Chapter 6

Determinants of outcome in non-septic critically ill patients with acute kidney injury on continuous venovenous hemofiltration

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Abstract

Background/Aims. In view of ongoing controversy, we wished to study whether patient characteristics and/or continuous venovenous hemofiltration (CVVH) characteristics contribute to the outcome of non-septic critically ill patients with acute kidney injury (AKI). **Methods.** We retrospectively studied 102 consecutive patients in the intensive care unit (ICU) with non-septic AKI needing CVVH. Patient and CVVH characteristics were evaluated. Primary outcome was mortality up to day 28 after CVVH initiation.

Results. Forty-four patients (43%) died during the 28-day period after the start of CVVH. In univariate analyses, non-survivors had more often a cardiovascular reason for ICU admission, greater disease acuity/severity and organ failure, lower initial creatinine levels, less use of heparin and more use of bicarbonate-based substitution fluid. The latter two can be attributed to high lactate levels and bleeding tendency in non-survivors necessitating withholding lactate-buffered fluid and heparin, respectively, according to our clinical protocol. In multivariate analyses, mortality was predicted by disease severity, use of bicarbonate-based fluids and lack of heparin, while initial creatinine and CVVH dose did not contribute. **Conclusion.** The outcome of non-septic AKI in need of CVVH is more likely to be determined by underlying or concurrent, acute and severe disease rather than by CVVH characteristics, including timing and dose

Key Words
- acute kidney injury - continuous venovenous hemofiltration – mortality – sepsis - timing/dose of hemofiltration

Introduction

Acute kidney injury (AKI) is common and associated with a high morbidity and mortality in the critically ill.[1-4] Renal replacement therapy is required in about 6% of patients and this is associated with a rise in mortality to about 60%.[2,4,5] Although improved therapy might help to decrease survival, the optimal timing, dose and type of renal replacement therapy, such as continuous venovenous hemofiltration (CVVH), the major treatment in Europe,[5] remain to be determined. Although septic AKI may differ from non-septic AKI, and the former may benefit more from higher CVVH dose compared with the latter,[4,6-8] patients have often been lumped together in prospective randomized trials, and as a result, timing, dose and the schedule of renal replacement therapy remain largely inconsistent.[6,8-17] In a retrospective analysis of both septic and non-septic patients, oligoanuria, acidosis and concomitant organ dysfunction at the time of initiation of renal replacement therapy were associated with high mortality.[18] Another observational retrospective study also did not reveal an effect of dose,[19] whereas higher creatinine levels at the start of CVVH suggested that late rather than early treatment was of benefit,[7] being in contrast to prospective and sometimes even randomized studies.[13,20-22] However, treatment guided by urea levels did not improve outcome in another prospective randomized study.[15] The contradicting results may partly relate to differences in patient recruitment and modes of renal replacement therapy across studies. Alternatively, the contribution of CVVH characteristics to outcome may be smaller than that of patient characteristics, including type and severity of the underlying disease and co-morbidity, but these issues have hardly been addressed in large observational studies using different renal replacement therapy modes previously.[5,18,19] Our recent retrospective analysis restricted to sepsis-induced AKI requiring CVVH suggested however that the dose delivered, rather than timing, mode of administration, azotemic control and concomitant organ failure, is an independent predictor of outcome.[23]

In the current retrospective study, we aimed to evaluate determinants of a favorable outcome in critically ill patients with AKI in need of CVVH. In an attempt to minimize differences attributable to patient selection, only non-septic AKI were studied. Our hypothesis was that outcome in non-septic AKI is determined by both patient and CVVH characteristics.

Patients and methods

All patients treated with CVVH between November 17, 2004, and January 31, 2006, in the intensive care unit (ICU) of a university hospital were retrospectively studied. AKI was

defined as a sudden creatinine and/or urea increase, loss of urine production or decreased renal clearance. Exclusion criteria were other indications for CVVH than AKI, such as a last known creatinine clearance (or estimated glomerular filtration rate using the abbreviated Modification of Diet in Renal Disease formula) <15 ml/min. Patients were excluded from the study if criteria of sepsis occurred within a 48-hour window after the start of CVVH. Sepsis was considered present if patients had clinical evidence of infection and at least two or more of the following conditions; temperature <36.0 or >38.0°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or mechanical ventilation, and/or white blood cells <4.0 or >12.0 × 10^9/l.[24]

Therapeutic protocol. Decisions regarding the time of initiation of CVVH were based on the opinion of the treating physicians and consulting nephrologists. The decision to start CVVH was based on the following parameters: diuresis, plasma urea and creatinine, plasma potassium and bicarbonate, and the occurrence of fluid overload. Other decisions included the use of anticoagulation, substitution fluid (lactate, bicarbonate or citrate buffer; table 1), post- or predilution, ultrafiltration and blood flow rates.

Table 1. Composition of substitution fluids.

	BH 504[®]	HF 32 Bic[®]	HF CitPre[®]
Sodium	140	140	139.9
Potassium	1.5	2.0	3.0
Magnesium	0.5	0.5	0.5
Calcium	1.5	1.75	-
Chloride	103	111.5	104.0
Glucose	11.0	1.0	5.0
Citrate	-	-	39.9
Bicarbonate	-	32.0	-
Lactate	42.0	3.0	-

In mmol/L.

To prevent frequent clotting of catheters or filters, patients were treated per protocol by heparin in order to reach an activated partial thromboplastin time between 55-65 s. Patients with increased risk of bleeding complications (defined as a platelet count <40 × 10^9/l, an activated partial thromboplastin time >60 s, a prothrombin time test (INR) >2.0, a recent major bleeding or significant active bleeding were not administered heparin. These patients were treated with anticoagulant-free CVVH (bicarbonate or lactate buffered) until the availability of citrate-based substitution fluid in May 2005, which then became the first choice

of treatment in case of a high bleeding risk. Furthermore, the choice of the substitution fluid, lactate or bicarbonate, was based on the occurrence of lactic acidosis. Patients are routinely treated with CVVH with lactate-buffered substitution fluid. In case of severe lactic acidosis (serum lactate >5 mmol/l), CVVH is performed with bicarbonate-buffered hemofiltration. The clinician almost always chooses predilution because of the possible positive effect on filter lifetime. CVVH is performed using a hemofiltration machine (Diapact; Braun, Melsungen, Germany). Vascular access is secured by inserting an 11-french double-lumen catheter (GamCath; Gambro, Hechingen, Germany) into one of the three large veins (jugular, femoral or subclavian). In all patients, a 1.9-m^2 highly permeable cellulose triacetate hemofilter is used (Nipro UF205; Nissho, Osaka, Japan). After 72 h, the filters are considered ineffective and are changed on a routine basis. In case of blood clots in the filter, an increased filter-membrane pressure, or therapeutic or diagnostic interventions, filters are changed earlier. Blood flow and flow of lactate- or bicarbonate-based substitution fluid were historically routinely set at 180 ml/min and 2 l/h, respectively, with the ultrafiltrate flow set by treating physicians. When using citrate-buffered substitution solution, the blood and substitution fluid flow is set per protocol at 180 ml/min and 2.4 l/h, respectively. CVVH was predicted to be not needed when diuresis and sufficient creatinine clearance had resumed, on clinical grounds and based on laboratory measurements, which is a commonly applied policy. If patients were indeed not in need of CVVH for >48 h, AKI was considered to have recovered. If CVVH had to be resumed within 48 h after discontinuation, a second episode of CVVH (after the initial episode) was defined.

Data collection. Patient characteristics, including age, gender, weight, height (for body mass index, BMI), co-morbidities and cause of AKI, were recorded. Data regarding Acute Physiology and Chronic Health Evaluation (APACHE II) and the sequential organ failure assessment (SOFA) score [1] were collected. The latter score was obtained on admission and day 0 (day of CVVH initiation). Co-morbid conditions are defined as follows: hypertension -- a diagnosis of hypertension mentioned in the medical record or the use of blood pressure-lowering agents; diabetes mellitus -- a diagnosis of diabetes mellitus mentioned in the medical record or the use of insulin or oral glucose-lowering agents; chronic renal failure -- a diagnosis of chronic renal failure mentioned in the medical record, without the need of renal replacement therapy (stages 1-4 chronic kidney disease), or chronic obstructive pulmonary disease -- a diagnosis of chronic obstructive pulmonary disease mentioned in the medical record or the use of medication for this indication. The reasons for ICU admission were

grouped as follows: cardiovascular disease, respiratory insufficiency, metabolic derangement, neurological disorders, hematological disorders, liver failure and gastrointestinal surgery. The reasons of AKI were categorized into four groups: prerenal/ischemic, contrast, rhabdomyolysis and miscellaneous reasons. Data concerning timing of CVVH initiation were retrieved; these include serum creatinine, urea, pH and bicarbonate, potassium and diuresis before CVVH initiation. The following CVVH characteristics were also recorded: the mode of CVVH (pre- or postdilution), blood flow, substitution flow, ultrafiltration flow, type of substitution fluid and of anticoagulation, filter life of all filters used, the hours CVVH actually performed, downtime, and prescribed and delivered dose. Downtime was defined as the interval that CVVH was prescribed but not applied due to circuit clotting or transport to the radiology or operating room. The prescribed and delivered doses were calculated. The former was defined as the ultrafiltration volume delivered per kilogram body weight before admission per hour; it was averaged per day and thus included downtime. The delivered dose was calculated by adjusting the prescribed dose for downtime.

To compensate the effluent dose based on losses due to predilution, the ultrafiltration flow per hour (Q_{uf}) was adjusted according to the following formula:

$$\frac{[Q_b \times 60 \times (1-Hct)]}{[(Q_b \times 60 \times (1-Hct)) + Q_s]} \times Q_{uf}$$

where Q_b = blood flow (ml/min) and Q_s = substitution flow (ml/h) and Hct = hematocrit.

The means for filter life, downtime, flow rate and dose were calculated for each patient per CVVH episode and for all episodes together, as well as the percent use of predilution CVVH, heparin and the different substitution fluids. A group median percentage of 0 thus implies that in most patients the respective mode was not used in all filters per patient.

Statistical analysis. Patients were grouped according to survival on day 28 after CVVH initiation. A power analysis was not performed for this retrospective analysis, but we estimated a mortality rate of 50% for the population in the study interval. The data were often non-normally distributed (Kolmogorov-Smirnov test: $p < 0.05$) and values are therefore summarized as medians and interquartile ranges (e.g. for the percentage of filters on certain modes per patient). The Mann-Whitney U test was used for continuous variables. For categorical data, Fisher's exact test was used. We performed multiple logistic regression using backward elimination to assess the independent value of initial creatinine and delivered dose

to predict 28-day mortality, including variables reaching statistical significance in univariate analyses ($p < 0.05$). The odds ratio and its 95% confidence interval (CI) were calculated. Similarly, we performed multiple proportional hazards (Cox) regression analysis for survival time and calculated hazard ratios (95% CI). We did not include filter time, a major determinant of the dose delivered, but forced initial creatinine and CVVH dose into the models. Exact p values are given if $p > 0.005$, and considered statistically significant if $p < 0.05$.

Results

Patient characteristics. A hundred and two consecutive patients were included. On day 28, 44 patients (43%) had died. Two patients died after ICU discharge within 28 days after the start of CVVH. Six patients had a second and 1 patient a third episode of CVVH. Fourteen patients received intermittent hemodialysis on the ward after ICU discharge. Outcome groups were comparable except for reasons of admission, their disease acuity and severity, and organ failure (table 2). Lactate levels were higher, and duration of CVVH and hospitalization shorter in non-survivors.

CVVH characteristics. Table 3 shows that in non-survivors, less heparin and lactate-buffered fluids and more bicarbonate-buffered fluids were used. Filter life and the number of filters used were decreased in non-survivors. Ultrafiltrate was somewhat greater in survivors at similar substitution fluid flows, suggesting greater fluid withdrawal. However, neither the prescribed nor the delivered CVVH dose, ranging between 12 and 46 ml/kg /h, differed among outcome groups. Table 4 shows that non-survivors had more severe metabolic acidosis, with similar oligoanuria, and initial creatinine and urea levels were lower and decreases occurred less often during (less prolonged) CVVH.

Table 2. Patient characteristics

	Survivors n=58	Non-survivors n=44	P
Age, year	70.5 (18.0)	69.5 (19.0)	0.71
Gender, female/male	26 (45)/32 (55)	16 (30)/28 (70)	0.15
Body weight, kg	78.5 (18.7)	80.0 (18.7)	0.78
Body mass index, kg/m^2	25.4 (4.1)	24.7 (4.7)	0.20
Co-morbidity			
Hypertension	31 (53)	12 (27)	0.01
Diabetes mellitus	12 (21)	7 (16)	0.61
COPD	9 (15)	3 (7)	0.22
CRF	8 (14)	5 (11)	0.46
APACHE II	24.5 (7.2)	32.5 (10.7)	<0.005
SOFA within 24 h	9.0 (3.0)	10.0 (3.0)	0.01
Elective ICU admission	35 (60)	17 (39)	0.04
Admission after surgery	41 (71)	21 (48)	0.02
Reason of admission to ICU			
Cardiovascular disease	24 (41)	24 (55)	0.01
Respiratory insufficiency	12 (21)	16 (36)	0.11
Metabolic derangement	6 (10)	12 (27)	0.03
Neurological disorders	1 (2)	8 (18)	0.01
Hematological disorders	2 (3)	8 (14)	0.03
Liver failure	3 (5)	4 (9)	0.40
Gastrointestinal surgery	2 (3)	2 (4)	0.49
Type of AKI			
Prerenal/ischemic	46 (79)	35 (80)	0.81
Contrast	3 (5)	1 (2)	0.46
Rhabdomyolysis	4 (7)	3 (7)	0.99
Miscellaneous	5 (9)	5 (11)	0.65
Mechanical ventilation within 24 h	51 (88)	43 (98)	0.13
Vasoactive drugs within 24 h	45 (78)	37 (84)	0.46
Lactate within 24 h, mmol/L	2.7 (2.9)	6.4 (7.9)	<0.005
Length of stay in hospital, d	14.0 (21.0)	5.0 (9.0)	<0.005

Median (interquartile range) or number (percentage) of patients, where appropriate. COPD, chronic obstructive pulmonary disease; CRF: chronic renal failure; APACHE II: the acute physiology and chronic health evaluation; ICU, intensive care unit; AKI: acute kidney injury; SOFA: sequential organ failure assessment.

Table 3. Characteristics of CVVH during stay in the ICU

	Survivors n=58	Non-survivors n=44	P
Time interval ICU admission and start CVVH, days	2.0 (1.2)	1.0 (1.0)	0.76
SOFA at start CVVH	11.0 (3.0)	14.0 (4.0)	<0.005
First episode of CVVH, duration, h	81.0 (90.5)	44.5 (109.5)	<0.005
Number of filters	3.0 (3.2)	1.0 (4.7)	0.01
Mean filter life, h	34.3 (27.7)	20.1 (25.2)	0.01
Mean downtime, h	1.5 (1.8)	0 (2.3)	0.01
Mean blood flow mL/h	180 (0)	180 (0)	0.42
Mean substitution flow, mL/h	2020 (332)	2000 (400)	0.78
Mean ultrafiltration flow, mL/h	2099 (350)	2040 (400)	0.04
Percentage on:			
predilution	100 (43)	100 (30)	0.95
heparin	74 (100)	0 (83)	<0.005
citrate	0 (59)	0 (11)	0.24
bicarbonate	0 (27)	55 (100)	<0.005
lactate	50 (100)	0 (69)	0.01
Mean prescribed dose, mL/kg/h	23.6 (6.8)	23.4 (6.0)	0.99
Mean delivered dose, mL/kg/h	21.8 (6.7)	22.2 (6.2)	0.36
Total CVVH, duration, h	84 (93)	45 (110)	<0.005
Number of filters	3.0 (4.2)	1.0 (4.7)	0.01
Mean filter life, h	33.9 (28.4)	20.1 (25.2)	0.01
Mean downtime, h	1.5 (1.8)	0 (2.3)	0.01
Mean blood flow mL/h	180 (0)	180 (0)	0.54
Mean substitution flow, mL/h	2075 (332)	2000 (400)	0.59
Mean ultrafiltration flow, mL/h	2108 (347)	2040 (400)	0.03
Percentage on:			
predilution	100 (40)	100 (30)	0.88
heparin	74 (100)	0 (83)	<0.005
citrate	0 (59)	0 (11)	0.24
bicarbonate	0 (23)	55 (100)	<0.005
lactate	59 (100)	0 (84)	0.01
Mean prescribed dose, mL/kg/h	23.5 (6.8)	23.4 (6.0)	0.99
Mean delivered dose, mL/kg/h	21.4 (6.7)	22.2 (6.2)	0.32

Median (interquartile range). CVVH, continuous venovenous hemofiltration; ICU, intensive care unit; SOFA, sequential organ failure assessment.

Table 4. Renal metabolic variables prior to and during CVVH

	Survivors n=58	Non-survivors n=44	P
Within 24 h prior to start CVVH			
Diuresis, mL/h	13.7 (16.5)	12.0 (19.7)	0.89
pH	7.26 (0.14)	7.19 (0.15)	<0.005
Bicarbonate, mmol/L	17.5 (5.0)	14.0 (4.4)	<0.005
Potassium, mmol/L	5.1 (1.1)	5.1 (1.1)	0.94
Creatinine, µmol/L	285 (129)	236 (120)	0.01
Urea, mmol/L	17.8 (11.4)	14.2 (13.4)	0.16
During CVVH			
Highest creatinine, µmol/L	285 (99)	177 (135)	0.01
Lowest creatinine, µmol/L	140 (80)	110 (84)	0.20
Change in creatinine, µmol/L	130 (117)	32 (123)	<0.005
Highest urea, mmol/L	18.5 (10.9)	10.3 (12.5)	0.04
Lowest urea, mmol/L	9.9 (5.6)	10.3 (10.9)	0.82
Change in urea, mmol/L	5.7 (12.1)	1.0 (2.7)	0.04

Median (interquartile range). CVVH, continuous venovenous hemofiltration

Multivariable analyses. Results of logistic and Cox regression analyses are depicted in table 5. In both models, initial lactate, changes in creatinine/urea or CVVH dose did not contribute to mortality prediction. In any case, both models suggest that mortality is determined by the underlying disease determining the mode of CVVH and anticoagulation rather than by timing, as judged from initial creatinine values, and dose. As data from patients with a poor prognosis can skew the results, we also analyzed the data after excluding patients who deceased within 48 h (n = 13). The results, however were similar regarding predicting contributions (p = 0.05 or less) by APACHE II score, and percentage on heparin and bicarbonate, but not regarding initial creatinine or CVVH dose.

Table 5. Multivariable (logistic and Cox regression) analysis of determinants of mortality in non-septic AKI needing CVVH

	Odds ratio (95% CI)	P	Hazard ratio (95% CI)	P
APACHE II	1.16 (1.06-1.27)	0.001	1.09 (1.04-1.14)	0.001
Initial creatinine, µmol/L	0.99 (0.99-1.00)	0.18	0.99 (0.99-1.11)	0.14
On heparin	0.98 (0.96-0.99)	0.007	0.99 (0.99-1.00)	0.04
Substitution fluid				
Lactate-buffered	1.02 (1.00-1.04)	0.04	not calculated	0.25
Bicarbonate-buffered	1.03 (1.01-1.05)	0.003	1.01 (0.99-1.01)	0.03
Delivered dose of CVVH, mL/kg/h	1.10 (0.99-1.21)	0.07	not calculated	0.25

AKI: acute kidney injury; CVVH, continuous venovenous hemofiltration; CI, confidence interval; APACHE II: acute physiology and chronic health evaluation. For logistic regression: Hosmer-Lemeshow test X^2 7.4, df 8, P=0.50, indicating good calibration

Discussion

This single-center retrospective study suggests that patient rather than CVVH characteristics contribute to the outcome of non-septic, critically ill patients with AKI on CVVH. This contrasts with the beneficial effects of a higher CVVH dose in the septic patients studied by us recently in the same time frame and with similar methodology.[23]

At the start of CVVH, creatinine and urea levels were higher in survivors than in non-survivors. Although this suggests that CVVH start was postponed in survivors compared to non-survivors, as observed before,[7] the difference disappeared in multivariable analyses, suggesting that timing was not a determinant of outcome in our patients,[c.f. 9,21] in contrast to suggestions that early institution may improve outcome.[14,20,22] The lower blood pH in non-survivors than in survivors can be attributed to higher lactate levels rather than more progressive renal failure. Since, per protocol, bicarbonate-buffered fluid is preferred to lactate-buffered fluid in case of lactic acidosis, the use of bicarbonate-buffered fluid predicted mortality in our models, and this is unlikely caused by a detrimental effect of the solution itself.[25] The absence of anticoagulation with heparin also predicted mortality, which is withheld in case of a bleeding tendency, which may be more severe in non-survivors. We cannot exclude that this contributed to the lower survival times of filters in non-survivors or that heparin has even exerted beneficial effects in our non-septic patients. The greater fall in creatinine and urea levels in survivors can be explained by the longer duration of CVVH. Downtime was decreased in non-survivors, which may be explained by the fact that in many patients in this group only one filter was used, which results in zero downtime.

Taken together, our results suggest that CVVH characteristics such as timing, dose and azotemic control did not determine outcome, while crude outcome and its patient-specific determinants of our study cohort roughly agree with other studies.[1-5,18,19,22] While large prospective studies either suggest or deny a benefit of higher- compared to standard-dose CVVH, many studies suggest that high-dose CVVH more likely benefits septic than non-septic patients, as judged from post hoc analyses, in the absence of prior stratified randomization.[6,8] Hence, a higher dose may, in line with observational studies [26] and our own results,[23] potentially be of benefit in septic patients with AKI only. Although underdosing (<20 ml/kg/h) is a potential threat,[16,23] this may, apparently, not have substantially affected outcome in our non-septic patients.

Obviously, the limitations of our study include its retrospective nature and the relatively small number of patients, so that conclusions should be drawn cautiously and a

small effect of CVVH characteristics on outcome cannot completely be excluded. They nevertheless represent a 'real-life' situation in a patient cohort treated with a single renal replacement therapy mode, and the observations may help to design and power future studies investigating timing and dose of CVVH in the critically ill. The results did not prompt us to change current CVVH practice for non-septic patients.

In conclusion, our retrospective data suggest that patient characteristics rather than the timing, dose and mode of CVVH and azotemic control are predominant determinants of outcome in critically ill non-septic patients with AKI.

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Disclosure statement

The authors declare that they have no competing interests.

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