Implementing a practice change: early initiation of continuous renal replacement therapy during neonatal extracorporeal life support standardizes care and improves short-term outcomes

Heidi J. Murphy¹ · John B. Cahill¹ · Katherine E. Twombly¹ · David J. Annibale¹ · James R. Kiger²

Received: 19 June 2017 / Accepted: 11 September 2017 / Published online: 30 October 2017
© The Japanese Society for Artificial Organs 2017

Abstract

Purpose We hypothesized that a standardized approach to early continuous renal replacement therapy (CRRT) during neonatal extracorporeal life support (ECLS) results in greater homogeneity of CRRT initiation times with improvements in fluid balance and outcomes.

Methods Retrospective analysis of data (2007–2015) obtained from neonates treated prior to (E1; $n=32$) and after (E2; $n=31$) a 2011 practice change: CRRT initiation within 48 h of ECLS.

Data from this project have previously been presented: (1) as an oral platform presentation at a Neonatology Fellows' conference: American Academy of Pediatrics 41st Southeastern Conference on Perinatal Research, Key Largo, Florida. February 2017; (2) as a poster presentation at: Pediatric Academic Societies Meeting, San Francisco, California. May 2017; (3) as a poster presentation at: 10th Annual Darby Children's Research Institute and Pediatrics Research Day, Medical University of South Carolina, Charleston, South Carolina. March 2017; (4) as a poster presentation at: Southern Society of Pediatrics Research Regional Meeting, New Orleans, Louisiana. February 2017. Abstract of this work was published as all abstracts presented at the SSPR annual meeting are published: Murphy H, Cahill J, Twombly K, Annibale D, Kiger J. Early Continuous Renal Replacement Therapy: Implementing a Practice Change in Neonatal Extracorporeal Life Support. Abstract. *J Invest Med.* 2017;65(2):545.

Results Birthweight, gestational age, ECLS mode, and age at ECLS initiation were similar to each epoch. Survival [E1: median 75%, E2: 71%] and length of ECLS [E1: median 221 h, E2: 180 h] were comparable. During E2, 100% of infants received CRRT (vs. E1: 37%; $p<0.001$) and 97% of infants initiated CRRT within 48 h of ECLS (vs. E1: 13%; $p<0.001$). Control charts demonstrate reduced practice variation. Elapsed time from ECLS to CRRT differed between Epochs [E1: median 105 h, E2: 9 h; $p<0.001$] as did weight at CRRT initiation [E1: 4.13 kg (29% above baseline), E2: 3.19 kg (0%); $p<0.001$]. Significant differences in weight change were noted on days 6 and 7 (E1: 14%, E2: 2%; raw data comparison yielded $p<0.05$) and curves were different ($p<0.05$).

Conclusions We successfully implemented a practice change, initiating CRRT within 48 h of ECLS cannulation, leading to decreased practice variation and improved short-term outcomes including decreased weight gain at CRRT initiation and faster return to baseline weight during the first 7 days of ECLS. We did not demonstrate changes in duration of ECLS, invasive ventilation, or survival.

Keywords Extracorporeal membrane oxygenation · Hemofiltration · Renal replacement therapy · Infant (newborn) · Hemodynamic

✉ Heidi J. Murphy
murphyh@muscc.edu

✉ John B. Cahill
cahilljb@muscc.edu

¹ Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Medical University of South Carolina, 165 Ashley Avenue, Charleston, SC 29425, USA

² Department of Pediatrics, University of Pittsburgh, Pittsburgh, PA, USA

Introduction

Extracorporeal life support (ECLS) is a lifesaving therapy that provides cardiopulmonary support to critically ill patients with select, potentially amenable diseases when conventional therapies have failed. Neonates constitute the largest group of patients who require ECLS, most commonly for congenital diaphragmatic hernia (CDH) and

respiratory failure [1]. Acute kidney injury (AKI) and refractory fluid overload often develop following ECLS initiation and significantly increase morbidity and mortality, particularly in neonatal patients [2–7]. In neonates with CDH, the incidence of AKI is particularly high, and if AKI progresses to kidney failure, these patients experience significant increases in duration of ventilation, duration of ECLS, and mortality [4]. Fluid overload complicates most neonatal ECLS courses with increases in body weight as well as increases in both extracellular fluid and total body water [8]. Mobilization of this fluid with return to near baseline weights has been shown to be associated with decreased duration of ECLS while failure to return to near baseline weights has been associated with decreased survival [9, 10]. Fluid restriction and diuretic therapy are typically trialed initially as fluid overload develops, but poor nutrition delivery and severe electrolyte disturbances commonly ensue [11]. Refractory fluid overload regularly occurs despite these measures necessitating continuous renal replacement therapy (CRRT).

CRRT can restore euvolemia in neonates receiving ECLS and improve outcomes without increasing long-term renal morbidity [11–14]. Specifically, CRRT use during neonatal ECLS has been shown to reduce duration of ECLS as well as duration of mechanical ventilation [12]. However, the optimal timing of CRRT initiation during neonatal ECLS is debatable, and CRRT is not universally utilized. A multicenter, international survey conducted by the Kidney Intervention during Extracorporeal Oxygenation study group revealed that nearly 25% of responding institutions do not use renal replacement therapy (RRT) during ECLS [15]. Of the institutions where RRT is used, the predominant indication for RRT was treatment of fluid overload (43% of respondents), while only 16% of respondents utilize RRT for prevention of fluid overload confirming that significant practice variations with regard to RRT utilization during ECLS exist. Our group has demonstrated improved nutrition delivery with CRRT during neonatal ECLS when CRRT is utilized early in the course [16].

Studies in pediatric patients have demonstrated a direct correlation between the degree of fluid overload at CRRT initiation and mortality [6, 17, 18]. Failure to return to dry weight has been associated with decreased survival in pediatric patients with respiratory failure [10]. Furthermore, once significant fluid overload has been established, efforts at fluid removal fail to improve mortality, underscoring the importance of prevention, and it has been suggested that intervening prior to the development of significant fluid overload may be the most effective strategy to improve outcomes [6]. Early CRRT, commonly defined as CRRT initiation within 48 h of ECLS cannulation, may prevent the complications incurred secondary to significant fluid overload and the associated mortality, but few studies have

examined outcomes in infants receiving early CRRT during ECLS [6, 19].

We evaluated our single-center experience with early CRRT use during neonatal ECLS. Using a multi-disciplinary approach including collaboration among neonatology, pediatric nephrology, perfusion specialists, ECLS coordinators, and nursing, we implemented a practice change in our neonatal intensive care unit in August 2011, aiming to initiate CRRT within 48 h of cannulation. We hypothesized that standardized, early initiation of CRRT during neonatal ECLS results in greater homogeneity of CRRT initiation times, improvements in fluid balance, and improvements in clinical outcomes.

Materials and methods

Demographics and data collection

We conducted a retrospective cohort study, collecting data from the medical records of neonates who received ECLS in the neonatal intensive care unit (NICU) at the Medical University of South Carolina, in Charleston, South Carolina. Infants were treated between January 1, 2007, and December 31, 2015. Patients were excluded if they were > 30 days of age at ECLS cannulation or if they required multiple runs of ECLS. Data including patient demographics, diagnosis requiring ECLS, mode of ECLS, duration of ECLS, mode of CRRT, weight at CRRT initiation, duration of CRRT, daily weights for first seven days of ECLS, duration of invasive ventilation, and survival were abstracted from patient charts. Percent fluid overload was calculated using the following formula based on the work of Selewski et al.: percent fluid overload = [(weight on day_x - weight at ECLS initiation) / weight at ECLS initiation] × 100% and recorded [17]. A similar formula was used to document percent fluid overload at CRRT initiation: percent fluid overload at CRRT initiation = [(weight at CRRT initiation - weight at ECLS initiation) / weight at ECLS initiation] × 100%. Duration of ventilation following decannulation as well as need for long-term renal replacement therapy, tracheostomy, or home ventilation were also recorded.

Practice change

A practice change occurred in August 2011 setting a goal for the initiation of CRRT within 48 h of cannulation (i.e., “early CRRT”) for all neonatal patients receiving ECLS. A stretch goal of CRRT initiation within 24 h of cannulation was also set. Comparisons were made between two Epochs: neonates who received ECLS prior to the practice change (Epoch 1; *n* = 32) and neonates who received ECLS following the practice change (Epoch 2; *n* = 31). Approval for this

study was obtained from the Medical University of South Carolina's Institutional Review Board; informed consent was waived.

ECLS with CRRT configuration

ECLS was managed by the neonatal attending of record with the co-management of an ECLS team composed of two additional neonatologists. Venovenous and venoarterial ECLS were both used during the study period at the discretion of the treating neonatologist. ECLS was provided using a roller head pump (SORIN GROUP USA, Incorporated; Arvada, Colorado) and QUADROX oxygenator (MAQUET Medical Systems, Wayne, New Jersey).

The most commonly used modes of CRRT in both groups during this study period were hemofiltration or hemodiafiltration at the discretion of the treating nephrologist. Prior to this practice change, CRRT was initiated on a case-by-case basis at the discretion of the neonatology team in consultation with our pediatric nephrology team; some infants received CRRT while others were managed with fluid restriction and diuretics alone. The new practice in our NICU was established in August 2011, and providers aimed to initiate CRRT within 48 h of cannulation for all neonatal patients receiving ECLS, preferably before the onset of significant fluid overload.

Initially, CRRT was provided using HF1000 polyarylethersulfone membranes with tubing (Gambro; Hechingen, Germany) added to the ECLS circuit in parallel to the pump and driven by the transpump pressure. The hemofilter access was attached to the ECLS circuit post-pump and pre-oxygenator, and the return from the hemofilter was attached to the circuit pre-pump and pre-oxygenator. Patient fluid removal rate was determined each day by the neonatology team in consultation with nephrology. In April of 2015, our institution began using the Prismaflex® system (Baxter International Incorporated; Deerfield, Illinois) with the access and return lines added pre-membrane in the ECLS circuit. Again, patient fluid removal rate was determined each day by the neonatology team in consultation with nephrology.

Outcome measures

We first analyzed the process of the quality improvement initiative itself comparing CRRT utilization in each Epoch. Using process control charting, we measured the effect of implementation of a practice change by analyzing the elapsed time from cannulation to CRRT initiation. Age and weight at CRRT initiation were also compared. Because the goal of early initiation of CRRT was to reduce volume overload, we hypothesized that early CRRT would result in less weight gain and a rapid return to pre-ECLS weight. Our primary outcome measure was average daily weight change

measured from the time of initiation of ECLS over the first 7 days of ECLS (or until discontinuation of ECLS if discontinued within 7 days). Percent fluid overload is reported; however, comparisons between groups were made utilizing raw weight data.

Additionally, to test the hypothesis that early CRRT improves clinical outcomes, we examined the duration of ECLS, duration of invasive ventilation, and survival rates. Because these selected clinical outcomes are strongly influenced by underlying diagnosis, comparisons were made between infants with similar diagnoses in one of the two subgroups, infants with CDH or infants with reversible pulmonary or pulmonary vascular pathology (including persistent pulmonary hypertension, meconium aspiration syndrome, or sepsis).

Statistical analysis

Quantitative data are shown as median (interquartile range) or mean $\pm$ standard deviation for continuous data and proportions for categorical variables. Univariate comparisons between Epochs were conducted using Chi square tests, Fisher's exact tests, or Wilcoxon rank sum tests, as appropriate. Analysis of the incremental weight change over the first seven days of ECLS was done based on repeated measures analysis of raw weight data, controlling for the baseline measurement (weight at ECLS cannulation). In this analysis, *p* values were adjusted for multiple comparisons using the Holm's stepdown approach. Linear regression using the repeated model measure was also performed (ECLS day 2–7). Process change was measured by sequential analysis of the time of initiation of CRRT after ECLS using process control charts. A *p* value of <0.05 was considered statistically significant. All analyses were performed using SPSS® Statistics, version 19 (IBM®, Armonk, New York), SAS®, version 9.4 (©SAS Institute Incorporated, Cary, North Carolina), and QI macros for Excel, version 2016.06 (Microsoft®, Redmond, Washington).

Results

Patients

A total of 63 neonatal patients were included, 32 patients in Epoch 1 and 31 patients in Epoch 2. The Epochs were similar when comparing diagnosis prompting ECLS, birthweight, gestational age, ECLS mode, and age at ECLS initiation; there was a significant gender difference (Table 1). Duration of ECLS as well as survival of ECLS and survival to discharge were comparable between groups (Table 1). Infants in both Epochs most commonly required ECLS

Table 1 Patient characteristics

	Epoch 1 (<i>n</i> = 32)	Epoch 2 (<i>n</i> = 31)	<i>p</i>
Diagnosis requiring ECLS, <i>n</i>			
CDH	8 (25%)	8 (26%)	1.0
Persistent pulmonary hypertension	9 (25%)	13 (42%)	0.25
Meconium aspiration syndrome	6 (19%)	5 (16%)	0.78
Sepsis	3 (9%)	1 (3%)	0.32
Other	7 (22%)	4 (13%)	0.51
Birth weight, kg	3.18 [2.81–3.51]	3.07 [2.8–3.31]	0.46
Gestation age, weeks	39 [37 ⁺² – 39 ⁺⁴]	38 ⁺⁴ [36 ⁺⁵ – 39 ⁺⁵]	0.62
Male, <i>n</i>	21 (66%)	12 (39%)	0.03
Venovenous ECLS, <i>n</i>	2 (6%)	7 (23%)	0.08
Age at ECLS initiation, h	35 [17–70]	30 [15–55]	0.52
Duration of ECLS, h			
All diagnoses	221 [148–362]	180 [117–372]	0.29
ECLS survivors	214 [141–341]	170 [112–267]	0.19
ECLS survival, <i>n</i>			
CDH	6 (75%)	5 (63%)	0.59
Reversible pulmonary/pulmonary vascular pathology	16 (94%)	17 (89%)	0.62
Other	6 (86%)	2 (50%)	0.49
Overall-all diagnoses	28 (88%)	24 (77%)	0.29
Survival to hospital discharge, <i>n</i>			
CDH	5 (63%)	4 (50%)	1.0
Reversible pulmonary/pulmonary vascular pathology	16 (89%)	17 (89%)	0.62
Other	3 (43%)	1 (25%)	1.0
Overall-all diagnoses	24 (75%)	22 (71%)	0.72

This table compares the baseline characteristics for infants in each Epoch. Continuous data are shown as median [interquartile range]. Categorical data are shown as proportions. Extracorporeal life support (ECLS)

for persistent pulmonary hypertension followed by CDH (Table 1).

Outcomes

Practice change was implemented in August 2011 which marks the transition from Epoch 1 to Epoch 2. During Epoch 1, 37% of patients received CRRT, while all patients received CRRT in Epoch 2 ($p < 0.001$). The distribution of time to CRRT initiation following cannulation was statistically different ($p < 0.001$) with initiation occurring later in Epoch 1 than Epoch 2 (Table 2). Process control charting illustrates that following this practice change, standardization of early CRRT initiation was achieved with a decrease in the variability of time elapsed from ECLS cannulation to CRRT initiation noted in Epoch 2 (Fig. 1).

We demonstrated statistically significant differences in elapsed time from cannulation to CRRT initiation [Epoch 1: median 105 h (28–178), Epoch 2: 9 h (4–22); $p < 0.01$] and weight at CRRT initiation [Epoch 1: 4.13 kilograms (3.73–4.95), Epoch 2: 3.19 kilograms (2.8–3.58); $p < 0.01$] (Table 2). Infants in Epoch 1 were more fluid overloaded at CRRT initiation than infants in Epoch 2 (Table 2).

Percent weight change over the first seven days of ECLS for patients in each Epoch is illustrated in Fig. 2. In both Epochs, we note a significant increase in weight following ECLS cannulation. However, in Epoch 2, we see a more dramatic decrease in weight during the second half of the first week of ECLS with a return to near baseline, while infants in Epoch 1 had a slower weight loss and remained $> 10\%$ fluid overloaded at ECLS day 7. Statistically significant differences in weight change were noted on days 6 and 7 of ECLS on repeated measures analysis of raw weight data. Using linear regression, a significantly more rapid decline in weight was noted from ECLS day 2 to ECLS day 7 in infants in Epoch 2 compared to those in Epoch 1.

There were no differences in additional select clinical outcomes including duration of ECLS, duration of invasive ventilation, or survival when comparing infants in Epoch 1 and Epoch 2 (Figs. 3, 4). Long-term morbidities are reported in Table 3.

Table 2 Analysis of practice change

	Epoch 1 (n = 32)	Epoch 2 (n = 31)	p
Most utilized CRRT modality	CVVH	CVVH	N/A
Use of CRRT			
Used	12 (37%)	31 (100%)	<0.001
Not used	20 (63%)	0 (0%)	
Time to CRRT ^a			
≤ 48 h	4 (13%)	30 (97%)	<0.001
> 48 h	8 (25%)	1 (3%)	
Elapsed time ECLS to CRRT, h	105 [28–178]	IQR [4–22]	<0.01
Weight at CRRT initiation, kg	4.13 [3.74–4.95]	3.19 [2.8–3.58] ^b	<0.01
Fluid overload at CRRT initiation ^d , percentage	29	0	N/A ^c
Birth weight, kg	3.18 [2.81–3.51]	3.07 [2.8–3.31]	0.46
Age at CRRT initiation, h	201 [87–234]	48 [24–78]	<0.01

This table compares the utilization of continuous renal replacement therapy (CRRT) infants in each Epoch

^a2 Patients (6%) of infants in Epoch 1 met our stretch goal and initiated CRRT < 24 h after cannulation compared to 24 patients (78%) in Epoch 2

^bOne patient in Epoch 2 excluded as no weights were available during the first 7 days of ECLS

^cPercent fluid overload at CRRT initiation was measured by the following formula: percent fluid overload at CRRT initiation = [(weight at CRRT initiation – weight at ECLS initiation)/weight at ECLS initiation] × 100%

^dPercent fluid overload is reported; however, comparisons between groups were made utilizing raw weight data. Continuous data are shown as median [interquartile range]. Categorical data are shown as proportions. Extracorporeal life support (ECLS)

Fig. 1 Process Control chart: time from extracorporeal life support to continuous renal replacement therapy. Process control chart (XMR chart) of time from extracorporeal life support (ECLS) cannulation to continuous renal replacement therapy (CRRT) initiation. Chart **a**: An X-chart (also known as an individual chart) demonstrates the hours

elapsed from ECLS to CRRT in each of the 12 patients that received CRRT in Epoch 1 and all 31 patients in Epoch 2. Chart **b**: A mR-chart (also known as a moving range chart) demonstrates the difference between consecutive data point measurements in each Epoch

Discussion

To our knowledge, this is the first study examining early CRRT utilization in exclusively neonatal patients receiving

ECLS and only the second study examining early CRRT utilization in a pediatric ECLS population. We report a successful change in practice at our institution, initiation of CRRT within 48 h of ECLS cannulation, with improved

Fig. 2 Outcome measure: weight change from baseline. Median percent weight change (including standard error bars) for patients in each Epoch for each of the first seven days of extracorporeal life support (ECLS) ($n = 32$ in Epoch 1 and $n = 30$ in Epoch 2; one patient in Epoch 2 excluded as weights were not recorded during the first 7 days of ECLS). Analysis using raw data is discussed within the manuscript

Table 3 Long-term complications and morbidities

	Epoch 1 ($n = 32$)	Epoch 2 ($n = 31$)	<i>p</i>
Duration of ventilation following decannulation, <i>n</i>			
CDH	266 [128–365]	399 [331–593]	0.13
Persistent pulmonary hypertension	58 [45–97]	114 [61–192]	0.06
Renal replacement therapy required after decannulation, <i>n</i>	3 (9%)	2 (6%)	1.0
Tracheostomy, <i>n</i>	1 (3%)	1 (3%)	1.0
Home ventilator, <i>n</i>	1 (3%)	1 (3%)	1.0

This table compares the long-term complications and morbidities for infants in each Epoch. Continuous data are shown as median [interquartile range]. Categorical data are shown as proportions. Congenital diaphragmatic hernia (CDH)

fluid management and short-term outcomes. Only one infant in Epoch 2 did not initiate CRRT within 48 h due to coordination of care difficulties.

Most studies examining the use of ECLS and CRRT during neonatal, pediatric, and adult ECLS were done when CRRT was initiated for an indication (fluid overload, acute kidney injury, electrolyte disturbances) rather than for prevention of complications and, not surprisingly, have shown conflicting results. Some studies have shown increased mortality, while others have demonstrated that CRRT was useful for the management of fluid overload and improved outcomes during ECLS [3, 6, 7, 19]. Emerging data suggest that the timing of CRRT initiation during ECLS may be an important factor driving these conflicting findings, but the optimal timing of CRRT initiation during neonatal ECLS is unknown [3, 6, 7, 14, 17, 20]. Two recent studies of early vs. delayed initiation of CRRT in adult patients have been completed, one suggesting an improvement in mortality associated with early CRRT utilization and the second suggesting no difference in mortality but decreased CRRT

utilization with the delayed strategy [21, 22]. However, these studies included only adult patients. In pediatric and neonatal patients, an association between fluid overload at CRRT initiation and mortality has been established; further, following the development of significant fluid overload, mortality is not improved by efforts at fluid removal for patients receiving ECLS [6]. This evidence led to our practice change of early CRRT initiation during neonatal ECLS, in August 2011, and our hypothesis that standardized early initiation of CRRT would result in greater homogeneity of CRRT initiation times and subsequently lead to improvements in fluid balance and clinical outcomes.

Through a multi-disciplinary, collaborative initiative, we successfully changed our practice in our NICU. Following the August 2011 practice change, 100% of infants in Epoch 2 received CRRT, a statistically significant increase compared to the 38% of infants in Epoch 1 that received CRRT. Ninety-seven percent of the infants in Epoch 2 received CRRT within our goal of 48 h of cannulation, and 78% of these infants met our stretch goal of CRRT initiation with

Fig. 3 Clinical outcome measures: duration of therapies. Box-plot: **a** Box-plot depicting the duration of extracorporeal life support for infants in each Epoch, analyzed in subgroups. Values in hours are represented by box with the lower boundary indicating 25th percentile, line within box marking median, the upper boundary indicating 75th percentile, whisker bars indicating 10th and 90th percentiles, and dots representing outliers. ^aCongenital diaphragmatic hernia (CDH; $n=8$ in Epoch 1 and $n=8$ in Epoch 2) and ^breversible pulmonary/pulmonary vascular pathology ($n=17$ in Epoch 1 and $n=19$ in Epoch 2). Box-plot: **b** box-plot depicts the duration of invasive

ventilation for infants in each Epoch, analyzed in the same subgroups. Values in hours are represented by box with the lower boundary indicating 25th percentile, line within box marking median, the upper boundary indicating 75th percentile, whisker bars indicating 10th and 90th percentiles, and dots representing outliers. ^cCDH— $n=8$ in Epoch 1 and $n=8$ in Epoch 2; ^dReversible pulmonary pathology— $n=16$ in Epoch 1 and $n=18$ in Epoch 2 (1 patient in each Epoch excluded—discharged to home with tracheostomy and home ventilator)

24 h of cannulation, a statistically significant increase from the 13% of infants in Epoch 1. This demonstrates that the practice of early CRRT is viable in an NICU setting when a multi-disciplinary team approach is applied. At our institution, ECLS coordinators attend all ECLS cannulations and ensure that the necessary equipment to perform CRRT as soon as possible after cannulation is available for NICU patients. Pediatric nephrology is contacted by the neonatology team after successful cannulation, and CRRT orders are placed; per protocol this must occur within 48 h of cannulation, and all team members including neonatology, pediatric surgery, pediatric nephrology, and ECMOlogists are aware that this will occur. As expected, we noted that infants treated after this practice change had significantly shorter time elapsed from ECLS cannulation to CRRT initiation than patients treated before the practice change. Statistical process control charting further illustrates standardization of early CRRT initiation with a decrease in the variability of time elapsed from ECLS cannulation to CRRT initiation

following August 2011 further demonstrating that early initiation of CRRT is feasible. To our knowledge, we are the first to report experience with early CRRT in a neonatal intensive care unit.

To determine the effect of this practice change on clinical outcomes, we compared differences in weight change from ECLS cannulation to CRRT initiation between Epochs with weight serving as a marker for fluid overload at CRRT initiation. Weight-based methods, rather than fluid balance methods, have been shown to be accurate markers of fluid overload [17]. Infants in Epoch 2 were noted to have a significantly lower weight at CRRT initiation compared to infants in Epoch 1; this suggests that infants in Epoch 2 had less fluid overload at CRRT initiation, as would be anticipated if early initiation of CRRT is effective. Infants in Epoch 2 did not have fluid overload at CRRT initiation compared to infants in Epoch 1 who experienced considerable fluid overload (29%). Studies in pediatric patients receiving ECLS and patients not receiving ECLS demonstrate a direct

Fig. 4 Clinical outcome measures: survival. Bar graph: **a** bar graph depicts the survival of extracorporeal life support for infants in each Epoch, analyzed in the same subgroupings (CDH- $n=8$ in Epoch 1 and $n=8$ in Epoch 2 [$p=0.59$]; Reversible pulmonary pathology- $n=17$ in Epoch 1 and $n=19$ in Epoch 2 [$p=0.62$]). Bar graph: **a** bar

graph depicts the survival to hospital discharge for infants in each Epoch, analyzed in the same subgroupings (CDH- $n=8$ in Epoch 1 and $n=8$ in Epoch 2 [$p=1.0$]; Reversible pulmonary pathology- $n=17$ in Epoch 1 and $n=19$ in Epoch 2 [$p=0.62$])

correlation between the degree of fluid overload at CRRT initiation and mortality [6, 17, 18]. In a study conducted by Selewski et al. of pediatric patients receiving ECLS, median fluid overload at CRRT initiation during ECLS was significantly lower in survivors vs. non-survivors, a finding that was consistent with reports from pediatric CRRT studies [6, 17, 18, 20]. Nonsurvivors had a median fluid overload at CRRT initiation of $>30\%$ while survivors had a median fluid overload at CRRT initiation of $<30\%$ [6]. This group also found that median fluid overload at CRRT discontinuation was significantly lower in survivors vs. nonsurvivors and that the average degree of fluid overload remained higher in nonsurvivors throughout the course of ECLS at all examined timepoints [6]. These findings were similar to the findings of Swaniker et al.: failure to return to a patient's dry weight during pediatric ECLS is associated with decreased survival [10]. Evaluation of our select, short-term clinical outcome, weight change over the first 7 days of ECLS, demonstrated statistically significant differences in weight change in days 6 and 7 of ECLS. Management of volume status and fluid balance was improved with early CRRT as demonstrated by a return to near baseline weight in infants in Epoch 2 (this was not observed in Epoch 1) and a more rapid trajectory of weight loss.

In addition to improvements in mortality, duration of ECLS has been shown to be increased due to AKI and fluid retention in pediatric and neonatal patients [2, 5, 9]. During neonatal ECLS specifically, CRRT use has been shown to reduce both duration of ECLS and mechanical ventilation [12]. Interestingly, weight in both groups increased after the

initiation of ECLS. We hypothesize that this increase might represent decompartmentalization of intravascular fluid and the formation of generalized edema that would be amenable to CRRT. It may also be secondary to the need for volume expansion that is common after the initiation of ECLS. Alternatively, because CRRT was initiated conservatively in anticipation of the need for volume expansion, it is possible that we underestimated the need for volume removal.

Because of these studies, we anticipated that the decreased fluid overload at CRRT initiation in Epoch 2 would be associated with decreased duration of ECLS and invasive ventilation along with improved survival. Although we achieved improved fluid management in patients in Epoch 2 and demonstrated less fluid overload at CRRT initiation and discontinuation, we did not demonstrate anticipated differences in duration of ECLS, duration of invasive ventilation or survival between Epochs. This could possibly be due to the fact that this was a retrospective study, and it was not powered to see the differences in clinical outcomes. Further prospective studies will be needed to assess these outcomes. Neonatal patients were included in many of the described studies; however, ours is the first study to examine CRRT use and fluid overload exclusively in a neonatal ECLS population. Further, many of the patients included in the above studies experienced cardiac disease and cardiac repair while our population of neonates primarily included respiratory diagnoses with no cardiac interventions required in either Epoch. Patients in Epoch 1 were noted to be 29% fluid overloaded at CRRT initiation, a level that did not reach the 30% level noted in other studies; our patients thus did not

experience fluid overload that was as severe as some patients included in the above mentioned fluid overload studies. Further, this study was not powered to assess these outcomes as a retrospective observational study. Lastly, at our institution, patients are taken off of ECLS as soon as possible regardless of fluid overload.

Since the initiation of our practice change in 2011, Wolf et al. published a report examining early CRRT use in pediatric patients receiving ECLS. To our knowledge, this is the only other study specifically evaluating early CRRT use in pediatric patients. The authors compared pediatric cardiac patients requiring ECLS alone with pediatric cardiac patients requiring ECLS with CRRT added within 48 h of cannulation (“early CRRT”) in response to fluid overload. The authors reported that early CRRT was independently associated with in-hospital death, and patients receiving ECLS with early CRRT had longer durations of ECLS. In that report, only 25% of patients receiving ECLS with early CRRT survived to hospital discharge while 60% of patients in the ECLS alone group survived to discharge ($p < 0.001$). Pediatric cardiac patients in the ECLS with early CRRT group had a mean duration of 11.2 days (median 9 days) of ECLS compared to patients in the ECLS alone group with a mean duration of 4.8 days (median 4 days) of ECLS ($p < 0.001$). The authors concluded that their findings did not appear to justify early CRRT use in cardiac ECLS patients [19].

Our report differs in several ways. We found no significant differences in duration of ECLS, duration of invasive ventilation, or mortality when comparing infants in our NICU who received ECLS with early CRRT (Epoch 2) with infants who received ECLS alone or ECLS with late CRRT (Epoch 1). Because underlying diagnosis has a significant impact on both mortality and duration of ECLS regardless of fluid management strategies, we evaluated infants by subgroups (CDH and reversible pulmonary/pulmonary vascular pathology), comparing infants with similar disease process in Epoch 1 to patients in Epoch 2. Significant differences between our study population and the pediatric cardiac patients studied by Dr. Wolf et al. likely contribute to these discordant findings. The pediatric cardiac patients in the study performed by Wolf et al. all had either congenital heart disease or medical cardiac disease necessitating ECLS; the majority of patients were postoperative from cardiac surgery. Additionally, a significant portion of patients in each group (> 30% overall) were cannulated via the extracorporeal cardiopulmonary resuscitation pathway (ECPR). Our study population comprised solely neonatal patients, most of whom were cannulated for respiratory disease, specifically persistent pulmonary hypertension (Table 1). No patients in our cohort had cardiac surgery before ECLS initiation, and none were cannulated via the ECPR pathway as most infants with cardiac disease at our institution are cared for

in a separate, pediatric cardiac intensive care unit. These populations were thus dissimilar and difficult to compare. The underlying physiology that led to ECLS in each study population was remarkably different and certainly affected outcomes profoundly regardless of fluid management strategies. Our findings correlate with the findings of Selewski et al. however. Our patients became > 10% fluid overloaded during the first week of ECLS despite early CRRT initiation, and although we were more successful in removing this excess fluid with early CRRT, we did not improve mortality [6]. However, we did not note the same worrisome findings of increased duration of ECLS and mortality demonstrated by Wolf et al. [19].

We recognize several limitations as well as confounders. This is a single-center study and retrospective in nature. A much larger study population would be required to provide improved power to assess our outcomes, particularly survival. Although infants were classified for comparison based on their indication for ECLS, many patients had significant co-morbid conditions (including diagnoses such as hypoxic ischemic encephalopathy and infection) that certainly affected each individual prognosis and contributed to long-term outcomes. Concurrent to this practice change, a multi-disciplinary ECLS team for neonatal patients was established including the primary neonatologist, with support from two neonatologists as well as select pediatric subspecialists including pediatric nephrology and pediatric surgery. Our NICU also began providing volume-guarantee modes of ventilation during 2014–2015, and a new protocol for initial treatment of infants with CDH was also introduced during the study period. While these changes could influence overall outcomes, fluid management (our primary outcome) was at the discretion of the neonatology attending of record. Importantly, our review includes patients treated over a nine-year period with multiple different modes of CRRT. Until 2015, a traditional model of an inline filter providing CRRT was most commonly used. Since April 2015, an integrated Prismaflex® system has been utilized for CRRT in our NICU during ECLS. Studies comparing inline filter ultrafiltration and integrated systems suggest that more accurate fluid removal occurs with integrated systems [6, 23]. At our institution, we found the more traditional mode of CRRT to be prone to fluid measurement error, and we believe that the Prismaflex® system has improved our accuracy in providing CRRT. Since this change to an automated CRRT system occurred relatively recently, only a small number of patients have received this type of therapy, and our results do not reflect this improved accuracy. With a larger cohort of patients receiving early CRRT during neonatal ECLS via the Prismaflex® system, improvements in our select clinical outcomes may be achieved.

Future studies focusing on better quantifying fluid overload and intravascular volume status throughout ECLS

courses, particularly examining outcomes for infants treated with early CRRT using the Prismaflex® system and those using the free flow system, are needed to better understand the full spectrum of effects of CRRT in neonatal patients receiving ECLS. Early CRRT utilization during ECLS may be justified, particularly in neonates requiring ECLS for respiratory failure, but requires more study. Additionally, further work to improve the fluid overload that occurs in the first few days following ECLS cannulation regardless of CRRT initiation timing must be done. Certainly, a multicenter randomized controlled trial to comparing outcomes among neonates and pediatric patients treated with early vs. late CRRT initiation during ECLS is necessary.

Conclusion

We successfully implemented a practice change, instituting CRRT within 48 h of cannulation, standardizing care in our NICU, and significantly reducing practice variation. This resulted in improved short-term clinical outcomes including decreased weight gain (reflecting decreased fluid overload) at time of CRRT initiation as well as a more rapid return to baseline weight with early CRRT initiation. No changes were found in duration of ECLS, duration of invasive ventilation, or survival.

Acknowledgements Monika Cardona, RN, BSN; Alisha Gibbs, RN, BSN; Mical Parker, RN, BSN, CCRN, Kristen Morella, MPH.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest; however, Dr. John B. Cahill owns stock in the following companies: General Electric, Medtronic, and Pfizer. Heidi J. Murphy, MD helped to conceive, plan, and perform the work leading to this manuscript and interpreted the evidence presented here. She wrote this report and approved the final draft. John B. Cahill, MD, Katherine E. Twombly MD, David J. Annibale, MD and James R. Kiger, MD helped to conceive, plan and interpret the evidence presented here. These authors contributed to revisions of this manuscript and approved the final draft.

References

1. ECMO: Extracorporeal Cardiopulmonary Support in Critical Care. 4th ed. ed.: Extracorporeal Life Support Organization
2. Smith AH, et al. Acute renal failure during extracorporeal support in the pediatric cardiac patient. *ASAIO J.* 2009;55(4):412–6.
3. Zwiers AJ, et al. Acute kidney injury is a frequent complication in critically ill neonates receiving extracorporeal membrane oxygenation: a 14-year cohort study. *Crit Care.* 2013;17(4):R151.
4. Gadepalli SK, et al. Acute kidney injury in congenital diaphragmatic hernia requiring extracorporeal life support: an insidious problem. *J Pediatr Surg.* 2011. 46.
5. Fleming GM, et al. The incidence of acute kidney injury and its effect on neonatal and pediatric extracorporeal membrane Oxygenation outcomes: a multicenter report from the kidney intervention during extracorporeal membrane oxygenation study group. *Pediatr Crit Care Med.* 2016;17(12):1157–69.
6. Selewski DT, et al. Fluid overload and fluid removal in pediatric patients on extracorporeal membrane oxygenation requiring continuous renal replacement therapy. *Crit Care Med.* 2012;40(9):2694–9.
7. Askenazi DJ, et al. Acute kidney injury and renal replacement therapy independently predict mortality in neonatal and pediatric noncardiac patients on extracorporeal membrane oxygenation. *Pediatr Crit Care Med.* 2011;12(1):e1–e6.
8. Anderson HL 3rd et al. Extracellular fluid and total body water changes in neonates undergoing extracorporeal membrane oxygenation. *J Pediatr Surg.* 1992. 27(8):1003–7 (**discussion 1007-8**).
9. Kelly RE Jr, et al. Pulmonary edema and fluid mobilization as determinants of the duration of ECMO support. *J Pediatr Surg.* 1991;26(9):1016–22.
10. Swaniker F, et al. Extracorporeal life support outcome for 128 pediatric patients with respiratory failure. *J Pediatr Surg.* 2000;35(2):197–202.
11. Hoover N, et al. Enhanced fluid management with continuous venovenous hemofiltration in pediatric respiratory failure patients receiving extracorporeal membrane oxygenation support. *Intensive Care Med.* 2008;34(12):2241–7.
12. Blijdorp K, et al. Haemofiltration in newborns treated with extracorporeal membrane oxygenation: a case-comparison study. *Crit Care.* 2009;13(2):R48.
13. Chen H, et al., Combination of extracorporeal membrane oxygenation and continuous renal replacement therapy in critically ill patients: a systematic review. *Crit Care.* 2014;18(6).
14. Paden ML et al. Recovery of renal function and survival after continuous renal replacement therapy during extracorporeal membrane oxygenation. *Pediatric Crit Care Med J Soc Crit Care Med World Federation Pediatric Intensive Critical Care Soc.* 2011;12(2):153–8.
15. Fleming GM, et al. A multicenter international survey of renal supportive therapy during ECMO: the Kidney Intervention During Extracorporeal Membrane Oxygenation (KIDMO) group. *Asaio J.* 2012;58(4):407–14.
16. Murphy HJ, Twombly CJ KE, Kiger JR. Early continuous renal replacement therapy improves nutrition delivery in neonates during extracorporeal life support. *Journal of Renal Nutrition.* 2017; p. Accepted for publication on June, 12 2017. Pending publication.
17. Selewski DT, et al. Weight-based determination of fluid overload status and mortality in pediatric intensive care unit patients requiring continuous renal replacement therapy. *Intensive Care Med.* 2011;37(7):1166–73.
18. Sutherland SM, et al. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. *Am J Kidney Dis.* 2010;55(2):316–25.
19. Wolf MJ et al. Early renal replacement therapy during pediatric cardiac extracorporeal support increases mortality. *Ann Thoracic Surg.* 96(3):917–22.
20. Modem V et al. Timing of continuous renal replacement therapy and mortality in critically ill children. *Crit Care Med.* 2014;42(4):943–53.
21. Zarbock A, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *Jama.* 2016;315(20):2190–9.
22. Gaudry S et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med.* 2016;375(2):122–33.
23. Symons JM et al. Continuous renal replacement therapy with an automated monitor is superior to a free-flow system during extracorporeal life support. *Pediatr Crit Care Med.* 2013;14(9):e404–8.