Effect of Dynamic Circuit Pressures Monitoring on the Lifespan of Extracorporeal Circuit and the Efficiency of Solute Removal During Continuous Renal Replacement Therapy

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Research

Keywords: Continuous renal replacement therapy, Circuit pressures, Extracorporeal circuit failure, Access outflow dysfunction, Solute removal efficiency

DOI: https://doi.org/10.21203/rs.3.rs-64086/v1

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Abstract

Objective: To observe the effects of dynamic pressure monitoring on the lifespan of the extracorporeal circuit and the efficiency of solute removal during continuous renal replacement therapy (CRRT).

Materials and Methods: A prospective observational study was performed at the West China Hospital of Sichuan University in the intensive care unit. Analyses of the downloaded pressure data recorded by CRRT machines and the solute removal efficiencies, calculated by $2*Ce/(C_{pre}+C_{post})$, where $C_e$, $C_{pre}$ and $C_{post}$ are the concentrations of the effluent, pre-filter blood, and post-filter blood, respectively, were performed. Samples were collected at 0, 2, 6, 12, 24 h after the initiation of CRRT. We measured the concentrations of creatinine, blood urea nitrogen (BUN) and β2-microglobulin in the plasma and effluent.

Results: Extracorporeal circuits characterized by moderate-severe (M-S) access outflow dysfunction (AOD) events, defined as access outflow pressure less than or equal to -200 mm Hg more than 5mins, had shorter lifespans with no anticoagulation (17.6±11.2 h vs. 35.1±17.1 h, $P=0.001$) or with regional citrate anticoagulation (RCA) (40.3±22.2 h vs. 55.9±21.7 h, $P=0.016$). Moreover, Cox regression analysis revealed that the lack of moderate-severe AOD events, RCA, or continuous veno-venous hemodialfiltration (CVVHDF) independently prolonged the circuit lifespan. All tested solutes removal efficiencies started to decline at 12h. Furthermore, efficiencies of all solutes removal dropped obviously at 24h when TMP $\geq$ 150mmHg.

Conclusion: RCA and CVVHDF predicted a longer circuit lifespan. Moderate-severe AOD events were associated with a shorter circuit lifespan when RCA or no anticoagulation was used. Replacement of extracorporeal circuit might be considered if TMP $\geq$ 150mmHg at 24h.

Introduction

Continuous renal replacement therapy (CRRT) slowly and effectively removes water and solutes from critically ill patients [1]. Prolonging the lifespan of CRRT circuits is fundamental for better therapeutic effects. The extracorporeal circuit, which is the key part of CRRT, consists of a vascular access outflow lumen, prefilter tubing, a filter, post-filter tubing, an air-trap chamber, pre-vascular inflow tubing and a vascular access inflow lumen. Frequent clotting in the extracorporeal circuit may lead to massive blood loss, shorter effective treatment times, and increased medical costs [2]. Many factors might influence circuit survival, including anticoagulation, vascular access, CRRT treatment parameters (e.g, modality, filter membrane, blood flow rate), hematocrit and blood coagulation [3–9]. However, the mechanisms of extracorporeal circuit failure are still not clear.

In the past, pressure data were obtained by manual recording every hour. With developments in science and technology, mainstream CRRT machines can continuously record changes in pressure, such as access outflow pressure (AOP), pre-filter pressure (PFP), effluent pressure (EP), and return inflow pressure (RIP), every minute during therapy and store the data on internal storage. A few trials have investigated the pressure changes during CRRT [10, 11], stored pressures data can be downloaded into an Excel
spreadsheet to obtain detailed pressure data and the precise circuit lifespan [12]. CRRT removes waste and maintains the electrolyte and acid-base balance via various techniques, such as dispersion, convection, ultrafiltration and adsorption. It is logical to believe that the removal efficiencies of diverse sizes of solutes are different due to their distinct characteristics and removal methods. Previous studies that focused on solute removal predominantly focused on modality and pre/post-dilution. Many influencing factors remain unknown. In addition, no trials have investigated the relationship between dynamic pressure monitoring and solute removal efficiency hindered by the extraction method. We hypothesized that continuous pressure changes during CRRT affect the extracorporeal circuit lifespan and solute removal efficiency.

**Materials And Methods**

**Study design**

This prospective, observational, cohort study was performed in the ICU of West China Hospital of Sichuan University, Chengdu China. The data were recorded from October 2018 to December 2019. The study was approved by Institutional Review Board of West China Hospital, Sichuan University (2017-06). Informed consent was obtained from the patient or responsible surrogate.

**Study population**

A total of 395 episodes of CRRT in 131 patients were included. These episodes represented 16,244.1 h of treatment. The study cohort included all patients who received at least one complete episode of CRRT. All therapies used a Prismaflex machine (Baxter, USA). Patients were excluded if (1) CRRT was performed using a non-Prismaflex machine, (2) the modality was not in continuous veno-venous hemofiltration (CVVH) or continuous veno-venous hemodiafiltration (CVVHDF), such as plasma exchange (PE), and (3) patients was pregnant, aged under 18 years, breastfeeding or patients had other special conditions. The severity of the illness in each patient was assessed by the sequential organ failure assessment (SOFA) score.

**CRRT protocol**

The CRRT equipment was Prismaflex (Baxter, USA) with the AN69 ST150 filter (Baxter, USA). All the patients used double-lumen venous catheters for vascular access. All femoral vascular access was achieved via 13F dual-lumen catheters (Baxter, USA), and jugular access was achieved via 11.5Fr catheters (Baxter, USA). The blood rate was maintained at 150 to 200 mL/min. CVVH was performed in the pre-dilution mode. CVVHDF was performed in the post-dilution mode, and the ratio of dialysate to replacement fluid was 1:1. The replacement fluid used was the standard bicarbonate-based solution (QINGSHAN LIKANG, China). RCA was the first choice in all circuits, with low-molecular-weight heparin (LMWH) or no anticoagulation as the alternative. Extracorporeal circuit cessation occurred when the circuit clotted or the circuit reached the maximum recommended use. The effective treatment period for each extracorporeal circuit was a maximum of 72 h.
Measurement of pressure dynamics in the extracorporeal circuit

The methods used to extract, store, and analyze the continuous pressure data were similar to those described in a previous publication [12]. The pressure variables included minute AOP, effluent pressure (EP), prefilter pressure (PFP), and return inflow pressure (RIP) from relevant circuit points. TMP was calculated from these data using the equation: 

\[ \text{TMP} = \frac{(\text{PFP} + \text{RIP})}{2} - \text{EP} \]

Access outflow dysfunction (AOD) was defined as an AOP − 200 mmHg according to a previous study[10]. We defined three types of AOD events on the basis of total minutes of AOD: mild (≤ 5 min), moderate (5 min < timing ≤ 60 min) and severe (time > 60 min).

Sample collection in the extracorporeal circuit during CRRT and measurement

Samples (blood and effluent) were obtained at 2, 6, 12, and 24 h when CRRT was used in the post-dilution CVVHDF modality. The concentrations of blood urea nitrogen (BUN), creatinine (Cr) and β2-microglobulin in the plasma and effluent were measured in the clinical laboratory of West China Hospital of Sichuan University. Solute removal efficiency = 2*Ce/(Cpre + Cpost), where Ce, Cpre and Cpost are the concentrations of the effluent, blood prefilter, and postfilter, respectively. The data of solute removal efficiency were matched with the accurate pressures data at the same timepoint.

Collection of patient characteristics

For each circuit evaluated, demographics, including sex, age, diagnosis, weight, height, and SOFA score, were collected. Laboratory tests before the initiation of CRRT were conducted, including assessments of hemoglobin, platelets, indexed normalized ratio (INR), and activated partial thromboplastin time (APTT). We obtained the following CRRT parameters: anticoagulation, modality, dose, vascular access site and the reason for extracorporeal circuit failure.

Statistical Methods

Variables are reported as the medians with standard deviation. Variability of pressures was defined as the standard deviation for all pressure. Comparisons between groups were performed using one-way analysis of variance or the chi-squared test. Variables associated with extracorporeal circuit lifespan were analyzed using the Cox regression model. A p value less than 0.05 was considered statistically significant. Data were analyzed using SPSS version 19.0 (SPSS Inc., Chicago, Ill., USA).

Results

Patients and extracorporeal circuits
A total of 395 episodes (Fig. 1) in 131 patients, accounting for 16,244.1 h of effective treatment time, were included in the study. Over the course of our study, 96 cases (24.3%) were electively ended (i.e., the circuit had been used for 72 h). Clotting of the filter or air-trap chamber occurred in 299 cases (75.7%). The average lifespan of the extracorporeal circuit was 41.1 ± 24.8 h. For anticoagulation, RAC was the primary choice (48.6%), followed by no anticoagulation (31.1%), and LMWH (20.3%). In the cluster of modality, the proportion of CVVHDF was 81.3%, and CVVH was 18.7%. The average prescribed dose of CRRT was 31.3 ± 3.2 ml/kg/h. The femoral vein accounted for 93.2% of vascular access. Right side femoral vein access was used in 61.6% of the cases, and the left side was used in 38.4% of the cases. Alternative vascular accesses included the jugular vein (6.8%), of which 88.2% of the cases were accessed on the right side. The details are reported in Table 1.

**Dynamic pressure changes during CRRT with different extracorporeal circuit failures (ECF)**

For further analysis, we defined three types of extracorporeal circuit failures [10] according to circuit lifespan, including early (≤ 12 h), intermediate (> 12 h, ≤ 24 h) and late (> 24 h). A total of 134 circuits (33.9%) experience early-intermediate failure, and 261 circuits (66.1%) experienced late failure. The mean changes in the AOP, PFP, EP, RIP and TMP data were completely distinct in the different groups. The Dynamic mean pressure curve graphs are shown in Fig. 2.

The negative value of AOP was smallest in the early group (-62.87 ± 2.31 mmHg), which was 23.5 and 4.87 mmHg lower than that in the late and intermediate groups, respectively. The overall changes in the PFP were also varied among the different types of ECF: the mean value in the early, intermediate and late groups were 133.43 ± 21.95 mmHg, 150.47 ± 28.09 mmHg and 104.92 ± 3.89 mmHg, respectively. About EPs, intermediate group had the smallest value of mean extracorporeal circuit data, followed by the late and early groups. In data of RIPS, the lowest and highest mean values were 46.38 ± 1.11 mmHg and 61.22 ± 7.74 mmHg in the late group and intermediate group, respectively. In cure graph of TMP, the line in the early and intermediate groups increased rapidly, with mean data of 98.12 ± 34.48 mmHg and 120.15 ± 38.891 mmHg, respectively. Moreover, the variability of late groups was statistically smaller than that compared to the other groups (P < 0.05) in all totally different extracorporeal circuit pressure cluster (AOP, PFP, EP, RIP, TMP). The detail variability data are shown in Table 2.

**Access outflow dysfunction (AOD) events under different anticoagulants**

A total of 143 circuits experienced at least one AOD episode, and no significant difference was found (41.0 ± 25.7 vs. 41.3 ± 23.6 h, P = 0.91) in the lifespan of the circuits in which no AOD event occurred. However, the circuits without moderate-severe AOD events were significantly prolonged compared to those with moderate-severe AOD events during CRRT (43.0 ± 24.4 vs. 28.6 ± 24.2 h, P = 0.003) (Fig. 3).

In our study, RCA was associated with longer circuits survival (31.3 ± 20.0 h vs. 23.9 ± 19.1 h vs. 54.6 ± 22.2 h, P < .05). Moreover, different anticoagulation strategies had distinct effects on moderate-severe...
AOD events in the circuit lifespan. When no anticoagulation was used, the lifespan of circuits without moderate-severe AOD events was significantly prolonged (17.6 ± 11.2 h vs. 35.1 ± 17.1 h, P = 0.001). The same effect existed when RCA was used (40.3 ± 22.2 h vs. 55.9 ± 21.7 h, P = 0.016). However, the effect of moderate-severe AOD events on circuit survival disappeared with the use of LMWH (24.4 ± 15.5 h vs. 24.9 ± 16.3 h, P = 0.96; Fig. 4).

Analysis of risk factors of extracorporeal circuit survival

Comparison between the early-intermediate and late groups revealed that circuits in the chronic group had a lower occurrence of moderate-severe AOD episodes (22.4% vs. 8.0%, P < 0.001), lower platelet count (102.67 ± 90.11 vs. 133.46 ± 84.86 *10^9/l, P = 0.011) and higher use of the CVVHDF modality (90.4% vs. 63.4%, P < 0.001). However, mild AOD events, hemoglobin, PT, INR, APTT and vascular access (P > 0.05) were not significantly different between these two groups (Table 3). Variables associated with a shorter lifespan of the extracorporeal circuit are shown in Table 4. According to the Cox regression model, moderate-severe AOD events (HR 1.893, 95CI% 1.300 to 2.756, P = 0.001) were risk factors for circuit survival during CRRT. RCA (HR 0.391, 95CI% 0.293 to 0.521, P < 0.001) and CVVHDF (HR 0.546, 95CI% 0.376 to 0.793, P = 0.001) were independently associated with a longer lifespan of the extracorporeal circuit.

Solute removal efficiency and dynamic pressure changes

The removal efficiency of medium-macro molecular solutes (β_2-microglobulin) was significantly lower than that of BUN and creatinine at different time during CRRT. All efficiencies of tested solutes removal (BUN, creatinine and β2-microglobulin) dropped gradually with operation time prolonged (Fig. 5). The details of solute removal efficiency in different anticoagulation modalities were presented in Supplementary Appendix File. According to the precise TMP data which was matched with sample collection time, two groups were formed: TMP < 150 mmHg and TMP ≥ 150 mmHg. The solute removal efficiency in the lower TMP group showed greater clearance ability than that in the higher TMP group. Moreover, this phenomenon significantly occurred between the TMP < 150 mmHg and TMP ≥ 150 mmHg group for BUN (0.92 ± 0.10 vs. 0.83 ± 0.16, P = 0.001), creatinine (0.77 ± 0.20 vs. 0.63 ± 0.23, P = 0.007), and β2-microglobulin (0.46 ± 0.11 vs. 0.29 ± 0.08, P < 0.001) at 24 h (Fig. 6).

Discussion

Main findings

We analyzed continuous pressure data from CRRT and found that, after classifying the different types of circuits failure, moderate-severe access outflow dysfunction was associated with a shorter lifespan of extracorporeal circuit compared to mild dysfunction. Moreover, when anticoagulation was performed with citrate or when anticoagulation was not performed, M-S was associated with shorter circuit survival compared to that observed when LMWH was used. We found that the use of CVVHDF and citrate and the absence of moderate-severe AOD events prolonged the lifespan of extracorporeal circuit. Our study
demonstrated distinct downtrend in small-molecule and macro-molecular solutes in removal efficiency under different anticoagulation modalities. Solute removal efficiency declined significantly at 24 h or TMP ≥ 150 mmHg. Meanwhile, removal efficiency declined when circuit survival up to 24 h while TMP ≥ 150 mmHg compared with those in TMP < 150 mmHg at 24 h.

**Relationship to Previous Studies**

**Lifespan of extracorporeal circuit**

Recent published studies [3, 4] suggested that citrate was superior to heparin for circuit survival and anticoagulation-related bleeding risk. However, the lifespan of extracorporeal circuit still varied greatly in studies despite whatever anticoagulant applied. A multicenter, randomized controlled study [13] of 174 patients compared circuit survival when different anticoagulants used, namely, citrate and heparin, during CRRT. The lifespans of the two groups were 37.5 ± 23 h and 26.1 ± 19 h, respectively. The standard deviation confirmed the variability in circuit survival. Matthew Brain [9] reported a meta-analysis about non-anticoagulant factors (such as vascular access, dialysis membrane, and modality) on the lifespan of extracorporeal circuit, but the value of this article decreased due to the biased problem. Factors influencing the lifespan of extracorporeal circuit are not exactly definite so further studies are needed. AOP is a major concern in circuit pressures monitoring on the lifespan of extracorporeal circuit. Access outflow pressure is measured between the catheter and the blood pump. Since the inner blood is sucked by extracorporeal circuit, the AOP is generally negative and less than −50 mmHg [14]. A recently published observational study [10] was the first study to acquire continuous pressure data accurately during CRRT, and these pressures accurately reflect the real state of each part of the extracorporeal circuit. This study suggested that an AOP less than or equal to -200 mmHg could be considered a dysfunction, and AOD events can shorten the survival of the extracorporeal circuit. The study still had some limitations, such as the inclusion of a narrow population (most were postoperative patients) and the lack of RCA data. A recent retrospective study [11] suggested that the occurrence of an AOD event within 4 h after the initiation of CRRT significantly reduced the lifespan of extracorporeal circuit by 12.9 h compared to the absence of an AOD event. COX analysis of two studies [10, 11] suggested that AOD events were independent risk factors for circuit survival, which indicates that AOP status warrants concern.

AOD events are quite common in the clinic, and these events are an indirect indicator of the quality and function of the vascular access. Several causes of AOD were proposed: 1. The patient’s body position may change frequently due to the needs of nursing or other therapy. The catheter may be suddenly bent or folded, which results in a sharp decrease in AOP and an extremely negative value. This interference is the most common reason for an AOD event in the clinic [15, 16]. 2. The formation of thrombus or fibrous sheath in the lumen of catheter or the collapse or thrombosis of the central vein where catheter was placed may cause an AOD event. 3. Blood flow exceeding the maximum allowable range of the double-lumen catheter (>350 or 400 ml/min) may also cause an AOD event. The occurrence of moderate-severe AOD events should be avoided as much as possible. The results of our study suggested that short-term
access outflow dysfunction (AOD) is not enough to affect the lifespan of the extracorporeal circuit. Only AOD that lasted a sustainable time (≥ 5 min), such as a moderate-severe AOD event, affected the extracorporeal circuit, especially circuits with citrate and no anticoagulation. Notably, this phenomenon did not indicate heparin were superior to RCA and no anticoagulation but only indicated that moderate-severe AOD events should be a concern. The possible explanation for this result is that different anticoagulants play distinct roles. Citrate prevents coagulation by complexing ionized calcium in the extracorporeal circuit. The part entering the human body is metabolized from one molecule of citrate into three molecules of bicarbonate in the mitochondria of the liver, skeletal muscle, and kidney [17]. Notably, complexed calcium is released, and lost calcium is supplemented in postfilter. Therefore, citrate, is an ideal regional anticoagulant that effectively maintains an anticoagulation effect in the extracorporeal circuit and avoids bleeding in the body. LMWH exerts systemic anticoagulant effects by enhancing antithrombin III activity and inhibiting thrombin (factor IIa) and factor Xa. The pharmacokinetics are complex. Therefore, the variability in the high risk of bleeding individuals is a disadvantage. In addition, COX analysis showed that moderate-severe AOD events were a risk factor for circuit survival.

**Solute removal efficiency**

Using of RCA has been verified to prolong the circuit survival and avoid a system "shutdown" because of the early clotting of the circuit. Nevertheless, a decrease in solute clearance occurs even if extracorporeal circuit functioning properly. From now no when should we replace the extracorporeal circuit accurately is a mystery and Even the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines do not have a suggestion about that point, and how and when does solute removal efficiency decay are still indeterminate. Therefore, it is very valuable to find an indicator to determine whether to replace extracorporeal circuit. Clogging of hemofilter membranes and clotting of the circuit are associated with the rise in TMP [14]. Compared with other pressures data, TMP is particularly important in the study of solute removal efficiency. The relationship between TMPs and solute removal efficiency has not been investigated. Previous trials have studied the effects of diverse filter membranes and dilution methods on removal efficiency [18, 19]. A large multicenter randomized controlled (RENAL) study [20] of 1508 patients investigated the effect of high-dose (40 ml/kg *ml) and low-dose (25 ml/kg* ml) on 90-day survival rate during CRRT and suggested no difference. A uniform CRRT dose was used in our study to exclude its effect on solute removal efficiency. A study [18] focused on the effect of membrane materials (Sureflux150E vs AV-400) on solute clearance; however, the results showed no difference between cellulose triacetate membranes and synthetic membranes on the removal of solutes (urea nitrogen and creatinine). Our study only used ST150 membrane (polyacrylonitrile material) to decrease an interference of materials. A small multicenter randomized controlled study [21] recently focused on effects of different modalities (CVVH vs. CVVHD), convection and diffusion, on solute clearance using similar doses. The results showed no significant difference at 0 h and 4 h (P > 0.05) for small solutes (urea nitrogen and creatinine) and medium-macro molecules (inflammatory mediators, such as IL-6). No study has analyzed the solute removal efficiency and continuous pressure in extracorporeal circuit because of the prior lack of effective data extracting methods. Therefore, our study is innovative.
Solute removal efficiencies due to unique characteristics. The kidney is the only excretory organ of β2-microglobulin (11.8 kD). A previous study[22] showed that the risk of death increased 11% when the concentration of β2-microglobulin increased by 10 mg/L in blood. Therefore, our study selected it as a representative medium-macro-molecular solute. It has been thought that small molecules, such as urea nitrogen, freely pass through the dialysis membrane for 100% removal. However, a randomized controlled study conducted by William D. LyndonD[23] revealed that the measured clearance rates of urea nitrogen and creatinine in a high-dose group during CRRT were significantly different from the achieved clearance rates of 7.1% and 13.9% (P < 0.001), respectively. The results showed that the clearance of urea nitrogen and creatinine was not 100%, and the ability to removing creatinine was significantly overestimated compared to urea nitrogen. However, this study had some limitations, such as the lack of a downward trend in the removal effects for diverse solutes. A recent prospective cohort study[24] investigated the effect of high-flux filters (surface area 1.8 m²) on the clearance of various solutes during CRRT. The results showed that the clearance of small molecule solutes (Cr and BUN) was not different at 72 h (0.99 ± 0.03 vs. 0.91 ± 0.16, P = 0.074; 1 ± 0 vs. 0.95 ± 0.17, P = 0.5), but β2-microglobulin changed substantially (0.61 ± 0.09 vs. 0.48 ± 0.13, P = 0.002). The results of this study are higher than our results at every sample collection time. The explanation for this phenomenon may be that the removal efficiency of the high-flux filter was higher than an ordinary filter. In addition, the lifespan of all the circuits were extreme (72 h), and no filter coagulation occurred with the use of citrate as the anticoagulation. Therefore, solute removal may decrease more slowly when the extracorporeal circuit is running well.

Strengths And Limitations

Our study has important clinical significance because continuous pressures data are still not completely utilized. In our study, we collected various modalities of anticoagulation and multiple RCA data (48.6%) compare to other trails[10, 11]. Moreover, we creatively combined the dynamic pressure monitoring with the solute removal efficiency during CRRT and offered a new idea for circuit replacement.

Our study also has several limitations. First, it was a single-center observational study, and the findings require verification by multicenter studies. In addition, our study used data from a single type of machine, modality, dose, dialyzer membrane so risk factors of circuit survival and the results of access outflow dysfunction need more various data to confirm the results.

Conclusion

RCA and CVVHDF prolonged circuit survival during CRRT. Moderate-severe AOD events should be concerned, especially when RCA or no anticoagulation used. With the prolonged using of extracorporeal circuit, all tested solutes removal efficiency started to significantly declined at 12 h. Besides with the increase of TMP, solute removal efficiency descended dramatically. Moreover, extracorporeal circuit might be replaced when lifespan up to 24 h if TMP ≥ 150 mmHg because of the decrease in solute removal efficiency.
Abbreviations

CRRT
continuous renal replacement therapy; AOD: access outflow dysfunction; BUN: blood urea nitrogen;
RCA: regional citrate anticoagulation; LMWH: low-molecular-weight heparin; CVVHDF: continuous veno-
venous hemodialfiltration; CVVH: continuous veno-venous hemofiltration; AOP: access outflow pressure;
PFP: pre-filter pressure; EP: effluent pressure; RIP: return inflow pressure; SOFA: sequential organ failure
assessment score; ECF: extracorporeal circuit failure; KDIGO: Kidney Disease: Improving Global Outcomes

Declarations

Acknowledgments
The authors acknowledge the help of the west China Hospital of Sichuan University and the CRRT
nursing staff for their assistance in the collection of electronic pressure data and samples during CRRT.

Authors’ contributions
All of the authors agree to the submission of this paper. L.Z., as the corresponding author of this paper,
was mainly responsible for program design and modification. P.L., L.L., X.T., M.G., T.W., L.C., were involved
in this clinical trial and vouch for the adherence of the trial to the protocol, for the accuracy of the data.
P.L. conducted the statistical analysis and wrote the first draft. All of the authors reviewed, revised, and
approved the final version of the manuscript.

Funding
This study was funded by 1·3·5 project for disciplines of excellence–Clinical Research Incubation Project,
West China Hospital, Sichuan University (18HXFH018).

Availability of data and materials
The data that support the findings of this study are not available due to the clinical study report being
finalized. However, the data will be available from the authors upon reasonable requests at a later time.

Ethics approval and consent to participate
The trial was approved by Institutional Review Board of West China Hospital, Sichuan University(2017-
06). Informed consent was obtained from either the patient or from the patient’s legally authorized
representative if the patient was unable to provide consent.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests

References

1. Ronco C, Cruz D, Bellomo R. Continuous renal replacement in critical illness. Contrib Nephrol. 2007;156:309–19.

2. Schiff H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. N Engl J Med. 2002;346(5):305–10.

3. Bai M, Zhou M, He L, Ma F, Li Y, Yu Y, Wang P, Li L, Jing R, Zhao L, et al. Citrate versus heparin anticoagulation for continuous renal replacement therapy: an updated meta-analysis of RCTs. Intensive care medicine. 2015;41(12):2098–110.

4. Liu C, Mao Z, Kang H, Hu J, Zhou F. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: a meta-analysis with trial sequential analysis of randomized controlled trials. Crit Care (London England). 2016;20(1):144.

5. Crosswell A, Brain MJ, Roodenburg O. Vascular access site influences circuit life in continuous renal replacement therapy. Critical care resuscitation: journal of the Australasian Academy of Critical Care Medicine. 2014;16(2):127–30.

6. Califano AM, Bitker L, Baldwin I, Fealy N, Bellomo R. Circuit Survival during Continuous Venovenous Hemodialysis versus Continuous Venovenous Hemofiltration. Blood purification. 2020;49(3):281–8.

7. Schetz M, Van Cromphaut S, Dubois J, Van den Berghe G. Does the surface-treated AN69 membrane prolong filter survival in CRRT without anticoagulation? Intensive care medicine. 2012;38(11):1818–25.

8. Fealy N, Aitken L, du Toit E, Lo S, Baldwin I. Faster Blood Flow Rate Does Not Improve Circuit Life in Continuous Renal Replacement Therapy: A Randomized Controlled Trial. Critical care medicine. 2017;45(10):e1018–25.

9. Brain M, Winson E, Roodenburg O, McNeil J: Non anti-coagulant factors associated with filter life in continuous renal replacement therapy (CRRT): a systematic review and meta-analysis. BMC nephrology 2017, 18(1):69.

10. Zhang L, Tanaka A, Zhu G, Baldwin I, Eastwood GM, Bellomo R. Patterns and Mechanisms of Artificial Kidney Failure during Continuous Renal Replacement Therapy. Blood purification. 2016;41(4):254–63.

11. Sansom B, Sriram S, Presneill J, Bellomo R. Circuit Hemodynamics and Circuit Failure During Continuous Renal Replacement Therapy. Critical care medicine. 2019;47(11):e872–9.

12. Zhang L, Baldwin I, Zhu G, Tanaka A, Bellomo R: Automated electronic monitoring of circuit pressures during continuous renal replacement therapy: a technical report. Critical care and resuscitation: journal of the Australasian Academy of Critical Care Medicine 2015, 17(1):51–54.

13. Hetzel GR, Schmitz M, Wissing H, Ries W, Schott G, Heering PJ, Isgro F, Kribben A, Himmele R, Grabensee B, et al. Regional citrate versus systemic heparin for anticoagulation in critically ill
patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. Nephrology dialysis transplantation: official publication of the European Dialysis Transplant Association - European Renal Association. 2011;26(1):232–9.

14. Michel T, Ksouri H, Schneider AG. Continuous renal replacement therapy: understanding circuit hemodynamics to improve therapy adequacy. Curr Opin Crit Care. 2018;24(6):455–62.

15. Kim IB, Fealy N, Baldwin I, Bellomo R. Premature circuit clotting due to likely mechanical failure during continuous renal replacement therapy. Blood purification. 2010;30(2):79–83.

16. Mandolfo S, Borlandelli S, Ravani P, Imbasciati E. How to improve dialysis adequacy in patients with vascular access problems. J Vasc Access. 2006;7(2):53–9.

17. Morita Y, Johnson RW, Dorn RE, Hall DS. Regional anticoagulation during hemodialysis using citrate. Am J Med Sci. 1961;242:32–43.

18. Pichaiwong W, Leelahavanichkul A, Eiam-ong S. Efficacy of cellulose triacetate dialyzer and polysulfone synthetic hemofilter for continuous venovenous hemofiltration in acute renal failure. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2006;89(Suppl 2):65–72.

19. de Sequera P, Albalate M, Pérez-García R, Corchete E, Puerta M, Ortega M, Alcázar R, Talaván T, Ruiz-Álvarez MJ: A comparison of the effectiveness of two online haemodiafiltration modalities: mixed versus post-dilution. Nefrologia: publicacion oficial de la Sociedad Espanola Nefrologia 2013, 33(6):779–787.

20. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, et al. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med. 2009;361(17):1627–38.

21. Chen LX, Demirjian S, Udani SM, Trevino SA, Murray PT, Koyner JL. Cytokine Clearances in Critically Ill Patients on Continuous Renal Replacement Therapy. Blood purification. 2018;46(4):315–22.

22. Okuno S, Ishimura E, Kohno K, Fujino-Katoh Y, Maeno Y, Yamakawa T, Inaba M, Nishizawa Y: Serum beta2-microglobulin level is a significant predictor of mortality in maintenance haemodialysis patients. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 2009, 24(2):571–577.

23. Lyndon WD, Wille KM, Tolwani AJ. Solute clearance in CRRT: prescribed dose versus actual delivered dose. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2012;27(3):952–6.

24. Siebeck M, Dimski T, Brandenburger T, Slowinski T, Kindgen-Milles D: Super High-Flux Continuous Venovenous Hemodialysis Using Regional Citrate Anticoagulation: Long-Term Stability of Middle Molecule Clearance. Therapeutic apheresis and dialysis: official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 2018, 22(4):355–364.

Tables
Table 1. Demographic and laboratory features of patients and the extracorporeal circuit
| Age (years)         | 56.7±14.0 |
|---------------------|-----------|
| Sex (male/female)   | 86/45     |
| SOFA score          | 14±2      |

**Diagnosis**

- Respiratory disease: 33
- Cardiovascular disease: 30
- Digestive diseases: 43
- Neurological disorders: 5
- Sepsis: 20

**Episodes of CRRT**: 395

**Extracorporeal circuit lifespan**: 41.1±24.8 h

**Use of anticoagulation** (%)

- LMWH/unfractionated heparin: 80 (20.3%)
- Regional citrate anticoagulation: 192 (48.6%)
- No anticoagulation: 123 (31.1%)

**Reason for changing extracorporeal circuit**

- Clotting of air-trap chamber: 38 (9.6%)
- Programmed change: 96 (24.3%)

**Vascular access**

- Right femoral veins: 227 (57.4%)
- Left femoral veins: 141 (35.8%)
- Internal jugular vein: 27 (6.8%)
- CVVH: 74 (18.7%)
- CVVHDF: 321 (81.3%)

**Dose of CRRT (ml/kg/h)**: 31.4±3.1

**Hemoglobin (g/L)**: 85.0±19.0

**Platelet (*10^9/L)**: 113.0±89.4

**INR**: 1.5±0.6

**APTT, s**: 45.1±21.7
Table 2 Pressure Data of different extracorporeal circuit failures

|                      | Early ECF       | Intermediate ECF | Late ECF        |
|----------------------|-----------------|------------------|-----------------|
| AOP, mmHg            | -86.37±13.03    | -67.69±8.20      | -62.87±2.31     |
| AOP variability, mmHg| 37.73±23.28     | 20.31±14.33      | 13.79±10.21     |
| PFP, mmHg            | 133.43±21.95    | 150.47±28.09     | 104.91±3.89     |
| PFP variability, mmHg| 32.86±12.33     | 37.89±15.20      | 12.67±8.12      |
| EP, mmHg             | -3.52±26.07     | -13.49±25.03     | -4.30±6.44      |
| EP variability, mmHg | 26.05±13.73     | 37.04±15.60      | 15.91±9.81      |
| RIP, mmHg            | 55.82±7.25      | 61.22±7.74       | 46.37±1.11      |
| RIP variability, mmHg| 14.88±8.39      | 15.53±9.14       | 9.97±5.99       |
| TMP, mmHg            | 98.12±34.48     | 120.15±38.89     | 80.79±8.11      |
| TMP variability, mmHg| 32.40±16.12     | 46.40±20.75      | 14.38±11.64     |

Table 3 Comparisons between the Intermediate and Late groups
### Table 4 Cox regression analysis of variables associated with shorter circuit survival

| Variables                           | HR (95%CI)     | P value |
|-------------------------------------|----------------|---------|
| Regional citrate anticoagulation    | 0.391 (0.293 0.521) | <0.001 |
| Moderate-severe AOD                 | 1.893 (1.300 2.756) | 0.001  |
| Hemoglobin>85 g/L                   | 0.819 (0.631 1.063) | 0.134  |
| Platelet>110*10^9/L                 | 1.168 (0.902 1.513) | 0.239  |
| CVVHDF                              | 0.546 (0.376 0.793) | 0.001  |
Figure 1

Numbers of CRRT Episodes Enrolled in the Study, Assigned to different extracorporeal circuit failures Group, and Included in the Analysis
Figure 2

Dynamic mean pressure curve of every minute over time by early, intermediate and late extracorporeal circuit failures. Shaded areas = 95% confidence of the mean. Lifespan of the early group ended at 11 h, the intermediate group ended at 23 h, and the late group ended at 24 h. AOP, PFP, EP, RIP and TMP are the average values of each pressure minute.
Figure 3

Circuit lifespans with different patterns of AOD events
Figure 4

Lifespan of extracorporeal circuits that experienced M-S AOD events in various anticoagulation conditions
Figure 5

Solute removal efficiency at different time

![Bar chart showing solute removal efficiency at different time with statistical significance levels.](image)

Figure 6

Solute removal efficiency in different TMPs groups at 24h

![Bar chart showing solute removal efficiency in different TMPs groups at 24h.](image)