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ABSTRACT

Continuous renal replacement therapy (CRRT) is a family of extracorporeal treatments which have evolved from simple to complex goals. It began as a monotherapy to lower intravascular volume in an already hemodynamically compromised hypotensive patient. Modern day therapies using the same catch-all name now have lofty goals of reversing the pathophysiology of intermediary metabolism and immunologic disorders. Over several decades a confusing set of abbreviations have emerged. Problems arise when the simpler forms are used for complex goals and vice versa. Presented here is an attempt to simplify the understanding of this heterogeneous therapy by a review of the historical evolution, a review of the goals of subtypes of CRRT, and a review of current cutting-edge therapies which combine renal replacement with other organ rescue therapies. This last management strategy is now becoming commonly known as tandem therapy or multi-system organ support (MOST) therapy. Tandem therapies combine two organ support modalities, and MOST therapy simultaneously uses more than two organ rescue treatments.

CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT) SIMPLIFIED

INTRODUCTION

Having practiced nephrology since 1976 I have seen the progressive improvements in dialysis technology for the past 40 years. I have published in some of the earliest manuals of dialysis procedures (1-3). I have also edited what I consider the first subspecialty textbook of geriatrics, Geriatric Nephrology and Urology (4). With this experience, my goal of this review is to simplify the principles behind the modalities of continuous renal replacement therapy. I plan to do so by discussing three different ways of analyzing CRRT.

1. Goals of elimination – convection, diffusion, together or individually
2. Historical evolution - no pumps to multiple pumps
3. Tandem therapies – CRRT + other eliminations in series

In each category there is a spectrum from gentle low efficiency mono therapy to aggressive high efficiency combined therapies. The terminology for these therapies has evolved as well, and abbreviations are numerous and confusing. Like dialects, there may be regional, national, and international variations. I plan to present an explanation for the goals of these therapies and the common abbreviations in this country and in our practice used to identify them.

GOALS OF ELIMINATION

The basic principles underlying CRRT of any type results from the manipulation of the two types of transfer or eliminations of fluids, electrolytes, or toxic substances from plasma during the common hemodialysis treatment:

conduction or convection, also known as diffusion or ultrafiltration respectively. The conduction or diffusion requires contact between the watery phase of plasma and the watery dialysate through the pores of a dialysis membrane. Conduction or diffusion transfers solutes from the higher concentration (most often the plasma water with high nitrogen or potassium) to the lower concentration (dialysate with zero or specified low concentration). This process reduces the concentration of abnormal toxic products or electrolytes in the plasma which is returned to the patient. Convection or ultrafiltration transfers water droplets with all solutes that are dissolved across the membrane without need of contact with dialysate by a pressure gradient. In most dialysis treatments the two transfers are combined. When blood solute concentrations are lowered there is often a transient gradient set up between the intracellular and extracellular concentrations which create an osmotic force to pull water intracellularly to create cellular edema. This produces symptoms called disequilibrium. See figure 1 below. Also this intracellular fluid shift sequesters fluid instead of allowing it to be eliminated and thus creates a resistance to lowering total body fluid. The rebound back to the intravascular space as solutes re-equilibrate then resists efforts to control fluid overload which may be embarrassing cardiac function or oxygenation of alveoli. CRRT began to isolate the convection or ultrafiltration so as to correct fluid overload states without worsening borderline blood pressure by avoiding the intracellular sequestration of fluid. In fact it was discovered to be well-tolerated and effective even in hypotensive patients without adding any further lowering of blood pressure and improving cardiac function by moving contractility back up the Starling curve.

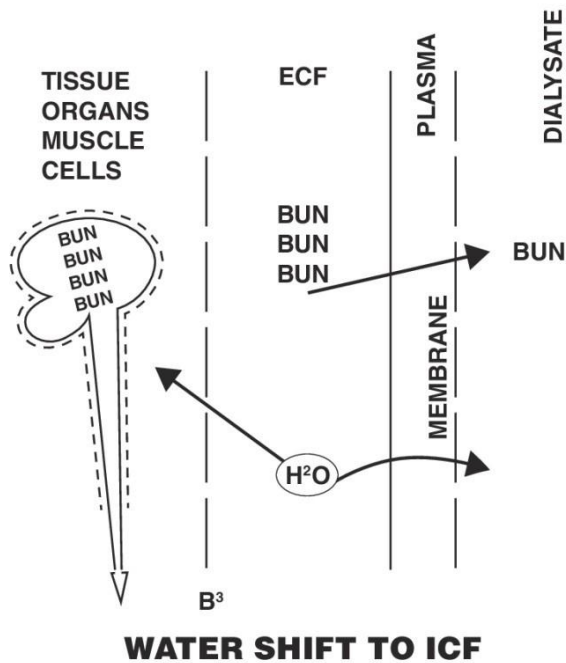


Figure 1. Disequilibrium from combined diffusion (conduction) and ultrafiltration (convection) to create organ internal fluid shifts, symptoms of organ (brain) edema, and hypotension (due to two-way fluid losses from intravascular volume). The abbreviation B3 represents blood brain barrier; ECF is extracellular fluid, ICF represents intracranial fluid; BUN is blood urea nitrogen.

HISTORICAL EVOLUTION – Mini-kidney to Hemodiafiltration

The beginning of CRRT occurred in the late 1970’s and early 1980’s. A highly porous dialysis-type membrane called a hemofilter was developed which could ultrafiltrate large

volumes of fluid with just a pressure gradient of mean arterial pressure compared to zero pressure in the filter(5). The red blood entered and the yellow (nitrogen rich) fluid flowed into a collection bag. Truly artificial urine was created. Originally, neither an infusion fluid nor heparinization was used, so the catheters, tubing, and filter were often laid in bed next to the patient, covered with the sheet and blanket, and the isolated ultrafiltration was invisible to the casual observer. This process became colloquially known as the mini-kidney, used first in the setting of cardiogenic shock to lower intravascular volume without the secondary shift of fluid in order to avoid further hypotension. As the heart muscle moved back up the Starling curve and the left ventricle was unloaded, the hypotension often improved with the fluid removal. Figure 2 illustrates a “mini-kidney.”

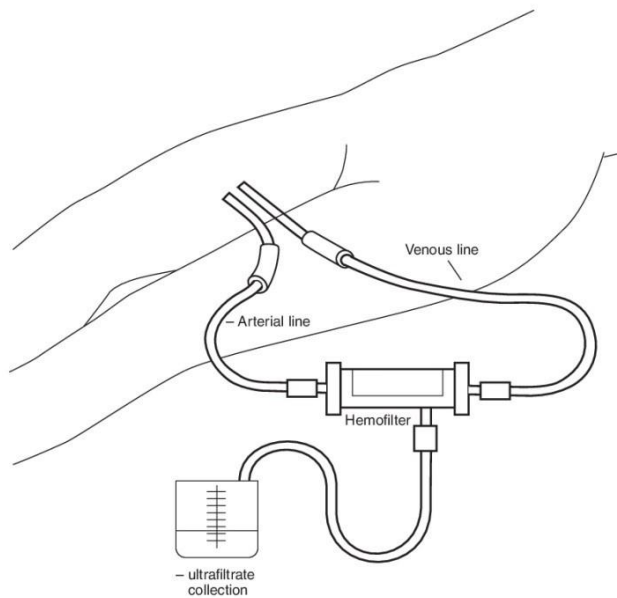


Figure 2. The patient's own mean arterial pressure delivers blood to the hemofilter and returns it to the patient by the venous line. The mean arterial pressure creates a positive pressure in the hemofilter to create transfer of plasma water (convection) into a collecting bag of artificial urine or ultrafiltrate.

The next step was using pumps to add or subtract fluid delivery to and from the hemofilter. This was originally done by pumps commonly used to deliver intravenous (iv) fluids. Thus was born convection with pre-filter

or post-filter dilution (continuous arteriovenous or continuous venovenous hemofiltration also known as CAVH or CVVH). Over time the simplicity of using double-lumen venous catheters led to the elimination of CAVH in favor of CVVH.

Figures 3-6 demonstrate where pumps were added to accelerate the various transfers and eliminations of fluids, low molecular weight solutes, middle molecular weight metabolic toxins, toxic drugs, toxic intermediary metabolites or immunologic substances which mediate inflammation, sepsis, and microangiopathic coagulation.

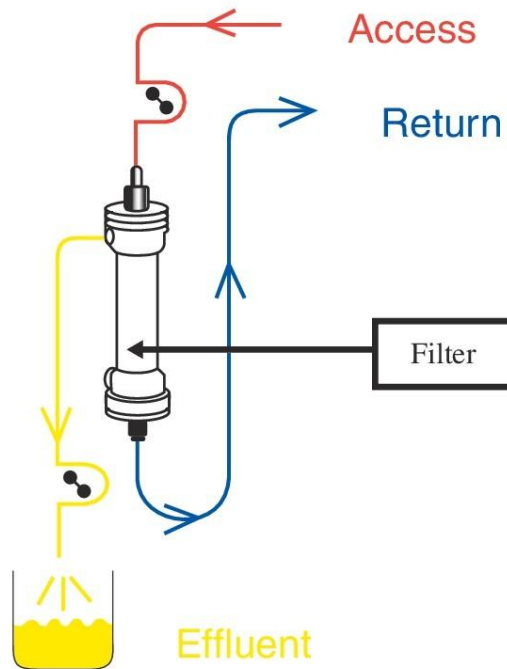


Figure 3 – Slow continuous ultrafiltration (SCUF). A pump was added to remove blood through vascular tubing at a modest flow rate from the patient (red line), deliver it to the hemofilter at approximately 250-300 cc/min, and push it back to the patient (blue line or tubing). A second pump

creates negative pressure in the hemofilter (convection) to ultra-filtrate blood into an artificial urine (effluent). A known coefficient is known for each hemofilter which when multiplied by the negative pressure created by the second pump will equal the cc/hour which will be delivered as effluent.

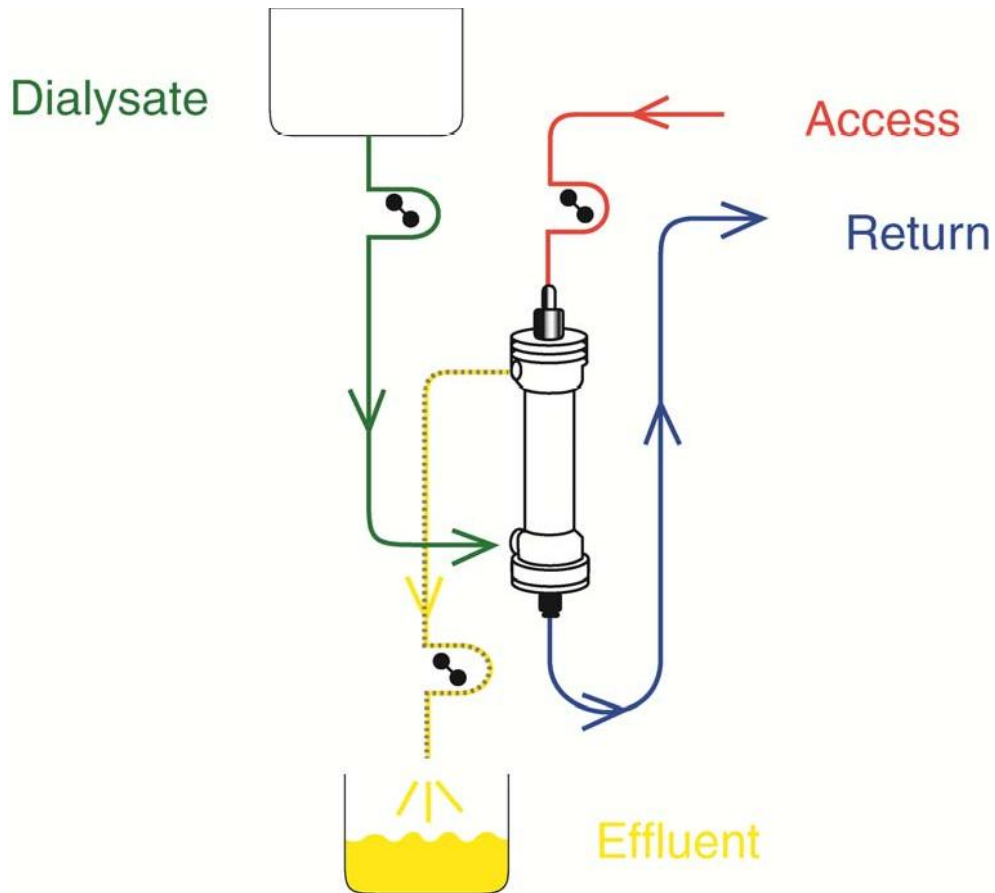


Figure 4. Continuous venovenous hemodialysis (CVVHD). Dialysate is delivered by a pump through the filter across the dialysate membrane from the blood, and ultrafiltration is accomplished by still an additional (negative pressure) pump. No pre-filter dilution is accomplished. This is similar

to a conventional dialysis, but at lower blood pump speeds and lower dialysate flow speeds. In this treatment dialysis and ultrafiltration are both occurring but less efficiently because both the blood delivery and dialysate delivery are very low, 200-250 cc/min blood flow and 200-600 cc/min dialysate flow.

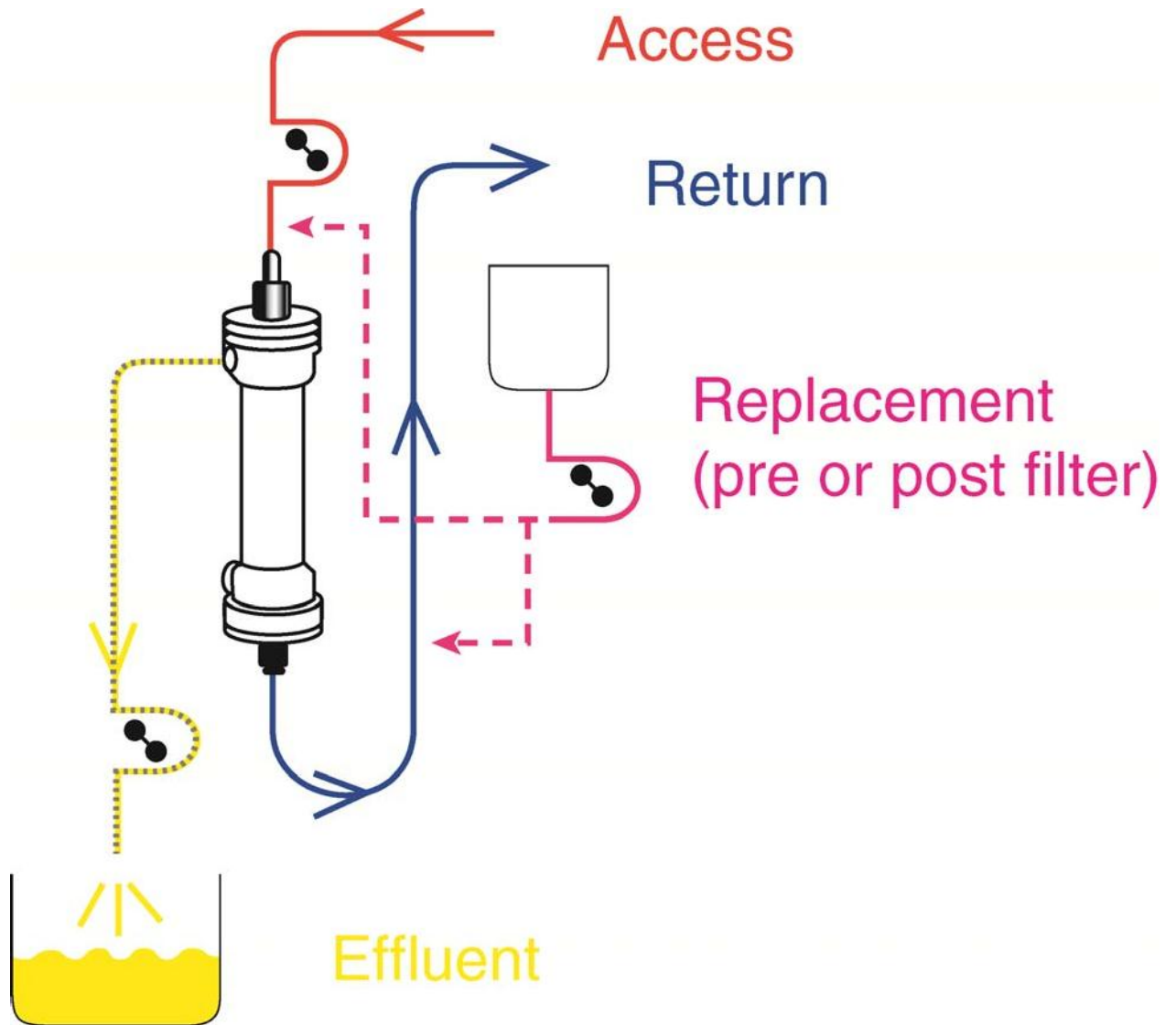


Figure 5. Continuous venovenous hemodiafiltration (CVVH) is a high convection rate (~35 mL/Kg/hour) combined with a prefilter hemodilution by a replacement solution. The high convection and large

prehemofilter allow removal and dilution of small molecular weight solutes as well as potentially toxic middle molecules (guanadino-succinic acid, interleukens, other pro-inflammatory molecules, and procoagulant precursors).

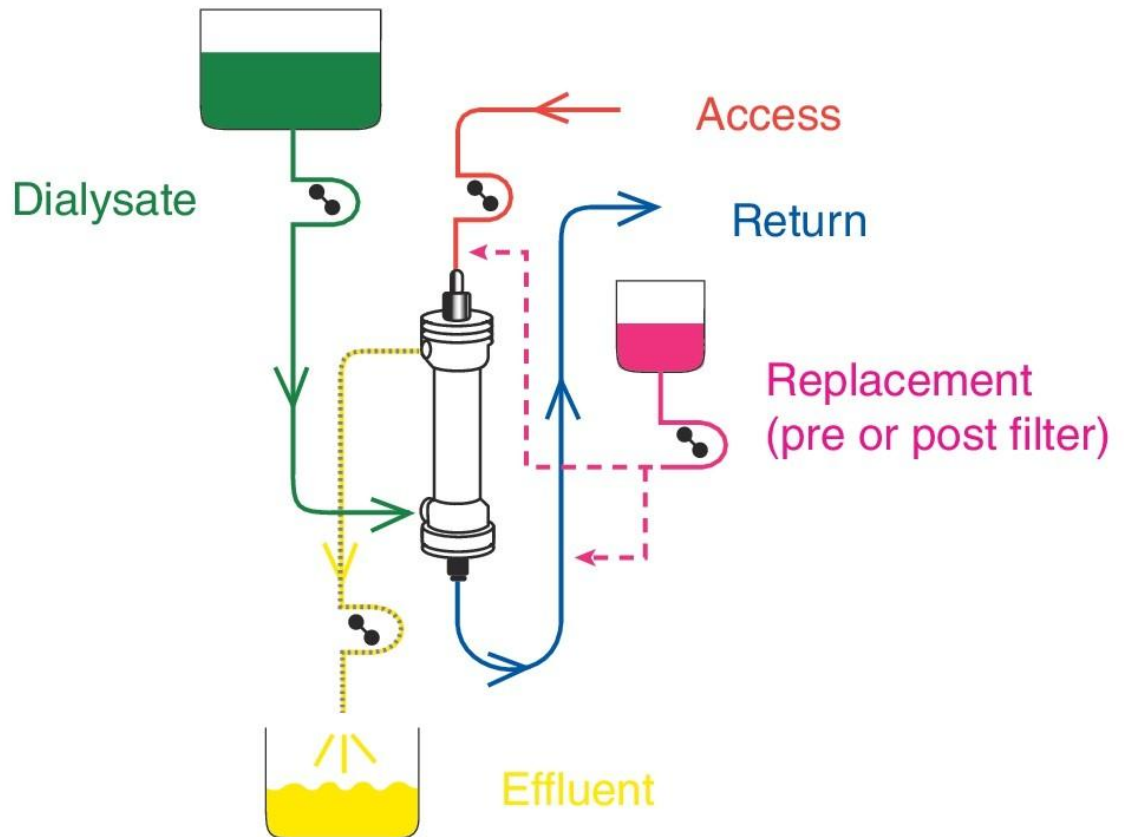


Figure 6. Continuous venovenous hemodia filtration and dialysis (CVVHDF) adds back some diffusion (conductive transfer) to the high rate of convection. This strategy will lower more rapidly small molecular weight solutes like potassium without creating as much disequilibrium as does a conventional dialysis. The dialysate and replacement fluids are clear solutions but are colored in this figure for ease of following the flow directions.

Later, machines were produced which consolidated all pumps into one computer coordinated device and to hold all the bags of administered solutions or eliminated fluids (Figure 7). There are several manufacturers of these CRRT machines which have a similar appearance and purpose – multiple pumps and multiple solutions/fluids.



Figure 7 –CRRT machine in which all pumps are located on one platform and all dilution solutions and collection bags are also in one location hanging from poles and hooks. As above there are several manufacturers of such equipment.

At present these machines provide 4 types of therapeutic modalities: slow continuous ultrafiltration (SCUF), continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), Continuous venovenous hemodia filtration (CVVHDF). All CRRT machines have the capability to perform any of these therapies with

the proper setup. Which therapy is chosen will be discussed later and depends on the needs of the patient and the preferences of the physicians ordering the therapy.

The subtypes of CRRT were discovered to accomplish different goals:

- 1) SCUF (also called pure ultrafiltration or PUF) is illustrated in Figure 3 and makes use of the isolation of ultrafiltration. In other words, no diffusion occurs because there is no dialysate flow, therefore no movement down a concentration gradient. As a result there are no secondary internal fluid shifts as described above for

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disequilibrium. SCUF will reduce the greatest amount of total body water volume with the least hypotension and is tolerated even in many hypotensive patients.

- 2) CVVH maximizes convective transfer (pressure driving water molecules and all that is dissolved in each droplet of water across the membrane). By administering a replacement fluid (usually pre-filter) to replace the convection fluid, there is a dilution of toxic middle molecular weight molecules (indoles, skatoles, guanadino-succinic acid), intermediary metabolites, immunologic inflammatory activators including interleukens, and coagulation activators. A convective rate and pre-filter replacement of 35 ml/kg/hour appears optimal for improvement of the pathophysiology of critical illness. Convective transfer reduces the total body burden of these substances, and the replacement isotonic fluid dilutes the residual amounts without changing standard electrolyte concentrations. This form of blood purification approaches a plasma exchange. This modality is shown in Figure5.
- 3) CVVHD is a slow gentle form of a usual dialysis treatment with very slow blood and dialysate flow rates and thus both diffusion and convection are of low efficiency. It would be equivalent to slow low efficiency diffusion or dialysis (SLED or SLEDD) therapy which

will be described in the next section. It will slowly and steadily remove small molecules but will not remove medium sized molecules and toxins from the body. The small molecules will include potassium, hydrogen ion, lithium, aspirin, small alcohols, phenobarbital, theophylline, and metformin than CVVH. This form of therapy works well to avoid a rebound of abnormal levels because once set up, it runs for many hours at a slow and steady pace. Rebound can occur when there is enterohepatic circulation, sustained metabolic acidosis, bezoars which sequester ingested substances, or lipophilic substances which have a high volume of distribution. This modality is shown in Figure4.

- 4) CVVHDF combines subtypes #2 and #3 forms of CRRT so there is the high rate of convection but also a low flow of dialysate. This form of therapy continues the convective transfer as described for CVVH but also adds back a gentle diffusion transfer which will more rapidly reduce concentrations of small solutes across the semipermeable membrane than convection and dilution alone. This form of CRRT does not avoid disequilibrium to the same extent as SCUF or CVVH and therefore will result in more hemodynamic in stability.

5) *SLEDD*

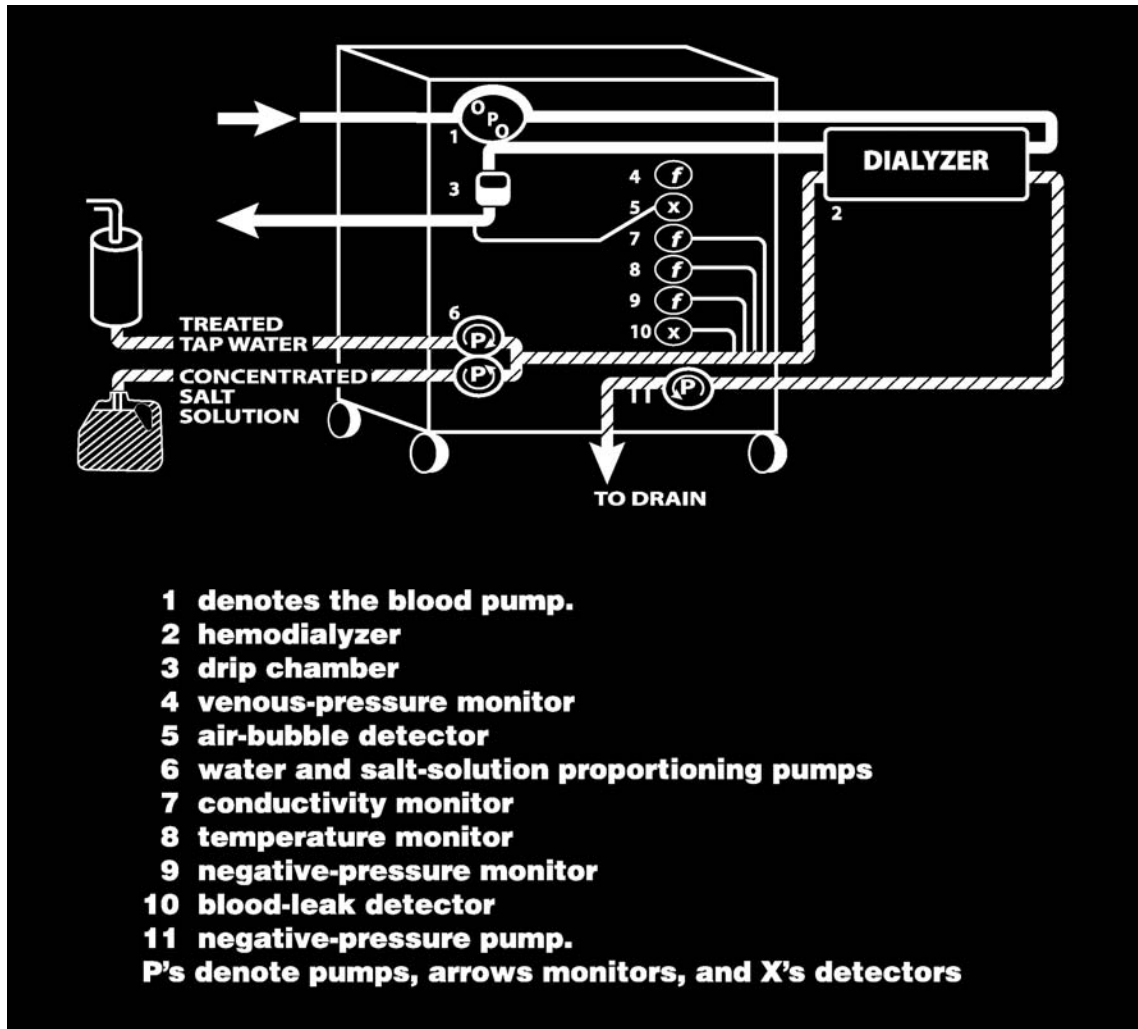
Is sustained low efficiency diffusion or dialysis. It is often shortened to slow low efficiency dialysis or SLED. It was developed when it was clear that the #3 type of CRRT could be implemented with a conventional

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hemodialysis machine (Figure 8) by slowing the blood and dialysate flow speeds markedly downward. Because of the slow speeds it was understood that once initiated, the dangers of a usual hemodialysis treatment would be minimal and easily correctable. The dangers of air emboli, blood leak, water treatment errors, dialysate mixture and delivery errors could easily and quickly stopped and corrected by intensive care unit (ICU) nurses with some

additional training. The hemodialysis team could set SLEDD up and move on to another patient while the ICU team managed the SLEDD. Also, there would be lack of need for capital expenditure for additional equipment besides the usual dialysis machines. The main drawback is that it is not as versatile in separating or combining ultrafiltration and convection from dialytic (diffusion) concentration reductions of electrolytes.

Medical Research Archives, Volume 5, Issue 5.May Issue.
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Figure 8. Conventional dialysis machine whose pumps can be slowed to create a CVVHD called slow low efficiency dialysis (SLED or SLEDD). This form of therapy uses the same machines as used in conventional dialysis, is better tolerated with less disequilibrium due to less efficient solute diffusion rates, and can run for a variable duration by bedside intensive care staff after being set up by the dialysis team.

A collaborative group of New York and Midwest dialysis centers compared several common practice variations of SLEDD in critically ill patient (6). The differences from one institution to another usually are due to the duration SLEDD is continued per treatment session. The collaborative group undertook a retrospective study to evaluate short and long-term duration of the daily SLEDD form of CRRT. Morbidity and mortality were compared in two groups, short-duration (St-SLEDD) and long-duration (C-SLEDD).

The significant differences in the two groups at the time SLED was initiated.

The St-SLEDD group ran for approximately 1 shift or 6 hours per day. The C-SLEDD group ran for approximately a whole day at a time or 21 hours per day. After SLEDD was initiated the urea was lowered significantly more in the C-SLEDD group. There were no significant differences in use of vasopressors, antibiotics, or nutrition. There was a trend toward lower mortality in the C-SLEDD group which did not reach significance as shown in the top panel of Figure 9 below. For further analysis, the patients were evaluated according to tertiles of risk assessment by the Acute Physiology and Chronic Health Evaluation (APACHE) scale on admission to the ICU (Figure 9 middle panel). This is also shown graphically using bar graphs in the same figure.

Comparison C- SLEDD vs St- SLEDD

	St-SLEDD	C- SLEDD	P value
Patients #:	52	32	
Admission Creatinine	3.66±4	3.54±6	NS
Hours/da on SLEDD	6.8±4	21.3	
Days on SLEDD	2.65±4	4.75±8	.0076
Vasopressors [%]	78.9	81.3	NS
Urea Reduction Ratio	38.6± 2.6	71.6±3.6	<.0001
Organ failure	2.3±1	2.56±.1	NS
Admission APACHE II	20.6± 1.2	21.6±1.6	NS
Pre-SLEDD APACHE II	25.4± 1.0	24.8±1.13	NS
Mortality risk	53.8	49.9	
Mortality	75%	65.6%	
Clotting	12%	38%	

**Combined Data
 APACHE tertiles**

Pre-SLEDD APACHE II	<20	20-25	>25
N	22	20	42
Pre- SLEDD APACHE II	17	23	31
APACHE II Mortality risk	25%	45%	73%
Mortality rate (total 71%)	40.9%	85%	81%
Deaths/total	9/22	17/20	34/42

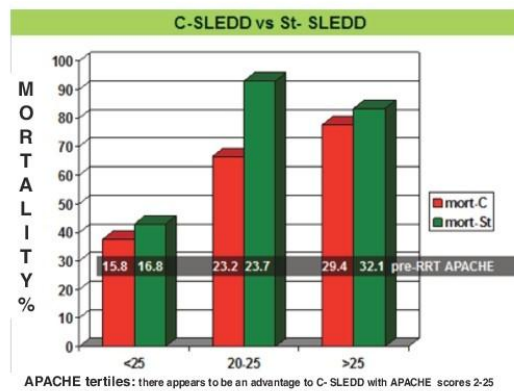


Figure 9. Comparison of shorter duration SLEDD (C-SLEDD) vs. long-duration SLEDD (St-SLEDD). Top panel shows the major differences between the groups: longer duration of therapy and greater reduction in the azotemia. The middle panel shows distribution of patients into tertiles of Acute Physiology and Chronic Health Evaluation (APACHE) risk stratification scores. The lower panel compares the mortality between the two groups in a bar graph format.

We concluded that the lowest APACHE group is at the least risk of dying and so duration of SLEDD likely does not matter since many will recover in either group. Similarly we interpreted the lack of difference in the highest mortality group to mean that this high mortality group will tend to die no matter what intervention is done. But importantly, in the intermediate mortality group with an APACHE score of 20-25, the long duration SLEDD had appeared to favor a better outcome. Obviously further study correctly

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powered to detect differences in outcomes between different durations of SLEDD will be needed. Our data serves as a set of clinical observations that leads to the hypothesis of improved outcomes with longer daily duration SLEDD treatments.

TANDEM AND MOST THERAPIES

When CRRT is combined with a second organ support system, it has recently been called tandem therapy. One of the earliest reports of combining two “life support” modalities was the performance of dialysis in series with cardiopulmonary bypass over 35 years ago(7). CRRT can be combined in series with oxygenation rescue therapies including extracorporeal membrane oxygenation (ECMO). It can be combined with left ventricular assist devices or intraaortic balloon pumps. Also CRRT can add a second filter such as an absorption filter for endotoxin or interleukins (Cytosorb^Tcorporation) or to filter out viral loads of Ebola, hepatitis B, or human immunodeficiency virus (HIV) such as produced by Aethlon^T Corporation. As mentioned above, when more than two organ support therapies are combined, the result has been called multi-system organ support or MOST therapy(8).

SUMMARY

A simple guide to the choice of these various modalities of CRRT is as follows:

SCUF – slow continuous ultrafiltration is used for fluid removal in heart, kidney, or liver failure patients even if they are hypotensive (Figure 3)

CVVH – continuous venovenous hemofiltration is the mainstay for life support in critically ill ICU patients with sepsis, pneumonia, or liver failure and may allow removal of toxic metabolites, toxic immunologic mediators, and toxic procoagulants (Figure 5)

CVVHD –continuous venovenous hemodialysis is not commonly used by our group as it is very similar to hemodialysis and forms the basis for SLEDD (Figure 4).

CVVHDF – continuous venovenous hemodia filtration with dialysis combined CVVH and CVVHD and is not often used by our group (Figure6).

SLEDD – sustained low efficiency dialysis is used when cost of new equipment precludes CVVH. It is not as versatile, using the conventional hemodialysis filter which is less porous than the usual CRRT hemofilter resulting less convection. The slower diffusion is often better tolerated due to less disequilibrium, but eventually sustains the slow correction of electrolytes and acid/base balance. It is thought that today’s conventional hemodialyzers remove more middle molecules and toxic immunologic substances than the first generation of hemodialysis filters (Figure 8).

CONCLUSIONS

Once thought of as a last ditch effort to “rescue” seriously ill patients, CRRT is now frequently used early in the management of acute kidney injury in patients in the ICU. The slow but steady nature of fluid/electrolyte and acid/base corrections are well-tolerated, and once set up they run mostly on automatic pilot for a shift or a day or two before requiring takedown and repeat set up. The monitoring can be handled by ICU bedside nurses with additional training which frees up the dialysis team to do other patient conventional hemodialysis treatments. In addition, CRRT modalities appear to have the added benefit of a more porous membrane which may remove toxic immunologic substances or procoagulant factors which promote organ failure. Expansion of the scope of therapy to tandem, MOST, newer absorption therapies, and new virus filtration therapies continue to add to their potential usefulness.

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