Continuous renal replacement therapy: a potential source of calories in the critically ill[1,2]

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ABSTRACT

Background: Overfeeding can lead to multiple metabolic and clinical complications and has been associated with increased mortality in the critically ill. Continuous venovenous hemofiltration (CVVH) represents a potential source of calories that is poorly recognized and may contribute to overfeeding complications.

Objective: We aimed to quantify the systemic caloric contribution of acid-citrate-dextrose regional anticoagulation and dextrose-containing replacement fluids in the CVVH circuit.

Design: This was a prospective study in 10 critically ill adult patients who received CVVH from April 2014 to June 2014. Serial pre- and postfilter blood samples (n = 4 each) were drawn and analyzed for glucose and citrate concentrations on each of 2 consecutive days.

Results: Participants included 5 men and 5 women with a mean ± SEM age of 61 ± 4 y (range: 42–84 y) and body mass index (in kg/m^2) of 28 ± 2 (range: 18.3–36.2). There was generally good agreement between data on the 2 study days (CV: 7–11%). Mean ± SEM pre- and postfilter venous plasma glucose concentrations in the aggregate group were 152 ± 10 and 178 ± 9 mg/dL, respectively. Net glucose uptake from the CVVH circuit was 54 ± 5 mg/min and provided 295 ± 28 kcal/d. Prefilter plasma glucose concentrations were higher in patients with diabetes (n = 5) than in those without diabetes (168 ± 12 compared with 140 ± 14 mg/dL; $P < 0.05$); however, net glucose uptake was similar (46 ± 8 compared with 61 ± 6 mg/min; P = 0.15). Mean ± SEM pre- and postfilter venous plasma citrate concentrations were 1 ± 0.1 and 3.1 ± 0.2 mmol/L, respectively. Net citrate uptake from the CVVH circuit was 60 ± 2 mg/min and provided 218 ± 8 kcal/d.

Conclusions: During CVVH there was a substantial net uptake of both glucose and citrate that delivered exogenous energy and provided ~512 kcal/d. Failure to account for this source of calories in critically ill patients receiving nutrition on CVVH may result in overfeeding. *Am J Clin Nutr* 2017;105:1559–63.

Keywords: nutrition, CRRT, CVVH, citrate, anticoagulation, caloric uptake

INTRODUCTION

Overfeeding is associated with multiple complications in critically ill patients, including hypercapnia, hepatic dysfunction, azotemia, altered immune function, and hyperglycemia (1). It is also associated with higher mortality in nonseptic mechanically ventilated patients in intensive care units (ICUs)[8] (2–4). The role of the counterregulatory response to stress and injury as a cause of hyperglycemia has been emphasized for many years, but there has been less emphasis on exogenous energy supply as a contributor to increased glucose concentrations, although hyperglycemia, which itself is associated with increased mortality, is a known consequence of overfeeding (5–7). In patients who require nutritional support, there is a strong relation between the amount of feeding administered and both hyperglycemia and insulin requirements (8). Continuous renal replacement therapy (CRRT) is now used universally in hemodynamically unstable individuals with acute and chronic kidney impairment, and it has been recognized as a potential source for macronutrient losses as well as macronutrient uptake, depending on the composition of the fluids used (9–12). However, to our knowledge, the possibility for net macronutrient uptake has not been mentioned in published guidelines from nephrology and nutrition societies (13–15). We aimed to quantify the energy supply from CRRT with the use of contemporary guideline-recommended low-lactate replacement fluids and citrate anticoagulation in continuous venovenous hemofiltration (CVVH) (14).

METHODS

Participants

After approval of the protocol by the Mayo Clinic Institutional Review Board, patients who received CVVH from April 2014 to June

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[2] Supplemental Figure 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[8] Abbreviations used: ACD-A, acid-citrate-dextrose formula A; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; ICU, intensive care unit.

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2014 were identified from a daily drug utilization report. Individuals aged ≥18 y admitted to an ICU and receiving CVVH with the use of regional citrate anticoagulation with acid-citrate-dextrose formula A (ACD-A) solution (2.2% sodium chloride citrate and 2.45% dextrose) (Baxter) were considered eligible. Patients were excluded if they were pregnant, were expected to receive <24 h CVVH therapy, were on concomitant extracorporeal membrane oxygenation therapy, had a BMI (in kg/m^2) >40, or had reversal of port connections on the dialysis catheter and dialysis circuit lines. A graphic depiction of the participant selection process is shown in **Supplemental Figure 1**. Written informed consent was obtained from the patients or legally authorized representatives.

Protocol

The clinical care of patients was managed by the ICU service, generally with the use of standard guidelines for initiating nutritional support (15). The participants were studied twice on consecutive days. CVVH therapy was initiated and managed per institutional CVVH protocol and per physician discretion. All patients were treated with CVVH with the use of the Prismaflex system (Gambro) and high-efficiency polyarylethersulfone HF 1400 disposable filter set (blood volume = 186; surface area = 1.4 m^2). Standard blood flow rates were 205 mL/min, ultrafiltration rates were $\sim 30 \cdot \text{mL}^{-1} \cdot \text{kg}^{-1}$ actual body weight, and ACD-A rates were 300 mL/h (5 mL/min), unless a calcium gap was present that required reducing the ACD-A infusion rate. Pre- and postfilter hemofiltration replacement fluids were administered as low- or high-bicarbonate solutions with minimal lactate (**Table 1**). Fifty percent of the replacement fluid was administered prefilter, and 50% was administered postfilter.

Between 12 and 36 h after the start of CVVH (T_1), the first set of 4 samples, each drawn 10 min apart, was obtained simultaneously from the pre- and postfilter sampling sites of the CVVH circuit (**Figure 1**) for measuring hematocrit, glucose concentration, and citrate concentration. The second set of samples was obtained ≥12 h later (T_2), 36–60 h after CVVH initiation.

Data collection and analysis

Baseline demographic data, including age, sex, race, weight, BMI, history of diabetes mellitus or hepatic cirrhosis, admitting diagnosis, and etiology of renal failure were recorded for each patient. Hospital and ICU admission and discharge dates and CVVH characteristics were also documented. Glucose concentrations were determined with the use of a glucose oxidase method (GM9 Analyzer; Analox Corp).

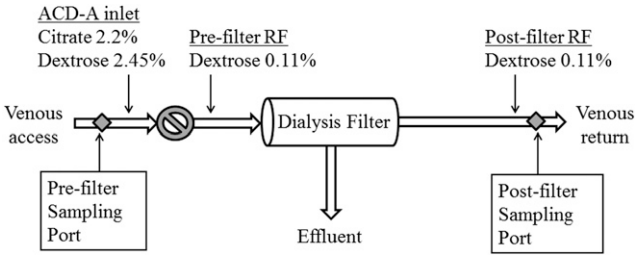

FIGURE 1 A diagram of the CVVH circuit and sampling sites used for obtaining glucose and citrate concentrations. The circle with a diagonal line represents the blood flow pump. ACD-A, acid-citrate-dextrose formula A; CVVH, continuous venovenous hemofiltration; RF, replacement fluid.

Plasma citrate concentration was determined with the use of liquid chromatography–tandem mass spectrometry.

Calculations

Net citrate and glucose uptake were calculated with the use of the concentrations and flow rates at each sampling site. Plasma flow [blood flow × (1 − hematocrit)] was used in citrate calculations because citrate does not distribute within erythrocytes; blood flow was used in glucose calculations (16). Flow delivered at pre- and postfilter ports were calculated with Equations *1* and *2*:

$$\text{Flow at prefilter sampling site (mL/min)}\left(Q_{\text{pre}}\right) = Q_{\text{b}} - Q_{\text{citrate}} \quad (1)$$

$$\text{Flow at postfilter sampling site (mL/min)}\left(Q_{\text{post}}\right) = Q_{\text{b}} - Q_{\text{removal}} \quad (2)$$

where Q_{b} is the blood flow rate, Q_{citrate} is the flow of ACD-A solution, and Q_{removal} is the net fluid removal rate.

Equations *3* and *4* were used to determine citrate and glucose uptake per hour:

$$\text{Citrate uptake (mmol/h)} : \left[Q_{\text{post}} \times \left(1 - \text{Hct}_{\text{post}}\right) \times C_{\text{post}}\right] - \left[Q_{\text{pre}}\left(1 - \text{Hct}_{\text{pre}}\right) \times C_{\text{pre}}\right] \quad (3)$$

$$\text{Glucose uptake (mg/h)} : \left[Q_{\text{post}} \times G_{\text{post}}\right] - \left[Q_{\text{pre}} \times G_{\text{pre}}\right] \quad (4)$$

where C_{post} is the concentration of the citrate postfilter sample site, C_{pre} is the concentration of citrate at the prefilter sample

TABLE 1
Content of replacement fluids

Component	Low-bicarbonate solution PrismaSate B22GK4/0[1]	High-bicarbonate solution PrismaSate BGK2/0[1]
Sodium, mEq/L	140	140
Potassium, mEq/L	4	2
Chloride, mEq/L	120.5	120.5
Sodium bicarbonate, mEq/L	22	32
Magnesium, mEq/L	1.5	1.5
Dextrose, mg/dL	110	110
Lactate, mEq/L	3	3

[1] Gambro.

site, G_{post} is the concentration of the glucose postfilter sample site, G_{pre} is the concentration of glucose at the prefilter sample site, Hct_{pre} is the prefilter hematocrit, Hct_{post} is the postfilter hematocrit, Q_{post} is the blood flow at the postfilter sample site, and Q_{pre} is the blood flow at the prefilter sample site. The sieving coefficient of glucose is 1; therefore, postfilter glucose concentrations were not adjusted for the ultrafiltration rate (17). Mean values for glucose and citrate concentrations for the 4 blood samples were used in all calculations. Daily energy uptake from CVVH-derived glucose was determined by multiplying glucose uptake (grams per day) by 3.8 kcal/g. Energy uptake from CVVH-derived citrate was determined by multiplying citrate uptake (grams per day) by 2.5 kcal/g (18).

Statistical analysis

Statistical analysis was performed with a *t* test with the use of Microsoft Excel 2010. Categorical data are expressed as frequencies and percentages. Continuous data are shown as means ± SEMs. $P < 0.05$ was considered significant.

RESULTS

Ten patients were studied. Thirty-six patients were excluded or did not provide consent (Supplemental Figure 1). Patient characteristics are summarized in **Table 2**. Most patients were postsurgical, including individuals who had undergone cardiovascular ($n = 5$) and abdominal ($n = 2$) procedures. Most patients ($n = 7$) started CVVH within 48 h of admission to the ICU. Five patients were on an insulin infusion before CVVH initiation; 6 patients were on an insulin infusion during CVVH initiation, including during sample collection. Estimated basal energy requirements equal to estimated basal energy expenditure (Harris-Benedict equation) were 1543 ± 81 kcal/d. CVVH characteristics are provided in **Table 3**. One patient was studied only on day 1 because CVVH was discontinued on day 2. Two patients received a lower ACD-A rate of 200 mL/h, 1 patient on both days and 1 patient only on the second day; the other 8 patients received ACD-A at 300 mL/h. There were no substantial interruptions in CVVH therapy between sampling times.

Plasma glucose and citrate concentrations on day 1 are depicted in **Figure 2**, which shows that steady-state conditions were achieved for both at both sampling sites. Mean glucose and citrate concentrations on days 1 and 2 are shown in **Figure 3**; results from 8 patients are shown because 1 patient was studied only on day 1 and another had different ACD-A flow rates on the 2 days. Results of the 2 study days in those 8 patients were reproducible, with CVs of 7–11% (data not shown). Postfilter citrate concentrations were not corrected for the sieving coefficient, which is <1, because the error that this introduces is negligible (19). Prefilter plasma glucose concentrations were higher in patients with diabetes ($n = 5$) (168 ± 12 compared with 140 ± 14 mg/dL; $P < 0.05$), but net glucose uptake was not different in patients with and without diabetes (46 ± 8 compared with 61 ± 6 mg/min; $P = 0.15$). Because of this, results in the diabetic and nondiabetic groups were combined for analysis. Mean pre- and postfilter glucose concentrations in the 10 patients were 152 ± 10 and 178 ± 9 mg/dL, respectively. Mean pre- and postfilter citrate concentrations were 1.0 ± 0.1 and 3.1 ± 0.2 mmol/L, respectively. Net glucose and citrate uptake from CVVH fluids are shown in **Table 4**. As can be seen, net energy uptake from glucose and citrate averaged 295 and 218 kcal/d, respectively, for a total of 512 kcal/d or 33% of the estimated basal energy expenditure.

DISCUSSION

We undertook this study to assess the role of CVVH as a source of exogenous energy in critically ill patients. We found that CVVH contributes substantially to total calorie intake primarily because of the uptake of citrate and dextrose from the ACD-A solution when low lactate replacement fluids are used (~512 kcal/d or ~30% of basal energy requirements). The caloric contribution of citrate and dextrose were roughly equivalent (218 and 295 kcal, respectively). Although glucose concentrations were higher in patients with underlying diabetes mellitus, total glucose uptake did not differ between individuals with and without diabetes.

Citrate is now widely used as a regional anticoagulant in CVVH to prevent hemofilter clotting caused by prolonged exposure of blood to foreign surfaces of the extracorporeal circuit (20). It is well tolerated and has been shown to reduce bleeding risk and improve circuit life compared with traditional systemic heparin anticoagulation (14, 21). Citrate, which exerts its anticoagulant effect by chelating calcium, is subsequently removed

TABLE 2
Patient characteristics[1]

Characteristic	Value
Age, y	61 ± 4
Men, *n*	5
Weight, kg	79 ± 5
BMI, kg/m^2	28 ± 2
Surgical, *n*	7
Comorbidities, *n*	
Diabetes mellitus	5
Cirrhosis	2
Etiology of AKI, *n*	
ATN	7
Multifactorial	3
Nutrition administration, *n*	
Oral diet or enteral	5
Parenteral	1
None	4
SOFA score	12.6 ± 1

[1] Values are means ± SEMs unless otherwise indicated. $n = 10$. AKI, acute kidney injury; ATN, acute tubular necrosis; SOFA, Sequential Organ Failure Assessment.

TABLE 3
CVVH characteristics[1]

Characteristic	Value
$Q_{citrate}$, mL/min	4.6 ± 0.2
Ultrafiltration rate, mL · kg^{-1} · h^{-1}	30 ± 2
$Q_{removal}$, mL/min	3.2 ± 0.7
Transmembrane pressure, mm Hg	92 ± 10.3

[1] All values are means ± SEMs. $n = 10$. CVVH, continuous venovenous hemofiltration; $Q_{citrate}$, flow rate of acid citrate dextrose solution; $Q_{removal}$, net volume removal rate.

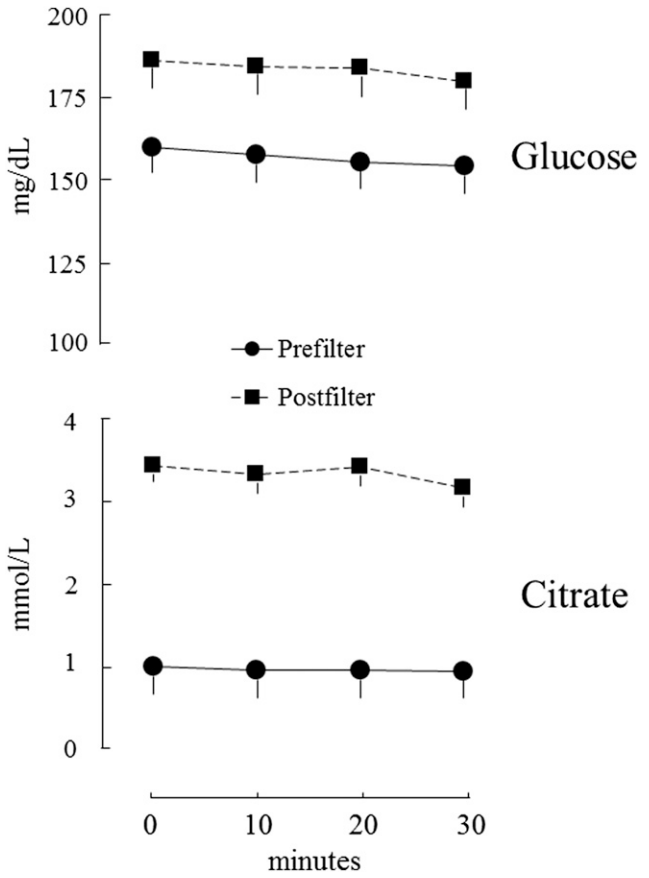

FIGURE 2 Mean glucose and citrate concentrations on day 1 (n = 10).

either through the dialysis filter or via rapid metabolism in various tissues, predominantly the liver (22).

The potential for energy exchange across the CRRT circuit has been recognized for many years. Monaghan et al. (12) reported the uptake of ≤300 g glucose/d from replacement fluids with a high glucose content (83 mmol/L). CRRT can potentially lead to both energy loss and gain depending on the fluids used (9). In this study, energy gain (~500 kcal/d) was caused almost exclusively by the uptake of dextrose and citrate from ACD-A. The contribution of replacement fluids was negligible because of their low lactate content. In the absence of high lactate delivery, a substantial gain or loss of energy would not be expected from the replacement fluids because of the small difference in glucose concentrations between these fluids and blood. The only previous demonstration of energy gain with the use of citrate for anticoagulation to our knowledge is that from Balik et al. (10, 11), who reported that when an acid-citrate-dextrose

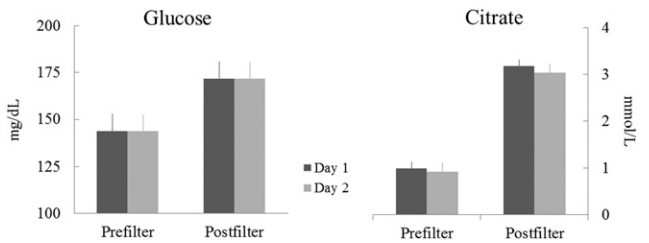

FIGURE 3 Comparison of glucose and citrate concentrations on days 1 and 2 (n = 8).

TABLE 4
Net macronutrient uptake[1]

Macronutrient	Uptake, mg/min	Energy gained, kcal/d
Glucose	54 ± 5	295 ± 28
Citrate	60 ± 2	218 ± 8
Total		512 ± 32

[1] Data are presented as means ± SEMs. n = 10.

solution is used with high lactate replacement fluids, CRRT can provide ≤1300 kcal/d. Our results are more relevant to the most recently published Improving Global Outcomes Acute Kidney Injury Work Group acute kidney injury guidelines (14), which recommend lactate-free replacement fluids.

Despite the potential for net energy accrual during CRRT, most authors have emphasized nutrient loss, including loss of glucose, micronutrients, and especially protein (23–26). The International Society of Nephrology clinical practice guideline for acute kidney injury emphasizes increased protein needs, partly because of the extracorporeal loss of amino acids, in CRRT patients (14). Similarly, the American Society for Parenteral and Enteral Nutrition guidelines for nutrition support in acute renal failure describe profound losses of calcium and magnesium in the dialysate effluent and emphasize higher protein requirements in CRRT but do not explicitly mention macronutrient losses (15). Net uptake of calories is not mentioned in either document.

To our knowledge, this study is the first to measure energy uptake from CVVH when low lactate replacement fluids are used. It should be emphasized that the content and amount of replacement fluids, the ACD solution used, and dialysis devices and filters used during CRRT differ among institutions. In the case of citrate anticoagulation fluids or replacement fluids that contain little or no dextrose, for example, the energy uptake would be much less. For this reason, our results should be generalized with caution.

These findings have important implications in the care of patients on CRRT who are receiving nutritional support. Energy requirements in the critically ill are not as high as once was thought, and overfeeding, especially with parenteral nutrition, is commonplace (7, 27). Our results indicate that CRRT, if not recognized as a source of calories, can increase total energy supply by ~33% in patients receiving full estimated basal energy requirements (which are similar to resting energy expenditure in many patients) via artificial nutrition (27). In fact, there is a role for underfeeding selected patients with obesity and diabetes because this approach results in less hyperglycemia (15, 27). Nonnutritional sources of energy such as dextrose-containing fluids used to treat hypernatremia or administered with intravenous medications, propofol, and the dialysis modalities used in the critically ill have received relatively little attention as sources of energy (28, 29). Our CRRT patients were not overfed because most of them were not receiving nutrition support. However, we did show a potential for overfeeding by demonstrating that the use of CRRT, if not taken into account, could dramatically increase total energy supply. Overfeeding, especially with carbohydrates, contributes to complications, such as hypercarbia, which may prolong mechanical ventilation, and hepatic steatosis (15, 27, 30, 31). Excessive calories may also increase the risk of refeeding and electrolyte abnormalities in severely malnourished patients (1). Overfeeding patients in

the ICU has been associated with increased mortality, morbidity, and length of stay (4, 30, 32, 33).

In this study, net energy uptake was measured in only 10 patients on CVVH; however, the study design was robust, including sequential sampling to improve precision and measurements on separate days to affirm reproducibility. Our findings are consistent with previous studies that have shown a net caloric gain from CRRT fluids and, as explained previously, relevant to current guidelines for CRRT use. The results should be interpreted in the context of local practices with regard to CRRT fluids and anticoagulation, infusion rates, etc. Additional studies are needed to clarify the impact of alternative CRRT protocols on energy balance.

In conclusion, CRRT is an important potential source of unrecognized exogenous calories. We estimated that the daily metabolic contribution of citrate and glucose from CVVH in critically ill patients is substantial at ~512 kcal/d. Given this important contribution, practitioners should consider the additional energy provided by CRRT when designing enteral or parenteral nutrition regimens in the context of institutional CRRT practices.

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