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ORIGINAL ARTICLE

Artificial Lung / ECMO

Early continuous renal replacement therapy during infant extracorporeal life support is associated with decreased lung opacification

Heidi J. Murphy[1,5] · Meryle J. Eklund[1,2] · Jeanne Hill[1,2] · Kristen Morella[3] · John B. Cahill[1] · James R. Kiger[4] · Katherine E. Twombley[1] · David J. Annibale[1,5]

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Abstract

Lung opacification on chest radiography (CXR) is common during extracorporeal life support (ECLS), often resulting from pulmonary edema or inflammation. Concurrent use of continuous renal replacement therapy (CRRT) during ECLS is associated with improved fluid balance and cytokine filtration; through modification of these pathologic states, CRRT may modulate lung opacification observed on CXRs. We hypothesize that early CRRT use during infant ECLS decreases lung opacification on CXR. We conducted a retrospective cohort study comparing CXRs from infants receiving ECLS and early CRRT ($n=7$) to matched infants who received ECLS alone ($n=7$). The CXR obtained prior to ECLS, all CXRs obtained within the first 72 h of ECLS, and daily CXRs for the remainder of the ECLS course were analyzed. The outcome measure was the degree of opacification, determined by independent assessment of two, blinded pediatric radiologists using a modified Edwards et al.'s lung opacification scoring system (from Score 0: no opacification to Score 5: complete opacification). 220 CXRs were assessed (cases: 93, controls: 127). Inter-rater reliability was established (Cohen's weighted $\kappa=0.74$; $p<0.0001$, good agreement). At baseline, the mean opacification score difference between cases and controls was 1 point (cases: 1.8, controls 2.8; $p=0.049$). Using mixed modeling analysis for repeated measures accounting for differences at baseline, the average overall opacification score was 1.2 points lower in cases than controls (cases: 2.1, controls: 3.3; $p<0.0001$). The overall distribution of scores was lower in cases than controls. Early CRRT utilization during infant ECLS was associated with decreased lung opacification on CXR.

Keywords Extracorporeal life support · Extracorporeal membrane oxygenation · Continuous renal replacement therapy · Renal support therapy · Lung opacification

✉ Heidi J. Murphy
murphyh@musc.edu

✉ David J. Annibale
annibald@musc.edu

1 Department of Pediatrics, Medical University of South Carolina, Charleston, South Carolina, USA

2 Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, South Carolina, USA

3 Department of Public Health Sciences, Medical University of South Carolina, Charleston, South Carolina, USA

4 Department of Pediatrics, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

5 Division of Neonatology, Medical University of South Carolina, 165 Ashley Avenue, MSC 917, Charleston, South Carolina 29425, USA

Introduction

Extracorporeal life support (ECLS), also known as extracorporeal membrane oxygenation, is a therapy that provides temporary cardiopulmonary support for patients with select disease processes who have failed conventional medical management and subsequently have increased risk of mortality. Neonatal respiratory failure is the most common indication for ECLS among all ages with a survival rate of approximately 62% [1]. Although life saving, patients receiving ECLS can suffer from several well-documented complications. Following cannulation, infants often experience an overwhelming inflammatory response, similar to systemic inflammatory response syndrome or acute respiratory distress syndrome, as well as fluid overload (FO) [2–4]. Both of these complications can contribute to opacification of the lungs on chest radiography (CXR) that has been found to accurately reflect decreased lung compliance and lung volume in infants on ECLS. [5–7].

Continuous renal replacement therapy (CRRT) is used in many centers during ECLS to optimize fluid balance in response to volume overload. At our institution in the neonatal intensive care unit (NICU), CRRT is started early to prevent the development of (FO) and the associated morbidities and mortality. CRRT use is associated with improvement in fluid balance during ECLS and inflammatory cytokine removal and, thus, may modify both the presence and degree of lung opacification on CXR [8–11]. However, to our knowledge, the effect of CRRT on lung opacification during ECLS has never been studied.

We aimed to determine if the use of early CRRT during infant ECLS was associated with changes in the degree of pulmonary disease, as assessed by lung opacification on CXR. We hypothesized that early CRRT use during infant ECLS decreases lung opacification on chest radiography.

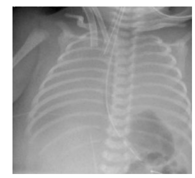
Materials and methods

We conducted a matched, retrospective cohort study comparing CXR from infants receiving ECLS and concurrent, early CRRT (“cases”; $n = 7$) to case-matched infants who received ECLS alone (“controls”; $n = 7$). Infants who received ECLS and concurrent CRRT were prospectively enrolled from a single level III NICU between 2016 and 2017. Patients were eligible if they received ECLS and early, prophylactic CRRT (within 48 h of ECLS cannulation) was utilized during the ECLS course; patients were excluded if they were > 12 months of age at ECLS initiation. Historical cases were matched with each case patient for ECLS indication, ECLS mode, gestational age (all term infants, or within 1 gestational week) and postnatal age (all cannulated within the 1st week of life with one exception) and selected from infants treated in the NICU at the Medical University of South Carolina (MUSC) between 2004 and 2011.

Data including basic demographics, duration of ECLS, time of CRRT initiation, pre-ECLS clinical variables (including alveolar–arterial oxygen tension difference ($AaD0_2$), oxygenation index (OI), presence of hypoxic ischemic encephalopathy, pre-ECLS mechanical ventilation duration, use of inhaled nitric oxide, FO at decannulation, survival) and CXRs were acquired from each patient’s electronic medical records. The last CXR obtained prior to ECLS cannulation (“baseline”), all CXRs obtained within the initial 72 h of ECLS, and daily CXRs for the remainder of the ECLS course were analyzed for each patient. Survival of ECLS was defined as survival for > 24 h after decannulation. The $AaD0_2$ was calculated using the following formula: [fractional inspired oxygen concentration × (atmospheric pressure (i.e., 760 mmHg) − water pressure (i.e., 46)) − (partial pressure of arterial carbon dioxide/0.8) − partial pressure of arterial oxygen). The OI was calculated using the following formula: [(mean arterial pressure × fractional inspired oxygen concentration)/partial pressure of arterial oxygen]. FO at decannulation was calculated using the following formula: %FO = [(ECLS decannulation weight − ECLS initiation weight)/ECLS initiation weight]. The primary outcome measure was degree of lung opacification determined by independent, blinded assessment of CXRs by two pediatric radiologist using a previously validated, lung opacification scoring system developed by Edwards et al. (Table 1) [12]. Modifications were made to the Edwards et al.’s scoring system including addition of ‘Score 0’ with associated findings (absence of granularity or opacification of lung fields, air bronchograms and sharp cardiac and diaphragmatic silhouettes) and elimination of the aeration category included in the original system. Both pediatric radiologists assigned a lung opacification score to each CXR; these scores were then averaged to result in an average opacification score (AOS) for each CXR. Based on presumed clinical severity of lung opacification, mild, moderate, and severe opacification categories were created to make these Edwards et al.’s scores more clinically meaningful. Clinical categories were created based on degree of lung opacification as judged by the neonatology co-authors: mild, moderate and severe (Table 3).

At our institution, ECLS is managed by the neonatal attending with consultation provided by an ECLS team including two additional neonatologists as well as the pediatric surgery and pediatric nephrology teams. Venovenous (VV) and venoarterial (VA) ECLS were both utilized in this study at the discretion of the ECLS team. ECLS was provided by a roller head pump (Sorin Group USA,

Table 1 Modified Edwards et al.'s lung opacification scoring system Adapted from Edwards et al. [12]

Characteristics	Lung opacification scores					
	Score 0	Score 1	Score 2	Score 3	Score 4	Score 5
Granularity and opacification	None	Faint, requiring close observation to detect	Easily seen	Prominent; light and dark areas of lung approximately equal	Marked; lung substantially more light than dark	Lungs essentially opaque
Air bronchograms	None	None beyond the center of the chest	Faint at the bases	Obvious	Marked	Sharp and distinct or absent
Cardiac and diaphragmatic silhouettes	Sharp	Sharp	Slightly fuzzy	Moderately fuzzy	Indistinct	Indiscernible
Example chest radiographs						

Addition of score 0 with associated findings (absence of granularity or opacification of lung fields, air bronchograms and sharp cardiac and diaphragmatic silhouettes) and elimination of original aeration category

Incorporated, Arvada, CO) and QUADROX oxygenator (Maquet Medical Systems, Wayne, NJ). CRRT modality was prescribed at the discretion of the consulting pediatric nephrologist. Following a practice change in August 2011, all patients treated in the NICU received CRRT following cannulation, with a goal of CRRT initiation within 48 h of cannulation (i.e., "early CRRT"). CRRT is continued throughout the entire course of ECLS. ECLS and CRRT configurations used have been previously described by our facility [13].

Specifically, CRRT is provided using an automated machine directly connected to circuit, with both access and return lines inserted pre-pump and pre-membrane, generally maintaining a euvolemic initial approach (fluid ins = fluid outs). As we transition to a net fluid removal strategy with clinical improvement, care is taken to avoid inadequate pump flow.

For demographic/group characteristics, quantitative data are shown as median [interquartile range] for continuous data and counts (proportions) for categorical variable data. Bivariate comparisons between groups were conducted using Student's paired *t* test, Fisher's exact test, and Wilcoxon rank sum test, as appropriate. Linear mixed modeling for repeated measures and Cochran–Armitage trend tests were used to analyze the primary outcome of lung opacification. Inter-rater reliability was established based on scores of all CXRs from both reviewers, and a Cohen's weighted κ was calculated. All analyses were conducted using SAS statistical software (version 9.4; SAS Institute, Cary, NC) and SPSS Statistics, version 24 (IBM©, Armonk, NY). Statistical significance was determined by comparing two-sided *p* values to alpha = 0.05. Approval for this study was provided by the MUSC Institutional Review Board.

Results

Fourteen patients were included, seven from each group. Case patients were enrolled sequentially. Controls were historical cases, matched based on the criteria described above. Although patients were carefully matched as described, baseline patient demographics and select clinical variables were similar between groups (Table 2). Twelve of the fourteen enrolled patients received VA ECLS; the remaining two patients received VV ECLS.

A total of 220 chest radiographs were assessed, 93 from the case group and 127 from the control group. There was a range of 5–32 CXRs per subject with a mean of 15.8 CXRs per subject. A weighted Cohen's $\kappa = 0.74$ ($p < 0.0001$) suggests the reviewers had good agreement and inter-rater reliability. Table 3 depicts results of initial comparisons of CXR opacification between groups. At baseline (i.e., comparing the last radiograph obtained prior to ECLS initiation), a mean AOS difference between cases and controls existed (cases: 1.8; controls: 2.8; $p = 0.049$ Student's *t* test). Because of the significant difference at baseline, the mixed model analysis for repeated measures was utilized, accounting for this difference at baseline. Using this model, the overall mean AOS, based upon comparison of all radiographs obtained subsequent to baseline, was 1.2 points lower in cases than controls (cases: 2.1, controls: 3.3; $p < 0.0001$ mixed modeling for repeated measures). When comparing

Table 2 Baseline patient characteristics

Demographics and select patient characteristics	Cases ($n=7$ infants)	Controls ($n=7$ infants)
Birth weight (kg)	2.7 [2.4–3.3]	3.2 [3.0–3.5]
Gestational age (weeks)	38 [36–39]	39 [38–39]
Male (*n*)	5 (71)	6 (86)
Diagnosis (*n*)		
MAS	1 (14)	1 (14)
ppHN	3 (43)	3 (43)
L CDH	3 (43)	3 (43)
Age at cannulation (days)	3 [2.5–5.5]	3 [2–5]
Alveolar–arterial oxygen tension difference ($AaD0_2$) at cannulation	619 [598–632]	613 [611–628]
Oxygenation index (OI) at cannulation	44 [35–59]	44 [36–81]
Duration of mechanical ventilation at cannulation (days)*	39 [15–53]	38 [15–40)]
Vasopressors/inotropes at cannulation (yes)	5 (71)	7 (100)
Inhaled nitric oxide at cannulation (yes)	4 (57)	4 (57)
Hypoxic ischemic encephalopathy (yes)	1 (14)	2 (29)
Fluid overload at decannulation (percentage)	23 [16–26]	22 [20–28]
Age at decannulation (days)	12 [7.5–22.5]	20 [15–23.5]
Duration of ECLS (days)	10 [4–12]	14 [11.5–20]
Survived ECLS (yes)	5 (71)	6 (86)
Survived to hospital discharge (yes)	2 (29)	5 (71)

Baseline demographics and select outcomes. No statistically significant differences were detected. Continuous data are shown as median [interquartile range]; categorical data are shown as counts (proportions)

kg kilograms, *MAS* Meconium aspiration syndrome, *ppHN* Persistent pulmonary hypertension, *L CDH* Left-sided congenital diaphragmatic hernia

*Two patients, one case and the matched control, were excluded from this analysis as they were cannulated much later in life than all other infants

Table 3 Chest radiograph opacification differences

Opacification analyses	Cases ($n=7$ infants)	Controls ($n=7$ infants)	*p* value
Baseline mean AOS	1.8	2.8	0.049
Overall mean AOS*	2.1	3.3	<0.0001
ECLS day 2/3 mean AOS**	1.8	4.4	<0.0001
Clinical AOS categories***	Cases	Controls	*p* value
Mild AOS (score 0–1.5)	31	9	<0.0001
Moderate AOS (score 2–3.5)	58	63	
Severe AOS (score 4–5)	4	55	

An average opacification score, AOS, was calculated by taking the mean of the scores given by each radiologist reviewer for each CXR. All opacification scores determined based on the modified Edwards et al.'s lung opacification scoring system (Edwards DK, et al. *Radiology* 1985)

*$n=220$ radiographs. Repeated measures analysis using mixed modeling

**$n=14$ radiographs, one radiograph/subject. Range of hours after cannulation: 33–75 h

***Distribution of average opacification scores (AOS) via clinical severity: "mild" opacification includes radiographs with scores of 0–1.5, "moderate" opacification includes radiographs with scores of 2–3.5, "severe" opacification includes radiographs with scores of 4–5. $n=220$ radiographs

mean AOS between groups on ECLS day 2–3, again there was a significant difference detected; the case group had a significantly lower mean AOS than controls at this time point (cases: 1.8, controls 4.4; $p<0.0001$ mixed modeling for repeated measures). The overall distribution of AOSs was lower in cases than controls (Fig. 1). The highest mean AOS achieved in each group on each day of ECLS is depicted in Fig. 2. A significant difference in the distribution of AOSs among these clinical categories was detected; CXRs obtained from the cases demonstrated significantly

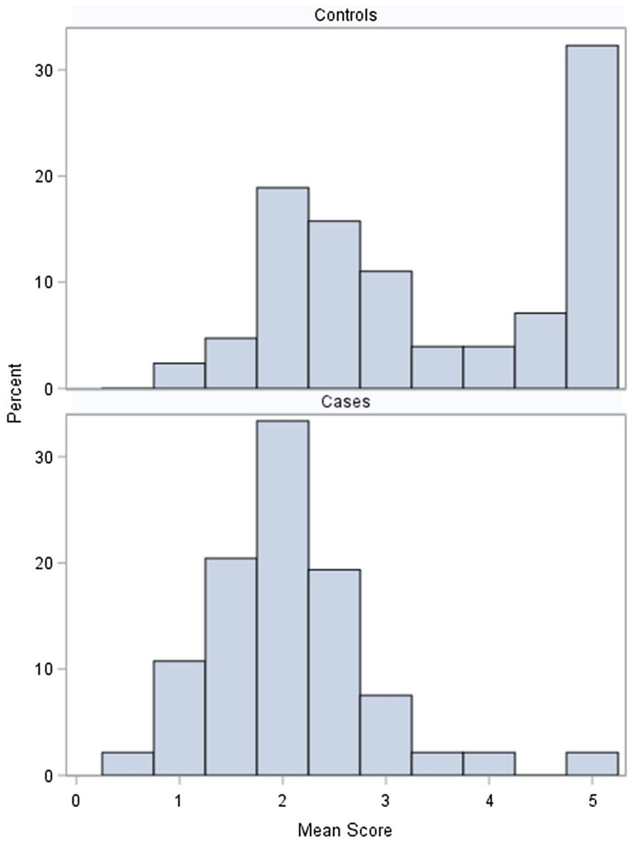


Fig. 1 Distribution of mean lung opacification score. Distribution of mean average lung opacification scores (obtained by averaging the lung opacification score obtained from two blinded, independent pediatric radiologists) by group, includes all chest radiographs obtained within 100 h of ECLS initiation. $n = 98$ radiographs (49 radiographs/group)

less "moderate" and "severe" opacification than CXRs obtained from controls (Table 3; $p < 0.0001$ Cochran–Armitage trend test).

Discussion

The lung opacification scoring system utilized here was first developed by Edwards et al. in 1985 and used to assess and quantify lung opacification on CXRs obtained from newborn infants with respiratory distress syndrome (RDS) [12]. Eighteen of the enrolled patients received endotracheal instillation of human surfactant, while the remaining 18 infants did not. CXRs from all patients were examined, and lung opacification was quantified using the original Edward's scoring system, then called the "RDS Severity Scoring System on Radiographs"; the authors found that treatment with human surfactant ameliorated radiographic findings of RDS.

One year later, Taylor et al. utilized a modified version of this scoring system for the first time in infants receiving ECLS and found that the degree of lung opacification, quantified by the Edwards et al.'s scoring system, did accurately reflect the markedly decreased lung compliance and lung volumes these infants experienced in the hours following ECLS cannulation [7].

Lung opacification can occur in infants during ECLS for a variety of reasons including atelectasis, FO with pulmonary edema, and inflammation. FO often complicates neonatal and infant ECLS, regardless of underlying diagnosis, worsening both morbidity and mortality [4, 14–17]. A recent study found that FO is independently associated with adverse outcomes in pediatric and neonatal patients receiving ECLS, including increased mortality and increased duration of ECLS [4]. CRRT utilization is commonly used to help manage fluid balance during ECLS in these populations, although the optimal timing and methodology for CRRT provision are unknown [18]. CRRT is associated with improved fluid balance during ECLS as well as removal of inflammatory cytokines that are known to circulate in high concentrations immediately following ECLS cannulation; through modification of these pathologic states, CRRT may change the degree of lung opacification observed on CXRs [2, 3, 9, 13, 18–20]. However, to our knowledge, CRRT-mediated effects on lung opacification have never been studied.

In our NICU, CRRT is initiated early in the course of ECLS (within 48 h of ECLS initiation) for all patients in an effort to prevent the development of significant FO and the associated increase in morbidity and mortality. Our group has previously evaluated the effects of early CRRT utilization in our neonatal ECLS patients and found that early CRRT use allows for provision of improved nutrition, particularly protein administration, without increasing length of ventilation, length of ECLS, or worsening survival [13, 21]. We believe this practice is safe and feasible, when fluid removal is cautiously advanced with clinical improvement. When incorporated into the ECLS circuit after prime, CRRT can be used in a volume neutral way to prevent FO (i.e., fluids in = fluids out) without removing excess volume from the patient. If a complication occurs with the machine, CRRT can be isolated from the circuit and a new CRRT filter re-primed with the same blood can be used for the initial prime, limiting patient exposure to blood products. We have ongoing work attempting to quantify the effects of concurrent CRRT and ECLS on inflammatory responses in neonates as well and have documented CRRT-mediated filtration of pro-inflammatory mediators (Murphy HJ unpublished). We hypothesize that early utilization of CRRT during infant ECLS will be associated with decreased lung opacification when compared to matched infants who did not receive CRRT.

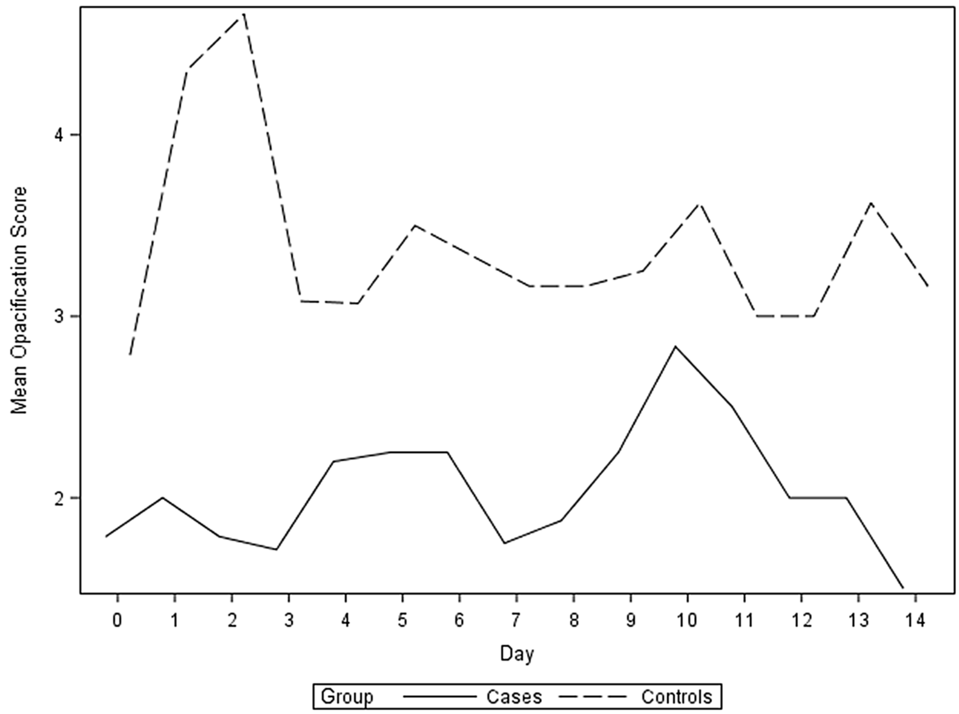


Fig. 2 Distribution of highest mean lung opacification score by day of extracorporeal life support (highest mean AOS (average opacification score) per day by group

We found no differences in birth weight, gestational age, gender, age at cannulation, decannulation or duration of ECLS (Table 2). We also collected pre-ECLS clinical variables to ensure cases and controls were clinically similar at ECLS cannulation. These variables included $AaDO_2$, OI, pre-ELS duration of mechanical ventilation, the use of inhaled nitric oxide, the use of vasopressors/inotropes, the presence of hypoxic ischemic encephalopathy, and no differences were found between groups in these variables suggesting that the groups were clinically similar at baseline. However, the baseline opacification scores were significantly different; patients who received CRRT (i.e., cases) had lower scores and thus less opacification on the last radiographs obtained prior to cannulation than non-CRRT receivers (i.e., =controls) (Table 3). The reason for this difference at baseline is not clear although there are several possible explanations. Infants enrolled in this study were treated between dates spanning 2004–2017, and there was no temporal overlap between the two populations (cases treated between 2004 and 2011; controls treated between 2016 and 2017). Over the course of this time period, multiple changes in the care of our ECLS patients have occurred, including a transition to volume-guaranteed mechanical ventilation and the development of protocols for management of infants with congenital diaphragmatic hernia and those with pulmonary hypertension, resulting in what we believe is improved care. These changes may be responsible for the decrease in lung opacification noted at baseline in case patients and may bias our results. These baseline differences in opacification were controlled for in the remainder of the analysis, though this may not eliminate all potential bias.

Overall, in our cohort, CRRT use during ECLS was associated with decreased lung opacification, both by radiographic scores and corresponding clinical scores. Mean AOS's were lower among case patients than control patients when all obtained radiographs ($n=220$) were evaluated (Table 3). This analysis was performed using repeated measures technique, additionally controlling for the baseline difference in opacification scores. The frequency distribution of scores is depicted in Fig. 1. To avoid over-representation of CXRs from any patient with extended ECLS duration, the frequency distribution is comprised of CXRs obtained during the initial 100 h of ECLS only (Fig. 1). During this time period, CXRs obtained from case patients most commonly had a mean AOS of 2; the most common mean AOS among CXRs obtained from control patients was 5 (Fig. 1). Here, CRRT use is clearly associated with decreased lung opacification.

Similarly, comparison of the radiographs obtained between ECLS day 2 and 3 (1 radiograph per patient; $n=14$) also demonstrated lower scores and thus less lung opacification among cases as compared to controls (Table 3). ECLS is known to illicit a significant inflammatory response similar to that seen in systemic inflammatory response syndrome and acute respiratory distress syndrome, particularly following cannulation [3, 22]. Furthermore, in a recent study conducted by the Kidney Interventions during Extracorporeal Membrane Oxygenation (KIDMO) study group, the epidemiology of FO during ECLS was characterized, and the median day of peak FO during ECLS was day 3 [4]. To observe the effects of these complications on the lungs, we chose to compare lung opacification at this particular time point (ECLS day 2–3). Even at a time when inflammation and FO are significant in typical patients, in our small cohort, CRRT use is associated with decreased lung opacification, even after adjusting for baseline differences noted between cases and controls.

CRRT-mediated improvements in opacification were observed throughout the entire course of ECLS. Figure 2 depicts the highest mean AOS score achieved in each group, cases and controls, for each day of ECLS. The highest scores achieved by case patients were persistently lower than the highest scores achieved by the non-CRRT-receiving control patients on each day of ECLS. We hypothesize that this reflects overall improved lung function, and with a larger sample size, these improvements in lung opacification may result in improvement in clinical outcomes such as duration of mechanical ventilation and duration of ECLS.

Multiple modalities of CRRT were utilized including continuous venovenous hemofiltration and continuous venovenous hemodiafiltration at the discretion of the treating pediatric nephrologist in both case and control patients. Each modality has different physiologic mechanisms that could also impact these outcomes. Modes that primarily rely on convection rather than diffusive clearance, in particular, are known to result in improved cytokine clearance [11].

Although this analysis included more than 220 CXRs, only 14 patients were enrolled, so assessment of clinical outcomes in this small sample size would be underpowered and thus of little utility. We have compared pre-ECLS clinical variables but acknowledge that there is a high risk of type II error given the small patient number. Future studies with broader enrollment are required to determine the relationship between changes in lung opacification on CXRs and clinical outcomes such as duration of ventilation, duration of ECLS, and survival in infants receiving ECLS. Based on these results from a small retrospective cohort, a larger prospective cohort study is justified to determine how these radiographic changes are related to clinical outcomes. Our group has previously published our single center experience with early CRRT use during neonatal ECLS and found no difference in survival among CRRT receivers versus non-CRRT receivers in a larger cohort [13]. The relationship between mortality and CRRT use in neonatal and pediatric patients receiving ECLS is unclear; the few studies currently available in the medical literature present conflicting findings [14, 23–25]. Larger, randomized studies are needed. Previous studies have demonstrated that the degree of lung opacification on CXR accurately reflects both lung volume and compliance in infants during ECLS and that edema and the mobilization of excessive fluid are important determinants of improved lung function and duration of ECLS [6, 7]. Clinically, worsening FO is predictive of higher peak OI in pediatric critical care patients with severe FO (> 15%) and independently associated with longer duration of ventilation [26]. This leads us to hypothesize that improvement in FO may be associated with decreased duration of ventilation. Although we did not detect differences in FO at decannulation between groups, our sample size limits the usefulness of this analysis. Furthermore, this single measure of FO is likely inadequate to fully address how fluid changes across ECLS courses impact outcomes and lung opacification. Lung opacification during ECLS and the associated improvement in opacification found with early CRRT utilization likely result from changes in both fluid balance and inflammatory cascades. The impact of CRRT-mediated improvements in lung opacification on clinical outcomes requires further investigation.

Conclusion

Early continuous renal replacement therapy utilization during infant extracorporeal life support is associated with significantly decreased lung opacification on chest radiographs. Future studies to determine the association between this continuous renal replacement therapy-mediated decreased lung opacification and both short- and long-term clinical outcomes are warranted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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