 weeks has been in infants with bronchopulmonary dysplasia who developed respiratory failure in the setting of pneumonia or sepsis. From 1990 to 1999, our institution cannulated 9 infants with GAs ranging from 24 4/7 weeks to 33 3/7 weeks; however, all infants had corrected to term prior to cannulation with age at cannulation ranging 105–383 days. Among these infants, the survival rate was comparable to most other ECMO populations; however, there were high rates of severe pulmonary and neurodevelopmental sequelae among this already vulnerable population [23].

In recent years, publications involving neonates of 32–34 weeks GA have reported improved survival and decreased ICH. As such, high-volume centers should consider ECMO on a case-by-case basis among neonates of 32–34 weeks GA to gain experience during the ECMO course and to perform careful neurodevelopmental follow-up to better inform practice changes on this select population.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.T.W. conceived and wrote the manuscript. H.L.H. conceived and edited the manuscript. N.E.R. conceived and edited the manuscript, provided oversight, and serves as the guarantor for the article.

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