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Membrane pressures predict clotting of pediatric continuous renal replacement therapy circuits

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Abstract

Background—Clotting of continuous renal replacement therapy (CRRT) circuits leads to inadequate clearance, decreased ultrafiltration, and increased resource use. We identified factors associated with premature clotting of circuits during CRRT in children.

Methods—In a retrospective cohort of 26 children (median age 11.8 years) receiving 79 CRRT circuits (51 heparin, 22 citrate, 6 using no anticoagulation), we captured hourly pressure, flow, and fluid removal rates along with all activated clotting time (ACT) and circuit ionized calcium measurements. Cox and logistic regression models were used to examine factors associated with premature circuit clotting before the scheduled 3-day circuit change.

Results—Of the 79 circuits, 51 (64.6%) underwent unplanned filter change due to filter clotting (median duration 18.25 h, interquartile range [IQR] 9.25, 33.5 h), and 28 (35.4%) underwent scheduled change (median duration 66 h, IQR 61.00, 69.00 h). Patient age, catheter size and location, blood flow rate, and the percentage of pre-filter replacement fluid were not associated with premature clotting. Heparin circuits were less likely than citrate circuits to clot prematurely. Each 1-mmHg increase in the transmembrane or filter pressure was independently associated with a 1.5% (95% confidence interval [CI] 1.0–2.0%) and 1.5% (95% CI 1.0–2.0%) higher risk of clotting, respectively. Higher ACTs were associated with lower transmembrane ($p = 0.03$) and filter ($p < 0.001$) pressures.

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Compliance with ethical standards The study was reviewed and approved by our Institutional Review Board who waived the requirement for informed consent.

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Conclusions—The majority of circuits in our cohort were subject to unplanned filter changes. Elevated transmembrane and filter pressures were associated with clotting. Our results suggest that maintaining higher ACT may decrease the risk of circuit clotting. Larger studies are needed to examine other factors that may prolong the lifespan of the CRRT circuit in this high-risk population.

Keywords

Anticoagulation; Continuous renal replacement therapy; Filter clotting; Membrane pressures; Pediatrics

Introduction

Acute kidney injury (AKI) occurs in >10% of children admitted to the intensive care unit [1]. Continuous renal replacement therapy (CRRT) is prescribed for the management of critically ill patients with severe AKI and fluid overload [2]. Compared to acute hemodialysis, CRRT provides continuous fluid removal with greater hemodynamic stability. However, circuits that prematurely clot can lead to lower delivered dialysis doses, exposure to additional blood products for priming, and increased resource utilization to restart the circuit [3, 4].

During CRRT, activation of the clotting cascade occurs when blood contacts the artificial surface [5–7]. Heparin or citrate anticoagulation is used to decrease circuit clotting. While initial reports found similar circuit life spans with heparin or citrate anticoagulation [8], more recent reports have shown that citrate anticoagulation is associated with longer CRRT circuit life spans in children [9–12]. Pre-dilution of blood flowing through the CRRT dialysis filter reduces the risk of intra-filter hemo-concentration, mitigating circuit clotting risk [13]. Among adults, higher filtration fraction [7] and transfusions [14] are associated with increased circuit clotting.

The few studies assessing factors associated with CRRT circuit duration in children have focused on catheter sizes, CRRT modality, and blood flow rates (BFR) [15–17]. Transmembrane pressure (TMP) is the pressure exerted on the dialysis membrane and reflects the pressure difference between the blood and fluid compartments. Filter pressure (FP) is an indication of the pressures in the hollow fibers of the filter. No prior pediatric studies have looked at changes in circuit pressures as a predictor circuit clotting risk. Our objective was to comprehensively assess clinical and circuit-related factors associated with premature clotting in children receiving CRRT to identify strategies that may prolong circuit lifespan, thereby preventing inefficient dialysis and wasted resources.

Materials and Methods

Patient population

We conducted a retrospective cohort study of critically ill children receiving CRRT over a 2-year period (January 2013 to December 2014) at the Children's Hospital of Philadelphia (Fig. 1). We included all circuits that were planned to last for 72 h before a scheduled change. We excluded circuits where a patient required extracorporeal membrane

oxygenation at the time of CRRT ($n = 5$ among 2 patients), those who received high-dose CRRT for inborn errors of metabolism ($n = 2$, for 1 patient), and those who underwent scheduled daily circuit changes ($n = 33$, for 1 patient). Additionally excluded were 33 circuits that were taken down due to patient death ($n = 4$), line malfunction ($n = 8$), and interruption for an acute procedure ($n = 21$). We also compared our data to data from the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry. Briefly, the ppCRRT Registry included data on 344 patients receiving CRRT at 13 different centers [18]. The study was reviewed and approved by our Institutional Review Board who waived the requirement for informed consent.

CRRT protocol

All patients received continuous veno-venous hemodiafiltration (CVVHDF) on a Prismaflex® (Gambro Renal Products, Lakewood, CO) machine. At our institution, CRRT is prescribed and managed by a nephrology team. The circuit is set up by a nephrology dialysis nurse, but run by the intensive care unit nurses who are specially trained in CRRT. When a patient is receiving CRRT, depending on the acuity of the patient, they are typically assigned their own nurse, which minimizes the risk of delays in alarm responsiveness.

The decision of which anticoagulation to use is determined after discussion with the critical care team and depends on the individual bleeding risk and liver function of the patient. Citrate is typically avoided in patients with severe liver dysfunction. When using citrate anticoagulation, calcium is returned through a separate lumen. In infants with minimal access, there is often no access available to return calcium, making citrate anticoagulation difficult to use. Heparin is avoided in subjects with known allergies, profound bleeding, or intracranial hemorrhage.

In this study, for heparinized circuits, we used an initial loading dose of 5–10 units/kg, followed by a continuous infusion of 5 units/kg/h. Activated clotting times (ACT) were measured every hour on a Hemochron® monitoring system (Accriva Diagnostics, San Diego, CA) and the heparin infusion rate changed accordingly. The target ACT range was 180–220 s with a tighter range maintained for patients at increased risk of bleeding. For citrate-anticoagulated circuits, the initial Anticoagulant Citrate Dextrose Solution, Solution A rate was 1.5-fold higher than the BFR (in ml/h) [18, 19]. Calcium gluconate (24 g in 1 L 0.9% saline) was administered through the return line at 40% of the initial citrate rate (in ml/h). Citrate and calcium rates were titrated based on the circuit ionized calcium levels (goal range 0.35–0.5 mmol/L) and patient ionized calcium levels (target range 1.11–1.3 mmol/L). Circuit ionized calcium concentrations were monitored at hours 1 and 2, and every 4 h thereafter. At our institution we follow a fixed protocol for titration of heparin or citrate/calcium infusions. Any changes to anticoagulation are based on the protocol, and the bedside nurse communicates any concerns with the nephrology team, as needed.

Explanatory variables

Patient demographics, including age, gender, body surface area (BSA), and indication for dialysis initiation, were retrieved from the medical record. We also collected data on the catheter size and location (upper vs. lower extremity), dialyzer size (M100 vs. M60;

Prismaflex® System; Gambro AB-Baxter International, Deerfield, IL), and type of anticoagulation (heparin vs. citrate versus none) used.

Circuit-related variables included the BFR (ml/min, ml/kg/min), dialysate flow (ml/h), pre- and post-filter replacement fluid rates (ml/h), and the proportion of the total replacement rate that was given pre-filter at the start of CRRT. For each circuit, we used the electronic medical record to capture hourly nurse-recorded TMP (mmHg), FP (mmHg), return pressure (mmHg), access pressure (mmHg), and actual patient fluid removal (ml/h, ml/kg/h). The ultrafiltration rate (UFR) (ml/h) and filtration fraction were calculated for each time point. Hourly ACTs (s) and circuit ionized calcium levels were collected for heparinized and citrate anticoagulated circuits, respectively.

Statistical analysis

Data were presented as medians and associated interquartile ranges (IQR). Circuits that underwent unplanned filter change due to filter clotting were compared to those that lasted until a scheduled circuit change. Univariate Cox regression models were fit to assess which factors were associated with time to premature clotting. An overall Wald test was used for nominal variables, while a trend test was used for ordinal variables. Because subjects could receive more than one circuit during the observation period, with multiple observations within a given circuit, we used robust standard errors to account for clustering at the subject level. Variables with univariate p of <0.10 were considered for inclusion in a multivariate model.

Using the multiple pressure, flow, and anticoagulation measurements captured on each circuit, we also fit multivariate logistic regression models with the goal of predicting premature clotting at any time point during the circuit lifespan by incorporating combinations of different observed covariates. In contrast to the Cox regression models, where we modeled circuit survival time, these logistic regression models allowed us to determine how well we could predict premature clotting at any given time during the circuit life span. As a benchmark, we fit a Gradient Boosting Machine (GBM) model, which is a data intensive machine learning classification technique [20]. GBM is an ensemble technique that iteratively combines many individual regression models and is a powerful prediction modeling tool. GBM can include multiple interrelated covariates and also effectively captures complex non-linear associations and interactions [21]. Specifically, we fit GBM with tree-regression models under a Bernoulli or Logistic loss function, where the number of iterations and shrinkage parameters were tuned through cross-validation. The cross-validation folds were defined at the subject level. In our GBM model, we included moving averages, moving maximums, moving minimums, and moving slopes/lags (up to 2 observations prior to a given time point) for all covariates that varied over time (including BFR, pressure measurements, UFR, and actual fluid removal). Given the small number of clotting events, we omitted ionized calcium levels and ACTs from these models, since these variables were only observed in citrate and heparin circuits, respectively.

Additionally, there were between 20 and 100 total observations missing for most of the covariates that varied over time. For each time-varying covariate that had missing values, we imputed the missing values using time-series splines (TS function in R) based on the whole

history of the time-varying covariate. In total, incorporating all baseline clinical covariates and time-varying circuit-related covariates, we included 102 potential covariates to predict circuit clotting. To assess the performance of all our predictive models, we calculated the fivefold cross-validation area under the curve (AUC), where a value closer to 1 indicates better predictive ability. We also reported the sensitivity, specificity, positive predictive value, and negative predictive value for each of our models using the observed data. For each model, these metrics were determined by calculating the probability cutoff that maximized the AUC, then applying this cutoff on the model predictions. We used generalized estimating equations with an independent working correlation structure and robust standard errors that were adjusted for age, BSA, and whether or not the circuit was heparinized, to determine which variables, lagged 1 h prior, could have been changed to prevent clotting.

Finally, to validate the data collected in our cohort, we compared the BSA, BFR, dialysate and replacement flow rate, mean FP (within circuit), mean UFR (within circuit) and mean ACT (within circuit) of patients/circuits in our cohort to those of the CVVHDF circuits (using the PrismaFlex® machine) in the ppCRRT cohort. Given that many of these variables were skewed, we tested whether the median values of these variables differed between our cohort and the ppCRRT cohort. *P* values were determined through a non-parametric permutation test where cohort assignments were randomly shuffled at the patient level 5000 times. All analyses were performed using STATA 13.0 (StataCorp LP, College Station, TX) and R version 3.2.3. A two-sided *p* value of <0.05 was considered to be statistically significant.

Results

Between January 2013 and December 2014, a total of 152 CRRT circuits were started at The Children's Hospital of Philadelphia (Fig. 1). We included 79 CRRT circuits among 26 patients in the analysis, of which 51 circuits (64.6%) underwent unplanned filter change due to filter clotting and the remaining 28 circuits (35.4%) underwent a scheduled change. The circuits undergoing an unplanned filter change lasted a median of 18.3 (IQR 9.3, 33.5) h while circuits undergoing a scheduled change ran a median of 66 (IQR 61, 69) h. The patients receiving the 79 circuits had a median age of 11.8s (IQR 3.5, 15.2) years, 58.2% were male, and their median BSA was 0.96 (IQR 0.54, 1.75) m². Age, gender, and BSA were not associated with the risk of premature clotting (each *p* > 0.2).

The characteristics of the 79 circuits are shown in Table 1. Neither the catheter size, catheter location, nor filter size were associated with premature clotting. BFR, replacement plus dialysis rate, and percentages of pre-filter replacement fluid measured at the start of CRRT were not associated with premature clotting. Even though filtration fraction was not associated with premature clotting in our models, we noted that only four CRRT circuits in our cohort had a filtration fraction of >25% and that all of these experienced unplanned filter changes.

We included 76 subjects in the ppCRRT registry who received 241 CVVHDF circuits using the Prismaflex® machine circuits (Table 2) [18]. In our cohort, 51 circuits (64.5%) clotted as

compared to 159 circuits (65.9%) in the ppCRRT cohort. With the exception of BSA, there was no significant difference in circuit characteristics between the two cohorts.

Using automatic data retrieved from the electronic medical record, we included over 3000 TMP, FP, return pressure, and access pressure measurements from our cohort at The Children's Hospital of Philadelphia, for a median of >33 measures per circuit. As shown in Table 1, circuits that clotted prematurely had higher hourly median TMP, FP, and return pressures than those that lasted to the scheduled change. Specifically, each 1-mmHg increase in the TMP, FP, or return pressure was associated with a 1.5, 1.5, and 1.1% higher risk of premature clotting, respectively (each $p < 0.001$). As shown in Fig. 2, TMP appeared to steadily increase over time in circuits that clotted prematurely, but remained relatively stable and was mostly <200 mmHg in the 28 circuits that did not clot. Figure 3 shows similar trends over time for FP when circuits that clotted prematurely are compared with those that did not.

Use of heparin anticoagulation (vs. citrate) was associated with a lower risk of clotting ($p = 0.006$). Of the 51 circuits that clotted prematurely, 26 (51.0%) used heparin, 20 (39.2%) used citrate, and five (9.8%) used no anticoagulation. There were 2048 ACT measurements for the 51 circuits using heparin, with a median of, 41 (IQR 15, 66) measurements per circuit. Over the lifespan of the circuit, the median ACT was higher in those circuits that did not clot and underwent only the scheduled change (216 s, IQR 198, 239 s) than in those that clotted early (197 s, IQR 183, 211 s). Each 1-s increase in the ACT was associated with a 2.1% lower risk of clotting ($p < 0.001$). There were 240 circuit ionized calcium measurements for the 22 circuits using citrate, with a median of ten (IQR 5, 16.5) measurements per circuit. Over the lifespan of the circuit, the median circuit ionized calcium was lower in the circuits that underwent the scheduled change (0.39 mmol/L, IQR 0.37, 0.41 mmol/L) than in those that clotted early (0.41 mmol/L, IQR 0.30, 0.46 mmol/L). Each 0.01-mmol/L increase in the circuit ionized calcium was associated with a 5.0% higher risk of clotting ($p < 0.001$).

Table 3 shows the multivariable Cox model results for the heparin circuits. TMP, FP, and ACT were associated with clotting risk. Adjusting for the other variables, each 1-mmHg increase in the TMP or FP was associated with a 1.1% ($p < 0.001$) and 1.2% ($p = 0.029$) higher risk premature clotting, respectively. Further, each 1-s increase in ACT was associated with a 3.3% decreased hazard of clotting ($p < 0.001$).

Table 4 shows the prediction results from various logistic regression models using the GBM technique. Based on the AUC results, the strongest predictor of premature clotting was TMP. The GBM model with only TMP yielded a fivefold cross-validation AUC of 0.837, while including only FP yielded a fivefold cross-validation AUC of 0.714. Adding additional covariates did not markedly increase the AUC. When lag time in hours and time-of-values of TMP, FP, and return pressure were used together, the AUC increased slightly to 0.85. The data intensive GBM approach yielded a slightly higher AUC of 0.860 and, relative to the other models, a markedly better positive predictive value of 16.1%. Finally, given that TMP and FP were strong predictors of circuit clotting, we analyzed how changes in other

variables, lagged 1 h prior, affected the TMP and FP. The ACT was negatively associated with changes in the subsequent hour's TMP ($p = 0.03$) and FP ($p < 0.01$).

Discussion

We retrospectively examined 79 CRRT circuits used to treat 26 critically ill children and included hourly pressure, flow, and anticoagulation methods and measurements to determine factors associated with a higher risk of circuit clotting. The majority of circuits (>60%) clotted prematurely, prior to a scheduled change. Higher TMP and FP and lower ACT measurements were independently associated with a higher risk of premature circuit clotting. In addition, TMP and FP were the strongest predictors of premature clotting, and higher ACTs were associated with a subsequently lower TMP and FP. We were unable to show that the filtration fraction was associated with the risk of clotting, possibly because the filtration fraction across both groups was low, with only four circuits having a filtration fraction of >20%.

There are few studies in pediatrics evaluating factors that contribute to premature clotting of CRRT circuits. In a cohort of children with liver failure, Goonasekera et al. concluded that CRRT circuits clotted in children despite patient clotting dysfunction due to liver disease [14]. Higher pre-filter replacement fluid rates have been associated with a lower risk of circuit clotting as pre-filter dilution decreases the concentration of serum proteins entering the filter, as well as the hematocrit and platelet counts [13, 22]. Due to the effect of positioning, CRRT circuits using lower extremity catheters are associated with an increased risk of clotting [16]. Increasing BFR improves clearance and may reduce the risk of clotting [22–24]. However, the ability to maximize BFR is limited by patient and catheter size.

We observed that in circuits clotting prematurely, the TMP and FP steadily increased over the lifespan of the circuit, similar to what has been reported in adults [25]. In contrast, CRRT circuits that did not clot showed relatively stable TMP and FP measurements, with most values remaining at <200 mmHg. In a study on five adult patients receiving 41 CRRT circuits, an increase of 26 mmHg in the TMP predicted circuit failure due to clotting [6].

The Gambro® CRRT machine is indicated for use in patients with a body weight of >20 kg. Higher BFRs as well as dialysate and replacement fluids help to maximize clearance. When the CRRT circuit pressure alarms are triggered due to high pressures, the alarms can be overridden. In order to prolong the lifespan of the CRRT circuit, changes may be made to the flow rates, including decreasing the BFR, increasing the proportion of pre-filter replacement fluid, and reducing the UFR. We did not observe that changes in the blood flow or replacement rates were associated with the risk of clotting or changes to the TMP or FP. However, we recognize the primary limitation of our study was the small sample size from a single center. We suggest that larger studies that include more clotting events are needed to establish pediatric-specific CRRT dosing guidelines that allow for adequate solute clearance while maximizing circuit lifespan for fluid removal, the most common indication for CRRT in children.

The anticoagulant used in CRRT should have the smallest effect on patient hemostasis, should be safe and easy to monitor, and should provide decreased risk of circuit clotting [10]. In recent studies in pediatrics and adults, citrate anticoagulation may be associated with longer circuit durations [9–12]. Similar to our study, most of these studies have a small sample size of citrate circuits. The ppCRRT Registry study found similar circuit lifespans between citrate and heparin circuits [8]. In contrast, we observed that heparin circuits were associated with a lower risk of clotting. Citrate binds to the calcium in the blood flowing through the CRRT circuit and provides regional anticoagulation as its effect is neutralized by replacing calcium in the return line. Heparinized circuits expose patients to a more systemic anticoagulation effect [20]. Hence, heparin should be used cautiously in patients with an increased risk of bleeding. The optimal choice of anticoagulant continues to be a patient-specific decision weighing such factors as systemic bleeding risk, liver dysfunction, and available patient access. Given the conflicting reports in the literature, further studies in children are needed to better determine the association between choice of anticoagulation and clotting risk/circuit lifespan.

In conclusion, we observed that a high percentage of CRRT circuits in children clot before reaching a scheduled change. This rate of premature clotting was similar to that found in the ppCCRT, a registry with similar demographic and dialysis settings as our cohort. Clinicians managing CRRT circuits, especially during high pressure alarms, are confronted with a wide array of settings and readings that can potentially be altered to maintain the circuit. Our findings support that by focusing on the TMP or FP, one can be reassured if the readings remain at <200 mmHg. Close attention to the ACT and consideration for sustaining the ACT at >200 s may help to prolong circuit lifespan in appropriately selected children at low risk for bleeding complications. Larger, multi-center studies incorporating automatic data capture from the electronic medical record and/or directly downloaded from the CRRT machine would help to optimize the prescription for children receiving CRRT.

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Fig. 1.
Flowchart of study cohort. *ECMO* Extracorporeal membrane oxygenation, *CRRT* continuous renal replacement therapy

Fig. 2. Changes in hourly transmembrane pressures (*TMP*) (*y-axis*) over time (*x-axis*, in hours) in circuits that clotted prematurely (*left panel*) as compared to circuits that lasted 3 days (*right panel*). *Black dots* indicate when a circuit clotted. *Red line* is a lowess line indicating overall trend. In circuits clotting prematurely, the transmembrane pressures increased steadily over time. In circuits lasting 3 days, the transmembrane pressures appeared to be more constant, with hourly values mostly <200 mmHg

Fig. 3. Changes in hourly filter pressures (*y-axis*) over time (*x-axis*, in hours) in circuits that clotted prematurely (*left panel*) as compared to circuits that lasted 3 days (*right panel*). *Black dots* indicate when a circuit clotted. *Red line* is a lowess line indicating overall trend. In circuits clotting prematurely, the filter pressures increased steadily over time. In circuits lasting 3 days, the filter pressures appeared to be more constant and with hourly values mostly <200 mmHg

Table 1

Characteristics of the 79 continuous replacement therapy circuits among 26 children

Variable	Circuit underwent scheduled change (<i>n</i> = 28 circuits)	Circuit underwent unplanned change due to filter clotting (<i>n</i> = 51 circuits)	Univariate HR (95% CI)	Univariate <i>p</i> value
Primary indication for dialysis				
Fluid overload	13 (46.4%)	33 (64.7%)	Reference	<0.001
Electrolyte abnormality	15 (53.6%)	14 (27.5%)	0.555 (0.262–1.17)	
Ingestion	0 (0%)	4 (7.8%)	4.567 (2.880–7.240)	
Upper extremity central line (vs. lower extremity)	25 (89.3%)	45 (88.2%)	1.131 (0.551–2.323)	0.74
Catheter size (French)				
<8	2 (7.1%)	3 (5.9%)	1.159 (0.741–1.815)	0.52
8–10	5 (17.9%)	9 (17.7%)		
10–12	16 (57.1%)	25 (49.0%)		
>12	5 (17.9%)	14 (27.5%)		
M100 dialyzer (versus M60)	9 (32.1%)	21 (41.2%)	1.347 (0.668–2.716)	0.41
Anticoagulation				
Heparin (<i>n</i> = 51)	25 (89.3%)	26 (51.0%)	0.39 (0.20–0.77)	Heparin vs. citrate:
Citrate (<i>n</i> = 22)	2 (7.1%)	20 (39.2%)	Reference	0.006
None (<i>n</i> = 6)	1 (3.6%)	5 (9.8%)	0.69 (0.36–1.30)	
Blood flow rate at CRRT start (ml/min)	90 [73, 138]	120 [80, 150]	1.006 (0.999–1.013)	0.10
Blood flow rate at CRRT start (ml/kg/min)	5.5 [2.4, 6.1]	3.9 [1.9, 5.5]	0.900 (0.743–1.091)	0.28
Replacement plus dialysate at CRRT start (ml/h/1.73 m ²)	2466 [1952, 2897]	2649 [2156, 3405]	1.000 (1.000–1.001)	0.20
Replacement plus dialysate at CRRT start (ml/kg/h)	41.4 [38.3, 71.3]	48.1 [42.2, 71.4]	1.001 (0.992–1.011)	0.76
Percentage pre-filter replacement fluid at CRRT start	66.7 [60, 70]	66.7 [60, 70]	0.976 (0.950–1.003)	0.08
Hourly transmembrane pressure during circuit (mmHg)	66 [46, 105]	118 [86, 164]	1.015 (1.010–1.020)	<0.001
Hourly filter pressure during circuit (mmHg)	136 [112, 159]	156 [127, 198]	1.015 (1.010–1.019)	<0.001
Hourly return pressure during circuit (mmHg)	76 [59, 91]	74 [56, 104]	1.011 (1.006–1.017)	<0.001
Hourly access pressure during circuit (mmHg)	–55 [–75, –44]	–84 [–97, –58]	0.995 (0.987–1.003)	0.23
Hourly ultrafiltration rate during circuit (ml/h)	592 [460, 1154]	1098 [944, 1670]	1.000 (0.999–1.001)	0.53
Actual patient fluid removal during circuit (ml/h)	93 [51, 163]	162 [83, 324]	1.001 (1.000–1.003)	0.10
Actual patient fluid removal during circuit (ml/kg/h)	3.6 [2.5, 5.4]	5.0 [2.7, 9.3]		
Activated clotting time during circuit (s)	216 [198, 239]	197 [183, 211]	0.979 (0.969–0.988)	<0.001
Circuit ionized calcium during circuit (mmol/L)	0.39 [0.37, 0.41]	0.41 [0.30, 0.46]	1.050 (1.025–1.076) ^a	<0.001
Filtration Fraction (%)	10.6 [7.3, 13.7]	12.7 [10.7, 14.7]	1.060 (0.984–1.143)	0.12

Data are shown as median with the interquartile range (IQR) given in square brackets or as a number with the percentage given in parenthesis HR, Hazard ratio; CI, confidence interval; CRRT, continuous renal replacement therapy

^a Ionized calcium HR is in terms of a 0.01 mmol/L increase

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Table 2

Comparison of demographic data of our cohort with that of subjects in the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) registry receiving circuits using the Prismaflex® CRRT machine

Variable	Our cohort		ppCRRT registry		<i>p</i> value ^a
	Circuit underwent scheduled change (<i>n</i> = 28 circuits)	Circuit underwent unplanned change due to filter clotting (<i>n</i> = 51 circuits)	Circuit underwent scheduled change (<i>n</i> = 82 circuits)	Circuit underwent unplanned change due to filter clotting (<i>n</i> = 159 circuits)	
Anticoagulation					
Heparin	25 (89.3%)	26 (51.0%)	16 (19.5%)	26 (16.4%)	
Citrate	2 (7.1%)	20 (39.2%)	65 (79.3%)	128 (80.5%)	
None	1 (3.6%)	5 (9.8%)	1 (1.2%)	5 (3.0%)	
Body surface area	0.67 [0.48, 1.72]	0.96 [0.73, 1.79]	0.46 [0.27, 0.80]	0.48 [0.27, 0.94]	0.009
Blood flow rate (ml/min)	90 [74, 131]	120 [83, 150]	100 [60, 120]	100 [60, 150]	0.271
Dialysate flow rate (ml/h)	663 [338, 1000]	868 [500, 1500]	1000 [500, 1500]	850 [500, 2000]	0.542
Replacement plus dialysate at CRRT start (ml/h/1.73 m ²)	2466 [1965, 2897]	2649 [2162, 3405]	3647 [2127, 4716]	2891 [2096, 3981]	0.178
Mean hourly filter pressure during circuit (mm Hg)	139 [113, 153]	159 [120, 209]	149 [119, 186]	198 [160, 263]	0.058
Mean hourly ultrafiltration rate during circuit (ml/h)	648 [492, 1152]	1087 [584, 1703]	1813 [787, 2500]	1500 [745, 2592]	0.232
Mean activated clotting time during circuit (s)	221 [200, 241]	199 [184, 213]	208 [199, 220]	203 [188, 227]	0.767

Data are shown as median with the IQR given in square brackets or as a number with the percentage given in parenthesis

^aThe *p* value (testing if medians between groups are equal) was determined through a non-parametric permutation test with 5000 resamples

Table 3

Multivariable Cox regression model showing factors associated with a higher risk of circuit clotting in the circuits using heparin

Variable	HR for clotting (95% CI)	p-value
Main indication for continuous renal replacement therapy		
Fluid overload	Reference	–
Electrolyte derangement	1.471 (0.20–10.64)	0.704
Ingestion	0.346 (0.01–14.75)	0.579
Blood flow rate at start (ml/min)	0.999 (0.98–1.02)	0.867
Percentage pre-filter replacement fluid at start	0.992 (0.95–1.04)	0.756
Hourly transmembrane pressure during circuit (mmHg)	1.011 (1.01–1.02)	<0.001
Hourly filter pressure during circuit (mmHg)	1.012 (1.001–1.02)	0.029
Hourly return pressure during circuit (mmHg)	1.006 (0.99–1.02)	0.344
Actual fluid removal during circuit (ml/h)	0.992 (0.98–1.00)	0.178
Activated clotting time during circuit (s)	0.967 (0.95–0.98)	<0.001

Model results shown are for the heparin circuit only; the results were similar when using all circuits

Logistic regression analysis to determine factors that may predict premature clotting of continuous renal replacement therapy circuits

Table 4

Logistic regression models	Fivefold cross-validation area under the curve	Specificity	Sensitivity	Positive predictive value	Negative predictive value
Logistic regression model: transmembrane pressure only	0.837	0.796	0.735	0.055	0.995
Logistic regression model: filter pressure only	0.714	0.784	0.612	0.044	0.992
Logistic regression model: transmembrane and filter pressure	0.841	0.824	0.816	0.070	0.996
Logistic regression model: transmembrane, filter, and return pressure values, lagged and time-of-values	0.852	0.848	0.800	0.078	0.996
Logistic regression model: transmembrane, filter, and return pressure values, running averages and time-of-values	0.822	0.804	0.800	0.062	0.996
Gradient boosting machine: all variables included (102 covariates)	0.860	0.922	0.918	0.161	0.999