Original Paper

Blood Purification

Blood Purif 2016;41:254–263
DOI: 10.1159/000441968

Received: August 20, 2015
Accepted: October 27, 2015
Published online: December 16, 2015

Patterns and Mechanisms of Artificial Kidney Failure during Continuous Renal Replacement Therapy

Ling Zhang[a, c] Aiko Tanaka[c] Guijun Zhu[b, c] Ian Baldwin[c]
Glenn M. Eastwood[c] Rinaldo Bellomo[c]

[a]Department of Nephrology, West China Hospital of Sichuan University, Sichuan, Chengdu, and [b]Department of Intensive Care Unit, Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China; [c]Department of Intensive Care Unit, Austin Hospital, Heidelberg, Australia

Key Words
Artificial kidney failure · Circuit pressure · Access outflow dysfunction · Transmembrane pressure · Critical illness

Abstract
Background: We aimed to describe the previously unstudied relationship between circuit pressures and circuit clotting, here labeled as 'artificial kidney failure' (AKF), in patients receiving continuous renal replacement therapy (CRRT). ***Methods:*** We performed an observational study of CRRT-treated critically ill patients to continuously record the multiple CRRT circuit pressures. ***Results:*** Three patterns of access outflow dysfunction (AOD) were also noted: severe, moderate and mild. Compared with circuits without AOD, circuits experiencing at least one AOD episode had shorter lifespans (14.2 ± 12.7 vs. 21.3 ± 16.5 h, p = 0.057). This effect was more obvious with moderate or severe AOD (8.7 ± 4.6 vs. 20.6 ± 15.7 h, p = 0.007). If any AOD events occurred within the first 4 h, the sensitivity and specificity in predicting early-immediate AKF were 53.4 and 94.4%, respectively. ***Conclusions:*** Early and intermediate AKF during CRRT is most likely dependent on AOD, which is a frequent event with variable severity.

Background

During continuous renal replacement therapy (CRRT), blood is pumped through a complex extracorporeal circuit. The circuit includes a double lumen catheter, its vascular access outflow lumen, pre-filter tubing, the filter itself, post-filter tubing, air-trap chamber, prevascular inflow tubing and, finally, the inflow lumen of the vascular access. Although anticoagulants such as heparin or citrate are commonly used, circuit clotting within the first 24 h of therapy remains frequent [1]. Such clotting may contribute to inadequate treatment, increased blood loss, greater cost of therapy and typically increases the nursing time dedicated to CRRT instead of direct patient care [1, 2].

CRRT is a prevalent modality of artificial kidney in critically ill patients, and 'artificial kidney failure' (AKF) occurs frequently during clinical practice. Although the main reason for AKF is circuit clotting [3, 4], mean circuit life can vary from 13 to 125 h despite anticoagulation with heparin or citrate [5] and circuit clotting occurs frequently even within the first 10 h of operation [6]. The mechanisms responsible for such variability in the incidence and timing of AKF remain unclear but may relate

KARGER

E-Mail karger@karger.com
www.karger.com/bpu

0253–5068/15/0414–0254$39.50/0

Rinaldo Bellomo, MBBS, MD (Hons), FRACP, FCICM, PG Dip Echo
Department of Intensive Care Unit
Austin Health, 145 Studley Road
Heidelberg, VIC 3084 (Australia)
E-Mail rinaldo.bellomo@austin.org.au

to flow reductions due to access dysfunction [7]. Such flow reductions, in turn, are logically reflected in circuit pressure changes. Thus, continuous monitoring of multiple circuit pressures may more clearly identify where and how AKF occurs. In this regard, modern CRRT machines can now provide such continuous pressure measurements at different points of the extracorporeal circuit [8].

Accordingly, we conducted a prospective pilot observational study and obtained minute-to-minute data on circuit pressures in a cohort of CRRT circuits and recorded filter functional life for each circuit studied. We aimed to test the hypothesis that AKF is not a uniform condition but occurs, instead, through several distinct patterns of circuit failure.

Methods

Study Design and Setting

We performed a single center prospective observational study of critically ill patients in a combined medical, surgical and cardiothoracic ICU in a tertiary institution from September 2014 through March 2015. The Human Research Ethics Committee approved the study (LNR/14/Austin/596) and waived the need for informed consent because the study was non-interventional and all data were de-identified.

Participants

A prospective cohort of adult (aged 18 years or older) patients who underwent CRRT using the Prismaflex machine (Gambro, Lund, Sweden) was included. Patients receiving CRRT were excluded if: (1) CRRT was performed with another machine, (2) the Prismaflex was used for plasma exchange and (3) expected duration of CRRT was <24 h.

CRRT Protocol

Criteria for initiation of CRRT were as reported in the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study [9]. CRRT was performed using the Prismaflex machine (version 4.10), with the corresponding AN69 membrane (Gambro Nephral ST™, Lund, Sweden). Continuous veno-venous hemofiltration (CVVH) (50% post-dilution) or continuous veno-venous hemodiafiltration (CVVHDF) (50% dialysate, 50% replacement fluid with post-dilution) were performed at a rate of 25–30 ml/kg/h of effluent flow. Blood flow rate was 200 ml/min, and occasionally, 150 ml/min was the choice when citrate was used as the anticoagulant. Bicarbonate-buffered solutions were used, including Hemosol-B0 (Gambro, Lund, Sweden) and Accusol (Baxter, Ill., USA). Heparin was the preferred anticoagulant. However, no anticoagulation CRRT was also prescribed in patients with bleeding diatheses. Otherwise, for patients with early circuit clotting, regional anticoagulation with heparin-protamine or citrate was given. However, the latter was administered only in the absence of severe liver dysfunction or in patients with severe lactate acidosis. Vascular access for CRRT was secured by means of 13.5-Fr dual-lumen catheters (Niagara, Vascath, Ont., Canada) or 13-Fr dual-lumen catheters (Dolphin, Gambro, Lund, Sweden).

Measurement of Dynamic Changes in Circuit Pressures

The details and illustrations of the methods used to obtain, store and analyze pressure data from the CRRT circuit have been previously published [10].

Data on circuit pressures including access outflow pressure (AOP), effluent pressure (EP), pre-filter pressure (PFP), return inflow pressure (RIP) and transmembrane pressure (TMP) were collected every minute from relevant circuit points (more details in online suppl. file 1; for all online suppl. material, see www.karger.com/doi/10.1159/000441968). We defined early AKF as circuit failure occurring in less than 10 h from initiation of CRRT, intermediate AKF as circuit failure occurring between 10 and 24 h from initiation of CRRT and late AKF as circuit failure occurring more than 24 h from initiation of CRRT.

Variables and Data Sources

All baseline demographics were collected prior to CRRT commencing, including diagnosis, age, sex, sequential organ failure assessment score and the need for mechanical ventilation. For each circuit evaluated, we obtained the following data: circuit lifespan (h), CRRT anticoagulation type, vascular access position, modality and dose, presence of mechanical ventilation, vasopressor support, mean artery pressure, temperature, hemoglobin (g/dl), platelet counts ($*10^3$/μl), international normalized ratio (INR), activated partial thromboplastin time (APTT), pH and ionized calcium.

Statistical Methods

Continuous variables are expressed as the mean ± SD or median (25th and 75th percentiles), as appropriate. Variability of pressures for access outflow or return inflow was defined as the standard deviation for all pressure measurements [11]. The frequency of access dysfunction episodes was expressed as events per 1,000 CRRT-hour. Comparisons of data from each group were performed using the one-way analysis of variance or chi-square test. Circuit survival was compared using the Kaplan–Meier survival statistics and Cox regression model. Differences at the level of p values <0.05 were considered significant. All statistical analyses were performed with SPSS version 19.0 (SPSS Inc., Chicago, Ill., USA).

Results

Participants and Descriptive Data

We studied 1,436 h of circuit lifespan from 79 circuits for 23 patients (13 men, mean age 52 years). The characteristics of the study patients are shown in table 1. Mean circuit lifespan was 17.8 ± 13.8 h. Anticoagulants were used for 45 (54.4%) circuits. All vascular access was via the femoral veins with catheter length of 20 cm. Cessation of the circuit was elective (no need of CRRT) for 3 circuits (3.8%) while the other 76 circuits

Table 1. Demographic and treatment features of patients and circuits

	Patients (n = 23)
Age, years	52±12
Gender, f/m	10/13
Sequential organ failure assessment score	9±2
Mechanical ventilation	15 (65.2)
Diagnostic category	23
Sepsis	5
Cardiovascular	8
Gastrointestinal	8
Respiratory	2
Circuits number	79
Circuit life, h	17.8±13.8
Anticoagulation	45 (54.4)
Heparin	40 (50.6)
Citrate	2 (2.5)
Heparin + protamine	1 (1.3)
No anticoagulation	36 (45.6)
Elective circuit change	3 (3.8)
Non-elective circuit change	76 (96.2)
Filter clotting	68 (89.5)
Access dysfunction	7 (9.2)
Clotting of air-trap chamber	1 (1.3)
Right femoral access	16 (69.6)
Left femoral access	7 (30.4)
CVVH	49 (62.1)
CVVHDF	30 (37.9)
CRRT dose, ml/h/kg	26.4±5.7
Hemoglobin, g/dl	93.5±13.4
Platelet count, 10^3/μl	154.1±37.8
INR	1.2±0.1
APTT, s	39.3±7.4

Values are mean ± SD or n (%).

(96.2%) experienced AKF. Filter clotting or clogging (defined as a TMP >250 mm Hg; 89.5%) was the main reason of AKF while 7 (9.2%) circuits were lost due to access dysfunction (unable to obtain blood flow), with 1 circuit lost because of clotting in the air-trap chamber (1.3%).

Patterns of AKF

As shown in figure 1, we assessed 3 patterns of AKF, namely, early (≤10 h), intermediate (>10, <24 h) and late (≥24 h). The mean lifespan with AKF was 17.6 ± 14.9 h. Overall, 28 (36.8%) circuits experienced early AKF with a lifespan of 6.1 ± 1.7 h, while 30 (39.5%) circuits experienced intermediate AKF with a lifespan of 15.4 ± 3.6 h and the remaining 18 (23.7%) circuits experienced late AKF with a lifespan of 41.4 ± 13.0 h (online suppl. file 2). There was a significant difference in circuit lifespan between these different AKF patterns ($p < 0.001$).

Patterns and Frequency of AOD

After evaluating the dynamic changes of circuit pressures, we found that when AOP decreased to –200 mm Hg or less (online suppl. file 3), dramatic changes in PFP, EP and TMP were found synchronously, indicating that CRRT did not 'work well' at that moment. According to such phenomenon, as shown in figure 2, we defined 3 patterns of access outflow dysfunction (AOD): severe (negative pressure <–200 mm Hg for ≥1 h or unable to obtain outflow), moderate (negative pressure <–200 mm Hg for >5 min but <1 h) and mild (negative pressure <–200 mm Hg for ≤5 min). Eighteen (78.3%) patients experienced at least 1 time of AOD. Among the 76 circuits, 34 (44.7%) circuits experiencing at least 1 episode of AOD and 19 (25%) circuits experienced moderate-severe AOD. As shown in figure 3, compared with circuits without AOD, those experiencing at least 1 episode of AOD had a shorter lifespan (14.2 ± 12.7 vs. 21.3 ± 16.5 h, $p = 0.057$). Similarly, circuits with moderate or severe AOD had a significantly shorter lifespan (8.7 ± 4.6 vs. 20.6 ± 15.7 h, $p = 0.007$). Furthermore, the mean 'remaining' lifespan of the 19 circuits (18 in early-immediate AKF group and 1 in late AKF group) after moderate-severe AOD events was only 2.37 ± 2.64 h.

Finally, a total of 129 AOD episodes per 1,000 CRRT-hour were observed during early or intermediate AKF circuits. These events included 14 episodes of severe, 9 of moderate and 106 of mild AOD. In contrast, no severe AOD episode was found in circuits that experienced late AKF, and we only observed 2 episodes of moderate AOD and 46 episodes of mild AOD per 1,000 CRRT-hour. As shown in online supplementary file 4, early or intermediate AKF were associated with significantly higher frequency of total AOD episodes than late AKF, as well as all 3 patterns ($p < 0.05$).

Sensitivity and Specificity of AOD Events in Predicting Early-Immediate AKF

As shown in figure 4, 80% of mild AOD events, 63.2% of moderate-severe AOD events and 76.4% as a total occurred within first 4 h in early-immediate AKF group; in contrast, only 1 (3%) mild AOD event as a total occurred within first 4 h in late AKF group ($p < 0.001$). From table 2, if any AOD events occurred within the first 4 h, the sensitivity and specificity in predicting early-immediate AKF was 53.4 and 94.4%, respectively, with the accuracy of 63.2%.

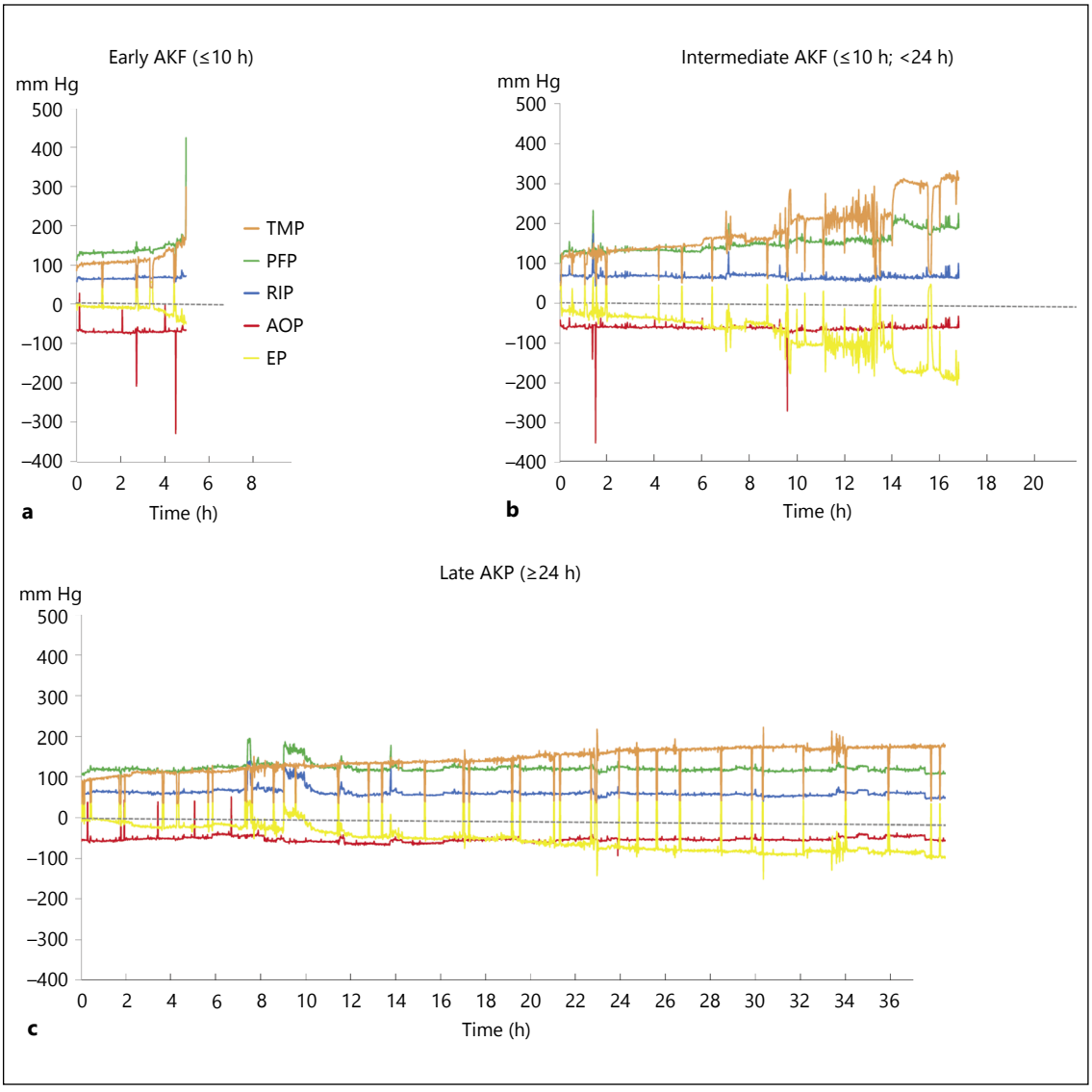


Fig. 1. Patterns of AKF. **a** The circuit lifespan was 4.0 h due to early AKF (filter clotting: TMP = 450 mm Hg) with rapid change in pressure. **b** The circuit lifespan was 16.7 h due to intermediate AKF (filter clotting: TMP = 316 mm Hg). **c** The circuit lifespan was 67.4 h due to late AKF with slow filter clotting over time (filter clotting: TMP = 395 mm Hg).

Changes of Pressures in Different Patterns of AKF during CRRT

As shown in table 3, a trend toward higher mean AOP was found in early AKF group ($p = 0.065$). However, there were significant baseline differences in AOP between the 3 groups ($p = 0.024$), as well as significant differences in AOP variability ($p < 0.001$). Early AKF was associated with higher baseline AOP, mean AOP and greater variability in such pressures than late AKF ($p < 0.05$). There were no differences in baseline, mean and variability of RIP between the 3 groups.

Although circuits had similar baseline TMP values, early or intermediate AKF circuits had a faster and steeper early TMP increases over time in comparison with late AKF circuits ($p < 0.01$). In addition, faster and steeper increases in PFP and negative EP were also found in the early or intermediate AKF groups ($p < 0.05$). There was a negative association between circuit lifespan and the early increase rate of TMP ($r = –0.681$, $p < 0.001$), as well as the early increase rate of PFP ($r = –0.617$, $p < 0.001$) and negative EP ($r = 0.623$, $p < 0.001$; online suppl. file 5).

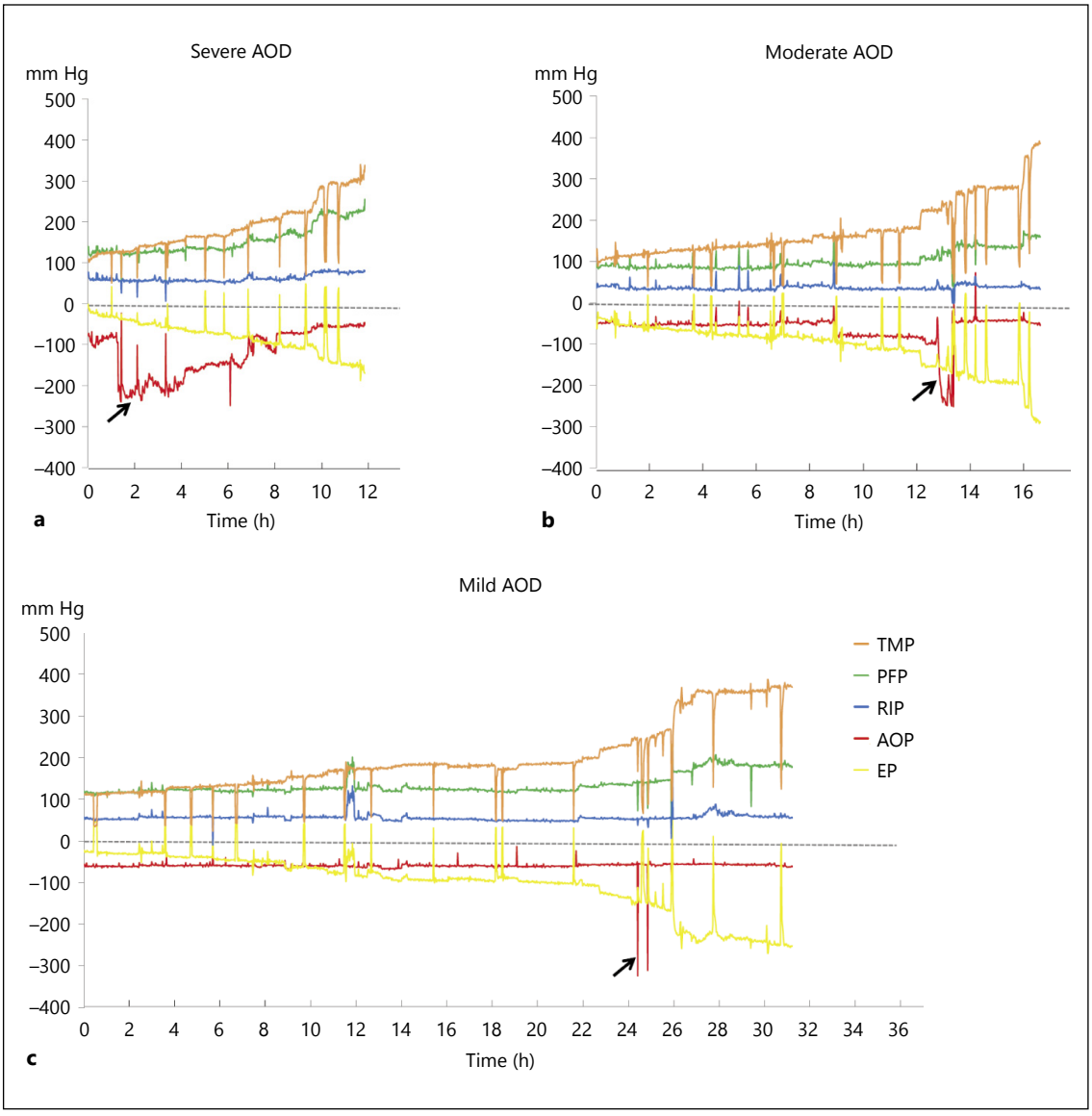


Fig. 2. Patterns of AOD. **a** There is major and sudden and prolonged increase in the negative pressure (from –100 to –250 mm Hg as indicated by arrow) required to achieve flow from the outflow lumen of the dialysis catheter after only a very short time of circuit function. Please note that the negative pressure needed to generate flow at baseline even before the episode of dysfunction is already approximately –100 mm Hg, while for the circuits in figure 1b and c the negative pressure at the baseline is approximately –50 mm Hg. **b** There is sudden and extended increase in the negative pressure (from –100 to –280 mm Hg as indicated by arrow) required in order to generate flow from the outflow lumen of the dialysis catheter after 12 h of stable function. **c** There are only 2 very short-lived deep increases (up to –350 mm Hg) in the negative pressure required to generate flow from the outflow lumen of the dialysis catheter at 24 h of circuit function with return to normal thereafter.

Factors Associated with Lifespan in Different Patterns of AKF

For further analysis, all 76 circuits experiencing AKF were divided into 2 groups: early-intermediate AKF group and late AKF group. The circuits in the late AKF group had a markedly longer lifespan than that in the early-intermediate AKF group (42.2 ± 12.3 vs. 10.6 ± 5.6 h, $p < 0.001$). The analysis of potential factors that may have influenced circuit lifespan is presented in table 4. Circuits in the late AKF group had a lower occurrence of moderate-severe AOD episodes (5.6 vs. 29.3%, $p = 0.029$), lower AOP variability (8.2 ± 3.6 vs. 20.5 ± 16.5 mm Hg, p =

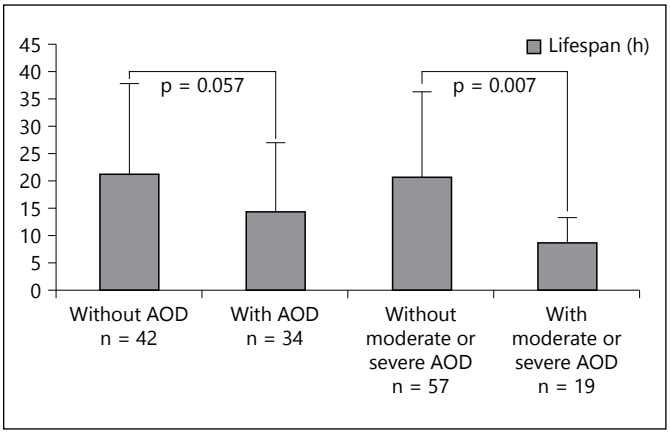
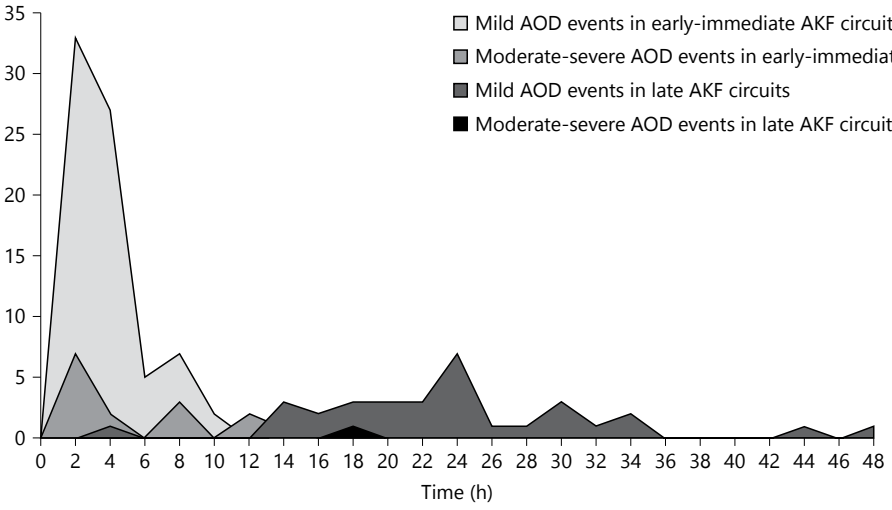


Fig. 3. Lifespan in different patterns of AOD.



	Early-immediate AKF	Late-AKF	p value
Mild AOD events within the first 2 h	31/70	0/32	<0.001
Mild AOD events within the first 4 h	56/70	1/32	<0.001
Moderate-severe AOD events within the first 2 h	7/19	0/1	0.452
Moderate-severe AOD events within the first 4 h	12/19	0/1	0.209
Total AOD events within the first 2 h	38/89	0/33	<0.001
Total AOD events within the first 4 h	68/89	1/33	<0.001

Fig. 4. Time window of AOD during CRRT.

0.006) and lower platelet count (104.6 ± 56.7 vs. 168.9 ± 75.3*10^9/l, $p < 0.001$). There were no significant difference in mild AOD episodes, baseline and mean AOP, use of anticoagulation, CRRT modality and dose, femoral access position, INR, APTT, pH, temperature and ionized calcium between the 2 groups ($p > 0.05$).

Similar results were obtained on Cox regression analysis (online suppl. file 6). Higher moderate-severe AOD episodes appeared to be associated with significantly shorter circuit survival (hazard ratio [HR] 0.33, 95% CI 0.15–0.72), but no difference was found between circuits with only mild AOD and circuits without AOD. Higher

Table 2. Sensitivity, specificity, accuracy, PPV and NPV of AOD events in predicting early-immediate AKF

	Number of circuits, %	Sensitivity, %	Specificity, %	Accuracy, %	PPV, %	NPV, %
Mild AOD event within the first 2 h	19/76 (25)	32.8	100	48.7	100	45.1
Mild AOD event within the first 4 h	26/76 (34.2)	44.8	94.4	56.6	98.2	68.9
Moderate-severe AOD event within the first 2 h	7/76 (9.2)	12.1	100	32.9	100	7.7
Moderate-severe AOD event within the first 4 h	9/76 (11.8)	15.5	100	35.5	100	12.5
Any AOD event within the first 2 h	24/76 (31.6)	41.4	100	55.3	100	39.3
Any AOD event within the first 4 h	32/76 (42.1)	53.4	94.4	63.2	98.6	60.4
Moderate-severe AOD event	19/76 (25)	31.0	94.4	32.9	94.7	29.8

PPV = Positive predictive value; NPV = negative predictive value.

Table 3. Changes of pressures in different patterns of AKF during CRRT

	Early AKF (n = 28)	Intermediate AKF (n = 30)	Late AKF (n = 18)	p value
Baseline AOP, mm Hg	−76.0±36.7	−58.9±15.8*	−59.5±8.2*	0.024
Mean AOP, mm Hg	−75.4±22.5	−64.8±2.5	−62.6±7.7*	0.065
AOP variability, mm Hg	26.0±17.6	17.2±12.5*, #	8.2±3.6*, #	<0.001
Baseline RIP, mm Hg	62.3±9.5	60.5±23.3	66.5±16.3	0.521
Mean RIP, mm Hg	64.8±13.0	61.6±21.6	66.1±10.5	0.643
RIP variability, mm Hg	7.5±3.8	10.3±9.0	10.4±6.2	0.225
Increase in TMP, mm Hg/h	43.4±20.7	15.2±6.8*, #	5.1±2.6*, #	<0.001
Increase in PFP, mm Hg/h	34.2±18.5	8.7±5.7*, #	1.2±1.1*, #	<0.001
Decrease in EP, mm Hg/h	−29.8±15.2	−12.0±4.1*, #	−4.4±2.1*, #	<0.001

* Significant differences when compared to early group ($p < 0.05$).
# Significant differences when compared to intermediate group ($p < 0.05$).

AOP variability (>10 mm Hg) was also an independent risk factor for shorter circuit lifespan with an HR of 0.40 (0.21–0.73). In contrast, a lower platelet count (<100*10^3/μl) was associated with a longer circuit survival time (HR 2.09, 95% CI 1.17–3.73). The Kaplan–Meier survival curves for groups between different patterns of AOD or AOP variability are shown in online supplementary file 5. They demonstrate significantly shorter circuit survival time in the moderate-severe AOD or high AOP variability (>10 mm Hg) groups.

Discussion

We performed a pilot observational study to clarify the possible patterns and mechanisms of AKF during CRRT by continuous monitoring of circuit pressures. We assessed 3 major patterns of AKF: early (≤10 h); intermediate (>10, <24 h) and late (≥24 h). There was a significant difference in the rate of increase in TMP and related pressures between the 3 patterns. Moreover, we also found 3 different patterns of AOD: severe, moderate and mild. Early or intermediate AKF were clearly associated with different patterns, greater incidence, greater variability and greater severity of AOD. If any AOD events occurred within the first 4 h, the sensitivity and specificity in predicting early-immediate AKF was 53.4 and 94.4%, respectively. These observations have important implications on logical circuit management by clinicians.

Many studies have compared different strategies of circuit anticoagulation to prevent clotting of the extracorporeal circuit [3, 4, 12–15]. However, a previous study found that 13.5% artificial kidneys clotted in a very short time (mean lifespan 8 h), even though common antico-

Table 4. Comparison of factors associated with circuit lifespan in early-intermediate AKF vs. late AKF

	Early-intermediate AKF (n = 58)	Late AKF (n = 18)	p value
Lifespan, h	10.6±5.6	42.2±12.3	<0.001
Total AOD episodes (yes vs. no)	32 (55.2)	6 (33.3)	0.105
Only mild AOD	15 (25.9)	5 (27.7)	0.872
Moderate-severe AOD	18 (29.3)	1 (5.6)	0.029
Baseline AOP, mm Hg	–67.9±29.2	–59.5±8.2	0.232
Mean AOP, mm Hg	–70.2±22.5	–62.6±7.7	0.166
AOP variability, mm Hg	20.5±16.5	8.2±3.6	0.006
AOP variability >10 mm Hg	39 (67.2)	3 (16.7)	<0.001
Anticoagulant use in CRRT	33 (56.9)	9 (50)	0.607
CRRT modality (CVVH/CVVHDF)	36/22	13/5	0.432
CRRT dose, l/h	2.5±0.5	2.3±0.2	0.704
Femoral access position (R)	42 (72.4)	11 (61.1)	0.362
Hemoglobin[#], g/l	84.5±21.4	89.3±20.4	0.271
Platelet count[#], 10^3/μl	168.9±75.3	104.6±56.7	<0.001
INR[#]	1.5±0.5	1.5±0.4	0.673
APTT[#], s	41.8±10.9	41.7±15.2	0.972
PH[#]	7.4±0.1	7.4±0.1	0.684
Temperature[#], °C	36.5±0.7	36.7±0.6	0.783
Ionized calcium, mmol/l[#]	1.2±0.1	1.2±0.2	0.988
Mean blood pressure[#], mm Hg	77.7±9.1	76.6±12.6	0.775
Mechanical ventilation[#]	46 (79.3)	15 (83.3)	0.708
Vasopressor support[#]	34 (58.6)	11 (61.1)	0.851

Values are maean ± SD or n (%).
[#] At the beginning of every new circuit during CRRT.

agulation strategies were used [6]. In the large RENAL study [9], a high standard deviation in the number of filters used daily was reported, which implies that many patients required 2 or more filters daily. Furthermore, in a recent randomized controlled trial comparing different anticoagulation strategies (citrate vs. heparin) in CRRT, major fluctuations in circuit life were found both in the citrate (37.5 ± 23 h) and the heparin group (26.1 ± 19 h) [13]. Another observational study found that the circuit life during CRRT was only 11 ± 11.5, 11.6 ± 6.6 and 7.4 ± 5.1 h in patients with acute liver failure, acute chronic liver disease and post-elective liver transplantation, respectively [16]. Clearly, early or intermediate AKF during CRRT is common. Our study provides an estimate of this syndrome at approximately 70% of all CRRT circuits.

Only a few studies have assessed changes in circuit pressure during CRRT. A previous study in 1990 [17] reported that an increase of 26 mm Hg or more in the transfilter pressure gradient (PFP-RIP) might predict circuit failure due to clotting and imminent cessation of function. However, only 41 circuits with continuous veno-venous hemodialysis were included in the study, pressures were not collected electronically or continuously; the effect of EP was not assessed, and crucially, the study reported no data on AOP, the major marker of access dysfunction. Another study [18] recorded circuit pressures manually on an hourly basis during CRRT and showed that different patterns of pressure profiles might be associated with different circuit lifespan. However, such hourly sampling is clearly suboptimal, misses important episodes of AOD within each hour and is open to selection bias as observers can choose pressures each hour that most closely represent their views of events. In contrast, we developed and applied a new method for the automated electronic monitoring of circuit pressures every minute during CRRT and described the characteristics of different patterns of AKF and their relationship to circuit pressures.

A multicenter randomized controlled study [19] reported that about 10% of patients experienced vascular access dysfunction during renal replacement therapy at either the femoral or jugular site. There are several potential reasons for access dysfunction. First, during physio-

therapy or positional changes, catheter position may suddenly change and lead to intermittent occlusion [6, 20]. Second, thrombus formation in the catheter, bending of the catheter or collapse of a central vein around the catheter, may also contribute to AOD [6]. Third, we speculate that, with increase in temperature of the vascular catheter after insertion, flexibility increases and lumen obstruction is more likely. By continuously monitoring pressures in our study, a total of >100 episodes of AOD were seen in 79 circuits, implying that many AOD episodes are not detected without continuous monitoring and silently contribute to AKF.

Our study demonstrates that CRRT circuits likely fail through different mechanisms. They suggest that for rapid circuit failure, a common preceding event is the occurrence of severe or moderate AOD. As AOD leads to strong negative pressures being applied, our findings imply that flow out of the catheter arterial lumen must be impaired or even absent. If the filtration process continues while there is no flow, hemoconcentration and stasis will occur and clotting and loss of function will take place. Being able to distinguish such access-related AKF from slow progressive filter clotting without AOD has clear therapeutic implications – the former requires repositioning or changing of the access catheter or greater attention during patient movement, the latter requires adjusted anticoagulant therapy. Importantly, increased aggressiveness of anticoagulation in the setting of access malfunction is unlikely to be useful and may increase patient risk.

By electronically assessing pressure recordings during CRRT for the first time, we have described a new convenient method to observe and record circuit pressures every minute during CRRT. In doing so, we have identified major patterns of AKF, as well as different patterns of vascular access malfunction. Moreover, by showing the dynamic changes in circuit pressures and their relationship with AKF, we were able to develop a new, more objective and likely more accurate approach to the investigation of AKF during CRRT. Finally, this methodology provides valuable clinical information that can inform decisions about access, anticoagulation and circuit management in a more logical and evidence-based fashion.

Our study, however, has several limitations. First, it is a single center, observational study. Therefore, more information from other centers is needed to confirm the external validity of our findings. However, we studied a heterogeneous cohort, which reflects the typical patients treated with CRRT in a modern ICU. Second, our description of patterns of AKF is, to a degree, arbitrary. However, it is based on striking and obvious differences in circuit lifespan and changes in TMP. The same problem applies to our description of patterns of AOD. However, our findings are also visually obvious, logical and in keeping with clinical suspicions. Third, in our study, all CRRTs were provided via a femoral vascular access, and the jugular and subclavian accesses were not observed. However, in the recent literature [19], similar catheter dysfunction rate was found between femoral and jugular site, indicating that the AOD problem might also be frequent in the jugular and subclavian site. Fourth, 20-cm-long catheters were used in the femoral position. However, such catheters remain commonly used in the world, and major manufacturers such as Gambro/Baxter do not market 24- or 25-cm-long catheters in Australia.

Solute removal may also be affected differentially by such changes in circuit pressures and this issue needs to be investigated. Moreover, different blood pump speeds, CRRT intensity, CRRT modalities may affect circuit pressure differently and require assessment. Finally, catheter size and location and anticoagulation strategies and their impact on circuit pressures need to be assessed to define the most successful technical approach to minimizing early circuit loss and the inherent cost of this.

In conclusion, in the first observational cohort study of continuous electronic monitoring of circuit pressure changes during CRRT, we were able to identify major patterns of AKF in CRRT. Our findings suggest that early or intermediate AKF during CRRT might be mostly dependent on vascular access outflow malfunction and that the severity and frequency of such malfunction could now be diagnosed. These observations have practical implications because vascular access malfunction might logically require a different approach to circuit management compared with slow progressive circuit clotting.

Acknowledgment

The authors acknowledge the help of the Austin Hospital, ICU nursing staff, for their assistance in the collection of electronic data of circuit pressures during CRRT.

Support

None.

Financial Disclosure

The authors declare that they have no relevant financial interests.

Author Contribution

R.B., as the corresponding author of this paper, was mainly responsible for program design and modification. L.Z. wrote the first draft. L.Z., G.Z. and A.T. enrolled the patients and collected the CRRT pressures and clinical data. I.B. and G.M.E. put their hands on study design and modification of the draft. Each author contributed important intellectual content during manuscript revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. L.Z. and R.B. take responsibility that this study has been reported honestly, accurately and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

References

1 Davenport A: The coagulation system in the critically ill patient with acute renal failure and the effect of an extracorporeal circuit. Am J Kidney Dis 1997;30(5 suppl 4):S20–S27.
2 Baldwin I: Factors affecting circuit patency and filter 'life'. Contrib Nephrol 2007;156: 178–184.
3 Oudemans-van Straaten HM, Bosman RJ, Koopmans M, van der Voort PH, Wester JP, van der Spoel JI, Dijksman LM, Zandstra DF: Citrate anticoagulation for continuous venovenous hemofiltration. Crit Care Med 2009; 37:545–552.
4 Monchi M, Berghmans D, Ledoux D, Canivet JL, Dubois B, Damas P: Citrate vs. heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study. Intensive Care Med 2004;30:260–265.
5 Wu MY, Hsu YH, Bai CH, Lin YF, Wu CH, Tam KW: Regional citrate versus heparin anticoagulation for continuous renal replacement therapy: a meta-analysis of randomized controlled trials. Am J Kidney Dis 2012;59: 810–818.
6 Kim IB, Fealy N, Baldwin I, Bellomo R: Premature circuit clotting due to likely mechanical failure during continuous renal replacement therapy. Blood Purif 2010;30:79–83.
7 Baldwin I, Bellomo R, Koch B: Blood flow reductions during continuous renal replacement therapy and circuit life. Intensive Care Med 2004;30:2074–2079.
8 Boyle M, Baldwin I: Understanding the continuous renal replacement therapy circuit for acute renal failure support: a quality issue in the intensive care unit. AACN Adv Crit Care 2010;21:367–375.
9 Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S: Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009;361:1627–1638.
10 Zhang L, Baldwin I, Zhu G, Tanaka A, Bellomo R: Automated electronic monitoring of circuit pressures during continuous renal replacement therapy: a technical report. Crit Care Resusc 2015;17:51–54.
11 Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Sever PS, Poulter NR: Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010;375:895–905.
12 Brophy PD, Somers MJ, Baum MA, Symons JM, McAfee N, Fortenberry JD, Rogers K, Barnett J, Blowey D, Baker C, Bunchman TE, Goldstein SL: Multi-centre evaluation of anticoagulation in patients receiving continuous renal replacement therapy (CRRT). Nephrol Dial Transplant 2005;20:1416–1421.
13 Hetzel GR, Schmitz M, Wissing H, Ries W, Schott G, Heering PJ, Isgro F, Kribben A, Himmele R, Grabensee B, Rump LC: Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. Nephrol Dial Transplant 2011;26:232–239.
14 Hwang SD, Hyun YK, Moon SJ, Lee SC, Yoon SY: Nafamostat mesilate for anticoagulation in continuous renal replacement therapy. J Artif Organs 2013;36:208–216.
15 Link A, Girndt M, Selejan S, Mathes A, Bohm M, Rensing H: Argatroban for anticoagulation in continuous renal replacement therapy. Crit Care Med 2009;37:105–110.
16 Agarwal B, Shaw S, Shankar Hari M, Burroughs AK, Davenport A: Continuous renal replacement therapy (CRRT) in patients with liver disease: is circuit life different? J Hepatol 2009;51:504–509.
17 Holt AW, Bierer P, Bersten AD, Bury LK, Vedig AE: Continuous renal replacement therapy in critically ill patients: monitoring circuit function. Anaesth Intensive Care 1996;24: 423–429.
18 Ejaz AA, Komorski RM, Ellis GH, Munjal S: Extracorporeal circuit pressure profiles during continuous venovenous haemofiltration. Nurs Crit Care 2007;12:81–85.
19 Parienti JJ, Thirion M, Mégarbane B, Souweine B, Ouchikhe A, Polito A, Forel JM, Marqué S, Misset B, Airapetian N, et al: Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. JAMA 2008; 299:2413–2422.
20 Mandolfo S, Borlandelli S, Ravani P, Imbasciati E: How to improve dialysis adequacy in patients with vascular access problems. J Vasc Access 2006;7:53–59.