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# **Faster blood flow rate does not improve circuit life in Continuous Renal Replacement**

## **Therapy: A randomized controlled trial**

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## **Abstract**

**Objective:** To determine whether blood flow rate influences circuit life in continuous renal replacement therapy.

**Design:** Prospective randomized controlled trial.

**Setting:** Single centre tertiary level intensive care unit.

**Patients:** Critically ill adults requiring continuous renal replacement therapy.

**Interventions:** Patients were randomized to receive one of two blood flow rates: 150 mL/min or 250 mL/min.

**Measurements and Main Results:** The primary outcome was circuit life measured in hours. Circuit and patient data were collected until each circuit clotted or was ceased electively for non-clotting reasons. Data for clotted circuits are presented as median (Inter-quartile range) and compared using the Mann Whitney U test. Survival probability for clotted circuits was compared using log-rank test. Circuit clotting data were analysed for repeated events using hazards ratio (HR). One hundred patients were randomised with 96 completing the study (150 mL/min, n=49; 250 mL/min, n=47) using 462 circuits (245 run at 150 mL/min and 217 run at 250 mL/min). Median circuit life for 1<sup>st</sup> circuit (clotted) was similar for both groups (150 mL/min: 9.1 [5.5, 26] hrs vs. 10 [4.2, 17] hrs; p=0.37). CRRT using blood flow rate set at 250 mL/min was not more likely to cause clotting compared to 150 mL/min (HR, 1.00 [0.60, 1.69]; p=0.68). Gender, Body Mass Index, weight, vascular access type, length, site, mode of CRRT or International Normalised Ratio had no effect on clotting risk. CRRT without anticoagulation was more likely to cause clotting compared to use of heparin strategies (HR 1.62, p=0.003). Longer Activated Partial Thromboplastin Time (HR 0.98, p=0.002] and decreased platelet count (HR 1.19 p=0.03] was associated with a reduced likelihood of circuit clotting.

**Conclusions:** There was no difference in circuit life whether using blood flow rates of 250 mL/min or 150 mL/min during CRRT.

**Key words:** Continuous Renal Replacement Therapy, filter life, circuit life, continuous hemofiltration, acute kidney injury, critical care

## Introduction

Acute kidney injury (AKI) is a complication of critical illness that affects up to 50% of intensive care patients.<sup>1-3</sup> The use of Renal Replacement Therapy (RRT) has evolved as the treatment for severe AKI and is required in 5-6% of all critically ill patients in intensive care units (ICUs).<sup>4</sup> Continuous Renal Replacement Therapies (CRRT) relies on the maintenance of extracorporeal circuit (EC) patency for as long as possible, however premature circuit failure due to clotting may cause blood loss, reduced therapeutic efficacy and increased workload and treatment costs.<sup>5-8</sup>

Clogging and clotting of the hemofilter membrane is the major mechanism of premature failure and circuit loss in CRRT.<sup>9,10</sup> It has been suggested that increasing blood flow rate (BFR) through the EC to speeds greater than 200 mL/min may reduce premature clotting.<sup>11</sup> One recent report demonstrated a reduction in filter lifespan when BFR was less than 200 mL/min concluding that the optimal blood flow rate during CRRT is between 250-300 mL/min.<sup>12</sup>

The impact of BFR on membrane clotting rate is potentially important and has not been examined in controlled studies. Despite suggestions to increase blood flow rates in the EC<sup>11,12</sup>, there remains great variability in the prescription of this setting worldwide. Although a recent survey of Australian and New Zealand ICUs indicated a BFR of 150-200 mL/min was the dominant setting, a faster rate of 200-250 mL/min was also commonplace in ICU's surveyed.<sup>13</sup> Observational studies and recent worldwide practice surveys of CRRT also demonstrate great variability in practice from 80 mL/min<sup>12</sup> to 350 mL/min.<sup>14-16</sup> While BFR may

be an important determinant of circuit life in CRRT, the most suitable speed to reduce clotting and optimise membrane life has not been identified. To address this question, we conducted a prospective randomized controlled trial (RCT). We tested the hypothesis that a faster blood flow rate (250 mL/min) would be superior to a slower blood flow rate (150 mL/min) in maintaining circuit patency in CRRT.

## **Materials and Methods**

### **Trial design and setting**

This study was a prospective, parallel group RCT conducted in a 24 bed, adult, tertiary intensive care in Melbourne, Victoria, Australia. The study was registered at the Australian New Zealand Clinical Trials Registry (ACTRN:12615001353583) and approved by Austin Health Human Research Ethics Committee (HREC project No. H2012/04772). Written informed consent was obtained from the patient or their next of kin prior to, or soon after enrolment.

### **Eligibility criteria**

Critically ill patients in ICU were eligible for the study if they fulfilled three criteria: 1) age  $\geq$  18 yrs, 2) AKI (RIFLE classification F)<sup>16</sup> requiring CRRT and 3) vascular access was via the femoral vein for standardisation. Patients were considered ineligible for the study if they fulfilled any of the following exclusion criterion: 1) required citrate anticoagulation (citrate protocol requires set blood flow rate of 150 mL/min), 2) expected stay in the ICU was less than 24 hours.

## Interventions

The study compared two blood flow rate settings on circuit life in CRRT. The intervention was a set BFR of 250 mL/min and the control was a set BFR of 150 mL/min. CRRT was performed using Continuous Venovenous Hemofiltration (CVVH) or Continuous Venovenous Hemodiafiltration (CVVHDF) modalities. Vascular access was via either Niagara 13.5 Fr-catheter (24cm) (Bard, Murray Hill, NJ, USA) or Gamcath Dolphin Protect 13.0 Fr-catheter (25 cm) (Gambro, Hechingen, Germany) dual lumen catheters. Treatment modality and choice of vascular access was at the discretion of the treating physician. Prismaflex with AN69ST (ST100) 1.0 m<sup>2</sup> membrane (Gambro Nephral TM, Lund, Sweden) or Infomed HF 440 with DF 140 Polyethersulfone 1.4 m<sup>2</sup> membrane (Infomed, Geneva, Switzerland) was used for all treatments. Bicarbonate buffered replacement and dialysis fluid (Baxter, Castlebar, Co. Mayo, Ireland) was used. In CVVH, replacement fluid was delivered into the EC before and after the filter (pre and post-dilution), with a ratio of 50% predilution and 50% postdilution. Dose in CVVH was standardised at 2000 mL/hour. In CVVHDF, the replacement fluid was all delivered postdilution. Dose in CVVHDF was standardised at 1000 mL/hour replacement and 1000 mL/hour dialysate.

Anticoagulation was provided according to a predefined ICU protocol and mandates no anticoagulation in patients at risk of bleeding from a coagulopathy or thrombocytopenia. Options for anticoagulation when used included regional heparinisation with unfractionated heparin (1000 IU/hour) delivered prefilter and protamine (10 mgs/hour) delivered in the return limb of the EC for reversal of heparin. Unfractionated heparin was used alone and



delivered pre-filter at 5-10 IU/kg/hour. CRRT was prescribed by the treating intensivist and delivered by ICU nurses. The decision to start or stop CRRT, and determining the reason for stopping, was done by ICU doctors and nurses respectively as is usual protocol for the ICU.

### **Data collection**

Baseline data relating to age, gender, weight, BMI, source of admission, severity of illness (Acute Physiology and Chronic Health Evaluation score II, III; Simplified Acute Physiology Score II), diagnostic group, presence of sepsis, mechanical ventilation, inotropes/vasopressors, and basic laboratory variables pertaining to renal function was collected.

### **Outcomes**

The primary outcome was circuit life (measured in hours) and recorded as clotted when; 1) Transmembrane pressure across the circuit exceeded 300 mmHg, 2) pre-filter pressure > 200 mmHg, 3) visible clot obstructing flow through the circuit and 4) the blood pump was unable to rotate due to clot obstruction in the membrane or for 'elective' reasons. e.g. CT, MRI, surgical intervention or cessation prior to clotting for native renal assessment.

### **Sample size**

Without supportive data to inform a power calculation for this study, 100 patients were chosen to ensure a sample that was sufficient to reflect usual ICU patient characteristics and allow recruitment completion in one year. Patients stayed in the BFR treatment group allocated at randomization. The treating physician prescribed the CRRT modality for each

patient (CVVH or CVVHDF) which was maintained/retained for all subsequent treatments. All circuits used for these patients were included and analysed accordingly.

### **Randomization**

Patients were screened and entered the study by ICU clinical staff. Patients were randomly assigned with stratification for mode (CVVH or CVVHDF). Once the treating physician prescribed CRRT and the mode of therapy, patients were randomized using a web based central randomization service. A variable block randomization with parallel allocation was used to allocate to each study group (150mL/min vs. 250 mL/min).

### **Statistical methods**

The primary outcome (circuit life) was analysed in a two-step process. First analysis: this excluded all electively removed or non-clotted circuits from the data. The distribution of data for all circuits meeting the defined clotting criteria was then assessed. As expected study variables were not normally distributed and non-parametric statistics were used with circuit life reported as median and IQR. Circuit life for the two groups (150 mL/min vs. 250 mL/min) was compared using Mann-Whitney *U*-test. Analysis of the two groups was then assessed for survival probability and presented graphically using Kaplan-Meier survival plots. A log-rank test was used to compare circuit life between the two groups. This analysis was not adjusted for any confounding variables.

Second analysis: included all circuits (clotted and those electively removed). Circuit life was analysed using repeated events survival analysis.<sup>7,17</sup> A proportional hazard conditional

frailty model<sup>17</sup> (an extension of cox regression) was used to test for within patient dependence. It was expected that there would be heterogeneity among individual trial patients. In addition, individual trial patients may contribute one or multiple circuits. It was assumed to be a correlation between an individual trial patient contributing multiple circuits and circuit life. The frailty model was used to test event dependence (where the event is a clotted circuit) within the trial patients. Event dependence in this study meant that an occurrence of one event (time to clotting of the circuit) may make further events (additional circuit clotting times) more or less likely. The advantage of this model is that it considers any within-cluster correlation of circuit life. Proportions were compared using a chi-square test.

First analysis was carried out using IBM SPSS statistics for Windows (v2, IBM Corp., Armonk, NY). Second analysis was performed using SAS (Enterprise Guide v5.1; SAS Institute Inc., Carey, NC).

## **Results**

### **Participants and recruitment**

One hundred patients were randomized between June 2013 and August, 2014. Two patients from each group were randomized but did not receive CRRT. The CONSORT diagram for patient enrolment is shown in **Figure 1**. Overall, 96 patients (49 in the 150 mL/min group and 47 in the 250 mL/min group) contributed a total of 463 study circuits: 245 in the 150 mL/min group and 218 in the 250 mL/min group. Median study circuits per patient was four (IQR 2, 6) and totalled 8206 CRRT treatment hours.

At randomization, patients were similar with respect of age, sex, severity of illness scores (APACHE II, III, SAPS II), admission source and diagnosis (**Table 1.**). There was a nine kg difference in patient weight between the two groups ( $p= 0.03$ ); however, BMI was similar for both groups. Pre-randomization renal laboratory variables were also similar for both groups.

### **Primary outcomes - Circuit Life**

The first analysis incorporated 369 defined clotted circuits. The median circuit life for these circuits ( $n=369$ ) was similar for both groups (150 mL/min,  $n=196$  [10 hrs IQR 6.0, 24]) vs. (250 mL/min,  $n = 173$  [11.5 hrs IQR 6.8, 18.3]  $p = 0.81$ ). For first analysis, there were 81 clotted first circuits. The median circuit life of these circuits was 9.1 hrs (IQR, 5.5, 26 hr) in the 150 mL/min group compared to 10 hrs (IQR, 4.2, 17 hr) in the 250 mL/min group,  $p=0.37$ . Second and third median circuit lives for those deemed to have clotted were also similar (**Table 2**). The probability of the first study circuit from each patient failing due to clotting did not differ between BFR groups (150 ml/min vs. 250 mL/min; HR, 0.85, log rank test = 0.46) (**Figure 2**).

The second analysis involved evaluation of all circuit terminations (clotted and electively removed) and revealed that a BFR of 250 mL/min was not more likely to cause clotting compared to 150 mL/min (HR, 1.00 [0.60, 1.69];  $p=0.68$ , variance of the random effect, 1.078 [0.23]) (**Table 3**). There were no differences in likelihood of clotting for: gender, BMI, weight, vascular access type, length or site, mode of CRRT or INR. CRRT without use of anticoagulation was more likely to cause clotting compared to use of heparin or heparin/protamine (HR 1.62, [1.18, 2.23],  $p=0.003$ ). Longer APTT (HR 0.98, [0.97, 0.99],

p=0.002) was associated with a lower likelihood of circuit clotting. Probability of clotting was higher in those patients with higher platelet counts (HR 1.19, [1.01, 1.40], p=0.03) (**Table 3**).

## **Discussion**

This is the first known prospective study to examine the effect of blood flow rate on circuit duration in both CVVH and CVVHDF. In a cohort of 100 ICU patients requiring CRRT three key findings have been identified: first, when blood flow rate is increased to 250 mL/min it does not increase circuit life during CRRT. Second, the use of an anticoagulation strategy and longer APTT's extends CRRT circuit life. Third, patients with higher platelet counts were more prone to premature circuit clotting in this study.

## **Relationship to previous studies**

The maintenance of circuit patency by prevention of clotting is the greatest challenge associated with providing CRRT for critically ill patients. As a result, many studies have focused on anticoagulation strategies to extend circuit life,<sup>7,18-27</sup> while many aspects of treatment and prescription setting have not been investigated. One RCT has included blood flow rate in the assessment of circuit clotting in CRRT, indicating that blood flow rates >125 mL/min did not improve circuit survival.<sup>28</sup> This study was conducted in CVVHD mode which is rarely used in current practice.<sup>13,15,29,30</sup> Pure diffusive modes of hemofiltration such as CVVHD have been shown to be associated with decreased procoagulatory activity in the dialyser membrane when compared to convective modes<sup>31,32</sup> and makes comparisons to CVVH and CVVHDF problematic.

One single centre study assessing 1332 treatments from 355 patients concluded that BFR did indeed affect circuit life.<sup>12</sup> In this retrospective audit, the authors suggest a BFR less than 200 mL/min significantly decreased circuit life compared to rates greater than 200 mL/min. They also determined that BFR greater than 300 mL/min led to lower median circuit lives and recommended an optimal BFR of between 250-300 mL/min.

### **Implications of study findings**

Our data provides evidence to suggest that a faster blood flow rate does not influence circuit life and prescription of rates greater than 150 mL/min makes no difference to the likelihood of clotting in either CVVH or CVVHDF. It has previously been suggested that blood flow should be maintained at 200 mL/min<sup>33-35</sup> and always be greater than 100 mL/min to avoid premature clotting.<sup>36</sup> The ability to maintain consistent and constant flow may be more critical, with the flow and resistance balance being more important. We have previously reported these mechanical factors and their adverse effect on circuit life.<sup>10,37,38</sup>

Despite many authors suggesting blood flow rates for CRRT of 200-250 mL/min<sup>12,33-35</sup> and international surveys indicating practical prescriptions of >200 mL/min; there has been no endorsements for this setting. The Acute Dialysis Quality Initiative (ADQI) consensus guidelines for operational characteristics from 2002 indicate that blood flow may be increased to augment solute clearance but do not include a recommendation for this prescription.<sup>39</sup> The more recent Kidney Disease Improving Global Outcomes (KDIGO) consensus guidelines outline settings for different RRT modalities indicating 150-250 mL/min is typically prescribed for CRRT modes such as CVVH and CVVHDF but make no recommendations for practice based

on evidence.<sup>40</sup>

The use of anticoagulants to prevent extracorporeal clotting and extend circuit life in CRRT has been used for decades.<sup>41</sup> Unfractionated heparin (UFH) remains the most commonly prescribed anticoagulant<sup>13,42</sup> worldwide and remains the standard against which other anticoagulant regimens are compared.<sup>7,21,22,24,25,43</sup> A regional heparin technique favours patient safety and anticoagulant free CRRT is used for a high risk of bleeding.<sup>44,45</sup>

We have previously reported on circuit life in CVVH when no anticoagulation was used compared to low dose UFH and a regional heparin technique.<sup>45</sup> This study of 300 filters described similar circuit lives for all three methods and has similarities to our findings which indicate the strong association between higher platelet counts and premature circuit clotting.

### **Strengths and Limitations**

This RCT of 100 patients presents for the first time the outcomes of an investigation into the effect of blood flow rate on circuit life in two commonly used modes of CRRT. This analysis is based on a large number of circuits and for 8206 hours of treatment time. This number of patients and treatment time is representative of a tertiary level intensive care unit and signifies important findings for current CRRT practice. The presentation of our analysis for first circuit (clotted) and the analysis of all circuits using repeated events survival analysis should be the new standard for studies reporting circuit life in CRRT where previously an all circuits analysis may have drawn conclusions not valid due to repeated measures effect. The study was not powered to detect a difference as there was insufficient historical data available

to make the appropriate group size calculation. One further limitation may be the defined blood flow rates used in this study. Blood flow rates less than 150 mL/min or greater than 250 mL/min may have yielded a different outcome. Circuit life (hrs) in both groups may be shorter due to the large proportion of patients enrolled have a diagnosis of liver failure and liver transplantation making comparisons to other ICU's difficult. Two membrane compositions were used and anticoagulation according to an established local policy. These two factors may have some influence on our findings.

## **Conclusions**

A blood flow rate of 250 mL/min does not improve CRRT circuit life compared with a blood flow rate of 150 mL/min. Independent factors that may extend circuit life include anticoagulation strategies, higher APTT and lower platelet counts.

## **Acknowledgements**

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**Figure 1.** Flow diagram of participants showing assessment of eligibility, enrollment, treatment allocation and follow-up in the trial. CRRT = Continuous Renal Replacement Therapy, CVVH = Continuous VenoVenous Hemofiltration, CVVHDF = Continuous VenoVenous Hemodiafiltration

**Figure 2.** Kaplan Meier estimate of the probability of continuous renal replacement therapy circuit survival for the first circuit – clotted circuits only





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**TABLE 1. Baseline demographic and clinical characteristics**

<b>ADMISSION VARIABLES</b>	<b>150 ML/MIN N = 49</b>	<b>250 ML/MIN N = 47</b>	<b>P-VALUE</b>
<b>AGE</b>	61.08 ± 15.96	60.77 ± 18.31	0.93
<b>GENDER (M/F)</b>	34/49 (69%)	24/47 (51%)	0.10
<b>BMI</b>	29.01 ± 5.48	27.59 ± 6.85	0.26
<b>WEIGHT</b>	85.19 ± 20.39	75.85 ± 20.30	<b>0.03</b>
<b>APACHE II</b>	22.16 ± 6.47	23.13 ± 6.55	0.47
<b>APACHE III</b>	85.65 ± 23.17	87.21 ± 26.28	0.76
<b>SAPS II</b>	56.22 ± 14.19	55.55 ± 15.21	0.82
<b>SOURCE OF ADMISSION - NO. /TOTAL</b>			



<b>NO. (%)</b>			
ED	13 (27.7%)	12 (25.5%)	
WARD	17 (34.7%)	17 (36.2%)	
POST OP (ELECTIVE)	7 (14.3%)	6 (12.8%)	
POST OP (EMERGENCY)	5 (10.2%)	4 (8.5%)	
TRANSFER OTHER ICU	5 (10.2%)	5 (10.6%)	
TRANSFER OTHER HOSPITAL	2 (4.1%)	3 (6.4%)	
<b>ADMISSION DIAGNOSIS - NO. /TOTAL NO. (%)</b>			
CARDIOVASCULAR	6 (12.2%)	5 (10.6%)	
CARDIAC SURGERY	11 (22.4%)	8 (17.0%)	
RESPIRATORY	0	1 (2.1%)	
GASTROINTESTINAL	6 (12.2%)	6 (12.8%)	
LIVER FAILURE	5 (10.2%)	6 (12.8%)	
LIVER TRANSPLANT	10 (20.4%)	13 (27.7%)	
ACUTE RENAL/GENITOURINARY	5 (10.2%)	5 (10.6%)	
HEMATOLOGICAL	4 (8.2%)	1 (2.1%)	

INFECTION/ABSCESS	2 (4.1%)	2 (4.3%)	
<b>MECHANICAL VENTILATION – NO. (%)</b>	41 (83.7%)	36 (76.6%)	0.44
<b>VASOPRESSOR/INOTROPE – NO. (%)</b>	41 (83.7%)	41 (87.2%)	0.77
<b>SEVERE SEPSIS – NO. (%)</b>	24/49 (49%)	26/47 (55.3%)	0.55
<b>LAB DATA PRIOR TO RANDOMISATION</b>			
SERUM CREATININE	317.20 ± 171.61	297 ± 181.54	0.16
SERUM UREA	23.62 ± 14.94	21.19 ± 10.03	0.33

Independent T-test and chi-square test

**TABLE 2. Circuit life duration – Clotted circuits only**

<b>CIRCUIT LIFE</b>	<b>150 ML/MIN N = 49</b>	<b>250 ML/MIN N = 47</b>	<b>P-VALUE</b>
<b>ALL CIRCUITS</b>	n = 196	n = 173	
<b>MEDIAN HRS (IQR)</b>	10 (6, 24)	11.5 (6.8, 18.3)	0.81
<b>1<sup>ST</sup> CIRCUIT</b>	n = 49	n = 47	
<b>MEDIAN HRS (IQR)</b>	9.1 (5.5, 26)	10 (4.2, 17)	0.37
<b>2<sup>ND</sup> CIRCUIT</b>	n = 35	n = 38	
<b>MEDIAN HRS (IQR)</b>	14 (8.5, 21)	13.8 (8.5, 16.7)	0.45
<b>3<sup>RD</sup> CIRCUIT</b>	n = 22	n = 23	
<b>MEDIAN HRS (IQR)</b>	17 (10.5, 28.5)	16 (12, 21.5)	0.52

Mann Whitney U test

**TABLE 3. Univariate and Multivariate analysis for all circuits**

COVARIATE	Effect	UNIVARIATE MODEL			MULTIVARIATE MODEL		
		HR (95% CI)	p- value	Random Effect Variance (sd)	HR (95% CI)	p- value	Random Effect Variance (sd)
<b>BLOOD FLOW</b>	250 mL/min vs. 150 mL/min	1.04 (0.65,1.69)	0.38	1.005 (0.20)	1.00 (0.60, 1.69)	0.68	1.078 (0.23)
<b>GENDER</b>	Male vs. Female	1.56 (0.97, 2.52)	0.07	0.905 (0.19)	1.76 (0.93, 3.33)	0.08	
<b>BMI</b>		1.02 (0.98, 1.06)	0.26	0.979 (0.20)	1.04 (0.95, 1.14)	0.42	

<b>WEIGHT</b>	for every 5kg increase	1.04 (0.98, 1.11)	0.19	0.957 (0.20)	0.96 (0.82, 1.12)	0.59
<b>VASCATH SITE</b>	Right Femoral vs. Left femoral	0.75 (0.55, 1.03)	0.07	1.075 (0.22)	0.94 (0.66, 1.34)	0.73
<b>VASCATH LENGTH</b>	20 cm vs. 15 cm	0.83 (0.31, 2.19)	0.10	1.091 (0.22)	0.92 (0.34, 2.50)	0.18
	24 cm vs. 15 cm	0.53 (0.22, 1.27)			0.17 (0.03, 1.16)	
<b>VASCATH DIAMETER</b>	13 Fr vs. 13.5 Fr	1.41 (0.96, 2.09)	0.08	1.055 (0.21)	2.66 (0.24, 29.91)	0.43

<b>CRRT MODE</b>	CVVHDF vs. CVVH	1.10 (0.68, 1.77)	0.70	0.993 (0.20)		
<b>ANTICOAGULATION</b>	None vs. Heparin/regional heparin	1.65 (1.21, 2.24)	0.001	1.148 (0.23)	1.62 (1.18, 2.23)	0.003
<b>PLATELETS (X 10<sup>11</sup>)</b>		1.13 (0.97, 1.31)	0.11	0.928 (0.19)	1.19 (1.01, 1.40)	0.03
<b>INR (RATIO)</b>		0.84 (0.65, 1.09)	0.19	0.993 (0.20)	1.05 (0.77, 1.42)	0.77
<b>APTT (SECONDS)</b>		0.98 (0.97, 0.99)	0.0003	0.898 (0.19)	0.98 (0.97, 0.99)	0.002







