Continuous Renal Replacement Therapy

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ABSTRACT: Continuous renal replacement therapy (CRRT) is a blood purification modality that uses a combination of convection and diffusion to eliminate uremic toxins and correct electrolyte imbalances. Although CRRT is usually associated with the treatment of acute renal failure, it can also be useful in treating many types of toxicoses and drug overdoses. Unlike intermittent hemodialysis, in which the patient is treated at set intervals for a specified number of hours, CRRT continues until kidney function is restored. CRRT's array of blood purification techniques and its slow, continuous nature more closely approximate normal kidney function than does intermittent dialysis. Although easier to maintain than traditional dialysis systems, CRRT requires specialized equipment, training, and nursing care.

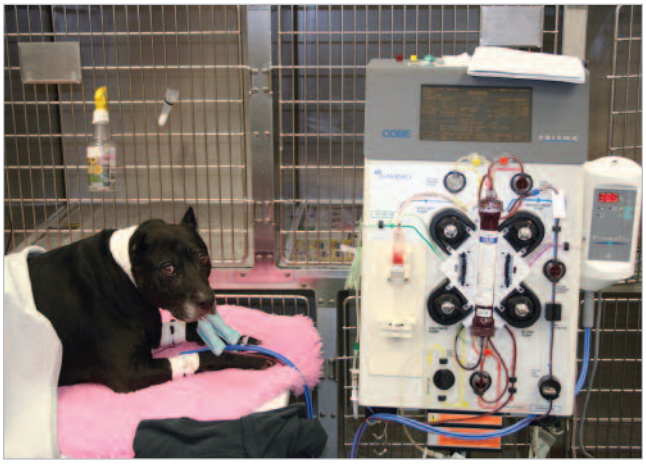
In 1913, John Abel, a pharmacologist at Johns Hopkins University, reported the first successful performance of dialysis in a dog.[1] In a procedure he referred to as *vividiffusion*, blood was diverted from an anesthetized animal, treated with a leech-derived anticoagulant, passed through semipermeable membranes suspended in saline solution, and then returned to the patient.[1] Although the vividiffusion apparatus appears rudimentary by today's standards, Abel's idea of using a semipermeable membrane to remove substances from blood remains the basis of all blood purification technology.

Until recently, all veterinary patients requiring blood purification treatment received intermittent hemodialysis. This is a primarily diffusion-based modality that is performed at set intervals, often several times a week, for 4 to 5 hours at a time.[2] More recently, a newer technology, called *continuous renal replacement therapy* (*CRRT*), has emerged.[3] As the name implies, this technique relies on continuous, gradual blood purification.[4] Both diffusion and convection are used to remove toxins from the blood. Once treatment has begun, the patient's blood is filtered until kidney function returns.

CRRT has several potential advantages over traditional intermittent dialysis. Because of its gradual nature and advanced filtering capabilities, CRRT more closely approximates normal kidney function; therefore, its control of uremia is superior to that of intermittent dialysis,[5] which uses fast blood and dialysate flow rates to achieve maximum blood purification in a relatively short period of time. Control of acidosis and electrolyte balance has also been reported to be superior in patients receiving CRRT.[6] In addition, the CRRT unit is completely self-con-

[a]Dr. Acierno discloses that he has received financial support from Hill's Pet Nutrition, Inc.

Figure 1. Keno, an anuric renal failure patient, received continuous venovenous hemofiltration.



Keno undergoing treatment in the Louisiana State University intensive care unit.

Keno 2 days after treatment ended.

tained, allowing it to be used cage-side (Figure 1). This is possible because the flow rates used in CRRT are slower, enabling the use of packaged fluids. Intermittent dialysis systems are not portable because they have specialized water purification requirements and require large quantities of dialysate that must be produced on-site, using complicated reverse-osmosis water treatment equipment.[2] While slightly more expensive, the use of prepackaged fluids significantly reduces the complexity of the CRRT process. Unlike traditional dialysis units that require extensive routine maintenance, the CRRT machine requires no special care.

Although CRRT involves sophisticated technology, the actual process of blood purification can be divided into four easily described steps: (1) blood is diverted from the patient to the CRRT unit, (2) anticoagulants are added to the blood, (3) uremic toxins are removed and electrolytes normalized, and (4) the blood is returned to the patient.

VASCULAR ACCESS

Blood removal and return are facilitated by sedating the patient and placing a dual-lumen temporary dialysis catheter in the jugular vein using the Seldinger technique.[7] These specialized catheters are designed to maximize blood flow and minimize the recirculation of processed blood.[8,9] Typically, an 11.5-Fr catheter is placed in medium and large dogs; small dogs and cats can receive a 7-Fr catheter. Because the blood flow requirements of CRRT are relatively modest, these easily placed catheters provide adequate access for the entire procedure. All CRRT catheters should be handled in an aseptic fashion and used exclusively for hemodialysis. A separate IV catheter should be placed for any other procedure requiring venous access, such as the administration of medications. The only vein suitable for the placement of a dialysis catheter is the jugular; therefore, these veins should not be used for any purpose in a patient that might later be referred for CRRT.

ANTICOAGULATION

As in intermittent dialysis, CRRT blood purification takes place in an artificial kidney known as a *dialyzer*. Although the dialyzer and its associated tubing are made of highly biocompatible materials, contact between these manmade structures and the patient's blood invariably leads to activation of the clotting cas-

Key Points

- Continuous renal replacement therapy consists of four blood purification modalities used to treat acute renal failure and toxin exposure. It may also be helpful in cases of congestive heart failure.
- Continuous renal replacement therapy is a gradual process in which patients with acute renal failure receive continuous treatment until normal kidney function returns.
- Because patients require days to weeks of continuous treatment, continuous renal replacement therapy requires a large pool of trained personnel.

cade. In the absence of adequate anticoagulation, clotting and clogging of the dialyzer is inevitable.[10] This is undesirable for several reasons. In a small patient, the blood volume in the CRRT circuit can be significant. Because clotted blood cannot be returned to the patient, significant blood loss can occur. Secondly, CRRT blood lines and dialyzers are expensive and, once clotted, must be replaced. Even tiny clots that become lodged in the dialyzer can have a significant effect on treatment efficiency and necessitate dialyzer replacement. Lastly, while setup of the CRRT unit is relatively quick and simple, the patient's blood cannot be filtered during this time. Therefore, significant effort is directed to preventing CRRT circuit clotting.

Two techniques are commonly used to prevent blood coagulation during CRRT. The most widely employed method is the systemic anticoagulation of the patient with a constant-rate infusion of heparin.[11] Heparin binds to and activates antithrombin, a circulating protease inhibitor that inhibits the active form of clotting factors IX, X, XI, and XII.[12] Many CRRT systems are designed with integrated heparin infusion pumps. The anticoagulation effects are monitored by periodically measuring activated clotting time[11] (Figure 2). The primary risk of systemic anticoagulation is uncontrolled hemorrhage; however, protamine sulfate can be given to reverse heparin's effects if activated clotting time becomes excessively prolonged.[11]

The use of citrate as an anticoagulant has also been described.[13] As blood enters the system, it is infused with citrate.[11] The citrate chelates serum calcium, which is an important enzyme cofactor at several steps in the clotting cascade.[14] This renders the blood unable to clot. Before the blood is returned to the patient, calcium chloride is added to return serum calcium to physiologic levels. Citrate therapy has the advantage of providing local anticoagulation in the circuit without systemic effects on the patient. However, there is a significant risk of hypocalcemia and metabolic alkalosis.[3,14,15] Therefore, the use of citrate requires periodic calcium and acid–base monitoring, which can be costly. Nevertheless, one human study has reported that regional citrate anticoagulation is associated with fewer complications and improved clinical outcomes.[16]

Figure 2. Automated coagulation timer. An accurate determination of coagulation status is critical to prevent clotting within the dialyzer and spontaneous bleeding in the patient.

BLOOD PURIFICATION

In a process reminiscent of John Abel's vividiffusion equipment, the dialyzer divides the patient's blood and directs it through thousands of straw-like semipermeable membranes that are suspended in a specially formulated fluid called *dialysate*.[17] Unlike intermittent dialysis systems, which rely primarily on diffusion, blood purification in the CRRT unit is accomplished by three mechanisms: diffusion,[4,18] convection,[4,18] and adsorption.[19] These mechanisms can be used individually or combined to take advantage of the particular strengths of each technique.

Diffusion is the tendency of molecules in a solution to move from an area where they are in a high concentration to an area where they are in a lower concentration.[18] This movement occurs because particles are constantly in motion and tend to disperse as they bounce off one another.[20] In patients with renal failure, uremic toxins such as blood urea nitrogen and creatinine accumulate to high concentrations in the blood. The semipermeable dialyzer membranes allow these toxins to diffuse freely into the dialysate.[18] However, the process of diffusion is limited by the size of the membrane pores; as the size of a molecule approaches the average pore size, its rate of diffusion decreases. The dialysate is continuously replenished in the direction opposite to that of the blood flow so that the concentration of toxins in the blood is always higher than that in the dialysate and diffusion of toxins from the blood into the dialysate proceeds continuously. Simultaneously, substances in the dialysate diffuse into the blood; therefore, the dialysate contains precisely measured concentrations of electrolytes and buffers and is carefully prepared to avoid contamination by metals, toxins, bacteria, and endotoxins.[17] The movement of substances into the blood can be regulated by manipulating their concentration in the dialysate. For example, renal failure patients

are often in a state of metabolic acidosis. Because the amount of bicarbonate in the dialysate is relatively high, it moves into the blood by diffusion and the acidosis is corrected.[20]

Convection also takes place in the dialyzer. In this process, blood traveling within the semipermeable membranes is exposed to a positive transmembrane pressure—that is, the pressure inside the membrane is positive relative to the pressure outside the membrane—and this pressure difference pushes fluid out of the blood and across the semipermeable membrane.[18,20] Toxins, electrolytes, and other molecules are carried across the membrane with this fluid, which is called *ultrafiltrate*.[18,20,21] This fluid is then removed from the dialyzer and disposed of as effluent. Convection is more technically challenging than diffusion because large amounts of fluid and associated electrolytes are rapidly removed from the blood. If they are not carefully replaced, the patient will quickly become dehydrated or experience electrolyte imbalances. The theoretical benefit of convection is that larger molecules are more effectively cleared by this process than by diffusion.[18,22]

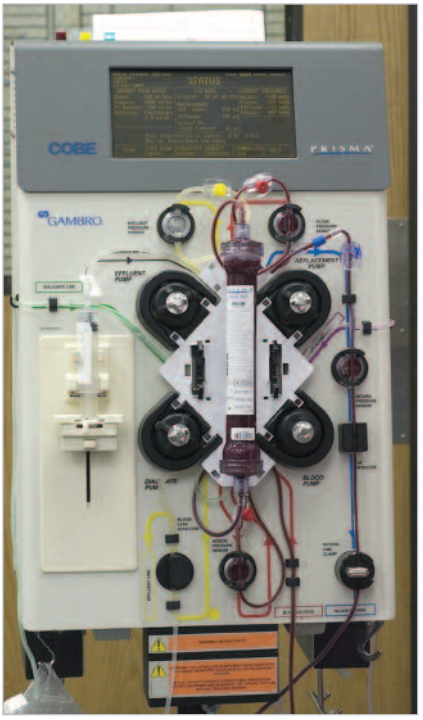


Figure 3. The Gambro Prisma unit is the most widely used CRRT unit in veterinary medicine. An integrated computer system coordinates the activity of a blood pump, a dialysis solution pump, a replacement solution pump, an effluent pump, and a heparin infusion pump. The speed of the pumps is electronically verified and adjusted. The dialysis solution, replacement solution, and effluent (dialysis solution and ultrafiltrate) are continuously weighed, and any deviation from the calculated values generates an alarm.

Adsorption occurs when molecules adhere to the dialysis membrane and are removed from circulation.[19,20] It has been shown that human patients with systemic inflammatory response syndrome who undergo CRRT have a significant drop in inflammatory mediators.[19] Some of these mediators leave the blood by diffusion or convection; others adsorb to the dialysis membrane.[19] This process has attracted great interest as a possible mechanism of reducing systemic inflammation.

SYSTEM FEATURES

Design

To safely provide a variety of blood purification modalities, CRRT systems are highly integrated and computerized (Figure 3). A central control unit coordinates the movement of as many as four peristaltic pumps: a blood pump, a dialysis solution pump, a replacement solution pump, and an effluent pump. The speed of the pumps is electronically verified and adjusted. The dialysis solution, replacement solution, and effluent (dialysis solution and ultrafiltrate) are continuously weighed. Because all fluids in the CRRT system are packaged, it is possible to calculate the expected weight of each fluid based on the unit's current settings. These calculations are compared with the actual weight, and any difference results in a system alarm. Many systems can forecast the times at which components will need to be replaced and the effluent bag emptied. In addition, they continuously calculate and monitor dozens of system parameters.

Modes of Operation

CRRT units use the principles of diffusion and convection to produce four different filtration modalities: slow continuous ultrafiltration (SCUF), continuous venovenous hemodialysis (CVVHD), continuous venovenous hemofiltration (CVVH), and continuous venovenous hemodiafiltration (CVVHDF).[23] SCUF is the least complex and most rapid of the CRRT modalities, lasting only a few hours (Figure 4). It consists purely of convection, in which transmembrane pressure forces fluid out of the blood. In this modality, the ultrafiltrate is not replaced, and the blood becomes more concentrated. In human medicine, SCUF has been used to treat congestive heart failure patients who do not respond to medical management.[18] The use of SCUF for treating veterinary patients is being evaluated.

CVVH is conceptually similar to SCUF in that convection forces fluid out of the blood. However, unlike SCUF, in CVVH, the removed fluids are replaced with a sterile, balanced electrolyte solution[18,24,25] (Figure 5). This solution, which keeps the blood from becoming too concentrated, can be added to the blood before[18,26] or after it travels through the dialyzer. In most cases, it is added after. In the postdialyzer configuration, ultrafiltrate leaves the blood as it travels through the dialyzer, and the blood becomes

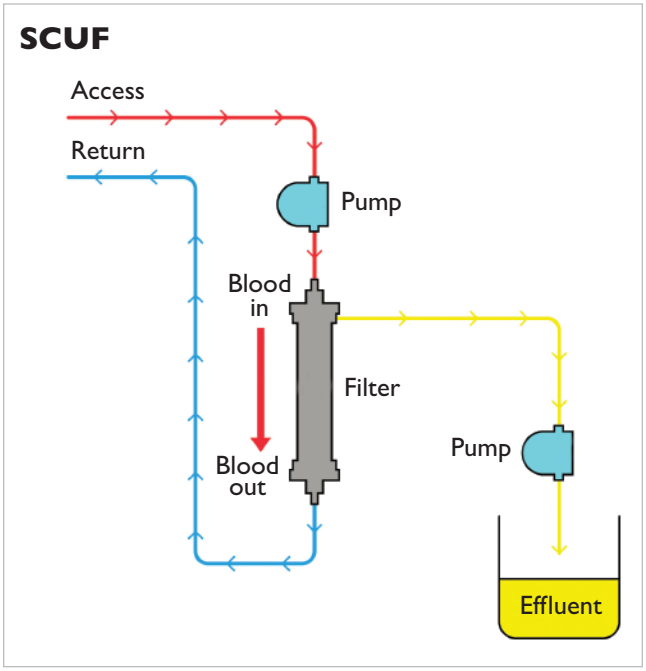


Figure 4. SCUF is a purely convective modality in which an increased transmembrane pressure generates large amounts of ultrafiltrate. This fluid is not replaced.

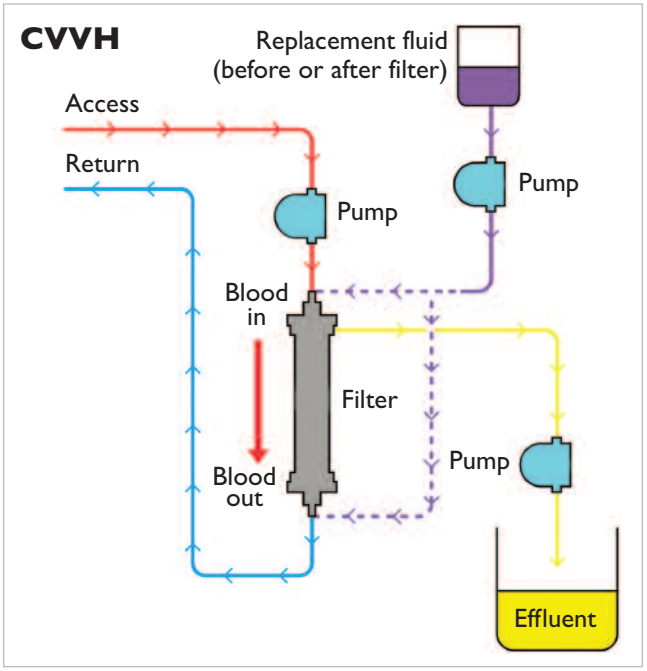


Figure 5. Like SCUF, CVVH is a convective modality that generates large amounts of ultrafiltrate due to an increased transmembrane pressure; however, in CVVH, the lost fluid is replaced with a sterile balanced electrolyte solution. This replacement fluid can be added before or after the dialyzer.

increasingly concentrated. This is an extremely effective way to remove toxins. However, as the hemoconcentration increases, there is a risk that blood will sludge, clot, and clog the dialyzer's membranes.[18] This risk is not as great in SCUF, in which the object of therapy is to correct volume overload and which takes much less time than CVVH, reducing the likelihood that the dialyzer membranes will become entirely clogged. In CVVH, increasing hemoconcentration limits the amount of fluid that can be removed to about 20% to 25% of the blood volume. Before the blood is returned to the patient, replacement fluids are added to restore the blood volume to normal. When fluids are added to the blood before it enters the dialyzer, the excess fluid is removed by convection. While less likely to result in clotted membranes, the prefilter arrangement is less effective in removing uremic toxins.[26]

CVVHD is a primarily diffusive therapy that is similar to intermittent hemodialysis[23] (Figure 6). Toxins (e.g., creatinine) and electrolytes that are in high concentrations in the blood diffuse across the dialysis membrane and enter the dialysate.[17] Beneficial substances that are in high concentrations in the dialysate (e.g., bicarbonate) diffuse across the membrane and enter the blood.[17]

CVVHDF combines the diffusive aspects of CVVHD with the convective properties of CVVH[23] (Figure 7). As the blood flows through the dialyzer's membranes, diffusion guides the movement of uremic toxins and electrolytes while a difference in the transmembrane pressure causes the movement of fluid and molecules out of the blood.[18] The ultrafiltrate mixes with the dialysate, is removed from the dialyzer, and is replaced with a sterile balanced electrolyte solution in the same manner as described for CVVH.[25] Because the diffusion and convection processes can be modified independently, CVVHDF gives the operator the greatest possible scope of treatment options.

* * *

It is not clear which CRRT modality provides the most effective blood purification. Earlier research suggested that the convective components of CVVH and CVVHDF provided a significant advantage in the removal of blood solutes.[18,22] Newer studies have shown that diffusive modalities, such as CVVHD, are just as effective at removing smaller solutes such as creatinine and blood urea nitrogen.[26,27] In addition, patients receiving CVVHD experience fewer dialyzer malfunctions.

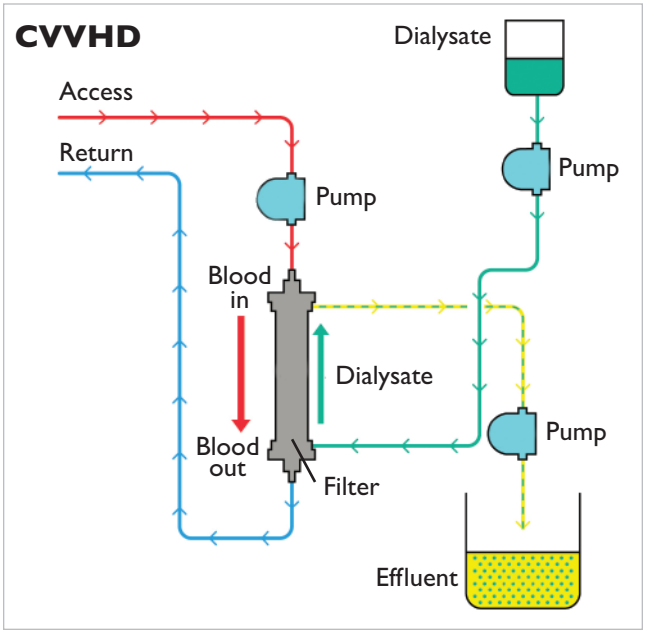


Figure 6. CVVHD is a primarily diffusive therapy in which uremic toxins and excess electrolytes diffuse out of the blood and into the dialysate. Beneficial substances that are in a high concentration in the dialysate (i.e., bicarbonate) diffuse across the membrane and enter the blood. The movement of substances can be controlled by their concentration in the dialysate.

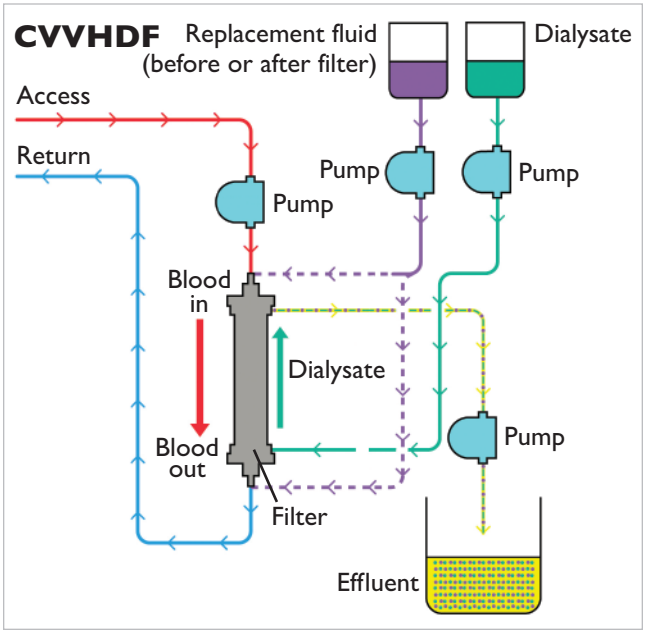


Figure 7. CVVHDF combines the diffusive aspects of CVVHD with the convective properties of CVVH. Diffusion guides the movement of uremic toxins and electrolytes while a difference in the transmembrane pressure causes the movement of fluid and molecules out of the blood.

However, the role of larger molecules in renal failure is less clear. It is possible that larger molecules are important in the pathogenesis of uremia or azotemia.

INDICATIONS

Treatment of acute renal failure is the most common application of CRRT in veterinary medicine. By removing uremic toxins and correcting electrolyte, acid–base, and fluid imbalances, CRRT temporarily replaces critical renal functions. This gives patients the time needed for their kidneys to heal. Unfortunately, it is usually not possible to determine how long CRRT will be needed or if normal kidney function will return.

The ability of CRRT to remove a substance such as a toxin or drug from the blood depends on several of the substance's molecular characteristics. For example, as molecules approach the membrane's pores in size, the ability to remove them decreases.[28] Only the free or non-protein-bound portion of a drug or toxin can be removed; therefore, substances that are highly protein bound are more difficult to remove from the blood.[28] The volume of distribution of the drug or toxin is another limiting factor. This is a measure of a substance's distribution throughout the body. The ability of CRRT to remove a toxin is inversely proportional to its volume of distribution because CRRT can remove only substances within the vasculature.[28] Data have been published on the degree to which many specific medications, illegal drugs, and toxins can be removed by intermittent dialysis and CRRT (see the box on this page). Most dialysis and CRRT centers maintain up-to-date copies of these lists.

In human medicine, CRRT has been used to treat inborn errors of metabolism, septic shock, and systemic inflammatory response syndrome.[19,29–31] The value of

Examples of Drugs and Toxins That Can Be Removed by Dialysis

Antibiotics/Antifungals
- Aminoglycosides
- Amikacin
- Gentamicin
- Tobramycin
- Vancomycin
- Fluconazole
- Amphotericin (limited)

NSAIDs
- Aspirin/salicylates
- Acetaminophen

Other drugs
- Phenobarbital

Toxins
- Ethylene glycol
- Ethanol

CRRT treatments in some of these conditions is under debate.[30,31] The use of CRRT for these conditions in veterinary medicine has not yet been evaluated.

PATIENT CARE AND MONITORING

To provide CRRT, a facility requires a pool of trained personnel capable of 24-hour patient monitoring for extended periods of time. The box on this page contains a list of centers that currently provide CRRT. Although the actual CRRT process is automated, patients require continuous monitoring until renal function returns, which may take more than 1 week. In addition, an advanced understanding of renal physiology and the mechanics of the CRRT unit is essential for troubleshooting and making treatment decisions.

Dialysis is a technically complicated endeavor that is compounded by the patient's size and critical condition. In our experience, problems associated with coagulation are perhaps the most challenging. Although activated clotting times are measured regularly, clots can form in the CRRT circuit. This is especially common in CVVH, in which concentrated blood can sludge in the dialyzer. Conversely, some patients develop significant bleeding at the catheter site. Hypotension is another potential complication of CRRT. While the exact cause is complex,[32] it is likely that the proportionally large amount of blood needed in the CRRT circuit (50 to 84 ml) as well as the reduction in blood volume caused by convection are primarily responsible.[32,33] In an attempt to address this problem, at the start of dialysis, larger patients receive an amount of crystalloid solution from the unit that is equivalent to the volume of blood needed to fill the circuit; smaller patients receive colloids or blood. While no data exist to indicate the minimum size a veterinary patient must be to receive CRRT, studies in children have shown that neonates weighing as little as 5 lb (2.3 kg) can be successfully treated.[34] We have successfully treated patients weighing as little as 2.4 kg. Dialysis disequilibrium syndrome occurs when osmotic changes occur rapidly and induce cerebral edema. This is a common concern in traditional intermittent hemodialysis.[2,35,36] Because of CRRT's slow and gradual nature, there are no reports of dialysis disequilibrium occurring in patients receiving this therapy.[37]

CONCLUSION

CRRT is a relatively new modality for the treatment of renal failure and toxicosis. Its slow, continuous blood processing and variety of blood purification techniques more closely approximate the normal function of the kidneys than does traditional hemodialysis. The units are portable, allowing for cage-side operation and monitoring. The judicious use of preformulated fluids eliminates the need for the cumbersome water treatment equipment often associated with intermittent dialysis. The CRRT units themselves are virtually maintenance free. Nevertheless, monitoring and care of the patient 24 hours a day until renal function returns is a significant undertaking. While CRRT has the potential to become more widely accessible than intermittent dialysis, its cost, required expertise, and intensive nature will likely limit its availability to a relatively small number of referral institutions.

Centers Offering Continuous Renal Replacement Therapy

Advanced Critical Care and Internal Medicine
Tustin, CA
949-654-8950
Dr. Ravi Seshadri

California Animal Referral and Emergency
Santa Barbara, CA
805-899-2273
Dr. Deanna Purvis

The Center for Specialized Veterinary Care
Westbury, NY
516-420-0000
Dr. Diane Levitan

Chicago Veterinary Kidney Center
Buffalo Grove, IL
847-459-7535
Dr. Jerry Thornhill

City of Angels Veterinary Specialty Center
Culver City, CA
310-558-6100
Dr. Richard Mills

Louisiana State University
Baton Rouge, LA
225-578-9600
Dr. Mark Acierno

Veterinary Specialists of South Florida
Cooper City, FL
954-432-5611
Drs. Jeff Toll, Brian Roberts, Stacy Armstrong

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ARTICLE #1 CE TEST

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1. The movement of molecules from an area of high concentration to an area of lower concentration is called

a. *diffusion.*
b. *convection.*
c. *adsorption.*
d. *ultrafiltration.*

2. Which feature is not common to all current blood purification techniques?

a. use of diffusion
b. use of semipermeable membranes
c. need for central venous access
d. need for anticoagulation

(continues on page 280)

Continuous Renal Replacement Therapy

(continued from page 272)

3. Which is not a complication associated with CRRT?

a. hypotension
b. spontaneous bleeding
c. dialysis disequilibrium
d. clot formation

4. CRRT regularly uses all of the following blood purification techniques except

a. diffusion.
b. adsorption.
c. convection.
d. hemoperfusion.

5. How does CVVH differ from SCUF?

a. SCUF uses diffusion as the primary blood purification technique.
b. CVVH replaces the ultrafiltrate.
c. CVVH uses adhesion as the primary blood purification technique.
d. CVVH is intended for the correction of overhydration only.

6. Which is the primary use for SCUF?

a. treatment of toxicosis
b. correction of overhydration
c. treatment of acute renal failure
d. treatment of inborn errors of metabolism

7. _____ is not an indication for CRRT.

a. Anuric renal failure
b. Toxin exposure
c. Chronic renal failure
d. Oliguric renal failure

8. Which CRRT modalities use diffusion to purify blood?

a. SCUF and CVVH
b. CVVH and CVVHDF
c. CVVHD and CVVHDF
d. SCUF and CVVHD

9. Which of the following is not an advantage of CRRT over intermittent hemodialysis?

a. cage-side use
b. superior uremic control
c. reverse osmosis water treatment facilities
d. high degree of control over electrolytes

10. The ability of CRRT to remove a toxin does not depend on the toxin's

a. ionic nature.
b. size.
c. protein binding.
d. volume of distribution.