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# Validation of a Protocol for Continuous Hemodiafiltration with Regional Citrate Anticoagulation with Omni®

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**Keywords**
Blood purification · Citrate · Hemodiafiltration · Renal replacement therapy · Urea clearance

**Abstract**
***Introduction:*** Omni® (B Braun, Melsungen, Germany) is able to run continuous renal replacement therapy (CRRT) in continuous veno-venous hemofiltration (CVVH), hemodialysis (CVVHD), and hemodiafiltration (CVVHDF) modes. However, to date, there is no validated protocol to guide the use of Omni® in CVVHDF mode with regional citrate anticoagulation (RCA). ***Methods:*** We designed a protocol for CVVHDF-RCA tailored for Omni®. This protocol was tested in patients included in an observational study conducted in our center between January and March 2021. For all study patients, we collected baseline characteristics, laboratory results, CRRT circuit lifespan as well as plasma and effluent samples at 12, 24, 48, and 72 h of CRRT circuit initiation. At each study time point, we computed urea, creatinine, and β2-microglobulin clearance as well as effluent/blood ratios. Data from circuits in CVVHDF-RCA mode are compared with those in standard therapy (CVVHD-RCA) with the same device. ***Results:*** We analyzed ten circuits (5 patients) in CVVHDF-RCA mode and 32 (13 patients) in CVVHD-RCA mode. No adverse events related to the therapy were observed. In CVVHDF-RCA mode, median circuit running time was 68 (IQR 8.1) hours versus 46 (IQR 9.0) in CVVHD mode, $p = 0.053$. Therapy adaptations (dialysate rate and/or blood flow) were required in one (10%) circuit (15.6% in CVVHD mode, $p = 0.56$). Compared to CVVHD, CVVHDF was able to achieve similar clearance and effluent/blood ratio for urea, creatinine, and β2-microglobulin across the entire duration of circuit lifetime. ***Conclusion:*** The proposed protocol for CVVHDF-RCA for Omni® was associated with similar circuit lifetime, number of required adaptations and clearances to standard CVVHD-RCA. It appears to be safe and feasible.

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## Introduction

Regional citrate anticoagulation (RCA) is now recognized as the method of choice for continuous renal replacement therapy (CRRT) [1, 2]. Several randomized controlled trials have established its superiority over other methods in terms of filter lifetime, delivered therapy, and nursing workload [3–5]. RCA increases to some degree the complexity of CRRT as it requires more solutions (citrate and calcium

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solutions). In order to avoid electrolyte and acid-base imbalances, a dedicated protocol, integrating device and solutions specificities must strictly be followed [6].

Omni® (B Braun, Melsungen, Germany) is a new CRRT device that was developed with improved user interface and usability in mind [7]. Omni® has been on the market since 2017 and is routinely utilized in many units throughout the world. As all current generation CRRT devices, Omni® is able to run CRRT in three modalities: continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), and continuous veno-venous hemodiafiltration (CVVHDF). To date, no modality has demonstrated its superiority over the others in terms of patients' centered outcomes [8, 9] and decision to choose one or the other mostly depends on clinician's experience and preference. Diffusion-based methods (CVVHD and CVVHDF) are however increasingly preferred with RCA since they require lower blood flows and therefore minimize the citrate load to the patient [6].

To date in the absence of a validated protocol, Omni® devices have not been used in CVVHDF with RCA[2–5]. We have designed such protocol based on the one proposed by Morgera et al. [10] After extensive in vitro testing suggesting a high level of safety, we report here the results of our first utilization in patients.

## Materials and Methods

*Study Design and Population*

This is a monocentric prospective observational study embedded within a larger observational study aiming to evaluate the performance of CRRT filters over time. It was conducted in the adult intensive care unit (ICU) of the Centre Hospitalier Universitaire Vaudois (CHUV), a tertiary, teaching hospital located in Lausanne, Switzerland between January and March 2021. To be considered for inclusion in the current study, patients had to fulfil all the following criteria: age >18 years old, admission to our ICU, receipt of CRRT with Omni® for either acute or chronic kidney injury for an expected duration of 72 h. Patients with poorly functioning dialysis catheter at the time of the study or already enrolled in another conflicting study were excluded.

*CRRT Delivery*

All therapies were delivered using Omni® (B Braun Medical) CRRT generators. Scheduled running time was 72 h as recommended by the manufacturer. Fluid removal was set by clinicians on a daily basis according to patients' hemodynamic status and fluid balance. Therapies were performed using OMNI set with Omnifilter 1.6 $m^2$ (Polyethersulfone; Bellco for CVVHD and polysulfone; Avitum for CVVHDF). Therapy adaptations were performed by the medical team in charge based on patients' metabolic values. Such adaptation might involve either an increase or decrease in blood flow or an increase or decrease in dialysate rate.

CVVHD-RCA (Standard of Care)

CRRT in CVVHD mode was delivered with RCA using standard solutions (Mexsol® calcium-free dialysate with 133 mmol/L of sodium and 20 mmol/L of bicarbonate, 118.9 mmol/L of chloride, 1 mmol/L of magnesium, 4 mmol/L of potassium) and 4% trisodium citrate (citrate 136 mmol/L, sodium 408 mmol/L) following an adapted protocol inspired by Morgera et al. [10]. Dialysate flow rate was set according to patients' dry weight aiming for a dose slightly above 25 mL/kg/h. Citrate solution flow was started at 4 mmol/L of blood and titrated according to post-filter ionized calcium measurements for a target value between 0.25 and 0.34 mmol/L. Calcium reinfusion solution consisted in 500 mmol/L $CaCl_2$ solution infused at a rate of 1.7 mmol/L effluent and titrated according to systemic ionized calcium measurements for a target value between 1.12 and 1.20 mmol/L. Total calcium was regularly monitored throughout the therapy.

CVVHDF-RCA (New Modality)

The study protocol is shown in Figure 1. As shown in Figure 2, CRRT in CVVHDF mode was delivered with RCA using standard solutions (Mexsol® calcium-free dialysate with 133 mmol/L of sodium, 20 mmol/L of bicarbonate, 118.9 mmol/L of chloride, 1 mmol/L of magnesium, 4 mmol/L of potassium and Duosol® as substitution solution with 1.5 mmol/L of calcium, 140 mmol/L of sodium and 35 mmol/L of bicarbonate, 4 mmol/L of potassium, 0.5 mmol/L of magnesium, 113 mmol/L of chloride). Citrate solution was a 4% trisodium citrate solution (citrate 136 mmol/L, sodium 408 mmol/L). Dialysate and substitution flow rate were set according to patients' dry weight aiming for a dose slightly above 30 mL/kg/h. The proportion of diffusion and convection delivered with this protocol was 2/3 (66.6%) and 1/3 (33.3%) of the total prescribed dose, respectively. Hence, the expected filtration fraction should be <15%.

Citrate solution flow was started at 5 mmol/L of blood and titrated according to post-filter ionized calcium measurements for a target value between 0.20 and 0.29 mmol/L. This is necessary due to the post-filter administration of a calcium containing substitution solution.

Calcium reinfusion solution consisted in 500 mmol/L $CaCl_2$ solution infused at a rate of 1.7 mmol/L effluent and titrated according to systemic ionized calcium measurements for a target value between 1.12 and 1.20 mmol/L. Total calcium was regularly monitored throughout the therapy.

Project Assessments and Procedures

For each patient, we collected baseline characteristics, as well as physiological parameters at circuit initiation as well as during CRRT. We collected filter lifespan and registered adverse events associated with the therapy. In addition, we collected blood and effluent samples at 12, 24, 48, and 72-h post circuit initiation. We measured urea, creatinine, and β2-microglobulin in these samples and computed their respective clearances using the following formula [11]:

$$\text{Clearance}(x) = \text{TEV} \times \frac{\left(\frac{E_x}{S_x}\right)}{W} (\text{mL/kg/h}),$$

where TEV stands for total effluent volume over a 24-h period, $E_x$ for the substance (urea, creatinine, or β2-microglobulin, respectively)

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| Patients' weight (kg) | Dialysate flow (mL/h) | Blood flow (mL/min) | Substituition flow (mL/h) | Citrate / blood ratio (mmol/L) | Calcium / effluent ratio (mmol/L) |
|---|---|---|---|---|---|
| <90 | 1,600 | 80 | 800 | 5.0 | 1.7 |
| 90 – 110 | 2,000 | 100 | 1,000 | 5.0 | 1.7 |
| >110 | 2,400 | 120 | 1,200 | 5.0 | 1.7 |

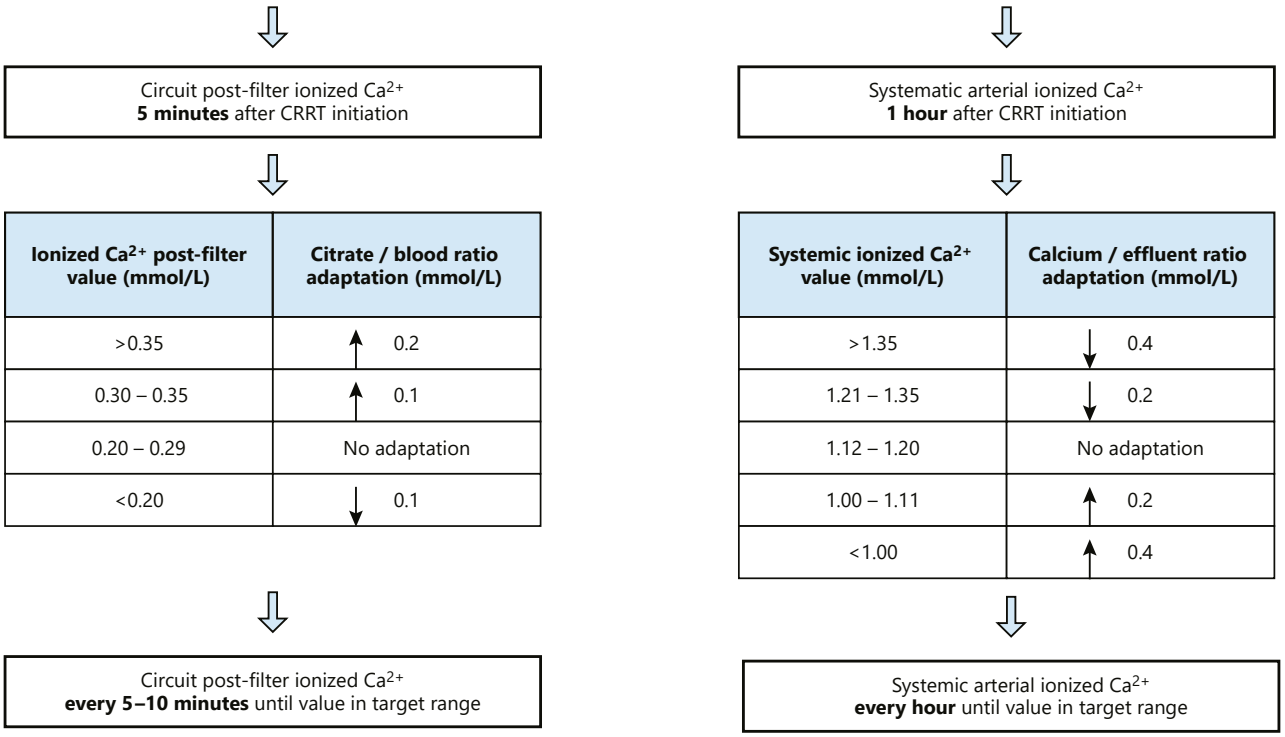


**Fig. 1.** CVVHDF-RCA Protocol. Initial setting and adjustments of therapy solutions (dialysate substitution solution, citrate, and chloride) according to patient's weight. Solution type and contents are described in Figure 2 and in the main body. CVVHDF, continuous veno-venous hemodiafiltration; RCA, regional citrate anticoagulation.

concentration in the effluent sample, $S_x$ for its concentration in the serum sample, and $W$ for patient's weight. In addition, for each molecule, we computed effluent/blood ratio at each study time point.

For each circuit, we calculated the mean filtration fraction using the following formula:

$$\text{Mean filtration fraction} = \frac{\text{Total effluent flow}}{\text{Mean blood flow}} \times 60 \times \left(1 - \text{Hematocrit}\right).$$

Group allocation was predetermined: CVVHDF was utilized in the last 5 patients enrolled in the "kinetics of small and middle molecule clearance during CRRT" study. Data obtained in patients who underwent CRRT in CVVHDF mode were compared to those obtained in patients who underwent CRRT in CVVHD mode.

We recorded all adverse events occurring during the therapy. In particular, we recorded metabolic, hematologic, catheter re-



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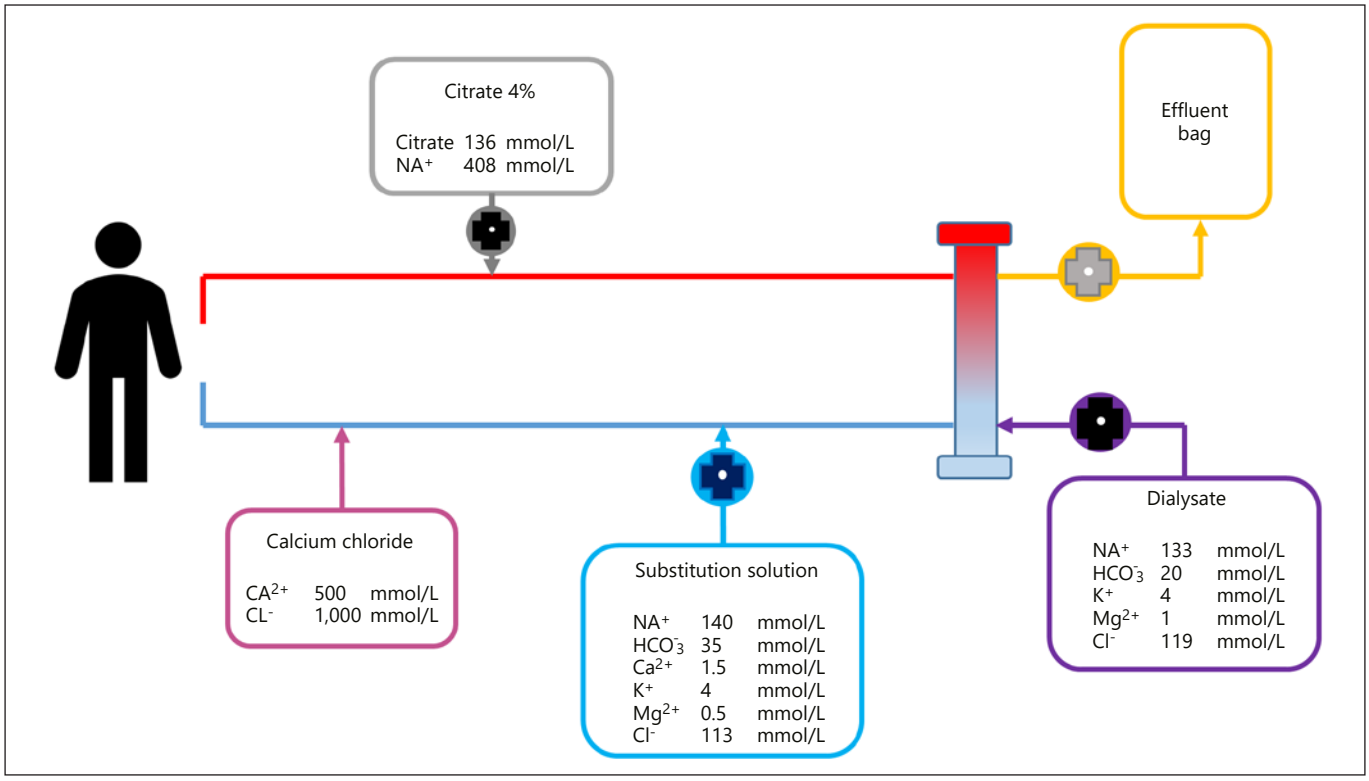


**Fig. 2.** CVVHDF-RCA circuit. Schematic CVVHDF-RCA circuit setup with detailed electrolyte composition of dialysate, substitution, calcium chloride, and citrate solutions. CVVHDF, continuous veno-venous hemodiafiltration; RCA, regional citrate anticoagulation.

lated and technical and other types of complications. Specific definitions used to define adverse events and serious adverse events are reported in the online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000524329). Alterations present at the beginning of the session (preexisting anomaly) were not considered.

*Statistical Analyses*

Categorical data are reported as number (percentage) and compared using $\chi^2$ or Fisher exact test. Continuous data are reported as mean (standard deviation) or median (interquartile range [IQR]) according to their distribution. Normally distributed data were compared using *t* test, paired *t* test or repeated measures ANOVA while non-normally distributed data were compared using Wilcoxon signed-rank test or Kruskal-Wallis. We used Kaplan-Meier method to estimate filter lifetime and log-rank regressions to assess group differences. A two-sided *p* value <0.05 was considered to be statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY, USA: IBM Corp.

*Staff Training*

In our unit, CRRT is run by ICU nurses. No particular training was delivered for the purpose of the study. The specificities of the CVVHDF-RCA protocol over the standard CVVHD-RCA were summarized in a short document that was distributed to the nurses managing a patient included in the sub-study.

## Results

*Patients' Characteristics*

Altogether, we included 18 patients in this analysis, 5 in the CVVHDF group, and 13 in the CVVHD group. Their characteristics are shown in Table 1. There were imbalances in baseline characteristics. Patients in the CVVHDF group were younger, heavier, and had less comorbidities. Similarly, their disease severity at admission ICU (SAPS and SOFA scores) tended to be lower. In these patients, we analyzed respectively 10 (CVVDHF group) and 32 (CVVHD group) circuits.

*Safety*

Adverse Events

Adverse events and serious adverse events recorded during the study period are reported in Table 2. The only serious adverse event encountered in the CVVHDF group is a gastrointestinal hemorrhage (defined as a need for transfusion of more than 2 units of blood). After clinical review, this complication appears unlikely to be attributable to the therapy.



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**Table 1.** Patients' characteristics

| | CVVHD ($n$ = 13) | CVVHDF ($n$ = 5) |
|---|---|---|
| Median age (IQR) | 68 (10) | 63 (11) |
| Sex, *n* (%) | | |
| Female | 0 (0) | 1 (20) |
| Male | 13 (100) | 4 (80) |
| Mean weight, kg (SD) | 75.7 (5.6) | 98.4 (7.6) |
| COVID-19, *n* (%) | 7 (53.8) | 3 (60.0) |
| Mean baseline creatinine, µcmol/L (SD) | 109 (16) | 92 (12) |
| Mean creatinine on admission, µmol/L (SD) | 237 (51) | 317 (136) |
| Median Charlson score (IQR) | 4 (4) | 2 (4) |
| Main diagnosis, *n* (%) | | |
| ARDS | 7 (53.8) | 2 (40) |
| Cardiogenic shock | 1 (7.7) | 0 (0) |
| Hemorrhagic shock | 1 (7.7) | 0 (0) |
| Hypovolemic shock | 1 (7.7) | 0 (0) |
| Septic shock | 2 (15.4) | 1 (20) |
| Other | 1 (7.7) | 2 (40) |
| Mean SOFA on admission (SD) | 9 (1) | 7 (1) |
| Mean SAPS on admission (SD) | 54 (4) | 40 (5) |
| Median number of circuits included (IQR) | 4 (2) | 1 (4) |
| Reason for RRT initiation, *n* (%) | | |
| Uremia | 4 (30) | 1 (20) |
| Fluid overload | 1 (7) | 1 (20) |
| Oliguria | 6 (13) | 2 (40) |
| Metabolic acidosis | 2 (15) | 0 |
| Hyperkalemia | 0 | 1 (20) |
| Median RRT duration days (IQR) | 16 (13) | 8 (23) |

ARDS, adult respiratory distress syndrome; RRT, renal replacement therapy; SD, standard deviation; IQR, interquartile range; SOFA, sequential organ failure assessment score; SAPS, simplified acute physiological score.

Circuit Lifetime

Median lifetime was 68 h (IQR 8.1) for circuits in CVVHDF mode. This was higher than median lifetime of circuits in CVVHD mode 46.0 h (IQR 9.0) although it did not reach statistical significance (log rank $p = 0.053$). Of note, as per manufacturer recommendations, circuits are terminated after 72 h of utilization irrespective of their performances.

Therapy Adaptations

In therapies performed in CVVHDF mode, 1 (10%) required therapy adaptation. In CVVHD mode, it was 5 (15.6%).

*Efficacy*

Biological Values

Key biological values measured during CRRT are shown in online supplementary Figure S1. Apart from baseline values, there was no significant difference between the two types of therapies in sodium, potassium, urea, or creatinine serum levels nor in arterial pH or bicarbonate levels.

Clearances and Effluent/Blood Ratios

Filter clearances for urea, creatinine, and β2-microglobulin are shown in online supplementary Figure S2. These values remained stable across the duration of the therapy and were similar in measurements obtained in CVVHDF and CVVHD mode.

The ratios of effluent/blood levels for urea, creatinine, and β2-microglobulin are shown in online supplementary Figure S3. These values remained stable across the duration of the therapy and were similar in measurements obtained in CVVHDF and CVVHD mode.

Fluid Removal

Incremental and cumulative volume removed during CRRT is shown in online supplementary Figure S4. Vol-

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**Table 2.** Adverse events

| | Adverse events | | Serious adverse events | |
|---|---|---|---|---|
| | CVVHD ($n$ = 32) | CVVHDF ($n$ = 10) | CVVHD ($n$ = 32) | CVVHDF ($n$ = 10) |
| Metabolic complications, *n* (%) | | | | |
| Total calcium/ionized calcium >2.5 | 0 | 0 | 1 (3.1) | 0 |
| Citrate accumulation | 0 | 0 | 0 | 0 |
| Hypocalcemia | 16 (50) | 7 (70) | 1 (3.1) | 0 |
| Hypercalcemia | 0 | 0 | 0 | 0 |
| Hypokalemia | 19 (59.3) | 5 (50) | 1 (3.1) | 0 |
| Hyperkalemia | 9 (28.1) | 5 (50) | 1 (3.1) | 0 |
| Metabolic acidosis | 0 | 0 | 0 | 0 |
| Metabolic alkalosis | 1 (3.1) | 0 | 0 | 0 |
| Hyponatremia | 0 | 0 | 0 | 0 |
| Hypernatremia | 2 (6.2) | 0 | 0 | 0 |
| Hypophosphatemia | 0 | 2 (20) | 0 | 0 |
| Hyperphosphatemia | 3 (9.4) | 3 (30) | 0 | 0 |
| Hypomagnesemia | 0 | 0 | 0 | 0 |
| Hypermagnesemia | 0 | 1 (10) | 0 | 0 |
| Hypoglycemia | 1 (3.1) | 0 | 0 | 0 |
| Hyperglycemia | 15 (46.9) | 7 (70) | 0 | 0 |
| Hemodynamic complications | | | | |
| Hypotension within 1 h of CRRT, *n* (%) | 1 (3.1) | 0 | 0 | 0 |
| Arrhythmia, *n* (%) | | | | |
| Atrial fibrillation | 0 | 0 | 1 (3.1) | 0 |
| Ventricular tachycardia | 0 | 0 | 0 | 0 |
| Ventricular fibrillation | 0 | 0 | 0 | 0 |
| Bradycardia | 0 | 0 | 0 | 0 |
| Asystole | 0 | 0 | 0 | 0 |
| Cardiac arrest | 0 | 0 | 0 | 0 |
| Hematologic complications, *n* (%) | | | | |
| New onset thrombocytopenia | | | 2 (6.3) | 0 |
| Hemorrhagic complication | | | 0 | 1 (10) |
| Catheter-related complications | | | | |
| Arterial puncture | 0 | 0 | 0 | 0 |
| Hematoma | 0 | 0 | 0 | 0 |
| Bleeding | 0 | 0 | 0 | 0 |
| Line-related infection | 0 | 0 | 0 | 0 |
| Technical complications | | | | |
| Machine dysfunction, *n* (%) | 1 (3.1) | 0 | 0 | 0 |
| Circuit air leak | 0 | 0 | 0 | 0 |
| Circuit blood leak in replacement fluid compartment | 0 | 0 | 0 | 0 |
| Other | | | | |
| Hypothermia, *n* (%) | 6 (18.8) | 1 (10) | 0 | 0 |
| Hyperthermia, *n* (%) | 2 (6.3) | 2 (20) | 0 | 0 |
| Hypersensitivity reaction | 0 | 0 | 0 | 0 |
| Vomiting, cramps | 0 | 0 | 0 | 0 |

CRRT, continuous renal replacement therapy; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration.

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ume removed by CVVHDF was very similar to those removed by CVVHD.

Delivered Dose

The total cumulative median delivered doses with CVVHDF were higher (169.5 L; IQR 25.9) than the doses delivered with CVVHD (151.2 L; IQR 21.4).

Filtration Fraction

The mean observed filtration fraction was 11.9% (standard deviation 1.6) in CVVHDF mode versus 7.3% (standard deviation 1.5) in CVVHD mode.

## Discussion

*Key Findings*

We performed CRRT in CVVHDF-RCA mode in 5 patients (10 circuits) with Omni® as a CRRT device. Overall, the therapy appeared safe, and no significant adverse events related to the therapy or used products have been recorded. The proposed protocol was highly feasible as only a limited number of therapy adaptations (10% of circuits) needed to be performed by the medical team in charge. Median circuit lifespan was very high (median 68 h), similar, or higher to circuits ran in the standard CVVHD-RCA mode. Regarding efficacy, Omni® in CVVHDF mode was able to deliver high clearances for small (urea, creatinine) and middle molecules (β2-microglobulin). These clearances were similar to those obtained in CVVHD mode and sustained over time. Changes in electrolytes (sodium,potassium) and acid-base status were similar to those observed during therapy performed in CVVHD mode. Finally, fluid removal could be performed in a similar extent to what was achieved in CVVHD mode.

*Comparison with Previous Studies*

Numerous protocols regarding CRRT with RCA have emerged over the years. The first, proposed by Mehta et al. [12], relied on continuous arteriovenous hemodialysis. This technique enabled volume, solute, and electrolyte control but was technically complicated and required very close monitoring.

Various subsequent protocols for CVVHDF have then been published (shown in online suppl. Table S1) [13–18]. The one proposed by Tolwani et al. [19] is commonly applied. It relies on a 0.5% trisodium citrate solution delivered as pre-dilution replacement fluid, a standardized saline dialysate and a calcium gluconate infusion administered through a separate central venous line. Its main advantage was to be based on standardized solutions thereby minimizing user's intervention and increasing safety. However, this protocol was tailored for specific CRRT devices and cannot directly be translated to the Omni®.

Another protocol proposed by Morgera et al. [10] for CVVHD is widely used throughout the world. This protocol includes a 4% trisodium citrate solution, a calcium-free dialysate, and a calcium chloride infusion. It has been shown to be very safe and easy to apply in many settings [20]. A modified version of this protocol to enable its utilization in CVVHDF mode has been proposed; however, it was never formally evaluated [21].

*Implication for Clinicians and Policy Makers*

The choice of RRT modality still largely depends on hospital policies, familiarity of the ICU clinicians with each therapy and must still be individualized and adapted to every patient within any specific clinical situation. Hence, we propose a protocol for CVVHDF-RCA with the Omni® device that is safe and efficacious. Of course, this should not restrain clinicians from identifying situations at risk of citrate accumulation such as acute liver failure, circulatory shock, and certain intoxications. In these situations, particular care is required and measures such as more frequent monitoring of total/ionized calcium, decreased citrate delivery by decreasing blood flow, or increasing dialysate flow must be considered. In centers with limited experience with citrate, these conditions might be considered as contraindications to the therapy [6].

*Strengths and Limitations*

This study has several strengths. First, it is the first to describe and report results on a new CVVHDF-RCA protocol applied to critically ill patients. Our data and sample collection were conducted in a strict manner with a very low rate of missing values. It includes detailed physiological parameters including serial clearances of small and middle molecules throughout therapy duration. It is however limited by the small number of patients and its monocentric nature. In addition, patients' allocation was not random and their baseline characteristics were not balanced. Finally, due to the limited number of patients only limited statistical comparisons could be performed.

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## Conclusion

The proposed protocol for CVVHDF-RCA for Omni® was associated with similar circuit lifetime, number of required therapy adaptations, and solute clearances to standard CVVHD-RCA. It appears safe and feasible in ICU patients suffering from adult respiratory distress syndrome and sepsis with AKI.

## Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki [22], the Human Research Act [23], the Human Research Ordinance [24] and followed the Strengthening the Reporting of Observational Studies in Epidemiology guideline [25]. This study protocol was reviewed and approved by the Ethics Committee Vaud (CER-VD 2020-01584). As this study involved patients in an emergency situation, oral and/or written informed consent was obtained from each patient or their next of kin before enrollment. This consent procedure was approved by the Ethics Committee Vaud.

## Conflict of Interest Statement

Dr. Schneider reported receiving grants from Leenaards Foundation and B Braun Avitum during the conduct of the study and speaking honorarium from Fresenius Medical Care CytoSorbents Corporation outside the submitted work. No other disclosures were reported.


## Funding Sources

The current investigation was financially supported by B Braun Avitum. It was however performed independently and the main investigator vouches for the integrity of the data. B Braun Avitum was allowed to read the draft of the report before submission but had no influence on its content or decision for submission.


## Author Contributions

Livia Whiting carried out data collection and drafted the manuscript. Livia Whiting, Karima Alouazen, Oliver Joannes-Boyau, and Antoine Schneider participated in study concept and design. Antoine Schneider carried out statistical analysis and obtained funding. All authors participated in interpretation of the data and critically reviewed the manuscript. All authors read and approved the final manuscript and agree to be personally accountable for their contribution.

## Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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