The Impact of Blood Flow Rate on Circuit Life in Continuous Renal Replacement Therapy (CRRT)

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Abstract

The impact of blood flow rate on Circuit Life and Solute Clearance in Continuous Renal Replacement Therapy (CRRT)

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Background: There is minimal evidence to inform blood flow rate (BFR) during continuous renal replacement therapy (CRRT).

Aims: We aimed to assess the effect of BFR on circuit life and solute maintenance during CRRT.

Design: A prospective randomised controlled trial.

Setting: Twenty-four bed, single-centre, tertiary-level intensive care unit.

Participants: Critically ill patients with acute kidney injury treated with CRRT (continuous venovenous haemofiltration [CVVH] or continuous venovenous haemodiafiltration [CVVHDF]).

Interventions: Patients were randomised to receive one of two BFRs: 150 mL/min or 250 mL/min.

Main outcome measures: The primary outcome was circuit life measured in hours. The secondary outcome was changes in urea and creatinine concentrations (changes from baseline), and delivered treatment for each 12 h period was used to assess solute maintenance.

Results: One hundred patients were randomised, with 96 completing the study (150 mL/min, n = 49; 250 mL/min, n = 47) using 462 circuits (245 runs at 150 mL/min and 217 runs at 250 mL/min).

Primary outcome: Circuit and patient data were collected until each circuit clotted or was ceased electively for non-clotting reasons. Data for clotted circuits were presented as median (interquartile range [IQR]) and compared using the Mann–Whitney U test. Survival probability for clotted circuits was compared using a log-rank test. Circuit clotting data were analysed for repeated events using hazard ratio (HR). Median circuit life for the first circuit (clotted) was similar for both groups (150 mL/min: 9.1 [5.5, 26] h vs. 10 [4.2, 17] h, $p = 0.37$). CRRT using a BFR set at 250 mL/min was not more likely to cause clotting compared with 150 mL/min (HR 1.00, 95% CI 0.60–1.69; $p = 0.68$). Gender, body mass index, weight, vascular access type, length, site, mode of CRRT and international normalised ratio had no effect on clotting risk. CRRT without anticoagulation was more likely to cause clotting compared with 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, $p = 0.03$] were associated with a reduced likelihood of circuit clotting.

Secondary outcome: There was a total of 426 12 h periods (150 mL/min, 208; 250 mL/min, 218). Mean hours of treatment per 12 h was 6.3 h (3.7) in the 150 mL/min group and 6.7 h (3.9) in the 250 mL/min group ($p = 0.6$). There was no difference between the two BFR groups for mean delta urea (−0.06 [SD 0.015] vs. −0.07 [SD 0.01], $p = 0.42$) or mean delta creatinine (−0.05 [SD 0.01] vs. −0.08 [SD 0.01], $p = 0.18$). Independent variables associated with less reduction in mean serum urea and creatinine were low haemoglobin level (−0.01 [SD 0.005], $p = 0.002$; 0.01 [SD 0.005], $p = 0.006$) and less hours treated (−0.023 [SD 0.001], $p = 0.000$; −0.02 [SD 0.002], $p = 0.001$). No effect for body weight was found.

Conclusion: There was no difference in circuit life or solute maintenance whether using a BFR of 250 mL/min or 150 mL/min during CRRT.

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Statement of Originality

This work has not previously been submitted for a degree or diploma in any University. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Nigel Goss Fealy

Contents

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List of Abbreviations

ADQI	Acute Dialysis Quality Initiative
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
ANZCTR	Australian and New Zealand Clinical Trials Registry
ANZICS	Australia and New Zealand Intensive Care Society
AORTIC	Australasian Outcomes Research Tool for Intensive Care
APACHE	Acute Physiology, Age and Chronic Health Evaluation Score
APTT	Activated Partial Thromboplastin Time
ARF	Acute Renal Failure
ATN	Acute Tubular Necrosis
BEST Kidney	Beginning and Ending Supportive Therapy for the Kidney
BFR	Blood Flow Rate
BMI	Body Mass Index
BUNC	Blood Urea and Creatinine
CAVH	Continuous Arteriovenous Haemofiltration
CIS	Clinical Information System
CKD	Chronic Kidney Disease
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRRT	Continuous Renal Replacement Therapy
CTG	Clinical Trials Group
CVVH	Continuous Venovenous Haemofiltration
CVVHD	Continuous Venovenous Haemodialysis
CVVHDF	Continuous Venovenous Haemodiafiltration
EC	Extracorporeal
ECMO	Extracorporeal Membrane Oxygenation
EDDf	Extended Daily Diafiltration
ESRD	End Stage Renal Disease
FF	Filtration Fraction
Fr	French Gauge
FUNC	Filtrate Urea/Nitrogen and Creatinine
GFR	Glomerular Filtration Rate
HITTS	Heparin-Induced Thrombocytopaenia and Thrombosis Syndrome

HR	Hazard Ratio
HREC	Human Research Ethics Committee
ICU	Intensive Care Unit
IHD	Intermittent Haemodialysis
INR	International Normalised Ratio
IQR	Interquartile Range
KDIGO	Kidney Disease Improving Global Outcomes
LMWH	Low Molecular Weight Heparin
MCF	Mechanical Circuit Failure
PD	Peritoneal Dialysis
PF4	Platelet Factor 4
RCA	Regional Citrate Anticoagulation
RCT	Randomised Controlled Trial
RIFLE	Risk Injury Failure Loss End Stage Renal Disease
RRT	Renal Replacement Therapy
SAPS	Simplified Acute Physiology Score
SLEDD	Slow Low-Efficiency Daily Dialysis
TEV	Total Effluent Volume
TMP	Transmembrane Pressure
TPE	Therapeutic Plasma Exchange

Acknowledgements

Included in this thesis are three papers in Chapters 3 and 5 that are co-authored with other researchers. My contribution to each co-authored paper is outlined at the front of the relevant chapter. The bibliographic details for these papers, including all authors, are:

Chapter 3, Publication 1: Nigel Fealy, Leanne Aitken, Eugene du Toit, Ian Baldwin. (2015). Continuous renal replacement therapy: Current practice in Australian and New Zealand intensive care units. *Critical Care and Resuscitation*, 17(2), 83–91.

Chapter 5, Publication 2: Nigel Fealy, Leanne Aitken, Eugene du Toit, Serigne Lo, Ian Baldwin. (2017). Faster blood flow rate does not improve circuit life in continuous renal replacement therapy: A randomized controlled trial. *Critical Care Medicine*, 45(10), e1018–1025.

Chapter 5, Publication 3: Nigel Fealy, Leanne Aitken, Eugene du Toit, Michael Bailey, Ian Baldwin. (2018). Evaluation of urea and creatinine change during continuous renal replacement therapy: Effect of blood flow rate. *Critical Care and Resuscitation*, 20(1), 41–47.

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(Date) 1/10/2019

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Chapter 1: Introduction

1.1 Introduction

Acute kidney injury (AKI) occurs in a significant number of patients in hospital and in approximately half of patients admitted to the intensive care unit (ICU).[2, 3] It is associated with significant mortality and morbidity.[4-8] Artificial kidney support known as renal replacement therapy (RRT) has evolved as treatment for severe AKI in critically ill patients.[9] Artificial kidney techniques such as RRT used in the management of AKI focus on replacing the primary functions of the kidney, including maintenance of fluid and acid–base balance, solute removal and electrolyte control. The various techniques of RRT include peritoneal dialysis (PD), intermittent haemodialysis (IHD) and continuous renal replacement therapy (CRRT). CRRT has emerged in recent decades to be the dominant RRT modality worldwide[10] and differs from other techniques as it is intended to be applied for 24 h per day in the ICU. Continuous modes of RRT rely on the blood-filled extracorporeal (EC) circuit being patent for as long as possible to provide this continuous therapy. However, circuits used for CRRT frequently clot so that therapy is interrupted, resulting in potential blood loss and inefficient treatment.[11, 12] The speed of blood flow through the EC circuit may be an important practical determinant of patency and longevity of each CRRT circuit and may affect the 'circuit life'.

This prospective study assessed the impact of blood flow rate (BFR) on circuit life in CRRT. In this chapter, an introduction to the study, including the background, research problem and significance of this study, is presented, as well as an overview of the chapters comprising this thesis.

1.2 Background

1.2.1 Acute kidney injury and critical illness

AKI is a significant clinical problem that complicates the stay of many hospitalised patients.[13] This abrupt loss of renal function may last for many days or weeks, and manifests clinically as an inability to maintain fluid and acid–base balance, biochemical stability and excretion of waste products. AKI is estimated to occur in approximately 20–200 individuals per million in the community, 7–18% of patients in hospital and 50% of patients admitted to the ICU.[2, 3] AKI is also associated with significant morbidity and

mortality; an estimated 2 million people worldwide die every year, and survivors have an increased risk of developing chronic kidney disease (CKD) or end stage renal disease (ESRD).[14, 15]

The aetiology of AKI in the ICU patient is usually multifactorial; however, haemodynamic instability, sepsis and drug toxicity are commonly implicated. The key causative process of AKI comprises complex interactions between vascular, tubular and inflammatory factors.[16] Kidneys appear to be vulnerable to injury or insult from toxins with or without ischaemia, resulting in vasoconstriction, endothelial injury and activation of inflammatory immune responses.[13, 17] This is a modification in understanding of AKI as traditional concepts concentrated on conditions that caused hypoperfusion, with a reduction in renal blood flow altering the delicate vascular tubular relationship in the renal medulla.[17] More recent studies have however demonstrated that AKI can develop during periods when renal blood flow is normal or even increased, as occurs in sepsis.[18] Inflammatory processes such as sepsis appear to cause dysfunction of the microcirculation in the glomeruli and peritubular capillaries, causing areas of hypoperfusion and micro ischaemia even after systemic haemodynamic stability has been restored in the critically ill patient.[19, 20] Sepsis is a major associated pathology linked to the development of AKI in the critically ill patient. The multinational Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study found sepsis in half the patients diagnosed with AKI in intensive care.[21] More recent studies have confirmed these findings, with high frequency of sepsis among critically ill patients diagnosed with AKI, ranging from 37% to 53%.[22, 23-25]

Apart from sepsis, or in association with it, other shock states induce ischaemia, causing a primary reduction in kidney function and resulting in insult to the nephron and development of acute tubular necrosis (ATN). Similar to sepsis, there are changes to the microcirculation, leading to endothelial dysfunction, cellular adhesion and interstitial oedema. Tubular epithelial cell injury may be the result of prolonged hypotension, exogenous products such as drugs (nephrotoxins), or endogenous molecules such as cytokines or other inflammatory mediators.[18, 26] Tubular injury often leads to structural changes, mitochondrial damage, necrosis, apoptosis and eventual cellular death.[18] The accumulation of the detached cells and necrotic debris in the lumen of the tubule contributes to obstruction, reduction in glomerular filtration, oliguria and eventual anuria.[17] During this phase of insult to the nephron, morphological and functional changes to the endothelial cells result in the recruitment of circulating neutrophils, lymphocytes

and macrophages, leading to release of chemicals such as nitric oxide and other proinflammatory mediators. These chemicals released by the nephron and the efferent vascular system lead to dilation, loss of normal glomerular filtration pressure, toxin retention, loss of urine production and eventual anuria.[27-29] While the development of AKI involves many complex pathophysiological processes, the clinical diagnosis of the disease process, and therefore management, has been the subject of much debate over the past two decades.

1.2.2 Definition, classification and clinical identification of acute kidney injury

Prior to 2004, there was no consensus or uniform clinical definition of what constituted acute renal failure (ARF),[30] as it was then termed, despite its importance for clinical care and research. The Acute Dialysis Quality Initiative (ADQI), a panel of leading intensivists and nephrologists, met in 2000 to establish consensus based on evidence and expert opinion pertaining to ARF and treatment modalities. In 2002, the ADQI reported that there were more than 35 definitions for ARF in the medical literature.[31] The inconsistency in the definition of ARF had led to a large discrepancy in the reported incidence rates of ARF, as well as mortality estimates.[32, 33] In 2004, the ADQI developed a consensus definition of ARF based on severity (Risk, Injury and Failure) and two outcome classes (Loss and End stage kidney disease), known as the RIFLE criteria.[34] The term ARF was replaced with the new term AKI at this time. The three severity grades are based on changes in baseline creatinine or urine output. The two outcome criteria are defined by the duration of the loss of kidney function.

The RIFLE classification system (Figure 1.1) articulates the relationship between glomerular filtration rate (GFR), creatinine and urine output criteria for the stratification of AKI. The classification system organises degrees of kidney insult by using either blood criteria (creatinine) or clinical criteria (urine output). Patients are stratified to ‘risk’ (RIFLE classification R), ‘injury’ (RIFLE classification I) and ‘failure’ (RIFLE classification F). Patients diagnosed with RIFLE classification F meet criteria for the institution of RRT in the ICU.

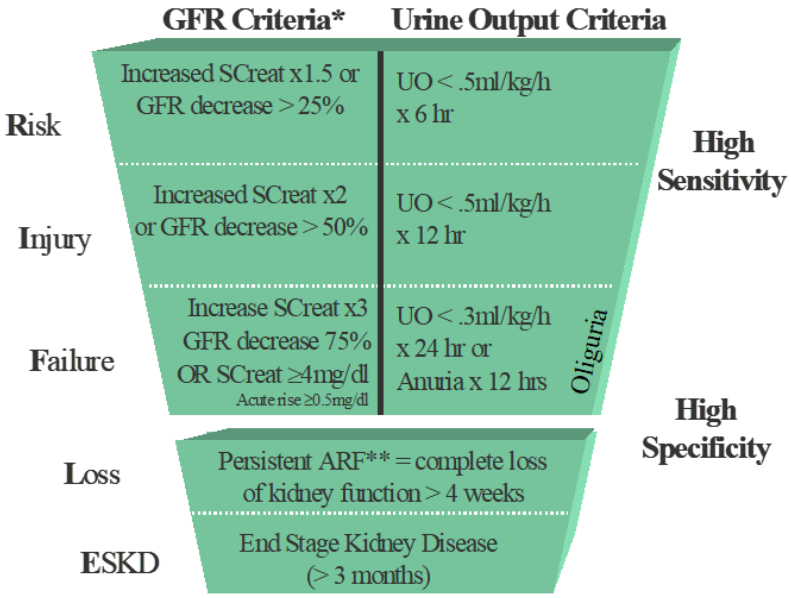


Figure 1.1: The RIFLE classification system for AKI.[35]

The RIFLE criteria were subsequently assessed in more than 550,000 patients to confirm validity of the definition.[36] The expected benefits of this more precise and universal definition of AKI were twofold: early detection of 'at risk' patients to aid their ongoing management and prevention of progression to failure, and establishment of standardisation within the research domain so that findings are more comparable for equivalence.[37]

In 2005, a new classification of AKI was proposed by the Acute Kidney Injury Network (AKIN) working group, comprising nephrologists and critical care physicians who specialise in AKI.[38] The AKIN classification system published in 2007 is a modification of the RIFLE classification with more emphasis on serum creatinine changes (and less on GFR) during the acute phase of the kidney dysfunction.[39] Stage 3 in this classification system corresponds to kidney 'failure' and directs the physician to initiate RRT in the ICU.

The focus on early diagnosis and management of AKI was further advanced in 2012 as a European expert group known as Kidney Disease Improving Global Outcomes (KDIGO) merged with the AKIN.[40, 41] This combined group provided clinicians with a more staged approach to the diagnosis of AKI using creatinine baselines, rise times and timing (Figure 1.2). In addition to progressing the identification of AKI for clinical practice and research, the AKIN and KDIGO groups provided clinicians with evidence-based guidelines for the management of AKI patients, including provision of artificial renal support or RRT.[40]

AKI Staging - KDIGO

AKI stage	Serum Creatinine criteria	Urine output criteria
1	SCr increase ≥ 26 µmol/L within 48hrs or SCr increase ≥ 1.5-2 X reference SCr within 1 week	< 0.5 mL/kg/hr for 6 consecutive hrs
2	SCr increase ≥ 2-3 X reference SCr within 1 week	< 0.5 mL/kg/hr for 12 hr
3	SCr increase ≥ 3 X reference SCr within 1 week or SCr increase ≥ 354 µmol/L or initiated on RRT (irrespective of stage at time of initiation)	< 0.3 mL/kg/hr for 24 hr or anuria for 12 hr

Figure 1.2: The AKIN/KDIGO classification/staging system of AKI.[39]

1.2.3 Management of acute kidney injury in the intensive care unit setting

When AKI is severe, recovery of function can take several days to weeks. During this time, the kidneys cannot maintain homeostasis of fluids, electrolytes, metabolic acids and waste products.[42, 43] The initiation of strategies to reverse or protect the kidneys largely depends on the severity of illness. In general, initial management of AKI in the intensive care setting is focused on haemodynamic optimisation, fluid resuscitation and pharmacological support of blood pressure.[44] In addition, the prevention of further kidney damage by limiting known nephrotoxic agents and instituting agents that protect the kidneys such as loop diuretics[45] are considered important interventions in the recovery from renal dysfunction.

Despite more meaningful definitions of AKI now being published, there are still no clear uniform criteria to inform practitioners about when the initiation or treatment of the disease process with RRT should commence.[46] The clinician determines initial medical management strategies and, if required, eventual artificial renal support according to the patient's individual clinical condition. It is generally accepted that those patients stratified as 'risk' would be subject to a list of protective strategies in an attempt to preserve existing renal function and prevent irreversible damage and progression of the illness.[47] In those patients stratified as 'injury' or 'failure', RRT may be instituted by the physician, depending on fluid, electrolyte and metabolic derangements, as part of a larger management plan.

The practice of treating AKI with CRRT was reported by the BEST Kidney study in 2005. The BEST Kidney study, a prospective multinational, multicentre observational kidney

study, reported an AKI incidence of 6% in 29,269 intensive care patients. Of this AKI group, 1260 patients were treated with CRRT.[48, 49] These data suggest that of all patients admitted to ICUs worldwide, 5% will be treated with a form of RRT during the course of their ICU stay. To illustrate the significance of this therapy, based on data from the Australia and New Zealand Intensive Care Society (ANZICS) database for 2016/17, 157,674 patients were admitted to ICUs across these two countries.[50] These data suggest that approximately 7884 patients treated in intensive care in Australia and New Zealand would have required a form of artificial renal support during their critical illness.

1.2.4 Kidney failure and extracorporeal therapies

Despite complex physiology, human kidney function can be replaced with an artificial process, which can temporarily sustain life. Normal kidney function is essential for the wellbeing of other key body organs such as the brain, heart, liver and lungs. With high levels of toxins in AKI, these organs also become dysfunctional.[51] Artificial kidney techniques used in the management of AKI focus on replacing the primary functions of the kidney, including maintenance of fluid and acid–base balance, solute removal and electrolyte control.[52]

The support of the failing kidneys in the critically ill individual requires the establishment of an EC blood-filled circuit where blood can be mechanically pumped through an artificial membrane or haemofilter acting as an artificial kidney. This treatment, known as CRRT, is only successful if the membrane and the EC circuit function without clotting.[53] In current experience, this means continuous function for more than 24 h before failure.[54]

1.2.5 Clotting in the extracorporeal circuit

Whenever blood is exposed to the plastic and 'foreign' components of the CRRT circuit, natural clotting mechanisms are activated.[55] Once clotting has been activated, circuit failure is inevitable as clotting occurs within the circuit filter. One of the interventions utilised to prevent activation of the clotting cascade and therefore increase EC circuit 'life' is to use anticoagulant drugs such as heparin.[56] However, despite the use of these anticoagulants, the desired result is often not achieved, and the circuit continues to clot prematurely (e.g., <6 h)[53, 57], which suggests that there are other important factors contributing to clot formation.

1.2.6 Blood flow and the extracorporeal circuit

Despite clot formation in the blood circuit compromising the efficacy of the CRRT system, adequate investigation into the factors that affect flow of blood through the CRRT system has not been reported. There are many resistance points in the EC circuit that have the potential to impede blood flow, induce turbulence and promote clot formation.[58] Only one study has demonstrated a correlation between unexpected flow variation within the blood-filled circuit and filter life.[59] It has been suggested that increasing BFR through the EC circuit to speeds greater than 200 mL/min may reduce the incidence of premature clotting particularly in the context of convective and combination modes of CRRT.[1] One recent retrospective report demonstrated a reduction in filter lifespan when the BFR was less than 200 mL/min, concluding that a BFR of 250–300 mL/min should be prescribed for CRRT.[60] Despite some recommendations, there is great variability in the BFR utilised in clinical settings worldwide—from 80 mL/min to 350 mL/min—which may be indicative of a lack of scientifically validated evidence to support clinical practice.[35, 60, 61] There have, to this point, been no controlled studies that focus on the impact of BFR on circuit/filter life in the success of the therapy. Optimum BFR for CRRT and its effect, if any, on circuit life, and therefore efficiency of treatment, has therefore not been adequately determined. BFR in the EC circuit may be an important independent factor affecting circuit or filter life and, ultimately, the success of the therapy.

1.2.7 Clinical and nursing implications of premature circuit clotting

Premature clotting of the membrane and circuit leads to lengthy periods when therapy is ceased to allow for preparation and reinstitution of the circuit. The implications of frequent circuit or membrane failure to the patient are now well recognised, with a direct correlation between the amount of time spent off therapy (downtime) and the extent of loss of solute and fluid balance control.[62] The more frequent the membrane and circuit failure, the greater the downtime and the less effective the treatment. The clinical importance of frequent membrane and circuit failures, and therefore shorter periods of effective treatment, cannot be underestimated in relation to patient outcomes.

This failure due to clotting also increases the nursing time and efforts required to reset the CRRT circuit, and has a further monetary cost as new sterile components are required each time.[63] The nursing work required to reset the CRRT circuit following failure includes sterile procedures and administration of additional IV fluids, as well as possible interruption to patient sleep, pressure care schedules and family visiting. A CRRT circuit

that clots may also result in the patient losing in excess of 120 mL of whole blood from the circuit. Blood transfusion may be required if several failures occur within a short period. With CRRT in the ICU, prevention of circuit clotting is a very important aim to improve patient safety and patient outcome.

1.3 Research problem

There is sufficient indication to suggest that BFR may be an important independent factor influencing circuit life in CRRT. Despite suggestions to increase BFR to extend circuit life, there remains great variability in clinical practice worldwide. The speed of blood flow in the EC circuit may have direct effects on clotting pathways, because of interactions with the CRRT circuitry and membranes, or indirect effects by triggering alarm conditions that stop the CRRT pump, thereby ceasing blood flow, causing blood stasis and activating clotting processes. The combination of these complex interactions may be directly linked to the set BFR, but the importance of this relationship is yet to be determined in any meaningful way.

1.4 Significance of the study

It is highly likely that the speed of blood flow through the EC circuit affects CRRT circuit life. The impact of BFR on circuit life has not been adequately explored thus far. A greater understanding and clarification of the role that BFR has on CRRT circuit life will inform bedside clinicians and provide data for worldwide clinical practice guidelines.

This work therefore seeks to:

1. provide prospective controlled data exploring the relationship between prescribed BFR and circuit life in CRRT
2. provide bedside clinicians with a better understanding of the importance of practical prescription parameters and efficiency of therapy
3. provide clinicians an evidence-based BFR prescription for optimal CRRT delivery.

Addressing these aims is important for several reasons. First, frequent circuit clotting decreases treatment efficiency as patients must often be removed from the therapy for potentially long periods of time to reset the machine and circuit tubing so that the therapy can be reinstituted. Any improvement to circuit life will reduce the frequency of interruptions and reduce potential complications associated with fluid balance, acid–base

and electrolyte instability. Second, with frequent circuit clotting, patients can lose a clinically significant amount of blood, possibly requiring blood transfusion. Optimised circuit life may prevent unnecessary blood loss and reduce requirements for blood transfusion and its associated risk in critically ill patients. Third, in many countries, intensive care nurses perform the set-up and maintenance of the therapy while also caring for the critically ill patient. Premature cessation due to circuit clotting affects nursing time and the ability of the bedside intensive care nurse to deliver timely care for ICU patients. Extension of each circuit life will allow the bedside nurse to deliver focused care with less interruptions to the most vulnerable patient population.

Overall, there is value in answering the questions addressed in this study because of the potential to improve clinical practice and patient outcomes, inform clinical guidelines for practice and provide a more efficient therapy, which is frequently prescribed in the intensive care patient.

1.5 Structure of the document

This thesis is presented in six chapters as follows:

Chapter 1: The background to this study, research problem and significance of the study are provided.

Chapter 2: A comprehensive and critical appraisal of the literature addressing the issue of BFR in CRRT is presented. The literature review is organised in four main sections: an introduction to the topic, circuit life in CRRT, BFR prescription in CRRT and a description of the research question.

Chapter 3: A description of current CRRT practice in Australia and New Zealand as assessed through a survey, including publication of the results, is provided.

Chapter 4: The research design and methods used to address the research question are described. Elements of the research methods outlined include design, settings, sample, interventions, ethical considerations, data collection and analysis for the study.

Chapter 5: The results of this study are presented. This section comprises an introduction to the results, followed by more detailed reporting of the results that have been published in two peer-reviewed publications. The discussion for each outcome variable is included within the published papers pertaining to the area of focus.

Chapter 6: The overall discussion and conclusion of the thesis, as well as the recommendations for clinical practice and future research, are presented. Strengths and limitations of this study are also provided.

1.6 Summary

An introduction to this study has been provided in this chapter, which explored the issue of AKI and critical illness, management of AKI with CRRT and implications of premature clotting of the EC circuit used in CRRT. The research problem and aims were presented, and an outline of the current inadequacies in BFR prescription and the impact it has on circuit life was provided. The significance of the study for clinical practice, education and future research was also presented. Last, an overview of the remaining chapters of the thesis was provided.

Chapter 2: Literature Review

2.1 Introduction

CRRT has been increasingly applied in the ICU since it was first described; however, the basic concept of the technique remains the same.[52, 64] CRRT is managed by the intensive care nurse who has specialised training in setting up the tubing circuit, connecting the circuit to the patient, and monitoring the replacement and removal of fluids.[65] The increasing use of RRT to treat critically ill patients has led to the development of both specialised nursing to manage this technology and many diverse machines to facilitate this therapy for the patient with AKI in the ICU setting.[66, 67]

One of the main problems with all current EC RRTs is their relatively high failure rate due to blood clotting—thrombogenicity.[68] Frequent thrombus formation is likely to result in treatment inefficiency. Contact between the blood and an artificial surface is the major factor initiating coagulation. This exposure of the blood to foreign or non-biological materials such as the circuit tubing and artificial membrane is thought to trigger platelet activation, which in turn initiates the coagulation cascade.[69, 70] Eventually, there are enough thrombi in the circuit or membrane, or both, to obstruct flow within the circuit, leading to high pressures and the diagnosis of circuit failure. Successful application of CRRT depends on adequate EC circuit life.

A review of the current literature pertaining to circuit failure (life) in CRRT is provided in this chapter, with a focus on three main areas:

1. the importance of preventing clotting in the EC circuit and the artificial membrane (filter) necessary to maintain the therapy
2. a review of the factors associated with, and strategies currently used, to prevent filter clotting and optimise circuit life
3. a focus on gaps in our current knowledge relating to blood flow mechanics and the potential influence on circuit life.

2.2 Methods

The search strategy for this literature review was developed by the student with the assistance of library staff at Austin Health. A search of Ovid MEDLINE and Ovid EMBASE libraries was initially performed in October 2011 to provide context for the

study, focus the research question and inform design for the study. A final search using the same strategy was conducted in March 2018 with no restrictions for using key words, variant spellings and wildcards (Table 2.1). Title and abstract searches were focused on terms relating to continuous forms of RRT, which is inherently specific to intensive or critical care settings. As a result, intensive care or critical care was not included in the search strategy.

Table 2.1: Search Strategy for Literature Review

Title and abstract search		Title and abstract search/MeSH terms
renal replacement therapy OR continuous renal replacement therapy OR RRT OR CRRT OR CVVH OR CVVHD OR CVVHDF OR CVVHDf	OR	continuous venovenous hemofiltration OR continuous venovenous haemofiltration OR continuous venovenous hemodialysis OR continuous venovenous haemodialysis OR continuous venovenous hemodiafiltration OR continuous venovenous haemodiafiltration
	AND	hemofiltration OR haemofiltration OR hemodiafiltration or haemodiafiltration
anticoagulants OR heparin OR citrate OR epoprostenol OR nafamostat OR hirudin	AND	regional heparin OR regional heparinisation OR low molecular weight heparin OR clexane OR dalteparin OR LMWH OR prostacyclin OR regional citrate anticoagulation OR regional anticoagulation
extracorporeal circulation OR circuit OR filter OR catheter OR vascular access catheter OR vascath OR blood flow	AND	circuit life OR filter life OR circuit survival OR filter survival OR clot OR thrombosis OR failure

2.2.1 Inclusion and exclusion criteria

Abstracts were screened for potential relevance, after which full-text versions of the papers were obtained. Literature included comparator studies, observational studies and reviews for variables that may lead to premature clotting of the EC, or strategies aimed at extending circuit life in continuous modes of RRT. Although the purpose of this study was to examine a non-anticoagulant factor and its relationship to circuit life, anticoagulant

strategies were included in the literature review as there may be an association between many of the factors that may contribute to the success or failure of the therapy.

The following studies were considered not relevant and excluded: abstracts relating to vascular access for intermittent dialysis therapies, IHD, extended daily diafiltration (EDDf) or slow low-efficiency daily dialysis (SLEDD). Also excluded were CRRT dosing or pharmacokinetic studies; studies relating to paediatric CRRT; and adjunct therapies associated with RRT, such as extracorporeal membrane oxygenation (ECMO), therapeutic plasma exchange (TPE) and blood purification therapies such as liver support systems and cytokine removal. In addition, studies aimed at timing of CRRT commencement, cessation or recovery of renal function after CRRT were excluded.

2.2.2 Literature search results

A total of 1037 abstracts were identified, of which 235 were selected for full-text analysis. The study selection process is outlined in Figure 2.1. The most common reason for exclusion was studies focused towards intermittent therapies (vascular access and anticoagulant strategies). Included literature was sorted and placed into two broad categories: anticoagulation strategies to extend circuit life (n = 165) and non-anticoagulation factors affecting circuit life in CRRT (n = 70). While the number of studies examining heparin appears low compared with citrate, a significant number of alternative anticoagulation strategies have used heparin as a comparator to identify efficacy of the therapy.

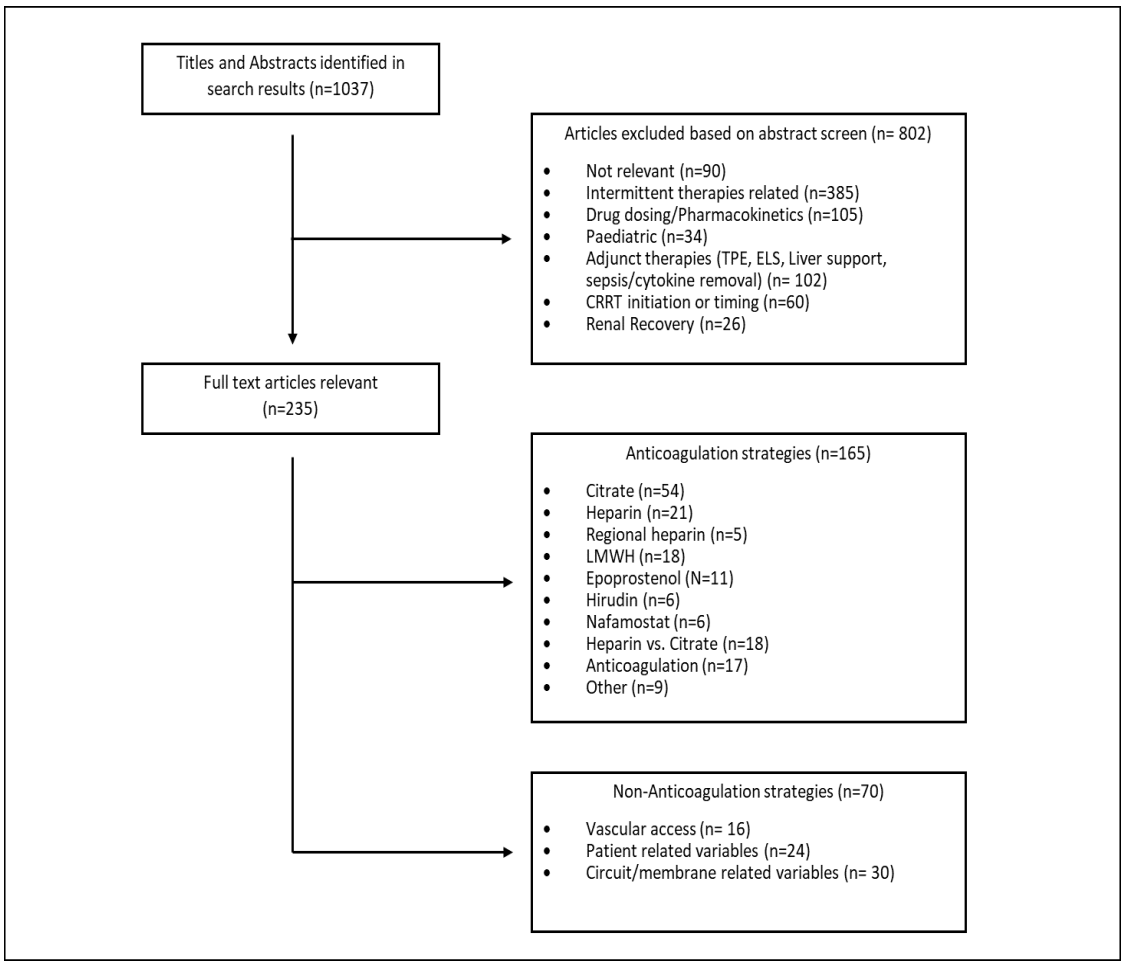


Figure 2.1: Article flow through the review process.

2.3 Anticoagulation strategies to extend circuit life

One mechanism utilised to prevent activation of the clotting cascade and increase EC function before clotting is the administration of anticoagulant drugs.[56] Despite the use of anticoagulants being administered to the patient via the CRRT circuit, the desired result is often not achieved and the circuit continues to clot prematurely.[53] This outcome is commonly related to the dose of anticoagulant being reduced to a low dose to minimise risk of bleeding following surgery or in the setting of neurological disorders where cerebral bleeding is a risk.[71, 72]

The use of anticoagulant agents to impede circuit clotting and extend circuit survival is balanced with the risk associated with administering these drugs to critically ill patients. The clinical 'mindset' is to achieve acceptable circuit life without increasing the risk of bleeding in this fragile patient cohort. Acceptable circuit life has traditionally been difficult to quantify because of individual and institutional practice and target variations.[73] As a quality indicator, circuit survival or life of 20–24 h without clotting or treatment

time of ≥20 h per day has been recently suggested as a benchmark target to assess therapy efficiency.[74]

2.3.1 Methods of providing anticoagulation

Clotting systems are activated as blood makes contact with plastic tubing and the filter membrane. Anticoagulant agents are designed to influence this process, delaying clot formation while the blood is outside the body and particularly within the filter fibres. There are three major drug types that are utilised to prevent blood clotting in the EC circuit and filter. They are factor Xa or thrombin inhibitors (unfractionated and low molecular weight heparin [LMWH]), antiplatelet agents (prostacyclin) and calcium chelators (citrate). As thrombin, blood platelet cell fragments and calcium are vital in clot formation, these drugs are targeted to one of these elements.

2.3.1.1 Unfractionated heparin

Heparin is the most commonly used anticoagulant for the prevention of clot formation in RRT.[53, 75, 76] Heparin increases clotting time by binding with antithrombin III, which inhibits clotting factors including thrombin and factor Xa.[76] There have been numerous studies focused on heparin as the sole anticoagulant in CRRT systems.[77-83] Most commonly, heparin is administered as a constant infusion into the 'arterial limb' or outflow limb of the EC circuit so that heparin is exposed to the blood prior to its flow through the artificial membrane. This administration of heparin is aimed at preventing coagulation in the circuit and membrane, but may also have a 'systemic' anticoagulant effect on the patient.[84]

Despite being considered the standard of care, the use, safety and efficacy of heparin in the critically ill patient has been questioned over the last decade.[85] Given high doses of heparin are sometimes required to prevent circuit clotting, systemic bleeding is a significant complication in this group of patients.[78, 82] When high-dose heparin is used for CRRT (>15 IU/kg), the risk of bleeding can be up to 50% of patients where used.[86-90]

The anticoagulant effect of unfractionated heparin depends on inhibition of antithrombin III. In critically ill patients, circulating levels of antithrombin III may be low because of consumption of the factor in conditions that activate the coagulation cascade, such as sepsis or other systemic inflammatory processes. 'Heparin resistance' has been used to describe the phenomenon where despite increasing doses of heparin there is no significant

increase in activated partial thromboplastin time (APTT) and a significant decrease in circuit life.[91]

An important consideration in prescribing heparin is the potential for critically ill patients to develop heparin-induced thrombocytopaenia and thrombosis syndrome (HITTS). Heparin binds to platelet factor 4 (PF4), which is released from platelets once activated.[85] Some patients develop antibodies to this heparin-PF4 bound complex, which induces excessive platelet activation, coagulation activation and resultant consumptive loss of circulating platelets, inducing a state of thrombocytopaenia.[91] This altered pathophysiological sequence can lead to a prothrombotic state and risk excessive clot formation with life-threatening thromboembolism.[85, 91]

Many centres have developed low-dose heparin regimens to minimise patient bleeding but provide an acceptable circuit life.[92-94] Despite using these low-dose heparin regimens, the reported incidence of bleeding episodes remains as high as 30%[82, 94], with mortality due to bleeding in one study being as high as 15%.[80] One retrospective analysis indicated a correlation with increased bleeding in patients and an APTT longer than 45 s.[82] For this reason, many ICU physicians opt for low-dose heparinisation (5–10 IU/kg) of CRRT circuits, with an APTT of 34–45 s to mitigate the bleeding risks associated with the therapy.[56]

2.3.1.2 Low molecular weight heparin

LMWH differs from unfractionated heparin in its molecular structure. LMWH binds to antithrombin III, but inhibits thrombin to a lesser degree (and factor Xa to a greater degree) than unfractionated heparin.[76] LMWH has a more predictable anticoagulant effect than heparin and has been reported to cause less bleeding compared with heparin.[76] Patients treated with LMWH appear to have a decreased incidence of HITTS, less activation of platelets and reduced activation of the PF4 complex than those treated with unfractionated heparin.[95-97] Few studies of LMWH efficacy in CRRT have been conducted.[98-100] One early randomised trial comparing heparin and LMWH demonstrated comparable circuit life and no increase in bleeding complications.[101] Since then, only one randomised controlled trial (RCT) has demonstrated superiority of the LMWH enoxaparin in prolonging circuit life compared with unfractionated heparin (31 h vs. 22 h, $p = 0.017$). Both these studies highlighted several practical issues that arise with the use of LMWH. Monitoring the efficacy of the drug requires an anti-Xa assay, which is expensive and not routinely performed in most centres.[97, 101, 102] In addition, LMWH has

no reversal agent or antidote, which limits its safety in critically ill patients, and is more expensive than standard heparin.[76, 97, 101] Therefore, because of these practical limitations, LMWH has not gained universal acceptance and is not widely used.

2.3.1.3 Regional heparin

If the circuit 'life' is deemed to be unacceptable (e.g., <6 h), a different anticoagulation method is indicated to prevent circuit clotting without increasing the risk of bleeding to the patient.[56, 72] The common alternative approach is to provide a high level of anticoagulation in the EC circuit only, without the patient receiving active drug.[103] This is known as circuit or 'regional' anticoagulation.[71] When using heparin, this involves administering the drug into the circuit as usual, but administering an antidote or drug (e.g., protamine) to eliminate the effect of the heparin just before the blood returns from the circuit to the patient.[103] In clinical practice, some of the complications associated with administration of unfractionated heparin are evident (HITTS, heparin resistance) as the dose of unfractionated heparin is often significantly increased in an attempt to prolong circuit longevity.[95] In addition, dosing of unfractionated heparin and the antidote can be complex for the bedside clinician as they differ in elimination half-life, making adjustments for effect difficult.[104] Despite the potential of a regional heparin technique to prolong circuit life, there appears variability in efficacy.[105] Some small studies have demonstrated practicability of the regimen without establishing any circuit life advantages over LMWH or regional citrate techniques.[106-108] A recent large multicentre RCT (212 patients, 857 CRRT circuits) comparing regional heparinisation and regional citrate technique in both continuous venovenous haemofiltration (CVVH) and continuous venovenous haemodiafiltration (CVVHDF) demonstrated a statistically significant increase in circuit clotting associated with regional heparin (hazard ratio [HR] 2.03, $p < 0.0005$), with an associated significant reduction in median filter life (22.8 h vs. 39.2 h, $p = 0.0037$). There were also more adverse events (11 vs. 2) in the regional heparin group, with HITTS the most common event. Given these latest findings, a regional heparin and protamine technique may have substantial limitations for both efficacy and safety in critically ill patients requiring CRRT.

2.3.1.4 Thrombin inhibitors

Thrombin (factor IIa) plays a central role in the generation of a clot or thrombus. Thrombin activates several clotting factors (V, VIII, XI) to further produce more thrombin and factor XIII, which facilitates clot stabilisation and stimulates platelets.

Direct thrombin inhibitors are a class of anticoagulants that inhibit free and clot-bound thrombin and that do not react to antibodies to heparin.[109] For this reason, direct thrombin inhibitors such as hirudin, argatroban, lepirudin and bivalirudin may be beneficial in critically ill patients with known or suspected HITTS.[110, 111] Observational studies have demonstrated the successful use of hirudin in critically ill patients diagnosed with HITTS.[112-114] However, despite the maintenance of circuit patency, hirudin was also associated with bleeding complications in up to 38% of patients.[113-115] The normal half-life of hirudin is short (1–2 h) but can be as long as 50 h in renal insufficiency[112], and because of its high molecular weight (>6000 Da), hirudin is not easily removed by convective or diffusive modes of CRRT.[116] Combined with a lack of any reversal agent, hirudin's potential for ongoing bleeding in this group of patients has discouraged its use.[116]

One study of 30 HITTS-positive patients treated with the second-generation thrombin inhibitor argatroban as the sole anticoagulant provided a satisfactory mean filter life of 24 h without significant bleeding events.[111] Argatroban differs from hirudin in that it is excreted by the liver; has a low molecular weight (500 Da), allowing for clearance with CRRT; and has actions that may be reversed with activated factor VII.[117] One recent single-centre RCT compared argatroban with hirudin in patients with known HITTS in continuous venovenous haemodialysis (CVVHD).[118] Twenty-eight patients received continuous dialysis with no difference in first circuit life between the two groups (33 h vs. 22 h, $p = 0.298$); however, bleeding requiring intervention was higher in the hirudin arm (4 vs. 11, OR = 3.9).[118] While argatroban may have some pharmacologic advantages over hirudin, patients with liver dysfunction, sepsis or multi-organ dysfunction could be prone to delayed clearance of the drug, leading to cautious use in this group for fear of unwanted bleeding events.[109]

2.3.1.5 Epoprostenol (prostacyclin)

Prostacyclin causes an anticoagulant effect by preventing the activation and aggregation of platelets.[81] Prostacyclin-based anticoagulation is usually utilised in patients where heparin therapy has been ineffective in prolonging circuit life or where heparin therapy is contraindicated.[66, 119] Some studies in patients requiring EC circuit anticoagulation with prostacyclin have demonstrated a reduced risk of haemorrhage and fewer bleeding episodes compared with heparin.[81, 120-122] The efficacy and safety of prostacyclin for maintaining circuit life has been compared with heparin as well as a prostacyclin/heparin

combination in one RCT.[119] Median circuit life for prostacyclin alone was 15–19 h, which increased to 21–22 h when combined with low-dose heparin.[119] In this study, prostacyclin alone was associated with greater haemodynamic instability compared with the other two methods.[119] Clinically, prostacyclin is now often combined with low-dose heparin or LMWH to increase efficacy.[66, 102] However, patients often exhibit unwanted systemic side effects such as hypotension[76] and an increase in intracranial pressure[81], which limits its safety in the critically ill patient.

2.3.1.6 Nafamostat mesilate

Nafamostat is a synthetic serine protease inhibitor that interferes with the coagulation cascade by inhibiting platelet aggregation and other coagulation factors. There are limited studies that demonstrate an improvement in circuit life with its use; however, this has not been demonstrated in large RCTs.[123-126] The use of nafamostat is limited to Asian countries, and it is not currently available in the United States, United Kingdom and Australia, which have limited evidence for its use as an effective anticoagulant in CRRT. A recent survey of CRRT practices in Japan indicates that nafamostat is the anticoagulant of choice, with over 80% of clinicians indicating the drug as their first preference for extending circuit life.[127] Similar to other platelet inhibitors, nafamostat has been associated with significant side effects such as anaphylaxis and agranulocytosis, which might have deterred clinicians from investigation outside this region.[128, 129]

2.3.1.7 Regional citrate anticoagulation

Citrate causes anticoagulation by binding to ionised calcium in serum. As ionised calcium is a major activating factor in the coagulation cascade, it decreases blood coagulability once bound. Therefore, an infusion of a solution containing citrate into the CRRT circuit can lead to anticoagulation of the circuit. When the blood returning from the circuit returns to the patient circulation, it mixes with systemic blood and the calcium concentration is partially restored to normal. In the liver, kidney and skeletal muscle, citrate is metabolised to yield carbon dioxide and bicarbonate,[130] with calcium being released back to the body. However, in CRRT, a significant amount of the bound citrate–calcium complex is lost in the ultrafiltrate (waste) and this calcium lost across the membrane needs to be replaced by a separate infusion to maintain the body calcium balance.[66] With this method, the EC circuit is anticoagulated, but the patient is not. Thus, filter clotting is prevented but the patient's risk of bleeding is very low. The metabolism

of citrate into bicarbonate means that citrate acts not only as an anticoagulant but also as an efficient buffer in patients with loss of acid–base control due to their AKI.

Regional citrate anticoagulation (RCA) can be performed in all modes of CRRT; however, in modes such as CVVHDF, the complexity of the application increases, with specific formulations of citrate, replacement and dialysate fluids and calcium replacement solutions required. Specific software applications are now available on modern CRRT platforms to simplify the practical application of RCA and allow for alteration in therapy dosing, BFR and citrate dose, and thereby prevent potential metabolic consequences.

Original observational studies of RCA therapy compared with unfractionated heparin anticoagulation reported significantly better circuit survival times and less bleeding episodes.[131-133] In 2004, Monchi and colleagues highlighted the potential of RCA as an effective anticoagulant by conducting a crossover-design RCT using heparin as the control in patients treated with CVVH.[87] This was one of the first RCTs to demonstrate statistical and clinical superiority in favour of citrate anticoagulation for not only circuit life (70 h vs. 40 h, $p = 0.0007$) but also adverse events such as major bleeding and transfusion requirements.[87] Since the Monchi study, there have been 10 RCTs investigating the effectiveness of RCA for circuit life in CRRT, with 972 patients and 1949 circuits studied.[88, 89, 108, 132, 134-139] The most recent RCT by Gattas and colleagues investigated two regional techniques (RCA vs. regional heparin) in two modes (CVVH and CVVHDF) across seven centres including 212 patients and 857 circuits analysed.[137] The first circuit analysis (n = 204 circuits) demonstrated a significant improvement in median circuit life with RCA compared with regional heparin (39.2 vs. 22.8, log-rank $p = 0.0037$). In addition, when all circuits were analysed (n = 857), those anticoagulated with a regional heparin technique were more likely to experience circuit clotting than those treated with a regional citrate regimen (HR 2.03, 95% CI 1.36–3.03; $p < 0.0005$).[139]

A recent meta-analysis of these 11 RCTs using regional citrate concluded that an RCA technique reduced the risk of circuit clotting compared with either regional heparin (HR 0.52, 95% CI 0.35–0.77; $p = 0.001$) or systemic heparin (HR 0.76, 95% CI 0.59–0.98; $p = 0.04$).[140] Citrate was also shown to reduce the incidence of filter failure (HR 0.70, 95% CI 0.50–0.98; $p = 0.04$).[110] The current KDIGO Clinical Practice Guidelines released in 2012 recommend the use of a regional citrate technique for anticoagulation in CRRT in patients who do not have contraindications to citrate (e.g., liver failure).[141] Since the publishing of these guidelines to aid clinical practice, there have been four RCTs

demonstrating circuit life advantages of RCA over heparin in CRRT for AKI, further validating citrate as the first choice anticoagulant to prevent premature clotting in the EC circuit.

2.3.2 No Anticoagulation

Given concerns about the costs and complications of various anticoagulation regimens, one simple technique in patients at risk of bleeding is to perform CRRT with 'no anticoagulation'. This technique has been reported in the literature in a sub-group of patients who require CRRT and who are considered at high risk of bleeding.[66, 72, 80] One prospective observational study identified that because of abnormal coagulation (auto-anticoagulation) status of critically ill patients, 50% of patients requiring CRRT received no anticoagulation.[142] Further, these EC circuits still achieved an acceptable lifespan (>15 h) with no increase in risk to the patient.[142]

2.3.3 Summary of anticoagulation strategies to extend circuit life in continuous renal replacement therapy

Anticoagulation is a necessary component of CRRT prescription and practice. For many years, unfractionated heparin represented the 'gold standard' and the method against which other anticoagulant agents were measured. While unfractionated heparin may be an effective agent in the prevention of premature clotting in CRRT, it has significant disadvantages for the critically ill patient. RCA for CRRT was established in the 1990s as an alternative to heparin, with the potential advantage of efficacy and reduced bleeding risk to patients. Despite theoretical advantages, citrate has not been readily adopted by clinicians because of its perceived complexity and association with single-centre and cohort studies. Over the past decade, the development of novel citrate formulations and diluted citrate solutions, and the advancement in specific CRRT machine software, have revolutionised the technique and given more opportunity for its application in many ICUs. As a result, large multicentre studies have demonstrated superiority of citrate over other anticoagulant techniques, and citrate should now be considered the 'first choice' CRRT anticoagulation method.

2.4 Non-anticoagulation factors that may influence circuit life

Thrombogenesis of the EC circuit is thought to be multifactorial but centred around platelet and intrinsic coagulation activation. The anticoagulation agents discussed may

play an important role in inhibiting this process and thereby extending circuit life. However, despite their perceived effectiveness, other non-anticoagulant factors may influence the success or failure in maintaining CRRT circuit patency. Vascular access, biocompatible membranes and circuits, circuit design characteristics, blood flow mechanics, CRRT modality, machine design and staff expertise may affect clotting activation and therefore may be considered independent factors in the duration of each circuit life. These variables will now be discussed in more detail.

2.4.1 Vascular access catheters

To establish CRRT, it is necessary to create a blood flow outside the body: an EC circuit. The blood is accessed from the venous circulation of the patient via a catheter placed in a large vein. Blood is withdrawn from the vein and returned to the same vein by means of a double-lumen (dual) catheter. This catheter must be small enough to be placed into a vein but large enough to provide blood flows of up to 300 mL/min into the CRRT circuit.[143] Placement of the catheter is usually in the femoral or internal jugular vein, and occasionally the subclavian vein.[144] A well-functioning vascular access catheter is a prerequisite for successful application of CRRT.[96, 145, 146] Access catheters are a common cause of circuit failure in CRRT, and many clinicians are unaware of the impact catheter design and placement have on patency of the EC circuit.[147]

Most temporary vascular access catheters are made of synthetic polymers such as polyurethane and silicone, which provide adequate structure, softness and biocompatibility.[145] Silicone is considered softer with less chance of vascular perforation and is the material of choice when longer-term access is required. Polyurethane catheters are considered semirigid, which makes the device easier to insert and less prone to kinking and therefore blood flow interruptions.[148] Semirigid catheters are favoured over more rigid catheters to avoid vessel wall damage or damage to surrounding epithelium during insertion, which may initiate the activation of the clotting cascade.[147] The materials used to manufacture access catheters may affect clotting and circuit life. While at present there is no evidence supporting greater circuit patency with a specific biocompatible material, one RCT has demonstrated better CRRT circuit patency rates with the addition of an antibacterial surface coating to a standardised polyurethane catheter compared with the same catheter without modification.[149] Meier and colleagues reported significantly less clotting and dysfunction in the surface-treated catheter as well as a significant reduction in infection rates.

For access catheters to be successful, they must provide reliable and constant blood flow. Access catheters vary in design (shape), length and diameter (French gauge, Fr). Venous access catheters that are used for CRRT are dual-lumen catheters, where blood is drawn into one lumen or 'tunnel' of the catheter and returned via a secondary parallel 'tunnel'. These lumens vary in shape from a side-by-side circular 'O' design (Figure 2.2) to a flatter 'D' design (Figure 2.3). Other designs termed 'coaxial' consist of two lumens that run non-parallel, where one inner lumen is surrounded by an outer lumen with side holes that draw blood into the catheter. Blood flow through catheters with an end-hole design such as the 'O' and 'D' is thought to be laminar, which is optimal, whereas flow through side holes is turbulent, which is thought to contribute to early clotting. One study suggests that the side holes, which are a characteristic of the coaxial design (Figure 2.4), cause sufficient resistance and negative pressure to draw the catheter tip against the vessel wall at higher BFRs, causing blood flow interruptions.[150]

The relationship between catheter design and resistance to blood flow has also been demonstrated, with the side-by-side 'O' design generating the least resistance to blood flow.[151] An ex vivo study by Naka and colleagues investigated catheters differing in terms of diameter and length, and found that the larger lumen catheters (14 Fr) had significantly lower resistance to blood flow than small gauge catheters (11.5 Fr).[152] The investigators also reported that despite popular belief that increasing the length of catheters would increase the blood flow resistance, there was no significant difference in resistance between 'short' (13.5 cm) and 'long' (24 cm) catheters.

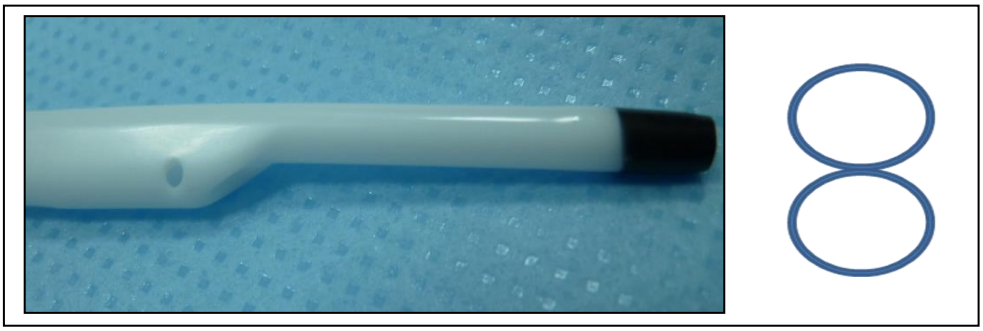


Figure 2.2: Bard Niagara catheter featuring double 'O' design.

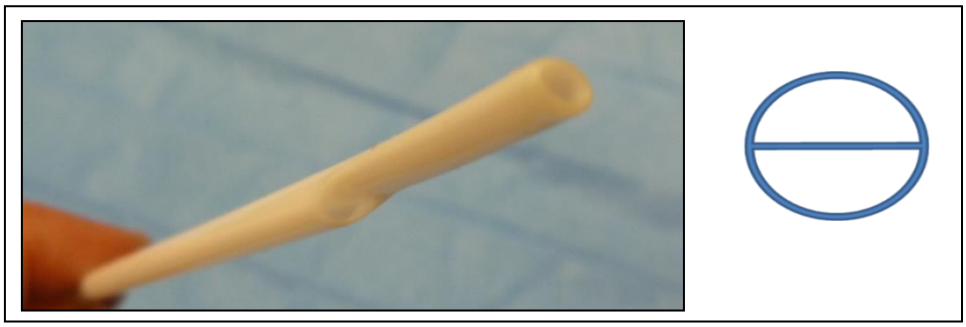


Figure 2.3: Gambro Dolphin Protect featuring double 'D' design.

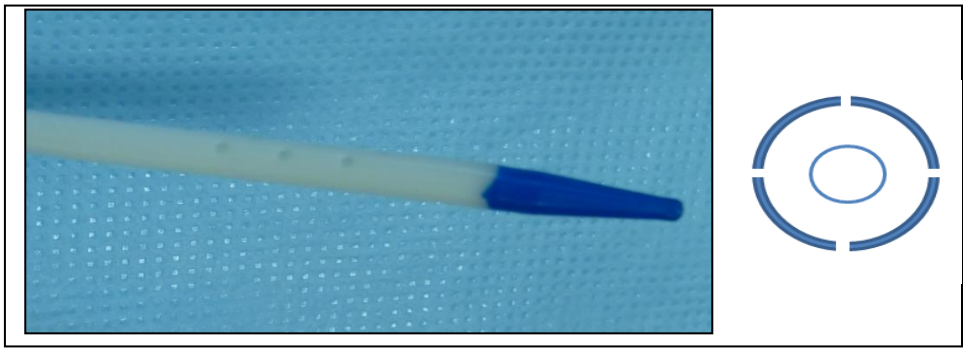


Figure 2.4: Arrow catheter featuring coaxial design.

2.4.1.1 Mechanical failure and vascular access catheters

Recent studies have highlighted the impact that access catheters may have on circuit life.[57, 153, 154] The term 'mechanical failure' has been used to describe either the terminal or intermittent failure of the access catheter to maintain blood flow at the prescribed rate. Terminal mechanical failure may be a result of clot formation within the access device or permanent kinking of the catheter leading to significant blood flow obstruction. Temporary failure may be the result of temporary kinking or obstruction due to patient movement during agitation, positional changes, excessive hip flexion with the use of femoral catheters or coughing with subclavian or jugular venous access. Baldwin and colleagues were the first to demonstrate that there was a relationship between nursing and patient care activities and reductions in blood flow that led to eventual circuit dysfunction.[150] They further reported that the blood flow reductions or even cessation of blood flow may not always trigger machine alarms to notify the bedside clinician to then make appropriate responses. In contrast to these findings, Wang et al.[155] investigated the impact of early mobilisation on CRRT and reported an increase in circuit life when patients were exposed to more frequent position changes including passive leg exercises, sitting and standing for physiotherapy.

Recently, a retrospective observational study set out to quantify for the first time the incidence of mechanical failure in one ICU. They reported that 'likely mechanical failure' was responsible for the loss of one in eight CRRT circuits when femoral venous access was solely used.[57] In a separate study, the same group investigated the relationship between insertion site and patient body position on circuit life in CRRT with femoral access catheters. They reported that circuit life was significantly longer in patients with right-sided femoral catheter insertion sites; however, no correlation between the patient's position (supine, right side lying or left side lying) and circuit longevity was observed.[154] Despite some evidence from observational and retrospective studies, there are no randomised studies in critically ill patients that evaluate catheter design or insertion site on circuit life in CRRT.[156] Without direct comparative studies for catheter location, a recent meta-analysis indicated a possible preference towards femoral site over internal jugular, with a 27% increase in circuit survival.[157] The review, using pooled data of 2173 circuits, reported that the subclavian access site was associated with significantly worse circuit life compared with the femoral access site, with the internal jugular position no different from femoral positioning.[157] These more recent findings are at odds with current KDIGO guidelines that recommend the right internal jugular vein as the preferred site for access for CRRT but may reflect the observational evidence available at their time of release.[158-160]

2.4.2 Modality and circuit life

It is generally accepted that a more diffusive-based CRRT approach is associated with longer circuit life than convective therapies.[161, 162] Convective techniques such as CVVH remove plasma water from the blood, increasing blood viscosity at the terminal end of the haemofilter, which in turn may lead to increased clogging and clotting at this site. In addition to haemoconcentrating the blood and altering serum haematocrit, the haemofilter fibres are exposed to a greater concentration of platelets and coagulation factors, which may further increase the likelihood of clotting.[102, 156] Diffusive modes of RRT, such as CVVHD and CVVHDF, allow for higher solute clearance despite requiring lower prescribed blood flow speed within the EC circuit, and may therefore also affect circuit survival.[156] There are two RCTs comparing the CVVH mode with the CVVHD and CVVHDF modes.[163, 164] In 2006, Ricci et al. conducted a prospective crossover study of 30 circuits comparing CVVH with CVVHD at a dose of 35 mL/kg/h. Median circuit lifespan was significantly longer in the CVVHD group (37 h vs. 19 h, $p = 0.03$).[164] In 2008, Davies et al. validated these findings in a similar crossover study comparing pre-

dilution CVVH with pre-dilution CVVHDF in 43 patients and 96 circuits with a dose of 35 mL/kg/min. In this study, CVVHDF was superior in terms of median circuit life (16 h vs. 6 h, $p < 0.001$); however, both groups had much reduced circuit longevity compared with the earlier study, without any discernible explanation.[163] A recent meta-analysis of non-anticoagulant factors by Brain and colleagues concluded that CVVHD and CVVHDF were associated with a 44% lower failure rate (clotting) compared with CVVH, confirming the theoretical advantages of diffusive modes with respect to circuit longevity.[157]

2.4.3 Machine design and extracorporeal circuit characteristics

From the initial adaptive technology, specific CRRT machines have been designed to enable safe and potentially reliable performance. These machines have made a significant number of technological advances since their development; however, many of the design features of both the machine and the circuit have remained from intermittent dialysis platforms. These features have been examined for their impact on circuit life and are discussed below in more detail.

2.4.3.1 Machine platforms

Although the first CRRT treatments were performed using circuits driven by native arterial blood pressure (continuous arteriovenous haemofiltration [CAVH]), it is in the form of roller-pumped venovenous therapy that CRRT became an accepted and widely used technology.[52, 67, 165] The adoption of this technology was based on improved solute clearance and the safety of not cannulating large arteries.[166] Initially, the machines or platforms utilised for CRRT were 'adapted' components from dialysis machines.[167] The rapid development in electronics in the early 1990s led to more purpose-built CRRT machines specifically designed for continuous therapies use in the ICU.[167, 168] These machines are now equipped with integrated safety alarms, fluid balancing controls and connected blood modules capable of performing CVVH, CVVHD and CVVHDF as well as adjunctive therapies such as plasma exchange and haemoperfusion.[168]

The integration of purpose-built hardware (machine) and continuously updated software has allowed the introduction of this therapy into most ICUs, where previously the patient might have required referral to larger metropolitan hospitals for treatment. Machines have been designed to provide easy set-up and treatment options, which have enabled units with less experienced staff to adopt the therapy for AKI. However, some machine and

software designs that instruct the bedside nurse 'through' the treatment do not easily allow for intervention or 'troubleshooting' and may limit the ability of the expert nurse to maintain the therapy during short-term technical issues such as mechanical problems. The more intuitive or sensitive the machine and the less reliant it is on clinician intervention, the more likely it is to impose 'rules' where the machine instructs the nurse to 'end treatment', often prematurely and in response to conditions that are temporary. This may lead to a reduction in circuit longevity in lieu of all other factors.

2.4.3.2 Roller pump

Most CRRT machines use a mechanical roller pump similar to cardiopulmonary bypass machines to draw blood from the 'access' or 'arterial' lumen of the access catheter and pump forward through the artificial membrane and the remaining EC circuit back to the 'return' or 'venous' lumen of the catheter. The roller pump design compresses plastic tubing as the pump head rotates, drawing blood into the roller pump tubing and expelling it forward into the EC circuit. The bedside nurse sets the BFR (e.g., 200 mL/min), which then determines the number of revolutions of the roller pump head. The use of roller pump designs to circulate blood may affect circuit life. It has been reported that despite setting the BFR at a predetermined level, the actual or real blood flow may vary by as much as 30–40 mL/min without operator awareness.[59] Baldwin and colleagues proposed that these blood flow variations and reductions create backflow of blood from the roller pump, blood flow stasis and eventual circuit clotting. In addition, the action of the roller pump compressing blood-filled tubing may cause blood cell stress (platelets and red cells) and therefore activation of the coagulation cascade within the EC circuit.[169]

2.4.3.3 Bubble trap—Venous (air trap chamber)

Many CRRT circuit designs incorporate a gas or air bubble trap into the venous side of the EC circuit as a safety mechanism to prevent air entering the patient. The bubble trap allows blood and replacement fluid to enter the circuit while providing a chamber for any inadvertent air to collect. At the bottom or exit path of the venous chamber is a microfilter to collect blood impurities and therefore prevent microthrombus entry into the patient's venous circulation. There are two recognised areas of clot formation within the venous chamber. First, at the top of the chamber there is a blood and gas interface so that blood has direct contact with air and carbon dioxide (Figure 2.5). This exposure of the blood to gases leads to activation of the coagulation cascade, and turbulent blood flow causes cell smearing and deposition of cells against the internal wall of the venous chamber.[169-171]

Eventually, there is blood clot formation, and ultimately obstruction to blood flow and circuit malfunction may occur. Second, a build-up of cells and debris at the bottom of the chamber leads to obstruction and clotting over the surface of the micro-aggregate filter (Figure 2.6).[172] There have been some attempts to limit clotting within the chamber by adding heparin or replacement fluid directly into the chamber during treatment, with limited success.[173, 174] Baldwin et al. in 2012 investigated the impact of a modified bubble trap design where blood entered the chamber horizontally to create a vortex effect within the space, but failed to demonstrate a circuit life difference compared with conventional designs.[175]

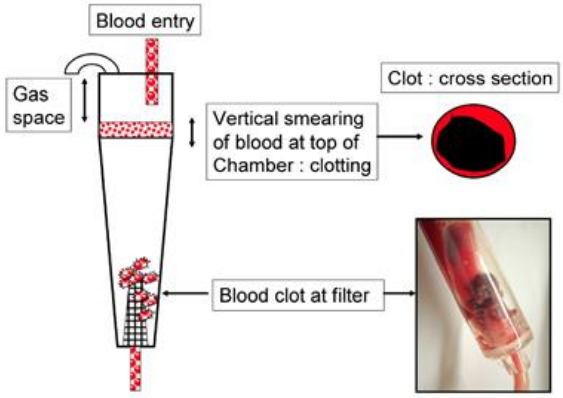


Figure 2.5: Venous bubble trap.

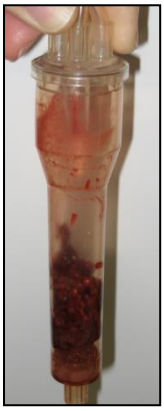


Figure 2.6: Clot formation on the micro-aggregate filter.

2.4.3.4 Membranes (haemofilter)

The properties of the artificial membrane (haemofilter) (Figure 2.7) may play an important role in determining circuit life. Modern CRRT machines incorporate biocompatible membranes that have been designed to decrease the reactivity of the blood to a large surface area of foreign material, which may initiate the intrinsic pathway of the

coagulation cascade.[69] Clotting processes within these haemofilters are influenced by the electro-negativity of the membrane, its ability to bind plasma proteins, activation of the complement system and adhesion of platelets to the membrane surface.[96] The addition of heparin to the EC circuit during the priming process to 'coat' the haemofilter is suggested by various authors to be a useful strategy to prevent clotting.[75, 102, 170] There is limited evidence to suggest this has an effect on all haemofilter membranes; however, plastic and membrane surfaces do adsorb heparin, particularly after treating to neutralise negative charge, and this procedure is therefore considered a worthwhile preventative measure to inhibit clotting.[176, 177]

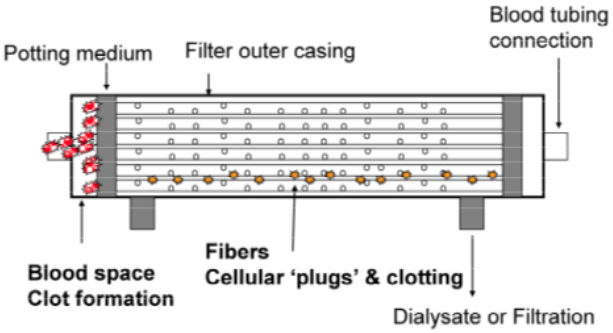


Figure 2.7: Membrane or haemofilter clotting process.

Few studies have evaluated the influence that various membrane materials such as polyacrylnitrile, polysulfone and polyethersulfone have on circuit life in CRRT. It has been reported in one non-randomised study that synthetic membranes with fewer adsorptive properties, such as polyamide, have a reduced tendency to clotting compared with acrynitrile.[90] Modification (so-called surface treatment) of existing membranes (AN 69 ST) to increase heparin binding has shown some promising results in increased circuit life.[176] However, when tested, there was no significant difference in circuit life compared with non-surface-treated membranes (AN 69) in two randomised studies.[178, 179] While newer synthetic membranes with various polyethersulfone materials are being developed to improve biocompatibility and decrease platelet and coagulation activation,[180] there have to date been no large RCTs to evaluate the type of membrane and its influence on circuit life in CRRT.

Another physical property that may influence circuit survival is the length and surface area of haemofilter. Theoretically, haemofilters with more fibres, which are shorter in length and result in larger surface areas, provide less resistance to blood flow and may

prevent clogging of the membrane.[181] However, this has not been demonstrated in two observational studies. Dungen and colleagues reported that when comparing two polysulfone haemofilters, the membrane with longer hollow fibres recorded lower transmembrane pressures (TMPs) and longer filter survival times.[182] In addition, one study comparing surface areas of 0.75 m^2 and 1.3 m^2 failed to demonstrate a difference in circuit patency times when it was hypothesised that a larger surface area with more fibres would provide less blood flow resistance and take longer for membrane fouling and clotting.[173]

2.4.4 Circuit patency and substitution fluids administration

In the CRRT modes of CVVH and CVVHDF, plasma water is removed from the blood across the semipermeable membrane of the haemofilter fibres in a process known as 'convection'. Convection requires pressure within the filter fibres to separate the blood, forcing plasma water and along with it solutes through the membrane and out of the haemofilter to be discarded as waste.[183] The waste is termed ultrafiltrate. To achieve higher solute clearance, the amount of plasma water removed or ultrafiltrate rate per hour must also increase.[184] To prevent hypovolaemia or intravascular plasma water depletion, the administration of an electrolyte replacement or substitution fluid is required to maintain the patient's intravascular volume status.[185] These replacement fluids can be administered into the blood-filled EC circuit ahead of the haemofilter (pre-dilution) or into the venous chamber after the haemofilter (post-dilution).

The pre-dilution method effectively dilutes the blood entering the filter, decreasing haemoconcentration, blood viscosity and serum haematocrit, and thereby reducing membrane fouling as plasma water is removed.[186] Pre-dilution theoretically decreases solute clearance as a significant portion of the plasma water removed across the membrane will be the pre-dilution replacement fluid containing few waste products.[187] One small randomised crossover-design study and one observational study found delayed filter clotting and improvement in circuit life in CVVH when pre-dilution was compared with post-dilution fluid replacement.[188, 189] Van der Voort and associates[107] however demonstrated that the post-dilution method was associated with a significantly higher solute clearance than the pre-dilution method, while Uchino and colleagues[190] reported no difference in daily creatinine levels and therefore no reduction in solute clearance over a 24 h period. If pre-dilution increases circuit life, then the time spent resetting the treatment after circuit clotting (downtime) is reduced. This reduction in downtime more

than compensates for the theoretical treatment efficiencies gained through the post-dilution method while also reducing costs associated with nursing time and consumables required.[188]

2.4.5 Staff training and expertise

Safe and skilled use of CRRT machines require structured nursing education and training activities with theoretical and practical components.[191] An inability to manage or correct simple alarm events contributes to stasis of blood flow, early filter clotting and perhaps patient harm.[156] Despite current sophisticated machines using advanced troubleshooting prompts and automated alarms to provide a safety net for bedside use, these are not absolute in respect to the human–machine interface.[192] The success of the therapy may be heavily influenced by staff that are not adequately trained or prepared to set up, manage, troubleshoot and monitor the therapy in use for a critically ill patient.[186]

A comprehensive education programme that has a foundation in theory and incorporates practical learning is best placed to meet the demands of critical care nurses who are novices in respect to CRRT.[193] For more advanced troubleshooting concepts, there are many strategies to train nurses, including simulation set-up of the machine and EC circuit, interactive video activities of these alarms and simple tutorial activities.[170, 194] All of these are useful towards providing safe and successful therapy and adjunctive strategies for maintaining circuit patency. Bedside records of circuit life are useful and important data to review the maintenance of expertise in the therapy.[192, 195] This type of circuit patency or circuit life audit provides useful feedback to teachers, particularly when circuit 'life' is poor (e.g., <6 h). Repeated events of this outcome can reflect the adequacy of nursing education and reiterate the current training needs.

2.5 Patient-related factors that may influence circuit life in continuous renal replacement therapy

Patient factors such as illness type, pathophysiology, pathology and coagulopathy may have a causal relationship on CRRT success and maintenance of circuit life. Alterations in circulating blood factors, anti-inflammatory or proinflammatory mediators, or toxins may lead to either an increase or a decrease in circuit life. In addition, the effect of anticoagulation drug strategies may be impaired or compromised because of major organ failures such as those involving the liver, bone marrow, vascular endothelium or haematological system.

2.5.1 Blood factors

There appears to be an association (inverse relationship) between platelet count and circuit life as outlined in a recent systematic review and meta-analysis.[157] Many papers investigating filter and circuit life have reported this as a secondary finding to the primary question or analysis.[190, 196-198] De Pont and colleagues have postulated the causative mechanism is due to shear stress within the membrane, where platelets are activated within the fibres, causing platelet deposition and excessive clotting.[199] They further contend the association between platelet count and premature clotting is more likely in post-dilution forms of CRRT, where higher haematocrit and blood viscosity may potentiate excessive platelet activation.[199]

There does not appear to be an association between haemoglobin level and circuit life; however, one single-centre study has suggested that higher white blood cell count (neutrophils) may lead to premature clotting in CRRT circuits.[200]

2.5.2 Coagulation parameters

While there are no observational studies focusing on APTT and hours to clotting in the CRRT circuit, pooled data suggest that for every 1 s increase in APTT, an increase in the odds of circuit survival exists.[157] There does not appear to be a similar association for international normalised ratio (INR) or prothrombin time.[157] Higher fibrinogen levels have been shown to induce premature clotting in one study[200]; however, this is not consistent with other reports that suggest no such correlation exists.[201]

2.5.3 Patient pathology

As previously suggested, there is a significant association between sepsis and the development of AKI in the critically ill patient.[22, 23-25] In early sepsis, activation of the coagulation system is triggered by proinflammatory cytokines that increase the expression of tissue factor endothelial cells and at the same time downregulate natural anticoagulants, thus initiating thrombin generation, subsequent activation of platelets and inhibition of fibrinolysis.[202] The influence of this proinflammatory, increased coagulation state of the patient and the interaction between artificial surfaces of the EC circuit and potential premature clogging and clotting is not well understood.[96] Despite the large cohort of patients requiring CRRT diagnosed with sepsis, there has been no report focused towards the direct influence of sepsis on circuit life in CRRT.

There appears to be a clear association between circuit lifespan and patients diagnosed with liver failure.[203] The complex pathology associated with the auto-anticoagulated state in liver failure and shortened circuit lifespan is well reported.[203-206] One large retrospective report from 79 patients and 539 circuits established correlations between MELD score, bilirubin level, APTT, platelet count and INR as significant variables associated with CRRT circuit life in this specific patient population.[206]

2.6 Influence of blood flow rate (blood pump speed)

The optimum BFR for CRRT is not well established. In the literature, BFRs have been reported between 80 mL/min[142] and 350 mL/min.[149] BFR may vary in accordance with the mode of CRRT (CVVH, CVVHD and CVVHDF), location (country and hospital), unit policies and guidelines, as well as individual clinician (medical and nursing) preference. A 2005 worldwide survey of 23 countries conducted by the BEST Kidney study investigators demonstrated great variability in practices, particularly in respect to mode of therapy and BFR.[48] Despite this worldwide variability in practice, they concluded that the most common setting for BFR in CVVH and CVVHDF was 150–200 mL/min.

A practice survey conducted in ICUs in Australia and New Zealand in 2004 concluded that the blood pump speed was consistent with the BEST Kidney study findings, with a common setting of 150–200 mL/min in both CVVH and CVVHDF.[66] It is generally accepted that a higher BFR (>200 mL/min) decreases the tendency for circuit clotting. With the advent of improved machine capabilities and the ongoing investigation into higher-intensity (dose) CRRT, there has been a gradual implementation of higher BFRs (>250 mL/min) to match increasing ultrafiltration rates.[207]

BFR appears to be central to every non-anticoagulant factor affecting circuit life. The prescribed speed of blood flow will have a direct effect on the ability of the vascular catheter to maintain access and flow of blood into and out of the EC circuit. Higher BFRs will highlight any flaws in access design, material, diameter and length. Higher BFRs require more revolutions of the roller pump and create more turbulent flow within the venous chamber, possibly promoting premature clotting within the circuit. The impact of blood pump speed on membrane design or size has not been established; however, higher BFRs theoretically create greater TMPs within the haemofilter—a clinical indicator that may prompt staff to cease treatment prematurely.

The requirement for faster blood flows may generate higher circuit pressures, leading to frequent alarm conditions exposing novice or inexperienced staff to troubleshoot unfamiliar machines. This may in turn lead to lengthy periods of blood stasis and activation of clotting within the circuit and haemofilter. If indeed mechanical failure is a significant issue relating to the 'success' of maintaining the therapy, higher BFRs may exacerbate frequency of temporary mechanical failures.

One RCT has included BFR in the assessment of circuit clotting in CRRT, indicating that a BFR of >125 mL/min did not improve circuit survival.[208] This study was conducted in CVVHD mode, which is rarely used in current practice.[208-213] Pure diffusive modes of haemofiltration such as CVVHD have been shown to be associated with decreased procoagulatory activity in the dialyser membrane compared with convective modes[164, 214] and make comparisons with CVVH and CVVHDF problematic.

One single-centre study assessing 1332 treatments from 355 patients concluded that BFR did indeed affect circuit life.[60] In this retrospective audit, the authors suggested that BFRs below 200 mL/min significantly decreased circuit life compared with rates above 200 mL/min. They also determined that BFRs above 300 mL/min led to lower median circuit life and recommended an optimal BFR of 250–300 mL/min.

Despite many authors recommending a BFR of 200–250 mL/min for CRRT[60, 195, 215] and international surveys indicating practical prescriptions of >200 mL/min, there has been no endorsement for this setting. The 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.[216] The more recent KDIGO consensus guidelines outline settings for different RRT modalities, indicating that 150–250 mL/min is typically prescribed for CRRT modes such as CVVH and CVVHDF but make no recommendations for practice based on evidence.[217]

2.7 Summary of literature review

Circuit life and patency of the CRRT EC circuit have been the subject of significant research in the past decades. Much of this literature has focused towards drug or anticoagulant interventions to extend circuit life to provide an uninterrupted form of the therapy to enhance treatment efficiency. In the past decade, citrate has emerged as the safest, and most cost efficient and effective form, of anticoagulation for CRRT and has been recommended in many worldwide practice guidelines.

In addition to testing anticoagulation strategies, many authors have recognised the impact that more practical aspects of the therapy may have on its successful application in the treatment of AKI in the critically ill patient. Vascular access, access site, mode of therapy, membranes, circuit design and staff training are variables that have been investigated for their impact on circuit life. This review has highlighted other patient-related factors such as illness type (patient pathology) and blood abnormalities that may interact with the treatment, causing premature failures and clotting.

What is clear is that the relationship between BFR and circuit patency has not been explored or tested adequately. While some authors have proposed or hypothesised the prescription of higher BFRs to prolong circuit life, this has been based on theoretical concepts, retrospective data or expert opinion. At present, there is no evidence from controlled studies to guide clinicians for this potentially important prescription setting. This represents a significant gap in the understanding of one of the pillars of any EC circuit—that is, what speed should the blood travel through the circuit. Evaluation of BFR and the impact (if any) on circuit life is vital to inform clinical practice, gain new understanding and potentially optimise the therapy in this vulnerable patient group. An evaluation of current prescription practices in respect to BFR settings in CRRT is an essential step in informing the methodology for this study and is explored in Chapter 3.

Chapter 3: Establishing Current Continuous Renal Replacement Therapy Practice in Australian and New Zealand Intensive Care Units

3.1 Statement of contribution to co-authored published paper

This chapter includes a co-authored paper. The bibliographic details of the co-authored paper, including all authors, are:

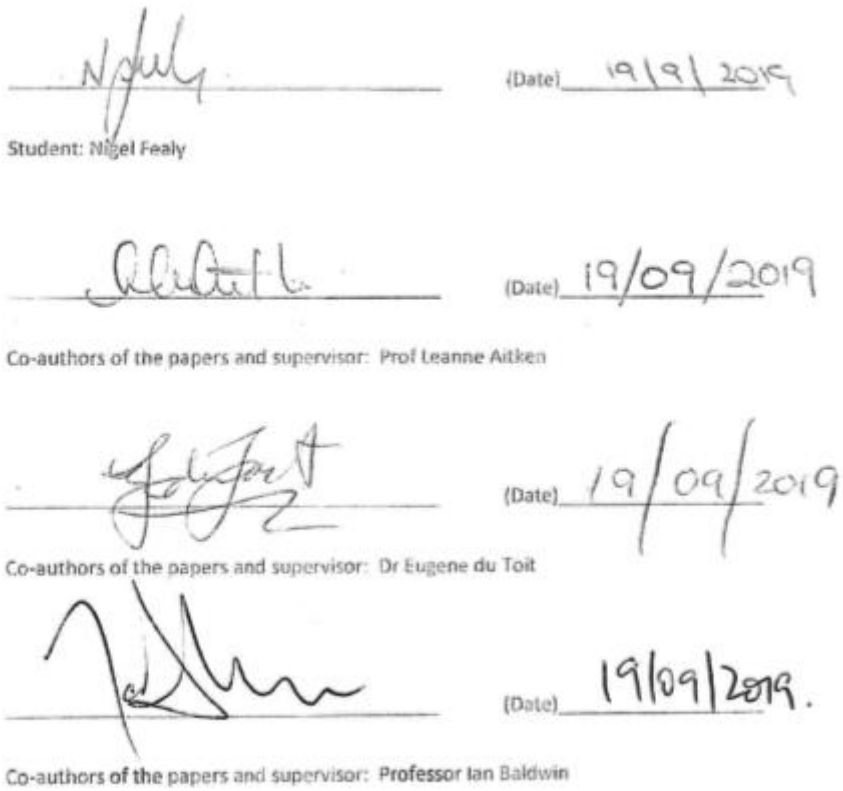
Publication 1: Nigel Fealy, Leanne Aitken, Eugene du Toit, Ian Baldwin. (2015). Continuous renal replacement therapy: Current practice in Australian and New Zealand intensive care units. *Critical Care and Resuscitation*, 17(2), 83–91.

My contribution to the paper involved:

- critical review of the literature to inform the design of the practice survey
- development of the survey method and survey tool (online)
- successful institutional ethics submission
- engaging three professional bodies (ACCCN, ANZICS Clinical Trials Group [CTG] and Intensive Care Coordination and Monitoring Unit [ICCMU])
- distribution of survey to potential participants
- data collection from returned surveys
- data analyses
- data interpretation
- writing of the manuscript
- revision of the manuscript
- approval of the final version.

I completed the research and writing of the paper with methodological and editorial advice from my PhD supervisors, Professor Leanne Aitken, Dr Eugene du Toit and Professor Ian Baldwin.

This publication is included in this thesis with copyright permission from the editors of *Critical Care and Resuscitation* in accordance with journal guidelines.



3.2 Introduction

Clot formation in the blood-filled circuit is a major obstacle for successful CRRT application. Blood flow during CRRT is set by the bedside clinician and the speed (flow rate, mL/min) is a potential important practical factor in the maintenance of a circuit where, if the flow is too slow or too fast, clotting is more likely to occur. Despite this, blood flow speed (rate) and the association of clot formation has not been well studied and reported in the literature. The BFR itself may be an important factor, or the speed of blood flow and its association with other machine and circuit variables that may promote premature clotting. To help inform our method for the intended study, it is important to establish the current practical applications of CRRT, including BFR prescription.

3.3 Understanding current clinical practice

Previous to the 'BEST Kidney' investigation into worldwide CRRT practice, little was known regarding the clinical and practical application of CRRT.[218] In 2008/9, two large multicentre RCTs (the RENAL and ATN studies) investigated the impact of CRRT

treatment ‘dose’ on mortality in critically ill patients diagnosed with AKI.[219, 220] Prior to both these seminal studies, surveys were conducted in 2003/2004 to inform investigators of the then current practice relating to technical aspects of CRRT delivery, and thereby guide trial design.[208, 221] Australian and New Zealand data from 2004 indicated a median BFR of 200 mL/min[208] with the BEST Kidney study[218], and the pre-practice US ATN study[221] reported a median rate of 150 mL/min. Interestingly, in the country breakdown, the median BFR in Japan was 80 mL/min, in contrast to 200 mL/min in Australia, the Netherlands, Portugal and the UK.

Following publication of the RENAL and ATN results, two international surveys were conducted into clinician CRRT practice to determine changes (if any) in response to these studies.[210, 222] These studies, however, focused on dose, modality and timing aspects of RRT rather than on the practical or technical application of the therapy. While no data on BFR from these recent practice surveys are reported, observational studies report practices between 100[223] and >300[60, 190] mL/min, indicating continued variability in this setting of the therapy. In addition to individual practice patterns, there has been significant enhancement in CRRT machine technology, which allows for BFRs of up to 400 mL/min. The impact that improved and more functional machines has on bedside prescription has not been established. To better advise our trial design and method, a prospective survey of the current practices of CRRT in Australian and New Zealand ICUs was conducted.

3.3.1 Ethics review

The approval of the Human Research Ethics Committees (HREC) of Austin Health was obtained prior to commencement of the practice survey. Austin Health HREC deemed the survey to be Low and Negligible Risk Research and approved the study without further review (see Appendix 1).

3.4 Publication 1: Continuous renal replacement therapy: Current practice in Australian and New Zealand intensive care units

Continuous renal replacement therapy: current practice in Australian and New Zealand intensive care units

Nigel Fealy, Leanne Aitken, Eugene du Toit and Ian Baldwin

ABSTRACT

Background: Large multicentre studies of continuous renal replacement therapy (CRRT) in critically ill patients may influence its bedside prescription and practical application. Despite this, many aspects of CRRT may not be informed by evidence but remain a product of clinician preference. Little was known about current CRRT practice in Australia and New Zealand and it is not known if the evidence from recent studies has been integrated into practice.

Design and setting: A prospective online survey of CRRT practice was sent to intensive care unit medical and nursing clinicians via three national databases in Australian and New Zealand ICUs in December 2013 to March 2014.

Results: There were 194 respondents from 106 ICUs; 49 ICUs (47%) were in tertiary metropolitan hospitals. One hundred and two respondents (54%) reported continuous venovenous haemodiafiltration as the most common CRRT technique, with a combination of predilution and postdilution of CRRT solutions. The prescription for CRRT was variable, with respondents indicating preferences for therapy based on L/hour (53%) or a weight-adjusted treatment in mL/kg/hour (47%). For all modes of CRRT, the common blood flow rates applied were 151–200 mL/minute and 201–250 mL/minute. Few respondents reported preferring flow rates < 150 mL/minute or > 300 mL/minute. Unfractionated heparin was the most commonly used anticoagulant (83%), followed by regional citrate. Femoral vein vascular access was preferred and, typically, a 20 cm length catheter was used. Bard Niagara and Arrow catheters were most frequently used. The Gambro Prismaflex was the dominant machine used (71%).

Conclusions: Our results provide insight into existing clinical management of CRRT. There is considerable variation in the prescription of CRRT in Australian and New Zealand ICUs.

Crit Care Resusc 2015; 17: 83–91

Acute kidney injury (AKI) is a significant and recognised complication of critical illness that affects 2%–7% of hospitalised patients[1-3] and up to 34% of critically ill patients.[4-6] AKI can result in severe derangements in fluid, electrolyte and acid–base balance requiring the intervention of supportive strategies. The use of renal replacement therapy (RRT) forms a key component in the treatment for severe AKI and its use is required in up to 5%–6% of all critically ill patients in intensive care units.[7]

The technical application of RRT has been highlighted in recent years with several large, multicentre, randomised controlled trials[8,9] investigating RRT technique and "dose", and its association with mortality as the primary outcome. In the Randomized Evaluation of Normal Versus Augmented Level (RENAL) study, 1464 patients receiving continuous renal replacement therapy (CRRT) (specifically, continuous venovenous haemodiafiltration [CVVHDF]) were explored at different dose intensities, and the results indicated no difference in the 90-day mortality.[8] Similarly, in the Acute Renal Failure Trial Network (ATN) study, 1124 patients receiving intermittent haemodialysis (IHD), slow low-efficiency daily dialysis (SLEDD) and CVVHDF, at different dose intensities, also showed no difference in the 60-day mortality.[9] Technical information on the application of RRT for the treatment of AKI was illustrated in several prestudy practice surveys.[10,11] Technical aspects such as modality, dose, dose prescription, replacement or dialysate fluid type, blood flow rate, predilution and postdilution for replacement fluid and machine types were explored in detail. More recently, two international groups have investigated the current management, practices and practitioner beliefs after the dissemination of results from the RENAL and ATN trials.[12,13] Of particular importance is whether CRRT practices have changed in response to these studies. These later surveys have concentrated on dose, modality and timing of RRT with limited information about practical or technical aspects of the application of therapy.

To date there have been no data published describing alteration in practice for Australian and New Zealand ICU clinicians following outcomes of the RENAL or ATN studies. In addition to practice changes following the results of these studies, there have been significant enhancements to capacity and flexibility in functionality of CRRT machines since the practice survey conducted in 2004 before the RENAL study. This improvement in machine design and functionality may have prompted changes to prescribing practices of CRRT in many Australian and New Zealand ICUs.

The aim of our survey was to establish the current practical prescription of CRRT in ICUs caring for adult and paediatric patients in Australia and New Zealand.

Table 1. Profile of survey respondents ($n = 194$)

Variable	*n* (%)
State, territory or New Zealand island	
Australian Capital Territory	3 (1.5%)
New South Wales	51 (26.3%)
Northern Territory	5 (2.6%)
Queensland	36 (18.6%)
South Australia	18 (9.3%)
Tasmania	5 (2.6%)
Victoria	53 (27.3%)
Western Australia	14 (7.2%)
North Island of New Zealand	8 (4.1%)
South Island of New Zealand	1 (0.5%)
Professional role	
Consultant intensivist	36 (18.6%)
Nurse unit manager (charge nurse)	11 (5.7%)
ICU-based educator	37 (19.1%)
Clinical nurse consultant	9 (4.6%)
Associate nurse unit manager (team leader)	12 (6.2%)
Clinical nurse specialist	47 (24.2%)
Registered nurse	42 (21.6%)
Hospital type	
Regional	53 (27.3%)
Metropolitan private	19 (9.8%)
Metropolitan public level 2	30 (15.5%)
Metropolitan public level 3	92 (47.4%)
ICU type	
Adult	134 (69.1%)
Paediatric	7 (3.6%)
Combined adult and paediatric	53 (27.3%)
Number of ICU beds	
0–5	8 (4.1%)
6–10	70 (36.1%)
11–15	47 (24.2%)
16–20	22 (11.3%)
> 20	47 (24.2%)
Annual CRRT treatments	
< 10	22 (11.3%)
11–25	32 (16.5%)
26–50	44 (22.7%)
51–75	18 (9.3%)
76–100	15 (7.7%)
> 100	49 (25.3%)
Don't know	14 (7.2%)

ICU = intensive care unit. CRRT = continuous renal replacement therapy.

Methods

Survey method

A descriptive online survey was distributed from December 2013 to March 2014 requesting information from clinicians about their current practical application of CRRT. A sample of ICU medical and nursing staff was accessed via three separate databases. The Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (CTG), the Intensive Care Coordination and Monitoring Unit (ICCMU) ICU Connect list server and the Australian College of Critical Care Nurses (ACCCN) databases were used to seek participants for the survey. Ethics approval was granted by the Austin Health Human Research Ethics Committee (project 04918) before study commencement. Consent to participate was implied by submission or return of the questionnaire.

Survey design

The survey was devised from the practice questionnaire used in the study of 34 Australian and New Zealand ICUs in 2004 and published in 2008, before the RENAL study.[10] The tool used for this survey was a modification of the 11-point questionnaire and consisted of 20 questions (see Appendix online at cicm.org.au/Resources/Publications/Journal). Questions on demographics included the practitioner's state or territory, study site (hospital), professional role (eg, intensivist, nurse unit manager) and type of ICU (adult or paediatric). Respondents were also asked to identify the number of beds and type of ICU (eg, metropolitan tertiary or private) and the number of patients they treated with CRRT each year. Twelve questions focused on the prescription of CRRT, including the modalities of CRRT used (ie, continuous venovenous haemofiltration [CVVH], continuous venovenous haemodialysis [CVVHD] and CVVHDF), prescribed blood flow rate, if CRRT was prescribed on the basis of patient weight or litres per hour, and if prescription was for replacement or combined with dialysate flow rates. Respondents were also asked to identify the preferred anatomical site for vascular access, the catheter type and usual length of catheter, the anticoagulation regimen used and type of machine used for CRRT.

Statistical analysis

Descriptive statistics were used for all demographic and clinical data and for all items in the survey. Data were cleaned and checked for missing values and invalid responses. The prime reporting statistics were expressed as frequencies and percentages. Statistical analyses were performed using Stata version 11 (Statacorp).

Table 2. Continuous renal replacement therapy regimens

Prescription variable	Frequency of use, *n* (%)			
	Never	Occasionally	Frequently	Always
Continuous venovenous haemodiafiltration				
Dose prescription, L/h (*n* = 156)				
1 (D) + 1 (R)	60 (38.4%)	35 (22.5%)	51 (32.7%)	10 (6.4%)
1.5 (D) + 1.5 (R)	52 (33.3%)	45 (28.9%)	56 (35.9%)	3 (1.9%)
2 (D) + 2 (R)	61 (39.1%)	55 (35.3%)	30 (19.2%)	10 (6.4%)
> 2 (D) + > 2 (R)	110 (70.5%)	34 (21.8%)	7 (4.5%)	5 (3.2%)
Dose prescription, mL/kg/h (*n* = 117)				
0–15	90 (77%)	18 (15.4%)	6 (5.1%)	3 (2.5%)
16–25	27 (23%)	23 (19.7%)	44 (37.6%)	23 (19.7%)
> 25	41 (35%)	30 (25.6%)	31 (26.6%)	15 (12.8%)
Blood flow rate, mL/min (*n* = 177)				
0–50	168 (94.9%)	6 (3.4%)	3 (1.7%)	0 (0)
51–100	152 (85.8%)	15 (8.5%)	10 (5.7%)	0 (0)
101–150	85 (48%)	62 (35%)	25 (14.1%)	5 (2.9%)
151–200	24 (13.6%)	48 (27.1%)	80 (45.2%)	25 (14.1%)
201–250	57 (32.2%)	39 (22.1%)	68 (38.4%)	13 (7.3%)
251–300	92 (52%)	44 (24.9%)	35 (19.8%)	6 (3.3%)
> 300	155 (87.6%)	17 (9.6%)	2 (1.1%)	3 (1.7%)
Continuous venovenous haemofiltration				
Dose prescription, L/h (*n* = 156)				
≤ 2	116 (74.4%)	29 (18.5%)	4 (2.6%)	7 (4.5%)
2–3	105 (67.3%)	20 (12.8%)	27 (17.3%)	4 (2.6%)
> 3	120 (76.9%)	22 (14.1%)	12 (7.7%)	2 (1.3%)
Dose prescription, mL/kg/h (*n* = 117)				
0–15	108 (92.3%)	8 (6.8%)	1 (0.9%)	0 (0)
16–25	89 (76%)	17 (14.5%)	9 (7.7%)	2 (1.7%)
> 25	86 (73.5%)	12 (10.3%)	16 (13.7%)	3 (2.5%)
Blood flow rate, mL/min (*n* = 89)				
0–50	82 (92%)	5 (5.6%)	2 (2.4%)	0 (0)
51–100	76 (85.4%)	11 (12.3%)	2 (2.3%)	0 (0)
101–150	53 (59.6%)	31 (34.8%)	5 (5.6%)	0 (0)
151–200	17 (19.1%)	19 (21.3%)	38 (42.7%)	15 (16.9%)
201–250	25 (28%)	20 (22.5%)	35 (39.3%)	9 (10.2%)
251–300	40 (45%)	25 (28%)	21 (23.6%)	3 (3.4%)
> 300	74 (83%)	11 (12.4%)	2 (2.3%)	2 (2.3%)

(D) = dialysis. (R) = replacement.

Results

Characteristics of the cohort

Survey invitations were emailed to 4105 potential participants via ACCCN (1853 participants), ICCMU (1652) and the ANZICS CTG (600) membership databases. There is likely to have been duplication between these databases, with an unknown number of people appearing on two or all three databases, so it was not possible to know the precise number of invitees. Respondents totalled 194, and 106 intensive or critical care units from Australia and New Zealand were represented. Most respondents came from New South Wales (26.3%) and Victoria (27.3%), and most worked in metropolitan ICUs (72.7%), with the largest group working in

Table 3. Preferred vascular access sites and catheter brands and lengths for continuous renal replacement therapy

Vascular access variable (*n*)	Frequency of use, *n* (%)			
	Never	Occasionally	Frequently	Always
Vein (194)				
Left internal jugular	15 (7.7%)	108 (55.7%)	69 (35.6%)	2 (1%)
Right internal jugular	7 (3.6%)	65 (33.5%)	121 (62.4%)	1 (0.5%)
Left femoral	2 (1%)	57 (29.4%)	132 (68%)	3 (1.5%)
Right femoral	3 (1.5%)	51 (26.3%)	137 (70.6%)	3 (1.5%)
Left subclavian	69 (35.6%)	98 (50.5%)	26 (13.4%)	1 (0.5%)
Right subclavian	66 (34%)	103 (53.1%)	24 (12.4%)	1 (0.5%)
Catheter brand				
Bard Niagara (133)	66 (49.6%)	16 (12%)	34 (25.5%)	17 (12.8%)
Gambro Dolphin (136)	85 (62.5%)	9 (6.6%)	18 (13.2%)	24 (17.7%)
Quinton Mahurkar (119)	114 (95.8%)	4 (3.4%)	1 (0.8%)	0 (0)
Medcomp (119)	110 (92.4%)	0 (0)	8 (6.7%)	1 (0.8%)
Arrow (137)	49 (35.8%)	30 (21.9%)	32 (23.4%)	26 (19%)
Cook (128)	84 (65.6%)	17 (13.3%)	19 (14.8%)	8 (6.3%)
Don't know (63)	–	–	–	–
Catheter access length	**15 cm**	**20 cm**	**24/25 cm**	
Internal jugular (150)	94 (62.7%)	55 (36.7%)	1 (0.6%)	–
Femoral (150)	4 (2.6%)	76 (50.7%)	70 (46.7%)	–
Subclavian (150)	85 (56.7%)	60 (40%)	5 (3.3%)	–
Don't know (44)	–	–	–	–

metropolitan level three tertiary institutions (47.4%), caring for adult patients only (69.1%) (Table 1). Consultant intensivists represented 18.6% of the total responses, 19.1% were ICU-based clinical educators, 24.2% were clinical nurse specialists, and 21.6% were registered nurses filling the larger part of nursing roles. About one-third (36.1%) of respondents worked in units of 6–10 beds with 24.2% working in ICUs of over 20 beds. About one-quarter of respondents (25.3%) indicated that their ICU treated over 100 patients per year with some form of CRRT.

CRRT mode and dose

There was obvious clinical variation in the dose prescription for CRRT. Fifty-three per cent of respondents indicated that the standard treatment dose of CRRT was prescribed in their ICUs in L/hour, and 47% indicated that prescriptions used a weight-based dosing strategy of mL/kg/hour. The most common CRRT technique was CVVHDF, with 54% of respondents indicating that they always used this mode of therapy. In contrast, 9% of respondents indicated that they always used CVVH, and 2% always used CVVHD in their ICUs.

CVVHDF, in combination with before-and-after fluid replacement (before-and-after dilution) was indicated by respondents as always prescribed in 29% of treatments, with predilution CVVHDF (13%) and postdilution CVVHDF (12%) the next most-used practices. If CVVHDF was prescribed in a standardised dose of L/hour, respondents reported a dose of 1 L/hour for dialysis (D) + 1 L/hour as replacement (R) fluid as being frequently or always used in 39.1% of treatments. A dose of 2 L/hour (D) + 2 L/hour (R) was nominated as frequently or always used in 25.6% of cases. CVVHDF set at 16–25 mL/kg/hour was the most common weight-based regimen, with 57.3% frequently or always prescribing this dose. A dose of > 25 mL/kg/hour (39.4%) was the next most-used dosing regimen (Table 2).

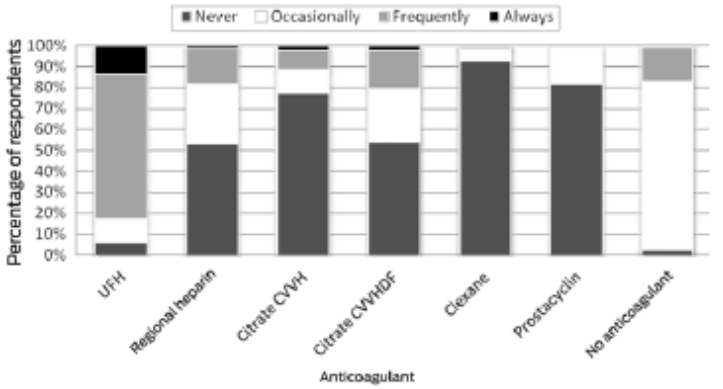
If CVVH was prescribed in a standardised dose of L/hour, respondents reported a dose of 2–3 L/hour as frequently or always used in 19.9% of treatments and a dose > 3 L/hour in only 9.0% of cases. CVVH set at > 25 mL/kg/hour was the most common weight-based regimen with 16.2% frequently or always prescribing this dose (Table 2).

Blood flow rate

A blood pump speed (set blood flow rate) of 151–200 mL/minute was frequently or always used in 59.3% of CVVHDF and 59.6% of CVVH treatments, respectively. A prescribed rate of 201–250 mL/minute was the next most-used range, with 45.7% of respondents frequently or always using it for CVVHDF, and 49.5% of respondents frequently or always using it for CVVH (Table 2). Fifty-one per cent of respondents suggested that the blood flow rate for CRRT was prescribed by unit policy or protocol, with 29% prescribed by medical staff and 20% set by the allocated bedside nurse.

The management of frequent CRRT machine alarms included the manipulation of blood flow rate in an attempt to decrease alarm conditions such as elevated transmembrane pressure and high return or venous pressures. Thirty-four per cent of respondents indicated that they frequently alter the pump speed to alleviate alarm conditions in an attempt to continue therapy.

Figure 1. Anticoagulant choices for continuous renal replacement therapy



UFH = unfractionated heparin. CVVH = continuous venovenous haemofiltration. CVVHDF = continuous venovenous haemodiafiltration.

Vascular access

The right and left femoral veins were most nominated as the access sites of choice for CRRT (Table 3). The next most common site was the right internal jugular vein, with few respondents indicating the use of subclavian veins. Bard Niagara and Arrow catheters were the most frequently used access devices, with a length of 20 cm preferred for all access sites.

Anticoagulation

Unfractionated heparin was the anticoagulant of choice, with 83% of respondents frequently or always using it to extend circuit life in CRRT. Regional techniques were less likely to be used; regional heparin (18%) and regional citrate in combination with CVVHDF (21%) were frequently or always used. Eighty per cent of respondents indicated that they occasionally used a no-anticoagulant strategy in place of drug-based anticoagulant treatment for CRRT (Figure 1).

Machines

The most commonly used CRRT machine was the Prismaflex (Gambro) (71%), followed by the Aquarius (Nikkiso) (27%), Prisma (Baxter Gambro) (8%) and the HF440 (Infomed) (5%).

Discussion

Summary of major findings

We assessed clinical practice prescriptions for the management of CRRT in Australian and New Zealand ICUs, and made five key findings. First, CVVHDF was the mode of CRRT most commonly used, typically using a combination of before-and-after filter fluid replacement. Second, about half the respondents indicated that their practice was to adjust the dose of therapy according to body weight (mL/kg/hour), while half used a standardised dose (L/hour). Third, the prescribed blood flow rate was highly variable, with 150–200 mL/minute being the most common rate for CVVH and CVVHDF. Fourth, a femoral vein was the most frequently nominated site for vascular access. Finally, unfractionated heparin is the most commonly used anticoagulant in CRRT.

Contrast with previous studies

The ANZICS Centre for Outcome and Resource Evaluation assumes that by ANZICS definitions for patient acuity managed,[14] all Australian and New Zealand level 2 and level 3 ICUs (public and private hospitals) are capable of performing RRT. If we continue this assumption, the cohort of RRT-capable ICUs would number 145. About three-quarters of these ICUs (73% [$n = 106$]) completed our survey, suggesting a strong representation of units capable of performing RRT in Australia and New Zealand. In 2001, Silvester and colleagues investigated aspects of RRT practice in 81 Australian ICUs and reported on the management and epidemiology of acute renal failure.[15] The technical aspects of their

study were limited to vascular access site, anticoagulant and mode of therapy. The only other reported study into local CRRT practices was before the RENAL study, which investigated 34 ICUs in Australia and New Zealand.[10] This study, conducted in 2004, investigated the technical and practical application of the therapy and provided important information for the conduct of our survey.

The Beginning and Ending Supportive Therapy for the Kidney study[1] investigated worldwide CRRT practice in 54 centres and 23 countries after the introduction of consensus guidelines and recommendations from the Acute Dialysis Quality Initiative (ADQI) in 2002. This multinational, multicentre study investigated technical aspects of CRRT including modality, dose, dilution method, membrane type and blood flow. The Department of Veterans' Affairs/National Institutes of Health ATN prestudy practice survey[11] reported the findings from 130 practitioners in 27 medical centres in the United States. Nine of the 26 questions specifically related to CRRT prescription, including estimation of frequency of use, vascular access (arterial or venous), mode, blood flow rates, type of fluids and dose prescription. Perhaps the largest survey investigating RRT practice involved 560 European critical care nephrology conference participants.[16] Most respondents were nephrologists (52%) with CRRT-prescribing doctors accounting for 25% of the responses. The technical aspects surveyed were limited to dose, modality and anticoagulant; technical prescription was not investigated.

Since the RENAL (2009)[8] and ATN (2008)[9] studies, there has been limited investigation of alteration in practice and prescription of CRRT, despite the publication of the respective findings from these two large and potentially influential studies. In 2010, the European Society of Intensive Care Medicine (ESICM) investigated the current practices associated with RRT from 272 doctors.[12] Despite a high number of respondents, the survey had limited technical descriptions of technique and prescription, but did provide insight into practices relating to dose, modality and intensivists' beliefs about optimal management of RRT. A survey of 167 intensivists in 2009 and 2010 investigated the management of AKI and RRT in the United Kingdom.[13] Modality and dose were addressed, with little information on specific technical prescription. Our survey, with a large representative sample from Australian and New Zealand ICUs, is the largest examination of the technical prescription of CRRT since publication of, and recommendations from, the RENAL and ATN studies.

Mode of therapy

The dominant mode of CRRT in Australia and New Zealand is CVVHDF, with 54% of respondents indicating that they always use it, and CVVH (9%) and CVVHD (2%) being less frequently favoured. Before the RENAL study, 62% of ICUs (21 of 34) indicated CVVHDF as their preferred mode.[10] ICUs had previously reported a higher use of CVVH, at 35% of ICUs (12 of 34), compared with our findings.[10] Internationally there remains great variation in practice in relation to modality of choice. The ESICM survey reported only a slight favour towards CVVHDF (50.9%) compared with CVVH (40.6%).[12] In the UK, CVVH is the dominant mode (56%) compared with CVVHDF (37%).[13] In the US, the pre-ATN practice survey conducted in 2003 indicated that 112 practitioners (86.2%) prescribed some form of CRRT in the 27 sites investigated.[11] Of these responders, most used CVVHD (78 of 112), followed by CVVHDF (67 of 112), with CVVH used in fewer than one-third of patients requiring continuous artificial renal support. It appears from these data that when nephrologists are prescribing and/or closely advising intensivists in the US, dialysate or diffusion is a mainstay for prescription by mode.

The use of CVVHDF and CVVH requires the administration of replacement solution. Our data suggest for both these modes that a combination of before-and-after dilution replacement is favoured by one-third of respondents. Historically, there is variability, with some ICUs exclusively using before-only (predilution) or after-only (postdilution) sites for substitution fluid administration. In contrast to our current findings, the Australian and New Zealand pre-RENAL practice survey conducted in 2004 reported 94% of ICUs using a predilution approach in CVVH and CVVHDF,[10] suggesting a change in practice over the past 10 years. The BEST Kidney study reported a slight favour for predilution (58%) compared with postdilution only (41%).[1] The recent ESICM and UK surveys[12,13] showed similar findings to our own: a combination of predilution and postdilution was most commonly used, with typically 30%–50% of replacement fluid delivered before dilution. It is likely, given the technological advancement of the machines used for CRRT, that this change in practice may be common. RRT machines now have the capacity to deliver replacement fluid before and after filtration, with new software and added roller pumps to achieve this dual pathway simultaneously. Therefore, the change may simply be because this is possible, or because when clotting occurs commonly in the filter or membrane and the postfilter bubble trap within the circuit, dilution into the blood path targets these two points to prevent clotting.[17]

Dose

In the pre-RENAL practice survey, no Australian or New Zealand ICU reported prescribing CRRT according to patient weight. During a similar period there was minimal prescribing of CRRT according to weight in other practice surveys.

In the US, fewer than 20% of practitioners based the dose on patient weight, with most (80%) prescribing at least 35 mL/kg/hour.[11] Ricci and colleagues described uncertainty, particularly among intensivists, about treatment prescription, but indicated a target dose of 35 mL/kg/hour or 2–3 L/hour.[16] The BEST Kidney study reported treatment doses in mL/hour with a median standardised CRRT dose of 2 L/hour and a calculated weight-adjusted dose of 20.4 mL/kg/hour.[1]

A decade on, we report that half the ICUs in Australia and New Zealand describe a weight-based dosing prescription of mL/kg/hour. Further, a CVVHDF dose of 16–25 mL/kg/hour was the most common dose, followed by > 25 mL/kg/hour. If CVVH was the mode of choice, a dose of > 25 mL/kg/hour was the most frequently used. For Australian and New Zealand ICUs prescribing in L/hour, a dose of 1 L/hour (R) and 1 L/hour (D) is the most common in CVVHDF, and 2–3 L/hour in CVVH mode. In contrast, the ESICM survey described a median CRRT dose of 35 mL/kg/hour, with < 15% of respondents prescribing a standard, fixed ultrafiltrate dose, irrespective of body weight.[12] As with the European survey, 73% of UK ICUs use a protocol for CRRT dose with a CVVH dose of 35 mL/kg/hour being the most frequent prescription.[13]

Blood flow rate

One aspect of practice with ongoing variation is the speed of blood flow in the extracorporeal circuit. Before more advanced CRRT technology, blood flow rates of 150–200 mL/minute were common. Certainly the Australian and New Zealand data from 2004 indicated a median blood flow rate of 200 mL/minute,[10] with the BEST Kidney study[1] and prepractice ATN study[11] reporting a median rate of 150 mL/minute. Interestingly, in the country breakdown, the median blood flow rate in Japan was 80 mL/minute, but in Australia, the Netherlands, Portugal and the UK, the median blood flow rate was 200 mL/minute. Our study showed that although 150–200 mL/minute was still the dominant setting for all CRRT modes, a faster rate of 200–250 mL/minute is now commonplace in Australian and New Zealand ICUs. We do not have any data on blood flow rates from more recent practice surveys, but observational studies report practices of using between 100 mL/minute and > 300 mL/minute, indicating great variability and limited evidence for best practice for this therapy.[18,19]

Vascular access

The site for vascular access for CRRT may be the most important variable for circuit life success.[20-22] There is much literature devoted to access site, type, design and catheter-related complications.[23-30] The internal jugular vein is the site traditionally considered preferable to femoral venous access,[20,31] and this choice is supported by the ADQI and Kidney Disease Improving Global Outcomes (KDIGO) consensus guidelines.[32,33] Despite this, femoral access catheters are frequently used in the delivery of CRRT[19,26] and may have a lower incidence of dysfunction and bacterial colonisation compared with jugular sites in patients with a lower body mass index.[26,27] Access sites in relation to right and left venous positions have also been investigated, with some studies suggesting that longer circuit lifespans may occur with use of the right femoral and right internal jugular veins, compared with a left-sided approach.[25,28] To our knowledge, there are no data to clarify clinician preference in relation to site, length or type. No previous or current RRT practice surveys have included vascular access as an item of interest. Our data from Australia and New Zealand indicate that the right and left femoral veins are the sites of choice, followed closely by the right internal jugular vein. A catheter length of 20 cm was the most commonly used, for all sites, with just under half the respondents indicating that 24–25 cm catheters were used in femoral veins. This may indicate that a longer catheter is not considered necessary by some, and that the 20 cm version can be used in both the femoral and internal jugular vein sites, making ordering and stocking of the device simpler. Others using the longer 24–25 cm catheter for femoral access in adults may use this to place the catheter tip closer to the right atrium and would need to order and stock both lengths.

Anticoagulants

Respondents indicated that CRRT is often performed without the aid of an anticoagulant. When patients received an anticoagulant, unfractionated heparin (UFH) was the most commonly used, with over 80% of ICUs using it to extend circuit life. This finding is consistent with previous practice surveys from a decade earlier which also indicated UFH as the anticoagulant of choice.[1,16] This approach is likely to be due to historical reasons, the predictability of outcomes and clinician familiarity with heparin use. Despite recent studies showing a better circuit life, and literature guiding the choice of CRRT anticoagulant towards use of regional techniques with citrate,[34-38] this has not translated into current practice patterns. Only a small proportion of respondents indicated that they frequently used the technique. Factors affecting citrate use may include less historical use, unfamiliarity with citrate compared with heparin, and cost.

Strengths and limitations

A strength of our study is the generalisability of the findings. Despite an unknown response rate, we gathered information from 106 hospitals in Australia and New Zealand, potentially representing 73% of all ICUs capable of performing RRT. This study therefore is the largest

investigation of Australian and New Zealand CRRT practice ever conducted.

Our study has several limitations. The accuracy of the responses could not be independently verified, as the prescription of CRRT practice was self-reported rather than by observation or collection of treatment data. The pre-RENAL,[10] ATN[11] and recent practice surveys have used a self-reporting approach. We did not obtain information about the use of, or prescribing practices associated with, alternative renal support therapies, such as IHD or SLEDD. Despite some increasing interest in prolonged intermittent therapies such as SLEDD, it has been previously reported that patients in Australian and New Zealand ICUs spend <5% of their renal support time receiving a therapy other than CRRT.[11] We received 194 responses from 106 ICUs, indicating multiple respondents from a single ICU and the potential for reporting disagreement. When multiple responses from one site were received, individual surveys from the site were checked for consistency of practice patterns. Five ICUs with multiple responses and some inconsistencies in self-reported practice were contacted for clarification of usual CRRT prescription.

Recommendations for research

We chose to determine current practices rather than explore clinicians' perceptions of the optimal approaches to CRRT prescription, or if they prescribe according to any published evidence. It would be useful to explore the opinions of individual clinicians about their practice of CRRT, with specific themes of initiation or optimal timing, dose prescription and modality choice for specific patient groups, as well as how technical or practical prescription settings are decided in ICUs. A cross-sectional study or point prevalence study would also provide more objective and reliable data for the prescription and delivery of RRT for Australian and New Zealand ICU inpatients, further highlight consistent or inconsistent current practices, and provide useful data that may help with the design of control groups for future trials. There is also a need to continue developing a data and evidence base for the most effective aspects of CRRT. There appears to be a need to examine effective strategies for implementing results of past studies into daily practice. Data from large published trials have not changed many aspects of practice in Australia and New Zealand.

Conclusion

Our prospective survey of 194 clinicians from 106 ICUs in Australia and New Zealand on technical and practical aspects of CRRT suggests that, a decade on from the last practice survey and the dissemination of dose findings from Australia and New Zealand, there remains a high variability in the practical prescription of CRRT. This lack of uniformity, particularly in blood flow rates, access catheter length and replacement fluid site, highlights the lack of adequate randomised controlled trials (RCTs) to provide evidence for CRRT guidelines. The variability in dose and dose prescription emphasises an inconsistent approach to therapy, despite large RCTs and recommendations on the management of CRRT from recently published KDIGO guidelines. Our study shows the lack of standardisation in the application of CRRT in the critically ill.

Competing interests

None declared.

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Appendix

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Continuous renal replacement therapy practice survey

1. Please identify the location of your hospital

- o North Island of New Zealand
- o South Island of New Zealand
- o Queensland
- o New South Wales
- o Victoria
- o Australian Capital Territory
- o South Australia
- o Tasmania
- o Western Australia
- o Northern Territory

2. To ensure hospital data is not duplicated, can you please type the name AND location of your hospital

_____

3. Indicate your position in your Intensive Care Unit

- o Consultant Intensivist
- o Medical (other)
- o Nurse Unit Manager (Charge Nurse)
- o ICU based Educator
- o Clinical Nurse Consultant
- o Associate Nurse Unit Manager (Team leader)
- o Research Nurse

- Clinical Nurse Specialist
- Registered Nurse

4. What best describes your Intensive care unit

   - Regional Hospital
   - Metropolitan Private Hospital
   - Metropolitan Public Level 2
   - Metropolitan Public Level 3

5. What best describes your Intensive care unit

   - Adult Intensive Care only
   - Paediatric Intensive Care only
   - Combined Adult Paediatric Intensive Care

6. What is the size (number of beds) of your Intensive care unit

   - 0-5 beds
   - 6-10 beds
   - 11-15 beds
   - 16-20 beds
   - > 20 beds

7. Estimate or approximate the number of patients treated with CRRT per year in your ICU
   - < 10
   - 11 – 25
   - 26 – 50
   - 51 – 75
   - 76 – 100
   - > 100
   - Don't Know

8. How often would you use the following modes of CRRT
   Please respond to all options in list below

	Never	Occasionally	Frequently	Always

CVVH (Predilution)

CVVH (Postdilution)

CVVH (Pre+Post dilution)

CVVHDF (Predilution)

CVVHDF (Postdilution)

CVVHDF (Pre+Post dilution)

CVVHD

9. The standard dose or treatment of CRRT in your ICU is measured in:

- mls/kg
- litres /hr

10. How often do you set the following prescription (Replacement and/or Dialysate) rate?
    Respond to all options in the list below

	Never	Occasionally	Frequently	Always
CVVH **≤ 2 Litres**				
CVVH **> 2 L but < 3 Litres**				
CVVH **≥ 3 Litres**				
CVVHDF **(1L Replacement + 1L Dialysate)**				
CVVHDF **(1.5L Replacement + 1.5L Dialysate)**				
CVVHDF **(2L Replacement + 2L Dialysate)**				
CVVHDF **(>2L Replacement + >2L Dialysate)**				

11. How often do you set the following exchange (Replacement and/or Dialysate) rate?
    Respond to all options in the list below

	Never	Occasionally	Frequently	Always
CVVH **0-15 mls/kg**				
CVVH **16-25 mls/kg**				
CVVH **>25 mls/kg**				
CVVHDF **0-15 mls/kg**				
CVVHDF **16-25 mls/kg**				
CVVHDF **>25 mls/kg**				

12. How often would you use the following blood pump speed (blood flow rate) in CVVH?

	Never	Occasionally	Frequently	Always
0-50 mls/min				
51-100 mls/min				
101-150 mls/min				
151-200 mls/min				
201-250 mls/min				
251-300 mls/min				
> 300 mls/min				

13. How often would you use the following blood pump speed (blood flow rate) in CVVHDF?

	Never	Occasionally	Frequently	Always
0-50 ml/min				
51-100 mls/min				
101-150 mls/min				

151-200 mls/min

201-250 mls/min

251-300 mls/min

> 300 mls/min

14. In response to frequent alarms (High TMP, Venous pressure, Low Access pressure), do you manipulate/alter the blood flow rate (pump speed) in order to continue treatment

Never Occasionally Frequently Always

15. How often would you use vascular access catheters (Vascaths) in the following locations

	Never	Occasionally	Frequently	Always
Left Internal Jugular				
Right Internal Jugular				
Left Femoral				
Right Femoral				
Left Subclavian				
Right Subclavian				
Other				

16. For the vascular access site indicated above, select the Vascath length you use (cms)

	15 cm	20 cm	24/25 cm
Internal Jugular			
Subclavian			
Femoral			
Other (please specify)			

17. Please indicate your Anticoagulation choice for CRRT in your ICU
    Please respond to all options below

	Never	Occasionally	Frequently	Always
Unfractionated Heparin				
Regional Heparin (heparin + protamine)				
Citrate CVVH				
Citrate CVVHDF				
Clexane				
Prostacyclin				
No Anticoagulation				
Other (Please specify)				

18. How often would you use the following vascular access types in your intensive care unit

	Never	Occasionally	Frequently	Always
Bard Niagara				
Gambro Dolphin				
Quinton Mahurkar				
Medcomp				
Arrow				
Cook				

Other

Don't know the access
make/type

19. Which of the following best describes how blood flow rates are chosen / prescribed?

    Nurse initiated

    Medical initiated

    Protocol or unit policy (standard)

    Other

20. Which of the following machines do you use for CRRT

    - Prisma
    - Prismaflex
    - Aquarius
    - Infomed HF440
    - Other

Chapter 4: Research Method and Design

4.1 Introduction

Multiple factors responsible for circuit life in CRRT were presented in Chapter 2. The review of the literature led to the identification in gaps in our current knowledge and the formulation of the research questions for this study. A prospective survey of CRRT practice was presented in Chapter 3. This information identified the current trends in practice and informed the design of the study. The methodological framework to answer the research question is presented in this chapter. First, the research design is outlined. Second, the characteristics of the sample (inclusion/exclusion criteria), sample size and setting, and randomisation for this study are described. Third, the study intervention and standardisation of CRRT technique are outlined. Fourth, data collection and data analysis procedures are discussed. Finally, the ethical considerations for this study are presented.

4.2 Research aims and questions

The overall aim of this study was to gain a better understanding of the impact of BFR on the application of CRRT in critically ill patients with AKI.

4.2.1 Aims

The aims of this study were to:

1. investigate the relationship between BFR and circuit life in patients treated with CRRT
2. determine if BFR affects solute maintenance in patients treated with CRRT
3. provide initial data to reliably inform the feasibility and sample size calculations of a larger future RCT.

4.2.2 Research questions

To meet the aims of the study, the following research questions have been developed:

1. Does a higher BFR improve circuit life in CRRT?
2. Does a higher BFR affect solute maintenance in patients treated with CRRT?
3. What sample size is required to conduct an appropriately powered RCT?

4. What important feasibility parameters are required to design an appropriately powered RCT?

4.3 Research design

A prospective randomised controlled experimental design was used for this study. The study was a parallel group design where one treatment variable (BFR) was applied simultaneously in two separate groups of participants. The intervention was a set BFR of 250 mL/min, and the control was a set BFR of 150 mL/min. For the purposes of the study, each participant was randomised and allocated to one of the two prescribed BFRs (150 mL/min or 250 mL/min) in either CVVH or CVVHDF.

The key dependent variable was *circuit life* and the key independent variable was *blood pump speed*. Other confounding variables of interest were:

- mode of CRRT
- femoral vascath position (left or right)
- treatment efficiency—waste clearance and serum levels of solutes such as urea (mmol/L) and creatinine (µmol/L)
- anticoagulation type and dose
- daily coagulation profile—INR (ratio) and APTT (s)
- blood count—platelets (number × 10^9/L)
- machine type/brand
- vascular access type, diameter and length
- patient weight and body mass index (BMI).

4.4 Definitions

For the purposes of the study, circuit failure was defined as the occurrence of one or more of the following:

1. TMP greater than 250 mmHg
2. pre-filter pressure greater than 200 mmHg
3. EC circuit clot obstructing blood flow
4. any machine alarm that advised that the filter was clotted.

These definitions describe the condition where the circuit has clotted or failed. The therapy was then temporarily ceased and, if treatment was still required, reset with a new

haemofilter and circuit. BFR was again set at the allocated rate determined from the randomisation process.

Circuits were also identified for data analysis as either:

1. electively removed for patient transport (e.g., CT scans, MRI or operating theatre)
2. electively removed for discontinuation of the therapy.

4.5 Study setting

The research project was undertaken in the Department of Intensive Care at the Austin Hospital in Melbourne, Victoria. The ICU is a 24-bed level-three tertiary and training referral centre for the management of critically ill patients. The department has 10 intensive care medical consultants, one critical care nephrologist and 215 nursing staff. This is considered a 'general intensive care' centre, which specialises in cardiac surgery, vascular surgery, neurosurgery and gastrointestinal surgery, as well as general medical and surgical patients requiring more advanced technologies and procedures. The department is also the state's referral centre for acute liver failure, liver transplantation and spinal cord injuries. The unit admits on average 2100 patients per year. Over the past decade, an average of 140 patients have required CRRT per year. The average number of RRT days for this period was 686 per year, which equates to each patient receiving an average of 5 days of CRRT.

4.6 Sample size

The sample was adult patients with AKI who required CRRT in the ICU. The sample was one of convenience, and although a single-centre study, these patients were considered representative of an adult intensive care population in a tertiary teaching facility in Australia. As there were no published studies investigating the relationship between blood flow speed and circuit life in CRRT, there were no data to inform sample size using power calculations for this study. As a pilot study, the sample size has been considered to collect sufficient data to inform a future power calculation and to identify issues relating to feasibility for a larger RCT. Torgerson et al. suggest that a well-designed pilot study requires a minimum sample size of 32 patients to observe a difference of one standard deviation between the two randomised groups with 80% power.[224] In this study, it was intended that 100 patients would be enrolled. This number was selected not only to gather

sufficient data for a sample size calculation but also to ensure recruitment in a period of 1 year.

4.7 Recruitment process

Any patient requiring RRT for the treatment of AKI was screened for eligibility.

4.7.1 Inclusion criteria

Patients were eligible for enrolment in the study if they:

- were ≥18 years of age
- developed AKI in accordance with the RIFLE classification (F) (grades of severity of AKI based on changes to serum creatinine and urine output and two clinical outcomes)[225]
- required CRRT as prescribed by the treating intensive care consultant
- qualified for vascular access via the femoral vein for standardisation of method.

4.7.2 Exclusion criteria

Patients were ineligible for the study if they:

- required citrate anticoagulation as prescribed by the treating consultant (citrate dose protocol in the study setting requires a set BFR of 150 mL/min)
- were anticipated to require a short stay in the ICU of less than 24 h.

4.8 Randomisation

After diagnosis of AKI and physician decision to initiate CRRT, the mode of treatment was prescribed by the treating intensive care physician. Once the mode of therapy was known (CVVH or CVVHDF), the BFR was randomly allocated to either 150 mL/min or 250 mL/min. The use of anticoagulation or non-anticoagulation was prescribed by the treating physician. Upon clotting of the first and subsequent circuits, a new circuit was prepared, and the participant continued treatment at the BFR allocated at randomisation. Termination of treatment was at the discretion of the treating ICU physician.

Randomisation was completed via the web-based randomisation service through the Clinical Trial Coordinating Centre (Griffith University). Randomisation was applied to the BFR group and stratified to mode (CVVH or CVVHDF). A variable block

randomisation with parallel allocation was used to assign the two study groups (150 mL/min or 250 mL/min). The randomisation procedure was completed solely by the principal investigator.

A standardised RCT methodology was adopted using guidelines based on the Consolidated Standards of Reporting Trials (CONSORT) statement.[226, 227] The CONSORT statement for this study is shown below (Figure 4.1).

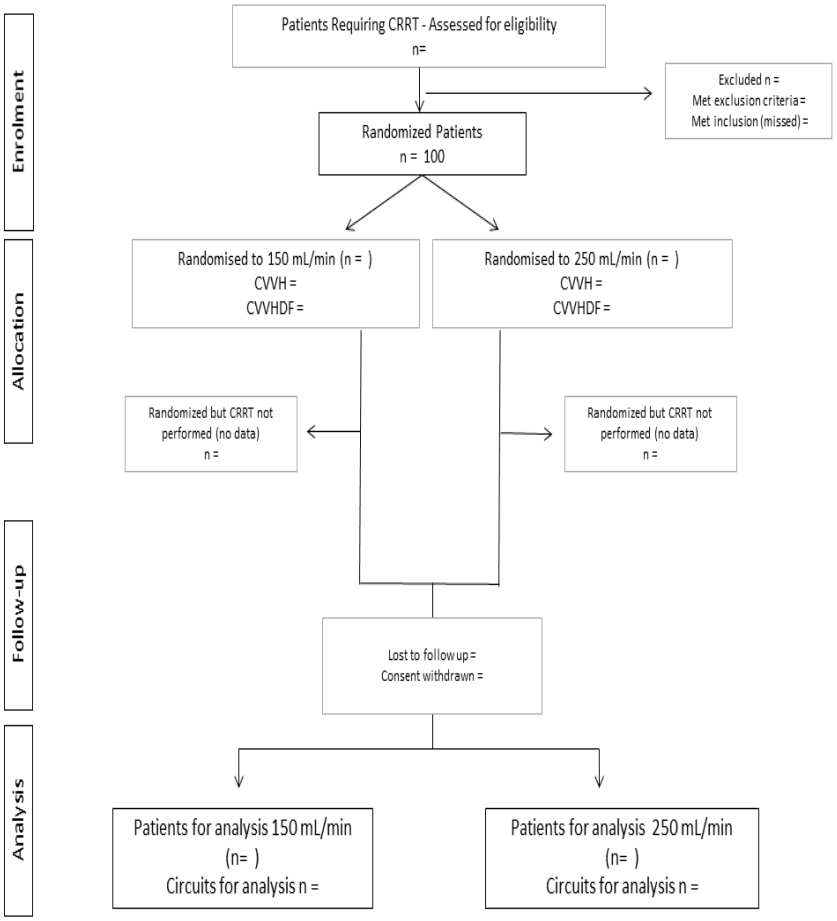

Figure 4.1: CONSORT diagram for study.

4.9 Standardisation of technique

As outlined in Chapter 2, there are a number of factors that may influence circuit life and longevity. These factors can lead to progressive circuit and membrane clotting, which may be mediated by anticoagulation strategies as well as variables relating to the practical application of the therapy. For this study, measures were taken to standardise the approach for CRRT so that any differences in circuit life were based on the variable of interest (BFR) and not confounded by factors identified in the literature. Factors that were

standardised included the make and model of CRRT machine, mode of therapy, dose of therapy, commercial brand of membranes (haemofilter) and vascular access catheters.

4.9.1 Continuous renal replacement therapy instrumentation: Machine and system

CRRT was achieved using either the Infomed HF440 (Geneva, Switzerland) or Baxter Gambro Prismaflex (Gambro, Lund, Sweden) platform (Figures 4.2 and 4.3).

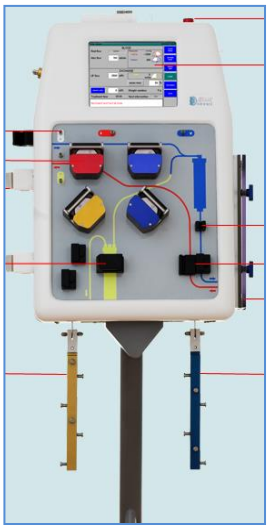

Figure 4.2: Infomed HF440. Figure 4.3: Gambro Prismaflex.

4.9.2 Mode of therapy and dose

CVVH was achieved using a standardised ultrafiltration rate of 2000 mL/h using bicarbonate buffered solutions as the replacement fluid (Accusol, Baxter, Irvine, CA, USA). Replacement solutions for CVVH were delivered into the EC circuit before and after the filter (i.e., pre-dilution and post-dilution) at a ratio of 50% pre-dilution and 50% post-dilution. Any prescribed fluid loss was determined by the treating physician. The circuit design for CVVH is illustrated in Figure 4.4.

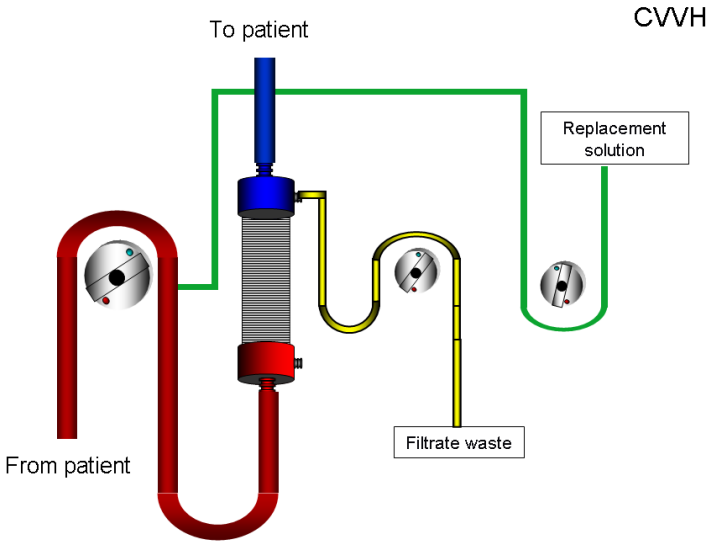

Figure 4.4: CVVH: EC circuit, replacement and filtrate (waste) pathways.

CVVHDF was achieved using a standardised dialysate flow rate of 1000 mL/h and ultrafiltration rate of 1000 mL/h using bicarbonate buffered solutions as the dialysate and replacement fluids (Accusol, Baxter, Irvine, CA, USA). Replacement solutions for CVVHDF were delivered into the EC circuit after the filter only (i.e., 100% post-dilution). Any prescribed fluid loss was determined by the treating physician. The circuit design for CVVHDF is illustrated in Figure 4.5.

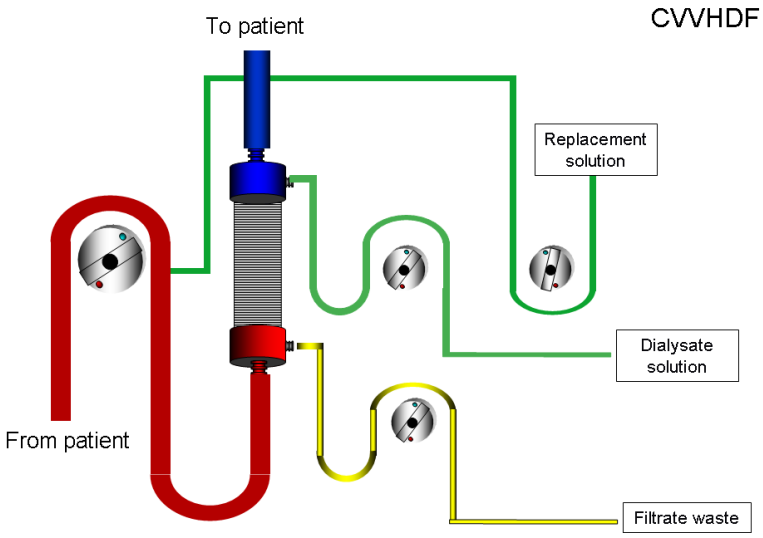

Figure 4.5: CVVHDF: EC circuit, replacement, dialysate and filtrate (waste) pathways.

4.9.3 Membranes (haemofilter)

Both CVVH and CVVHDF treatments were achieved using the AN 69 ST (ST 100) 1.0 m^2 membrane (Gambro, Lund, Sweden), specifically designed for use with the Gambro Prismaflex platform. When the Infomed HF440 platform was used for both modalities, an Infomed DF 140 1.4 m^2 polyethersulfone membrane (Infomed, Geneva, Switzerland) was used. These membranes are used worldwide and no clinical differences with respect to clotting have been reported.[156]

4.9.4 Vascular access

For the study, femoral vein access was the standardised approach to access with a dual-lumen vascular access device. The treating physician could select from two readily available access catheters in the ICU: the Niagara 13 Fr × 24 cm dual-lumen catheter (Bard, Ontario, Canada) or the Gamcath Dolphin Protect 13.5 Fr × 25 cm dual-lumen catheter (Gambro, Henchingen, Germany). No internal jugular or subclavian catheters were used for this study. Catheters were inserted under strict aseptic conditions using standard Seldinger guide wire technique. Both access devices are polyurethane material and have similar double 'D' or 'O' design profiles.

4.9.5 Anticoagulation

When used, type of anticoagulant and dose were at the discretion of the treating ICU physician. Usual prescribing practices at the study site included no anticoagulation, unfractionated low-dose heparin, regional heparinisation (with the reversal agent protamine delivered into the EC circuit post-filter) and RCA. For this study, patients requiring RCA were not eligible for enrolment in the study. As stated, 'regional citrate' anticoagulation requires a set blood pump speed of 150 mL/min in CVVH only, thereby contrary to the study protocol. The type of anticoagulant, dose and effect on participants' coagulation profile were recorded for analysis.

4.10 Intention to treat

The intention to treat principle was adopted for this study. First, all patients with AKI who required CRRT were screened for eligibility and the possibility of enrolment. This ensured that the sample was a representative sample from a typical ICU population that required RRT. Further, in this design, the responsibility for treatment mode was designated to the treating ICU physician. It was foreseeable that there might have been

unequal treatment distribution between CVVH and CVVHDF during enrolment and data collection. The incorporation of an intention to treat principle allowed the analysis of data to be undertaken irrespective of the sequence of treatments.[227] In addition, this principle allowed data to be collected from participants despite non-adherence to the intervention. During the study period, it was intended that data be collected irrespective of protocol deviations or irregularities in the non-compliance of protocols or in the withdrawal of participants.

4.11 Data collection

4.11.1 Patient demographic characteristics

Each participant was assigned a study identifying number with characteristics of their illness and admission recorded. The Acute Physiology, Age and Chronic Health Evaluation II and III score (APACHE II, III) as well as the Simplified Acute Physiology Score II (SAPS II) were determined by utilising universally accepted tools. As a standard feature of the ICU literature, severity of illness scoring is utilised as a means of describing patients included in a study at baseline (equivalence) or as a predictor of mortality before a given intervention. APACHE II, III and SAPS II scoring occurs in every ICU in Australia. The numerical value is ascertained from a collection of predetermined criteria that enable the severity of illness to be classified. The score provides a risk of death calculation and enables groups of patients with critical illness to be compared in an objective manner between ICUs nationally and internationally.

In addition to severity of illness scores, baseline characteristic data were collected for each study participant. These included:

- age
- gender
- weight
- BMI
- source of admission
- diagnostic group
- presence of sepsis
- treatment with mechanical ventilation
- treatment with inotropes or vasopressors
- pre-randomisation serum renal biochemistry values (urea and creatinine).

4.11.2 Circuit life data

After randomisation and allocation to intervention (BFR), and treatment commencement, data collection occurred using a standardised paper-based case report form (CRF) (Appendix 2). Data for the dependent variable (circuit life) as well as the independent variable of BFR were gathered for each CRRT circuit as follows:

- randomised BFR
- circuit number
- circuit start date/time
- circuit finish date/time
- circuit life
- modality (CVVH or CVVHDF)
- vascular access type
- vascular access length
- vascular access gauge
- vascular access site (right or left femoral position)
- machine platform (Infomed or Prismaflex)
- anticoagulation type
- anticoagulation dose
- circuit discontinuation reason (clotting or elective).

On the CRF, bedside staff were prompted to identify the reason for each circuit's removal (clotting or elective). Staff were asked to diagnose clotting with reference to the definitions previously outlined. In addition to the CRF, bedside staff were asked to record BFR, cumulative hours of circuit life, TMP, and anticoagulation type and dose every hour on the patient's observational chart. This chart was digitally scanned into the patient's electronic medical record and was used to cross-reference against the CRF. A Microsoft Excel™ (Redmond, Washington) database was developed and used to record all variables collected.

4.11.3 Evaluation of solute clearance

Small-solute maintenance, as measured by blood plasma concentrations of delta urea and creatinine, was calculated for two predefined 12 h periods each day. For all patients, twice-daily (at 0500 and 1700) measurement of biochemical parameters (serum creatinine and urea) was performed. Haemoglobin was also measured. Circuit life was documented

for each CRRT circuit as cumulative hours. Given this information, delivered treatment hours could be calculated for each 12 h period (T1 [0500–1700] and T2 [1700–0500]).

4.12 Data analysis

4.12.1 Data cleaning and preparation

The initial statistical work required building the database and categorising the number of variables collected. A database was established to store categorical and continuous variables. Each variable was coded with an accompanying codebook to provide a description of the values included in the database. Following data entry, the database was examined for missing or out-of-range data. Following transcription into an electronic database, each entry was crosschecked by a second investigator. Accuracy of data points were evaluated by assessing the distribution of continuous data and clarifying the accuracy of significant outliers. Accuracy of data fields that are categorical text fields was assessed by ordering such fields alphabetically and checking for repeated/inaccurately spelt forms. A data query list was generated, and a log was completed for the response to each query. New databases were then created and dated with each episode of cleaning to permit an audit trail of all changes made.

4.12.2 Primary outcome—Circuit life

The primary outcome of circuit life was analysed using a two-step process:

4.12.2.1 First analysis

This analysis 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. Analysis of all clotted circuits as well as a comparison of the first, second and third circuit life data for the two groups (150 mL/min vs. 250 mL/min) was carried out using the Mann–Whitney U test. Analysis of the two groups (first circuit only) 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. The first analysis was carried out using SPSS Statistics for Windows (version 20.0; IBM, Chicago, IL, USA).

4.12.2.2 Second analysis

The second analysis included all circuits (clotted and those electively removed). Circuit life was analysed using repeated-events survival analysis.[139, 228] A proportional hazard conditional frailty model (an extension of Cox regression) was used to test for within-patient dependence.[228] It was expected that there would be heterogeneity among individual trial patients. In addition, individual trial patients might have contributed one or multiple circuits. It was assumed that there was 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 was that it considered any within-cluster correlation of circuit life. Proportions were compared using a chi-square test. In the final model, and in all other analyses, a *p*-value of <0.05 was set to indicate statistical significance. The second analysis was performed using SAS (Enterprise Guide v5.1; SAS Institute Inc., Carey, NC, USA).

4.12.3 Secondary outcome—Solute maintenance

Linear regression analysis was performed to identify independent variables that may be associated with change in small-solute serum levels. Independent variables included modality of CRRT, gender, BMI, weight, haemoglobin and number of hours treated in each 12 h period. Repeated measures ANOVA was used on the independent variables demonstrating significance. The advantage of this model is that it considered within-subject measures over multiple time points. In this study, patients contributed multiple 12 h periods measuring solute percentage change over these periods. Data lacking normality of distribution were presented as median with IQR (25% and 75%) using the Wilcoxon rank-sum test, and normally distributed data were presented as mean with SD using Student's *t* test, the chi-square test and Fisher's exact test; $p < 0.05$ was considered significant. SPSS (version 21.0; IBM, Chicago, IL, USA) software was used for all data analysis.

4.12.4 Feasibility outcomes and power calculation

In addition to inferential statistical analysis, a feasibility examination of the study was performed to inform the practicability of a larger RCT. Aspects including numbers of

patients screened, eligibility and eventual enrolment were examined to enlighten time frames and challenges to the enrolment process in critically ill patients. As written consent was required by the hospital's HREC, consent rates and any impediment to consent were also examined. All protocol violations were assessed for repetitive impediments and considerations for any future study. In addition, results from the study were used to calculate the minimum sample size required for a statistically powered RCT in the future.

4.13 Ethical considerations

Permission to undertake the study was sought from the HREC of Griffith University as well as the HREC of Austin Health, where the study was conducted (Appendix 3 and Appendix 4). Permission was also sought from the Medical Director and Director of Research from the Department of Intensive Care at Austin Health. Clinical research involving the critically ill presents many challenges as this group of patients are vulnerable and rely on intensive care physicians and nurses to manage treatment and delivery of care. The major concerns regarding research in this vulnerable patient population surround issues of patient safety and the requirement for consent.[229]

In this study, the general values and principles set out in the National Statement on Ethical Conduct in Human Research were applied.[230] These principles are respect, research merit and integrity, justice and beneficence. In this study, this included informed consent, data storage, anonymity and confidentiality. In addition to local institutional and University HREC permission, the study was also listed with the Australian and New Zealand Clinical Trials Registry (ANZCTR) (Appendix 5).

4.13.1 Informed consent

Written informed consent was sought from the participant prior to enrolment in the study. If the participant was unable to provide consent because of his/her illness, consent was sought from the person responsible for the participant prior to enrolment. In the event that neither the participant nor the person responsible for the participant was able to provide consent prior to enrolment, a delayed consent process was undertaken. For the purposes of the study, enrolment and randomisation were undertaken and clinical guidelines (methodology) outlined in this protocol were performed. Delayed consent was then sought from either the participant or the person responsible for the participant for inclusion in the research project. The consent was voluntary and could have been withdrawn at any time without repercussion or penalty. The participant and person

responsible for the participant information sheet and consent forms used in this study are presented in Appendix 6 and Appendix 7.

All patients (included and excluded patients) requiring CRRT during the study period received the usual or standard therapy per ICU policy and ICU consultant discretion. All patients were treated equally and fair in this respect, and no groups were afforded special care or consideration. The principal of beneficence was also maintained as patients received therapy that is considered standard for the treatment of AKI, and the procedure of CRRT used in this study did not add additional risk to the participating patients.

4.13.2 Data storage

All data collected were stored in a locked cupboard in a locked office at Austin Health during the study period. Upon completion of the study, records pertaining to the study will be kept in a secure location in the same facility for a period of 7 years and then destroyed in a method consistent with the National Health and Medical Research Council guidelines.

4.13.3 Anonymity and confidentiality

The data were collected in a potentially re-identifiable manner and then were de-identified for analysis, reporting and publication purposes. Each patient's key was stored separately to the data and all data sheets and CRFs only contained study ID. Only the researcher had access to the patients' information. Publications and presentations were prepared in such a manner as to maintain the confidentiality and anonymity of all study participants.

4.14 Summary of chapter

In this chapter the methodological framework used for the study was presented. Chapter 5 presents the findings and discussion of this research through two peer-reviewed journal publications.

Chapter 5: Results

5.1 Statement of contribution to co-authored published papers

This chapter includes two co-authored papers. The bibliographic details of the co-authored papers, including all authors, are:

Publication 2: Nigel Fealy, Leanne Aitken, Eugene du Toit, Serigne Lo, Ian Baldwin. (2017). Faster blood flow rate does not improve circuit life in continuous renal replacement therapy: A randomized controlled trial. *Critical Care Medicine*, 45(10), e1018–1025.

My contribution to the paper involved:

- critical review of the literature to inform the design of the study
- development of the study protocol and method
- successful institutional and university ethics submission and review process
- registration and set-up of the web-based clinical trials randomisation service
- registration of the study with the ANZCTR
- development of the CRFs and data collection tools
- screening of patients for eligibility and education of bedside staff for screening out of hours
- enrolment of participants, including randomisation
- explanation of study to potential participants or persons responsible for the participant and gaining consent
- data collection and validation of CRF with patient medical records
- data analyses
- data interpretation
- writing of the manuscript
- revision of the manuscript
- approval of the final version.

I completed the research and writing of the paper with methodological and editorial advice from my PhD supervisors, Professor Leanne Aitken, Dr Eugene du Toit and Professor Ian Baldwin. Additional statistical support, analysis and interpretation was provided by Dr Serigne Lo.

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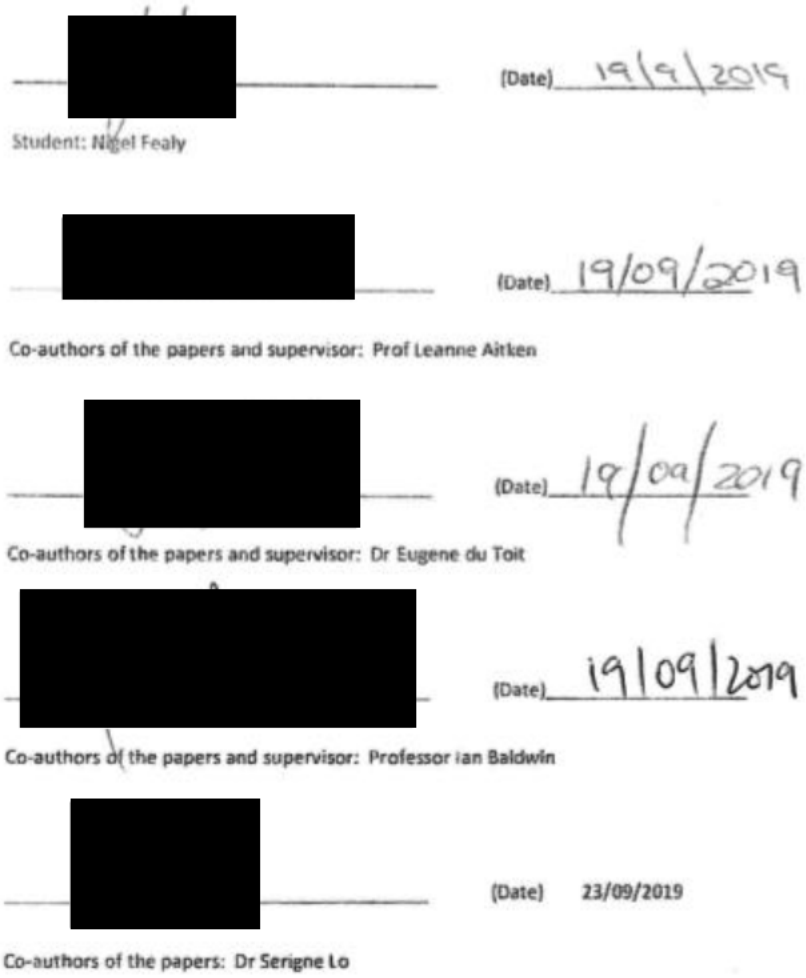

Publication 3: Nigel Fealy, Leanne Aitken, Eugene du Toit, Michael Bailey, Ian Baldwin. (2018). Evaluation of urea and creatinine change during continuous renal replacement therapy: Effect of blood flow rate. *Critical Care and Resuscitation*, 20(1), 41–47.

My contribution to the paper involved:

- critical review of the literature to inform the design of the study
- development of the study protocol and method
- successful institutional and university ethics submission and review process
- registration and set-up of the web-based clinical trials randomisation service
- registration of the study with the ANZCTR

- development of the CRFs and data collection tools
- screening of patients for eligibility and education of bedside staff for screening out of hours
- enrolment of participants, including randomisation
- explanation of study to potential participants or persons responsible for the participant and gaining consent
- data collection and validation of the CRF with patient medical records
- data analyses
- data interpretation
- writing of the manuscript
- revision of the manuscript
- approval of the final version.

I completed the research and writing of the paper with methodological and editorial advice from my PhD supervisors, Professor Leanne Aitken, Dr Eugene du Toit and Professor Ian Baldwin. Additional statistical support, analysis and interpretation was provided by Dr Michael Bailey.

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[redacted] (Date) 19/9/2015

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5.2 Introduction

This chapter will describe findings of the study from data collected between June 2013 and August 2014. The aim of this study was to investigate the relationship between BFR prescribed in CRRT and the impact (if any) on both circuit life and maintenance of solute control in critically ill patients with AKI. Data are presented as two peer-reviewed published co-authored papers and report findings from the two initial research questions:

- Does a higher BFR improve circuit life in CRRT?
- Does a higher BFR affect solute maintenance in patients treated with CRRT?

Additional data not included in published papers are addressed with reference to the third and fourth research questions:

- What sample size is required to conduct a powered RCT?
- What important feasibility parameters are required to design a powered RCT?

5.3 Publication 2: Faster blood flow rate does not improve circuit life in continuous renal replacement therapy: A randomized controlled trial

Faster Blood Flow Rate Does Not Improve Circuit Life in Continuous Renal Replacement Therapy: A Randomized Controlled Trial

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

Design: Prospective randomized controlled trial.

Setting: Single center tertiary level ICU.

Patients: Critically ill adults requiring continuous renal replacement therapy.

Interventions: Patients were randomized to receive one of two blood flow rates: 150 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 nonclotting reasons. Data for clotted circuits are presented as median (interquartile range) and compared using the Mann-Whitney *U* test. Survival probability for clotted circuits was compared using log-rank test. Circuit clotting data were analyzed for repeated events using hazards ratio. One hundred patients were randomized 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 first circuit (clotted) was similar for both groups (150 mL/min: 9.1 hr [5.5–26 hr] vs 10 hr [4.2–17 hr]; $p = 0.37$). Continuous renal replacement therapy using blood flow rate set at 250 mL/min was not more likely to cause clotting compared with 150 mL/min (hazards ratio, 1.00 [0.60–1.69]; $p = 0.68$). Gender, body mass index, weight, vascular access type, length, site, and mode of continuous renal replacement therapy or international normalized ratio had no effect on clotting risk. Continuous renal replacement therapy without anticoagulation was more likely to cause clotting compared with use of heparin strategies (hazards ratio, 1.62; $p = 0.003$). Longer activated partial thromboplastin time (hazards ratio, 0.98; $p = 0.002$) and decreased platelet count (hazards ratio, 1.19; $p = 0.03$) were associated with a reduced likelihood of circuit clotting.

Conclusions: There was no difference in circuit life whether using blood flow rates of 250 or 150 mL/min during continuous renal replacement therapy. (*Crit Care Med* 2017; 45:e1018–e1025)

Key Words: acute kidney injury; circuit life; continuous hemofiltration; continuous renal replacement therapy; critical care

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Acute kidney injury (AKI) is a complication of critical illness that affects up to 50% of intensive care patients (1–3). 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 ICUs (4). Continuous renal replacement therapies (CRRTs) rely 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 (5–8).

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

The impact of BFR on membrane clotting rate is potentially important and has not been examined in controlled studies. Despite suggestions to increase BFRs in the EC (11, 12), 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 ICUs surveyed (13). Observational studies and recent worldwide practice surveys of CRRT also demonstrate great variability in practice from 80 mL/min (12) to 350 mL/min (14–16). Although BFR may be an important determinant of circuit life in CRRT, the most suitable speed to reduce clotting and optimize 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 BFR (250 mL/min) would be superior to a slower BFR (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 enrollment.

Eligibility Criteria

Critically ill patients in ICU were eligible for the study if they fulfilled three criteria: 1) greater than or equal to 18 years old, 2) AKI (Risk, Injury, Failure [F], Loss, and End-stage kidney disease classification F) (16) requiring CRRT, and 3) vascular access was via the femoral vein for standardization. Patients were considered ineligible for the study if they fulfilled any of the following exclusion criteria: 1) required citrate anticoagulation (citrate protocol requires set BFR of 150 mL/min) and 2) expected stay in the ICU was less than 24 hours.

Interventions

The study compared two BFR 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 veno-venous hemofiltration (CVVH) or continuous veno-venous hemodiafiltration (CVVHDF) modality. Vascular access was via either Niagara 13.5F catheter (24 cm) (Bard, Murray Hill, NJ) or Gamcath Dolphin Protect 13.0F catheter (25 cm) (Gambro, Hechingen, Germany) dual lumen catheters. Treatment modality and choice of vascular access were at the discretion of the treating physician. Prismaflex with AN69ST (ST100) 1.0 m^2 membrane (Gambro Nephral TM, Lund, Sweden) or Infomed HF 440 with DF 140 Polyethersulfone 1.4 m^2 membrane (Infomed, Geneva, Switzerland) was used for all treatments. Bicarbonate buffered replacement and dialysis fluid (Baxter, Castlebar, County Mayo, Ireland) was used. In CVVH, replacement fluid was delivered into the EC before and after the filter (pre and postdilution), with a ratio of 50% predilution and 50% postdilution. Dose in CVVH was standardized at 2,000 mL/hr. In CVVHDF, the replacement fluid was all delivered postdilution. Dose in CVVHDF was standardized at 1,000 mL/hr replacement and 1,000 mL/hr dialyzate.

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 heparinization with unfractionated heparin (UFH) (1,000 IU/hr) delivered prefilter and protamine (10 mg/hr) delivered in the return limb of the EC for reversal of heparin. UFH was used alone and delivered prefilter at 5–10 IU/kg/hr. 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, body mass index (BMI), source of admission, severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] score II, III; Simplified Acute Physiology Score [SAPS] II), diagnostic group, presence of sepsis, mechanical ventilation, inotropes/vasopressors, and basic laboratory variables pertaining to renal function were collected.

Outcomes

The primary outcome was circuit life (measured in hours) and recorded as clotted when 1) transmembrane pressure across the circuit exceeded 300 mm Hg, 2) prefilter pressure greater than 200 mm Hg, 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, for example, 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 1 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 analyzed 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 (150 vs 250 mL/min).

Statistical Methods

The primary outcome (circuit life) was analyzed in a two-step process. First analysis: this excluded all electively removed or nonclotted 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 nonparametric statistics were used with circuit life reported as median and interquartile range (IQR). Circuit life for the two groups (150 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 analyzed using repeated events survival analysis (7, 17). A proportional hazard conditional frailty model (17) (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 IMB SPSS statistics for Windows (v2; IBM, Armonk, NY). Second analysis was performed using SAS (Enterprise Guide v5.1; SAS Institute, Cary, 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 Consolidated Standards of Reporting Trials diagram for patient enrollment is shown in **Figure 1**. Overall, 96 patients (49 in the 150 mL/min group and

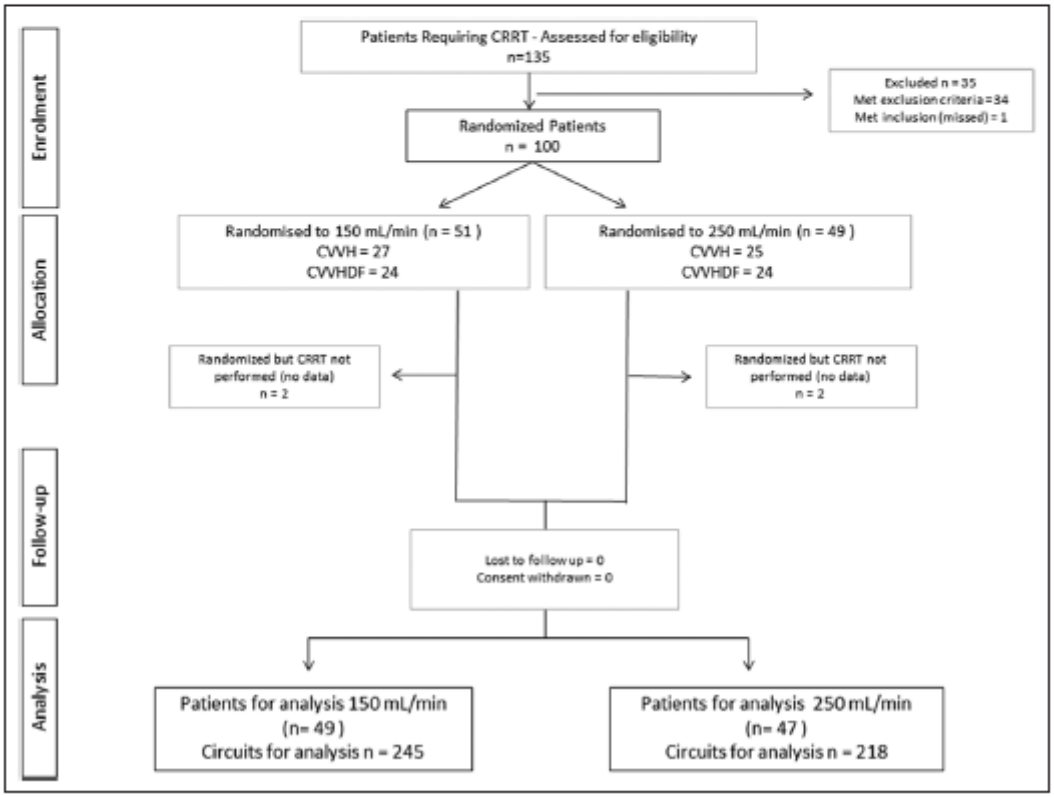

Figure 1. Flow diagram of participants showing assessment of eligibility, enrollment, treatment allocation, and follow-up in the trial. CRRT = continuous renal replacement therapy, CVVH = continuous veno-venous hemofiltration, CVVHDF = continuous veno-venous hemodiafiltration.

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 were four (IQR, 2–6) and totaled 8,206 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 9 kg difference in patient weight between the two groups ($p = 0.03$); however, BMI was similar for both groups. Prerandomization 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 hr: IQR, 6.0–24]) vs (250 mL/min, $n = 173$ [11.5 hr: 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 hours (IQR, 5.5–26 hr) in the 150 mL/min group compared with 10 hours (IQR, 4.2–17 hr) in the 250 mL/min group, p value equals to 0.37. Second and third median circuit lives for those deemed to have clotted

TABLE 1. Baseline Demographic and Clinical Characteristics

Admission Variables	150 mL/min ($n = 49$)	250 mL/min ($n = 47$)	p
Age	61.08 ± 15.96	60.77 ± 18.31	0.93
Gender (male/female)	34/49 (69%)	24/47 (51%)	0.10
Body mass index	29.01 ± 5.48	27.59 ± 6.85	0.26
Weight	85.19 ± 20.39	75.85 ± 20.30	0.03
APACHE II	22.16 ± 6.47	23.13 ± 6.55	0.47
APACHE III	85.65 ± 23.17	87.21 ± 26.28	0.76
Simplified Acute Physiology Score II	56.22 ± 14.19	55.55 ± 15.21	0.82
Source of admission—*n*/total no. (%)			
Emergency department	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)	
Admission diagnosis—*n*/total no. (%)			
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)	
Hematalogical	4 (8.2)	1 (2.1)	
Infection/abscess	2 (4.1)	2 (4.3)	
Mechanical ventilation—*n* (%)	41 (83.7)	36 (76.6)	0.44
Vasopressor/inotrope—*n* (%)	41 (83.7)	41 (87.2)	0.77
Severe sepsis—*n* (%)	24/49 (49)	26/47 (55.3)	0.55
Lab data prior to randomization			
Serum creatinine	317.20 ± 171.61	297 ± 181.54	0.16
Serum urea	23.62 ± 14.94	21.19 ± 10.03	0.33

APACHE = Acute Physiology and Chronic Health Evaluation.
Independent *t* test and chi-square test.

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 vs 250 mL/min; hazards ratio [HR], 0.85; log-rank test = 0.46) (**Fig. 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 with 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, and mode of CRRT or international normalized ratio. CRRT without use of anticoagulation was more likely to cause clotting compared with use of heparin or heparin/protamine (HR, 1.62 [1.18–2.23]; $p = 0.003$). Longer activated partial thromboplastin time (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).

TABLE 2. Circuit Life Duration–Clotted Circuits Only

Circuit Life	150 mL/min ($n = 49$)	250 mL/min ($n = 47$)	p
All circuits	$n = 196$	$n = 173$	
Median hours (IQR)	10 (6–24)	11.5 (6.8–18.3)	0.81
First circuit	$n = 49$	$n = 47$	
Median hours (IQR)	9.1 (5.5–26)	10 (4.2–17)	0.37
Second circuit	$n = 35$	$n = 38$	
Median hours (IQR)	14 (8.5–21)	13.8 (8.5–16.7)	0.45
Third circuit	$n = 22$	$n = 23$	
Median hours (IQR)	17 (10.5–28.5)	16 (12–21.5)	0.52

IQR = interquartile range.
Mann-Whitney *U* test.

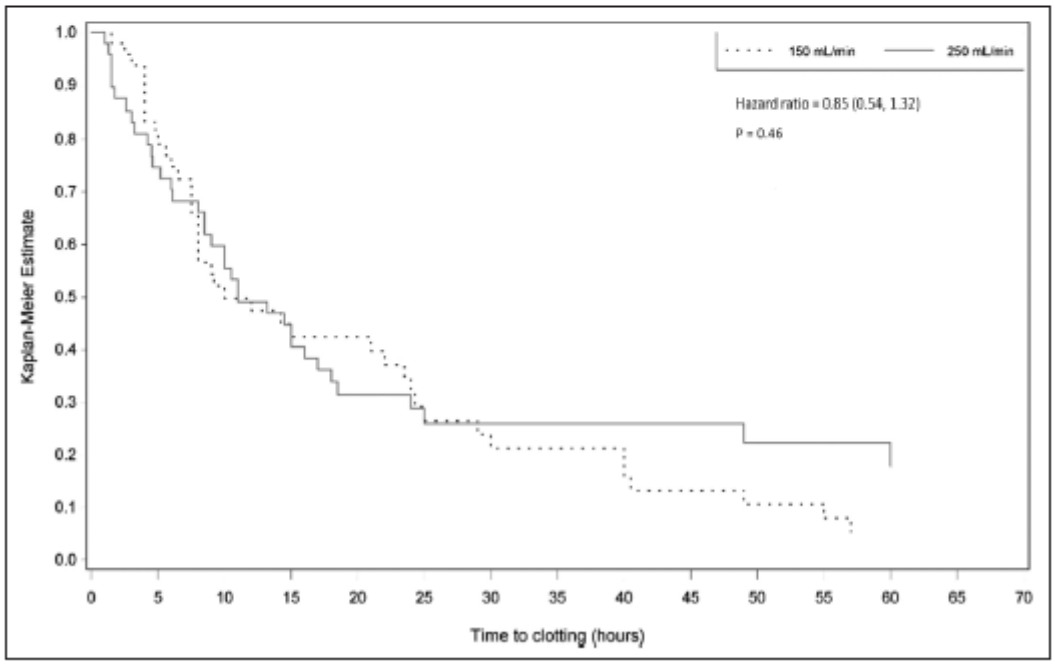

Figure 2. Kaplan-Meier estimate of the probability of continuous renal replacement therapy circuit survival for the first circuit—clotted circuits only.

TABLE 3. Univariate and Multivariate Analysis for All Circuits

		Univariate Model			Multivariate Model		
Covariate	Effect	HR (95% CI)	p	Random Effect Variance (SD)	HR (95% CI)	p	Random Effect Variance (SD)
Blood flow	250 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)
Gender	Male vs Female	1.56 (0.97–2.52)	0.07	0.905 (0.19)	1.76 (0.93–3.33)	0.08	
Body mass index		1.02 (0.98–1.06)	0.26	0.979 (0.20)	1.04 (0.95–1.14)	0.42	
Weight	for every 5 kg increase	1.04 (0.98–1.11)	0.19	0.957 (0.20)	0.96 (0.82–1.12)	0.59	
Vascath site	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	
Vascath length	20 vs 15 cm	0.83 (0.31–2.19)	0.10	1.091 (0.22)	0.92 (0.34–2.50)	0.18	
	24 vs 15 cm	0.53 (0.22–1.27)			0.17 (0.03–1.16)		
Vascath diameter	13F vs 13.5F	1.41 (0.96–2.09)	0.08	1.055 (0.21)	2.66 (0.24–29.91)	0.43	
Continuous renal replacement therapy mode	Continuous veno-venous hemodiafiltration vs continuous veno-venous hemofiltration	1.10 (0.68–1.77)	0.70	0.993 (0.20)			
Anticoagulation	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	
Platelets ($\times 10^{11}$)		1.13 (0.97–1.31)	0.11	0.928 (0.19)	1.19 (1.01–1.40)	0.03	
International normalized ratio (ratio)		0.84 (0.65–1.09)	0.19	0.993 (0.20)	1.05 (0.77–1.42)	0.77	
Activated partial thromboplastin time (s)		0.98 (0.97–0.99)	0.0003	0.898 (0.19)	0.98 (0.97–0.99)	0.002	

HR = hazards ratio.

DISCUSSION

This is the first known prospective study to examine the effect of BFR 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 BFR is increased to 250 mL/min, it does not increase circuit life during CRRT. Second, the use of an anticoagulation strategy and longer APTTs 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 (7, 18–27), whereas many aspects of treatment and prescription setting have not been investigated. One RCT has included BFR in the assessment of circuit clotting in CRRT, indicating that BFRs greater than 125 mL/min did not improve circuit survival (28). This study was conducted in CVVHD mode which is rarely used in current practice (13, 15, 29, 30). Pure diffusive modes of hemofiltration such as CVVHD have been shown to be associated with decreased procoagulatory activity in the dialyser membrane when compared with convective modes (31, 32) and make comparisons to CVVH and CVVHDF problematic.

One single center study assessing 1,332 treatments from 355 patients concluded that BFR did indeed affect circuit life (12). In this retrospective audit, the authors suggest a BFR less than 200 mL/min significantly decreased circuit life compared with 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 and 300 mL/min.

Implications of Study Findings

Our data provide evidence to suggest that a faster BFR 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 (33–35) and always be greater than 100 mL/min to avoid premature clotting (36). 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 effects on circuit life (10, 37, 38).

Despite many authors suggesting BFRs for CRRT of 200–250 mL/min (12, 33–35) and international surveys indicating practical prescriptions of greater than 200 mL/min, there has been no endorsements for this setting. The Acute Dialysis Quality Initiative 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 (39). The more recent Kidney Disease Improving Global Outcomes 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 makes no recommendations for practice based on evidence (40).

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

We have previously reported on circuit life in CVVH when no anticoagulation was used compared with low-dose UFH and a regional heparin technique (45). 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 BFR on circuit life in two commonly used modes of CRRT. This analysis is based on a large number of circuits and for 8,206 hours of treatment time. This number of patients and treatment time is representative of a tertiary level ICU and signifies important findings for current CRRT practice. The presentation of our analysis for first circuit (dotted) 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 BFRs used in this study. BFRs less than 150 mL/min or greater than 250 mL/min may have yielded a different outcome. Circuit life (hours) 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 ICUs 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 BFR of 250 mL/min does not improve CRRT circuit life compared with a BFR of 150 mL/min. Independent factors that may extend circuit life include anticoagulation strategies, higher APTT, and lower platelet counts.

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5.4 Circuit distribution

Examination of the primary outcome (circuit life) involved a two-stage analysis of the data. The first stage included analysis of first circuits only. Any circuits that were terminated prior to the diagnosis of clotting (for procedural or other elective reasons) were then censored. Assessment established that circuit life data lacked normal distribution, and non-parametric analysis was used. Circuit life was then reported as median and IQR. Assessment of any second and third circuit life data (clotted only) was then conducted using the same process and reported. Circuit survival probability for the first circuits only (clotted) was then conducted and reported using the Kaplan–Meier curve, log-rank test and HR.

The examination of clotted first circuits only endeavoured to apply rigour to the analysis of circuit life. Each patient was thought to contribute at least one circuit that could be used for analysis. Each patient might have had a pathology or pathophysiology that might have influenced the clotting process for each circuit. The first-stage analysis of one circuit from each patient intended to remove any bias from individual patients to the primary outcome if individual patients were able to contribute multiple circuits. In this study, there was a wide range of distribution in the number of circuits per patient (Figure 5.1).

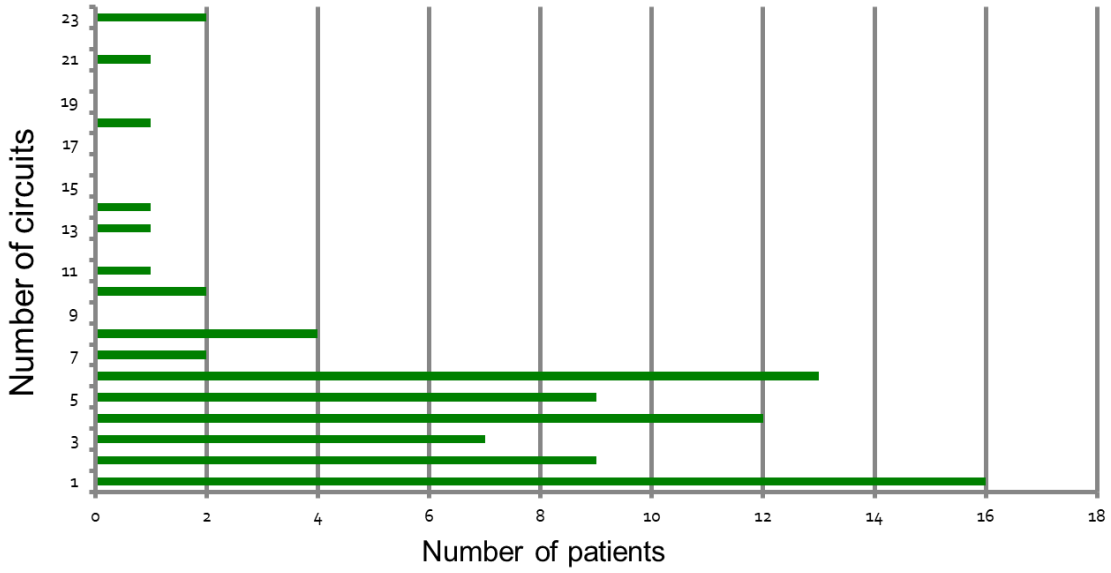

Figure 5.1: Distribution of circuits for study patients.

Sixteen patients in this study supplied only one circuit for analysis, whereas two patients supplied 23 circuits, which equates to 10% of the total number of circuits (n = 463). The

analysis of all circuits might have been misleading if patients contributing >20 circuits had a propensity for premature clotting or alternatively lengthy circuit life.

The secondary analysis did include all circuit life data (elective cessation and clotted circuits) for analysis. The issue of one patient contributing multiple circuits was addressed by using repeated-events survival analysis. Event dependence was tested, meaning that the occurrence of one event (premature or extended circuit life in an individual patient) might have made it more likely for this to occur repeatedly in the same patient because of their pathology, genetics or pathophysiology. The advantage of this model and analysis is that it considered any within-cluster correlation of circuit life and accounted for the variable distribution seen in Figure 5.1.

5.5 Anticoagulation use

Univariate and multivariate analysis indicated that the use of an anticoagulation strategy (unfractionated heparin or regional heparin and protamine) extended circuit life in CRRT compared with no anticoagulation (HR 1.62, 95% CI 1.18–2.23; $p = 0.003$). Further, any increase in APTT that might have been endogenous or from an anticoagulation strategy such as unfractionated heparin was also an independent factor in prolonging circuit life (HR 0.98, 95% CI 0.97–0.99; $p = 0.002$). Table 5.1 outlines the use of a no-anticoagulation strategy in comparison with anticoagulation strategies.

Table 5.1: Anticoagulation Use and Circuit Life for Study Circuits

Circuit life/Anticoagulation	150 mL/min n = 49 patients	250 mL/min n = 47 patients
All circuits (elective & clotted)	n = 245	n = 218
No anticoagulation, no. (%)	67 (27.3)	176 (80.7)
Unfractionated heparin, no. (%)	93 (38.0)	32 (14.7)
Heparin/Protamine, no. (%)	85 (34.7)	10 (4.6)
All circuits (clotted)	n = 196	n = 173
No anticoagulation, no. (%)	92 (46.9)	100 (58.5)
Median circuit life, h (IQR)	10 (6.0, 24.0)	11.5 (6.8, 18.3)
First circuit	n = 49	n = 47
No anticoagulation, no. (%)	37 (75.6)	35 (74.6)
Unfractionated heparin, no. (%)	10 (20.4)	9 (19)
Heparin/Protamine, no. (%)	2 (4)	3 (6.4)
Median circuit life, h (IQR)	9.1 (5.5, 26)	10 (4.2, 17)
Second circuit	n = 35	n = 38
No anticoagulation, no. (%)	23 (66)	23 (60.7)
Unfractionated heparin, no. (%)	6 (17)	13 (34)
Heparin/Protamine, no. (%)	6 (17)	2 (5.3)
Median circuit life, h (IQR)	14 (8.5, 21)	13.8 (8.5, 16.7)
Third circuit	n = 22	n = 23
No anticoagulation, no. (%)	13 (59.4)	12 (52.3)
Unfractionated heparin, no. (%)	6 (27)	9 (39)
Heparin/Protamine, no. (%)	3 (13.6)	2 (8.7)
Median circuit life, h (IQR)	17 (10.5, 28.5)	16 (12, 21.5)

The use of an anticoagulation strategy for all circuits in both intervention arms for this study was below 50%. In other words, more than half of all study circuits were not prescribed any anticoagulation by the treating ICU team. On examination of all circuits used in this study, there was a difference between the two BFR groups in relation to anticoagulation use. There was more anticoagulation use in the 150 mL/min group overall, with 178 circuits out of a possible 245 circuits anticoagulated with unfractionated heparin or regional heparin (72.6%). In the 250 mL/min group, anticoagulation was only used in 42 circuits out of 218 (19.2%), which equates to less than one in five circuits that were prescribed any anticoagulant regimen.

The use of any anticoagulation for the patient's first CRRT circuit was low for both groups, with a non-anticoagulation strategy prescribed in 75.6% and 74.6% in the 150 mL/min and 250 mL/min groups, respectively. For each patient prescribed CRRT, the prescribing team deemed the patient not able to receive an anticoagulant for the first circuit in two-thirds of cases. If patients required additional RRT after the initial first circuit, the prescription of an anticoagulation strategy remained under 40% for the second and third circuits by the treating ICU team.

5.6 Publication 3: Evaluation of urea and creatinine change during continuous renal replacement therapy: Effect of blood flow rate

Evaluation of urea and creatinine change during continuous renal replacement therapy: effect of blood flow rate

Nigel Fealy, Leanne Aitken, Eugene du Toit, Michael Bailey and Ian Baldwin

Acute kidney injury (AKI) is a complication of critical illness that affects up to 50% of intensive care patients.[1-3] The use of renal replacement therapy has evolved as the treatment for severe AKI, and is required in up to 5–6% of all critically ill patients in intensive care units (ICUs).[4] Continuous renal replacement therapy (CRRT) is the most common dialytic therapy used to treat AKI worldwide.[5] CRRT techniques are instituted by clinicians with the aim of achieving homeostasis of water, electrolytes, acid base and removal of waste products in this group of patients.[6] Solute control and maintenance have long been key priorities in the provision of CRRT and has been an area of research and focus since the first Acute Dialysis Quality Initiative consensus meeting.[7,8] Subsequently, two large multicentre randomised controlled trials definitively showed that there was no survival benefit in increasing the dose of CRRT from the common dose of 25 mL/kg/h.[9,10]

While a greater CRRT dose does not lead to improved patient outcomes, solute removal (particularly small solutes, such as urea and creatinine) remains an important aim of the therapy. For prescribing CRRT, clinicians continue to target a prescription dose and best settings to achieve solute removal for each 24-hour period, to remove excessive toxins and maintain solute balance for each individual patient.[8] In addition to a prescribed effluent rate, other clinical variables may contribute to solute clearance in CRRT, including "down time", membrane composition, membrane fouling and frequent circuit clotting.[11] The Acute Dialysis Quality Initiative has recently recommended research objectives aimed at identifying optimal techniques and practical prescriptions for solute removal.[8] Blood flow rate (BFR) and a modality of CRRT — that is, continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD) or continuous venovenous haemodiafiltration (CVVHDF) — are two common bedside prescriptions that may have a direct impact on solute removal, but have not been assessed in any randomised controlled study. An increase in BFR in convective modes, such as CVVH, may directly assist solute removal by increasing transmembrane pressure, exposing additional plasma water to the dialyser per effluent dose and assisting solvent drag across the membrane. Indirectly, a faster BFR may decrease blood viscosity in the membrane,

ABSTRACT

Objective: To determine if faster blood flow rate (BFR) has an effect on solute maintenance in continuous renal replacement therapy.

Design: Prospective randomised controlled trial.

Setting: 24-bed, single centre, tertiary level intensive care unit.

Participants: Critically ill adults requiring continuous renal replacement therapy (CRRT).

Interventions: Patients were randomised to receive one of two BFRs: 150 mL/min or 250 mL/min.

Main outcome measures: Changes in urea and creatinine concentrations (percentage change from baseline) and delivered treatment for each 12-hour period were used to assess solute maintenance.

Results: 100 patients were randomised, with 96 completing the study (49 patients, 150 mL/min; 47 patients, 250 mL/min). There were a total of 854 12-hour periods (421 periods, 150 mL/min; 433 periods, 250 mL/min). Mean hours of treatment per 12 hours was 6.3 hours (standard deviation [SD], 3.7) in the 150 mL/min group, and 6.7 hours (SD, 3.9) in the 250 mL/min group ($P = 0.6$). There was no difference between the two BFR groups for change in mean urea concentration (150 mL/min group, –0.06%; SD, 0.015; *v* 250 mL/min group, –0.07%; SD, 0.01; $P = 0.42$) or change in mean creatinine concentration (150 mL/min, –0.05%; SD, 0.01; *v* 250 mL/min, –0.08%; SD, 0.01; $P = 0.18$). Independent variables associated with a reduced percentage change in mean serum urea and creatinine concentrations were low haemoglobin levels (–0.01%; SD, 0.005; $P = 0.002$; and 0.01%; SD, 0.005; $P = 0.006$, respectively) and less hours treated (–0.023%; SD, 0.001; $P = 0.000$; and –0.02%; SD, 0.002; $P = 0.001$, respectively). No effect for bodyweight was found.

Conclusions: Faster BFR did not affect solute control in patients receiving CRRT; however, differences in urea and creatinine concentrations were influenced by serum haemoglobin and hours of treatment.

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increase filtration fraction and decrease membrane fouling with eventual clotting. In diffusive modes, such as CVVHD and CVVHDF, faster BFR may assist with solute removal by maximising concentration gradients between blood (plasma) flow and dialysate flow rates, decreasing dwell time and sustaining diffusive movement of solutes across the membrane.[12]

We aimed to test our hypothesis that faster BFR increases small solute removal (eg, urea and creatinine) in critically ill patients receiving CRRT. To address this question, we report additional findings from our recently published randomised controlled trial comparing two BFRs and the effect on circuit life in patients treated with CRRT.[13]

Methods

Trial design and setting

This study was a prospective, parallel group randomised controlled trial conducted in a 24-bed, adult, tertiary referral ICU 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 from the patient or their next of kin was obtained before or soon after enrolment.

Eligibility criteria

Critically ill patients in ICU were eligible for the study if they fulfilled the following criteria:

- age ≥ 18 years; and
- AKI (RIFLE [risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage kidney disease] classification = F)[14] requiring CRRT.
- Patients were considered ineligible for the study if they fulfilled any exclusion criterion:
- required citrate anticoagulation (citrate protocol requires a set BFR of 150 mL/min); or
- expected to stay in the ICU for < 24 hours.

Interventions

The study compared two BFR settings and the effect on small solute control in CRRT. BFR was either 250 mL/min or 150 mL/min using CVVH and CVVHDF modes. Vascular access was either Niagara 13.5 Fr catheter (24 cm) (Bard, Murray Hill, NJ, USA) or GamCath Dolphin Protect 13.0 Fr catheter (25 cm) (Gambro, Hechingen, Germany) dual lumen catheters. Machines used were Prismaflex with AN69 ST (ST100) 1.0 m² membrane (Gambro Nephral TM, Lund, Sweden) or Infomed HF440 with DF140 Polyethersulfone 1.4 m² membrane (Infomed, Geneva, Switzerland) for all treatments respectively. We used bicarbonate buffered replacement and dialysis fluid (Baxter, Castlebar, Co. Mayo, Ireland). In CVVH, the replacement fluid was delivered into the extracorporeal circuit before and after the filter (pre- and post-dilution), with a ratio of 50% pre-dilution and 50% post-dilution. The dose in CVVH was standardised at 2000 mL/h. In CVVHDF, the replacement fluid was delivered 100% post-dilution. The dose in CVVHDF was standardised at 1000 mL/h replacement and 1000 mL/h dialysate. CRRT was prescribed by the treating intensivist and provided by ICU nurses.

Data collection

We collected baseline data regarding age, gender, weight, body mass index (BMI), source of admission, severity of illness (APACHE [Acute Physiology and Chronic Health Evaluation] II and III score; SAPS [Simplified Acute Physiology Score] II), diagnostic group, presence of sepsis, mechanical ventilation, inotropes and vasopressors, and basic laboratory variables pertaining to renal function.

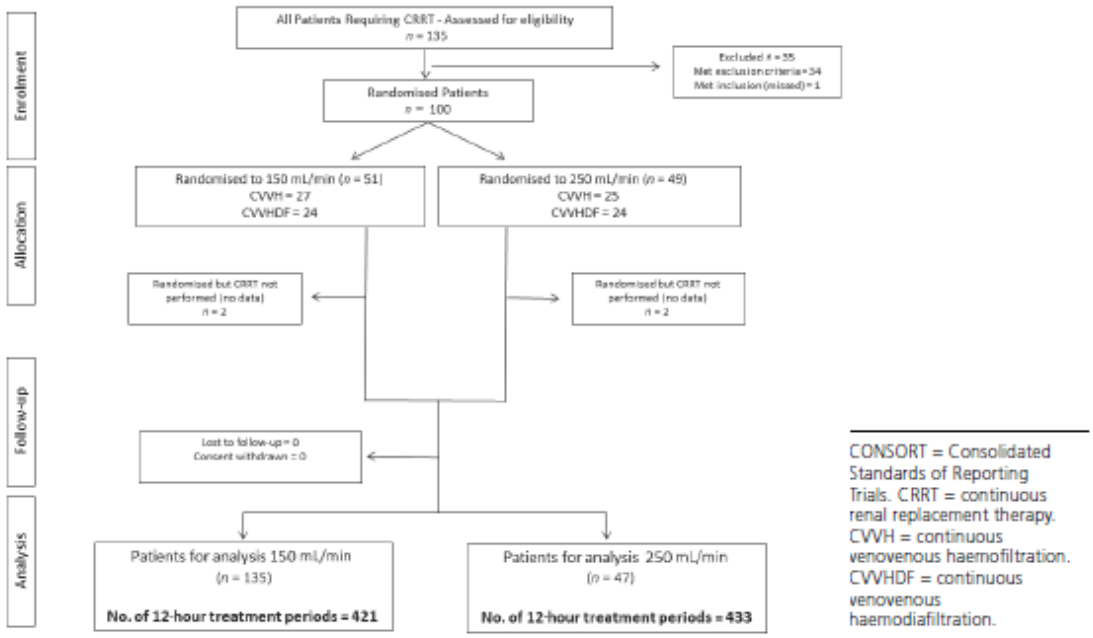
Outcome measurements

For all patients, twice-daily (0500 and 1700 hours) measurement of haemoglobin and biochemistry (serum creatinine and urea) was performed. The primary outcome was small solute maintenance estimated by the change in urea and creatinine concentrations over these two predefined 12-hour periods each day (percentage of change in serum levels over time). Circuit life was documented for each CRRT circuit as cumulative hours, so that delivered treatment hours could be calculated for each 12-hour period (T1, 0500–1700 hours; and T2, 1700–0500 hours).

Randomisation

Patients were screened and entered into the study by ICU clinical staff. Patients were assigned randomly with stratification for modality. Once the treating physician prescribed CRRT and the mode of therapy, patients were randomised using a web-based central randomisation service (Griffith University Clinical Trial Coordinating Centre). A variable block randomisation with parallel allocation was software-generated, with inbuilt concealment to allocate participants to each study group (150 mL/min *v* 250 mL/min). Patients stayed in the treatment group allocated at randomisation and modality (CVVH or CVVHDF) for treatment throughout their ICU stay. The sample size was without power calculation, was of convenience and was associated with the primary investigation.[13]

Figure 1. CONSORT diagram for patient enrolment



Data analysis

Linear regression analysis was performed to identify independent variables that may be associated with change in small solute serum levels. Independent variables included modality of CRRT, gender, BMI, weight, haemoglobin level and number of hours treated in each 12-hr period. Repeated measures analysis of variance (ANOVA) was used on the independent variables showing significance. The advantage of this model is that it considers within-subject measures over multiple time points. In this study, patients contributed multiple 12-hour periods measuring solute percentage change over these periods. Data lacking normality of distribution are presented as median with interquartile range (IQR) (25% and 75%), using the Wilcoxon rank sum test or mean with standard deviation (SD) when normally distributed, and using the Student *t* test, χ^2 test and the Fisher exact test. A $P < 0.5$ was considered significant. SPSS Statistics 21.0 (IBM, Chicago IL, USA) software was used for all data analysis.

Results

Participants and recruitment

All patients receiving CRRT in the study ICU ($n = 135$) were screened for eligibility between June 2013 and August, 2014. From this screening, 100 patients were considered eligible and randomised to the study; and two patients from each group were randomised but did not receive CRRT. Figure 1 shows the CONSORT diagram for patient enrolment. Overall, 96 patients (49 in the 150 mL/min group, and 47 in the 250 mL/min group) contributed a total of 854 12-hour treatment interval periods (421 in the 150 mL/min group, and 433 in the 250 mL/min group). Of the patients studied, 50 received CVVH compared with 46 treated with CVVHDF.

At randomisation, patients were similar with respect to age, sex, severity of illness scores (APACHE II and III; SAPS II), admission source and diagnosis (Table 1). There was a slight weight difference, with patients in the 150 mL/min group being heavier ($P = 0.03$); however, BMI was similar for both groups. Pre-randomisation renal function was also similar for both groups.

Primary outcomes: solute maintenance

A total of 7745.5 treatment hours were recorded from both groups (3840.7 hours in the 150 mL/min group, and 3904.8 hours in the 250 mL/min group) (Table 2). The mean treatment hours for each 12-hour period was similar (150 mL/min group; 6.3 hours; SD, 3.7; 52.5%, *v* 250 mL/min group; 6.7 hours; SD, 3.9; 55.8%; $P = 0.6$) as well as total number of 12-hour periods for each BFR group (Table

Table 1. Baseline demographic and clinical characteristics*

Admission variables	150 mL/min (*n* = 49)	250 mL/min (*n* = 47)	*P*
Age	61.08 ± 15.96	60.77 ± 18.31	0.93
Gender (male/female)	34/49 (69%)	24/47 (51%)	0.10
BMI	29.01 ± 5.48	27.59 ± 6.85	0.26
Weight	85.19 ± 20.39	75.85 ± 20.30	0.03
APACHE II	22.16 ± 6.47	23.13 ± 6.55	0.47
APACHE III	85.65 ± 23.17	87.21 ± 26.28	0.76
SAPS II	56.22 ± 14.19	55.55 ± 15.21	0.82
Source of admission			
ED	13 (27.7%)	12 (25.5%)	
Ward	17 (34.7%)	17 (36.2%)	
Post-operative (elective)	7 (14.3%)	6 (12.8%)	
Post-operative (emergency)	5 (10.2%)	4 (8.5%)	
Transfer from other ICU	5 (10.2%)	5 (10.6%)	
Transfer from other hospital	2 (4.1%)	3 (6.4%)	
Admission diagnosis			
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 failure/ genitourinary disorder	5 (10.2%)	5 (10.6%)	
Haematological	4 (8.2%)	1 (2.1%)	
Infection/abscess	2 (4.1%)	2 (4.3%)	
Mechanical ventilation	41 (83.7%)	36 (76.6%)	0.44
Vasopressor/inotrope	41 (83.7%)	41 (87.2%)	0.77
Severe sepsis	24/49 (49.0%)	26/47 (55.3%)	0.55
Laboratory data before randomisation			
Serum creatinine	317.20 ± 171.61	297 ± 181.54	0.16
Serum urea	23.62 ± 14.94	21.19 ± 10.03	0.33

APACHE = Acute Physiology and Chronic Health Evaluation. BMI = body mass index. ED = emergency department. ICU = intensive care unit. SAPS = Simplified Acute Physiology Score. * Independent *t* test and χ^2 test.

2). The median number of 12-hour periods per patient was also similar for both groups (150 mL/min; 6; IQR, 4–12; *v* 250 mL/min; 7; IQR, 4.5–12; *P* = 0.4).

Blood plasma concentrations of urea and creatinine were similar for time interval (T1 and T2), BFR and modality (Table 2). Linear regression analysis showed no difference in the change in urea and creatinine concentrations for BFR groups, modality of CRRT, gender, BMI and weight. Repeated measures analysis of variance (ANOVA) revealed no difference between the two BFR groups for change in mean urea concentration (150 mL/min; –0.06%; SD, 0.015; *v* 250 mL/min; –0.07%; SD, 0.01; *P* = 0.42) (Figure 2) or change in mean creatinine concentration (150 mL/min; –0.05%; SD, 0.01; *v* 250 mL/min; –0.08%; SD, 0.01; *P* = 0.18) (Figure 3) There was a significant correlation between the 12-hourly percentage change in the serum concentration of these two small solutes, with decreased haemoglobin levels (150 mL/min; –0.01%; SD, 0.005; *P* = 0.002; *v* 250 mL/min; 0.01%; SD, 0.005; *P* = 0.006) and less hours of CRRT during the 12-hour period (eg, more down time) (150 mL/min; –0.023%; SD, 0.001; *P* = 0.000; *v* 250 mL/min; –0.02%; SD, 0.002; *P* = 0.001).

Discussion

Key findings

In a cohort of 96 patients requiring CRRT, three key findings have been identified. First, analysis of the data from this study failed to support the hypothesis that faster BFR would improve small solute clearance. Second, there was an association with number of hours treated with CRRT and change in serum solute levels. Third, lower serum haemoglobin levels are an independent factor associated with difference in urea and creatinine levels.

Table 2. Continuous renal replacement therapy treatment times and solute levels

	150 mL/min		250 mL/min	
	CVVH	CVVHDF	CVVH	CVVHDF
12-hour time periods	169	252	261	172
Total treatment time (hours)	1527.7	2313	2331.3	1573.5
Hours of treatment (12-hour periods); mean (SD)	6.3 (3.7)		6.7 (3.9)	
Urea level, mmol/L				
T1 (0500–1700); mean (SD)	15.7 (7.6)	16.7 (8.7)	13.2 (5.9)	13.1 (6.2)
T2 (1700–0500); mean (SD)	15.2 (7.5)	16.4 (7.7)	12.7 (5.2)	13.4 (6.1)
Creatinine level, µmol/L				
T1 (0500–1700); mean (SD)	217.0 (127.3)	226.7 (152.7)	167.8 (82.8)	209.1 (126.2)
T2 (1700–0500); mean (SD)	218.3 (144.9)	216.6 (118.8)	165.0 (87.1)	202.3 (102.9)

CVVH = continuous venovenous haemofiltration. CVVHDF = continuous venovenous haemodiafiltration. min = minute. SD = standard deviation

Figure 2. Urea change by grouping (repeated measures analysis of variance [ANOVA])

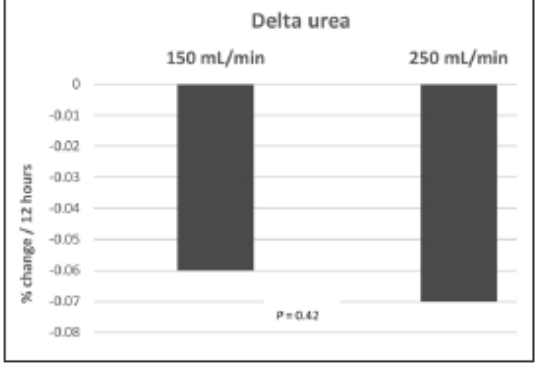
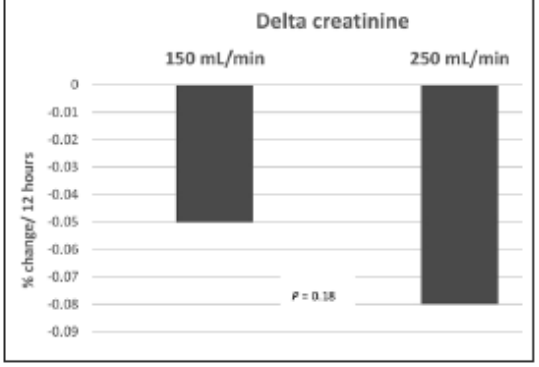


Figure 3. Creatinine change by grouping (repeated measures analysis of variance [ANOVA])



Relationship to previous studies

The efficiency of solute removal in CRRT has been a key focus since it started to be used for treating critically ill patients with AKI.[15,16] Foundation studies for small solute removal in CRRT were often unable to report BFR, as this was determined by arterial blood pressure in continuous arteriovenous circuits or as a low fixed rate (100 mL/min) determined by primitive blood pumps in the first venovenous circuits. These early reports identified that effluent rates (dialysate or ultrafiltration rates) were the most important determinants of small solute removal, as the volume of effluent would approximate the clearance.[15,16] Today, despite significant advances in CRRT technology, dosing or solute clearance in CRRT is still expressed as total effluent volume per weight and unit of time (mL/kg/h),[11] indicating that other factors may be less important in the clearance of solutes across the semi-permeable membrane.

One aspect of CRRT technology that has changed over time is clinicians prescribing a faster BFR. A recent survey of Australian and New Zealand ICUs indicated a BFR of 150–200 mL/min was the dominant setting; however, faster rates of 200–250 mL/min were now commonplace in the ICUs surveyed.[17] Observational studies and recent worldwide practice surveys of CRRT also show great variability in practice, from 80 mL/min[18] to 350 mL/min.[19,20] The prescription of BFR in intermittent haemodialysis (IHD) has long been seen as integral to therapy prescription for dosing (solute removal) in direct relation to dialysate flow rates, and is well established and standardised for the treatment of chronic kidney disease with dialysis.[21] Blood flow rates of ≥ 300 mL/min are prescribed typically with matching or higher dialysate flow rates (300–500 mL/min) to achieve azotemic control in this group of patients.[22,23] One key important difference between IHD and CRRT is the ability to achieve higher BFR during IHD with the use of long term large bore vascular access catheters and arteriovenous shunts, which both allow high BFR prescriptions aimed at targeted dosing regimens accordingly.

Historically, the prescription of BFR in CRRT has been based on the experience gained from IHD therapies, and a BFR of 200 mL/min has been common without any evidence for this.[24,25] However, limiting factors for blood flow in CRRT have been the use of short term small bore catheters in haemodynamically unstable patients[26] and the machine technology used to pump venous blood through the extracorporeal circuit. Unlike IHD, the setting of BFR in CRRT has been focused towards extracorporeal circuit patency and prevention of premature clotting (eg, < 6 hours) of the circuit.[13,19,27] The prescription of faster BFR in recent times may be attributed to improvements in vascular access catheters and machine capability rather than concern for solute clearance.

One retrospective review of 15 patients has examined any association with blood flow rates and clearances of urea and creatinine concentrations in CVVHDF.[28] Four BFR groupings were audited, with a mean rate of 125 mL/min that ranged between 35 mL/min and 175 mL/min. A comparative finding was that a BFR of 135–145 mL/min showed a difference in urea and creatinine concentrations compared with lower BFR ranges in this mode of CRRT. Consistent with our findings, Gilbert and colleagues[28] report that differences in change in urea and creatinine concentrations were best predicted by number of hours treated.

The acronym CRRT suggests that therapy is continuous and without interruption; however, down time and failure occurs frequently.[29] Reasons for interruptions to treatment are clotting, or when the patient requires procedures outside the ICU, or when native assessment of kidney function is trialled.[30] In this study, we identified an effective treatment time approximating 50% (6.3 hours and 6.7 hours/12 hours). The delivery therapy time is similar, with previously reported prescription versus delivery data.[24-33]

Similar to this study, it has also been shown that there is a direct correlation between reduction in hours of treatment and loss of small solute control in critically ill patients.[11,29,31] While there has been comparative prescribed versus actual delivered dose and therapy reports, it remains unclear which is the optimal number of CRRT hours per day to maintain small solute control in this group of patients. However, there is recent acknowledgement that clinicians who prescribe CRRT should be aware of the effect of delivery time in comparison to prescribed treatment, and should form an integral quality indicator measure in process reassessment, monitoring, reporting and benchmarking for CRRT.[34]

Based on the results identified in this study, we suggest that the number of hours of active treatment should be routinely reviewed as a component of practice. This information should be reviewed twice daily and then be considered in the context of solute levels and planned activities that might lead to down time, with CRRT prescriptions altered accordingly.

In this study, we report that low serum haemoglobin levels are an independent variable that affects small solute removal. Patients with lower serum haemoglobin count showed a smaller reduction in serum urea and creatinine levels over a 12-hour period. To our knowledge, this is the first study to report such finding.

Strengths and limitations

This randomised controlled trial of 100 patients presents, for the first time, an investigation into the effect of BFR on solute maintenance in two commonly used modes of CRRT. The analysis is based on 7745 hours (> 300 days) of treatment time. This number of patients and treatment time is representative of a tertiary level ICU and provides important findings for current CRRT practice. The study has some limitations. Solute clearance was reported as the percentage change in serum level over time. A direct measurement of serum solute levels and effluent solute levels would provide a more precise indication of control and represent a closer assessment for clearance. However, we did not measure effluent biochemistry.

The study was conducted in a single tertiary level ICU, where training and expertise among nurses for their ability to troubleshoot alarm conditions may influence delivered time (12 hours) compared with other centres, where circuits may terminate prematurely due to low skill level, or where the delays in reinstitution of therapy may be due to poor training. One further limitation may be the defined BFR used in this study. We chose 150 mL/min and 250 mL/min as a result of current intensive care practices. BFRs < 150 mL/min or > 250 mL/min may have yielded a different finding.

Conclusions

A BFR of 250 mL/min does not improve solute clearance compared with a BFR of 150 mL/min in CVVH or CVVHDF. Independent factors that affect solute removal include hours of effective treatment and haemoglobin levels.

Competing interests

None declared.

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* Please note. There is a typographical on Page 42 of the publication. This sentence is contained within the peer reviewed publication. The sentence should state "A faster BFR may decrease blood viscosity in the membrane, **decrease filtration fraction** and decrease membrane fouling with eventual clotting".

5.7 Informing statistical power

The primary research question for this study was the hypothesis that a higher BFR may increase circuit life in CRRT (CVVH and CVVHDF modes). Because of a lack of historical and supportive data to inform a power calculation for this research question, 100 patients were chosen to ensure a sample that was sufficient to reflect the usual characteristics of the ICU population. In addition, a recruitment period was chosen of 1 year to inform future studies of enrolment data. This study is therefore considered a pilot study, and data from it may now be used to determine a sample size to detect a significant association or difference between the experimental (250 mL/min) and control (150 mL/min) groups. Adequately powered studies enable the estimation of the likelihood of detecting significant effects at a given probability of a type II error. A power analysis calculates the sample size needed to adequately represent the target population (Table 5.2).

5.7.1 Power calculation for future randomised controlled trials

- Hypothesis: A higher BFR (250 mL/min) may increase circuit life in CRRT compared with the conventional BFR (150 mL/min).

Table 5.2: Power Calculation Based On First Circuit (Clotted Only) Data

Study parameters	150 mL/min	250 mL/min
Median circuit life, h (IQR)	9.1 (5.5, 26.0)	10.0 (4.2, 17.0)
Mean circuit life, h (SD)	20.1 (22.31)	17.65 (23.24)
Alpha = 0.05		
Power = 0.8		
Sample size	1302	1302
Total	2604 participants	

Sample size calculation revealed that assuming alpha = 0.05 and power = 0.8 and based on the circuit life data obtained in this study, a sample of 2604 participants are required to assess the impact of BFR on circuit life in CRRT.

5.8 Feasibility parameters for future randomised controlled trials

A further aspect of pilot studies is to potentially refine or modify the research method to develop large-scale powered studies. To assess the success of feasibility, broadly classified criteria require examination. These criteria can be categorised under processes, practicalities, management and scientific. In the following section, these criteria are examined in relation to this study.

5.8.1 Processes

5.8.1.1 Recruitment rates

The target for recruitment was 100 patients in a 1-year time frame. A pre-study education process was undertaken for intensive care consultant and registrar medical staff and senior and bedside nursing staff. The education process was aimed at involving the ICU team in the identification of potential study participants and screening processes prior to randomisation and allocation. CRRT is initiated throughout the 24 h cycle, so other screening practices (e.g., daily) would not have captured participants prior to first circuit commencement. One hundred and thirty-five patients were screened for eligibility between June 2013 and August 2014. One hundred and one patients met the inclusion criteria, with 100 patients randomised from this number. Only one patient assessed for eligibility and meeting inclusion criteria during the 14-month period missed randomisation, with CRRT commencing prior to the procedure. Approximately 25% of all patients assessed for eligibility were excluded from the study. The major reason for exclusion was vascular access located in sites other than the femoral vein, required for standardisation of technique. Recruitment was achieved in the expected time frame in this single-centre study. An adequately powered study would require multicentre enrolment to complete and acquire similar recruitment sites and rates achieved for the RENAL study investigating dose and mortality in CRRT.[219]

5.8.1.2 Eligibility criteria

Inclusion criteria required adults (≥18 years), RIFLE classification F (Failure) requiring CRRT, and vascular access in the femoral vein location. RIFLE criteria F with physician

decision to treat with CRRT provided enough participant numbers in this study. A future study may apply updated and accepted AKIN guidelines (stage 3) to identify patients with AKI requiring CRRT, particularly if multiple centres are required to complete the study. Limiting vascular access to the femoral vein excluded approximately 25% of patients receiving CRRT. A future RCT may include patients with vascular access in the internal jugular or subclavian position and include these variables in univariate and multivariate analysis, similar to vascular access type, diameter, position and length as analysed in this study. Exclusion criteria included CRRT with citrate anticoagulation as this regimen required a fixed BFR to maintain the dose in CVVH mode only. Current citrate protocols allow for alteration in BFR, but are applied almost exclusively in CVVHDF mode with significant increase in pre-dilution volume. CRRT with citrate may be included in future RCTs with appropriate univariate and multivariate analysis, as used in this study.

5.8.1.3 Consent

Written informed consent was required by either the participant or the person responsible for the participant. As all patients were treated in the ICU and >75% of participants in both study groups required mechanical ventilation, many consents were obtained from next of kin. There was no failure to consent or withdrawal of consent in this study (100% consent rate and 0% withdrawal). One important consideration that enabled high randomisation rates was the ability to gain delayed consent from either the participant or the person responsible for the participant. CRRT is often commenced out of hours or as an emergency therapy. Delayed consent allowed first for randomisation and interventions to commence and, second, for the consent process to be undertaken in a less stressed and time-sensitive manner. The number of consents obtained using the delayed process was 92 out of the possible 100 (92%). The high number of delayed consent processing might have been due to multiple factors. Often, the initiation of CRRT is time-sensitive, and there is limited opportunity to effectively communicate to the patient (participant) or the person responsible for the participant, where an informed process and time to review the study information prior to commencement of therapy are essential. In addition, critically ill patients in the ICU may be unable to provide consent because of their illness, and relatives or next of kin may not be immediately available prior to initiation of the therapy to undertake the consent process. All consents were performed by the primary investigator, and this single person reference as well as the high delayed consent process might have contributed to the high consent rate in this study.

5.8.1.4 Retention rates

Four out of 100 patients (two in each intervention arm) failed to complete the study. Randomisation was undertaken only after femoral vascular access was attended and physician decision to commence CRRT for AKI. For these four participants, CRRT was not commenced post-randomisation because of physician change in treatment strategy. This barrier to retention represents a small proportion (4%) of the randomised population and appears unavoidable in future studies. This may also indicate that the sequence of randomisation in the enrolment phase of the study has merit.

5.8.2 Practicalities

5.8.2.1 Resources—Machine platforms

The study ICU is a 24-bed general ICU treating an average of 140 patients per year with CRRT. The department has eight CRRT machines for 686 days of treatment per year, equating to each machine being in use for 85 days per year. This demonstrates sufficient capacity to treat current patient numbers and for potential increase in CRRT workload. During the study period, there were no occurrences of an inability to randomise or perform the intervention due to machine availability.

5.8.2.2 Integration with routine care

CRRT prescription including machines, mode, vascular access, haemofilter membranes, replacement, and dialysate fluids and dose were standardised to usual care for the duration of the study. Anticoagulation was prescribed according to unit policy for no anticoagulation, heparin alone or regional heparin regimens. The interventions of a set BFR of 250 mL/min and control set at 150 mL/min were the only alterations to routine delivery of CRRT in the ICU. Fluid loss prescription and cessation of therapy were also at the discretion of the treating intensive care physician so that bedside clinicians were comfortable that unit-based standard care was delivered to each patient included in the study.

5.8.3 Management

5.8.3.1 Randomisation method

Randomisation was achieved using a web-based clinical trial randomisation service through the Clinical Trial Coordinating Centre at Griffith University. At the study site,

icons for the randomisation service were placed on bedside computers with instructional sheets for log in and passwords. Following vascular access insertion and decision for mode of CRRT, clinicians were then asked to log on to the web-based service. Randomisation was stratified for mode (CVVH or CVVHDF), and with patient study number, allocation for BFR was achieved. An automated email was then sent to the principal investigator for each patient, which included study ID, mode and randomised BFR. The web-based randomisation service allowed for efficient and timely randomisation, particularly out of hours, and has the advantage of being able to be accessed across several centres for a multicentred study. In addition, the service allowed for logging of participants and up-to-date progress of the study.

5.8.3.2 Data collection

Once randomised, bedside clinicians could access study packs within the ICU. The pack included prescription charts for mode and BFR allocation, CRFs (Appendix 2), and bedside information regarding the aims and research questions of the study. On the CRF, basic demographic data were recorded, including pre-treatment urea and creatinine. The bedside nurse was then instructed to record the date and time of circuit start and stop times for each circuit applied to the patient. For each circuit, the nurse recorded details for anticoagulation type and dose, vascular access type and site, circuit life and reason for cessation of treatment (elective or clotting). For clotted circuits, the nurse was asked to classify from a defined list (e.g., TMP >300 mmHg) the identification of clotting occurrence. In addition, the nurse was asked to record BFR, cumulative circuit life (h) and TMP each hour, and circuit cessation reason on the patient's observation record. This record was then scanned post-discharge from the ICU into the patient's digital record. Data reliability was maintained by this two-step collection process (CRF and patient observation chart), which allowed confirmation of data queries and values from the alternate source. A larger future RCT may utilise an updated clinical information system (CIS) where the CRF may be validated against a machine data card or direct link to the CIS.

5.8.3.3 Data entry

Data entry for this study was undertaken by the principal investigator. Demographic data were obtained from the study hospital's digital CIS and scanned medical record system in accordance with HREC approval. Additional classification data were obtained from the Australian and New Zealand intensive care database Australasian Outcomes Research

Tool for Intensive Care (AORTIC). An Excel database was created, including a data dictionary, to record study, demographic, circuit life, and other circuit variable information including blood chemistry and coagulation data. Any missing data, out-of-range data or queries were transferred from the CRF to the digital information record at this time. This method allowed for accuracy of recording because of single data entry; however, a larger RCT may require monitoring of data using a statistical programme to validate the reliability of the data in a larger study population.

5.8.4 Scientific

5.8.4.1 Protocol—Implementation and compliance

There were no reported protocol violations during the study period. Standardisation of technique reflected the study ICU normal prescriptions and protocols except for BFR. In usual CRRT practice, BFR is a static prescription and is rarely altered by the bedside nurse. On occasion, the bedside nurse may alter the BFR to extend circuit life if pre-filter pressure or TMP causes alarm conditions and blood pump stoppages. For the study, nurses were instructed not to alter the BFR despite circuit pressure alarms and potential for clotting. For each hour, the nurse was asked to validate and record the BFR on the patient observation chart so that any variation or violation to the rate could be detected. The study ICU has a long history of performing CRRT research and this might have contributed to the high compliance rate in this study.

5.8.4.2 Treatment effect

There were no reported adverse events to patients because of study participation. Standard practice in the study ICU is to assess biochemistry and haematology at 0500 and 1700 to assess effectiveness and safety of the therapy. There were no occasions where the treating physician instructed the removal of the participant from the study because of ineffective therapy.

5.9 Summary of results

The results presented and discussed in these publications and chapter help establish the impact of BFR on CRRT efficiency. One measure of treatment efficiency is circuit longevity. In this study, our data suggest that a higher BFR does not improve circuit life in CVVH or CVVHDF or affect the likelihood of premature clotting. There were independent factors that were associated with increased circuit life, such as the use of an

anticoagulant regimen and patients with prolonged APTT. Patients with higher platelet counts were more likely to have circuits prematurely cease because of clotting.

A second measure of treatment efficiency is solute clearance. The results of this research suggest that higher BFR does not improve small-solute clearance; however, therapy delivery time is associated with improved efficiency of treatment. Lower serum haemoglobin level was an independent factor in small-solute clearance. Patients with lower haemoglobin levels treated with CRRT demonstrated smaller reductions in small-solute clearance for prescribed time intervals.

As there are no controlled studies assessing the impact of BFR on circuit life in CVVH or CVVHDF, this was considered an under-powered study. After assessment of the data, we determined that a future study would require the inclusion of 2604 patients to conduct an adequately powered RCT. The experimental design and methodology used in this study may be useful in designing a future trial, with many aspects demonstrating feasibility. Key areas of enrolment, randomisation and consent were successful in this study; however, alterations to inclusion criteria may be required for larger trial proposals. Amendment of AKI classification in relation to updated KDIGO guidelines would be required, particularly if a multi-site study is a consideration. Inclusion of internal jugular and subclavian vascular access would increase enrolment numbers by approximately 25%, decreasing study duration times.

Chapter 6: Discussion

6.1 Introduction

In a cohort of 100 ICU patients requiring RRT for the treatment of AKI, an increase in BFR to 250 mL/min from 150 mL/min did not increase circuit life in either CVVH or CVVHDF. However, this RCT did establish a strong association between the use of an anticoagulation strategy and circuit life in these modes of therapy. In addition, a relationship between the patient's coagulation profile and circuit life was confirmed, with higher platelet counts associated with premature clotting of the EC circuit. In assessing secondary outcomes of this study, a relationship between BFR and small-solute clearance was not established. Independent factors that were associated with small-solute clearance included number of hours of effective treatment and haemoglobin level.

CRRT is an integral component of the suite of therapies available in the ICU to support renal function in critically ill patients. However, strategies to optimise delivery of CRRT remain poorly defined. While anticoagulation approaches to optimise circuit life have been investigated in multiple RCTs, practical prescription settings relating to the CRRT system have not been investigated to the same degree of rigour. The impact of BFR through the membrane and EC circuit has not been adequately investigated to determine its impact on patency. The findings from this RCT and how they relate to our current knowledge of CRRT delivery are discussed in this chapter. These findings are also discussed for their importance in CRRT methodology and prescribing; the role of anticoagulation in CRRT prescription; and the methodological challenges in the measurement, reporting and analysis of filter and circuit life. Consideration of how CRRT may be prescribed within a new proposed model of precision concludes this section.

First, a review and discussion of the key findings from the studies presented in the results chapter are provided. These include:

1. the role of BFR and current best practice for BFR setting(s)
2. the role of anticoagulation-, patient- and intervention-related factors in determining CRRT circuit life
3. data and analysis strategies to determine circuit life in future research studies.

In addition, recommendations for future research, practice and education are outlined and the strengths and limitations of this study provided.

6.2 Relationship between blood flow rate and optimal continuous renal replacement therapy

In all blood purification techniques such as CRRT, there is a requirement for blood to be removed from the patient and passed through an EC circuit and membrane before finally being returned to the patient. The 'why' for these therapies is now well established.[231] The 'how' and 'when' remain areas of some debate and controversy.[1, 232] The evolution of technology over the past four decades has led to purpose-built CRRT machine platforms; however, circuit life has not significantly increased with the introduction of this higher-performing purpose-built equipment. Despite advances in technology, the essential elements of the system remain the same (Figure 6.1). The interaction or relationship between these three elements is likely to determine the success in maintaining continuity of therapy.

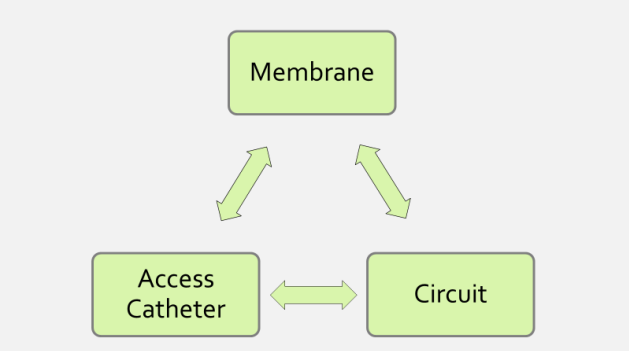

Figure 6.1: CRRT system dynamics.

This study aimed to examine whether the BFR itself (rate of flow) is an independent factor in maintaining circuit patency, as well as the impact of the BFR on the EC circuit, machine and functional aspects of the system. The influence of BFR in this study and relationships to current evidence and knowledge pertaining to therapy and circuit dynamics are explored in this section.

6.3 Significance of blood flow rate in continuous renal replacement therapy prescription

The primary aim of this research study was to measure and compare the effect of BFR on circuit life in the two most common modes of CRRT. There was no statistically significant

difference in either circuit life or probability of premature clotting with a BFR of 150 mL/min compared with 250 mL/min. In addition, an examination of first circuit life (expressed as hours) revealed a difference in duration of less than 1 h, which is neither statistically nor clinically significant. The examination of all clotted circuits (n = 369) as well as second and third circuits further demonstrated a difference of only 0.2–1.5 h. The secondary aim of this study was to assess the impact of BFR on small-solute control in patients receiving CRRT. Data from this study do not provide evidence that a higher BFR affects serum urea or creatinine concentrations in convective and diffusive modes of CRRT.

6.3.1 Impact of blood flow rate on circuit life

> Possible solutions to reduce filter clotting and deterioration in membrane permeability are the maximisation of blood flow rate (Qb) and optimisation of the ultrafiltration-to-blood flow ratio—filtration fraction (FF) percentage—for post dilution. Today, Qb values of greater than 200 mL/min are easily achievable, and FF percentages of less than 20% are advised.[1]

Ronco and colleagues recently hypothesised that faster blood flow through the EC circuit by setting higher BFR could prolong circuit life by minimising stasis of blood.[1] This view of the potential influence of BFR on circuit life is shared by other CRRT experts.[195, 233] Until the current study, there has been no RCT solely investigating the impact of BFR on circuit life in CRRT. One RCT conducted by Prasad and colleagues did randomise 34 patients to different BFRs (125 mL/min vs. 200–250 mL/min), but the data were confounded by the addition of saline flushing regimens (100 mL every hour vs. 100 mL every 30 min) to both the control and the intervention arms of the study. In addition, the study was conducted in the CVVHD modality, which is rarely used in the clinical setting.[209, 208, 234] Different modes of CRRT have been shown to alter procoagulatory activity within the haemofilter membrane, which may make comparisons between the purely diffusive mode of CVVHD and the modes of CVVH and CVVHDF, used in this study, difficult to assess.[164, 214, 235, 163]

A recent meta-analysis of non-anticoagulant factors associated with circuit life using pooled data from both adult and paediatric studies suggested that their modelling favoured higher BFR (HR 0.942, $p = 0.009$, $I^2 = 25.8\%$).[137] They further established that every 10 mL/min increase in BFR equates to a 5.8% increase in circuit survival. Despite these assertions, the authors did conclude that none of the studies used to come to these

conclusions were based on direct comparison studies using blood flow as the control or intervention and therefore should be viewed as supportive data only.[137] A recent audit by Dunn and Sriram of 355 patients and more than 1300 circuits in CVVHDF, conducted in a tertiary ICU, concluded that circuit life was affected by BFRs below and above 200 mL/min.[60] This retrospective review reported that circuit life markedly increased if BFR was maintained above 200 mL/min and proposed a target for clinicians should be 250–300 mL/min.[60] Dunn and Sriram's assertions provide an alternate perspective to the data presented in this RCT and use significant numbers of patients and circuits to inform conclusions. Despite the large dataset, the retrospective method used by Dunn and Sriram makes comparisons with the current RCT difficult.

6.3.2 Continuous renal replacement therapy system dynamics

Despite a 100 mL/min difference in BFR between the two interventions tested in the current study, this RCT has not demonstrated a clinical or statistical difference in circuit life in CVVH and CVVHDF. In formulating the initial research hypothesis, we proposed that the speed of blood flow in the EC circuit may have direct effects on clotting pathways due to interactions with the CRRT circuitry and membranes or indirect effects by triggering alarm conditions that stop the CRRT pump, thereby ceasing blood flow, causing blood stasis and activating clotting processes. One indirect interaction may be the relationship between BFR, mode and blood viscosity in the CRRT membrane and circuit. The combination of these elements is represented by a calculation known as filtration fraction, which may be used to determine optimal settings for mode, BFR and dilution pathways for replacement solutions if used. Filtration fraction may be a useful gauge of CRRT performance for solute clearance as well as a potential indicator of membrane clogging and premature clotting.

6.3.2.1 Membrane—Filtration fraction

Speed of blood flow through the CRRT membrane (dialyser) has been thought to influence both solute transportation (treatment efficiency) and blood composition (treatment longevity). In this RCT, we clinically tested this notion by specifically altering the BFR and, by extension, the plasma (water) flow rate available to the membrane. This complex interaction between the BFR and the mechanisms involved in solute removal and effect on filtration fraction are the basis for this RCT. The hypothesis that a higher BFR (250 mL/min) should enhance circuit life and solute clearance in CVVH and CVVHDF was not established in this RCT, and now questions such theoretical

assumptions regarding the utility of filtration fraction as a guide to treatment efficiency or circuit longevity.

For the same dose, different modes of CRRT traditionally require different BFRs to achieve 'adequate' solute clearance.[96, 216] This is largely due to the mechanism of solute removal in convective and diffusive modes of CRRT (Figure 6.2). CVVH solute removal is based on pure convection, where plasma water from the blood is forced across the semipermeable membrane of the haemofilter. The convective process of plasma water removal across the membrane (solvent drag) results in the movement of dissolved solutes and waste products and the creation of water loss as ultrafiltrate. The ability to effectively separate the plasma water from blood cells and plasma proteins requires a significant pressure gradient in the haemofilter membrane. This pressure gradient is achieved by setting a higher BFR in convective modes such as CVVH.

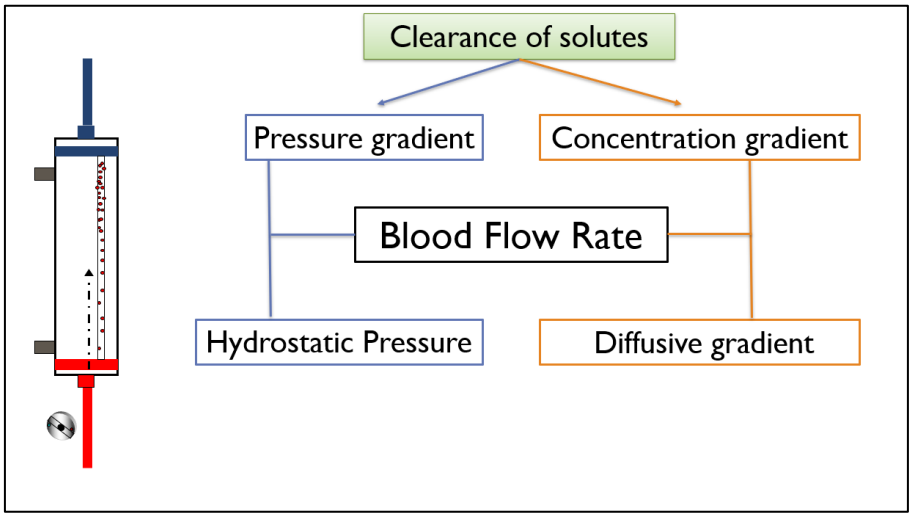

Figure 6.2: Mechanisms of solute removal in CRRT.

CVVHD solute removal is based on pure diffusion, where the CRRT system instils an electrolyte solution (dialysate) around the hollow fibres of the haemofilter counter-flow to the direction of blood flow within the fibres. Solute exchange occurs across the semipermeable membrane depending on the size of the molecule and the concentration gradient that exists between solutes in the blood and solutes in the dialysate. In this process, there is no movement of plasma water across the membrane. Higher BFRs are not required in this process as a pressure gradient is not essential to the movement of solutes or waste products. The CVVHDF mode relies on both convective and diffusive mechanisms, requiring both a pressure and a concentration gradient to remove excess solutes and waste products.

In convective modes such as CVVH and to an extent CVVHDF, the BFR determines the plasma flow rate into the haemofilter and the ultrafiltrate rate governs the filtration fraction (Figure 6.3).

Filtration fraction (FF) = Ultrafiltration rate (Quf)/Plasma flow (QPf)

Plasma flow = Blood flow − Haematocrit (Hct)

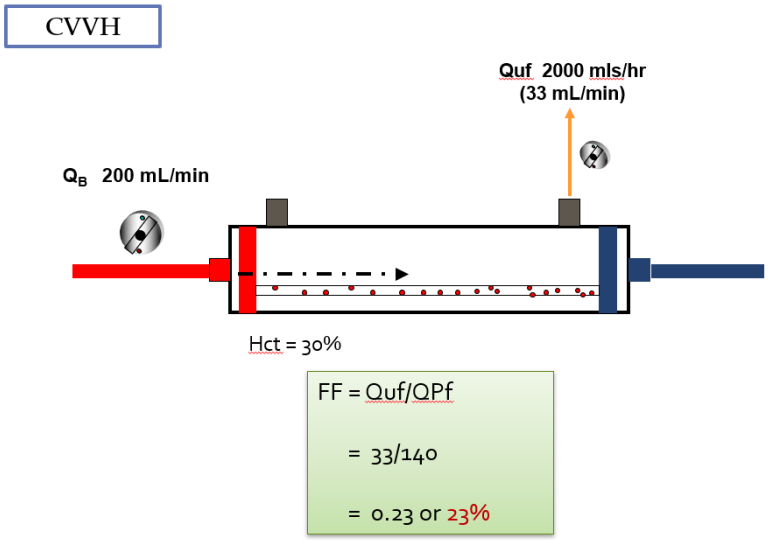

Figure 6.3: Filtration fraction in CVVH.

The concept of filtration fraction and potential impact on premature clogging and clotting in the EC circuit is now well established.[1, 233, 236] Modern CRRT machines are optioned for haematocrit level to be imputed at the beginning of each circuit and daily from pathology testing. Target filtration fraction ranges from 20% to 25%, with higher values than 30% indicating unacceptable haemoconcentration in the haemofilter and venous limb of the EC circuit, with increased risk of clotting.[1, 237] Machines installed with filtration fraction functionality will alert the bedside nurse if the current calculation of filtration fraction is greater than the default warning setting (e.g., 30%). The machine software will advise the nurse to decrease the current filtration fraction with the instruction for higher BFR. The effect of filtration fraction and, by extension, the risk of membrane and circuit clotting should now be a consideration in CRRT prescription of both dose and BFR.[237]

In this RCT, both the dose (Quf) and the BFR were fixed according to randomisation and standardisation of therapy in the trial. The patient's haematocrit level may change over time depending on haemoglobin level and intravascular volume status. If we assume a normal haematocrit level of 30%, the influence of the two BFR settings on filtration

fraction in this study can be calculated. A set BFR of 250 mL/min (Pf = 220 mL/min) and 2000 mL ultrafiltration rate (33 mL/min) equates to a filtration fraction of 15%, well below the desired level and which 'should' minimise the risk of clotting. In contrast, a set BFR of 150 mL/min (Pf = 120 mL/min) and 2000 mL ultrafiltration rate (33 mL/min) equates to a filtration fraction of 27.5%, immediately placing the circuit at risk of clotting.

One variable that was at the physician's discretion during this RCT was the prescription of fluid loss or removal depending on clinical requirements (fluid overload, interstitial lung oedema or peripheral oedema). Clinicians prescribe fluid loss for any external positive fluid gain such as intravenous therapies and nasogastric feeding. This fluid loss setting on the CRRT platform increases the ultrafiltration volume and consequently increases the filtration fraction and plasma water removal across the membrane, potentiating haemoconcentration and risk of clotting. One strategy to decrease the influence of filtration fraction issues is pre-dilution of the replacement solution in CVVH. The protocol for this study required a 50% pre-dilution ratio, which should have reduced filtration fraction in both BFR groups and might have influenced circuit life outcomes. In CVVHDF, the effect of filtration fraction remains for the convective component of the modality; however, with standardisation of dosing in this mode, this effect might have been smaller on circuit life outcomes as the ultrafiltration rate was reduced to 16 mL/min. A second confounder in CVVHDF was the standardisation of 100% post-dilution of the replacement solution, which might have led to haemoconcentration and higher blood viscosity in the haemofilter membrane.

Despite the possibility that filtration fraction may play a role in membrane and circuit clotting, univariate and multivariate analysis failed to demonstrate any association with BFR, modality (CVVH or CVVHDF) or circuit life in this study. The study data fail to support the current focus or theoretical assumptions placed on filtration fraction as a guide to premature clotting. Further, the automated advice and software alarm mechanisms in modern CRRT machines to increase BFR to reduce the likelihood of clotting in the membrane and circuit may not be an evidence-based remedy. It is important to note however, that this theoretical relationship between BFR, filtration fraction and circuit life is difficult to assess in day to day circuit function. Despite a numerical representation for each circuit, the numeric relies on manually inputted haematocrit data once or twice per day from blood pathology. The haematocrit level can change rapidly with intravenous fluid administration or increased ultrafiltrate or fluid loss. Without accurate and real-time

(continuous) haematocrit data input into the CRRT platform, the influence of filtration fraction on circuit life was not considered a useful variable for analysis in this study.

6.3.2.2 Vascular access

In this study, enrolment was limited to patients with femoral vascular access only as it is the preferred insertion site in the study ICU. Neither univariate nor multivariate analysis revealed any increase in the likelihood of clotting for vascular access insertion site (right vs. left femoral), vascath diameter (13.0 vs. 13.5 Fr gauge) or vascath length (20 cm vs. 15 cm or 24 cm vs. 15 cm). In addition, despite variants in alarm controls for the two CRRT machine platforms used in the study site, there was no difference between the Baxter Gambro Prismaflex and Infomed HF440 in propensity for premature clotting or clotting overall.

An essential component of the circuit dynamics is the potential influence of vascular access on treatment success measured by therapy continuity and circuit life. In this current study, femoral vascular access was standardised. However, because of different patient sizes, clinicians were able to choose from two different vascular access types. These access catheters differed from each other in respect to length and internal diameter. These essential differences might have been independent factors in establishing consistent blood flow from the vessel and therefore circuit life. CRRT requires large-bore, dual-lumen central-venous vascular access catheters to enable blood to enter and return from the EC circuit. Vascular access is a key component to the success of instituting CRRT and maintenance of adequate and consistent blood flow into the EC circuit.[236] Poorly positioned access catheters can lead to insufficient flow of blood into the EC circuit and may lead to variations in circuit pressures (negative access or arterial pressures), with resultant blood pump stoppages.[238] Blood pump cessation requires immediate nursing intervention to prevent prolonged blood stasis and likely EC clotting. Blood flow interruptions from the access catheter can be obvious (alarm condition) or undetected variations in blood flow in the circuit, and correlate to reductions in circuit life.[238, 239]

This investigation of BFR and its impact on circuit life has focused on all elements of the CRRT circuit, including vascular access. The hypothesis that higher BFR may improve circuit life was reasonable only if the vascular access could sustain consistent and stable blood flow into the EC circuit. The term mechanical circuit failure (MCF) has previously been described to highlight the impact that inconsistent BFR has on circuit life in CRRT.[239] The investigation of vascular access and MCF related to previous studies

demonstrated that major decreases in circuit blood flow occurred during physical movement of critically ill patients.[238] Such decreases can last many minutes, can be recurrent and can take place without machine alarms alerting the bedside nurse.[238] Accordingly, without alarm activation, no corrective action is taken. This sequence of events depends in part on the machines used and how such machines respond to excessively low pressure in the circuit between the access catheter and the blood pump, which is associated with flow reduction (low arterial pressure alarm). Some machines (Baxter Gambro Prismaflex, Lyon, France) detect the low pressure but continue to track the pressure as it worsens, simply resetting the alarm level. In this situation, no blood pump stoppages occur until the situation exceeds a defined machine-preset absolute level. Other machines (Infomed HF440, Geneva, Switzerland) have an alarm level that nurses can set. When this level is exceeded, the blood pump stops. The machine blood pump may restart if the situation resolves itself or requires resetting by the bedside nurse. These events where the blood pump stops and is then restarted result in temporary circuit blood flow failure. This flow instability may induce stasis and haemoconcentration, and contributes to red blood cell shear stress and eventual circuit clotting.[239]

The BFR settings used in this study were considered to test the impact of blood flow in the membrane and circuit, as well as the ability of the vascular access to cope with the higher BFRs seen in current clinical practice.[234] A potential confounder for our hypothesis that higher BFR may increase circuit life was the potential for a rate of 250 mL/min to induce more alarm conditions due to inconsistent blood flow, resulting in circuit and membrane blood stasis and eventual premature clotting. Regardless of suggestions that the machine, vascular access and nurse reaction time to alarms may influence premature clotting and shorter circuit life duration, this relationship was not established in this study.

Despite the potential importance of the site/location of vascular access to the overall success of the therapy, there remain no randomised controlled studies evaluating the effect of catheter design or access site on circuit life in critically ill patients requiring CRRT. There is conflicting evidence from observational studies for best access site. Three studies assessing access site and catheter dysfunction in CRRT concluded that right internal jugular access demonstrated the least malfunction compared with femoral and subclavian sites.[158, 240, 241] A recent meta-analysis of pooled data indicates that the grouped effect estimate of studies reporting time to event outcomes (circuit clotting) trended favourably towards the femoral site, with an associated 27% increase in filter survival.[157] Two large retrospective audits (486 patients, 1202 circuits) comparing access site and

circuit life reported superiority of femoral access over internal jugular and subclavian sites, concluding that femoral vascular access should be the preferred site in ICU patients. Current KDIGO practice guidelines recommend in order of preference: first, right jugular vein and, second, femoral vein.[141] Despite this, femoral access remains the most commonly used site for CRRT vascular access.[157]

6.3.3 Importance of blood flow rate on solute control

The timing or initiation of CRRT for critically ill patients with a diagnosis of AKI remains a matter of debate and an area of high priority for new knowledge in critical care and nephrology.[242, 243] The commencement of therapy is time-critical, but adequacy of the treatment is paramount to prevent further complications and avoid adverse outcomes. Despite diagnosing AKI, physicians will often be guided by clinical criteria to determine the timing of commencement of CRRT in critically ill patients. Physiological derangements, such as oliguria, anuria and fluid overload, and altered biochemical measures, such as serum urea, creatinine, potassium and acid–base imbalance, are often associated with the timing of therapy initiation in the clinical setting. Some physicians will commence CRRT prior to significant derangement in these measures, with an observation that the patient's progression of critical illness and acuity to multi-organ failure are evident. Often, however, the decision to commence CRRT is considered urgent because of clinical instability (hyperkalaemia, acidaemia, acute pulmonary oedema and uraemia).

Solute clearance appears to be dependent on three key variables: modality, BFR and total effluent volume (TEV). Historically in the clinical setting, treatment goals for the first 6–12 h were based on reduction in small-solute levels to prevent potential adverse outcomes, such as haemodynamic instability, and restore homeostatic balance. Evidence of success in the initial therapy timeline was based on reduction in serum urea and creatinine, control of serum potassium and restoration of acid–base status. After stabilisation in small-solute control, physicians will target a prescription that maintains solute removal and balance for each 24 h period. BFR is a treatment-related variable that has been implicated in the effectiveness of small-solute clearance, either by its relationship with the modality or in combination with mode and circuit/membrane integrity. Consensus guidelines for CRRT, including ADQI and KDIGO, do not recommend a BFR for optimal circuit life or solute removal. They instead outline typical setting ranges that may be used according to mode, and reflect a lack of focus or indecision.[141, 216] The endorsements for BFR and mode have

been reasonably consistent with these consensus practice guidelines in more recent literature; however, there appears great variation in minimum and maximum BFR for each mode.[244, 245]

In addition to mode and BFR, the third key prescriptive component of solute clearance is 'dose'. The first described measurements of clearance or dose were the effluent rates achieved (dialysate and ultrafiltrate), where the total effluent rate approximated the small-solute clearance.[246, 247] In the late 1980s and early 1990s, it was accepted that the greater the effluent volume settings (either by diffusion or convection), the better the solute clearance that is achieved. The limiting factor during this time was the inability of the technology to alter effluent volumes. The machine platforms were often adapted technology, with intravenous pumps controlling volumes, or alternatively primitive purpose-built machines with limited capacity to increase TEV. Practice surveys conducted in the early 2000s indicate that effluent volume prescription was often a set measure and not routinely altered according to individual patient requirements.[208, 221] The investigation of 'dose' or intensity of continuous therapies with mortality led to a weight-based description of TEV and, by extension, solute clearance.[219, 220, 248] Today, solute clearance is still expressed as TEV per weight and unit of time (mL/kg/h), with many CRRT machine platforms and ICU specific protocols using and targeting this expression of small-solute clearance.[234]

In the purely convective mode of CVVH, the sieving coefficient (ease with which a solute passes with the plasma water across the membrane) for small solutes is approximately 1.0 so that the clearance is equal to the ultrafiltration rate if the replacement rate is delivered 100% post-dilution.[249] Small-solute clearance may be restricted by any variable that limits ultrafiltration. One important limiting variable is filtration fraction. A high filtration fraction in this scenario may cause concentration polarisation within the fibre, haemoconcentration and clogging, leading to impairment in the ratio of ultrafiltration rate.[208] The maintenance of a filtration fraction less than 30% in CRRT is twofold: reduced risk of increased viscosity and haemoconcentration causing premature membrane and circuit failure, and maintenance of fibre and pore integrity and filter permeability to maintain consistent ultrafiltration rate and solute removal. As we have already established, filtration fraction is most easily manipulated by increasing the BFR, allowing greater exposure of plasma water flow inside the membrane fibres to ultrafiltrate flow so that efficient solute removal is maintained.

Effluent (dialysate and ultrafiltrate) is not as limited by filtration fraction in CVVHDF as in CVVH, and the prescribed BFR may be less important to solute clearance in this modality. However, for CVVHDF in this study, the replacement fluid accounting for the convective plasma water loss was all administered post-dilution at a fixed rate of 1000 mL/h. Theoretically, filtration fraction and BFR may be less influential in CVVHDF for solute clearance in comparison with CVVH; however, the differences in replacement fluid dilution (CVVH, 50% pre and post; CVVHDF, 100% post) in this study may make any evaluation of clearance between modes difficult.

Dose-related outcome studies have dominated CRRT research over the past 10–15 years. Two of the largest CRRT RCTs ever conducted failed to demonstrate a relationship between intensity of dose and survival early and after 90 days in critically ill patients treated with RRT.[219, 220] The quantity of dose in these studies used historical weight-based effluent rates (TEV) as a measurement of solute clearance. The examination of these trials has led to further investigation into the accuracy of effluent volume representing solute clearance or dose in CRRT.[250] There has been a suggestion that solute clearance may be compromised in delivering the prescribed dose in continuous therapies because of variation in practice and circuit dynamics.[251] Practical prescription differences, such as volume or fluid administration setting for pre-dilution or post-dilution, dilution differences between modalities, individual circuit longevity and function, membrane fouling and concentration polarisation, have all been implicated in the discussion regarding more accurate dose and solute clearance metrics for CRRT.[245, 250, 252-254]

Dialytic techniques such as IHD have used metrics for evaluating small-solute clearance for many years. The marker Kt/V for IHD is used to quantify the adequacy of the treatment (K = BFR, t = time and V = volume of distribution of 'urea', which is equivalent to the patient's total body water in association with their weight). This measurement has not been applied to CRRT because of perceived problems with urea volume of distribution, increased metabolic rates, fasting or enteral protein intake, abnormal fluid distributions in critically ill patients with AKI and an inability to easily weigh patients in the ICU.[255] Despite this, a modified version of Kt/V in conjunction with effluent-based dosing has been suggested.[254, 255] New dosing metrics specifically designed for CRRT that incorporate pre-dilution and post-dilution variables as well as adjustments for modality (CVVH or CVVHDF) have been proposed.[252, 254] For all old and new metrics designed to quantify the efficacy of solute clearance in CRRT, there is one constant value determining intensity and adequacy of therapy: BFR. The higher the

prescribed BFR in each calculation to determine dose assessment, the greater the solute clearance.

It was hypothesised that higher BFRs would increase small-solute removal in CRRT in the clinical application of the therapy. The outcome measure to evaluate solute removal efficiency was the change in patient small-solute serum concentrations (urea and creatinine) over time. Using routine blood tests performed twice daily at predefined 12 h time periods (0500 and 1700), the percentage change in serum urea and creatine was calculated. In addition, the number of hours of actual CRRT treatment over each 12 h period was calculated. In contrast to international practice guidelines, and historical and new metrics, indicating that a higher BFR should improve solute clearance, this investigation failed to demonstrate a correlation between BFR and change in patient serum urea and creatinine. Further, the study failed to demonstrate that modality is a significant independent variable in solute clearance. Data from this study did however demonstrate that total hours of effective treatment time per day (24 h) is associated with reductions in small-solute measurement.

The beginnings of treatment for AKI with more continuous techniques of RRT were based on slow and constant removal of small solutes to prevent complications associated with the condition. The clinical measure of success was the reduction and maintenance of normalised small-solute balance measured by daily blood tests. The techniques and modalities developed were based on dialytic techniques (convection and diffusion) and adapted to the continuous method. Unlike in IHD, clinicians did not directly measure small-solute clearance and metrics of dose were not considered important in the context of a continuous therapy. In this study, the percentage reduction method of small solutes in the patient's blood to evaluate clearance for BFR and modality was used. Much of the literature and guidelines purport the use of higher BFR to increase solute clearance in CRRT; however, this association has not been established in this RCT. One potential explanation is the indirect measurement of clearance. A more direct measurement such as measuring the filtrate urea/nitrogen and creatinine (FUNC) compared with the blood urea and creatinine (BUNC) as a ratio (FUNC:BUNC) might have given a more accurate measure of the influence of BFR on solute transport across the haemofilter. The sieving coefficient or transport of urea is 1.0 so that a direct measure of urea in the pre-filter blood and ultrafiltrate at each 12 h period to determine clearance for BFR might have yielded more instantaneous and precise measurements. This would, however, have required a

significant increase in lab testing for each study participant outside the normal testing regimen conducted in this study.

One consistent finding for solute clearance in CRRT is the effective treatment time in hours.[245, 250, 254-256] Known causes of reduced treatment time or 'downtime' include frequent circuit clotting, set-up and priming of the circuit, and procedural activities that require elective cessation of the therapy.[11, 12, 250, 256] Current approximations for prescribed versus delivered treatment over 24 h indicate a loss of effective treatment time of 4–6 h per day.[11, 257] This estimation of downtime has been included as a dose-related goal in CRRT practice guidelines to maximise effective solute clearance over each 24 h period, with a recommended dose of 25 mL/kg/h.[141] In this study, a lower than expected mean treatment time per 12 h period (6.3 vs. 6.7 h) was found, which equates to just over 50% effective treatment delivery. These data are inconsistent with previous reports at the same study site where greater than 75% effective treatment delivery has been described.[11, 12] The most likely cause of the reduced treatment hours in this study was short circuit life with more frequent removal, set-up, repriming and reconnection of new circuits.

In summary, the measurement of solute clearance in CRRT remains a complex dynamic, yet to be fully understood.[245, 250, 254, 255] The notion of dose in CRRT is a reasonably new concept highlighted by intensity and mortality trials. Prior to these trials, clinicians were more likely to prescribe standardised treatments to all patients with CRRT for the management of AKI. The standardisation of the dose in ICU settings was related to a prescription for the major determinants of solute clearance, including BFR, modality and effluent volume. Today, it is more likely that these variables, in particular dose and BFR, are altered for each individual patient, making estimations of solute clearance problematic.[234] In addition, unlike quantification of dosing in intermittent therapies, CRRT presents different challenges associated with greater treatment time per membrane and circuit (e.g., concentration polarisation, platelet adherence, fibre clogging, reduction in membrane and pore integrity, and inflammatory mediator adsorption) and influences of variation in technique (modality and pre/post-dilution). Just one of these variables, location of dilution, has been associated with a reduction in solute clearance as high as 30–40% in CVVH compared with post-dilution.[258] This study failed to demonstrate a difference in the maintenance of small-solute balance despite BFR differences; it also failed to demonstrate differences in many other variables now associated with clearance performance. With ongoing variation in technique and prescription, as well as influences

of circuit time, the accurate quantification of solute clearance in CRRT will continue to be an area of research and investigation in the future.

6.4 Impact of anticoagulation, and patient- and intervention-related factors, on the maintenance of continuous renal replacement therapy patency

6.4.1 Anticoagulation versus auto-anticoagulation

Two key findings of this study were that the use of an anticoagulation strategy and prolonged APTT were independent factors associated with prolonged circuit life in CRRT. This study demonstrated a statistically significant prolongation of circuit life when either a systemic unfractionated heparin or a regional heparin/protamine strategy was used. These data emphasise the importance of initiating anticoagulation in conjunction with CRRT to maintain a successful and patent EC circuit. The prescription of anticoagulation, however, was extremely low in this study. More than half of the 463 circuits applied in this study were not prescribed anticoagulation to optimise circuit longevity. Further, there was a discrepancy between the two groups (all circuits) for unfractionated heparin and regional heparin prescription, with the 150 mL/min group receiving four times the rate of anticoagulation compared with the 250 mL/min group. Both the low overall lack of prescription and the discrepancy may be easily explained. It should be noted that more than one-third of the patients in this study were diagnosed with a form of liver failure/transplantation. Despite the frequent clotting and short circuit life associated with these patients, clinicians are reluctant to prescribe any form of anticoagulation for CRRT to prevent life-threatening bleeding in this high-risk cohort. These patients often have prolonged ICU length of stay, and requirement for CRRT may require more treatment days (and therefore more circuits), compared with other patient groups. A breakdown for number of circuits per patient diagnosis might have confirmed this proposition.

The high percentage of liver failure/transplantation representation in the study may be attributed to both the study centre being a referral centre for liver failure/transplantation and exclusion criteria. In this study, patients who were prescribed RCA were excluded. Citrate anticoagulation at the time of enrolment required a fixed BFR of 150 mL/min and was conducted in CVVH mode only. Citrate is contraindicated in patients with liver dysfunction as hepatocellular function is required to metabolise the citrate compound

returned to the patient as part of the regional technique.[136] Citrate molecules are metabolised and converted by the liver to bicarbonate molecules. The exclusion of citrate anticoagulation–treated patients might have excluded other surgical and general ICU patients with AKI from the study and skewed data collection towards liver failure and transplantation cases where citrate would not be used.

In addition to a high number of liver failure/transplant patients included in our study, there were four more patients in the 250 mL/min group (15 vs. 19) than the 150 mL/min group who were diagnosed with failure or transplantation, equating to a 10% difference in patient numbers between the intervention groups. This difference in patient diagnosis may partly explain anticoagulation prescription disparity; however, more than 50% difference in overall prescription and more than 80% 'no anticoagulation' prescription in the 250 mL/min group may not be solely attributed to patient diagnosis. If the differential in anticoagulation prescription was due to patient diagnosis, this might have been more evident in the evaluation of first circuit treatments. For both groups, there was an equal prescription of a precautionary 'no anticoagulation' strategy, with 75% of both arms either failing to prescribe or deliberately not prescribing an anticoagulant. This similarity in non-prescription for the first circuit does cast some doubt that the patient diagnosis is fully responsible for the overall variation in anticoagulation prescription between the two groups.

Eighty-three per cent of patients required more than one circuit during their CRRT therapy. For those patients who required ongoing CRRT after the first circuit in this study, hours of function prior to clotting did increase. Median circuit life of clotted second circuits was 14 h (150 mL/min, n = 35) versus 13.8 h (250 mL/min, n = 38), and further increased to 17 h (150 mL/min, n = 22) versus 16 h (250 mL/min, n = 23) in patients requiring third circuits. One explanation for improvement in circuit life duration over multiple circuits may be the increased percentage of anticoagulation used over time. Initial first circuit anticoagulation prescription was similar for both groups (24% vs. 25%) and increased in frequency with each subsequent circuit with little variation between the two interventions (34% vs. 39% and 40% vs. 48%). The cause of this improvement in anticoagulation use over time may be multifactorial. Often, CRRT is started out of hours, and therapy and anticoagulation may be prescribed by trainee intensivists with limited or no experience in CRRT. Despite unit-based practice guidelines and policies to guide prescription, the junior intensivist may choose the 'safest' option in initial treatments and choose a strategy of no anticoagulation. Consultant intensivists with more experience may

be more likely to prescribe anticoagulation on the basis of protocol and experience, even in patients perceived as high risk.

Hours of circuit longevity reported in this study are short compared with other recent interventional studies and a meta-analysis of RCTs assessing circuit life in CRRT.[139, 140, 259, 260] Recent worldwide studies have reported circuit life exceeding 30 h.[137-139, 261, 262] In contrast, several studies have reported circuit life of less than 12 h.[203, 263, 264] This variability in reported circuit life may be due to a myriad of factors. The prevalence of citrate anticoagulation strategies and the multitude of studies demonstrating statistical and clinical advantages of this regimen over traditional anticoagulation techniques have been significant influences in maintaining patency in continuous therapies. As a result, several working groups including KDIGO, the Canadian Society of Nephrology and the Italian Society of Nephrology have endorsed regional citrate as the anticoagulant of choice for CRRT.[141, 265, 266]

6.4.2 Patient pathology/pathophysiology and influence on circuit life

In addition to anticoagulation prescription, a further potential explanation for increasing circuit life over time seen in this study may be the complex interaction between CRRT membranes and the patient's blood. Haemofilter (dialyser) technology has evolved with an improvement in biocompatibility. The structure and adsorptive properties of these new membranes have been examined both in vivo and in vitro.[267 268, 269] Investigation of membrane proficiency largely centres on the convective or diffusive clearance of small and middle molecular weight substances (e.g., electrolytes, urea, creatinine and inflammatory mediators) and the adsorptive properties of the membranes to proinflammatory mediators (e.g., cytokines) in patients with sepsis-related AKI. The process of fibre and eventual haemofilter clotting involves initial protein adherence, activation and deposition to the membrane walls, initiating a 'fouling' or 'clogging' of the hollow fibres.[178, 256, 267, 270] This complex process has led to the investigation of membrane structure and properties that may inhibit protein adherence and delay eventual clotting onset and progression.[178, 271, 272]

The adsorptive properties associated with newer membrane types may play a role in premature fouling of membranes in patients with high circulating levels of cytokines and other inflammatory mediators.[251, 268, 273, 274] In this study, 50% of patients randomised were diagnosed with severe sepsis and a significant number of patients had severe sepsis and concomitant liver failure. Sepsis leads to endothelial cell activation with release of

factor VIII, von Willebrand factors and tissue factor.[233] Patients with liver failure, despite having prolonged laboratory coagulation tests and reduced concentrations of natural anticoagulants such as antithrombin III and protein C, are more prone to thrombin generation because of release of tissue factor from the liver.[275] It may be plausible to suggest that initial circuits and membranes are exposed to increased levels of inflammatory proteins, factors and mediators that adsorb to the membrane, initiating premature fouling and eventual clotting. With potential convective and diffusive clearance and adsorption to the membrane, these proteins and mediators may reduce in blood concentrations over time. With each new circuit and cumulative hours of treatment and other ICU therapies, a reduction in these markers may not induce the same degree of fouling, and circuit life may improve with each new subsequent circuit.

6.4.3 Intervention-related variables

There are other factors that may contribute to hours of circuit life other than those reported or examined in the literature. We have suggested from this study that contributing factors might have included patient diagnosis and experience level of the prescriber, and even non-adherence to unit-based policies and protocols for potential safety concerns. Data from different centres may reflect outcomes linked to their specific patient demographic—trauma, surgical, medical, cardiac and surgical ICUs may all report diverse circuit life data irrespective of anticoagulation intervention or BFR being utilised. Public hospitals, which have a broader demographic cohort, may have poorer circuit life outcomes compared with private hospitals, with more homogeneous and healthier patient groups. Despite two large RCTs demonstrating no mortality difference in higher-intensity CRRT, there remains great variability in the prescription of dose in Australia and New Zealand.[234] To date, there are no reported data on the influence of dose (TEV and subsequent dialysis and replacement fluid rates) on circuit life. However, the impact of higher prescribed dose (convectively and/or diffusively) may alter circuit dynamics and membrane pressures, and this may result in reduced circuit life.

6.4.4 Generalisability of the study findings

The aim of this study was to establish the relationship (if any) between BFR (mL/min) through the EC circuit and two key measurements associated with adequacy of therapy: circuit life and solute control. This study was conducted in a single tertiary ICU, with the intention of recruiting a representative sample of critically ill patients with AKI requiring CRRT. One hundred and thirty-five patients were screened, resulting in 100 randomised

during the study period. Of the randomised patients, 96 completed the study (150 mL/min, n = 49; 250 mL/min, n = 47), with two from each intervention arm not receiving CRRT because of physician decision. The patients randomised to each group were similar in terms of age, gender, severity of illness scores, admission source, diagnosis and renal laboratory values. There was, however, a discrepancy in weight between the two groups.

As a single-centre RCT, the sample may be typical of the study ICU but may not be generalisable to critically ill patients with diagnosed AKI managed with CRRT in Australia or worldwide. To explore the external validity of our findings, a comparison of our baseline clinical characteristic data to two seminal RCTs examining CRRT dose or intensity was conducted (Table 6.1). The RENAL study[219] remains the largest multicentre RCT involving CRRT (CVVHDF) worldwide. It was conducted in Australia and New Zealand (2005–2008) and investigated the relationship between intensity of CRRT and mortality in critically ill patients diagnosed with AKI. The RENAL study was conducted across 35 ICUs in Australia and New Zealand, with 1508 patients randomised during the study period. The VA/NIH ATN study[220] (2003–2007) was also a dose-related mortality RCT, which included other dialysis methods such as IHD and SLEDD in conjunction with CRRT. The ATN study was conducted in 27 veterans' affairs and university affiliated centres in North America and included the randomisation of 1124 patients with diagnosed AKI and ATN requiring RRT. To date, these are the two largest RCTs to investigate CRRT in critically ill patients for the treatment of AKI.

Table 6.1: Comparison of Patient Characteristic Data with Multicentre Studies

	BFR 2013/14 (2017)		ATN 2003/07 (2008)		RENAL 2005/8 (2009)	
No. of centres	**1**		**27**		**35**	
Admission variables	**150 mL/min**	**250 mL/min**	**Intensive RRT**	**Less-intensive RRT**	**High-intensity CRRT**	**Low-intensity CRRT**
	n = 49	**n = 47**	**n = 563**	**n = 561**	**n = 722**	**n = 743**
Age, years	61.1 ± 15.9	60.8 ± 18.3	59.6 ± 15.3	59.7 ± 15.2	64.7 ± 14.5	64.4 ± 15.3
Gender (male sex), no. (%)	34/49 (69)	24/47 (51)	409/563 (72.6)	384/560 (68.6)	474/722 (65.7)	472/743 (63.5)
Weight, kg	85.2 ± 20.4	75.8 ± 20.3	84.1 ± 19.6	84.1 ± 18.9	80.8 ± 12.7	80.5 ± 13.1
APACHE II*	22.2 ± 6.5	23.13 ± 6.55	26.6 ± 7.2	26.1 ± 7.5		
APACHE III*	85.6 ± 23.2	87.21 ± 26.28			102.5 ± 25.9	102.3 ± 25.5
Source of admission, no. (%)						
Emergency department	13 (27.7)	12 (25.5)			163 (24.3)	185 (26.4)
Ward	17 (34.7)	17 (36.2)			210 (31.3)	177 (25.3)
Postoperative (elective)	7 (14.3)	6 (12.8)			80 (11.9)	84 (12.0)
Postoperative (emergency)	5 (10.2)	4 (8.5%)			93 (13.9)	113 (16.1)
Transfer from other ICU	5 (10.2)	5 (10.6%)			51 (7.6)	60 (8.6)
Transfer from other hospital	2 (4.1)	3 (6.4%)			73 (10.9)	81 (11.6)

	BFR 2013/14 (2017)		ATN 2003/07 (2008)		RENAL 2005/8 (2009)	
No. of centres	**1**		**27**		**35**	
Admission variables	**150 mL/min**	**250 mL/min**	**Intensive RRT**	**Less-intensive RRT**	**High-intensity CRRT**	**Low-intensity CRRT**
	n = 49	**n = 47**	**n = 563**	**n = 561**	**n = 722**	**n = 743**
Admission diagnosis, no. (%)						
Cardiovascular	6 (12.2)	5 (10.6)			268 (37)	266 (35.8)
Cardiac surgery	11 (22.4)	8 (17.0)			122 (16.9)	147 (19.8)
Respiratory	0	1 (2.1)			79 (10.9)	67 (9)
Gastrointestinal	6 (12.2)	6 (12.8)			85 (11.8)	88 (11.8)
Liver failure/transplant	15 (30.6)	19 (40.4)				
Acute renal/genitourinary	5 (10.2)	5 (10.6)			120 (16.6)	109 (14.6)
Mechanical ventilation, no. (%)	41 (83.7)	36 (76.6)	453 (80.5)	452 (80.7)	531 (73.5)	551 (74.2)
Severe sepsis, no. (%)	24/49 (49)	26/47 (55.3)	358 (63.6)	350 (62.4)	360 (49.9)	363 (48.9)
Laboratory data prior to randomisation						
BUN**, mg/dL	66.3 ± 41.9	59.43 ± 28.13	65.9 ± 30.2	66.7 ± 35.2	67.9 ± 37.3	63.9 ± 34.2
Serum creatinine, µmol/L	317.2 ± 171.6	297 ± 181.54			291 ± 192	279.5 ± 197
Serum urea, mmol/L	23.6 ± 14.9	21.19 ± 10.03			24.2 ± 13.3	22.8 ± 12.2

* Acute Physiology, Age, Chronic Health Evaluation; ** Blood urea nitrogen.

At randomisation, patients in all three studies were similar in many respects including age, weight, severity of illness scores, incidence of mechanical ventilation and importantly the pre-RRT renal laboratory values. There is a discrepancy between the prevalence of males in the North American study compared with the Australian studies; however, this may be explained by veterans' affairs study sites in the ATN study. The RENAL study reported a slightly older age demographic of 4–5 years compared with the ATN and this study. There is also a higher percentage of patients diagnosed with severe sepsis in the ATN study compared with the Australian and New Zealand studies. The ATN study did not include admission diagnoses or source of admission; however, the RENAL data are very similar to the current study except for patients categorised on admission as cardiovascular. This may be due to coding of patients in a larger study database or discrepancy associated with a single-site study versus 35 sites and categorisation of patients.

Overall, the baseline characteristics and demographic data for patients in this study (n = 96) are very similar to two published large multinational, multicentre RRT-based RCTs (n = 2589).[219, 220] This demonstrates that the types of patient randomised in this study are comparable to other Australian and North American studies investigating CRRT. This does suggest that our sample is representative of critically ill patients with AKI requiring CRRT and the findings, while statistically under-powered, may be clinically generalisable to other ICUs worldwide.

6.5 Methodological challenges in examining time data for continuous renal replacement therapy circuit function

CRRT has become an important treatment modality for critically ill patients with AKI, volume overload, and acid–base and electrolyte derangement. However, the therapeutic effectiveness of CRRT is heavily dependent on continuity of the treatment. There has been significant investigation into optimising circuit patency worldwide, often led by single-site studies such as this one. The design, method and reporting of circuit life studies also remain varied, making comparisons and judgements regarding efficacy of individual studies difficult to interpret. This section examines this current study in relation to previous literature and examines the challenges in assessing this and other reports investigating circuit life in CRRT.

6.5.1 Data defining circuit life

6.5.1.1 Measurement of circuit time or filter life

The primary question addressed in this study was to explore whether there was a relationship between BFR and circuit life in the two prevailing modes of CRRT (CVVH and CVVHDF). The primary outcome measure was circuit life in cumulative hours of patency prior to clotting and eventual cessation of the therapy. Although the median circuit life for all clotted circuits in this study was 10.0 h in the 150 mL/min group and 11.5 h in the 250 mL/min group, with similar results on first circuit assessment (9.1 h vs. 10.0 h), there was no significant statistical or clinical difference in circuit survival. This study does, however, report short circuit life compared with other recent circuit life studies.[91, 97, 138, 139, 208, 276] In comparison, these studies and the meta-analysis of RCTs report a circuit life range of 25–72 h. An adequate or acceptable circuit life for continuous therapy in hours is not well described in the literature. Despite the multitude of studies focused towards circuit life as a primary outcome, neither the ADQI[216, 277] nor the KDIGO[217] guidelines have established a consensus reference for adequate circuit life for CRRT. It has been previously suggested that a circuit life of 24 h may be a useful target for clinicians to assess the success of strategies aimed at optimising circuit life.[278] It has also been proposed that an average circuit life of 20 h per day if circuits are ceased because of clotting should be considered an acceptable outcome and a measurement representing success.[236]

If a circuit life of 20–24 h is considered a reasonable reference, the circuit life presented in this study only reached approximately 50% of this target. There may be several explanations for this result. The reported circuit life of less than 24 h is consistent with previous observational and controlled studies conducted at the study site.[108, 175, 190, 196, 206, 241, 279-284] One possible explanation is the demographic and baseline characteristics of patients admitted to the study ICU. The ICU is a tertiary referral centre for patients with acute liver failure, acute-on-chronic liver failure and liver transplantation. It has been previously reported that the incidence of these patients can be as high as 50% of the total ICU patient population.[284] Patients with liver failure have a high risk of simultaneous bleeding and clotting due to altered coagulation pathology (prolonged APTT, elevated INR and thrombocytopaenia), which makes the prescription of any anticoagulant problematic for the treating clinician.[201] Such patients' anticoagulant/procoagulant state makes circuit clotting frequent, resulting in circuit life of less than 10 h. In liver

failure/transplantation patients and similar circumstances, other investigators have reported similarly short circuit life.[203] Despite altered coagulation processes, which often inhibit the patient from normal clot development and may inhibit clotting in the EC circuit, procoagulant factors in these patients may initiate clotting progression in the CRRT circuit and lead to shortened circuit life.[203, 206]

In this study, 15 patients in the 150 mL/min group (30.6%) were classified as having liver failure or liver transplantation, as well as 19 patients in the 250 mL/min group (40.4%). In context, 34 out of the total 96 (35%) patients enrolled in the study were diagnosed with liver dysfunction, failure or transplantation. The relationship between shortened circuit life and patients with liver failure has been previously established by Chua and colleagues, who reported a median circuit life of 9–12 h in this patient group despite evidence of coagualopathy.[206]

6.5.1.2 Focus on circuit life

Clotting in the EC circuit has been one of the major challenges in the development and application of continuous forms of RRT since the late 1970s. Over the intervening four decades, a significant amount of enquiry and research has been dedicated to the exploration and development of the therapeutic approach, with particular reference to its practical application.[232] The efficiency measure of CRRT has largely centred on circuit longevity and maintaining patency of the EC circuit. This RCT continues to build a body of evidence for circuit life and the practical settings inherent in the application of the therapy.

A large number of prospective observational studies were available as potential designs of choice testing interventions to prolong circuit life in CRRT prior to guiding the method for this study.[12, 105, 190, 238, 280-282, 285-304] These studies have inherent value and contribute to a large database used for evidence-based guidelines. In intensive care patients, however, sample bias and variability in treatment-related variables make assessment of such studies challenging. In the last decade, there has been an increase in RCTs to test the effectiveness of an intervention that may improve circuit longevity and prolong functional patency in CRRT circuits.[87, 89, 97, 107, 108, 115, 125, 132, 137-140, 163, 197, 199, 260, 305, 306] Of interest, all of these studies test an anticoagulation hypothesis in an RCT design using unfractionated heparin as the control arm. RCTs in the ICU setting eliminate bias in the study sample and allow greater control over confounding variables in this complex group of patients.

A recent meta-analysis assessing circuit life and non-anticoagulant factors identified 364 full-text publications for review. Only 14 (3.9%) of these publications assessing vascular access, modality, circuit-related factors and patient-related variables were RCTs.[157] One potential explanation may be the difficulty in controlling the intervention in non-anticoagulant studies. The randomisation and application of an anticoagulant control or intervention may be easier to practically facilitate than dynamic mechanical, machine and circuit-related variables such as vascular access, modality and membrane. CRRT remains a complex practical therapy to instigate and maintain, with many aspects of delivery and application of the technique exposed to variability. Therefore, the results of studies designed to provide evidence for best practice may remain open to interpretation and scrutiny. The requirement for robustness and rigour were integral to the design of this RCT, and the feasibility component may help guide future non-anticoagulant CRRT circuit longevity studies.

6.5.1.3 Reporting and analysis of circuit life

The measurement and description of circuit life in the literature has also made studies with similar interventions difficult to interpret. In the current study, a rigorous data analysis plan based on a recent Australian multicentre RCT investigating the effect of two anticoagulation strategies (regional citrate and regional heparin) in patients receiving CRRT for AKI was used.[139] The analysis plan included the censoring of circuits terminated for elective and diagnosis-of-clotting reasons. Distribution of all clotted circuits was then assessed and, as expected, variables were not normally distributed and non-parametric tests were used, with circuit life reported as median and IQR. Statistically and clinically, there is great variability in circuit life in the practical setting. The censoring of circuits and assessment of distribution should be the initial steps in any rigorous data analysis plan assessing circuit life. The reporting of median circuit life, and use of non-parametric tests, should be considered essential for these studies, providing more accurate presentation, analysis and discussion of data.

For many circuit life studies, however, the reported duration is not procedurally censored for clotted-only circuits and data are not assessed for distribution. The reporting of mean or average circuit life is common in all study designs including some RCTs.[87, 105, 239, 241, 287, 290, 296, 307-309] It is unlikely that the distribution of circuits will be normal as vascular access issues often lead to premature circuit changes after commencement of the therapy (1–4 h). In contrast, some circuits may last several days despite previous circuits in the

same patient, using the same therapy, failing or apparently clotting after shorter time frames (e.g., <10 h). These unpredictable and variable circuit life patterns are common in the clinical setting, making the reporting of mean or average circuit life less meaningful. This study reports a median circuit life for the first circuit (clotted) of 9.1 and 10 h. In contrast, the reporting of mean circuit life for the same data would have revealed a circuit life of 20.1 and 17.7 h, respectively. With previous discussion of an adequate circuit life approaching 24 h, the mean circuit life, if reported, might have been misleading in the evaluation of this study and this sample of patients.

Some RCTs have examined circuit life as the primary outcome and reported median circuit life.[89, 107, 108, 197, 199, 299] However, these studies provide no information in the method or results for discrepancies in circuit count per patient, or the potential implications of individual patients providing multiple circuits to the data analysis. Only one previous circuit life RCT, conducted by Gattas and colleagues, has described a statistical methodology to determine the effect using repeated-events survival analysis.[139] The unique statistical model used by Gattas et al. and this study allows not only the interpretation of multiple circuit life data but also the inclusion of censored data (elective circuit cessation) in the data analysis. It may be that this staging statistical model provides the most accurate representation of trial data for any interventional study in circuit life associated with CRRT; therefore, this model may be the optimal model and analysis standard for future RCTs.

6.6 Strengths and limitations

This RCT investigating the impact of BFR on clinically important outcomes has made a significant contribution to a new understanding of CRRT practice. A significant strength of this study was the high enrolment and consent rates and zero withdrawal rate from the study. Data collection methods used in this study ensured that high-quality information was available for analysis. Importantly, this study has resulted in three publications in peer-reviewed journals, increasing the awareness of the influence that practical mechanisms of CRRT may play in the success or failure of therapy. The first publication is the largest investigation into CRRT practice ever conducted in Australia and New Zealand. It has informed clinicians and researchers of the current practical aspects of this therapy, with emphasis on BFR, dose, vascular access management, machine technology, anticoagulation and modality choice. It will serve as a significant reference for future investigations into CRRT research. The second and primary publication is a report of the

first RCT to assess the impact of BFR on circuit life in CVVH and CVVHDF. Despite evidence-based guidelines suggesting optimal BFR for mode and the potential significance of BFR on circuit life outcomes, this is the first study to critically investigate this prescription parameter in any meaningful way. Importantly, the data analysis method used in this study to assess circuit life should be considered the standard against which all CRRT circuit life studies should be considered and measured. The third publication from this study has informed an area of CRRT under current investigation. Quantification of solute clearance and dose remains an area of much debate, and our data, which conflicts with previous understandings and suggested metrics of clearance, should contribute to a greater investigation in adequacy measures.

The most important limitation of this RCT is sample size. Without data to support an adequately powered study, a period of 1 year was chosen to complete this study. While the patients studied, and total treatments performed in each group, provided useful clinical findings, a larger cohort of patients in each group, resulting in adequate power, would enable a rigorous examination of the study question related to efficacy. For an adequately powered circuit life study, more than 2600 patients would be required—to conduct such a study will require the involvement of multiple centres and significant financial support. A further potential methodological limitation to the study was a lack of procedural stardardisation in aspects of CRRT delivery. Due to practical implications at the study site, uniformity in relation to CRRT machine and kit-based membrane and vascular access type was not able to be achieved. In addition, CRRT mode was left to clinician discretion, however randomisation was stratified for mode in this study. Anticoagulation (or no anticoagulation) was also left to the treating clinician in this study. The lack of CRRT protocol uniformity should be a consideration in the interpretation of these results. In this study we investigated the influence of two BFRs on circuit life and solute clearance. Although in our survey on current practice, a small number of ICUs indicated they used BFR < 150 mL/min and some ICUs as < 100 mL/min as well as > 250 mL/min. This study did not explore the impact of these lower or higher flow rates on the effectiveness on the primary and secondary outcomes and therefore cannot comment on the efficacy, or otherwise, of these rates.

The method used to assess our secondary outcome of solute clearance was limited in its capacity to fully quantify the impact of BFR. A more direct measurement test such as filtrate urea (creatinine) and blood urea (creatinine) or FUNC:BUNC for each BFR group would have provided a more accurate assessment of solute movement and provided more

insights into changes in solute clearance over time in continuous methods of RRT. Another limitation of the study was that it was not possible to blind the independent variable of BFR, resulting in the possibility for bias to occur when a BFR of 250 mL/min may be thought to extend circuit life more than 150 mL/min. Although guidelines on what constituted a natural circuit life were clearly defined, the method used remained open to interpretation by the bedside clinical nurse. By the nature of the investigation, any attempt at blinding the study would have been impracticable and unavoidable since awareness of treatment parameters was necessary to perform CRRT (both groups) safely. The large percentage of patients enrolled in the study with a diagnosis of liver failure or liver transplantation might have influenced the circuit life reported in this study because of these patients' complex pathophysiology. A limitation of the analysis strategy in the current study may be a lack of inclusion of diagnostic grouping in the univariate and multivariate analysis of circuit clotting. In the development of an analysis plan for a larger RCT, a recommendation for diagnostic categorisation should form part of the strategy.

6.7 Recommendations for clinical practice

BFR does not appear to affect traditional efficiency indicators of circuit life and solute clearance. Despite this, clinicians should continue to be aware that prescription settings such as BFR may influence treatment adequacy of each individual patient. This project has emphasised areas of interest for the bedside clinician and the clinical researcher.

6.7.1 How to prescribe blood flow rate for continuous renal replacement therapy

In this study, I examined the influence of two BFR prescriptions (150 mL/min vs. 250 mL/min). The data demonstrate that a higher BFR yields a clinical benefit of neither extended circuit life nor improved solute clearance. This study has not examined the influence of a BFR of less than 150 mL/min or greater than 250 mL/min. Based on these data, a prescription of BFR between these two ranges will be sufficient to meet the needs of applying CRRT in the critically ill patient diagnosed with AKI. Irrespective of modality, the prescribing physician should feel confident that the BFR setting will not reduce the adequacy of the treatment. Perhaps more importantly, BFR should be matched to the individual patient condition and current understanding of circuit pressures in relation to the vascular access in use. If circuit life is deemed to be shorter than the accepted norm and mechanical failure is suspected because of persistent access pressure alarms, the clinician can alter BFR without compromising clinical care outcomes. All treating and prescribing clinicians should be aware that success of the therapy is largely

based on consistent and constant blood flow in the EC circuit and that decisions before treatment commencement may affect the efficacy of the therapy more than will the BFR setting.

The data from this study can also be used to guide ICU protocols for CRRT. In this study, the relationship between BFR and regional citrate methods of anticoagulation was not specifically investigated; however, most new RCA software programmes have linked citrate dosing and BFR algorithms. This linkage means that any increase in pre–blood pump citrate dose may result in an increase in BFR. An understanding that BFR is not an independent factor associated with circuit longevity should form part of any RCA prescription or policy when introducing the method in the ICU.

6.7.2 Prescription of anticoagulation

One of the key findings of this study is the impact that an anticoagulation strategy has on prolonging circuit life. While the anticoagulation prescription rate was low in both arms of the study, there is a demonstrated statistically significant superiority of circuit life when either a systemic unfractionated heparin or a regional heparin/protamine strategy was used. In this study, there was a high percentage of liver failure cohort, and as a result, there might have been some reluctance to prescribe an anticoagulation method because of the perceived clinical risk of bleeding. Apart from in this patient group or other patients deemed at high risk of bleeding, a focused anticoagulation strategy will inhibit premature circuit clotting and extend circuit life, minimise circuit downtime and improve treatment efficiency. The prescription or intentional non-prescription of an anticoagulation strategy should be based on individual patient assessment or unit-based guidelines based on the patient's coagulation profile so that patients may be identified as able to receive anticoagulation and maximum prescription applied.

6.7.3 Treatment assessment

Circuit life is an important indicator of CRRT treatment efficiency. The ability to regain and maintain solute control is also an important consideration in measuring the efficacy of the therapy. This study has highlighted the significance of optimising circuit life to provide continuous therapy in this group of patients. In addition to circuit life, this study has emphasised a need for clinicians to not only optimise individual circuit longevity but also maximise the number of hours of treatment in each 24-hour cycle. One key area for clinicians to focus on when assessing solute control in patients receiving CRRT is the

delivered therapy time in comparison with the desired prescription time (continuous or 24 h). While frequent circuit clotting may affect actual delivered treatment time, the effect of 'downtime' due to procedural activities, interdepartmental diagnostic activities or vascular access replacement may lead to long periods of non-treatment and determine solute control. This study highlights the need for treating clinicians to perform structured ongoing assessment of CRRT goals by using targeted endpoints and different measures such as delivered time per 24 h to govern success of the therapy.

6.8 Recommendations for future research

The primary research question for this study was the hypothesis that a higher BFR may increase circuit life in CRRT (CVVH and CVVHDF modes). Because of a lack of historical and supportive data to inform a power calculation for this research question, this study was considered a pilot and feasibility investigation. Data from this study should be used to inform a potential adequately powered RCT investigating the impact of BFR on circuit life in CRRT. A power calculation indicates a sample size of 2604 patients required to definitively answer the primary research question. Study enrolment rates in this study of 75% of eligible patients may be enhanced by some alteration to the inclusion criteria such as RCA and vascular access site amendments.

Anticoagulation strategies and vascular access sites were assessed in the statistical analysis of this study and the inclusion of citrate anticoagulation and jugular vein access could be evaluated in the same univariate and multivariate models. In this study, anticoagulation was identified as an important confounder on the primary outcome – circuit life. The incorporation of this variable in the design of a larger definitive study should be an important or essential element of any future study. The large sample size required will require significant funding support and multiple ICU sites with similar recruitment rates to other large-scale CRRT investigations to complete an RCT of this magnitude. The experimental design and methodology used in this study has been shown to be feasible and represents a useful guide in designing any future CRRT trial. The statistical analysis plan should act as a standard for any prospective RCT assessing circuit life in CRRT.

The relationship between haematocrit, pre and post-dilution filtration fraction in convective modes of CRRT and circuit life are yet to be definitively evaluated. With improvements in real time haematocrit measurement and accurate estimation of filtration fraction within the dialyser (haemofilter), the influence of these measurements on

outcomes such as circuit life and solute clearance should be an area of future investigation.

This study has identified that clinicians need more information about the potential impact of BFR on outcomes such as circuit life and solute control. This may be provided through a concept of a 'dashboard' or screen metrics view for clinicians to easily see (machine and/or bedside CIS) and consider the efficiency for a treatment in progress and be able to consider the possible consequences for any change in settings such as BFR. Circuit life data for the two blood pump speeds from this study with measurement of solute clearance could inform a predictive model to allow for situations where clinicians are changing settings such as BFR and CRRT dose but are unsure of the possible consequences to circuit life and function. Further investigation into predictive modelling platforms or data-based artificial intelligent systems for CRRT efficacy to determine effect on clinician decision-making, and subsequent CRRT practice and patient outcomes, should be a priority for researchers focused towards precision-based CRRT practice.

6.9 Concluding statement

Blood flow through the EC circuit and membrane formed the basis of CRRT 40 years ago. Despite its importance to the success of therapy, this is the first RCT to thoroughly examine the influence of BFR on circuit life and solute control. These outcomes are vitally important to every bedside clinician applying CRRT for the management of AKI, where technology plays a vital role in the further evolution and improvements in CRRT provision. The ability of purpose-built machines and advances in vascular access have enabled the prescription of higher BFRs similar to intermittent therapies. There has been an accepted and adopted theoretical advantage of prescribing higher BFRs for CRRT to yield longer circuit life and enhanced solute clearance. Until now, this theoretical benefit has not been tested in the clinical setting in any meaningful way.

The aims of this study were to investigate the relationship between BFR and circuit life in patients treated with CRRT. Secondary aims were to determine if BFR affects solute maintenance in patients treated with CRRT and to provide initial data to reliably inform the feasibility and sample size calculations of a larger future RCT. To address these aims, a prospective RCT design was used for this study. The intervention was a set BFR of 250 mL/min compared with a control BFR of 150 mL/min in either CVVH or CVVHDF.

When considering circuit life, data from 100 ICU patients requiring CRRT (CVVH, CVVHDF) revealed the following key findings: First, when BFR was increased to 250 mL/min, it did not increase circuit life in these CRRT modes. Second, the use of an anticoagulation strategy and longer APTT extended CRRT circuit life. Third, patients with higher platelet counts were more prone to premature circuit clotting in this study.

When specifically examining solute maintenance, faster blood flow did not improve small-solute clearance compared with slower blood flow. There was an association between number of hours treated with CRRT and change in serum solute levels, with lower serum haemoglobin level identified as an independent factor associated with difference in urea and creatinine levels.

The findings of this pilot and feasibility study suggest that higher BFR does not improve CRRT efficiency or adequacy of treatment. Overall, this project has demonstrated originality in an area of CRRT research for study design, data analysis, data presentation and scientific worth that should help the bedside clinician gain a better understanding of prescription variables as well as guide a more definitive RCT. This thesis provides a significant contribution to our understanding of the clinical application of CRRT. Data from this investigation into current practice for CRRT may enable future researchers and expert panels to develop focus areas of inquiry into practical elements of CRRT prescription. Finally, the findings and recommendations of this study may help bedside clinicians better apply and understand the importance of focus-based prescription and assessment of CRRT delivery to optimise outcomes in this group of patients.

Appendices

Appendix 1: Human Research Ethics Committee Austin Health Practice Survey Approval Form

Austin Health

Austin Hospital

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TO: Mr Nigel Fealy
Intensive Care Unit
Austin Health

PROJECT: CRRT Practice Survey

PROJECT No: 04918

Date: 05 December 2012

Re: Consideration of CRRT practice survey
Documents: CRRT Practice Survey template

Thank you for providing the above documentation for consideration by the Office for Research at Austin Health.

Provided that participation in the survey is voluntary, the data collected is non-identifiable and those that participate are able to contact yourself or another independent person if they have any concerns/complaints there appears to be negligible risk with the survey being conducted.

Based on the above, we do not feel that ethics review is required. Should any of the above conditions change, please contact the Office for Research for further assessment.

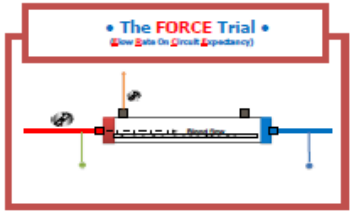
Good luck with the conduct of the survey,

[redacted]

Dr Jodie Palmer
Research Governance Officer
Office for Research
Austin Health
HSB 6, Studley Rd,
Heidelberg VIC 3084.
E: ethics@austin.org.au
P: 03 9496 2901

Appendix 2: Bedside Data Collection Case Report Form

The Impact of Blood Flow Rate on Circuit Life in CRRT Bedside Data Form



Patient Study Number |__|__|__| **Patient weight** .....**kgs** **Height** .....**cms**

Intervention: Randomised to: Blood Flow 150 mL/min ☐ OR 250 mL/min ☐

	CIRCUIT NO	1	2	3	4	5	6	7
	DATE/TIME: START __/__/__ hh:mm	__/__/__ __:__	__/__/__ __:__	__/__/__ __:__	__/__/__ __:__	__/__/__ __:__	__/__/__ __:__	__/__/__ __:__
	DATE/TIME: FINISH __/__/__ hh:mm	__/__/__ __:__	__/__/__ __:__	__/__/__ __:__	__/__/__ __:__	__/__/__ __:__	__/__/__ __:__	__/__/__ __:__
	Mode of CRRT √	CVVH __ CVVHDF __	CVVH __ CVVHDF __	CVVH __ CVVHDF __	CVVH __ CVVHDF __	CVVH __ CVVHDF __	CVVH __ CVVHDF __	CVVH __ CVVHDF __
	Machine: Infomed / Prismaflex							
	New **Vascath** this circuit	Y N	Y N	Y N	Y N	Y N	Y N	Y N
	Reason for new Vascath (eg. Dysfunction – short filter lives, access issues, suspected infection etc							
	Site: Right Femoral **(RF)** Left Femoral **(LF)**							
	Vascath: Brand/Type 1. Bard Niagara 2. Gambro Dolphin Protect							
	Vascath: Gauge/Length							

	Anticoagulation A. None B. Heparin C. Heparin + Protamine	Circuit 1_____	Circuit 2_____	Circuit 3_____	Circuit 4_____	Circuit 5_____	Circuit 6_____	Circuit 7_____

	Why Change Circuit (May be more than one reason e.g(a, b or a+g etc) a) TMP > 250mmHg b) Pre-filter pressure > 200mmHg (check Prismaflex wording) c) Clotting: stopping pump rotating, d) Machine states filter clotted e) Venous chamber clot f) Machine alarm/**specify below in comments……** g) Other….CT/OT h) Elective (Trial Off)	Circuit 1_____	Circuit 2_____	Circuit 3_____	Circuit 4_____	Circuit 5_____	Circuit 6_____	Circuit 7_____
	Comments							

Appendix 3: Griffith University Human Research Ethics Committee Approval Form

Mr Nigel Fealy

The Griffith Ethics Application Database has sent the conditional approval for prior review of "NRS/55/12/HREC The Impact of Blood Flow Rate on Circuit Life in Continuous Renal Replacement Therapy (CRRT)" to the nominated contact, Prof Leanne Aitken. I have recorded that you are the contact in the database records but the system record cannot be altered without deleting and resubmitting your application. I felt this would be unnecessary impost and further delay in approving you application.

A copy of the email text is set out below.

"GRIFFITH UNIVERSITY HUMAN RESEARCH ETHICS COMMITTEE

07-Jan-2013

Dear Prof Aitken

I write further to your application for ethical clearance for your project PR: The Impact of Blood Flow Rate on Circuit Life in Continuous Renal Replacement Therapy (CRRT)" (GU Ref No: NRS/55/12/HREC). This project has been considered by Human expedited review 1.

The Chair resolved to grant this project conditional ethical clearance, subject to you resolving the following matters:

As per the expectations articulated in the National Statement on Ethical Conduct in Human Research (2007) and Booklet 8 of the Griffith University Research Ethics Manual, because of the prior review by another HREC, this research has been subject to a special administrative review.

Please provide an assurance that the Manager, Research Ethics, Griffith University will be promptly notified if any adverse events occur, or if any concerns or complaints are received about the ethical conduct of this research, or if the project is discontinued for any reason.

Please arrange for an appropriate authorising officer, who is not a member of the research team, to complete and sign the s18 declaration (available from the forms page of the Griffith University Human Research Ethics web site or upon request from the Office for Research)."

This decision was made on 07-Jan-13. Your response to these matters will be considered by the Office for Research.

The ethical clearance for this protocol runs from 07-Jan-13 to 10-Oct-15.

Please forward your response to Rick Williams, Manager, Research Ethics, Office for Research, as per the details below.

It would be appreciated if you could give your urgent attention to the issues raised by the Committee so that we can finalise the ethical clearance for your protocol promptly. To assist you a copy of the S.18 form is attached.

Regards

Rick Williams
Manager Research Ethics and Integrity
Office for Research
Griffith University
Nathan
Brisbane QLD 4111
Tel: (07) 373 54375
Mob: 0418 638 911
Email: Rick.Williams@Griffith.edu.au

Appendix 4: Austin Health Human Research Ethics Committee Approval Document

Austin Hospital

145 Studley Road
PO Box 5555 Heidelberg
Victoria Australia 3084
Telephone 03 9496 5000
Facsimile 03 9458 4779
www.austin.org.au

TO: Prof Ian Baldwin
Dept. Intensive Care Unit
Austin Health

PROJECT: The impact of blood flow rate on circuit life in continuous renal replacement therapy (CRRT)

PROTOCOL No:
PROJECT No: H2012/04772

Date: 27 September 2012

Approval Period: **10 October 2012** to **10 October 2015**

Re: Approval of Low Negligible Risk Research
Approved documents: **(1) Application form v1.0** **(2) Protocol v1 dated June 2012** **(3) Participant Information and Consent Form (PICF) v 1.10.2012** **(4) Person Responsible ICF v1.10.12**

I wish to inform you that the Austin Health Human Research Ethics Committee (**HREC**) has approved your above mentioned project.

Austin Health HREC approval is granted from **10 October 2012** providing the following conditions being met:

1. Conditions

The Austin Health HREC will be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.

The Principal Investigator will provide an annual progress report to the Office for Research for the period July 1 – June 30 each year by the end of September. These are to be submitted electronically to: ethics@austin.org.au using templates provided at: http://www.health.vic.gov.au/cchre/applications/applications_how_to.htm. A final report is required upon the completion of your study.

Should your study not commence twelve (12) months from the date of this letter this

approval will lapse. A resubmission to the Human Research Ethics Committee would then be necessary before you could commence.

2. **Adverse Events**

The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including any unforeseen events that might affect continued ethical acceptability of the project. Serious Adverse Events must be notified to the Committee **within 48 hours of the event** by the Principal Investigator. In addition the Principal Investigator must provide a summary of the adverse events, in the specified format, including a comment as to suspected causality and whether changes are required to the Participant Information Sheet and Consent Form. In the case of Serious Adverse Events occurring at the local site, a full report is required from the Principal Investigator, including duration of treatment and outcome of event.

3. **Amendments**

If there is an event requiring amendments to be submitted you should follow the instructions found on the following website: http://www.austin.org.au/researchethics/

Should you have any queries about the Austin Health HREC's consideration of your project please contact Research Ethics Unit on (03) 9496 4090 or email ethics@austin.org.au. The Austin Health HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from http://www.austin.org.au/researchethics/ or from the Research Ethics Unit.

Yours Sincerely,

[redacted]

Jodie Palmer
Research Governance Officer
Officer for Research
L6, Harold Stokes Building
Austin Hospital
Phone: (03) 9496 2901
E-mail:ethics@austin.org.au

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice annotated with TGA comments (July 2008) and the applicable laws and regulations; and the Health Privacy Principles in The Health Record Act 2001.* The process this HREC uses to review multi-centre research proposals has been certified by the NHMRC.

Appendix 5: Australian and New Zealand Clinical Trials Registration

Dear Nigel Fealy,

Re: The impact of prescribed blood flow rate on circuit life in critically ill patients receiving continuous renal replacement therapy (CRRT) in intensive care

Thank you for submitting the above trial for inclusion in the Australian New Zealand Clinical Trials Registry (ANZCTR).

Your trial has now been successfully registered and allocated the ACTRN: ACTRN12615001353583

Web address of your trial: http://www.ANZCTR.org.au/ACTRN12615001353583.aspx
Date submitted: 9/12/2015 6:00:45 PM
Date registered: 14/12/2015 2:31:01 PM
Registered by: Nigel Fealy

****Please note that as your trial was registered after the first participant was enrolled, it does not fulfil the criteria for prospective registration and will therefore be marked as being Retrospectively Registered on our website.****

If you have already obtained Ethics approval for your trial, could you please send the ANZCTR a copy of at least one Ethics Committee approval letter? A copy of the letter can be sent to info@actr.org.au (by email) OR (61 2) 9565 1863, attention to ANZCTR (by fax).

Please be reminded that the quality and accuracy of the trial information submitted for registration is the responsibility of the trial's Primary Sponsor or their representative (the Registrant).
The ANZCTR allows you to update trial data, but please note that the original data lodged at the time of trial registration and the tracked history of any changes made will remain publicly available.

The ANZCTR is recognised as an ICMJE acceptable registry (http://www.icmje.org/faq.pdf) and a Primary Registry in the WHO registry network (http://www.who.int/ictrp/network/primary/en/index.html).

If you have any enquiries please send a message to info@actr.org.au or telephone +61 2 9562 5333.

Kind regards,
ANZCTR Staff
T: +61 2 9562 5333
F: +61 2 9565 1863
E: info@actr.org.au
W: www.ANZCTR.org.au

Appendix 6: Austin Health Participant Information and Consent Form

Austin Health

Place Patient Label Here

FAH016179

Participant Information Sheet/Consent Form

Title	***The impact of blood flow rate on circuit life in Continuous Renal Replacement Therapy***
Protocol Number	***04772***
Coordinating Principal Investigator/ Principal Investigator	***Professor Ian Baldwin***
Associate Investigator(s)	***Professor Leanne Aitken*** ***Mr Nigel Fealy***
Location	***Austin Health***

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have ***Acute Kidney Injury*** and the clinical team plan to commence a treatment known as continuous renal replacement therapy. Continuous renal replacement therapy is a type of artificial kidney that takes over some of the functions of the kidneys until they recover.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Purpose of this study?

The purpose of this study is to determine the best method of delivering continuous renal replacement therapy in critically ill patients in the intensive care unit with acute kidney injury.

Background Information

Many patients admitted to the intensive care unit with a critical illness suffer from acute kidney injury. This often requires the use of an artificial kidney therapy known as continuous renal replacement therapy.

Continuous renal replacement therapy requires the establishment of a blood filled circuit (tubing) to enable the pumping of blood through an artificial kidney (also called a filter). This form of renal replacement therapy uses a blood pathway (circuit) and filter very similar to that used for outpatient dialysis. This artificial kidney system often fails to work because blood clotting occurs. Ideally this artificial kidney should function without clotting for at least 24 hours.

Some recent clinical observations and studies have suggested that this premature clotting of the circuit may be in some part due to recurrent interruption to the blood flow by mechanical factors such as the position of the vascular access device, patient movement and positional changes. These mechanical factors can cause rapid reductions in blood flow or even temporary cessation of blood flow. This reduction in blood flow causes blood flow stasis promoting clot formation and eventual circuit failure.

There is great variability in the setting of the speed of the blood flow (blood flow rate) through the circuit between intensive care units in Australia. The speed of blood flow may be influential in the promotion of clotting due to the mechanical factors described earlier. We propose to make some comparisons between two blood flow rates (150 mL/min vs. 250 mL/min) currently being used within the intensive care unit at Austin Health.

The aim of this audit is to prospectively collect information to identify any advantage (if any) of one blood flow rate setting over another. Therefore this investigation simply requires that the patient is prescribed either one of the two accepted blood flow rate speeds for the duration of time they require artificial kidney support. Advantages in this case may include the length of time the circuit was able to function (circuit life) before clotting of the circuit occurred.

The study is being conducted exclusively at Austin Health and will involve 48 participants being recruited into the study.

This pilot study would be submitted to Griffith University (Brisbane) and examined for the award of Doctor of Philosophy (PhD).

3 What does participation in this research involve?

We kindly ask that you read this information sheet about this research study. If you are satisfied that it would be in your interest to participate in the study, please provide your consent on the form provided.

Following your diagnosis with acute kidney injury the clinical team will decide to commence continuous renal replacement therapy. This is routinely performed in the intensive care unit

and is setup and managed by the intensive care nurse. As a routine the blood flow rate is prescribed by the treating clinical doctors prior to commencement of the therapy. Normally this blood flow rate would range anywhere from 150 mL/min to 250 mL/min.

For the purposes of this study we would allocate the blood flow rate to either 150 mL/min or 250 mL/min. Allocation to one of these two groups will be randomised meaning that you have a 1 in 2 chance, like flipping a coin, to be allocated to either group. Apart from the allocation of the blood flow rate, the remaining prescription for the continuous renal replacement therapy will be decided by the treating clinical team as part of their standard or usual practice.

No additional blood tests or procedures are required for the completion of the study and all other care will be delivered per normal in the intensive care unit. To assess the impact of the blood flow rate on the circuit life, we are also asking for permission to obtain information from each participant's medical record. Your involvement with this study will continue for the duration of time renal replacement therapy is required to treat your kidney injury in the intensive care unit, or up to the point a decision is made to withdraw from the study by you, or at the discretion of the medical staff.

You will not incur any cost for your participation in this study or receive any payment.

4 What do I have to do?

Apart from the study procedures described above, you will receive standard care with no additional requirements placed on you.

5 Other relevant information about the research project

Continuous renal replacement therapy is commonly used for the treatment of acute kidney injury. We are investigating if the prescribed speed of the blood flow through the circuit affects the likelihood of early clotting and therefore decreasing the 'life' of each circuit. You will receive continuous renal replacement therapy for the treatment of your kidney injury even if you are not enrolled in the study or not.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the Austin hospital.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. If you decide not to participate in this study then renal replacement therapy will be performed as per usual care. The blood flow rate would be left to the discretion of the treating intensive care doctor or the bedside nurse.

8 What are the possible benefits of taking part?

There may be no immediate benefit to you from participating in this study. Participation in this study does not allow you to receive any compensation or other financial benefit. The results from this study are anticipated to benefit future patients.

9 What are the possible risks and disadvantages of taking part?

All medical procedures involve some risk of injury. If you decide not to participate, continuous renal replacement therapy will be performed according to the direction of the clinical team. The speed of the blood flow through the circuit is routinely prescribed between 150 mL/min to 250 mL/min. In this study we (the investigators) are wanting to prescribe the blood flow rate to see the effect (if any) on premature clotting in the circuit. The blood flow rate would not be prescribed slower or faster than what is considered routine for this therapy. Therefore there are no additional risks to you from your participation in the study.

10 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. Participation in the study is purely voluntary. If you decide to withdraw from the study, the treatment for acute kidney injury would continue with continuous renal replacement therapy until the clinical team decides it is no longer required.

Should you wish to discontinue your participation in this study, you are free to do so at any time without penalty. Consent to participate in the study does not exclude you from your rights under the law.

If you do withdraw your consent during the study, the study investigators will not collect additional information. We will ask you whether we can use the data already collected for study purposes. If consent is not obtained, collected data will be destroyed.

11 What happens when the research project ends?

If you give us your permission by signing the consent document, we plan to discuss and publish the results from this study in a peer reviewed journals, conference presentations and other professional forums. In any publication or discussion, information will be provided in such a way that you cannot be identified.

Part 2 How is the research project being conducted?

12 What will happen to information about the participant?

By signing the consent form you consent to the study investigator, collecting and using personal information about you the participant, for the study project. Any information obtained in connection with this study project that can identify you will remain confidential. Each Participant will be allocated a unique code and this unique code will be used to identify them in all matters relating to the study. Your information will only be used for the purpose of this study project and it will only be disclosed to you except as required by law. Access to this information will be restricted to study staff and will be housed in a locked room/cabinet accessible only by the study staff.

Data will be stored both on paper and electronically on computers. The computer records will be password protected and accessible only to the research staff. These records will be stored in a locked research office and at the completion of the study will be archived in a secure facility for fifteen years. After this time, the records will be destroyed.

Information about you may be obtained from their health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing your health records, if they are relevant to your participation in this study.

Your health records and any information collected and stored by the study doctor during the study may be reviewed (for the purpose of verifying the procedures and the data) by the ethics committee which approved this study, regulatory authorities, the Austin Hospital, or as required by law. By signing the consent form, you as the Participant, authorise release of, or access to, this confidential information as noted above.

It is anticipated that the results of this study will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

Information about your participation in this study may be recorded in your health records. In accordance with relevant Australian and/or Queensland privacy and other relevant laws, you have the right to request access to the information collected and stored by the study team about yourself. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

13 Complaints and Compensation

If you the participant suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment for yourself. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital. In addition the Manager, Research Ethics, Griffith University, will be notified immediately if any concerns or complaints are received by the primary Research Ethics Committee of Austin Health.

14 Who is organising and funding the research?

The Coordinating Principal Investigator for this study is Professor Ian Baldwin from The Austin Hospital. Professor Baldwin will be assisted by Mr Nigel Fealy from the Austin Hospital and Professor Leanne Aitken from Griffith University. There is no funding for the research project.

FAM010170

15 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee. The ethical aspects of this research project have been approved by Austin Health's human research ethics committee. In addition the project has been submitted to Griffith University's Human Research Ethics department for review.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

16 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if the participant has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor on 9496 5000 or any of the following people:

Clinical contact person

Name	*Professor Ian Baldwin*
Position	*Course Coordinator – Intensive Care Nursing*
Telephone	*9496 5000*
Email	*Ian.baldwin@austin.org.au*

For matters relating to research at the site at which the participant is participating, the details of the local site complaints person are:

Complaints contact person

Name	Austin Health
Position	*Dr Sianna Panagiotopoulos, Manager, Office for Research*
Telephone	*9496 5088*
Email	*ethics@austin.org.au*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Austin Health
HREC Executive Officer	*Dr Sianna Panagiotopoulos, Manager, Office for Research*
Telephone	*9496 5088*
Email	*ethics@austin.org.au*

Austin Health

Place Patient Label Here

Local HREC Office contact (Single Site - Research Governance Officer)

Name	Austin Health
Position	*Dr Sianna Panagiotopoulos, Manager, Office for Research*
Telephone	*9496 5088*
Email	*ethics@austin.org.au*

FAHB16179

Consent Form

Title	***The impact of blood flow rate on circuit life in Continuous Renal Replacement Therapy***
Protocol Number	***04772***

Austin Health

Place Patient Label Here

Coordinating Principal Investigator/ Principal Investigator	***Professor Ian Baldwin***
Associate Investigator(s)	***Professor Leanne Aitken*** ***Mr Nigel Fealy***
Location	***Austin Health***

FAN010170

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Austin Health concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Appendix 7: Austin Health Person Responsible for the Participant Information and Consent Form

Austin Health

Place Patient Label Here

FAN016170

Person responsible Information Sheet/Consent Form

Title	***The impact of blood flow rate on circuit life in Continuous Renal Replacement Therapy***
Protocol Number	***04772***
Coordinating Principal Investigator/ Principal Investigator	***Professor Ian Baldwin***
Associate Investigator(s)	***Professor Leanne Aitken*** ***Mr Nigel Fealy***
Location	***Austin Health***

Part 1 What does participation involve?

1 Introduction

Your relative/friend is invited to take part in this research project. This is because your relative/friend has ***Acute Kidney Injury*** and the clinical team plan to commence a treatment known as continuous renal replacement therapy. Continuous renal replacement therapy is a type of artificial kidney that takes over some of the functions of the kidneys until they recover.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want your relative/friend to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish for your relative/friend to take part, they don't have to. They will receive the best possible care whether or not they take part.

If you decide you want your relative/friend to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Purpose of this study?

The purpose of this study is to determine the best method of delivering continuous renal replacement therapy in critically ill patients in the intensive care unit with acute kidney injury.

Background Information

Many patients admitted to the intensive care unit with a critical illness suffer from acute kidney injury. This often requires the use of an artificial kidney therapy known as continuous renal replacement therapy.

Continuous renal replacement therapy requires the establishment of a blood filled circuit (tubing) to enable the pumping of blood through an artificial kidney (also called a filter). This form of renal replacement therapy uses a blood pathway (circuit) and filter very similar to that used for outpatient dialysis. This artificial kidney system often fails to work because blood clotting occurs. Ideally this artificial kidney should function without clotting for at least 24 hours.

Some recent clinical observations and studies have suggested that this premature clotting of the circuit may be in some part due to recurrent interruption to the blood flow by mechanical factors such as the position of the vascular access device, patient movement and positional changes. These mechanical factors can cause rapid reductions in blood flow or even temporary cessation of blood flow. This reduction in blood flow causes blood flow stasis promoting clot formation and eventual circuit failure.

There is great variability in the setting of the speed of the blood flow (blood flow rate) through the circuit between intensive care units in Australia. The speed of blood flow may be influential in the promotion of clotting due to the mechanical factors described earlier. We propose to make some comparisons between two blood flow rates (150 mL/min vs. 250 mL/min) currently being used within the intensive care unit at Austin Health.

The aim of this audit is to prospectively collect information to identify any advantage (if any) of one blood flow rate setting over another. Therefore this investigation simply requires that the patient is prescribed either one of the two accepted blood flow rate speeds for the duration of time they require artificial kidney support. Advantages in this case may include the length of time the circuit was able to function (circuit life) before clotting of the circuit occurred.

The study is being conducted exclusively at Austin Health and will involve 48 participants being recruited into the study.

This pilot study would be submitted to Griffith University (Brisbane) and examined for the award of Doctor of Philosophy (PhD).

3 What does participation in this research involve?

We kindly ask that you read this information sheet about this research study. If you are satisfied that it would be in your relative/friends interest to participate in the study, please provide your consent on the form provided.

Following your friend/relatives diagnosis with acute kidney injury the clinical team will decide to commence continuous renal replacement therapy. This is routinely performed in the intensive care unit and is setup and managed by the intensive care nurse. As a routine the blood flow rate is prescribed by the treating clinical doctors prior to commencement of the therapy. Normally this blood flow rate would range anywhere from 150 mL/min to 250 mL/min.

For the purposes of this study we would allocate the blood flow rate to either 150 mL/min or 250 mL/min. Allocation to one of these two groups will be randomised meaning that they have a 1 in 2 chance, like flipping a coin, to be allocated to either group. Apart from the allocation of the blood flow rate, the remaining prescription for the continuous renal replacement therapy will be decided by the treating clinical team as part of their standard or usual practice.

No additional blood tests or procedures are required for the completion of the study and all other care will be delivered per normal in the intensive care unit. To assess the impact of the blood flow rate on the circuit life, we are also asking for permission to obtain information from each participant's medical record. Your friend/relatives involvement with this study will continue for the duration of time renal replacement therapy is required to treat their kidney injury in the intensive care unit, or up to the point a decision is made to withdraw from the study by you as the person responsible for your friend/relative, or at the discretion of the medical staff.

Your friend/relative will not incur any cost for your participation in this study or receive any payment.

4 What do I have to do?

Apart from the study procedures described above, your friend/relative will receive standard care with no additional requirements placed on them.

5 Other relevant information about the research project

Continuous renal replacement therapy is commonly used for the treatment of acute kidney injury. We are investigating if the prescribed speed of the blood flow through the circuit affects the likelihood of early clotting and therefore decreasing the 'life' of each circuit. Your friend/relative will receive continuous renal replacement therapy for the treatment of their kidney injury even if they are enrolled in the study or not.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish your friend/relative to take part, they do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide for your friend/relative to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether your friend/relative will take part or not to take part, or to take part and then withdraw, will not affect their routine treatment, their relationship with those treating them or their relationship with the Austin hospital.

7 What are the alternatives to participation?

Your friend/relative does not have to take part in this research project to receive treatment at this hospital. If you decide for them to not participate in this study then renal replacement therapy will be performed as per usual care. The blood flow rate would be left to the discretion of the treating intensive care doctor or the bedside nurse.

8 What are the possible benefits of taking part?

There may be no immediate benefit to your friend/relative from participating in this study. Participation in this study does not allow them to receive any compensation or other financial benefit. The results from this study are anticipated to benefit future patients.

9 What are the possible risks and disadvantages of taking part?

All medical procedures involve some risk of injury. If you decide for your friend/relative not to participate, continuous renal replacement therapy will be performed according to the direction of the clinical team. The speed of the blood flow through the circuit is routinely prescribed between 150 mL/min to 250 mL/min. In this study we (the investigators) are wanting to prescribe the blood flow rate to see the effect (if any) on premature clotting in the circuit. The blood flow rate would not be prescribed slower or faster than what is considered routine for this therapy. Therefore there are no additional risks to your friend/relative from their participation in the study.

11 What if I withdraw from this research project?

If you decide to withdraw your friend/relative from the project, please notify a member of the research team before you withdraw. If you decide to withdraw from the study, the treatment for acute kidney injury would continue with continuous renal replacement therapy until the clinical team decides it is no longer required.

Should you wish to discontinue your friend/relatives participation in this study, you are free to do so at any time without penalty. Consent to participate in the study does not exclude them from your rights under the law.

If you do withdraw your consent during the study, the study investigators will not collect additional information. We will ask you whether we can use the data already collected for study purposes. If consent is not obtained, collected data will be destroyed.

12 What happens when the research project ends?

If you give us your permission by signing the consent document, we plan to discuss and publish the results from this study in a peer reviewed journals, conference presentations and other professional forums. In any publication or discussion, information will be provided in such a way that your friend/relative cannot be identified.

Part 2 How is the research project being conducted?

13 What will happen to information about the participant?

By signing the consent form you consent to the study investigator, collecting and using personal information about your friend/relative, for the study project. Any information obtained in connection with this study project that can identify them will remain confidential. Each Participant will be allocated a unique code and this unique code will be used to identify them in all matters relating to the study. Their information will only be used for the purpose of this study project and it will only be disclosed to them except as required by law. Access to this information will be restricted to study staff and will be housed in a locked room/cabinet accessible only by the study staff.

Data will be stored both on paper and electronically on computers. The computer records will be password protected and accessible only to the research staff. These records will be stored in a locked research office and at the completion of the study will be archived in a secure facility for fifteen years. After this time, the records will be destroyed.

Information about your friend/relative may be obtained from their health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing their health records, if they are relevant to their participation in this study.

Your friend/relatives health records and any information collected and stored by the study doctor during the study may be reviewed (for the purpose of verifying the procedures and the data) by the ethics committee which approved this study, regulatory authorities, the Austin Hospital, or as required by law. By signing the consent form, you on behalf of your friend/relative as the Participant, authorise release of, or access to, this confidential information as noted above.

It is anticipated that the results of this study will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that they cannot be identified.

Information about your friend/relatives participation in this study may be recorded in their health records. In accordance with relevant Australian and/or Queensland privacy and other relevant laws, they have the right to request access to the information collected and stored by the study team about themselves. They also have the right to request that any information with which they disagree be corrected. Please contact the study team member named at the end of this document if your friend/relative would like to access their information.

14 Complaints and Compensation

If your friend/relative suffers any injuries or complications as a result of this research project, you should contact the study team as soon as possible and they will be assisted with arranging appropriate medical treatment for themselves. If they are eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

15 Who is organising and funding the research?

The Coordinating Principal Investigator for this study is Professor Ian Baldwin from The Austin Hospital. Professor Baldwin will be assisted by Mr Nigel Fealy from the Austin Hospital and Professor Leanne Aitken from Griffith University. There is no funding for the research project.

FAHB16179

16 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee. The ethical aspects of this research project have been approved by Austin Health's human research ethics committee.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

17 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if your frien/relative has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor on 9496 5000 or any of the following people:

Clinical contact person

Name	*Professor Ian Baldwin*
Position	*Course Coordinator – Intensive Care Nursing*
Telephone	*9496 5000*
Email	*Ian.baldwin@austin.org.au*

For matters relating to research at the site at which the participant is participating, the details of the local site complaints person are:

Complaints contact person

Name	Austin Health
Position	*Dr Sianna Panagiotopoulos, Manager, Office for Research*
Telephone	*9496 5088*
Email	*ethics@austin.org.au*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Austin Health
HREC Executive Officer	*Dr Sianna Panagiotopoulos, Manager, Office for Research*
Telephone	*9496 5088*
Email	*ethics@austin.org.au*

Local HREC Office contact (Single Site - Research Governance Officer)

Austin Health

Place Patient Label Here

Name	Austin Health
Position	*Dr Sianna Panagiotopoulos, Manager, Office for Research*
Telephone	*9496 5088*
Email	*ethics@austin.org.au*

FAN010170

Consent Form

Title ***The impact of blood flow rate on circuit life in Continuous Renal Replacement Therapy***

Austin Health

Place Patient Label Here

Protocol Number	***04772***
Coordinating Principal Investigator/ Principal Investigator	***Professor Ian Baldwin***
Associate Investigator(s)	***Professor Leanne Aitken*** ***Mr Nigel Fealy***
Location	***Austin Health***

FAHB10179

Declaration by the person responsible for the Participant

I have read the person responsible Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Austin Health concerning my friend/relatives disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to my friend/relatives participation in this research project as described and understand that I am free to withdraw them at any time during the study without affecting their future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

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