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Continuous Hemofiltration/Dialysis: Current Status and Future Directions

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Introduction

There is a growing consensus that continuous renal replacement therapy[1-4] is preferable to intermittent renal replacement in treating patients with acute renal failure (ARF). Continuous therapies are not associated with the rapid «unphysiologic» shifts in fluid and solutes which characterize intermittent hemodialysis (IHD). Conventional IHD utilizes diffusion based transport of solutes and fluid across cellulose acetate and cuprophane membranes. New membranes which use polysulphone, polyacrylonitrile or polyamide as the basic material are more permeable than IHD membranes and have a higher molecular weight cut off for enhanced clearance of middle molecules[5]. Alternate renal replacement therapies have evolved with the availability of these membranes[6]. Continuous arteriovenous hemofiltration/dialysis (CVH/CAHD) is a new therapy rapidly gaining acceptance worldwide as the treatment of choice for ARF in critically ill, hemodynamically unstable, patients[7-10]. This review describes the current status of these techniques and discusses the newer developments in this area.

Evolution and nomenclature

Althoug the concept of continuous dialysis was advocated as early as 1960 by Scribner and his colleagues[11], intermittent hemodialysis (IHD) became the standard therapy and remains the commonest form of treatment for ARF. Peritoneal dialysis (PD) was the first form of continuous renal replacement (CAPD, CCPD) became available largely because it uses a highly permeable natural membrane. While useful for chronic renal replacement, its utility in ARF is limited[12]. All continuous renal replacement use membranes highly permeable to water and low molecular weight solutes. In its most basic form, termed **Slow Continuous Ultra-Filtration (SCUF),** fluid is removed by ultrafiltration. The ultrafiltrate has the composition of normal plasma and is not replaced. Solute clearance is minimal. SCUF is used predominantly for fluid management in patients undergoing cardiac surgery[13]. In **Continuous Arteriovenous Hemo-Filtration (CAVH),** the ultrafiltrate removed is replaced by a solution with an electrolyte composition similar to that of plasma[14]. Net fluid removal is determined by the amount of replacement fluid administered. One modification to improve clearance of small molecules **Continuous arterio-venous hemodialysis (CAVHD),** incorporates diffusive transport by circulating dialysis fluid through the filter using gravity, thereby enhancing solute clearances[15]. In standard CAVHD as described by Geronemus et al[15], fluid removal is tailored to individual requirements and a replacement fluid is not generally used. Solute clearances are thus more dependent on diffusive transport and less on convective transfer. **Continuous Arterio-Venous Hemodiafiltration (CAVHDF)** further enhances uultrafiltration rates and maintains fluid balance by adjusting the amount of replacement fluid, thereby maximizing convective and diffusive mechanisms for solute clearance[16].

If adequate arterial access is not available, the external blood pumps used in standard hemodialysis machines can provide the driving force and permit veno-venous access for blood delivery to the hemofilter. Counterparts of the above techniques are **Continuous Veno-Venous Hemofiltration (CVVHD)[17] (similar to CAVH); Continuous Veno-Venous Hemodialysis (CVVHD)[18]** which simulates CAVHD, and **Continuous Veno-Venous Hemodiafiltration** (CVVHDF)[19] which is similar to CAVHDF. Blood pumps permit continuous therapy in patients with poor arterial access but add complexity and cost to an otherwise simple procedure. Table I summarizes the key features of the above techniques.

Two other techniques occupy another classification niche. These techniques are variations of intermittent dialysis using hemodialysis machines. These therapies are significantly different from the continuous therapies described above and are mentioned here only because they provide prolonged dialysis. Simpson et al[20] used a continuous, volumetrically controlled, machine-driven ultrafiltration device with continuous bicarbonate hemodialysis across a polysulphone membrane and termed the process **Continuous Ultrafiltration Plus Intermittent Hemodialysis (CUPID).** Hombrouckx et al[21] described **Go Slow-Dialysis,** which uses a single-needle blood pump with a blood flow of 80 ml/min and a closed recirculating low volume bicarbonate dialysate system to dialyze patients for 8-12 hours per day. Neither method has gained wide acceptance at present.

Table I. Continuous Renal Replacement Therapy: Comparison of Techniques

	SCUF	CAVH	CVVH	CAVHD	CAVHDF	CVVHD
Access	A-V	A-V	V-V	A-V	A-V	V-V
Pump	No	No	Yes	No	No	Yes
Dialysate	No	No	No	Yes	Yes	Yes
Filtrate (ml/hr)	100	600	1,000	300	600	800
Filtrate (L/day)	2.4	14.4	24	7.2	14.4	19.2
Replace fluid (L/day)	0	12	21.6	4.8	12	16.8
Urea clear. (ml/min)	1.7	10	16.7	21.7	26.7	30
Simplicity*	4	3	2	3	3	2
Cost #	1	2	4	3	3	4

* 1 = least simple; 4 = most simple; # 1 = least expensive, 4 = most expensive.
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Operational characteristics

All continuous renal replacement therapies seek to harness the capability of highly permeable membranes to filter large volumes of fluid at relatively low pressures[5]. The hemofilter offers a low resistance to blood flow and the driving force for ultrafiltration is the mean arterial pressure (MAP) of the patient, which is opposed by the oncotic pressure. Nef filtration is dependent on the transmembrane pressure (TMP) difference generated. The generation of a TMP gradient within the filter is influenced by several factors including a patient's mean arterial pressure, serum protein concentrations, hematocrit and the length of the filtrate column[5]. In general the goal is to minimize the hydrostatic pressure drop across the filter by using a large bore access and short lines. Ultrafiltration is also optimized by adjusting the height of the filtrate bag and reducing oncotic pressure and viscosity within the filter. Some recent investigations in this area are described below.

1) *Component Modifications*

a) *Access:* Blood flow is determined by hemodynamic status of the patient, site and type of vascular access (catheter, Scribner shunt, A-V fistula), and diameter of the decive being used[22,23]. Olbricht et al[22] found blood flows were higher and overall pressure drop across the filter was smaller (70 ± 13 mmHg) for femoral artery catheters as compared to a Scribner shunt (90 ± 12 mmHg), confirming that femoral arterial access appears to be preferable. Ahmad[24] developed longer term access by externally connecting two catheters tunneled subcutaneously into the femoral artery and vein respectively. Venous access can be via single or double lumen catheters in the femoral or subclavian vein. A double lumen catheter offers flexibility for use in hemodialysis if CAVHD is discontinued[16].

b) *Membrane Characteristics and Filter Design:* A variety of membranes are currently available in different configurations[5]. Several investigators studied the role of filter design on filter performance. Yohay et al[25] compared the effect of filter geometry in CAVHD and found that parallel plate AN69 dialyzer provided similar UF rates but better diffusive clearance than the larger polyamide FH66 hollow fibers. When the resistance of the AN69 0.6 m^2 PAN membrane was compared was to a 0.23m^2 polysulphone capillary dialyzer, the capillary geometry resulted in higher resistances[26]. Ronco et al[27] found that an increase in the inner diameter of a polysulphone hollow fiber from 200u to 250u resulted in a 39 % increase in blood flow with similar filtration rates and fewer clotting problems and lower heparin requirements. These data suggest that flat plate configuration appears to offer less resistance to blood flow and may require less anticoagulation. Ultrafiltration rates tend to to decrease with time even when other factors are constant[28]. First attributed to a decline in filter permeability, possibly related to protein coating the membrane, it now appears that permeability decay is not related to membrane protein exposure but depends on membrane characteristics[29]. A large exponential decay in permeability within the first 6 hours is followed by a more gradual decay. Polysulphone membrane permeability appears to decrease most markedly, both initially and in later periods, while PAN and polyamide membranes have minimal decays after the initial decline. The reduction in performance is also seen in pumped systems and is similar in flat plate and hollow fiber configurations[30]. Other investigators[22] also demonstrated that hydraulic membrane permeability (Lp) significantly affects ultrafiltration rates; polyamide membranes had a higher Qf than polysulphone membranes. Thus the type of membranes used should be based on the clinical situation. If the primary indication is fluid removal a polyamide or polysulphone membrane would suffice, but if solute control is desired, a membrane with better diffusive characteristics (such as AN69 [PAN]) is preferable.

2) *Operational Enhancements*

a) *Fluid Balance:* Continuous therapy removes large volumes of fluid with relative ease even in hemodynamically unstable patients. Two general approaches can be used to adjust the ultrafiltration rate. We maintain UF rates of 8-12 ml/min by varying the length of the filtrate column[16]. Others regulate the volume of filtrate by a peristaltic pump placed on the dialysate outflow line[28]. The former method is simple but requires more monitoring; the latter adds another pump to the system but maintains more consistent ultrafiltration rates. Other investigators have developed closed dialysate systems which permit regulation of ultrafiltrate removed[31-33]. Uldall et al[31] utilize a non-compliant 30 liter dialysate container with a non-permeant plastic liner separating fresh dialysate from used dialysate. The desired amount of ultrafiltrate is removed by a separate pump. Dyson et al[32] use a similar desing but have the inflow and outlow of dialysate controlled by two mechanically linked occlusive pumps, whereas Tesio et al[33] control ultrafiltration and hence net fluid removal by placing the spent dialysate bag and replacement solution in a rigid container so that removal of dialysate above a predetermined volume results in infusion of replacement fluid. Ronco et al[34] have developed a new method termed continuous high flux dialysis (CHFD) which combines diffusive and convective clearance and controls ultrafiltration by back filtration across the membrane. All these systems require more complex setups and training and do not appear to reduce the need for ccurate monitoring. In CAVH and CAVHDF net fluid balance is achieved by varying the amount of replacement fluid administered. Replacement fluid always lags behind reconstitution of plasma volume, so there is a potential for volume depletion. Flow sheets can minimize this problem but this is labor intensive. Several new systems automate fluid balancing and follow for real time replacement of filtrate removed. Amicon's Equaline system (Amicon publication # 261) uses two load cells (one for the infusate and one for the filtrate) to continually provide weight data to a microprocessor programmed to control infusion rate. This system provides accurate real time fluid replacement, but was designed for CAVH and not CAVHD or CAVHDF, both of which require dialysate infusions. Additionally, the load cells are sensitive and lose their accuracy if bumped. Other balancing devices are used[35,36] and other investigators[37,38] have developed a computer operated system which gives graphical information of fluid balance. One of the most exciting developments in this area is the use of a computerized closed loop control of fluid replacement[39]. This system utiilizes data acquired by a computer in real time to determine mean systemic filling pressure which is used as a guide to fluid therapy. There is a computer of open-shut valve for fast fluid administration thereby eliminating the need for hourly fluid balance charting. Parkin et al[39] have used this in 8 critically ill patients over 525 hours and have maintained hemodynamic stability and fluid balance in all patients. This technique has a lot of promise as it would significantly reduce the work involved in hourly fluid balance calculations and allow accurate fluid balance.

b) *Solute clearances:* Siegler et al[28] significantly enhanced our current understanding of the processes involved in solute removal in continuous renal replacement systems. In CAVH, solutes are removed purely by convective transport[5]; additional diffusive transfer is added in CAVHD and CAVHDF[15]. The total solute clearance in CAVHD and CAVHDF is the sum of the convective and diffusive clearances[28]. Since the molecular weight cut off for the membranes is >20,000 daltons, most low and middle molecular weight substances have sieving coefficients (SC) of 1. Clearance is = Qf × SC for most middle molecules and is directly proportional to the amount of filtrate produced. Small molecules are less dependent on convective clearance and are more effectively transferred by diffusion[7]. CAVHD and CAVHDF dialysate flow rates are between 16.7-33.2 ml/min (1-2 L/Hr), which is much lower than blood flow rate (50-120 ml/min). This allows for complete saturation of the dialysate fluid with solutes. Thus the limiting factor for solute removal by diffusion is the dialysate flow rate and not the blood flow rate as is with conventional hemodialysis. Blood flow rates are not limiting until they are below 50 ml/min[40]. Dialysate flow rate of up to 3 L/Hr do not appear to affect the UFR in spite of higher pressure within the dialysate compartment. Such low dialysate flow rates usually prevent backfiltration of fluid to the blood compartment[41].

Several methods enhance solute clearance in CAVH. Kaplan[42] demonstrated that suction applied to the ultrafiltrate port enhanced filtrate volumes, increased effective filter life and was even more efficacious in conjunction with predilution. Replacement fluid administered prefilter dilutes blood prior to entry in the filter. This reduces the viscosity of blood within the filter, promotes superior filtration rates and increases urea clearances by facilitating transfer of BUN from the intraerythrocytic compartment. If an external pump is applied to the circuit (as in CVVH), the limitation of low ultrafiltration rates is overcome as 20-40 liters of filtrate can be easily produced in 24 hours[17]. This method requires adequate monitoring to prevent volume depletion and air embolism. Dialysate used across the membrane markedly improves clearances and retains the simplicity of the procedure. Solute clearances can be further enhanced in CAVHD by increasing the dialysate flow rate to 2 L/Hr[43]; predilution with traditional CAVHD enhances convective and diffusive solute transport, resulting in CAVHDF. Using this method we have had mean BUN clearances in the range of 23-30 ml/min even in hypotensive patients[44]. Other investigators reported similarly good results with CAVHDF. The advantage of this approach over CAVHD is that convective transfer contributes to middle molecule clearance, an important factor in removing mediators seen in ARF (such as tumor necrosis factor [TNF] and Interleukin 1 [IL1])[44,45]. The composition of the dialysate and replacement fluid is an important factor to be considered. Lactate based dialysis and femofiltration solutions may result in hyperlactatemeia and worsening of acid-base status[46]. Additionally lactate buffered substitution fluids used in CAVH tend to have higher urea generation rates as compared to bicarbonate solutions[47].

These data are intriguing and raise the question of which buffer is most suitable for use in continuous therapies. Further investigation is required in this area.

c) *Drug clearances:* The disposition of drugs in patients on CAVH largely depends on the sieving coefficient of the drug, the degree of protein binding, and the ultrafiltration rate since convective transfer is the main mechanism of solute removal. Several investigators described the pharmacokinetics of different drugs in CAVH and developed guidelines for dosing[48-50]. Davies et al[43] measured the effect od dialysate flow rates on the removal of some of the commoner drugs in patients on CAVHD. They found that increasing dialysate flow rate from 1 to 2 liters per hour did not make a significant impact on clearance of most antibiotic. Other investigators found that clearances of theophylline, phenytoin, digoxin and vancomycin were progressively enhanced when dialysate flow rates were increased from 5 ml/min to 16.7 ml/min[51]. Slugg et al[52] and others[53, 54] found that higher doses of vancomycin are required for both CAVH and CAVHD but no major kinetic differences appeared between CAVH and CAVHD. Clearance of vancomycin in CVVH ranges from 6.7-13.3 ml/min, however, total clearance is 28.5 ± 6.4 ml/min suggesting that non-renal clearance of this drug is preserved early on in ARF[55]. Tobramyacin removal is well documented in CAVH[56] and in CAVHD appears to depend more on the Qf than on dialysate flow rate[57]. The effect of these therapies on some newer antibiotics and anesthetics has also been recently studied[58-62]. Table 2 lists current recommendations on drug dosing in CAVHD.

Anticoagulation

Anticoagulation is essential to prevent clotting within the circuit[63]. Insufficient anticoagulation leads to deterioration of filter performance and eventual clotting[64], contributing to blood loss. Excessive anticoagulation, on the other hand, may cause bleeding complications. This subject has been reviewed recently[65] and elsewhere in this monograph.

Table II. Effect of dialysate flow (Qd) on Drug clearance (Cl) in CAVHD*

Drug	Qd 1 L/Hr Cl (ml/min)	Qd 2 L/Hr Cl (ml/min)	Recommended Dose (mg/Hr)
Cefuroxime.............	13.97	16.22	500-700/12
Ceftazidime.............	13.11	15.24	1,000/24
Ciprofloxacin...........	16.31	19.93	200/8
Vancomycin.............	11.7	15.6	1,000/48
Tobramycin.............	11.1	14.85	60-80/24
Gentamycin.............	20.5	25.9	80-100/24
Digoxin....................	10.0	11.0	0.125/24
Fluconazole.............	7.0	9.68	200/24
Doxycycline.............	6.99	12.11	200/24

* Modified from Davies et al.[43].

Indications and contraindications

Continuous therapies provide all of the common features of intermittent hemodialysis but are best utilized in the ICU setting. Since fluid and solute removal can both be controlled easily and are done continuously these methods have a significant advantage in the hemodynamically unstable patient. In addition to providing renal replacement these techniques permit unlimited fluid administration thereby allowing nutritional repletion in critically ill patients. Patients with ARF in the presence of multiple organ failure, sepsis, burns cardiogenic shock are all likely to be better managed with these methods. Cosentino et al[67] recently described their results in a randomized trial of CAVH in ARDS and reported a trend of enhanced survival in CAVH recipients. Similarly Garzia et al[68] found improved hemodynamics in patients treated with continuous theraphy for ARDS. CAVH has particular advantage in reducing intracranial pressure in patients with oliguric ARF with fulminant hepatic failure as the process is more gradual and less likely to produce hypotension and reduced cerebral perfusion pressure[69]. Since CAVH membranes provide an effective clearance for myoglobin this may be preferable to conventional hemodialysis[70]. There has been some interest to combine continuous therapies with other methods of solute removal such as hemoperfusion[71] and plasmapheresis[72] to widen the application of these methods for treatment of sepsis and multiple organ failure without the traditional indication of ARF. Initial results appear promising but at this time use of these methods for treating the sepsis syndrome remains experimental.

Absence of an adequate arterial access is a significant contraindication however pumped systems should be usable in this setting once they are developed further. Since large volumes of fluid can be removed quickly meticulous monitoring is essential and requires a nursing to patient ratio of at least 1:1 if not more. These procedures are difficult to perform in the non-ICU setting and are not recommended for the patient with uncomplicated ARF. Complications associated with continuous therapies are mostly due to the potential for volume depletion particularly if monitoring is inadequate and calculations inaccurate. Access related problems include peripheral embolism and dissection resulting in limb ischemia with arterial catheters. Fortunately this is rare but it is to be emphasized that arterial catheter should be of an appropriate size and be placed by experienced personnel[22]. Connections should be taped to provent accidental disconnection.

Results with continuous therapies

Continuous renal replacement modalities have been available for at least a decade but have not yet found widespread use. This is because of a) these are new techniques; b) there is a learning curve, and c) there is a lack of controlled comparisons with IHD. As the techniques evolve results must be considered in the following categories a) the efficiency of these modalities to achieve solute and fluid balance; b) effect on the nutritional status, and c) the impact on overall patient outcome.

a) *Efficacy:* Several investigators have utilized CAVH to treat ARF in the ICU setting. Over the last 10 years the procedure has been done in over 600 ARF patients for periods ranging from a few hours to several days. The majority of these investigators reported minimal difficulty in achieving fluid balance; however, solute balances were controlled only when high ultrafiltrate volumes could be maintained. In some patients CAVH has been found to be inadequate for small solute removal[10,14] and the procedure may not be able to maintain BUN concentrations below 120-150 mg/dl in severely catabolic patients. This is because the clearance achieved by CAVH is largely dependent on convective transport of solutes. Better solute clearances and metabolic control have been reported for CAVHD in comparison to CAVH[7,74,75]. Siegler et al[28] studied solute transport characteristics in 15 critically ill patients treated with CAVHD and found whole blood clearances of urea, creatinine and phosphate averaged 25.3, 24.1 and 21.3 ml/min, respectively. These clearances are a marked improvement over those achieved with CAVH alone (BUN 8.1 cc/min) or CAVH with predilution replacement solution and suction (18 cc/min)[36]. Pattison et al[76] were able to maintain BUN levels at 40-60 mg/dl and serum creatinine 1.4-4.0 md/dl in hypercatabolic ARF patients. Similarly other investigators[8,9] used CAVHD to achieve solute and volume control in patients with multiple organ failure and provide adequate nutrition. In our experience CAVHDF provides superior fluid and solute control than CAVHD. We have routinely achieved solute control with urea clearances ranging from 23-30 ml/min in hypercatabolic patients[16]. Similar results have been obtained by other investigators with CAVHD[77] and with pumped systems. Macias et al[78] have used CVVH in 25 patients and achieved solute control in all but one hypercatabolic patient. There were 4 episodes of volume responsive hypotension during the 193.5 treatment days.

Both CAVH and CAVHD have been used successfully in children[79,80] and have been associated with an improvement in pulmonary gas exchange in combined renal and respiratory failure[81]. CAVHD was found to be more efficacious than CAVH in managing ARF in critically ill children[82]. Zobel and co-investigators[83] reported their experience with 5 different A-V replacement modalities in 23 pediatric patients. Urea clearances were 5.6 ± 2.1 ml/min/m^2 for CAVH and 15.3 ± 3.7 ml/min/m^2 for CAVHD. Other investigators have used this technique successfully in select patient populations including congenital heart disease[84], hyperammonemia[85] and severe hyperkalemia[86]. CVVH has been used in the management of ARF in the neonate[87] and for inborn errors of metabolism[88].

b) *Effect on Nutrition:* Continuous therapies have a major advantage over IHD in permitting unlimited nutrition as fluid removal is not a limiting factor. Barlett et al[89] found that nutritional status was better in patients on CAVH and this factor may result in an improvement in survival. Similarly Chima et al[90] found that nutritional status improved in all 16 patients on CAVH, however 14 were in negative nitrogen balance. In our experience CAVHDF allowed better nutritional support and we were able to match or exceed the nutritional goals for patients treated with this modality whereas this was not possible in patients on IHD[96]. Other investigators have had similar results[81,92]. Urea kinetics have been done in 8 patients on CVVH and revealed that the normalized protein catabolic rate (NPCR) was 1.46 ± 0.54 g/kg/day and the nitrogen deficit was large >8 g/day reflecting deficiencies in non-protein energy administration[93]. In the overall nutritional balance of the patient two other factors need to be recognized. The dialysate fluid used in CAVHD has 1.5-2.5 % glucose which can be absorbed during the procedure (154-270 g/day) and contributes to the caloric load[28,94]. This must be considered in the nutritional prescription. A second factor is the loss of amino acids across the filter which range from 2.7-8.9 g at low flow rates (<102 g/24 hrs) and 30 g at higher flow rates[95]. Losses appear to depend more on the serum levels than the underlying clinical status of the patient[96,97].

c) *Outcome:* Despite significant advances in the management of ARF over the last four decades, the associated mortality has not changed significantly[98]. Mortality rates range from 30 % in nephrotoxic drug induced ARF and 90 % in severe multiple organ faulure[99,100]. The use of intermittent hemodialysis has reduced the 100 % mortality of ARF to its current level but has not been without its

Table III. Results with CAVH (CVVH) for Acute Renal Failure

Author	Year	Ref. #	Patients	‰ Surviv.
Kramer	1981	1	20	40
Olbricht	1982	109	34	26
Kaplan	1984	3	15	27
Kler	1985	110	182	22
Domoto	1985	111	36	25
Frisch	1986	112	27	41
Bartlett	1986	94	32	28
Mault	1987	113	61	18
Lieberman	1987	114	23	35
Paganini	1988	13	20	19
Weiss	1989	4	100	45
Wendon	1989	17	(28)	(52)
Alarabi	1990	115	112	52
Scherier	1990	117	49	35
Sluiter	1990	118	89	44
Zobel	1990	119	32(15)	63(27)
Bishof	1990	89	4	50
Canaud	1990	120	(32)	(16)
Korner	1990	121	(15)	(40)
Storck	1991	110	48(68)	12.5(29.4)
Macias	1992	78	(25)	(16)

Modified fron Mehta[159].

Table IV. Results with CAVHD (CVVHD) for Acute Renal Failure

Author	Year	Ref. #	Patients	% Surviv.
Schneider	1988	7	41	24
Pattison	1988	86	5	40
Barzilay	1988	122	6	50
Gibney	1988	8	15	33
Stevens	1988	73	36	31
Tam	1988	108	(16)	(56)
Voerman	1990	98	17	29
Geronemus	1990	123	111	24
Keller	1990	124	18	11
Hirasawa	1990	116	36	44
Schafer	1990	125	(38)	(33)
McDonald	1990	96	22	18
Bastien	1990	126	(34)	(50)
DiCarlo	1990	88	8	38
Bellomo	1990	9	12	42

Modified from Mehta[159].

own problems. The effect of continuous renal replacement therapy (CAVH, CAVHD) on overall patient outcome is still unclear. Tables III and IV summarize the major studies using CAVH and CAVHD and the actual mortality figures. Some investigators record hospital discharge as an outcome whereas others have used a definition of ICU survival thus resulting in differences in mortality statistics. The absence of an effect on mortality may represent an initial bias in selection of patients as generally continuous therapies have until recently only been utilized in patients who were hemodynamically unstable and «too sick» to receive intermittent HD. A second consideration is that very few studies[8,9,13] have used severity of illness scoring systems[105] to assess the impact of renal replacement therapy for ARF. Paganini et al[13] calculated the APACHE II scores retrospectively in 162 patients treated with continuous, combined or intermittent therapies in the ICU and found that patients with continuous therapies had a greater incidence of multisystem involvement and the highest scores. Dobkin et al[102] retrospectively calculated the APACHE II scores in 100 patients receiving hemodialysis in the ICU between 1982-1986. The scoring system was found to accurately predict a risk of death greater than 70 % with 100 % specificity. A third factor is the role of nutrition on outcome. Bartlett et al[89] found that nutritional status was improved in 56 patients with ARF treated with CAVH and resulted in an improved trend for survival in the CAVH group (CAVH 28 % survivors, HD 12 %). This is an important area for further investigation.

Critical evaluation of CAVH and CAVHD in comparison with IHD is scanty[103]. Recently, Bosworth et al[104] summarized their experience with 320 patients with ARF in the ICU over three years 1986, 1988 and 1989. 29.7 % were treated with continuous therapy (SCUF, CAVH or CAVHD) alone, 27.3 % had combined continuous and intermittent (HD) therapy and 43 % received intermittent HD alone. The continuous group had better hemodynamic stability and lower BUN's, however the overall mortality was similar in all three groups and ranged from 76 % for the combined group to 81 % of the intermittent group. They calculated the ratio of APACHE II scores at admission to ICU and at the time of renal consult and found that this ratio was >1 patients on continuous therapies suggesting that sicker patients were treated with continuous therapies. Siaberth[105] found continuous therapies reduced mortality in high risk patients but were not superior to intermittent therapy. These data suggest an overall poor prognosis in patients with multisystem failure and ARF in the ICU setting and this is reflected by other studies also[7-9,72]. However, there is little information regarding the impact of these therapies in a controlled trials.

Kierdorf[106] carried out a retrospective study comparing 73 patients treated by continuous hemofiltration over two years with 73 patients treated with intermittent hemodialysis. They found a significantly lower mortality in the CVVH group (57 deaths) versus the intermittent HD group (68 deaths). Other retrospective studies[107,109] have shown a trend for higher survival in continuous therapies. We retrospectively analyzed the effect of CAVH and IHD on the mortality of ICU patients with ARF during two consecutive 8 month periods following initiation of a CAVHD program[91]. In the initial 8 months the CAVHD program was being established and CAVHD was used predominantly hemodynamically unstable patients who would not tolerate IHD. For the first 8 months mortality rates were 67 %, 86 % and 91 % for IHD alone, IHD + CAVHD and CAVHD alone respectively. Overall mortality declined 13 % during the second 8 month period. Those receiving IHD alone had a 12 % increase in mortality (67 % to 75 %) whereas mortality decreased in patients crossing over from IHD to CAVHD (86 % to 67 %) and those receiving CAVHD initially (91 % to 73 %). Although our numbers are small and do not permit statistical comparison, we are encouraged by the trend in better outcomes. We believe that CAVHD is preferable to IHD in treating ARF in the ICU setting and we are currently conducting a prospective randomized trial to further assess the relative efficacy of these two therapies.

An additional area of investigation is the efficiency of different forms of continuous therapies and their impact on outcome. Storck et al[110] compared spontaneous hemofiltration (CAVH) to pump driven hemofiltration (PDHF) and found that both treatments adequately controlled uremia and fluid overload however, survival was significantly higher with PDHF as compared to CAVH (29.4 % vs 12.5 %). Since ultrafiltrate volumes were higher with PDHF as compared to CAVH it is postulated that improved middle and large molecule clearance may have had a salutary effect on survival. However, Journois et al[110] failed to find a relatiohip between ultrafiltrate volumes and patient outcome but found a negative correlation between ultrafiltrate volume produced and recovery from oliguria. Kierdorf et al[106] compared CAVH to CVVH in the treatment of multiple organ failure (MOF) and found CVVH to be clearly superior in controlling uremia and fluid balance. These data and those from other investigators all suggest that CAVH alone is inadequate for treating ARF associated with MOF. By contrast CVVH, CAVHD, CVVHD are all efficacious in solute and fluid control in this setting however, it is still not clear whether any one of these therapies is clearly superior in terms of improved outcome. Further research is warranted in this area.

Future directions

Continuous renal replacement therapy is still evolving and the next few years will undoubtedly bring in new modifications to make the technique applicable to a broader group of patients. Some of the areas where advances are likely to be made are as follows:

a) *Techical Issues:* One of the major concerns with these therapies has been the requirement of an arterial access. Pumped systems currently available have generally been those used for conventional dialysis machines with minor modifications. This has made them bulky, and relatively limited in capabilities. New pumped systems are being designed specifically for continuous therapies to control fluid removal and replacement and allow stable blood flows from a venous access. These systems will be smaller and more user friendly to allow for acceptance into the cramped ICU arena. Computerized closed loop control of fluid replacement[39] should allow integration of continuous therapies into the ICU setting.

b) *Biocompatibility:* Membrane interactions leading to complement activation and neutrophil sequestration has been described predominantly for intermittent HD[132], however since the exposure time to the membrane is considerably greater in continuous therapy this may be an important factor influencing outcome. Although various membranes have been shown to have different intensities of complement activation[132, 133] polysulphone and polyacrylonitrile membranes do not appear to result in this activation[130]. Recent data also suggests that anticoagulation may play an important role in complement activation and subsequent neutrophil sequestration independent of the membrane. It appears that citrate anticoagulation inhibits neutrophil activation by chelating calcium even in cuprophane membranes[135]. Previous studies[136] have shown similar results suggesting that changes in membrane biocompatibility are likely to be dependent on anticoagulation. Development of newer membranes with heparin bonding[137, 138] are promising however have been associated with increased complement activation[139]. Whether biocompatibility issues will influence outcome is still unclear, however data from Schulman et al[140] suggests that exposure of blood to cuprophane membranes resulted in a delay of recovery from acute renal failure in a rat model, whereas exposure to a polyacrylonitrile (AN69S) membrane was similar to controls. Similary residual renal function was better maintained in surgical ablation 5/6 nephrectomy model of renal failure when PAN membranes were used in contrast to cuprophane membranes[141]. These data support the role of selecting biocompatible membranes for continuous therapies even though cuprophane membranes could be utilized for pumped circuits[142].

c) *Cytokine modulation:* An additional area of intense interest is the effect off these techniques in removing mediators of inflammation such as TNF alpha, Interleukin 1, and Interleukin 6. Since the membranes used for continuous therapies have much higher molecular weight cut off's these mediators are likely to be cleared from the circulation. It has been previously shown that TNF alpha and IL-1 are removed from the circulation by CAVHD[143, 144]. We have recently demonstrated that cytokine extraction may be dependent on the membrane used. In an in-vitro model of CAVH/D the AN69-s PAN membrane was 2-3 fold more efficient in removing TNF as compared to the polysulphone and polyamide membranes[145]. Since these cytokines are an integral component of the response to sepsis and mediate some of the detrimental hemodynamic consequences it is possible that their removal may be beneficial. Hemofiltration has been found to be useful in initial studies from animal models of sepsis[146-147] and in some patients[72, 148]. If this area of investigation is successful it will open a new area of application for this therapy.

d) *Non-Renal applications:* The versatility of membrane filtration offered by continuous techniques lends itself to many different applications. Since fluid removal is efficient and easily regulated these therapies have been utilized in the treatment of pulmonary edema and cardiac failure[149-150]. Most patients treated with this appear to have improved diuresis and hemodynamic parameters. This may represent simple volume shifts allowing better cardiac performance or removal of other factors including catecholamines[151-152]. The ease of use of continuous therapies makes them a logical choice for emergencies in natural disasters such as earthquakes and for evacuation from high altitude areas[153].

Another area of application of these therapies is in the treatment of patients with cancer to limit drug induced toxicity. Extracorporeal hemofiltration of a hepatic venopus effluent reduced systemic toxicity of intraarterial infused in the hepatic artery of mongrel dogs[154]. Other investigators have shown that removal of a 10,100 mol wt factor in rabbits with VX-2 carcinoma by ultrafiltration resulted in improved survival[155]. It is likely that future research in these areas will result in a broader application of these therapies as adjuncts to cancer chemotherapy. CAVHD has also been utilized for the treatment of ARDS and results in improved hemodynamics and oxygenation[68], however a randomized controlled trial[67] did not show a major effect however, these data are from a small number of patients. Hepatic transplants provide another application for continuous therapy as fluid and electrolyte problems are commonly encountered in this group of patients and they are usually hemodynamically unstable[156, 157]. Patients treated with CAVH intraoperatively had decreased PEEP and FiO_2 requirements and lower cardiac filling pressures postoperatively[158]. Continuous therapies can thus serve as an important tool for maintaining metabolic and hemodynamic stability in this situation.

Summary

Continuous renal replacement therapies have emerged as treatment options for acute renal failure over the last decade. Several different methods are now in use. They have in common the use of a highly permeable membrane which allows removal of fluid and solutes in the presence of low driving pressures. Its major advantages over HD have been a) it is a continuous form of therapy that allows more stable maintenance of volume and composition of body fluids; b) water and electrolyte balance can be controlled; c) unlimited hyperalimentation is possible as there are no restraints in fluid volumes which can be administered; and d) patients are more hemodynamically stable and tolerate the procedure well. CAVHD is increasingly the first line of treatment used for acute renal failure in critically ill patients. Randomized trials comparing this techniques with standard intermittent hemodialysis are already under way but will need to be done at several centers. The impact of these therapies on outcome and nutritional status will be awaited with great interest.

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