The relationship between commencement of continuous renal replacement therapy and urine output, fluid balance, mean arterial pressure and vasopressor dose

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ABSTRACT

Background and objectives: The effect of initiating continuous renal replacement therapy (CRRT) on urine output, fluid balance and mean arterial pressure (MAP) in adult intensive care unit (ICU) patients is unclear. We aimed to evaluate the impact of CRRT on urine output, MAP, vasopressor requirements and fluid balance, and to identify factors affecting urine output during CRRT.

Design: Retrospective cohort study using data from existing databases and CRRT machines.

Setting: Medical and surgical ICUs at a single university-associated centre.

Participants: Patients undergoing CRRT between 2015 and 2018.

Main outcome measures: Hourly urine output, fluid balance, MAP and vasopressor dose 24 hours before and after CRRT commencement. Missing values were estimated via Kaplan smoothing univariate time-series imputation. Mixed linear modelling was performed with noradrenaline equivalent dose and urine output as outcomes.

Results: In 215 patients, CRRT initiation was associated with a reduction in urine output. Multivariate analysis confirmed an immediate urine output decrease (–0.092 mL/kg/h; 95% confidence interval [CI], –0.150 to –0.034 mL/kg/h) and subsequent progressive urine output decline (effect estimate, –0.01 mL/kg/h; 95% CI, –0.02 to –0.01 mL/kg/h). Age and greater vasopressor dose were associated with lower post-CRRT urine output. Higher MAP and lower rates of net ultrafiltration were associated with higher post-CRRT urine output. With MAP unchanged, vasopressor dose increased in the 24 hours before CRRT, then plateaued and declined in the 24 hours thereafter (effect estimate, –0.004 μg/kg/min per hour; 95% CI, –0.005 to –0.004 μg/kg/min per hour). Fluid balance remained positive but declined towards neutrality following CRRT implementation.

Conclusions: CRRT was associated with decreased urine output despite a gradual decline in vasopressor and a positive fluid balance. The mechanisms behind the reduction in urine output associated with commencement of CRRT requires further investigation.

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Continuous renal replacement therapy (CRRT) is a common intervention in the intensive care unit (ICU) for patients with acute kidney injury (AKI) and is associated with a 40–60% mortality.[1,2] Commencement of CRRT likely has haemodynamic and solute concentration consequences, which may affect urine output.[3-8] For example, hypotension on commencement of CRRT has been described in children and animal models[6,8-10] as well as in the adult ICU population.[11] However, the impact on mean arterial pressure (MAP) may be complex, and may include both positive effects (removal of pro-inflammatory mediators, correction of pH, potential cooling effects on metabolism) and negative effects (removal of anti-inflammatory mediators and vasopressors, bioincompatibility, fluid removal-related intravascular hypovolaemia, rapid shifts in osmolality, CRRT-associated myocardial stunning, and cooling-induced vasoconstriction).[4,12]

Rapid changes in MAP, however, are likely to be particularly injurious to the kidneys in patients with AKI, who have impaired autoregulatory mechanisms,[12,13] with such injury manifesting itself as decreased urine output. In turn, reduced urine output in AKI has been associated with poor outcomes, including in patients requiring CRRT.[14-16] Yet, no studies have systematically assessed the early (first 24 hours) impact of starting CRRT on urine output with consideration of simultaneous changes in MAP.

Objectives

Accordingly, the objectives of this study were to evaluate the impact of CRRT initiation on urine output, MAP, vasopressor requirements and fluid balance, and to identify factors that might

modulate any changes in urine output in the first 24 hours of treatment with CRRT.

Methods

Design

We performed a retrospective cohort study in three surgical and medical ICUs within a university-associated tertiary referral adult ICU system. This non-interventional observational study received Human Research Ethics Committee approval and did not require consent (HREC LNR/16/Austin/400).

Participants and CRRT protocol

Between June 2015 and August 2018, we included adult patients undergoing CRRT if they had a recorded treatment on the Prismaflex (Gambro/Baxter, IL, USA) device. Patients underwent CRRT based on accepted clinical indications (acidaemia, electrolyte management, drug intoxication, volume overload and uraemia). CRRT was prescribed at a standard intensity of 30 mL/kg/h as continuous venovenous haemodiafiltration (CVVHDF; 1:1 dialysis to filtration, predominantly pre-dilution) or continuous venovenous haemodialysis (CVVHD) with heparin, low molecular weight heparin, heparin-protamine, or no circuit anticoagulation. Fluid removal was at the discretion of the treating clinician. Blood flow (Qb) was generally 200–250 mL/min (CVVHDF) or 120–130 mL/min (CVVHD).[17] Each patient was included once only.

Variables and data sources

CRRT-related data (blood flow, effluent rate, net ultrafiltration rate [NUF], the hourly effluent volume less the dialysate and replacement volumes[18]) were extracted from the Prismaflex data cards and analysed using "R" software[19] (R packages are listed in the Online Appendix, table 1). Patient baseline and admission data were obtained from the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS CORE) Adult Patient Database,[20] and hourly urine output, vasopressor requirements, MAP and hourly fluid balance were obtained from medical records for 24 hours before and 24 hours following commencement of CRRT. Hourly vasopressor requirements were converted to noradrenaline equivalent, the sum of all vasopressor drug doses converted to a noradrenaline dose (Online Appendix, table 2).

Statistics

Baseline and process observations were summarised as proportions, means (95% confidence interval [CI]) or medians (interquartile range [IQR]) as appropriate. Urine output, fluid balance and MAP were imputed, where missing, by univariate time series imputation with Kalman smoothing,[21,22] using the "R" package imputeTS.[23] Mean (95% CI) MAP, noradrenaline equivalent dose, change in noradrenaline equivalent dose and fluid dynamic variables (urine output, fluid balance, NUF) were presented graphically with a simple linear model prediction or LOWESS smoother curves plotted.

Multivariate analyses were performed with mixed linear modelling with the patient as a random effect and outcomes of interest including urine output (with predictors of time, CRRT status, noradrenaline equivalent dose, MAP, NUF, among others) and noradrenaline equivalent dose in the post-CRRT commencement period. NUF was separated into tertiles (0, 0.1–1.15 and > 1.15 mL/kg/h) and noradrenaline equivalent dose was split into 0, and non-0 tertiles (0.01–0.10, 0.11–0.20 and > 0.20 μg/kg/min).

Results

Patient baseline and treatment-related variables

The patient baseline and treatment data are presented in Table 1. We studied 215 patients (138 males) with a median age of 61 years and an Acute Physiology and Chronic Health Evaluation (APACHE) III estimated Risk of Death (ROD) of 51%. Admission diagnosis was predominantly medical, with sepsis or other medical conditions accounting for 76% of cases. Most patients were oliguric (71%) at commencement of CRRT, with a median urine output of 18 mL/h. Although the prescribed effluent rate was 30 mL/kg/h, the effective delivered effluent rate was lower due to down time related to clotting or stoppages for imaging and procedures (mean, 20.20 mL/kg/h; 95% CI, 18.97–21.43 mL/kg/h).

Urine output data were available for 8084 hours within the 48 hours studied, requiring imputation of 2451 hours (23%); fluid balance data were available for 8018 hours with imputation of 2517 hours (24%); and MAP data were available for 8763 hours with imputation of 1772 hours (17%). Most imputation was performed in the pre-CRRT period (38% *v* 10% urine output; 36% *v* 11% fluid balance; 27% *v* 7% MAP; $P < 0.001$).

Urine output and CRRT initiation

After commencement of CRRT, there was a stepwise reduction in urine output, with a flattening of the rate of change over time (Figure 1, A). When stratified by urine output group at commencement of CRRT (severe oliguria, mild-to-moderate oliguria, non-oliguric) patient characteristics were

Table 1. Patient characteristics and selected treatment related variables

Variable	Value
Total number of patients	215
Sex, male	138 (64%)
Age, years, median (IQR)	61.00 (46.52–70.00)
Weight, kg, median (IQR)	82.0 (72.0–100.0)
APACHE III ROD, %, median (IQR)	51.45% (28.608–75.062%)
Creatinine at admission, μmol/L, median (IQR)	293.5 (173–503)
Urea at admission, mmol/L, median (IQR)	18.6 (10.88–28.02)
Diagnosis category at admission	
Cardiac surgical	18 (8%)
Other surgical	35 (16%)
Sepsis	68 (32%)
Other medical	94 (44%)
Urine output at CRRT commencement, mL/kg/h, median (IQR)	0.22 (0.03–0.62)
Urine output status at CRRT commencement*	
Severe oliguria	52 (24%)
Mild-to-moderate oliguria	101 (47%)
Non-oliguric	62 (29%)
Time from ICU admission to CRRT start, hours, median (IQR)	15.4 (6.3–43.6)
CRRT treatments, median (IQR)	2 (1–4)
Treatment time, hours, median (IQR)	45 (20.6–95)
Proportion time on treatment in first 24 hours, median (IQR)	79 (54–96)
CRRT mode†	
CVVHDF	90 (42%)
CVVHD	125 (58%)
Effluent rate (delivered), mL/kg/h, mean (95% CI)‡	20.20 (18.97–21.43)
NUF (total), mL/h, mean (95% CI)‡	102.9 (93.44–112.35)
NUF (total, per kg), mL/kg/h, mean (95% CI)‡	1.24 (1.12–1.36)
NUF (24 h) mL/h, mean (95% CI)‡	89.63 (77.75–101.52)
NUF (24 h, per kg), mL/kg/h, mean (95% CI)‡	1.08 (0.93–1.22)

APACHE = Acute Physiology and Chronic Health Evaluation; CRRT = continuous renal replacement therapy; CVVHD = continuous venovenous haemodialysis; CVVHDF = continuous venovenous haemodiafiltration; ICU = intensive care unit; IQR = interquartile range; NUF = net ultrafiltration rate; ROD = risk of death. * Severe oliguria, urine output 0 mL/kg/h at CRRT commencement; mild-to-moderate oliguria, urine output 0.1–0.5 mL/kg/h at CRRT commencement; non-oliguric, urine output > 0.5 mL/kg/h at CRRT commencement. † CVVHDF circuits were at blood flow 200–250 mL/min, CVVHD circuits were at blood flow 120–130 mL/min. ‡ Values shown are for all treatment and for the first 24 hours of treatment.

similar; however, there were differences in APACHE III ROD, admission urea and fluid balance (Online Appendix, table 3). Following CRRT commencement, the severely oliguric group showed a gradual increase in urine output to match the mild-to-moderate oliguric group by 24 hours. In the mild-to-moderate oliguria group, urine output decreased steadily in the 12 hours before CRRT commencement, fell further proximate to CRRT commencement, and then was maintained around 0.25 mL/kg/h during CRRT. In the non-oliguric group, with preserved urine output > 0.5 mL/kg/h before commencement of CRRT, urine output decreased minimally before CRRT commencement but there was a marked fall in urine output in the 6 hours following CRRT commencement (Figure 2). When measured in 6-hourly windows, non-oliguric patients had the largest fall in urine output from between time zero and 6 hours after commencement of CRRT (Online Appendix, table 4).

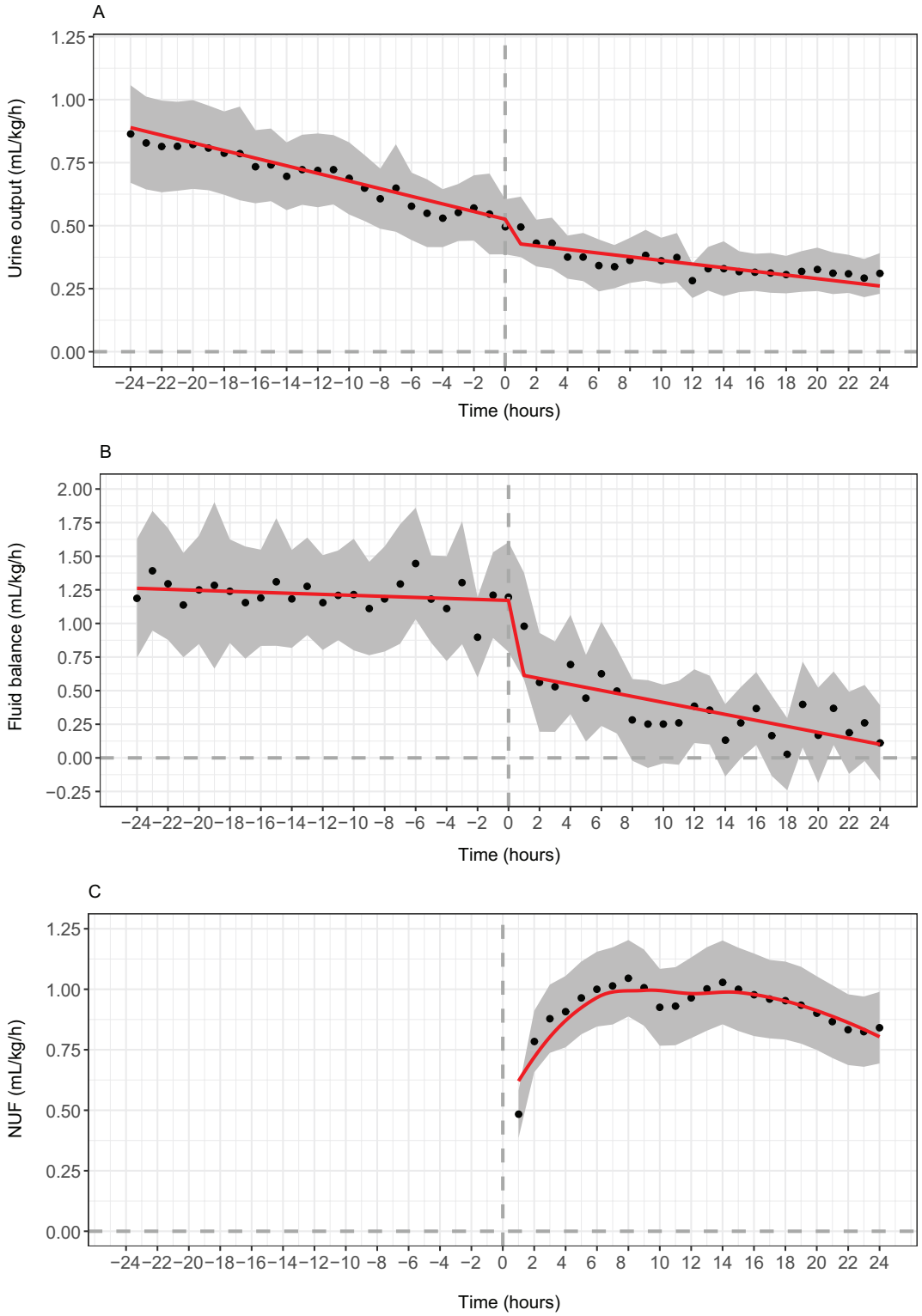
Fluid balance

Fluid balance was notably positive throughout, but after commencement of CRRT, fluid balance approached neutrality at 24 hours, suggesting a projected negative balance by 24–48 hours (Figure 1, B). Although remaining positive, the drop in fluid balance does mirror the drop in urine output observed.

There was sharp increase in NUF in the first 2 hours, followed by a more gradual increase between 2 and 6 hours and then a gradual decline in NUF from around 1 mL/kg/h to 0.75 mL/kg/h between 6 and 24 hours (Figure 1, C).

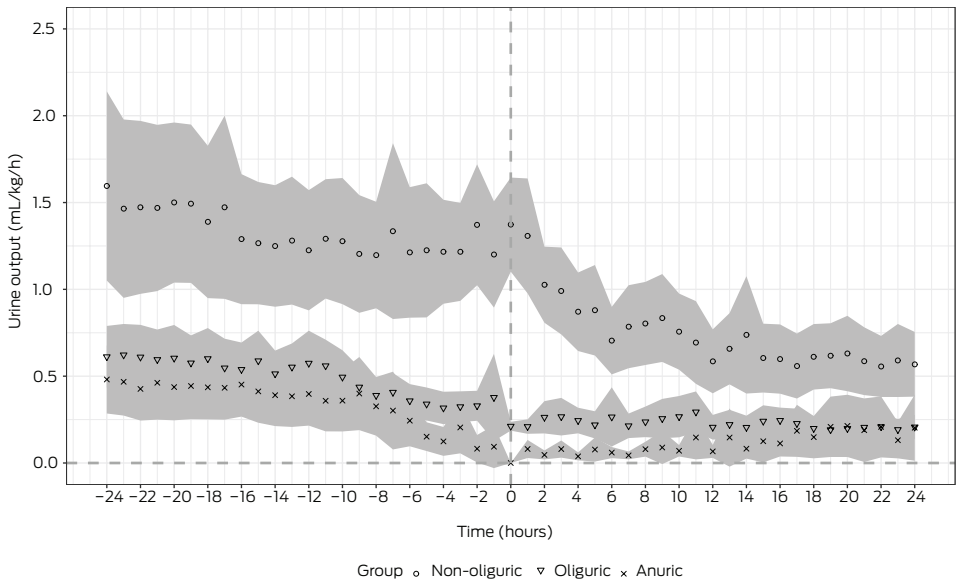
When stratified by urine output group, non-oliguric patients had a lower fluid balance gradually rising to +1000 mL, which remained stable following CRRT commencement; oliguric patients showed an increase to +3000 mL, followed by a divergence, where mild-to-moderate oliguric patients maintained stable fluid balance, and severely oliguric patients had an increase in fluid balance to +5500 mL at 24 hours (Online Appendix, figure 1).

Figure 1. Fluid dynamics parameters 24 hours before and 24 hours after continuous renal replacement therapy commencement



NUF = net ultrafiltration. Points indicate mean parameters hourly; shaded area shows 95% CI; lines in (**A**) and (**B**) indicate linear model prediction with interaction term for time and CRRT status, and in (**C**) LOWESS plot.

Figure 2. Urine output over time stratified by urine output at commencement of continuous renal replacement therapy



Multivariate analysis (Table 2) confirmed that, after CRRT commencement, there was a reduced urine output (effect estimate, –0.092 mL/kg/h; 95% CI, –0.150 to –0.034 mL/kg/h; $P = 0.002$), correcting for the reduction seen with time (effect estimate, –0.012 per hour [95% CI, –0.015 to –0.010] before CRRT commencement; –0.006 per hour [95% CI, –0.002 to –0.011] after CRRT commencement; $P < 0.001$). Urine output decreased with older age (effect estimate, –0.009; 95% CI, –0.015 to –0.003; $P = 0.006$) and higher vasopressor dose (0.01–0.10 μg/kg/min: effect estimate, –0.135 [95% CI, –0.182 to –0.087]; 0.11–0.20 μg/kg/min: effect estimate, –0.183 [95% CI, –0.233 to –0.133]; > 0.20 μg/kg/min: effect estimate, –0.238 [95% CI, –0.287 to –0.189]; all $P < 0.001$). Urine output increased with higher MAP (effect estimate, 0.053 per 10 mmHg; 95% CI, 0.041–0.065 per 10 mmHg; $P < 0.001$). CRRT mode, admission creatinine level, admission diagnosis and sex were not associated with a change in urine output. Low levels of NUF (0.1–1.15 mL/kg/h) were associated with a increase in urine output of 0.076 mL/kg/h (95% CI, 0.022–0.130 mL/kg/h) compared with a NUF of 0, but this effect was not seen with higher NUF (> 1.15 mL/kg/h).

Mean arterial pressure and vasopressors over time and association with CRRT

As expected, MAP remained relatively constant over time (Figure 3, A). The noradrenaline equivalent dose increased before and just after commencement of CRRT, followed by a plateau and more gradual decline, although it remained higher at 24 hours than at 12 hours before CRRT (Figure 3, B). Multivariate analysis (Online Appendix, table 5) showed a decrease in vasopressor requirements over time following commencement of CRRT (effect estimate, –0.004 μg/kg/min per hour; 95% CI, –0.005 to –0.004 μg/kg/min per hour).

Admission creatinine level, age, sex, CRRT mode (and therefore low–high Qb) and NUF rates were not associated with variation in vasopressor dose, but high severity of illness (APACHE III ROD ≥ 75%) was associated with a higher noradrenaline equivalent.

Discussion

Key findings

To our knowledge, this study is the first to report a detailed assessment of changes in urine output, MAP, vasopressor therapy, fluid balance, and NUF following the commencement of CRRT. We found that urine output rapidly decreased after initiation of CRRT, particularly in non-oliguric patients. Moreover, we found logical associations of urine output with higher MAP (increased urine output), higher vasopressor dose (decreased urine output) and age (reduced urine output). We also found that vasopressor dose increased before and immediately following CRRT, but plateaued and decreased within the first 24 hours, and that higher rates of NUF were not associated with higher vasopressor dose or greater decreases in urine output. Finally, the decrease in urine output appeared to occur despite the presence of a cumulatively positive fluid balance.

Relationship to previous studies

Residual renal function, which includes urine output, has been seen to decline in patients with intermittent haemodialysis.[24-26] This phenomenon is thought to be mediated by intradialytic reductions in renal perfusion.[27]

Table 2. Urine output: multivariate analysis

Variable	Effect estimate (95% CI)	*P*
CRRT status (after *v* before)	–0.092 (–0.150 to –0.034)	0.002*
Time (per hour)		
Before CRRT	–0.012 (–0.015 to –0.010)	< 0.001*
On CRRT	–0.006 (–0.002 to –0.011)	< 0.001*
Noradrenaline equivalent†		
0.01–0.10 μg/kg/min	–0.135 (–0.182 to –0.087)	< 0.001*
0.11–0.20 μg/kg/min	–0.183 (–0.233 to –0.133)	< 0.001*
> 0.20 μg/kg/min	–0.238 (–0.287 to –0.189)	< 0.001*
MAP (per 10 mmHg)	0.053 (0.041 to 0.065)	< 0.001*
NUF		
0.1–1.15 mL/kg/h	0.076 (0.022 to 0.130)	0.006*
> 1.15 mL/kg/h	0.011 (–0.039 to 0.061)	0.6674
Mode/blood flow‡	–0.015 (–0.215 to 0.184)	0.8808
Admission creatinine level, μmol/L§	0.004 (–0.036 to 0.044)	0.8442
Admission diagnosis¶		
Other surgical	–0.017 (–0.452 to 0.419)	0.94
Sepsis	0.100 (–0.322 to 0.522)	0.64
Other medical	0.100 (–0.294 to 0.494)	0.62
Sex, male	–0.069 (–0.277 to 0.139)	0.52
Age, years	–0.009 (–0.015 to –0.003)	0.006*
APACHE III ROD**		
30–49%	–0.279 (–0.577 to 0.019)	0.0686
50–74%	–0.073 (–0.377 to 0.231)	0.64
≥ 75%	–0.173 (–0.476 to 0.13)	0.26
CRRT commenced day 1††	0.116 (–0.094 to 0.326)	0.28

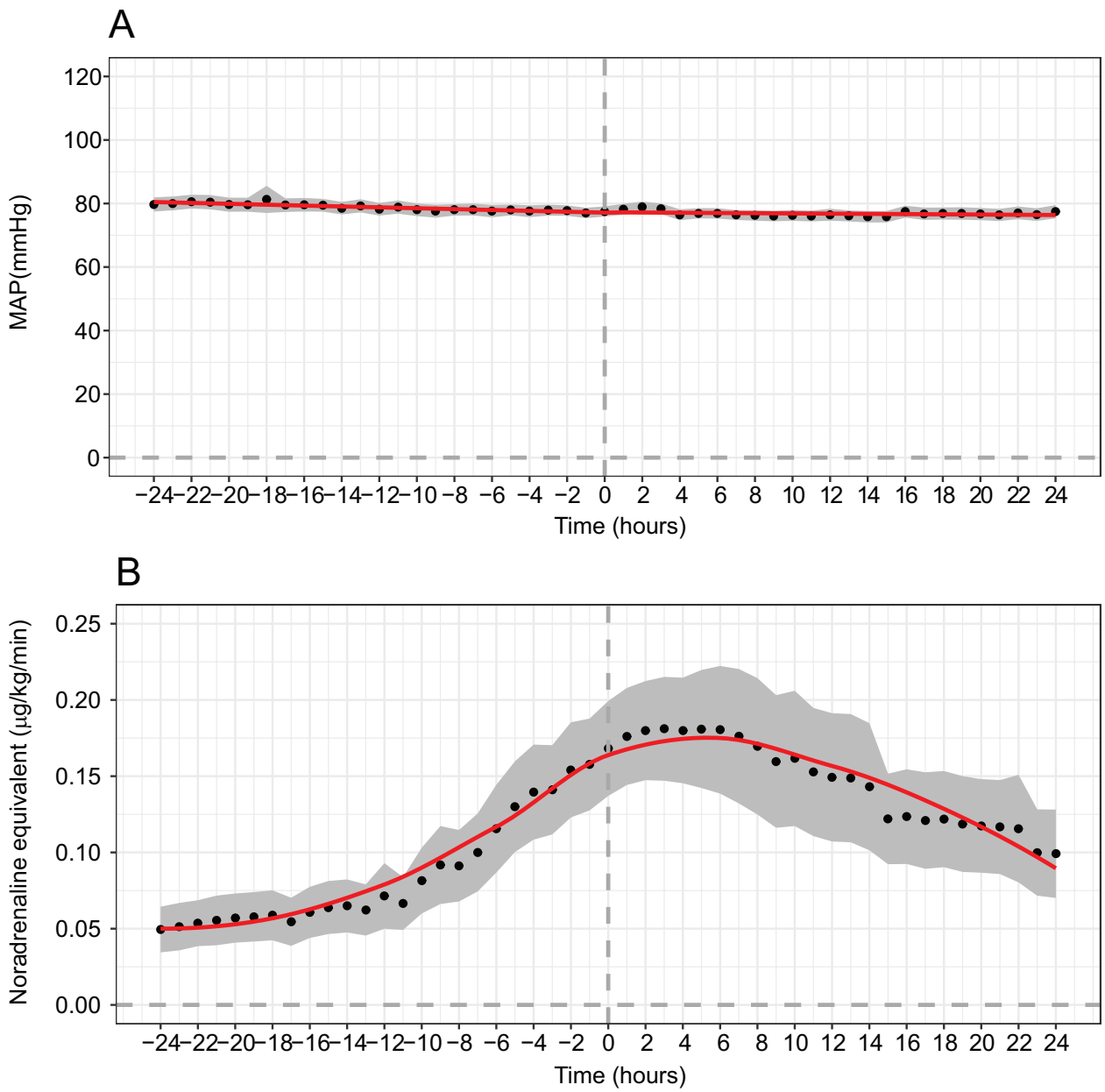
APACHE = Acute Physiology and Chronic Health Evaluation; CRRT = continuous renal replacement therapy; ICU = intensive care unit; IQR = interquartile range; MAP = mean arterial pressure; NUF = net ultrafiltration rate; ROD = Risk of Death. * $P < 0.05$. † Versus 0 μg/kg/min noradrenaline equivalent, measured hourly at the time of the urine output measurement. ‡ Mode and blood flow are interlinked, continuous venovenous haemodiafiltration (CVVHDF) protocol was blood flow 200–250 mL/h, continuous venovenous haemodialysis (CVVHD) was 120–130 mL/h, estimate is for CVVHDF versus CVVHD. § Effect estimate in increments of 1 μmol/L; ¶ Versus cardiac surgical. ** Versus 0–29%. †† Versus day 2 or later. Day 1 is defined as CRRT commencing with 24 hours of ICU admission.

Such an effect, however, has not been demonstrated in the acute setting during CRRT. Nevertheless, the acute decrease in urine output seen in the first few hours of CRRT in our cohort, particularly in non-oliguric patients, is consistent with the findings from re-analysis of the Acute Renal Failure Trial Network (ATN) study data,[4] which showed a daily decline in urine output in non-oliguric patients undergoing more intensive (35 mL/kg/h) renal replacement therapy.[4] Unfortunately, the ATN study findings represented the combined impact of both intermittent haemodialysis and CRRT, making it uncertain whether CRRT itself can induce such changes in urine output.

In this regard, this study is the first to show in detail that there appears to be an effect predominantly in the first few hours. Such fall in urine output, however, is consistent with data from animal models,[8] which found a 50% reduction in urine output following CRRT, similar to our finding in non-oliguric patients starting CRRT. Such experimental work also found a small reduction in cardiac output while on CRRT but increased renal blood flow, two variables not measured in our investigation.

Higher NUF rates were not associated with any reduction in urine output or change in vasopressor requirements. This contrasts with the findings in chronic intermittent haemodialysis where residual renal function appears to decline more rapidly at higher NUF rates.[28] An important caveat is that, in the period studied, fluid balance remained positive, which might explain why NUF was not associated with a change in vasopressors or urine output. NUF in our study population was also lower than NUF in patients in the RENAL study, suggesting a tendency to less aggressive fluid removal in our cohort. However, our finding that fluid balance positivity reduces following commencement of CRRT is logical, and that a negative balance is not achieved until around 24 hours is consistent with reports of others.[29] Reductions in urine output have been associated with poor outcomes in AKI, including in patients undergoing CRRT.[15,16] CRRT appears to be associated with a sudden drop in urine output, which may be harmful or indicative of CRRT-induced kidney injury. In this regard, patients undergoing accelerated renal replacement therapy (mostly CRRT) have been found to have an increased dependence on renal replacement therapy at 90 days.[30] It is thus possible that renal replacement therapy may exacerbate AKI with the early drop in urine output evidence of this effect.

Figure 3. Haemodynamic parameters 24 hours before and 24 hours after continuous renal replacement therapy commencement



Points show mean parameters hourly; shaded area illustrate 95% CI; lines in (**A**) show the linear model prediction with interaction term for time and CRRT status, and in (**B**) LOWESS plot.

Implications

Our findings imply that CRRT initiation induces a decrease in urine output. They also imply that such decrease occurs despite fluid balance remaining positive in the first 24 hours and MAP remaining stable after the start of CRRT. Thus, they suggest that volume depletion or hypotension may not be an explanation for the decrease in urine output. Urine output did not drop as markedly after CRRT commencement in patients with oliguria, potentially allaying concerns regarding possible harms in this group, but the underlying

processes that cause a drop in urine output in non-oliguric patients may be occurring nonetheless. Moreover, our finding that a higher NUF was not associated with decreased urine output or higher vasopressor requirement is logical in the presence of an overall positive fluid balance and suggests it is potentially acceptable to maintain higher NUF rates earlier. Finally, although reduced urine output has been found to have a strong association with poor outcomes, it remains unclear whether this association is maintained in patients with CRRT-related reduction in urine output.[14-16]

Strengths and limitations

To our knowledge, this study is the first to simultaneously report on hourly urine output, fluid balance, NUF, MAP and vasopressor dose immediately before and after the start of CRRT in adult ICU patients. These findings corroborate those of animal studies and clinical experience. We included a mixed cohort of ICU patients (increasing generalisability) who are at significant risk of morbidity and mortality and included hourly measurements of fluid balance, urine output, MAP and vasopressor requirements, implying a degree of data granularity. Moreover, the findings show robust effect sizes with strong associations, which may be clinically meaningful.

We acknowledge several limitations. Given its retrospective observational nature, confounding may have affected our findings. Furthermore, data were obtained from a single centre, which may reduce external validity. Moreover, none of the patients underwent CRRT with regional citrate anticoagulation, but this technique is unlikely to influence the findings. Data were only collected for 24 hours before and following CRRT commencement, and we are unable to comment on changes outside of this time window. In addition, up to 24% of measurements were imputed, the majority of which were in the pre-CRRT period. Such imputation may have reduced the validity of the findings. This concern, however, is countered by the use of an established time series imputation technique, which was applied uniformly to data before and after the start of CRRT, thus minimising bias. Another limitation of this study was that the administration of diuretics was not accounted for in the analysis. Finally, the data were extracted in hourly intervals and the minutely acute changes in MAP and vasopressor dose at initiation of CRRT were not captured. Therefore, more granular studies are needed to identify whether very early changes in MAP or vasopressor therapy are associated with subsequent changes in urine output.

Conclusions

After the start of CRRT, urine output decreased over a 24-hour window in this patient cohort, and vasopressor requirements rose before and after initiation of CRRT, followed by a gradual decline. In particular, commencement of CRRT was associated with a rapid near halving of urine output in non-oliguric patients despite a persistently positive fluid balance and a stable MAP. The mechanisms behind such a clear decrease in urine output are unknown, but our observations suggest that they may be independent of hypotension and fluid removal.

Competing interests

All authors declare that they do not have any potential conflict of interest in relation to this manuscript.

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