Catheter Port Reversal in Citrate Continuous Veno-Venous Hemofiltration

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Introduction: Knowledge of effects of catheter port reversal (CathPR), when blood is withdrawn from the venous port and returned via the arterial port, often used in dysfunctional catheters in renal replacement therapy, is limited in the setting of citrate continuous veno-venous hemofiltration (CVVH).

Methods: In this open trial, post-filter ionized calcium (PfCa), post-filter citrate concentration (PfCC), catheter recirculation, and solute clearance were measured before, during, and after 6 hours of CathPR, in well-functioning catheters. All other settings, including citrate settings, were left constant during the study.

Results: Twenty-three patients were included. Mean PfCa before CathPR of 0.36 mmol/L (SD 0.06) decreased to 0.31 (0.04) after 2 hours ($P = 0.002$), 0.31 (0.04) ($P = 0.002$) at 4 hours, and 0.31 (0.04) at 6 hours ($P = 0.001$). Return to normal increased mean PfCa to 0.34 (0.06) ($P = 0.006$). Mean PfCC rose from 592 mg/L (SD 164) before CathPR to 649 mg/L (190) after 2 hours ($P = 0.045$), to 696 mg/L (192) after 4 hours ($P < 0.001$), and to 657 mg/L (214) after 6 hours ($P = 0.018$). Return to normal decreased mean PfCC to 598 mg/L (184) ($P = 0.024$). Mean recirculation increased during CathPR (from 4.3% [0–8.7] before to 13.8% [9.7–22.2], $P < 0.001$). Urea, potassium, and creatinine clearances dropped significantly, but calcium clearance was unaffected.

Conclusion: CathPR caused a significant decrease in PfICA and increase in PfCC. Calcium handling differs from other solutes because of increases caused in citrate concentration and subsequent effects on calcium chelation. In citrate CVVH, CathPR in dysfunctional catheters should be limited in time, with intensive follow-up. Trial registration: ClinicalTrials.gov: NCT024600416. Registered 9 November 2015.

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The effects of arterial and venous CathPR in renal replacement therapy have been studied mainly in patients undergoing chronic hemodialysis therapy. When blood flow is inadequate in hemodialysis catheters (i.e., <300 ml/min), a temporary strategy to increase flow is to reverse catheter configuration (in which blood is withdrawn from the venous port and returned via the arterial port). Although studies have borne out that this increases recirculation (5% to even more than 15%),3–7 the improved blood flow due to line reversal may improve the overall clearance in dysfunctional catheters. In one study of 14 patients with dysfunctional catheters in a chronic hemodialysis population,3 line reversal markedly increased access recirculation (0% to 25%) but led to a significant increase in the mean urea clearance (128 ml/min at a flow of 200 ml/min to 157 ml/min at maximal blood flow). However, blood flows used in CVVH are lower and
knowledge of the effects of CathPR in this setting are limited. Methods of measuring recirculation are either non-urea-based indicator dilutional methods (among others thermal dilution, ultrasound velocity dilution, differential conductivity), or urea-based, although the former are generally not available in the intensive care unit (ICU). The urea-based method is relatively insensitive at high flow and is therefore more suitable for the relatively low blood flows encountered in CVVH, especially when using the low blood flow technique, according to the Kidney Disease Outcomes Quality Initiative guidelines. Recirculation above 10% by the urea-based method, or above 5% in the non-urea-based methods is deemed to be abnormal. In the era of citrate-based regional anticoagulation in CVVH, no studies describing the effects of catheter reversal on citrate metabolism, circuit ionized Ca, solute clearance, and circuit patency had been published, irrespective of the fact that (citrate) recirculation may affect all these factors. The goal of this study was to determine the effects of CathPR on postfilter ionized calcium concentration, postfilter citrate concentration, solute clearance, and recirculation in ICU patients undergoing citrate CVVH in nondysfunctional catheters.

**METHODS**

This single-center prospective open study (NCT024600416) was performed in the mixed medical-surgical ICU of Ziekenhuis Oost Limburg, Genk, Belgium, a large nonuniversity teaching hospital. The study was approved by the local ethical committee and written informed consent was obtained from the patient or legal representative. The study included intensive care patients receiving CVVH with citrate for acute kidney injury stage 2 or 3. According to the local protocol, citrate was the first-line anticoagulant for continuous renal replacement therapy, but not in patients with suspected liver failure. Patients not expected to survive the next 24 hours and patients already receiving renal replacement therapy at the time of admission to the ICU were excluded. Patients with dysfunctional catheters for renal replacement therapy were excluded, as were patients who had already undergone CathPR. Prophylactic or therapeutic doses of low molecular weight heparin were not a reason for exclusion. All patients on citrate CVVH received low molecular weight heparin for thromboprophylaxis or in therapeutic range if indicated, according to the standard ICU protocol.

The trial was designed to study the effects of CathPR in central venous catheters in patients undergoing citrate CVVH. Diuresis was preferably either minimal or the patients were anuric so that effects of changes in clearance due to renal clearance were minimalized and did not influence study outcomes. Patients had undergone CVVH for a substantial period, ensuring good metabolic control, so that possible short-term loss of clearance due to CathPR in this study had no detrimental effects. Catheters for renal replacement therapy were placed using ultrasonographic guidance in (in order of preference) the right jugular vein, the femoral vein, or in the subclavian vein. All catheters placed in the jugular and subclavian position were 15 cm in length. All catheters in the femoral position were 20 cm in length (GamCath 12 F × 15 cm and Gamcat 13 F × 20 cm, respectively; Gambro Kathetertechnik, Hechingen, Germany). For catheters placed in the jugular and subclavian position, a chest radiograph was performed to check positioning in the superior vena cava above the level of the pericardial reflection, before initiating circuit flow. All catheters placed in the femoral location were similarly placed under ultrasound guidance. However, tip location in femoral catheters was not checked. All circuits had been running for at least 24 hours without any signs of catheter-related malfunction.

At inclusion, patients were being treated according to our standard citrate protocol, with a citrate dose maintaining PfiCa between 0.25 and 0.35 mmol/l (1.0 and 1.4 mg/dl) and a urea clearance targeted at 25 ml/kg per hour. During the study, all settings, including citrate dosing, remained unadjusted to facilitate the study effects of CathPR, especially on citrate and calcium metabolism.

Citrate CVVH was performed using the Prismaflex (Baxter International Inc., Deerfield, IL; formerly Gambro Lundia AB, Lund, Sweden) and a 1.5-m² AN69 HF dialyzer (Kuf 37 ml/h/mm Hg). Blood flow rate was set according to body weight, and CVVH clearance was set for a total 25 ml/kg per hour after correction for predilution. As prefilter citrate buffer, Prisomicitrate 18/0, a dilute citrate-containing anticoagulation solution, was used containing 18 mmol citrate/l. Postfilter substitution was performed using a calcium-free substitution fluid, prismOcal B22. Prismaflex compensates the extracorporeal loss of free calcium and calcium bound in calcium-citrate complexes using a standardized closed-loop system for the dosing of calcium postfilter (Ca-chloride 550 mmol/l). Calcium compensation was set at 100%, which is also standard practice according to our citrate CVVH protocol, and remained so during the whole study period. Extra calcium supplementation was protocolized, our standard of care dictating a systemic iCa of more than 1.0 mmol/l. Net ultrafiltration rates were targeted according to individual needs while keeping them constant throughout the study period. Vascular access was established by
ultrasonography-guided placement of a 12-F hemodialysis catheter in the jugular, femoral, or subclavian vein (in order of preference).

Data Collection
Demographic and clinical data of all included patients were collected: age, gender, weight, acute kidney injury stage, use of vasoactive therapy, and ventilation. Based on clinical data, the APACHE II (Acute Physiology and Chronic Health Evaluation; a validated score for severity of illness) and SOFA score (Sequential Organ Failure Assessment; a score measuring organ failure) were calculated. Location of catheter placement for the extracorporeal circuit was noted, as well as circuit patency and filter survival during the study. All parameters for the extracorporeal circuit were noted (blood flow, prefilter citrate dose, postfilter substitution, ultrafiltration values, and effluent volume).

Study Design
Three separate aspects of extracorporeal circuit dynamics before, during reversal (for a total of 6 hours), and after return to normal configuration after 6 hours were studied.
- PfICa, PfCC, and necessity for change of citrate dosing.
- catheter recirculation (for urea and creatinine).
- clearance of the following substances: urea, creatinine, potassium, and calcium.
  Blood and effluent fluid were drawn for assay at the following times (a total of 6).
  - 1 hour before CathPR (to ensure steady state of circuit and parameters)
  - immediately before CathPR
  - 2 hours and 4 hours after CathPR
  - 6 hours after CathPR, immediately before return to normal configuration of the catheter
  - 1 hour after return to normal configuration
  At every time point, the following assays were obtained:
  - PfICa
  - PfCC
  - urea, potassium, creatinine, and total calcium from
    - the patient arterial line, as well as
    - effluent
  CathPR was performed as follows, by ICU nurses, after instruction and under supervision of a board-certified nephrologist/intensivist:
  - The venous port and arterial port were reversed (the access line and return line were switched).
  - The ports, access, and return lines were unclamped and the blood pump was restarted.

Calculations
The following techniques and formulas were used for determination of recirculation and clearance:
- Measuring Urea Recirculation
  \[
  \text{% Recirculation} = \left( \frac{\{P - A\}}{P - V} \right) \times 100
  \]
  where \( P \) = peripheral (from arterial line), \( A \) = from port before dialyzer (venous), and \( V \) = from port post dialyzer (venous).
  The peripheral line sample (from the arterial line) was drawn after decreasing the blood pump to 50 ml/min for 30 seconds. Recirculation was calculated at 1 hour before and immediately before CathPR; 2, 4, and 6 hours after CathPR; and 1 hour after return to normal configuration.
- Measuring Clearance
  \[
  K_{\text{solute}} = \frac{\text{TEV} \times \left( \frac{E_{\text{solute}}}{B_{\text{solute}}} \right)}{W}
  \]
  where solute can be urea, creatinine, potassium, or calcium;
  TEV = total effluent volume ; \( E \) = effluent concentration; \( B \) = arterial blood concentration; and \( W \) = weight.
  PfCCs were measured using the following assay: Citrate Reagent Set (Enzymatic Method, ref. 2881), produced by Firma InstruChemie BV, Delfzijl, The Netherlands. Controls: Citrate/Oxalate control (Normal and High): ref. 3085.

Statistics
Statistics were performed using SPSS Statistics version 26 (IBM Corp, Armonk, NY). Descriptive statistics were performed whereby normally distributed values were reported as mean (SD), not-normally distributed values as median (25th–75th percentile). Because of limited sample size, normality was determined by the Shapiro-Wilk test. Independent samples t-test or the Mann-Whitney U test were used as appropriate. The paired samples t-test or the Wilcoxon signed-rank test were used as appropriate to analyze values per patient comparing before and after CathPR and return to normal configuration after 6 hours. To compare categorical data, the Pearson \( \chi^2 \) was used. Correlations were calculated using Pearson’s coefficient of correlation or Spearman’s coefficient of correlation, depending on normality. A \( P \) value of less than 0.05 was considered statistically significant.

RESULTS
General
A total of 23 patients were included in this study. Patient and CVVH characteristics are summarized in
Table 1. Patient characteristics

| Characteristic                                      | Value          |
|-----------------------------------------------------|----------------|
| Male/female, n (%)                                  | 13/10 (56.5/43.5) |
| Mean age (y)                                        | 67.5 (11.4)    |
| Mean weight (kg)                                    | 88.6 (22.8)    |
| Acute kidney injury stage, n (%)                    |                |
| 2                                                   | 4 (17.4)       |
| 3                                                   | 19 (82.6)      |
| Invasive ventilation, n (%)                         |                |
| 2                                                   | 4 (17.4)       |
| 3                                                   | 19 (82.6)      |
| Noninvasive ventilation, n (%)                      |                |
| 2                                                   | 4 (17.4)       |
| 3                                                   | 19 (82.6)      |
| Vasopressive therapy, n (%)                         |                |
| 2                                                   | 4 (17.4)       |
| 3                                                   | 19 (82.6)      |
| APACHE II score                                     | 25.2 (7.9)     |
| SOFA score                                          | 13.1 (3.6)     |
| Catheter placement, n (%)                           |                |
| Femoral                                             | 12 (52.2)      |
| Jugular                                             | 9 (39.9)       |
| Subclavian                                          | 2 (8.7)        |

Continuous veno-venous hemofiltration

| Blood flow (ml/min)                                  | 130 (120–150)  |
| Citrate dose (mmol/l)                                | 3.5 (3.5–4.0)  |
| Effluent flow (ml/h)                                 | 2740 (673)      |

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, sequential organ failure assessment.

Table 1. One circuit was lost due to clotting of the filter after return to normal configuration and at one time point values for urea concentrations at the ports before and after the dialyzer were lost (see Supplementary Table S1).

PfCa and PfCC

Arteriovenous port reversal had a significant effect on PfCa. The mean PfCa before switch of 0.36 mmol/l (SD 0.06) dropped to 0.31 mmol/l (SD 0.04) after 2 hours (P = 0.002), 0.31 mmol/l (SD 0.039) (P = 0.002) at 4 hours, and 0.31 mmol/l (SD 0.039) at 6 hours (P = 0.001). The switch back to normal configuration caused a significant increase from a mean of 0.31 mmol/l (SD 0.001) to a mean of 0.34 mmol/l (SD 0.06) (P = 0.006). These values are illustrated in Figure 1. Although PfCa initially decreased after switch, no further statistically significant decrease was observed after the initial decline after 2 hours (3–5: P = 0.559, 3–7: P = 0.333, 5–7: P = 0.992). A comparison of PfCa 1 hour before and immediately before CathPR showed no significant difference (mean 1 hour before 0.36 mmol/l [SD 0.05], mean immediately before 0.36 mmol/l [SD 0.06], P = 0.273). There was no significant difference between PfCa at either 1 hour before CathPR or immediately before CathPR and PfCa after return to the normal configuration (P = 0.078 and P = 0.263, respectively).

CathPR had a significant effect on PfCC (see Figure 2). The mean PfCC before switch of 592 mg/l (SD 164) rose to 649 mg/l (SD 190), after 2 hours (P = 0.045), to 696 mg/l (SD 192), after 4 hours (P < 0.001) and to 657 mg/l (SD 214), after 6 hours (P = 0.018). The switch back to normal configuration caused a decrease from 657 mg/l (SD 214) to a mean of 598 mg/l (SD 184), which was significant (P = 0.024). A comparison of PfCC 1 hour before and immediately before CathPR showed no significant difference (mean 1 hour before 623 mg/l [SD 128], mean immediately before 592 mg/l [SD 164], P = 0.584). No significant difference between the values for PfCC during the period of switch was demonstrated, nor was there a significant difference between PfCC at either 1 hour before CathPR or immediately before CathPR and PfCC after return to normal configuration.

Effect of CathPR on Clearance

The highest baseline clearance was seen for urea (median 26.5 ml/kg per hour [24.7–29.2]) followed by potassium (median 25.4 ml/kg per hour [21.2–28.3]), calcium (median 23.7 ml/kg per hour [19.5–24.7]) and creatinine (median 22.0 ml/kg per hour [19.9–24.2]). After CathPR, urea clearances decreased by a mean of 5.4% (SD 11.4) at 2 hours (P = 0.054), 9.4% (SD 9.2) at 4 hours (P < 0.001), and 10.0% (SD 9.9) at 6 hours (P = 0.256), compared with baseline. A return to normal configuration again increased urea clearance by 0.6% (P = 0.852). After CathPR, potassium clearances decreased by a mean of 1.0% at 2 hours (P = 0.181), 9.4% at 4 hours (P < 0.001), and 1.0% (P = 0.256) at 6 hours.
hours, compared with baseline. A return to normal configuration increased potassium clearance by 0.6% (SD 11.5) (P = 0.852). In creatinine, clearances dropped by 12.5% (SD 13.25) at 2 hours (P < 0.001), 14.8% (SD 10.9) at 4 hours (P < 0.001), and 11.9% (SD 15.5) after 6 hours (p = 0.003). After return to normal configuration, creatinine clearance increased by 7.1% (SD 11.2) (P = 0.025). After CathPR, calcium clearance conversely increased at 2, 4, and 6 hours, compared with baseline, without reaching statistical significance. Return to normal configuration caused an insignificant change in calcium clearance.

Recirculation
To compare recirculation generally and based on catheter position, means were calculated pre-CathPR (2 values), during CathPR (3 values), and 1 hour after return to normal configuration (1 value). In Table 2, recirculation percentages are given, both in total and subdivided per catheter position.

Based on these values, there were significant differences both between the values pre CathPR and during CathPR, as well as comparing during CathPR and the value 1 hour after return to normal configuration (both P values < 0.001). There was no difference between pre- and post- CathPR (P = 0.514). Although there was a rise in recirculation during CathPR in all 3 catheter positions, the values in the femoral position (n = 12) differed significantly. During CathPR, recirculation was significantly higher in the femoral position than in the jugular position (P = 0.005). Values for each time point for urea concentrations are provided in Supplementary Table S1.

As described in Table 1, values for blood flow (Qb) varied between 120 and 170 ml/min (median 130 ml/min [120–150]), based on a weight-based protocol for determining Qb. There was no correlation between Qb and recirculation, either before (r = –0.249, P = 0.253) during (r = –0.349, P = 0.111), or after CathPR (r = –0.099, P = 0.661) when studying all results together (n = 23). Findings were similar when femoral and jugular positions were studied separately.

DISCUSSION
Arterial and venous port reversal of the catheter (CathPR) in which blood is withdrawn from the venous port and returned via the arterial port in citrate CVVH, caused a statistically significant decrease in PfCC. This phenomenon occurred in clinically well-functioning catheters and can be ascribed to increase in recirculation with a consequent increase in circuit citrate concentration despite unchanged citrate CVVH settings. In this setting of increased recirculation, calcium clearance increased (because of increased chelation to citrate and consequent loss via effluent), whereas clearance of urea, potassium, and creatinine decreased. Although the changes demonstrated have limited clinical repercussions, this study demonstrates proof of concept of the effects of citrate accumulation in case of increased recirculation in a citrate CVVH circuit.

Table 2. Recirculation (in %)

|                | Pre CathPR | CathPR | Post CathPR | Pre to CathPR | CathPR-post | Pre-post CathPR |
|----------------|------------|--------|-------------|---------------|-------------|----------------|
| Total (n = 23) | 4.3 (0–8.7) | 13.8 (9.7–22.2) | 0 (0–8.3) | <0.001 | <0.001 | 0.514 |
| Femoral (12)   | 3.3 (0–14.7) | 18.3 (13.1–26.9) | 0 (0–7.4) | 0.002 | 0.003 | 0.237 |
| Jugular (9)    | 4.3 (0.7–8.7) | 8.7 (4.0–10.3) | 4.8 (0–12.5) | 0.208 | 0.499 | 0.767 |
| Subclavian (2) | 4.7 (3.6–4.7) | 14.1 (13.7–14.1) | 4.2 (0–4.2) | - | - | - |
| P value jugular vs femoral | 0.972 | **0.005** | 0.331 |

CathPR, Catheter port reversal.
Values in median (25%–75%). Bold indicates statistically significant, P value <0.05.
To our knowledge, the phenomenon and effects of recirculation in a citrate CVVH circuit have been described previously in only 2 case reports: the first described a pediatric patient after CathPR using a femoral line,13 the second due to deep vein thrombosis leading to significant recirculation in a patient undergoing citrate CVVH, also via a femoral catheter.14 In the former, CathPR was implemented because of catheter dysfunction, which is common clinical practice. Our study demonstrates that this phenomenon is present, even if CathPR is implemented in seemingly well-functioning venous catheters. This effect will undoubtedly be more pronounced in dysfunctional catheters with increases in level of recirculation.

In citrate CVVH, calcium citrate complexes not removed through the hemofilter are returned via the venous port to the patient to be metabolized.2 If, however, a percentage of this citrate reenters the circuit because recirculation, circuit citrate rises. This is the case after CathPR in our study, without changes in either blood flow or citrate dose. Consequently, more iCa is chelated and PfCa falls and PfCC rises in the circuit. When CathPR is implemented in a normally functioning catheter, clearance decreases, as demonstrated for clearances of urea, creatinine, and potassium. However, because of changes of calcium citrate dynamics in the circuit, loss of calcium clearance due to less effective blood flow in the circuit is offset by higher citrate concentration in the circuit and consequent higher calcium clearance through the hemofilter. The fact that after the initial changes in PfCa and PfCC after 2 hours, there were no further changes in either during CathPR, most likely indicates that a new equilibrium is reached for citrate within the circuit.

Recirculation in venous catheters has been described previously and seems to be most prominent in those placed in the femoral position.15,16 Although numbers in our study were small, findings were similar, with significant changes in recirculation both when applying CathPR (increase) and when returning to normal configuration (decrease) in the femoral position. Similar increases and subsequent decreases were found on other catheter positions, but these were not statistically significant. Our study was not designed to study the effect of blood flow (Qb) on recirculation, and these values remained unchanged per patient during the study. There was no significant correlation between blood flow (Qb) and recirculation, most likely because the blood flow values used in CVVH in our study were low compared with those in hemodialysis and because the range of values was limited.

CathPR is routinely used in dysfunctional catheters to maintain adequate blood flow for clearance, and studies in the past have focused on the hemodialysis population, using higher blood flows (> 300 ml/min) than used in citrate CVVH in the ICU setting (median 130 ml/min in this study). Although a number of (hemodialysis) studies have demonstrated lower recirculation rates at the lowest blood flow settings,3,6,7 reported recirculation was always >10%. We studied the effects of CathPR for a limited period (6 hours) in nondysfunctional catheters, both mitigating factors. The continuous nature of continuous renal replacement therapy in the ICU and the fact that CathPR is executed in dysfunctional catheters could both exacerbate the effects of citrate recirculation found in our study.

Our study has a number of limitations. As stated, in this small, single-center study, we describe the effects of CathPR for a limited period (6 hours) in nondysfunctional catheters, and only studied the effects of return to normal configuration after 1 hour. This may explain why clearances do not return to the values measured before CathPR, although there might be deterioration of the filter during the study or changes in blood solute concentrations. Finally, recirculation was measured using a urea-based technique, which, as described in the introduction, has its limitations. However, in the ICU setting, this method is readily available to the clinician, in contrast to the other methods described and has been used to measure the effects of CathPR elsewhere.3,4,17

In conclusion, this study demonstrates that CathPR, a frequently used maneuver in dysfunctional catheters, has significant effects on postfilter ionized calcium concentration and PfCC, even for a short period in nondysfunctional catheters and demonstrates proof of concept of the effects of citrate accumulation in case of increased recirculation in a citrate CVVH circuit. Using this maneuver to maintain adequate blood flow in case of dysfunctional catheters in the setting of citrate CVVH could cause inappropriate changes in citrate settings in CVVH and delay timely replacement of a dysfunctional continuous renal replacement therapy catheter. Calcium handling in CathPR differs from other solutes because of increases caused in citrate concentration and subsequent effects on calcium chelation. In citrate CVVH, clinicians should be aware of the possible consequences of CathPR and we suggest CathPR in dysfunctional catheters should be limited in time, with intensive follow-up and prompt replacement.

**DISCLOSURES**

All the authors declared no competing interests.

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This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Ethical review board: the study protocol was approved by the local institutional review board (Commissie Medische Ethiek, Ziekenhuis Oost-Limburg, approval no. 15/060 U).

Informed consent to participate in the study was obtained from either the patient participants or legal guardian.

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

**AUTHOR CONTRIBUTIONS**

WB: conception and design of the study; the acquisition of data and data analysis, interpretation of data; drafting of and substantive revision of the manuscript. MVT: the acquisition of data and data analysis; substantive revision of the manuscript. MVL: the acquisition of data, substantive revision of the manuscript. KE: the acquisition of data, interpretation of data. IM: the acquisition of data and data analysis, interpretation of data. PJ: conception and design of the study, interpretation of data, substantive revision of the manuscript. All authors have approved the submitted version.

**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)

Table S1. Urea values used for recirculation calculations.

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