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Hypotension within one-hour from starting CRRT is associated with in-hospital mortality

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ABSTRACT

Purpose: To investigate early hemodynamic instability and its implications on adverse outcomes in patients who require continuous renal replacement therapy (CRRT).
Materials and methods: A retrospective study of patients admitted to the intensive care unit (ICU) and underwent CRRT at Mayo Clinic, Rochester, Minnesota between December 2006 through November 2015.
Results: Multivariate logistic regression was performed to identify predictors of in-hospital mortality and major adverse kidney events (MAKE) at 90 days. Hypotension was defined as any of the following criteria occurring during the first hour of CRRT initiation: mean arterial pressure < 60 mmHg, systolic blood pressure (SBP) <90 mmHg or a decline in SBP >40 mmHg from baseline, a positive fluid balance >500 mL or increased vasopressor requirement. The analysis included 1743 patients, 1398 with acute kidney injury (AKI). In-hospital mortality occurred in 884 patients (51%). Early hypotension occurred in 1124 patients (64.6%) and remained independently associated with in-hospital mortality (OR 1.56, 95% CI: 1.25–1.9).
Conclusion: Hypotension occurs frequently in patients receiving CRRT despite having a reputation as the dialysis modality with better hemodynamic tolerance. It is an independent predictor for worse outcomes. Further studies are required to understand this phenomenon.

1. Introduction

Acute kidney injury (AKI) is associated with higher risk of mortality in hospitalized patients. In critically ill individuals who require continuous renal replacement therapy (CRRT), the rate of in-hospital mortality has been steadily reported to be 50–60% over the past two decades [1,2]. There have been multiple predictors of mortality reported in patients on CRRT. These included older age, liver failure [3], fluid overload [4-6], mechanical ventilation [7] and severity of illness (measured by the use of vasopressors or other organ support devices) [1].

Intradialytic hypotension and its impact on patients on maintenance hemodialysis are described by National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) as "a decrease in systolic blood pressure (BP) by ≥ 20 mm Hg or a decrease in mean arterial pressure by 10 mm Hg associated with symptoms that include abdominal discomfort; yawning; sighing; nausea; vomiting; muscle cramps; restlessness; dizziness or fainting; and anxiety" [8]. The occurrence of intradialytic hypotension in patients on maintenance hemodialysis may be due to serious conditions such as infection (or sepsis in general), myocardial infarction, a reaction to the dialyzer membrane, or high ultrafiltration rates [9]. In most instances, it is due to incorrectly prescribed target weight, combinations of prescribed medications or autonomic neuropathy [10]. Severe intradialytic hypotension can lead to bowel ischemia, stroke and MI [9]. The occurrence of intradialytic hypotension is also associated with higher mortality rates and major adverse cardiac events [11,12].

The occurrence of intradialytic hypotension during CRRT is not well described in the literature. One reason may be that the KDOQI definition of intradialytic hypotension does not seem to be appropriate for patients on CRRT as it relies on a patient's ability to report symptoms to meet criteria for intradialytic hypotension. Another reason is that most studies reporting intradialytic hypotension in critically-ill patients with AKI requiring dialysis do not differentiate between modalities

Abbreviations: AKI, Acute kidney injury; CI, Confidence interval; CRRT, Continuous renal replacement therapy; CVVH, Continuous venovenous hemofiltration; DBP, Diastolic blood pressure; ESRD, End-stage renal disease; ICU, Intensive care unit; KDOQI, Kidney Disease Outcomes Quality Initiative; MAKE, Major adverse kidney events; MAP, Mean arterial pressure; OR, Odds ratio; SBP, Systolic blood pressure; SOFA, Sequential organ failure assessment.

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used. Given the variability in defining hypotension, it is challenging to estimate its prevalence in patients receiving CRRT. In one study, the incidence of hypotension within the first hour of CRRT initiation was found to be 43% when defining intradialytic hypotension as a “new/sudden decrease in systolic blood pressure (SBP) >40 mm Hg, a mean arterial pressure (MAP) of <60 mm Hg, or SBP <90 mm Hg; initiation or increased dosing of vasoactive drugs, or the need for intravenous fluid boluses within the first hour of CRRT” [13]. While the factors influencing intradialytic hypotension in patients undergoing maintenance hemodialysis as discussed above are better understood, the contributing factors to such phenomenon in critically-ill patients might be harder to delineate given vasodilatory state, decreased circulating volume, critical illness induced cardiomyopathy or other reasons. This could be the reason why Kidney Disease Improving Global Guidelines (KDIGO) in its Clinical Practice Guidelines for Acute Kidney Injury recommended “using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients” [14].

The detrimental impact of intradialytic hypotension in patients with AKI undergoing intermittent hemodialysis has been previously described. Intradialytic hypotension has been associated with decreased likelihood of renal recovery [15]. In another study, new lesions of acute tubular injury have been described as a result of intradialytic hypotension [16]. In animal model studies, the underlying mechanism is attributed to impaired renal autoregulation in the setting of kidney injury and the inability to maintain adequate renal perfusion even with small hemodynamic variations [16,17]. Hypotension during intermittent dialysis has also been associated with increased mortality in patients with AKI undergoing intermittent hemodialysis in the intensive care unit (ICU) [15]. In a retrospective study that included ICU patients undergoing dialysis (43.1% intermittent hemodialysis, 44.5% receiving CRRT, and 12.4% receiving slow low-efficiency dialysis), hypotension during dialysis was associated with increased mortality but not with renal recovery [18].

Although there is strong evidence that there is no significant difference in hemodynamic stability for patients treated with intermittent hemodialysis and CRRT, CRRT is usually the modality of choice when hemodynamically unstable patients develop AKI and require renal replacement therapy [19,20]. Some authors have suggested that the potential beneficial impact of CRRT may be apparent after a prolonged follow-up, where patients might have a favorable renal recovery attributable to improved hemodynamic tolerance [21] . To better understand the incidence and clinical impact of hypotension during the first hour of CRRT, this study investigated the incidence of hypotension in patients requiring CRRT along with its impact on in-hospital mortality and other relevant outcomes. This potentially provides a platform to identify modifiable risk factors for high mortality rates that have been consistently observed among CRRT-requiring AKI critically ill patients [1,2].

2. Materials and methods

2.1. Study design

This was a retrospective analysis of a cohort of adult (≥18 years of age) patients admitted to all ICUs at Mayo Clinic in Rochester, MN from 12/9/2006 through 11/11/2015 who underwent CRRT. The ICUs can be broadly categorized as Medical, Surgical, Coronary/cardiac ICU, Cardiovascular surgery ICU, and others included under miscellaneous (including neurology, respiratory care unit, etc..). The institutional review board approved this project and waived the need for informed consent for patients who provided research authorization for minimal risk chart review studies. We excluded patients who were pregnant or who did not provide research authorization.

2.1.1. Continuous renal replacement therapy standards and definitions

Continuous venovenous hemofiltration was the standard mode of CRRT for all enrolled patients. At Mayo Clinic, the following settings are considered standard: blood flow rate of 200 mL/min and replacement fluid rate of 30 mL/kg/h (50% is delivered as pre-filter).The replacement fluid is calcium-free, and 22 mEq/L or 32 mEq/L bicarbonate concentration solutions (PrismaSATE, BGK 4/0/1.2 and PrismaSATE, B22GK 4/0; Gambro1) is used for the replacement. We refer to the solution with bicarbonate concentration of 32 mEq/L as the high-bicarbonate and the one with bicarbonate concentration of 22 mEq/L as the low-bicarbonate solution. Regional citrate anticoagulation with a dextrose citrate solution formula A (ADC-A) is the standard for anticoagulation for all patients unless there is an absolute contraindication. All patients were also receiving continuous intravenous calcium chloride infusion to maintain normal serum ionized calcium levels concomitantly. In order to achieve appropriate regional anticoagulation, 3 mmol of citrate is delivered for each liter of blood flow with a dose adjustment in patients with severe liver failure. Dose adjustments are made based on the ratio of total to ionized calcium measured 4 h after CRRT initiation. We use normal saline solution to prime the circuit. CRRT was prescribed and managed by a dedicated nephrology-intensive care group. While dialysis nurses set up and periodically assess the CRRT circuit, intensive care nurses handled bedside CRRT management.

We defined hypotension within the first hour of CRRT initiation as a new mean arterial pressure (MAP) <60 mmHg, systolic blood pressure (SBP) <90 mmHg or a decline in SBP >40 mmHg from baseline, or a positive fluid balance >500 mL or increased vasopressor requirement. The reason for choosing the positive fluid balance or increased need of vasopressors is to account for clinically significant hypotension that required an intervention (or at least clinically meaningful change in the patients' course). We did not exclude patients who had a low blood pressure before CRRT initiation. We chose the minimum value recorded for SBP and MAP in determining patients who develop hypotension.

2.2. Statistical analysis

Depending on the normality of the data distribution we summarized continuous variables as mean and standard deviation or median and interquartile range (IQR). Categorical variables were presented as counts and percentages. The two-way independent *t*-test or Wilcoxon rank sum test was used for continuous variables, and the Chi-squared test or the Fisher's exact tests was utilized for categorical variables. Odds ratios (OR) were reported with the 95% confidence interval (CI). The primary outcome was in-hospital mortality. Secondary outcomes included ICU and hospital lengths of stay (LOS) and major adverse kidney events (MAKE) at 90 days. MAKE is a composite outcome of need of renal replacement therapy, doubling the serum creatinine from baseline or death at 90 days. Multivariate logistic regression was performed to identify independent predictors of in-hospital mortality. We also planned to investigate potential predictors of the occurrence of early hypotension. For that analysis, independent variables were chosen based on the clinical relevance. We performed the following sensitivity analyses when evaluating the association between hypotension and in-hospital mortality: 1) excluded patients who had fluid overload <5% of admission body weight before CRRT initiation, 2) excluded patients who had a minimum MAP≤55 mmHg one-hour prior to CRRT initiation, 3) included cumulative fluid balance, net ultrafiltered volume and duration of CRRT in the full model..

We used a conversion scale previously published by Murugan et al. [22] to standardize the different vasopressor types and doses given within 1 h prior to CRRT initiation to norepinephrine equivalent units. We used the maximum dose of each vasopressor within that hour. The conversion scale was adapted from the medical literature as cited by Murugan et al. [22-25]. Statistical significance was determined when the *p*-value was <0.05. All analyses were performed using JMP statistical software version 13.0 (SAS Institute Inc., Cary, NC, USA). We used RStudio: Integrated Development Environment for R (RStudio

Table 1
Study demographics.

Characteristics		Values
Age, years [mean (Sd)]		61 (15)
BMI, kg/m^2 [mean (Sd)]		31.5 (15)
SOFA score on CRRT initiation day [mean (Sd)]		11.77 (3.7)
Modified shock index (HR/MAP) [mean (Sd)]		1.3 (0.4)
ICU days when CRRT initiated [median (IQR)]		1 (IQR 0–2)
Charlson Comorbidity Index [median (IQR)]		5 (IQR 3–7)
Female [count (%)]		699 (40)
ESRD [count (%)]		345 (19.8)
AKI [count (%)]		1398 (80.2)
Mechanical Ventilation [count (%)]		1257 (72.1)
ICU type [count (%)]	Medical	836 (48)
	Coronary/cardiac	136 (7.8)
	Surgical	307 (17.6)
	Cardiovascular surgery	447 (25.7)
	Miscellaneous	13 (1)
Vasopressors used within 1st hour of CRRT initiation [count (%)]	Norepinephrine	865 (50)
	Vasopressin	759 (43.5)
	Epinephrine	424 (24.3)
	Milrinone	221 (12.6)
	Dopamine	124 (7.1)
	Phenylephrine	104 (6)
	Dobutamine	77 (4.4)

Team, 2016, Boston, MA, USA) to perform Hosmer and Lemeshow goodness of fit test.

3. Results

The analysis included 1743 unique adult patients, 345 (19.8%) with end-stage renal disease (ESRD) and 1398 (80.2%) with AKI. The mean age was 61($\pm$15) years with 699 (40%) female, median Charlson comorbidity index (CCI) of 5(IQR 3–7) and the mean sequential organ failure assessment (SOFA) score on the day of CRRT initiation was 11.77 ($\pm$ 3.7) (Table 1).

Overall in-hospital mortality occurred in 884 (51%) of the patients. Among the predictors of in-hospital mortality that were found to be statistically significant on univariate analysis were age (OR 1.01 per 1 year increase, 95% CI: 1.01–1.02), SOFA score (OR 1.13 per 1 unit increase, 95% CI: 1.10–1.16), hypotension within 1 h (OR 1.6, 95% CI: 1.3–1.9), AKI compared to ESRD (OR 1.9, 95% CI: 1.5–2.5), use of high bicarbonate replacement fluid (OR 1.71, 95% CI: 1.36–2.12). On multivariate analysis, hypotension within one hour of CRRT initiation remained independently associated with in-hospital mortality (OR 1.54, 95% CI: 1.25–1.92, $p < .001$), after adjusting for age, SOFA score, mechanical ventilation, fluid balance between ICU admission and CRRT initiation, Charlson comorbidity index, AKI vs ESRD, replacement fluid used and time of CRRT initiation (Table 2). We also performed a sensitivity analysis by defining hypotension based only on the blood pressure criteria, without the increase in vasopressor requirement or a positive fluid balance of >500 mL. There were 981(56%) patients who met this definition. While also including baseline MAP within one hour from CRRT initiation and the fluid removal rate within the first hour of CRRT initiation in the full model, hypotension within one-hour from CRRT initiation remained an independent predictor of in-hospital mortality (OR 1.32, 95% CI [1.05–1.65], p.016). We performed another sensitivity analysis by including the presence of cardiogenic shock as a covariate in the model. Hypotension remained independently associated with mortality (OR 1.49, 95% CI [1.2–1.85], $p < .001$). There was no interaction for the diagnosis of cardiogenic shock and hypotension. None of the other sensitivity analyses performed changed the nature or the statistical significance of the association between hypotension and in-hospital mortality (data not shown). Hosmer and Lemeshow goodness of fit test resulted in a p-value = .11, indicating appropriate calibration.

Among 1398 patients who had AKI, MAKE90 occurred in 913 patients (65.3%). Hypotension was also independently associated with

Table 2
Predictors of in-hospital mortality.

Predictors	Unadjusted OR (95% CI)	P-value	Adjusted[a] OR (95% CI)	P-value
SOFA score (per 1 unit)	1.13 (1.10; 1.16)	<0.001	1.13 (1.1,1.16)	<0.001
Age (per 1 year)	1.01 (1.01, 1.02)	<0.001	1.02 (1.01, 1.02)	<0.001
CRRT initiation day (per 1 day delay)	1.02 (1, 1.04)	0.048	1.1 (1.06, 1.15)	<0.001
Mechanical ventilation	1.16 (0.94; 1.4)	0.14	0.87 (0.7,1.1)	0.25
Hypotension in the first hour of CRRT initiation	1.6 (1.3–1.9)	<0.001	1.54 (1.25,1.92)	<0.001
AKI compared to ESRD	1.9 (1.5–2.5)	<0.001	1.54 (1.17, 2.04)	<0.001
Use of high bicarbonate replacement fluid[b]	1.71 (1.36, 2.12)	<0.001	1.52 (1.21, 1.93)	<0.001

[a] Model adjusted for age, SOFA score, mechanical ventilation, fluid balance between ICU admission and CRRT initiation, Charlson Comorbidity Index, AKI vs ESRD, use of high bicarbonate replacement fluid at the start of CRRT and timing of CRRT initiation (as ICU day number when CRRT was initiated).
[b] Compared to low bicarbonate replacement fluid (22 meq/L).

MAKE90 in the multivariate model (Table 3). In addition, among 913 patients who had MAKE90 in the original data, 61 patients (6.6%) met the criteria for doubling of creatinine only. When analyzing the data for MAKE 90 without the criteria for doubling of creatinine, the results showed a similar relationship between hypotension and MAKE90: 1.5 (95% CI: 1.14–1.99, $p = .003$).

Hypotension within the first hour of CRRT initiation occurred in 1124 patients (64.6%). Thirty percent of the patients met only one criterion for hypotension: 38 patients (2.1%) only had positive fluid balance, 124 patients (7%) only had increased vasopressor requirement and 362 patients (21%) only had drop in blood pressure. Patients who became hypotensive received less fluid between ICU admission and CRRT initiation (3.5 L, IQR 0.7; 9.1 vs. 5.7 L, IQR 1.6; 12 $p < .001$). They also had higher SOFA scores (12.1 vs. 11.1, $p < .001$), higher modified shock index (1.41 vs. 1.21, $p < .001$), higher lactate levels (5.35 vs. 3.41 mg/dL, $p < .001$), INR (1.91 vs. 1.72, $p = .001$) and norepinephrine doses within one hour before CRRT initiation (0.15 vs 0.12 μg/kg/min, $p = .001$). Also, hypotension was more likely to occur when any high bicarbonate replacement fluid was used [OR 1.6, 95% CI 1.27, 2.04; $p < .001$] when compared to the use of only low bicarbonate replacement fluid. This comparison was done for the type of replacement fluid used at the start of CRRT. In addition, hypotension occurred more frequently in the coronary/cardiac ICU (69%) and the cardiovascular surgery ICU (84%) versus the medical (58%) and general surgical (52%) intensive care units, $p < .001$. Patients with and without hypotension did not differ in age, sex, body mass index (BMI), ICU and hospital LOS, mechanical ventilation at CRRT initiation, AKI vs. ESRD, Charlson comorbidity index, presence of cirrhosis, baseline serum creatinine, serum bicarbonate, hemoglobin, sodium, chloride, and phosphorous levels. (Table 4).

Table 3
Predictors of MAKE90.

Predictors	Unadjusted OR (95% CI)	P-value	Adjusted [a] OR (95% CI)	P-value
SOFA score (per 1 unit)	1.11 (1.07; 1.14)	<0.001	1.12 (1.08, 1.16)	<0.001
Age (per 1 year)	1.02 (1.01, 1.02)	<0.001	1.02 (1.01, 1.03)	<0.001
CRRT initiation day (per 1 day delay)	1.05 (1.01, 1.09)	0.005	1.08 (1.04, 1.13)	<0.001
Hypotension in the first hour of CRRT initiation	1.48 (1.18–1.86)	<0.001	1.34 (1.05,1.71)	0.01
Use of high bicarbonate replacement fluid[b]	1.61 (1.24, 2.07)	<0.001	1.5 (1.14, 1.97)	0.002

[a] Model adjusted for age, SOFA score, mechanical ventilation, fluid balance between ICU admission and CRRT initiation, Charlson Comorbidity Index, use of high bicarbonate replacement fluid at the start of CRRT, baseline serum creatinine and timing of CRRT initiation (as ICU day number when CRRT was initiated).
[b] Compared to low bicarbonate replacement fluid (22 meq/L).

Table 4
Characteristics of patients with early hypotension.

Characteristics	Hypotension ($N = 1124$)	No hypotension ($N = 619$)	P-value
In-hospital mortality	617 (54.9%)	267 (43%)	<0.001
MAKE 90[a]	613 (68.6%)	300 (59.5%)	<0.001
Hospital LOS, median days (IQR)	21 (9;38)	21 (11;38)	0.07
ICU LOS, median days (IQR)	9 (4;17)	9 (5;16)	0.52
ICU day number when CRRT was initiated[b]	1 (0;2)	1 (1;3)	<0.001
Fluid balance before CRRT initiation (liters)[b]	3.5 (0.7;9.1)	5.7 (1.6;12)	<0.001
SOFA	12.1 (3.6)	11.1 (3.8)	<0.001
Modified shock index	1.41 (0.44)	1.21 (0.30)	<0.001
MAP within one-hour before CRRT initiation (mmHg)	67 (11)	77 (12)	<0.001
SBP within one-hour before CRRT initiation (mmHg)	98 (21)	119 (19)	<0.001
Heart rate closest to CRRT initiation (beats/min)	92 (22)	92 (18)	0.5
Fluid removal rate within 1-h after CRRT initiation (mL/Kg/Hour)[b]	1.32 (0.3; 3.2)	1.6 (0.6; 3.3)	0.02
Invasive ventilation at time of CRRT initiation	828 (73%)	429 (69%)	0.05
High-bicarbonate replacement fluid	323 (29.5%)	125 (20.6%)	<0.001
Low-bicarbonate replacement fluid	772 (70.5%)	478 (79.3%)	
CHF diagnosis	586 (52%)	230 (37%)	<0.001
CV surgery ICU	377 (84%)	72 (16%)	<0.001
Cardiac and coronary ICU	94 (69%)	42 (31%)	
Medical ICU	489 (58%)	348 (42%)	
General surgery ICU	160 (52%)	147 (48%)	
Sepsis	577 (51%)	335 (54%)	0.27
Diagnosis of cirrhosis or moderate-severe liver disease	95 (8.5%)	66 (10.6%)	0.14
Serum Albumin, g/dL	2.96 (0.7)	3.09 (0.77)	0.05
Ionized calcium mg/dL	4.24 (0.67)	4.35 (0.72)	0.002
Arterial pH on first day prior to CRRT	7.31 (0.1)	7.33 (0.1)	<0.001
Serum Bicarbonate, mmol/L	19.5 (4.6)	20.3 (4.3)	0.003
Serum lactate, mg/dL[b]	5.55 (2.6;11.6)	3.4 (1.7; 7)	<0.001
INR[b]	2.35 (1.6; 3.5)	1.8 (1.4;2.9)	0.001
Bilirubin, mg/dL[b]	3.7 (1.4; 13.1)	2.7 (1;8.6)	0.002
Norepinephrine drip mcg/kg/min[b,c]	0.15 (0.07; 0.35)	0.12 (0.06; 0.2)	0.001
Epinephrine drip mcg/kg/min[b,c]	0.05 (0.03; 0.1)	0.05 (0.03; 0.1)	0.36
Dopamine drip mcg/kg/min[b,c]	4.83 (3;8)	4 (3; 6.7)	0.81
Milrinone drip mcg/kg/min[b,c]	0.25 (0.14; 0.33)	0.25 (0.2; 0.41)	0.2
Phenylephrine drip mcg/kg/min[b,c]	0.75 (0.43; 1.88)	0.58 (0.31; 1.94)	0.49
Vasopressin drip U/min[b,c]	0.04 (0.03; 0.04)	0.04 (0.03; 0.04)	0.75
Dobutamine drip mcg/kg/min[b,c]	5 (2.75;7.5)	5 (2.5; 5.6)	0.45
Vasopressor standardized to norepinephrine within one-hour before CRRT initation (mcg/kg/min)[b]	0.18 (0.08; 0.38)	0.15 (0.1; 0.27)	0.08

[a] Measured in AKI subpopulation only.
[b] Using Wilcoxon given non-normal distribution. Values represent median and IQR.
[c] Values represent the doses one hour before CRRT initiation for patients who were receiving that vasopressor.

Predictors for hypotension occurring within the first hour of CRRT initiation were investigated, the following were found to be significant in the multivariate model: use of high bicarbonate replacement fluid alone (OR 1.45, 95% CI 1.11–1.9, $p = .001$), CHF diagnosis (OR: 1.9, 95% CI 1.5–2.5, $p < .001$), ionized calcium before CRRT initiation was inversely associated with hypotension (OR 0.72, 95% CI 0.61–0.85, $p < .001$, for every 1 mg/dL increase in ionized calcium), the same was true for blood pH (OR: 0.67, 95% CI 0.63, 0.77, $p < .001$, for every 0.1 unit increase in pH). The model was adjusted for age, fluid balance between ICU admission and CRRT initiation, mechanical ventilation, AKI vs. ESRD, time of CRRT initiation, presence of congestive heart failure diagnosis, use of high bicarbonate replacement fluid at the start of CRRT and arterial pH, serum bicarbonate and ionized calcium before CRRT initiation. (Table 5).

Table 5
Predictors of Hypotension within one-hour of CRRT initiation.

Predictors	Adjusted OR[a] (95% CI)	P-value
Use of high bicarbonate replacement fluid at the start of CRRT [b]	1.45 (1.11, 1.9)	0.001
CHF diagnosis	1.9 (1.5, 2.5)	<0.001
Invasive ventilation	1.27 (0.97, 1.67)	0.07
pH at start of CRRT	0.67 (0.63, 0.77)	<0.001
Ionized calcium	0.72 (0.61, 0.85)	<0.001

[a] Model adjusted for age, fluid balance between ICU admission and CRRT initiation, mechanical ventilation, AKI vs. ESRD, time of CRRT initiation, presence of congestive heart failure diagnosis (CHF), use of high bicarbonate replacement fluid at the start of CRRT, arterial pH, serum bicarbonate and ionized calcium before CRRT initiation.
[b] Reference group was low-bicarbonate replacement fluid.

4. Discussion

This is one of the largest studies to examine the prevalence of early hypotension after initiation of CRRT and to evaluate the association between this phenomenon and short-term mortality and major adverse kidney events. Nearly two-thirds of patients developed hypotension within one hour after CRRT initiation. In-hospital mortality in this critically-ill cohort of patients who require CRRT was 51%, and was higher among patients with early hypotension. After multivariate adjustment, we found that hypotension within one hour of CRRT initiation was associated with 1.54 times increased odds of in-hospital mortality and 1.36 times increased odds of MAKE90. This association remained significant even after adjusting for severity of illness; indicating that it is an important predictor of worse outcomes that can identify patients early (within one hour from starting CRRT) who are likely to have worse outcomes.

Intradialytic hypotension has been reported in multiple studies to range between 17 and 87% [18,26-29]. It is important to mention that previous studies have used different definitions for intradialytic hypotension and did not always specify the dialysis modality. Studies using the KDOQI definition can miss episodes of intradialytic hypotension, as it does not account for RRT delivery in the ICU where symptoms may not be reported due to altered mental status or mechanical ventilation. More importantly, the KDOQI definition does not account for the use of -or increased need for- vasopressor support to maintain systemic blood pressure during RRT [30]. For this reason, depending on the definition used, the incidence of intradialytic hypotension during CRRT can range between 0 and 87% [18,31] and 12.5%–45% [13,31], with the latter range being more similar to our definition of hypotension (decrease in MAP or any hypotensive episode prompting an increase in the dose of vasopressor infusion or need for fluid bolus). In one trial, intradialytic hypotension occurred in 35% of the patients on CRRT compared to 39% of patients on intermittent hemodialysis, a statistically nonsignificant difference. However, guidelines to improve hemodynamic tolerance in intermittent hemodialysis were followed; these included: simultaneous connection of both lines of the circuit filled with saline, gradual escalation of ultrafiltration, minimal duration session of 4 h use of cool dialysate (35 °C) with high sodium concentration [32]. All of these measures could have played a role in lowering the incidence of intradialytic hypotension, but more importantly, it shows that preventive measures could be standardized to guide patient care.

We have shown that hypotension was independently associated with mortality and MAKE90 even after adjusting for statistically significant and clinically relevant known confounders. In regards to MAKE90, in patients with AKI that are dialysis-dependent, intradialytic hypotension has been linked to new ischemic injury resulting in delayed recovery [16,33]. This is thought to be the result of loss of renal autoregulation, making the kidneys susceptible to small hemodynamic perturbation that will eventually lead to the new renal ischemic injury [16,17]. Evidence from studies comparing the different dialysis modalities has found an association between intradialytic hypotension and mortality. In a randomized clinical trial comparing CRRT (specifically, continuous veno-venous hemodialysis) to intermittent hemodialysis, when the whole cohort was analyzed, using Cox proportional hazard for time to death, a change in MAP after initiating dialysis was associated with increased mortality [Hazard ratio: 1.06 (1.01–1.10)] [15]. In another study, Augustine et al. showed that greater changes in MAP on dialysis and higher number of vasopressors at baseline remained associated with decreased survival times [15]. One confounder associated with increased hospital mortality frequently occurring in patients with AKI requiring CRRT is volume overload [30,34-36]. While recognizing this risk factor and including it in the model as a confounder, hypotension remained independently associated with both in-hospital mortality and MAKE90. This suggests that hypotension within one-hour of CRRT initiation might be contributing to worse outcomes through a different mechanism, which may not be solely explained by fluid gains. While acknowledging it is a different patient population, the underlying mechanism of the association between intradialytic hypotension and worse outcomes in ESRD patients on maintenance hemodialysis has been thought to be multifactorial. Intradialytic hypotension in this population has been associated with myocardial stunning [37], fixed reduction in systolic function [38], brain injury [39] and bowel ischemia leading to increased endotoxin translocation from the gut and eventually leading to reduced survival [40].

While most of the patient-specific factors that may contribute to intradialytic hypotension have been investigated in patients on maintenance hemodialysis, little is known about patients requiring CRRT in the ICU. In patients on maintenance hemodialysis, a rapid diffusive solute loss has been suggested to cause intradialytic hypotension through rapid drops in plasma osmolality, leading to movement of water intracellularly and eventually leading to a decrease in extracellular volume [41]. Autonomic dysfunction is a well-known risk factor for intradialytic hypotension in patients on maintenance hemodialysis; however, in critically-ill patients, compensatory mechanisms such as increasing sympathetic tone and cardiac output can also be impaired and contribute to intradialytic hypotension [30]. Endothelial dysfunction assessed with flow-mediated dilation of the brachial artery after upper arm occlusion has also been shown to be associated with intradialytic hypotension in patients on maintenance hemodialysis [42]. In our study, the use of high bicarbonate replacement fluid was independently associated with the occurrence of hypotension. This phenomenon may be difficult to explain given the non-conclusive data in human studies. In a small cross-over study in patients with ESRD on maintenance hemodialysis, the use of high (32 mmol/L) vs low (26 mmol/L) was associated with lower intradialytic systolic blood pressure [43]. In an observational study in patients with ESRD on maintenance hemodialysis, higher dialysate bicarbonate was associated with intradialytic hypotension (hazard ratio: 1.12 per 4 mEq/L higher bicarbonate concentration, 95% CI: 0.96–1.32) [44]. The authors in the latter study attribute the lack of statistical significance to low incidence of intradialytic hypotension in their population (3%). It is important to mention that while high bicarbonate replacement fluid may be used more often in sicker patients with lower pH, and thus these patients might be in a vasodilatory state, there may also be some additional inherent deleterious impacts that are directly associated with the use of high bicarbonate solution. Previously, Kashani et al. investigated the effect of using high bicarbonate replacement fluid in continuous veno-venous hemofiltration in a propensity score-matched analysis [45]. They showed that the use of higher bicarbonate replacement fluid was associated with worse outcomes irrespective of the pH and other comorbidities (including severity of illness). Despite that, we did account for several measures of disease severity when assessing the outcomes of mortality and MAKE90 (blood pH, invasive ventilation, AKI, CCI, and SOFA scores). It is important to mention that the diagnosis of sepsis or liver cirrhosis or moderate-severe liver disease were not different between patients who had hypotension and those who did not develop hypotension. A higher ionized calcium concentration before CRRT initiation was associated with less hypotension in our cohort. Measuring ionized calcium in the ICU is a common practice; however, some argue that it does not change management or impact outcomes since ionized hypocalcemia can be prevalent in critically-ill patients [46]. The relationship between ionized calcium and blood pressure is controversial, especially in the ICU. In a post-hoc analysis of a randomized trial involving AKI patients in the ICU that required dialysis, MAP during ICU stay was not dependent on absolute values of ionized calcium [47]. In an older and smaller observational study involving ICU patients, ionized calcium showed a dose-response effect with lower values correlating with lower blood pressure [48]. In a different patient population, higher dialysate calcium prevented the occurrence of intradialytic hypotension in patients receiving intermittent hemodialysis, though the study was small [49]. The situation in patients starting CRRT is peculiar as they will be subjected to citrate and might be at higher risk of iatrogenic ionized hypocalcemia. The chance of this occurring is minimized universally through concomitant calcium chloride infusion and by checking ionized calcium after CRRT initiation. It is important to mention that most patients being started on CRRT have some degree of metabolic acidosis and correction of metabolic acidosis, through the infusion of bicarbonate in the replacement fluid, may lead to ionized hypocalcemia [50]. Still, pre-CRRT ionized calcium in our cohort remained independently associated with early hypotension after accounting for dialysate and serum bicarbonate. It remains premature to make any recommendations based on this study and this association needs to be confirmed with prospective randomized trials before adopting any change in the usual clinical practice.

We acknowledge several limitations in this study. It is a retrospective study and is subject to unmeasured biases and unknown confounders that are inherent to the observational nature of the study. Although we included a relatively large number of patients, it remains the experience of only one center. We speculate that the impact of modality would not have changed the results; however, our results might not be generalizable to other institutions as all patients in our cohort received CVVH as the CRRT modality. In contrast, to our knowledge, this is the first study that identifies hypotension within the first hour of CRRT initiation to be independently associated with short and long-term outcomes. Although we cannot infer a causal relationship between hypotension within the first hour of CRRT and adverse outcomes, this phenomenon remained independently associated with worse outcomes after accounting for other indices of severity of illness. Providers might use it in identifying high risk patients especially in situations where goals of care remain unclear and time-limited trials are being considered. This is mainly because this phenomenon seems to be adding information about how patients would fair other than what is already known about the patient, in terms of multi-organ failure, severity of illness and comorbid conditions. We have also identified predictors of hypotension such as the replacement fluid used and pre-CRRT ionized calcium. Also, we measured the effect of early hemodynamic instability at a specific interval and thus are not able to determine whether the duration of hypotension or the development of delayed hypotension may have influenced the association between hypotension within the first hour and both mortality and MAKE90.

5. Conclusion

In conclusion, hypotension is a significant independent risk factor for in-hospital mortality and occurs frequently in patients receiving CRRT. Further studies are required to help understand this phenomenon given its implications on short and long-term outcome in a population with grave prognosis.

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Author contribution

K.B·K, J.J.D., J.C.J, B.M.W., A.W·W and R.C.A designed the study; K.S., P·K and K.B·K. analyzed the data; K.S., P.K. and K.B.K. drafted the paper; K.B.K, J.J.D., J.C.J, B.W., A.W·W and R.C.A revised the paper; all authors approved the final version of the manuscript.

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All of the authors have disclosed that they do not have any conflicts of interest.

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