

Continuous Renal Replacement Therapy in Dogs and Cats

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KEYWORDS

- Continuous renal replacement therapy • CRRT
- Acute kidney injury • Dialysis

In the early 1900s, a young pharmacologist at the Johns Hopkins University School of Medicine performed a series of experiments that would lay the foundation for all extracorporeal blood purification technologies developed during the next 100 years. Abel and colleagues¹ directed arterial blood from animal patients, mixed it with an anticoagulant, passed it through a device that divided the blood into strawlike semi-permeable membranes that were suspended in fluid, and then directed the blood back to the patient (**Fig. 1**). Abel demonstrated that the subject's blood could be altered by changing the composition of the fluid. This process, referred to as vividifusion, relied on the properties of diffusion and became the basis for intermittent hemodialysis (IHD).

Continuous renal replacement therapy (CRRT) is a more recently developed blood purification modality. As the name implies, CRRT is a continuous process, and once treatment begins, therapy continues until renal function returns or the patient is transitioned to intermittent dialysis. CRRT is similar to IHD because patient blood is divided into thousands of strawlike semipermeable membranes contained within a dialyzer; however, whereas IHD is primarily a diffusive therapy, CRRT uses diffusion, convection, and, to a lesser extent, adhesion.

CRRT has several significant advantages compared with IHD. The slow and gradual nature of the technique provides better control of electrolytes and acid-base balance.² The continuous operation more closely approximates the functioning of a normal kidney.³ Use of convection in CRRT provides a significant advantage in the removal of larger molecules than can be achieved with diffusion. These larger molecules are closer in size to those that are normally filtered by the kidney. The goal of IHD is to make dramatic changes in a patient's uremic, acid-base, and fluid status over short periods using diffusion; therefore, significant quantities of pure dialysate must be produced onsite. This technique requires a sizeable investment in the purchase and

The author has nothing to disclose.

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Vet Clin Small Anim 41 (2011) 135–146

doi:[10.1016/j.cvsm.2010.09.001](https://doi.org/10.1016/j.cvsm.2010.09.001)

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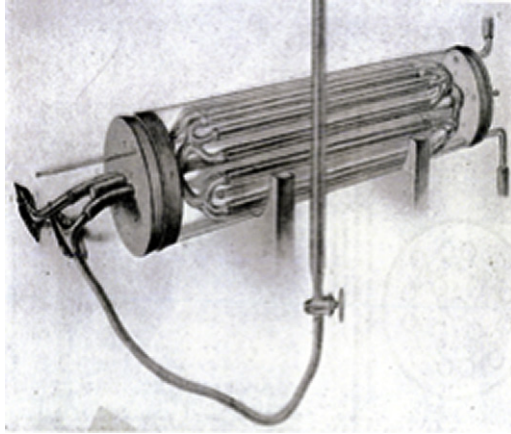


Fig. 1. Dr John Abel directed arterial blood from animal patients, mixed it with an anticoagulant, directed it through the device that divided the blood into strawlike semipermeable membranes that were suspended in fluid, and then directed the blood back to the patient. He demonstrated that the subject's blood could be altered by changing the composition of the fluid. (From Abel J, Rowntree L, Turner B. On the removal of diffusible substances from the circulating blood of living animals by dialysis. *J Pharmacol Exp Ther* 1914;5:285; with permission.)

maintenance of specialized water treatment facilities.⁴ In contrast, the efficient use of diffusion and convection in CRRT allows for the use of prepackaged sterile fluids and makes CRRT units virtually free of maintenance between treatments.

INDICATIONS

The most common indication for CRRT is the treatment of acute kidney injury (AKI) in cases in which renal function is expected to return in the near future or for patients who are to be transitioned to IHD. The author has used CRRT for patients with leptospirosis, tumor lysis syndrome, heatstroke, pre- and postsurgical support of ureteral obstructions, as well as aminoglycoside and melamine toxicities. CRRT can also be used to remove certain drugs and toxins. The ability of any extracorporeal therapy to remove a substance depends on the size of the molecule, its volume of distribution, as well as its degree of protein binding.⁵ A small molecule with a minimal volume of distribution and low protein binding would be most amenable to removal. The extent to which many drugs, toxins, and substances of abuse can be removed by CRRT or IHD has been published.⁶ CRRT has also been used to treat people with diuretic-resistant congestive heart failure; however, this treatment has not yet been evaluated in companion animals.⁷

BLOOD PURIFICATION

The basis of all extracorporeal blood purification is the dividing of a patient's blood into thousands of strawlike semipermeable membranes contained in the dialyzer. While traveling through the dialyzer's semipermeable membranes, blood is purified by diffusion, convection, and, to a lesser extent, adhesion. Diffusion is the tendency of molecules in solution to move from an area of higher concentration to that of lower concentration.⁷ As Abel demonstrated almost a century ago, by bathing the dialyzer's

semipermeable membranes in solution, the movement of substances can be facilitated in or out of the patient's blood by altering the solution's composition. This principle remains the basis of IHD.

Convection also takes place in the strawlike semipermeable membranes of the dialyzer; however, convection involves exposing the blood to a positive transmembrane pressure. This can be accomplished by creating a relative negative pressure around the membranes, a positive pressure within the membranes, or a combination of the 2 processes. Fluid, called ultrafiltrate, is pushed out of the blood and across the semipermeable membrane. Toxins, electrolytes, and other small molecules are then carried with the ultrafiltrate, which is then discarded.^{7,8} Fluids and electrolytes must be replaced with great accuracy because dehydration, overhydration, or severe electrolyte imbalances can quickly develop. The benefits of convection are 2-fold. First, convection makes more economical use of fluids than diffusion. Second, larger molecules are more effectively cleared by convection than by diffusion.⁹

Adsorption also plays a role in blood purification and occurs when molecules adhere to the membrane and are removed from circulation. Human patients with systemic inflammatory response syndrome who undergo CRRT experience a significant decrease in circulating inflammatory mediators.¹⁰ Some of these mediators leave the blood by diffusion or convection, whereas others become adhered to the semipermeable membrane. Although this technique has attracted interest as a possible treatment of systemic inflammatory syndrome, it is not clear if the reduction in mediators correlates to decreased morbidity or mortality.

MODES OF OPERATION

CRRT combines diffusion and convection to produce 4 distinct treatment modalities: slow continuous ultrafiltration (SCUF), continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). SCUF is the least complicated of the treatment modalities (**Fig. 2**). It is a purely convective modality in which blood enters the dialyzer, is divided into thousands of strawlike semipermeable membranes, and is exposed to a positive transmembrane pressure. Ultrafiltrate is forced out of the blood into the intermembrane space and is then discarded as effluent, and the hemoconcentrated blood is returned to the patient.¹¹ SCUF is used in human medicine for patients with nondiuretic responsive congestive heart failure.⁷

Similar to SCUF, CVVH is also a purely convective modality in which blood enters the dialyzer, is divided into thousands of strawlike semipermeable membranes, and then exposed to a positive transmembrane pressure; however, in CVVH, a sterile balanced electrolyte solution is used to replace the ultrafiltrate (**Fig. 3**).¹¹ The electrolyte solution can be added before or after the dialyzer, but in either case it is called the replacement fluid. When the replacement fluid is added before the dialyzer (predialyzer configuration), the patient blood is diluted and then convection within the dialyzer restores the blood to its normal physiologic volume. When the replacement fluid is added after the dialyzer (postdialyzer configuration), the blood is first hemoconcentrated within the dialyzer and then a sterile balanced electrolyte solution is added before the blood is returned to the patient. The benefit of operating in postdialyzer configuration is that it is efficient; however, as the blood becomes increasingly concentrated within the dialyzer, there is a risk of sludging and clotting.¹² Although the predialyzer configuration has a lower risk of clotting, it is much less efficient.¹³ Because a filtration fraction $[(\text{ultrafiltrate rate mL/min} \times 100)/(\text{blood flow rate mL/min} \times [1 - \text{hematocrit value}])]$ of 25% to 30% can be achieved before the risk of clotting significantly increases. Other

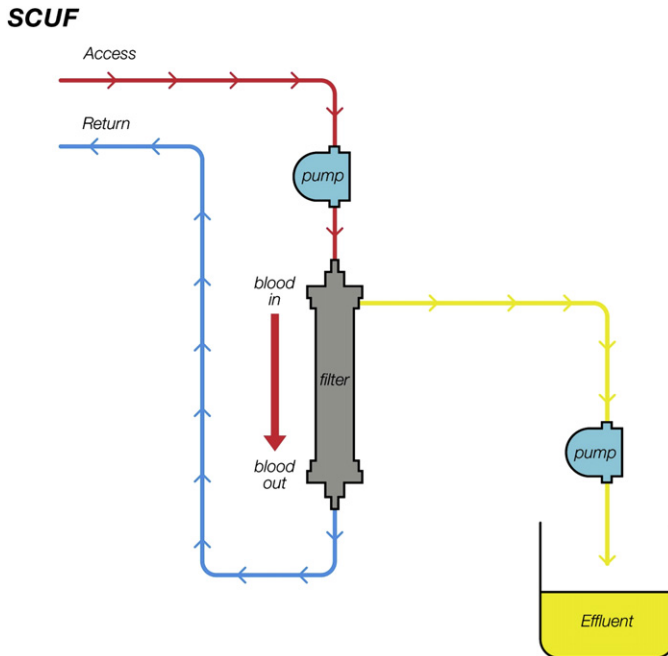


Fig. 2. SCUF, a purely convective modality, generates ultrafiltrate that is not replaced. (From Acierno MJ, Maeckelbergh V. Continuous renal replacement therapy. *Compend Contin Educ Vet* 2008;30(5):269, copyright 2008, Veterinary Learning Systems, Yardley, Pennsylvania; with permission.)

investigators report good success using the predialyzer configuration (Cathy Langston, personal communication, 2010).

CVVHD is a diffusive therapy that closely resembles IHD (**Fig. 4**).¹⁴ Blood enters the dialyzer and is divided into thousands of strawlike semipermeable membranes that are bathed in a solution (dialysate) that flows countercurrent to the blood flow. Toxins that are in high concentration in the blood diffuse across the membrane and enter the dialysate, whereas substances in a high concentration in the dialysate (eg, bicarbonate) diffuse into the blood. The exhausted dialysate is then disposed of as effluent. Although CVVHD is similar to IHD, the slow dialysate flow rates of CVVHD allow the use of prepackaged sterile dialysate.¹⁵

CVVHDF combines the diffusive characteristics of CVHD with the convective properties of CVVH (**Fig. 5**).¹⁴ Blood enters the dialyzer and is divided into thousands of strawlike semipermeable membranes, which are bathed in the dialysate, while the blood is exposed to a positive transmembrane pressure. Diffusion guides the movement of smaller uremic toxins and electrolytes, whereas the positive transmembrane pressure facilitates the movement of fluid and larger molecules. A sterile balanced electrolyte solution is used to replace the ultrafiltrate. Because the amount of convection and diffusion can be adjusted independently, this modality offers the greatest treatment flexibility.

At present, it is not clear which CRRT modality is most effective in the treatment of AKI. Although convective modalities (CVVH, CVVHDF) have an advantage in the clearance of larger molecules,¹⁶ diffusive therapies (CVVHD) are just as effective in the clearance of smaller molecules such as urea and creatinine.¹⁷ The exact role that larger

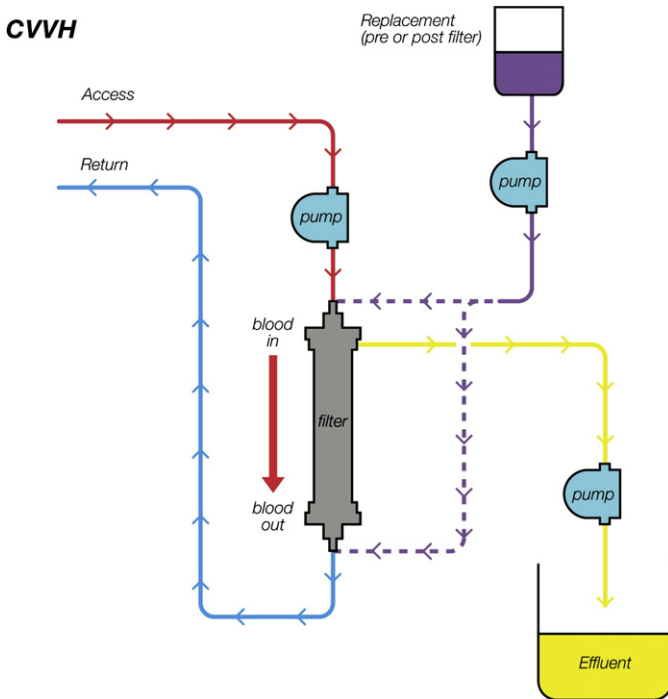


Fig. 3. CVVH is a purely convective modality in which ultrafiltrate is replaced with a sterile balanced electrolyte solution. (From Acierno MJ, Maekelbergh V. Continuous renal replacement therapy. *Compend Contin Educ Vet* 2008;30(5):269, copyright 2008, Veterinary Learning Systems, Yardley, Pennsylvania; with permission.)

molecules play in the pathogenesis of AKI or signs associated with uremia is not known. In addition, diffusive therapies are associated with lower incidence of CRRT circuit clotting.¹³ Nevertheless, in most instances, convective therapies (CVVH or CVVHDF) are used, with good results.

EQUIPMENT

Gambro Renal Systems (Lakewood, CO, USA) manufactures virtually all CRRT systems used in veterinary medicine. Although most veterinary facilities use the older Prisma unit, the new more advanced Prismaflex has replaced it. These units are highly integrated and computerized. A central computer coordinates the movement of 4 peristaltic pumps: a blood pump, a dialysis solution pump, a replacement solution pump, and an effluent pump. The actual speed of these pumps is electronically verified and adjusted. All fluids (dialysate, replacement, effluent) are continuously weighed and compared with calculated expected weights. Any difference between the actual and expected weight results in a system alarm. Dozens of system parameters are continuously calculated, monitored, and displayed. These systems incorporate a heparin infusion system, although the Prismaflex also has integrated supports for citrate anticoagulation.

BLOOD ACCESS

In all but the smallest patients, a dual-lumen temporary dialysis catheter is placed in the jugular vein using the Seldinger technique.^{18,19} These specialized catheters are

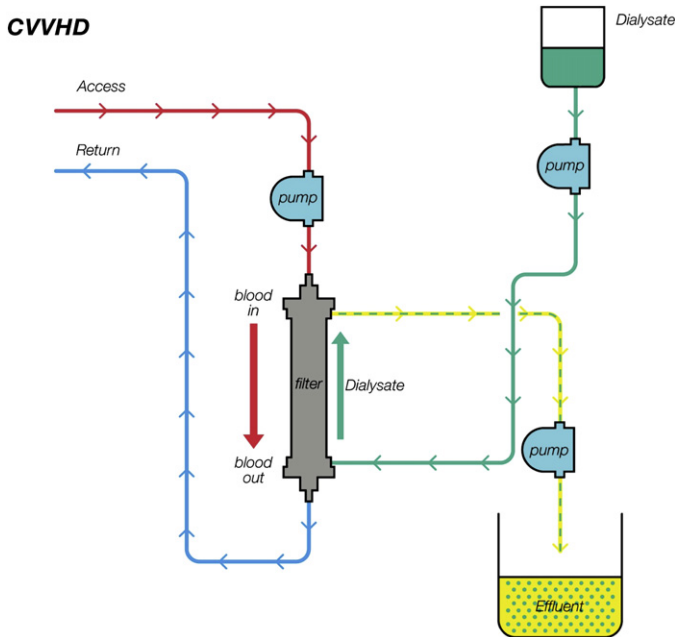


Fig. 4. CVVHD is a diffusive therapy similar to IHD. (From Acierno MJ, Maeckelbergh V. Continuous renal replacement therapy. *Compend Contin Educ Vet* 2008;30(5):270, copyright 2008, Veterinary Learning Systems, Yardley, Pennsylvania; with permission.)

designed to maximize blood flow and minimize blood recirculation. Typically, an 11.5F dual-lumen temporary dialysis catheter is placed in very large dogs, whereas an 8F catheter is placed in smaller dogs. In the smallest patients, a single-lumen 5F dialysis catheter is placed in each jugular vein. A more extensive discussion of the proper selection and care of vascular access catheters by Chalhoub and colleagues can be found elsewhere in this issue.

ANTICOAGULATION

Although CRRT tubing and dialyzers are made from highly biocompatible material, clotting is inevitable in the absence of adequate anticoagulation. Formation of clots in the CRRT circuit results in a significant loss of patient blood, requires the replacement of an expensive CRRT circuit, and results in time that the patient is not receiving treatment. Anticoagulation of the CRRT circuit is usually accomplished with heparin or citrate.

A constant rate infusion (CRI) of heparin has historically been the most widely used method of anticoagulation in patients undergoing CRRT,¹⁹ and most CRRT systems have integrated heparin syringe pumps. Heparin increases the activity of antithrombin, a circulating protease inhibitor. Because the patient's blood is systemically anticoagulated, there is a risk of uncontrolled bleeding; however, monitoring activated clotting time (ACT) and actively managing heparin infusion rates can minimize this risk (**Box 1**). Because of the low per-sample cost and minimal blood volume requirements, ACT devices manufactured by Medtronic (Minneapolis, MN, USA) are the most commonly used for monitoring ACT in veterinary CRRT.

Calcium is an essential cofactor required throughout the clotting cascade. Before the patient's blood enters the CRRT circuit, citrate is infused, which chelates the

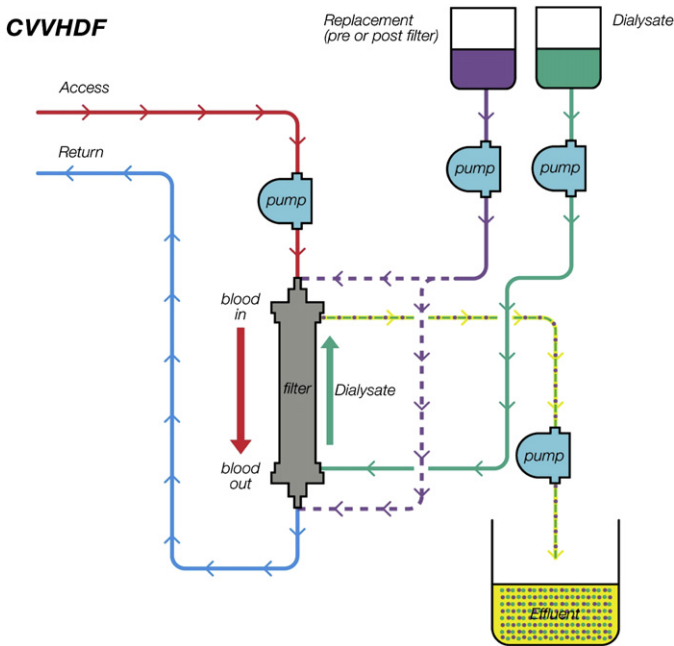


Fig. 5. CVVHDF combines the diffusive aspects of CVVHD with the convective properties of CVVH. (From Acierio MJ, Maeckelbergh V. Continuous renal replacement therapy. *Compend Contin Educ Vet* 2008;30(5):270, copyright 2008, Veterinary Learning Systems, Yardley, Pennsylvania; with permission.)

calcium and renders the blood unable to clot. Many of the resulting calcium-citrate complexes are lost through the dialyzer as effluent, while the remaining citrate returns to the patient and is metabolized by the liver into bicarbonate. The patient's physiologic calcium levels are maintained by infusing calcium directly to the patient. Citrate anticoagulation has advantages in that anticoagulation is limited to the CRRT unit and circuit lifespan may be extended²⁰; however, alkalosis from citrate metabolism as well as hypocalcemia and hypercalcemia are common life-threatening complications in both human and veterinary patients.^{21,22} Therefore, the patient's serum calcium concentration and acid-base status must be frequently monitored.²¹ Because of lower cost and ease of use and based on personal experience, heparin anticoagulation is used at the author's facility.

TREATMENT ADEQUACY

Although the toxins responsible for the uremia are not known, serum urea is easily measured and commonly used as a surrogate for all small molecules removed in CRRT.²³ The formula Kt/V is a commonly used measure of CRRT treatment adequacy. It represents the urea clearance over time, normalized for the patient's volume of distribution. In this calculation, K represents urea clearance in milliliters per minute. Total solute removal per period (Kt) is the product of clearance (K in milliliters per minute) and time (t in minutes) that the patient receives treatment per day. Kt is then normalized by dividing urea clearance over time by the patient's volume of distribution (V in milliliters). Urea is approximately equally distributed in all body fluid compartments, and its removal by CRRT is so gradual that significant differences

Box 1**Louisiana State University heparin work sheet**

Start of therapy

Check ACT

In the absence of coagulopathy (ACT>150), give 25-unit/kg heparin bolus

Record total units given _____

Recheck ACT. If less than 180, repeat bolus (maximum 3 total boluses)

Record number of boluses given _____

ACT at start of therapy _____

During CRRT

Start heparin infusion, 20 units/kg/h

If ACT<180, increase heparin by 1 unit/kg/h

If ACT>220, decrease heparin by 1 unit/kg/h

If ACT<170, bolus 10 unit/kg heparin and increase CRI

If ACT<160, bolus 15 unit/kg heparin and increase CRI

Monitor ACT every 30 minutes after any change

Monitor ACT every 2 hours once stable

do not develop between compartments; therefore, V is equal to total body water in milliliters (60% of body weight in kilograms \times 1000). Studies in humans suggest that a Kt/V of 1.4 or more may be associated with decreased morbidity and mortality.^{23,24} Although studies in companion animals are lacking, the author has found that a Kt/V of 1.4 produces satisfactory reductions in the concentration of urea and provides adequate control of acid-base and electrolyte balance in oliguric and anuric patients. Values for K can be estimated before treatment starts (K_{calc}) and then actual K calculated (K_{del}) once treatment begins.

As an example, a male neutered pit bull weighing 27 kg presents for treatment of AKI secondary to tumor lysis syndrome. A decision is made to treat the patient with CVVH in a postdialyzer replacement fluid configuration. To optimize treatment, it is ensured that the calculated Kt/V is at least 1.4. As a starting point, blood flow rate (Q_b) is estimated to be set at 100 mL/min (a little more than 3 times the weight in kg), and ultrafiltration rate is 20%; therefore, ultrafiltrate production rate is 20 mL/min. Although CRRT is theoretically an uninterrupted modality, patients need to be walked and the system needs attending. From experience, it was estimated that the patient should receive 1320 minutes (22 hours) of therapy per day. From **Box 2**, the formula for $K_{\text{calc CVVH}} = \text{ultrafiltrate (20 mL/min)}$. Therefore $Kt/V_{\text{calc CVVH}} = 1.65$ (20 mL/min \times 1320 min)/16,000 mL. Although this is an acceptable Kt/V, it should be ensured that the filtration fraction is not greater than 25% to 30%. If the packed cell volume of the patient is 30, the filtration fraction is 28% [(20 mL/min \times 100)/(100 mL/min \times [1–0.30])]. By decreasing the ultrafiltration rate to 17% (Q_{uf} = 17 mL/min), $K_{\text{calc CVVH}}$ would be a respectable 1.4, whereas filtration fraction decreases to a more comfortable 24%.

Once treatment has begun, actual Kt/V_{del} can be calculated to determine if treatment parameters require adjustment. To calculate K_{del} for the aforementioned patient, urea and ultrafiltrate values are needed. According to the laboratory tests, patient

Box 2**Kt/V formula**

K_{calc} = Calculated (estimated) urea clearance

K_{del} = Actual delivered urea clearance

CVVH: postdialyzer replacement fluid

K_{calc} = Ultrafiltration rate (mL/min)

K_{del} = Ultrafiltrate urea concentration (mg/dL) \times Ultrafiltration rate (mL/min)/Predialyzer urea concentration (mg/dL)

CVVH: predialyzer replacement fluid

K_{calc} = Ultrafiltration rate (mL/min)/(1+[Fluid replacement (mL/min)/Blood flow rate (mL/min)])

K_{del} = Ultrafiltrate urea concentration (mg/dL) \times Ultrafiltration rate (mL/min)/Predialyzer urea concentration (mg/dL)

CVVHD

K_{calc} = Dialysate rate (mL/min)

K_{del} = Postdialyzer dialysate urea concentration (mg/dL) \times Dialysate rate (mL/min)/Prefilter blood urea level (mg/dL)

CVVHDF: postdialyzer replacement fluid

K_{calc} = Ultrafiltration rate (mL/min) + Dialysate rate (mL/min)

K_{del} = Ultrafiltrate urea concentration (mg/dL) \times (Ultrafiltration rate [mL/min] + Dialysate rate [mL/min])/Predialyzer blood urea level (mg/dL)

serum urea nitrogen was 88 mg/dL and ultrafiltrate 80 mg/dL. Using the formula in **Box 2**, $K_{\text{del}} = 15.45$ mL/min (ie, $[80 \text{ mg/dL} \times 17 \text{ mL/min}]/88 \text{ mg/dL}$), and therefore, $Kt/V_{\text{DEL}} = 1.27$. Because this value is less than the ideal, the blood flow rate can be increased to 110 mL/min. Ultrafiltration rate will continue to be 17%; therefore, ultrafiltrate production will be 18.7 mL/min, and $Kt/V = 1.54$ ($[18.7 \text{ mL/min} \times 1320 \text{ min}]/16,000 \text{ mL}$). Filtration fraction will continue to be an acceptable 24% ($[18.7 \text{ mL/min} \times 100]/(110 \text{ mL/min} \times [1 - 0.30])$).

COMPLICATIONS

The most significant complications involve coagulation. Despite appropriate heparin management, clotting of the CRRT circuit is inevitable. To minimize treatment disruptions and the unavoidable loss of patient blood caused by an unexpected circuit clot, system parameters, such as filter and transmembrane pressure, are monitored carefully and the entire circuit is replaced if values unexpectedly change. Although the author has had success with circuits lasting more than 70 hours, the entire CRRT blood pathway is routinely replaced every 48 hours. Clots forming in or around the dialysis catheter can present a challenge to maintaining adequate blood flow. Proper care and troubleshooting of these catheters has been covered elsewhere. Some patients develop bleeding or oozing at the catheter site. This complication is most pronounced in cases in which previous jugular vein trauma precluded placement of the catheter by the Seldinger technique; however, this has not proved to be clinically significant except in small patients. Hypotension is another potential complication. Although the cause of the blood pressure drop at the start of therapy is likely to be multifactorial, the amount of blood needed to fill the CRRT circuit is at least partly the reason.²⁵

SPECIAL CONSIDERATIONS FOR SMALL PATIENTS

Continuous renal replacement circuits typically require 50 mL to 84 mL of blood to fill the tubing and dialyzer. This volume can represent a significant portion of a smaller patient's total blood volume and can lead to an unsafe drop in blood pressure at the start of treatment. One way to overcome this problem is to prime the CRRT circuit with whole blood or fresh frozen plasma and packed cells before the start of therapy. As blood is taken from the patient, they simultaneously receive a transfusion so that they have no change in blood volume. A problem arises because the strawlike semi-permeable membranes of most CRRT dialyzers are composed of acrylonitrile and sodium methallyl sulfonate copolymer (AN69). When exposed to acidic blood, these membranes activate bradykinins, which can potentiate life-threatening hemodynamic instability.^{26,27} Because stored blood products typically have a low pH, such blood primes can prove fatal. This problem can be circumvented by attaching both the CRRT patient-access and patient-return lines to the bag containing stored blood products and allowing the CRRT machine to correct the pH and remove the activated bradykinins. Thus, the bag of blood receives treatment as if it were a patient (**Fig. 6**). After approximately 30 minutes, the treatment is paused, the bag is disconnected, and the patient is connected. Using this strategy, patients weighing as little as 2.5 kg have been treated. It is important to properly anticoagulate the blood being treated because the replacement fluids/dialysate typically contain calcium. A similar hemodynamic instability has been reported in human patients who are treated with

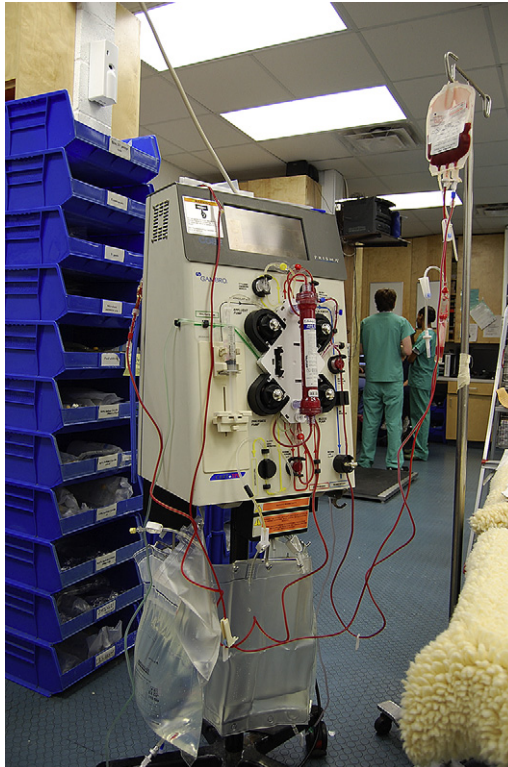


Fig. 6. Whole blood being dialyzed to correct pH.

angiotensin-converting enzyme inhibitors and receive CRRT²⁸; therefore, care should be taken when treating such patients.

PATIENT CARE

Providing properly trained, technically competent patient care is the most challenging aspect of providing CRRT. Once the patient has begun therapy, there is an obligation to continue treatment 24 hours a day until the patient recovers, is transitioned to IHD, or is euthanized. Advanced knowledge of renal physiology and the mechanics of the CRRT unit are essential for treatment decisions. The pool of adequately trained doctors and support staff is likely to be limited even in the largest practice. When patients require more than a few days of treatment, the staffing issues can become challenging. In the author's hospital, a doctor and a specially trained veterinary student constantly attend to the patient. These professionals are busy ensuring not only that the functioning of the CRRT unit is being monitored and analyzed but also that the hydration status of the patient is carefully scrutinized. Overhydration is an independent predictor of death in people with AKI. This overhydration is likely to be true in companion animals as well; therefore, attempt is made to account for every milliliter of fluid that enters or leaves patients undergoing CRRT on a continuous basis. There are likely to be a limited number of centers throughout the country that can provide the necessary level of care.

SUMMARY

CRRT is a relatively new extracorporeal blood purification modality for the treatment of AKI, fluid overload, and toxin exposure. Although CRRT has both therapeutic and operational advantages compared with IHD, its intensive nature and the need for specialized 24-hour care will likely limit the availability of this modality to a small number of referral institutions.

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