Fluid overload and fluid removal in pediatric patients on extracorporeal membrane oxygenation requiring continuous renal replacement therapy*

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Objective: **In pediatric patients, fluid overload at continuous renal replacement therapy initiation is associated with increased mortality. The aim of this study was to characterize the association between fluid overload at continuous renal replacement therapy initiation, fluid removal during continuous renal replacement therapy, the kinetics of fluid removal and mortality in a large pediatric population receiving continuous renal replacement therapy while on extracorporeal membrane oxygenation.**

Design: **Retrospective chart review.**

Setting: **Tertiary children's hospital.**

Patients: **Extracorporeal membrane oxygenation patients requiring continuous renal replacement therapy from July 2006 to September 2010.**

Interventions: **None.**

Measurements and Main Results: **Overall intensive care unit survival was 34% for 53 patients that were initiated on continuous renal replacement therapy while on extracorporeal membrane oxygenation during the study period. Median fluid overload at continuous renal replacement therapy initiation was significantly lower in survivors compared to nonsurvivors (24.5% vs. 38%, $p = .006$). Median fluid overload at continuous renal replacement therapy discontinuation was significantly lower in survivors compared to nonsurvivors (7.1% vs. 17.5%, $p = .035$). After adjusting for percent fluid overload at continuous renal replacement therapy initiation, age, and severity of illness, the change in fluid overload at continuous renal replacement therapy discontinuation was not significantly associated with mortality ($p = .212$). Models investigating the rates of fluid removal in different periods, age, severity of illness, and fluid overload at continuous renal replacement therapy initiation found that fluid overload at continuous renal replacement therapy initiation was the most consistent predictor of survival.**

Conclusions: **Our data demonstrate an association between fluid overload at continuous renal replacement therapy initiation and mortality in pediatric patients receiving extracorporeal membrane oxygenation. The degree of fluid overload at continuous renal replacement therapy discontinuation is also associated with mortality, but appears to reflect the effect of fluid overload at initiation. Furthermore, correction of fluid overload to ≤10% was not associated with improved survival. These results suggest that intervening prior to the development of significant fluid overload may be more clinically effective than attempting fluid removal after significant fluid overload has developed. Our findings suggest a role for earlier initiation of continuous renal replacement therapy in this population, and warrant further clinical studies. (Crit Care Med 2012; 40:2694–2699)**

Key Words: acute kidney injury; continuous renal replacement therapy; extracorporeal membrane oxygenation; fluid overload; pediatric intensive care

Extracorporeal membrane oxygenation (ECMO) is a life-saving therapy for pediatric patients with severe cardiac and respiratory failure. For patients on ECMO, the development of acute kidney injury (AKI) and the fluid overload (FO) are associated with increased mortality (1–7). As such, continuous renal replacement therapy (CRRT) has become an important tool in managing severe AKI in patients undergoing ECMO (2, 4, 8, 9).

FO is a clinically important target for intervention with CRRT in patients requiring ECMO (3, 5). FO at the initiation of CRRT is independently associated with increased mortality in a variety of clinical scenarios (10–13), although the ECMO population has not been independently examined. FO is a key component of the cardiorenal syndrome, which makes it of particular importance for patients on ECMO with cardiac dysfunction (14). CRRT provides flexibility and control in the management of fluid balance, and CRRT enhances the ability to achieve dry weight and negative fluid balance during ECMO (15, 16).

The impact of different CRRT fluid removal strategies on outcomes in AKI

***See also p. 2729.**

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patients has not been extensively studied. Michael et al (17) studied patients following stem-cell transplants who developed AKI and showed that the ability to maintain or achieve dry weight was associated with improved survival. Bouchard et al (18) found in adults that greater duration of FO while on renal replacement therapy was associated with higher mortality. To date, there have been no prospective randomized clinical trials comparing different CRRT fluid management strategies. The question remains as to whether CRRT can truly correct preexisting FO and whether such correction improves outcomes.

The aim of this study was to characterize the association between FO and outcomes in pediatric ECMO patients receiving CRRT. In particular, we sought to determine the impact of FO on survival at both CRRT initiation and discontinuation. We also examined the kinetics of CRRT-mediated fluid removal as a potential predictor of outcomes. We hypothesized that the ability to remove fluid and restore fluid balance with CRRT would be associated with improved survival.

METHODS

Study Population. We conducted a retrospective review of all pediatric patients undergoing concurrent CRRT and ECMO between July 2006 and October 2010 at the University of Michigan. For patients with multiple CRRT episodes separated by >24 hrs while on ECMO, the first episode was included. Patients on CRRT prior to ECMO were excluded. The institutional review board at the University of Michigan approved this study.

Prior to September 2009, ECMO was provided by a servo-regulated roller-pump system with a silicone lung as described by Swaniker et al (5). Subsequently, ECMO was performed using a centrifugal pump (Centrimag, Levitronix LLC, Waltham, MA). Prior to 2007, we used only Medtronic Silicone membrane oxygenators (Meditronic Inc., Minneapolis, MN); from 2007 through 2009, we used Quadrox oxygenators (Maquet, Hirrlingen, Germany) on all children over 10 kg because of lack of experience with Quadrox oxygenators on the smaller children. We converted to Quadrox oxygenators for all patients in November of 2009. The method of bypass performed was at the discretion of the treating physician. Typically, patients requiring ECMO for cardiac failure were placed on venoarterial bypass, and those requiring respiratory support were placed on venovenous bypass.

Patients received continuous venovenous hemofiltration by having a dialysis filter placed in parallel to the ECMO circuit by connecting to the ECMO circuit preoxygenator, until December 2008. After December 2008, we performed continuous venovenous hemodiafiltration using the Prismaflex system (Gambro, Lund, Sweden) similarly in parallel. For patients weighing <25 kg, CRRT was performed using an AN-69 M60 filter (Hospal, France). Otherwise, polysulfone HF 400 (Renalflo II, MN) or Optiflux (Fresenius, Germany) filters were used in line based on body surface area. Prior to 2008, heparin was used for anticoagulation in patients requiring CRRT in line with ECMO. Anticoagulation was performed using a standardized regional citrate protocol after December 2008 to standardize the institutional Prismafelx CRRT protocols (19).

Data Collection. Data collection included demographic data, laboratory data, and characteristics of the intensive care unit (ICU) course (Table 1). Pediatric Risk of Mortality III (PRISM III) scores at ICU admission for all patients and Risk Adjusted Congenital Heart Surgery-1 scores for cardiac surgical patients were calculated (20, 21). The indication for CRRT and ECMO was determined from the pediatric nephrology and critical care notes. The timing of CRRT initiation was at the treating physician's discretion.

FO was determined using daily patient weights obtained during CRRT with the ICU admission weight as baseline. The standard of care at our institution is to weigh ECMO patients daily, in a standardized manner similar to patients not on ECMO with care taken to monitor the cannulas during the procedure. The following previously reported formula was used to calculate percent FO at CRRT initiation (13):

Initiation FO = [(CRRT initiation weight – ICU admission weight)/(ICU admission weight)] × 100

Similarly, FO at CRRT discontinuation was calculated as follows:

Discontinuation FO = [(CRRT discontinuation weight – ICU admission weight)/(ICU admission weight)] × 100

The change in FO while on CRRT was determined as follows:

Change in FO = Initiation FO – Discontinuation FO

FO was also examined as a categorical variable using a cut-off of 10% (≤10% vs. >10%) and 20% (≤20% vs. >20%) based on published literature (10, 22). The primary outcome was ICU mortality.

Statistical Methods. Due to skewness of data, continuous variables are presented as median (interquartile range). Univariate comparisons were made using the Mann–Whitney *U* test and chi-square or Fisher's exact tests, as appropriate. Pearson correlation coefficients were computed to assess the linear relationship between initiation and discontinuation FO. Logistic regression models were used to assess the relationship between FO at each time point, the rate of fluid removal in various intervals, and ICU mortality while adjusting for age and PRISM score. Separate models were used to evaluate the impact of FO as a continuous variable and as a categorical variable. Multicollinearity was ruled out in all multivariate models using estimates of the variance inflation factor for each predictor. When examining fluid removal kinetics, the degree of FO on each day of CRRT was calculated, and a rate of change was determined by calculating the slope of a linear regression model for each patient. Rates were determined for the following periods: the first 3 days on CRRT, the first 7 days on CRRT, and the entire course of CRRT. Analyses were performed in SAS 9.2 (SAS Institute, Cary, NC) and R 2.10.1 (R Foundation for Statistical Computing, Vienna,

Table 1. Baseline patient characteristics overall and by survival status

Variable	Overall	ICU Survival		*p*
		Yes (N = 18)	No (N = 35)	
Age (months)	0 (0, 10)	10.5 (0, 112)	0 (0, 1)	<.001
Sex: female	21 (39.6)	5 (27.8)	16 (45.7)	.206
ICU admission weight (kg)	3.6 (3.2, 8.0)	10.5 (3.5, 63.7)	3.4 (3.0, 4.3)	.002
Hospital days prior to CRRT	6 (3, 11)	4.5 (3, 6)	9 (4, 13)	.035
ICU days prior to CRRT	5 (3, 10)	4.5 (3, 6)	6 (3, 11)	.299
Hours on extracorporeal membrane oxygenation	244 (151, 347)	281 (186, 369)	233 (138, 345)	.320
Hours extracorporeal membrane oxygenation prior to CRRT	43 (21, 92)	48.5 (29, 74)	40 (19, 94)	.614
Days on CRRT	7 (4, 12)	8 (6, 16)	7 (4, 12)	.385
More than two vasoactive medications at initiation	34 (64.2)	5 (27.8)	29 (82.9)	<.001
Number of vasoactive agents at initiation	3 (2, 4)	1.5 (1, 3)	4 (3, 4)	<.001
Diuretic exposure	48 (90.6)	16 (88.9)	32 (91.4)	.765
Diuretic infusion	35 (66)	12 (66.7)	23 (65.7)	.945
Therapeutic plasma exchange	6 (11.3)	4 (22.2)	2 (5.7)	.072
Pediatric Risk of Mortality III score at ICU admission	15 (9, 20)	16 (5, 19)	13 (9, 22)	.660

ICU, intensive care unit; CRRT, continuous renal replacement therapy;.

Continuous variables are expressed as median (interquartile range). Categorical variables are expressed as count (%).

Austria) (23), and statistical significance was set at $p \leq .05$.

RESULTS

Patient Characteristics. A total of 203 patients underwent ECMO during the study period and 57 (28%) of these patients received concurrent CRRT. Four patients received CRRT prior to ECMO and were excluded. Forty-six (87%) patients received venoarterial ECMO, and 7 (13%) patients received venovenous ECMO. One patient received multiple runs of CRRT. This study included 33 neonates (1 month of age or younger) and median patient age was 0 (0, 10) months. Baseline characteristics of the study population are summarized in Table 1.

The indications for the initiation of CRRT were FO (48 patients), electrolyte abnormalities (three patients), and multiple indications (two patients). The indication for ECMO was respiratory failure (19 patients, 36%), cardiac arrest (8 patients, 15%), low cardiac output syndrome (12 patients, 23%), and failure to separate from bypass following surgery (14 patients, 26%). The most common underlying diagnosis was surgical heart disease (N = 28, 53%; Table 2).

Outcome Data. Survival for patients requiring ECMO during the study period was 58%. For ECMO patients requiring CRRT, survival to ICU discharge was 34%. Survival was lower in the 36 patients that received CRRT with the filter placed in parallel with the ECMO circuit (prior to December 2008) compared to the 17 who received CRRT with the Prismaflex machine (25% vs. 52.9%, $p = .045$). Neonates (≤1 month) had a significantly lower rate of survival to ICU discharge (15.1% vs. 65%, $p < .001$). Additional variables that were significantly different between survivors and nonsurvivors included age, ICU admission weight, and number of vasoactive medications at CRRT initiation (Table 1). The median initiation FO was significantly lower in survivors compared to nonsurvivors (24.5% vs. 38.0%, $p = .006$; Table 3). Similarly, the median discontinuation FO was significantly lower in survivors compared to nonsurvivors (7.1% vs. 17.5%, $p = .035$).

Univariate analysis demonstrated a significant association between initiation FO and increased mortality (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.01–1.08; Table 4), and between discontinuation FO and increased mortality (OR 1.04, 95% CI 1.00–1.07; Table 4). In other words, for each 1% increase in FO at CRRT initiation or discontinuation, the odds of mortality increased by 4%. Multivariate analysis correcting for patient age and PRISM III score at ICU admission demonstrated a borderline significant association between initiation FO and mortality (OR 1.05, 95% CI 1.00–1.10, Table 4). In a similar model, discontinuation FO was associated with increased mortality (OR 1.06, 95% CI 1.00–1.12). Because we observed a high correlation (Pearson correlation 0.62) between degree of FO at CRRT initiation and discontinuation, we were unable to directly assess their individual effects in the same model. In order to assess the association between fluid removal and mortality, we examined the change in degree of FO during CRRT while adjusting for FO at CRRT initiation. This model revealed that change in percent FO was not significantly associated with mortality (OR 0.96, 95% CI 0.89–1.03; Table 4).

A subgroup analysis was performed on the patients with underlying surgical cardiac disease (n = 28). The survival to ICU discharge was significantly different in patients with underlying surgical cardiac disease (11% vs. 60%, $p < .001$). There were no differences between survivors and nonsurvivors in age, sex, timing of ECMO initiation, or duration of ECMO (data not shown). Median Risk Adjusted Congenital Heart Surgery score was 4 (3, 6) and was not predictive of mortality ($p = .608$). The degree of FO at CRRT initiation was significantly higher in nonsurvivors compared to survivors (38.0% vs. 14.0%, $p = .039$). FO at CRRT discontinuation was not significantly different between survivors and nonsurvivors (3% vs. 14.8%, $p = .248$).

We sought to describe the daily fluid removal while on CRRT by measuring the mean daily FO in survivors and nonsurvivors from initiation (Fig. 1). The average degree of FO remained higher in nonsurvivors compared to survivors at all timepoints examined. The FO curves of survivors and nonsurvivors remained parallel, suggesting that fluid removal was similar in both groups. Multivariate analysis accounting for patient age, PRISM III score at ICU admission, and rate of fluid removal during three different intervals from CRRT initiation demonstrated a consistently significant association between initiation FO and ICU mortality (Table 5). In the same models, a higher rate of fluid removal during

Table 2. Primary underlying disease necessitating extracorporeal membrane oxygenation

	N = 53	
Primary Disease	Number	% of Total Patients
Primary myocardial failure	8	15.1
Postoperative myocardial failure	28	52.8
Primary renal disease	1	1.9
Sepsis	7	13.2
Congenital diaphragmatic hernia	6	11.3
Other	3	5.7

Table 3. Fluid overload among extracorporeal membrane oxygenation patients requiring continuous renal replacement therapy, overall and by survival status

Variable	Overall	Survival		*p*
	N = 53	Yes (N = 18)	No (N = 35)	
% FO at CRRT initiation	30 (21, 49)	24.5 (7, 29)	38 (26, 51)	.006
% FO at CRRT discontinuation	13.8 (2.6, 28.9)	7.1 (-3, 18.4)	17.5 (6.7, 40.6)	.035
	Patients with surgical heart disease			
	N = 28	Yes (N = 3)	No (N = 25)	
% FO at CRRT initiation	37.5 (25, 49.5)	14 (2, 27)	38 (30, 50)	.039
% FO at CRRT discontinuation	14.3 (1.1, 29.3)	3 (-11.3, 18.3)	14.8 (4.3, 29.8)	.248
	Patients without surgical heart disease			
	N = 25	Yes (N = 15)	No (N = 10)	
% FO at CRRT initiation	26 (16, 41)	25 (7, 31)	35 (21, 60)	.162
% FO at CRRT discontinuation	13.3 (2.6, 24.6)	9.7 (-3, 20.9)	29.2 (11.1, 44.2)	.034

FO, fluid overload; CRRT, continuous renal replacement therapy.
Variables are expressed as median (interquartile range).

Table 4. Logistic regression models of fluid overload at continuous renal replacement therapy initiation, discontinuation, and change in fluid overload as predictors of mortality

Variable	Odds Ratio	95% Confidence Interval	*p*
Univariate Analysis[a]			
FO at CRRT initiation	1.04	1.01, 1.08	.018
FO at CRRT discontinuation	1.04	1.00, 1.07	.046
Multivariate Analysis Correcting for Age and PRISM III at ICU Admission[a]			
Variable			
FO at CRRT initiation	1.05	1.00, 1.10	.063
FO at CRRT discontinuation	1.06	1.00, 1.12	.047
Multivariate Analysis Evaluating Age, PRISM III Score at ICU Admission, and FO at CRRT Initiation[a]			
Variable			
PRISM III score	1.19	1.00, 1.40	.044
Age in months	0.95	0.89, 1.01	.077
FO at CRRT initiation	1.08	1.01, 1.16	.033
Change in % FO	0.96	0.89, 1.03	.212
Multivariate Analysis Correcting for Age and PRISM III at ICU Admission[a]			
Variable			
CRRT initiation <10% FO[b]	0.02	0.00, 0.77	.035
CRRT initiation >10% FO and CRRT Discontinuation <10% FO[b]	1.22	0.13, 11.1	.860
Variable			
CRRT initiation <20% FO[c]	0.21	0.02, 2.6	.221
CRRT initiation >20% FO and CRRT Discontinuation <20% FO[c]	0.53	0.13, 3.87	.687

FO, fluid overload; CRRT, continuous renal replacement therapy; PRISM, Pediatric Risk of Mortality; ICU, intensive care unit.

[a]Interpretation of odds ratios is odds of ICU mortality per 1% change in FO at the specified timepoint; [b]reference group for analysis was those patients with >10% FO at CRRT initiation and >10% FO at CRRT discontinuation; [c]reference group for analysis was those patients with >20% FO at CRRT initiation and >20% FO at CRRT discontinuation.

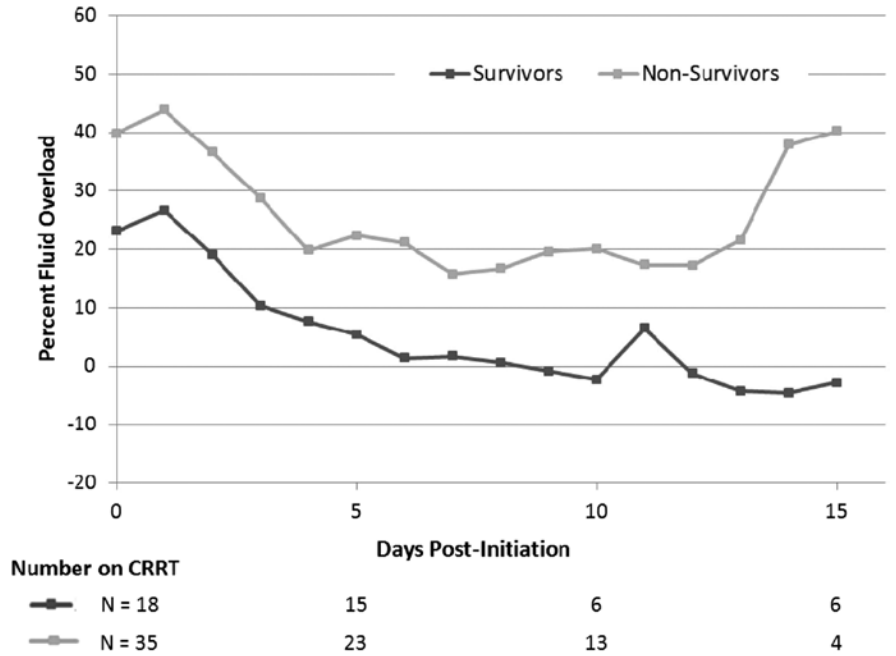

Figure 1. Mean fluid overload by day post-initiation of continuous renal replacement therapy (*CRRT*).

each period was not significantly predictive of lower mortality (Table 5). Average fluid removal rates were significantly higher in neonates compared to non-neonates on day 7 and over the entire CRRT course. Fluid removal rates were not significantly different after the change to utilizing the Prismaflex system for CRRT on ECMO.

To further examine the impact of fluid removal on outcome, we compared patients that achieved a clinically significant improvement in degree of FO (defined as FO <10% at CRRT discontinuation) vs. those that remained >10% FO. Nine patients initiated CRRT at <10% FO, and this group had an ICU survival of 55.6%. The survival to ICU discharge of the 44 patients initiating CRRT at >10% FO was 29.5%, and this did not seem to vary by the degree of fluid removal achieved. Compared to patients starting with >10% FO and ending with <10% FO (n = 13), patients starting and ending CRRT with >10% FO (n = 31) had similar survival rates (38.5% vs. 25.8%, $p = .478$, Fig. 2). In univariate analysis, the overall ICU survival was not statistically different between the three groups ($p = .251$). In a multivariate model adjusting for age and PRISM score, starting <10% FO was associated with a lower risk for mortality compared to the reference group of patients starting and ending with >10% FO (OR 0.02, 95% CI 0.00–0.77), while starting with >10% FO and achieving <10% FO did not appear to confer any different mortality risk (OR 1.22, 95% CI 0.13–11.1) (Table 4). A similar analysis was performed using 20% FO as the defining point and did not yield significant results (Table 4).

DISCUSSION

In pediatric patients requiring ECMO, AKI is an independent risk factor for mortality (1, 4, 5), and CRRT is an important therapy (2, 24). Previous pediatric studies have found an association between FO at CRRT initiation and subsequent mortality (10–13, 22, 25), and we have confirmed this association in an exclusive ECMO population (13). We demonstrate that CRRT was effective at improving fluid balance in the majority of patients. In addition, we present the first study to investigate the kinetics of fluid removal after CRRT initiation and the impact on mortality. Our data raise important questions about the clinical benefit of fluid removal once significant FO is established.

While the clinical significance of initial FO has been described, few studies have examined the impact of CRRT-mediated fluid removal on outcomes. In a study of 116 patients with multiorgan dysfunction, Goldstein and colleagues (25) noted a significant difference in survival between patients that achieved their dry weight vs. those that remained FO while on CRRT (76% vs. 36%, $p < .001$). The Program to Improve Care in

Table 5. Logistic regression models for mortality incorporating daily rate of change in fluid overload

Variable	Odds Ratio	95% Confidence Interval	*p*
Rate of Fluid Removal During First 3 Days			
Fluid overload at initiation	1.1	1.01, 1.12	.031
Rate of fluid removal	0.79	0.62, 1.02	.066
PRISM score	1.16	0.97, 1.38	.101
Age, months	0.89	0.76, 1.04	.130
The median (interquartile range) rate of fluid removal was 2.34%/day (0.10, 8.69)			
Rate of Fluid Removal During First 7 Days			
Variable			
Fluid overload at initiation	1.07	1.00, 1.14	.046
Rate of fluid removal	0.74	0.53, 1.04	.085
PRISM score	1.15	0.98, 1.35	.094
Age, months	0.87	0.71, 1.06	.165
The median (IQR) rate of fluid removal was 3.31%/day (1.61, 5.89)			
Rate of Fluid Removal Over Entire Continuous Renal Replacement Therapy Treatment			
Variable			
Fluid overload at initiation	1.08	1.01, 1.15	.034
Rate of fluid removal	0.75	0.55, 1.03	.079
PRISM score	1.16	0.98, 1.37	.092
Age, months	0.88	0.73, 1.06	.187
The median (interquartile range) rate of removal in this period was 1.87%/day (0.56, 4.62)			

Rate of fluid removal is defined as the % change in fluid overload per day during the period evaluated. Neonate defined as up to 1 month of age.

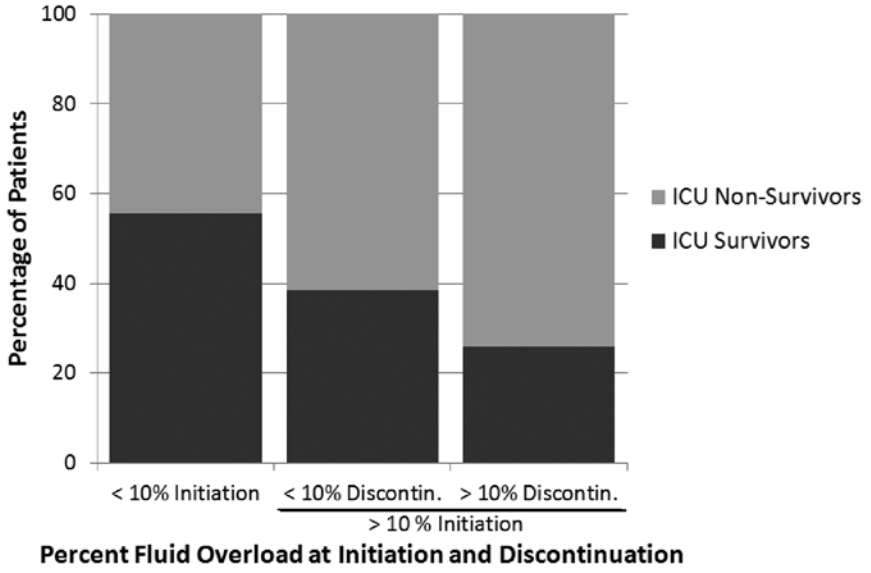

Figure 2. Change in the degree of fluid overload from initiation to discontinuation. *ICU*, intensive care unit.

Acute Renal Disease study noted increased mortality among adult patients with persistent FO at cessation of dialysis compared to those with resolved FO (35% vs. 56%, $p < .001$); similarly, longer duration of FO during dialysis was associated with worse outcomes (18). The implications of FO for patients on ECMO include increased mortality (5) and increased ECMO duration (3). We found that a lower degree of FO at CRRT discontinuation for patients on ECMO was associated with improved survival. However, this finding appeared to result from the high correlation between initiation and discontinuation FO. When directly assessing the impact of fluid removal, the change in percent FO from initiation to discontinuation of CRRT was not a significant predictor of outcome. The degree of FO improved in a parallel fashion in both survivors and nonsurvivors, demonstrating that fluid removal was equally achievable in both groups. Furthermore, after significant (>10%) FO was established, restoration of fluid balance to <10% FO during CRRT did not appear to significantly improve outcomes compared to patients that remained >10% FO. These data suggest that prevention of significant FO is likely to be more effective at improving outcomes than attempting fluid removal once significant FO is established. The exact definition of "clinically significant" FO remains undefined, but when examining a threshold of 20% FO, we did not observe a significant difference between FO groups with respect to mortality, suggesting that 20% may be too high a threshold level.

Our study is among the first to examine the kinetics of fluid removal following CRRT initiation. When viewing FO as a pathologic state, a more rapid improvement in the degree of FO may limit damage from this condition or may reflect clinical improvement. We hypothesized that a higher rate of fluid removal would be associated with lower mortality. In contrast, we observed that the rate of FO correction was similar between survivors and nonsurvivors (Fig. 1), and the rate of fluid removal was not a significant predictor of mortality when considered in either early (first 3 days) or later (first 7 days or entire course) periods following CRRT initiation. In all the models we examined, the degree of FO at CRRT initiation remained the most consistent predictor of mortality. These findings suggest that efforts at fluid removal may not be effective once significant FO is established, and are consistent with our other observations that correction of FO did not appear to be associated with improved outcomes. Clinical trials are needed to test whether prevention of FO may result in better outcomes.

The clinical importance of FO prevention is particularly relevant in patients on ECMO when one considers that trials off ECMO are more successful if patients are near their dry weight. At our institution, it is standard of care to remove no greater than 3 mL/kg/hr (6%–7% of dry weight/day) of fluid while on CRRT based on the dry weight, a practice consistent with other institutions (4). Patients receiving CRRT in our study were a median 30% FO at the initiation of CRRT. At a fluid removal rate of 3 mL/kg/hr, it would take 4–5 days for these patients to achieve their dry weight, as compared to 1–2 days if the patient was 10% FO at CRRT initiation. Therefore, the degree of FO at CRRT initiation may in part drive the duration of ECMO and contribute to morbidity resulting from prolonged therapy.

We included a large pediatric cardiac patient population in this study; in whom FO may be of particular importance given

the complex interplay between renal and cardiac dysfunction in the cardiorenal syndrome (14, 26–28). The finding that initiation FO was not significantly predictive of mortality in noncardiac patients further highlights the cardiac subgroup as a potentially high-yield target population. Early CRRT following cardiac surgery in adult studies has been shown to potentially improve outcomes (29). Such studies are lacking in the pediatric cardiac patient population, and our study suggests that 10% FO may be a potential target for future prospective interventional studies.

Limitations of this study include that it is a single center retrospective analysis. Although we were able to find statistically significant associations, our small sample size limited the precision of our estimates in subpopulations. In addition, we were not able to completely stratify for severity of illness or multiple organ dysfunction as there is not a defined severity of illness score for patients on ECMO (PRISM III score at ICU admission served as a surrogate). During the study period, two methods were used to perform CRRT for patients on ECMO, and these patients had significantly different rates of survival, but no differences in fluid removal. This finding likely reflects improvements in institutional practices and not the precision of FO measurements by pumps, but warrants further multicenter investigation. We acknowledge that there is no standardized protocol for the timing of the initiation of CRRT at our institution, which likely contributed to study heterogeneity. Lastly, as an observational study, we cannot offer firm clinical recommendations, but we hope to generate interest in prospective clinical trials.

CONCLUSIONS

We have demonstrated an association between FO at CRRT initiation and increased mortality not previously reported in an exclusive pediatric ECMO patient population. The degree of FO at CRRT discontinuation is also predictive of survival, but likely reflects the effect of FO at initiation, as correction of FO during CRRT did not appear to improve outcomes. In addition, we observed that the kinetics of fluid removal were actually similar between survivors and nonsurvivors. Taken together, these results suggest that intervening prior to the development of significant FO may be more clinically effective than attempting fluid removal after significant FO has developed. Our findings suggest a role for earlier initiation of CRRT in this population, and further clinical study is warranted in this area.

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