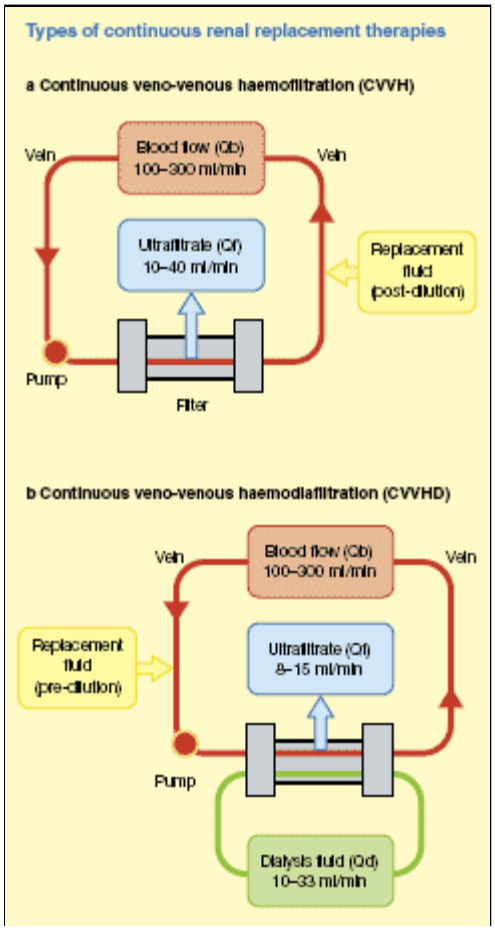
Renal replacement therapy

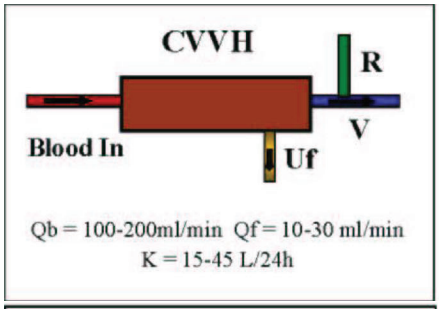
Size of molecules cleared by continuous renal replacement therapies (CRRT)

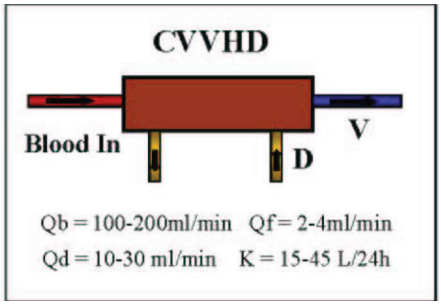
Type of molecule	Size	Example	Mode of removal
Small	< 500 Da	Urea, creatinine, amino acids	Convection, diffusion
Middle	500–5000 Da	Vitamin B_{12}, inulin, vancomycin	Convection better than diffusion
Low molecular weight proteins	5000–50,000 Da	β_2 microglobulin, cytokines, complement	Convection or absorption (on to filter)
Large proteins	> 50,000 Da	Albumin	Only minimal removal by standard CRRT

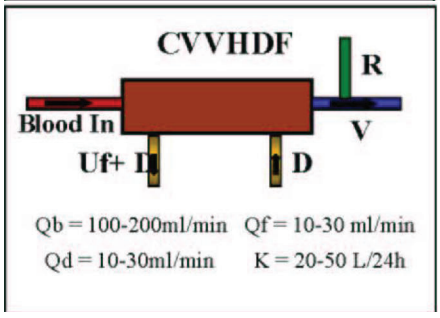
Da = Daltons

Blood is usually pumped through the dialysis circuit at the highest achievable flow rate (100–200 ml/minute); this depends on the quality of vascular access and the patient's haemodynamic state. A specialised, sterile fluid (replacement fluid) replaces the large volume of ultrafiltrate removed. There is no consensus on how long or how fast haemofiltration should be undertaken, but an ultrafiltration rate of at least 35 ml/kg/hour has been associated with improved survival compared with 20 ml/kg/hour. In practice, about 2 litres of ultrafiltrate are removed each hour. Either all or part of the ultrafiltrate is replaced, depending on the desired overall fluid balance.









Convective techniques such as continuous venovenous hemofiltration (CVVH)

generally utilize ultrafiltration rates of 1 to 3 liters per hour. However, high-volume hemofiltration with 6 liters of ultrafiltrate produced every hour has been used to remove middle- and large-molecular-weight cytokines in sepsis

In contrast to intermittent hemodialysis (HD) and slow low- efficiency dialysis (SLED), diffusion-based continuous techniques have dialysate flow rates that are significantly slower than the blood flow rates (17–34 mL/min versus 100–200 mL/min); this difference results in complete saturation of the dialysate.

Small molecules are preferentially removed by these methods.

Solute removal in CRRT is governed by the characteristics of the membrane, the force applied (convection, diffusion, adsorption, or a combination), and the site of infusing the replacement fluid (pre versus post filter). The sieving coefficient [SC = solute concentration in ultrafiltrate (UF)/(solute concentration in plasma at filter inlet plus plasma concentration at filter outlet/2)] describes the properties of the membrane that dictates solute removal in convective circuits. Protein-bound solutes or those that exceed the molecular weight cutoff (generally 20,000 daltons for polysulfone and polyacrylonitrile membranes) have sieving coefficients less than 1.

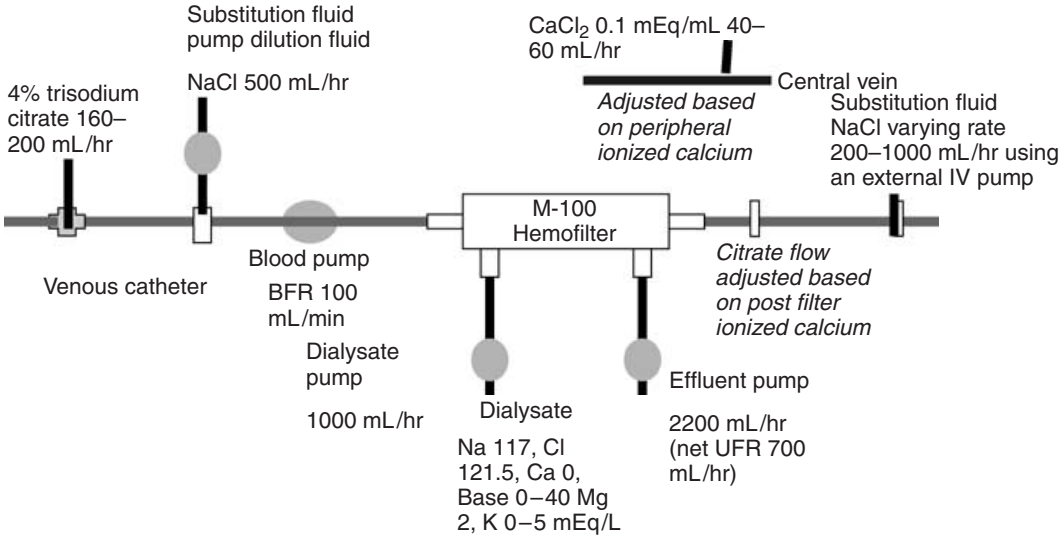
In all forms of CRRT, the "effluent" from the filter represents the end product of the filtration process and comprises the ultrafiltrate in CVVH, the spent dialysate in CVVHD, and the combination of the ultrafiltrate and spent dialysate in CVVHDF.

Continuous renal replacement therapy techniques vary in their ability to remove small and middle molecules. For small-sized solutes (for example, urea nitrogen, creatinine, phosphates), filter clearances were directly proportional to the effluent volume and did not vary significantly with convective or diffusive removal across a spectrum of effluent volumes (0.5–4.5 L/hr)

Drug removal largely depends on the sieving coefficient of the drug, the degree of protein binding, and the ultrafiltration rate.

Clearance of molecules in CRRT circuits also depends on the site of replacement

solution administration either pre or post filter (Fig. 1). Removal of ultrafiltrate across the filter concentrates the cellular elements and proteins in the blood emerging from the filter and is directly proportional to the ratio of ultrafiltrate to plasma flow rate (filtration fraction = FF). Previous studies have demonstrated that FF >20% contributes to reduced filter performance and filter clotting. Consequently, if UF rates are increased, the blood flow rate should be increased to maintain FF less than 20%.



. 1. CRRT circuit using regional citrate anticoagulation with the Gambro PRISMA machine and M-100 filter.

Table 1. Comparison of techniques

	IHD	SLED/EDD	SCUF	CVVH[a]	CVVHD[a]	CVVHDF[a]	PD
Access	VV	VV	AV or VV	VV	VV	VV	Peritoneal catheter
Membrane permeability	Variable	Variable	High	High	High	High	Peritoneal
Anticoagulation	Short	Long	Prolonged	Prolonged	Prolonged	Prolonged	None
Blood flow rate *mL/min*	250–400	100–200	<100	200–300	100–200	100–200	–
Dialysate flow *mL/min*	500–800	100	0	0	16.7–33.4	16.7–33.4	0.4
Filtrate *L/day*	0-4L	0-4L	0-4L	24–96	0	24–48	2.4
Replacement fluid *L/day*	0	0	0	21.6–90	4.8	23–44	0
Effluent saturation%	15–40	60–70	100	100	85–100	85–100	
Dialysate base	Acetate + bicarbonate	Acetate + bicarbonate	–	–	Lactate, bicarbonate, none (citrate)	Lactate, bicarbonate, none (citrate)	Lactate, bicarbonate
Replacement fluid base	–	–	–	Lactate, bicarbonate	–	Lactate, bicarbonate	–
Solute clearance mechanism	Diffusion	Diffusion	Convection	Convection	Diffusion	Both	Both
Urea clearance *mL/min*	180–240	75–90	1.7	16.7–67	21.7	30–60	8.5
Duration *hours*	3–4	8–12	Variable	>24	>24	>24	>24

Abbreviations are: SCUF, slow continuous ultra-filtration; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration. Modified from Mehta RL [87].

[a] In the absence of pumps, arteriovenous circuits can be utilized to provide continuous therapy (CAVH, continuous arteriovenous hemofiltration; CAVHD, continuous arteriovenous hemodialysis; CAVHDF, continuous arteriovenous hemodiafiltration). A key limitation of AV methods is that the blood flow rate cannot be controlled and, consequently, the ultrafiltration rates and solute clearances are variable.

When replacement fluid is infused post filter, solute clearance is equal to SC × Qef.

Dialysate "flow across" the membrane markedly improves clearances by diffusion and retains the simplicity of the procedure. Combining convection and diffusion allows flexibility in enhancing middle- and small-molecule clearances by increasing the volume of ultrafiltrate and dialysate, respectively [3, 4, 12, 13]. Additionally, since overall solute clearance is derived from both convective and diffusive components, it is easier to maintain FF within the optimal range at a relatively low blood flow rate. Adsorptive clearances depend upon the selective or non-selective binding of molecules to the filter membrane. In general, the adsorptive capacity varies and, depending on the membrane's surface area and binding characteristics, saturation of adsorptive sites will occur before the filtration capacity is reduced. Adsorptive clearances for middle molecules are time-dependent, with maximal values occurring in the initial few hours of therapy [6]. In septic patients treated with CRRT, filter adsorption was saturated within 6 to 8 hours

Table 2. Comparison of small, middle and large solute clearances across various modalities

		Parameter	Modality	
Solute		CVVH	Daily HD	SLED
Urea Nitrogen	TAC	40.3	64.6	43.4
	EKR	33.8	21.1	31.3
Inulin	TAC	25.4	55.5	99.4
	EKR	11.8	5.4	3.0
Beta 2 Microglobulin	TAC	9.4	24.2	40.3
	EKR	18.2	7.0	4.2

Abbreviations are: TAC, time averaged concentration (mg/dL); EKR, equivalent renal clearance (mL/min) = G/TAC; CVVH, 31/hr, pre-dilution; Daily HD, BFR 350 mL/min, dialysate flow rate 600 mL/min, 4 hrs session 6 times per week; SLED, BFR 200 mL/min, dialysate flow rate 100 mL/min, 12 hrs session 7 days per week.

G = generation based on a 70 kg patient with initial volume excess of 10 liter, initial blood urea nitrogen (BUN) 90 mg/dl, initial inulin 100 mg/L, initial β2M 20 mg/L, nPCRv 1.8 g/kg/d, inulin G 0.3 mg/min, β2M G 0.17 mg/min.

Modified from Liao Z [15].

A consequence of all CRRT methods is the ongoing loss of bicarbonate and electrolytes across the filter generally equivalent to the plasma concentration of these solutes times the total effluent (ultrafiltration and dialysate) flow rates [20]. Bicarbonate losses can be replaced by addition of sodium bicarbonate or other base (for example, lactate, acetate, citrate)

When base solutions other than bicarbonate are used, replacement of buffer stores depends on the metabolic rate for conversion to bicarbonate. In the absence of lactic acidosis, endogenous lactate clearance does not appear to be impaired. However, the filter clearance of lactate accounts for only 2.4% of overall lactate

clearance [28].

The beneficial role of bicarbonate as buffer instead of lactate has been investigated [29]. Hilton et al [25] have shown that bicarbonate-based solutions are associated with improved hemodynamic stability, although no difference was found by Thomas et al [26], who compared lactate- and bicarbonate-based solutions. Additional clinical studies have confirmed that lactate-based substitution fluids foster hemodynamic stability [30].

One practical issue with the use of bicarbonate-based solutions is that it is difficult to store premixed bicarbonate solutions.

Another factor to consider is that premixed solutions containing calcium and bicarbonate show evidence of microprecipitation of calcium carbonate crystals, and this should be avoided [35]. Citrate-based anticoagulation offers an alternate method for acid-base management, as the citrate is converted in the liver and muscle to bicarbonate. The combination of citrate anticoagulation and bicarbonate-containing solutions has been used effectively to manage complex acid-base disorders [23, 36–39].

The ultrafiltration rate used depends on two factors: the type of technique and the fluid balance requirements of the patient. Most modern CRRT pumped systems have a wide range of ultrafiltration rates that depend on the modality used. In convective techniques (CVVH), the ultrafiltration rate can vary from 0.5 to 12.0 L/hr, although most centers use a range of 1.0 to 3.0 L/hr. When dialysate is used (CVVHDF), almost all the current machines limit ultrafiltration rate to a maximum of 2 L/hr. These operative ranges are more than sufficient to achieve adequate fluid removal in almost all patients.

Table 4. CRRT prescription using the Gambro PRISMA machine and M-100 filter

	Setting	Rationale
Machine	Gambro PRISMA	Available machine
Modality	CVVHDF	Allows combination of diffusive and convective clearance. Consequently, UF rates can be limited and do not require high blood flow rates for filtration fraction (FF).
Membrane	M-100	0.9 m^2 AN69 polyacrylonitrile membrane adequate for clearances required.
Blood flow rate	100 mL/min	Not constrained by access, adequate flow for maintaining filtration fraction <25%.
Anticoagulation	4% tri-sodium citrate	At access exit through three-way stopcock to chelate ionized calcium and prevent clotting. Rate 160-200 mL/hr adjusted to maintain post-filter ionized calcium 0.25–0.4 mmol/L. Provides base from conversion of citrate to bicarbonate.
	0.1 mEq/mL calcium chloride	Replaces calcium removed across filter, administered through separate central line at initial flow rate of 40–60 mL/hr and adjusted to maintain peripheral ionized calcium of 1.12–1.32 mmol/L.
Effluent volume	2.2 L/hr	Allows small solute clearance of approximately 37 mL/min, adequate clearance to compensate for catabolic state and for reduction due to partial pre-dilution.
Dialysate flow rate	1 L/hr	Slower than blood flow rate with complete saturation of dialysate for small solutes. Diffusive clearance = 16.7 mL/min.
Pre-dilution fluid	0.5 L/hr	Administered pre-filter, pre-pump dilutes blood entering the filter with filtration fraction of 25%.
Post-filter replacement fluid	0.7 L/hr	Administered post filter in venous circuit. Volume greater than all anticipated intake to allow fixed effluent volume and clearance. Volume adjusted hourly to achieve desired fluid balance.
Dialysate fluid composition	0.45% saline + 40 mEq of Na as $NaHCO_3$ or NaCl + Mg 2.0 mEq/L + 2–5 mEq/L KCl + 0.1% dextrose	Low sodium (117 mEq/L) allows removal of sodium load in tri-sodium citrate (Na = 420 mmol/L, citrate 140 mmol/L), varying amounts of bicarbonate added to provide extra base for correction of acidosis and compensate for bicarbonate loss across filter, no calcium allows removal of citrate-calcium chelate.
Pre-dilution fluid composition	0.9% saline	Isotonic for diluting blood.
Post-filter fluid composition	0.9% saline, 0.45% saline + 75 mEq/L of sodium bicarbonate, sterile water + 150 mEq/L of sodium bicarbonate	Normal saline adequate to maintain normal sodium levels. Additional bicarbonate added to solutions depending on acid-base status and bicarbonate requirement.
Monitoring	Serum electrolytes and blood gases	Initially every 12 hours then every 24 hours, adjust solutions composition.
	Post-filter ionized calcium	Every 12 hours: adjust citrate flow rates.
	Peripheral ionized calcium	Every 12 hours: adjust $CaCl_2$ drip.
	UF/plasma urea nitrogen	Every 12 hours: assess filter efficacy and allow pre-emptive change in filter if ratio <0.6.
	Fluid balance	Set goals q 24 hours and monitor and adjust fluid balance by varying amount of replacement solution hourly to achieve target balance desired.

Two factors tend to dissuade nephrologists from initiating dialysis in the intensive care unit. First, there are well known risks of the dialysis procedure, including hypotension, arrhythmia, and complications of vascular access placement [40]. Second, there is a strong concern that some element of the dialysis procedure will slow the recovery of renal function and increase the risk of end-stage renal failure [41, 42]. Long-standing data have showed renal lesions consistent with fresh ischemia in experimental animals and humans dialyzed without systemic hypotension, long after their initial renal injury [43, 44].

CVVHDF was selected to provide diffusive and convective clearance of 37 mL/min (approximately 30 mL/kg/hr).

The present case would require an ultrafiltration rate of about 2520 mL/hr by Dr. Ronco's previous study [67]. But even in that paper only 80% or 85% of the

patients were able to achieve that 35 mL/kg of ultrafiltration. And in practice, some patients weigh 90 kg or more. How do you technically achieve such a high ultrafiltration rate considering that the Gambro Prisma has a maximal blood flow rate of 180 mL/min that would allow an ultrafiltration rate of up to 1000 mL/hr at usual settings?

So we got the same amount of solute clearance but the equivalent convective clearance of 1500 mL/hr. That's one way to get around it if you are looking purely at small solute clearance. If you wanted to achieve 35 mL/kg/hr of middle molecule clearance, then certainly you would have to ratchet up the blood flow rates. And the current versions of some of the machines do make it limiting for the blood flow rate.

Studies have demonstrated, however, that changing the filters every 12 hours might be required to reduce cytokine levels [13, 14]. However, the difficulty is knowing when

Yes; several published studies, including our own experience, clearly demonstrate that citrate anticoagulation offers better filter life, better filter performance, and less bleeding risk in comparison to heparin [23].

When the creatinine clearance was about 15 mL/min, that seemed to be a cutoff when you could easily stop CRRT.

GAMBRO

- Small molecules easily pass through a membrane driven by diffusion and convection.
- Middle and large size molecules are cleared primarily by convection.
- Semi-permeable membrane remove solutes with a molecular weight of up to 50,000 Daltons.
    - **A sieving coefficient of 1 will allow free passage of a substance; but at a coefficient of 0, the substance is unable to pass.**
        - **.94 Na+**

    - **1.0 K+**
    - **1.0 Cr**
    - **0 albumin will not pass**
- **Hemofilter membrane are composed of:**
    - **High flux material**
    - **Synthetic/biocompatible material**
- **Structural design is characterized by:**
    - **High fluid removal**
    - **Molecular cut-off weight of 30,000-50,000 Daltons.**

Other stuff

Lactate has a low molecular weight, and is therefore readily ultrafiltered and dialyzed. Its elimination is comparable with that of urea, with an extraction ratio of nearly 25%. Its elimination by hemofilter is proportional to the blood lactate concentration, leading to a lactate clearance of nearly 25 mL/min. Although the extraction ratio for lactate by the hemofilter is high, the amount of lactate removed by continuous venovenous hemofiltration with dialysis is negligible when compared with the whole plasma lactate clearance. Continuous venovenous hemofiltration with dialysis was responsible for <3% of the total lactate clearance in our critically ill patients. Therefore, continuous venovenous hemofiltration with dialysis cannot mask an overproduction of lactate, and the blood lactate concentration remains a reliable marker of tissue hypoxia in these patients.

We found a lactate-sieving coefficient close to 1, which means that lactate hemofilter clearance was comparable with the ultradiafiltration flow rate.

The importance of clearance of middle-molecular-weight solutes (500 to 30,000 daltons) with respect to clinical outcomes has long been debated.[10] Current high-f lux hemodialysis membranes have larger pores than did earlier-generation membranes, and they permit the passage of larger uremic toxins. Since the β_2-microglobulin concentration is easy to measure, it is frequently used as a marker solute for middle-molecular-weight solutes. Several retrospective, observational studies have suggested an association between the use of high-f lux hemodialysis membranes and reduced mortality.[11-14] However, increased clearance of middle-molecular-weight solutes has not been conclusively shown to be an important factor in a well-powered, prospective, randomized trial.

the rate of death during the first year of hemodialysis therapy exceeding 20%

Pathophysiology of RRT

Although considerable attention has focused on the perceived benefits of CRRT, there has been less emphasis on the possibility that CRRT might confer increased risk [38]. As a continuous extracorporeal therapy, CRRT requires continuous contact of patient's blood with foreign surfaces. This event activates the coagulation and complement cascade, leukocytes and platelets [39]. Activated leukocytes release inflammatory mediators and induce oxidative stress, transforming lipids and proteins and contributing to endothelial injury. Activated platelets aggregate and stimulate thrombin generation. Thus, bio-incompatibility of RRT materials potentially enhances coagulation and inflammation pathways that are already triggered in the critically ill patients and that RRT is called to treat.

RRT has important metabolic consequences because it is associated with large nonselective solute shifts. In the normal kidney, tubular modification of the glomerular filtrate includes re-absorption of beneficial substances such as amino acids, water-soluble vitamins and trace elements. During RRT these substances are lost, thereby reducing antioxidant defense. Amino acids are lost through the filter and it has been estimated that they represent at most approximately 10% of overall amino acid supplementation [41]. A negative balance of water-soluble vitamins, glutamine, carnitine, selenium and copper has been shown [42]. Zinc is also lost, but total balance appeared to be positive, because the replacement solution contained zinc. These micronutrients are crucial for antioxidant defense [43]. Consequently, patients on RRT need a sufficient intake of protein and micronutrients to compensate for increased losses. Moreover, CRRT corrects metabolic acidosis by removing metabolic acids and replacing buffer. In addition to citrate, lactate and bicarbonate are the most frequently used buffers. If liver function and tissue perfusion are not severely disturbed, and CRRT dose is sufficient, lactate buffering is generally safe and adequate. However, the generation of buffer from lactate requires three molecules of oxygen for each molecule of bicarbonate. Furthermore, with the exclusive use of lactate-based fluids patients develop hyperlactatemia [44]. Even if it is generally postulated that hyperlactatemia is not harmful, it indicates that the infused amount of lactate (about 150–300 g a day depending on CRRT dose) overcomes metabolic capacity [45]. If exogenous lactate supply exceeds the capacity of the citric acid cycle, a higher proportion of lactate is used for gluconeogenesis, which is not energy-effective. In patients with multiple organ failure, lactate buffering (compared with bicarbonate buffering) increased glucose intolerance [45]. Furthermore, RRT may alter actual serum lactate level and impair the utilization of this molecule as a

marker of metabolic acidosis or systemic hypoperfusion.