Continuous Renal Replacement Therapies for the Critically Ill

INTRODUCTION

Since its introduction in 1977, continuous renal replacement therapy (CRRT) has advanced considerably and is now widely used in the management of renal insufficiency in critical illness. Acute kidney injury (AKI) affects from 3.2% to 18.3% of hospitalised patients, and 35% of critically ill patients (VA/NIH Acute Renal Failure Trial Network, Palevsky et al. 2008; Selby, Crowley et al. 2012). Whatever the underlying cause, AKI is associated with increased mortality and is a frequent reason for escalation to critical care for renal replacement therapy.

INDICATIONS

CRRT is commenced when renal insufficiency has led to complications that are refractory to medical management, such as acidaemia, electrolyte disturbances, and more commonly oliguria unresponsive to diuretics, uraemia and volume overload (Table 1) (Kellum, Lameire et al. 2012; Silvester, Bellomo et al. 2001). In the UK CRRT is usually delivered by the critical care team with minimal input from nephrologists, unlike practices in other countries.

There are no universally accepted levels of urea, potassium or pH at which to start CRRT, but commonly used parameters are outlined in Table 1. Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that initiation of CRRT should depend on the presence of modifiable conditions and biochemical trends, rather than individual urea and creatinine thresholds (Kellum, Lameire et al. 2012).

PRINCIPLES OF HAEMOFILTRAITON

The two main types of renal replacement therapy are dialysis (which is intermittent) and filtration (which is continuous), the key differences are described in Table 2. Both systems draw blood from a large vein using a pump to stream it through an extracorporeal circuit, and return processed blood into the venous system. Solutes are removed from the blood across a semi-permeable membrane either by diffusion, (in hemodialysis), by convection (in haemofiltration) or by a combination of both (in haemodiafiltration) (Figures 1 and 2).

Diffusion-based dialysis systems use synthetic polysulfone membranes and are more effective at removing small molecules e.g. urea, creatinine and electrolytes (<300 Daltons)

than haemofiltration. Convective clearance is the ultrafiltration of large volumes of fluid, mainly plasma water, down a pressure gradient forcing a concomitant 'drag' of solutes across the membrane. As in the glomeruli**,** a pressure gradient from the blood compartment to the filtrate drives fluid across the membrane. Convection is more effective at clearing middle and larger sized molecules (500 to 20,000 Daltons). Large molecule clearance depends on the pore size of the membrane. High flux membranes, usually made of synthetic polymers, are used in continuous veno-venous haemofiltration (CVVHF) to remove molecules up to 20,000 Daltons. Most membranes need to be replaced after 24-72 hours of filtration, due to the accumulation of particles (often protein) in the filter, a process known as fouling. Filtered waste (ultrafiltrate) is discarded into bags by the machine. To maintain a neutral fluid balance, sterile isotonic replacement fluid**,** equal to the ultrafiltrate loss, must be added to the extra-corporeal circuit. This can be done before or after the membrane; termed pre-dilution or post-dilution. Typically, the total fluid volume is divided equally between pre- and post-dilution, but the ratio can be altered. Increasing pre-dilution dilutes the blood in the membrane, thus prolonging the membrane life, but reducing solute clearance. A balance must be made between these factors and patient specific needs (Velayutham & Columb 2005).

HYBRID THERAPIES

Filtration methods can be adapted to optimise solute or fluid clearance. Haemodiafiltration combines convection and diffusion to achieve a balanced rate of filtration of both large and small solutes, consequently it is the most commonly used modality. Slow, continuous ultrafiltration (SCUF) is used solely to remove plasma water. Unlike haemofiltration or haemodiafiltration, there is no fluid replacement during SCUF. Slow, continuous, low efficiency daily dialysis (SLEDD) provides extended IHD for 8-12 hours. Studies indicate that haemodynamic instability during SLEDD is less than in IHD, and comparable to CVVHF (Ronco, Ricci et al. 2015). KIDGO guidance recommends that the choice of renal replacement modality is based on availability and experience with specific modality and the patients haemodynamic stability (Kellum, Lameire et al. 2012).

HAEMODYNAMICS AND INTRAVASULCAR VOLUME CONTROL

Haemodynamic instability (common in critically ill patients) generally requires CRRT rather than intermittent haemodialysis (IHD) as the rapid removal of fluid and solutes in IHD can cause profound hypotension. During CRRT, blood pressure is less affected than during IHD,

because CRRT allows sufficient time for compensatory fluid shifts from the intersitium to maintain intravascular volume. A Cochrane systematic review reported that CRRT achieved better haemodynamic stability than IHD and decreased the need for vasopressors (Rabindranath, Adams et al. 2007).

During CRRT, intravascular volume control is titrated according to the patient's clinical needs. This is achieved by altering the daily balance of fluid removal and replacement, prescribed as a 24hr positive or negative balance. Balance can also be adjusted on an hourly basis to account for acute changes in clinical status. This facilitates the administration of intravenous fluid and medications to be given in the context of fluid overload.

TIMING

In the absence of life threatening complications directly related to renal failure, the decision of when to initiate CRRT is a topic of much debate. This decision is further complicated by the fact that the terms 'early' and 'late' are open to individual interpretation, as demonstrated by the varied definitions used in clinical trials. It is arguable that early initiation of CRRT may achieve better control of fluid volume and electrolytes and improve the removal of uraemic toxins. However, early initiation may unnecessarily expose patients to CRRT who would have otherwise spontaneously recovered. Two meta-analyses have concluded that 'early' initiation of CRRT reduces mortality (Seabra, Balk et al. 2008; Karvellas, Farhat et al. 2011). However, much of the data came from retrospective cohort studies with significant pre-intervention differences between study groups. Whereas more recent randomised controlled trials showed no difference in results (Gaudry, Hajage et al. 2016; Zarbock, Kellum et al. 2016). The pilot study of a multicenter randomized controlled trial attempting to resolve this issue, found no difference in mortality between early or late therapy (Wald, Adhikari et al. 2015).

DOSE OF RENAL REPLACEMENT THERAPY

The dose (or intensity) of CVVHF refers to the volume of ultrafiltrate produced per hour. It is commonly prescribed as an hourly exchange rate (e.g. 1500 ml/hr). The flow rate should be tailored to a patient's ideal body weight (ml/kg/hr). Considerable, but inconclusive, research has been devoted to determining the best dose for the critically ill. A widely used dose is 25ml/kg/hr (RENAL Replacement Therapy Study Investigators, Bellomo et al. 2009; VA/NIH Acute Renal Failure Trial Network, Palevsky et al. 2008). KDIGO guidelines recommend 20-

25ml/kg/hr in CRRT for AKI however to achieve this it may be necessary to use higher doses while minimizing interruptions total filter time (Kellum, Lameire et al. 2012).

The use of high volume haemofiltration (HVHF) in the treatment of sepsis is an area of interest to critical care physicians. Initially, the removal of soluble inflammatory mediators seemed a promising hypothesis, but this approach has not improved clinical outcomes (Bouman, Oudemans-Van Straaten et al. 2002). Ronco et al (2000) demonstrated better survival with 35ml/kg/hr compared to 20ml/kg/hr in sepsis, but no survival benefit from increasing filtration rates to 45ml/kg/hr. Subsequent multiple randomized controlled trials have not demonstrated any benefit (RENAL Replacement Therapy Study Investigators, Bellomo et al. 2009; Tolwani, Campbell et al. 2008; Joannes-Boyau, Honoré et al. 2013). A recent Cocharane systematic review concluded that HVHF (35 to 48ml/kg/hr) increased the risk of hypothermia without reducing mortality or furthering kidney recovery. Sub group analysis in septic patients discerned no benefits from high dose filtration (Fayad, Buamscha et al. 2016). Higher doses use more replacement fluid, may shorten membrane life and are more costly, which needs to be considered if there is little evidence for any clinical benefit.

INTRAVENOUS ACCESS

Early methods of CRRT used arterio-venous access with arterial flow providing the driving pressures for the extracorporeal circuit and filtration. Modern CRRT uses double lumen central venous access (10-14 Fr Catheter) and a pump in the machine to circulate blood. This avoids the risks associated with large bore arterial cannulation and leads to better controlled rates of filtration (Bellomo & Ronco 2000). Table 3 describes the advantages and disadvantages of different central venous access sites.

ANTICOAGULATION

Interruption of CRRT ranges from 8%-28% of total filtration time. The most frequent cause is clotting within the membranes of the circuit filter. Maintaining extracorporeal circuit patency with anticoagulation minimises breaks in filtration, reduces the differences between prescribed and delivered filtration doses, and lessens the blood loss that results from circuit changing. When blood comes into contact with artificial surfaces, the clotting cascade is activated. Anticoagulation helps to reduce this and increases the life of circuits and membranes. Commonly used anticoagulants include unfractionated heparin, sodium citrate and prostaglandins. KDIGO recommends the use of regional citrate anticoagulation for CRRT,

and unfractionated heparin for patients with contraindications to citrate. Sodium citrate achieves anticoagulation by chelating calcium which inhibits clot formation in the extracorporeal circuit. Sodium citrate anticoagulation can be achieved by using a number of different methods depending on the machine and fluids used.

Unfractionated heparin is given as a bolus, then as a continuous infusion (5-10 IU/kg/hr) into the extracorporeal circuit, prior to the membrane (Kishen, Blakeley et al. 2009). Its benefits are its low cost, reversibility (with protamine), ease of monitoring (through APTT), short half-life of 90 min and extensive clinical experience (Ronco, Ricci et al. 2015). Regional anticoagulation with heparin can be achieved by infusing protamine after the filter. Prostacyclin inhibits platelet aggregation and can be used with or without heparin. Prostacyclin is significantly more expensive than heparin, can cause vasodilation and hypotension but has a shorter half-life.

Anticoagulants should be avoided in patients with impaired coagulation (international normalized ratio >2.5, activated partial thromboplastin time >60 seconds, platelets $<60x10^{-3}$/litre) and also those who have had recent surgery (Kishen, Blakeley et al. 2009). In such cases, higher pump speeds and pre-dilution can reduce circuit and membrane clotting.

PHARMACOKINETICS

AKI impedes the clearance of many drugs, but once CRRT is initiated, the removal of water-soluble drugs is accelerated. Commonly used drugs removed by CRRT are outlined in Table 4. Drug clearance is increased by high filtration rates, long filtration sessions, high flux membranes, post-dilution and the patient's residual renal function. In addition, critically ill patients often have low albumin levels and volume overload, reducing the proportion of protein bound drug. Higher levels of unbound soluble drug result in greater clearance and lower therapeutic levels (Vaara, Pettila et al. 2012). Without standardised dosage, the pharmacokinetic effects of CRRT are difficult to gauge accurately. Ideally, drugs should be individually titrated to measured blood levels. However, therapeutic levels of many medications cannot be measured and therefore dosage is based on old pharmacokinetic models (Vaara, Pettila et al. 2012).

WHEN TO STOP

Decisions to stop CRRT are hindered by the unpredictability of kidney recovery in critically ill patients and the challenges of assessing renal function during CRRT. While receiving CRRT the blood markers of kidney function (creatinine and urea) are the combined result of CRRT and underlying renal clearance. Current guidelines recommend stopping CRRT when intrinsic kidney function has been restored; i.e. when creatinine clearance is at a minimum of 20ml/kg, and electrolytes, fluid and pH, are normal (Kellum, Lameire et al. 2012). In the Acute Renal Failure Trail Network Study renal support was ceased when creatinine clearance >20ml/min, urine flow >20ml/hr or a spontaneous fall in serum creatinine level. Studies have shown that urine output is the is the safest indicator for cessation (Ronco, Ricci et al. 2015). Urine output exceeding 400ml/day, in the absence of diuretics, has a positive predictive value for successful discontinuation in >80% of patients (Uchino, Bellomo et al. 2009). Whereas reinitiating CRRT is associated with increased mortality (Uchino, Bellomo et al. 2009). Whether too early discontinuation of CRRT with subsequent re-initiation is by itself harmful or an indicator of disease severity, requires further investigation. Withdrawal of CRRT must also be considered when kidney function fails to recover and the patient is not suitable for long term renal replacement.

COMPLICAITIONS OF CRRT

Before initiating CRRT, the benefits must be weighed against risks e.g. common complications include haemodynamic instability, volume and electrolyte disturbances. Intravascular catheter-related complications such as pneumothorax and arterial cannulation have been reduced with ultrasound guidance. Other line compilations include arrhythmias**,** thrombosis, infection and stenosis from repeated line insertion. Extracorporeal circuits risks include air emboli, sensitivity reactions, hypothermia, thrombosis and thrombocytopenia. Continuous anticoagulation can cause bleeding and heparin-induced thrombocytopenia, however the use of regional anticoagulation has reduced these risks (Kishen, Blakeley et al. 2009).

OUTCOMES

After a critical illness complicated by AKI requiring CRRT it is difficult to predict which patients renal function will return to normal, and which will have chronic renal impairment. Follow up of patients who have received CRRT is poor, as demonstrated by Kirwan (2015) who assessed the follow up of patients that received CRRT for AKI; 57% of patients had their creatinine measured 3-6 months post discharge and only 12% received specialist nephrology

follow up. When renal function was assessed, the rate of chronic kidney disease, stage 3 or greater, rose from 49% to 70% (Kirwan, Blunden et al. 2015).

Current literature on the impact of CRRT on long term kidney function is limited and complicated by large variations in study design and patient heterogeneity. A systematic meta-anaylsis assessing renal recovery in survivors of critical illness who received CRRT or IHD, found that IHD was associated with a higher rate of dialysis dependence compared with CRRT. However, this finding was limited to observational studies and no difference was found when analysis included randomised controlled trials (Schneider, Bellomo et al. 2013). More recently Wald (2014) demonstrated an association between CRRT, used in the treatment of AKI, and a lower risk of chronic dialysis when compared to IHD (Wald, Shariff et al. 2014). To understand outcomes there is a need for more detailed follow up and a largescale investigation into long-term complications.

COSTS

Continuous therapies cost considerably more per day than intermittent therapies, with haemofiltration sterile fluid and staffing costs contributing much of this. Consequently, some intensive care units opt to switch patients requiring CRRT to IHD once they are haemodynamically stable.

FUTURE DEVLOPMENTS

Current biomarkers of renal function are often inconsistent. A creatinine rise is only seen once kidney damage has taken place, and during CVVHF the levels are not representative of renal function. More reliable biomarkers to determine the onset, severity and treatment response of renal failure are necessary. Biomarkers currently under investigation (e.g. neutrophil gelatinase-association lipocalin, cystatin C, interlukin 8 and kidney injury molecule 1) should be considered in future studies.

CONCLUSION

There is no doubt that without CRRT, most critically ill patients would be unable to receive adequate renal replacement therapy. However, there remain a number of areas of uncertainty in its optimum use, including clarity on when to start and stop therapy, and the optimum dose in different cases. A thorough understanding of the theory and practice of CRRT is essential for anyone working on a critical care unit.

KEY POINTS

- AKI is common amongst critically ill patients
- For hemodynamically unstable patients CRRT should be used rather than intermittent therapies.
- The administration of CRRT should be tailored towards individual patient needs, based on current best evidence available.
- Circuit durability depends on good vascular access, adequate anticoagulation, and appropriate machine and blood pump settings.
- The effect of CRRT on drugs must be taken into consideration in order to avoid under or overdosing
- Survivors of AKI who received CRRT should routinely be followed up, ideally by a nephrologist
- No one system of CRRT has been shown to be consistently superior to another in the setting of critical illness

TABLES

Renal
•Fluid overload unresponsive to diuretic therapy •Hyperkalemia refractory to treatment •Rapidly increasing urea (urea > 30mmol/L) •Acidaemia (pH <7.1) •Oligouria (<200ml/12hr or Anuira <50ml/12hr) •Uraemic complicatons e.g. bleeding, pericarditis, encephalpoathy
Non Renal
•Drug overdose with a dialysable toxin •Liver failure (raised ammonia) •Patients requiring large amounts of blood products but at risk of developing pulmonary oedema or ARDS •Cardiac failure with severe fluid overload/pulmoary odema •Hyperthermia and Hypothermia

Table 1 - Table of renal and non-renal indications for CRRT (Kishen, Blakeley et al. 2009)

	CVVHF	IHD
Patient cohort	Critically ill	Chronic renal failure
Duration	Continuous, 24hrs	Short sessions 3 times a week
Blood flow	50-200ml/min	300-400ml/min
Mode of molecule clearance	Convection	Diffusion
Size of molecules cleared	Small-medium	Small
Anticoagulation	Required	Not needed
Access	Central venous access, Vascath	IV fistula or long-term tunneled haemodialysis line
Solute control	Good electrolyte and fluid balance control	More rapid fluid and electrolyte shifts
Fluid balance control	Used in haemodynamically unstable patients	Used in stable patients, hypotension is common
Water supply	Packaged sterile water (expensive)	Filtered water (cheaper)

Table 2 - Comparison table between CVVHF and IHD

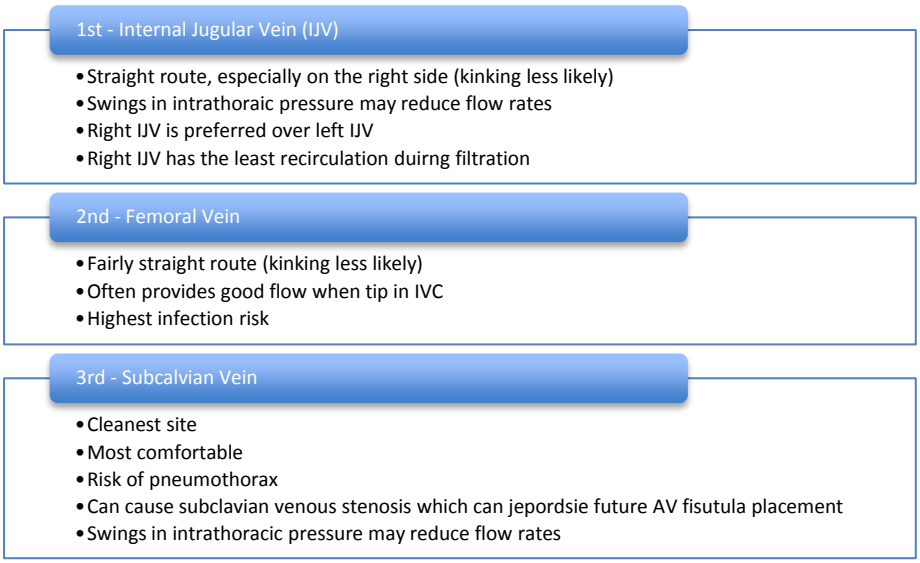

Table 3 - Central venous access in order of preferred site and describing the risks and benefits of each site.

Removed
• Lithium • Methanol • Ethylene glycol • Salicylates • Barbituates • Metformin • Aminoglycosides • Carbapenems • Cephalosporins • Penicllins • Metronidazole

Not removed
• Digoxin • Tricyclics • Phenytoin • Gliclazide • Betablockers (except atenolol) • Benzodiazepines • Warfarin • Macrolide • Quinolones

Table 4 - Table of drugs that removed by CRRT

FIGURES

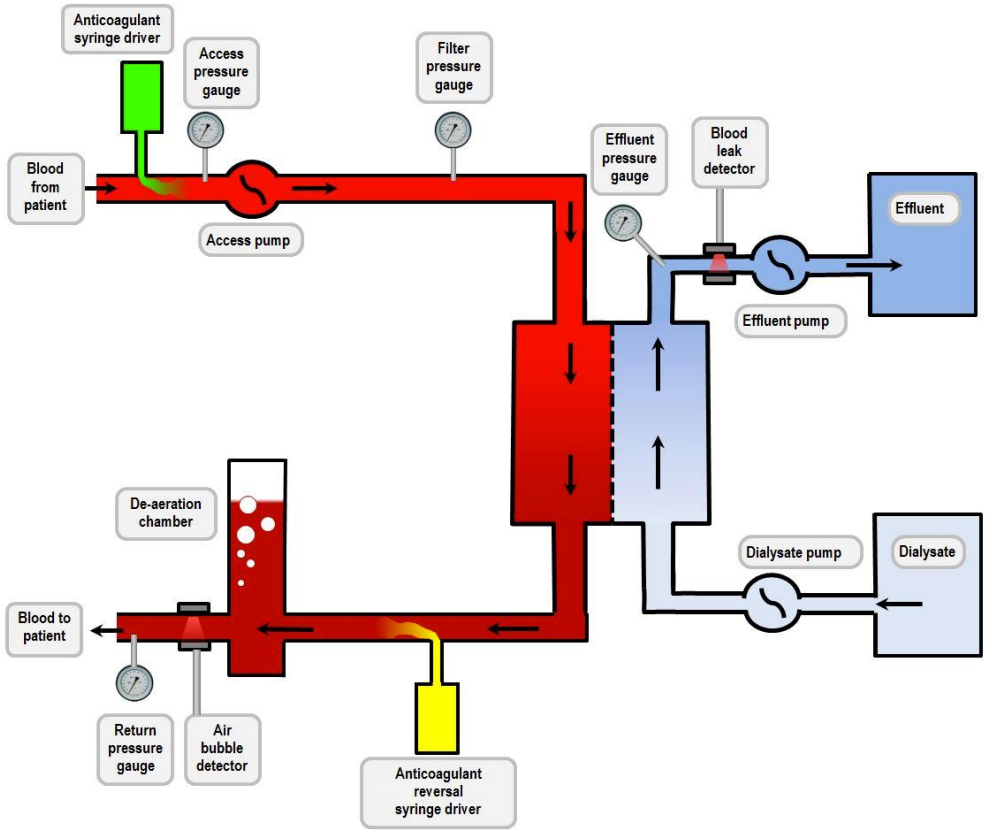

Figure 1 – Diagram of haemodialysis circuit. Solutes move via diffusion from a high concentration in the blood compartment to a low concentration in the dialysate. The speed of movement depends on the magnitude of the diffusion gradient, which is maintained by a

countercurrent. IHD machines have pumps, air detectors, and pressure monitors throughout the circuit (Yartsev 2016).

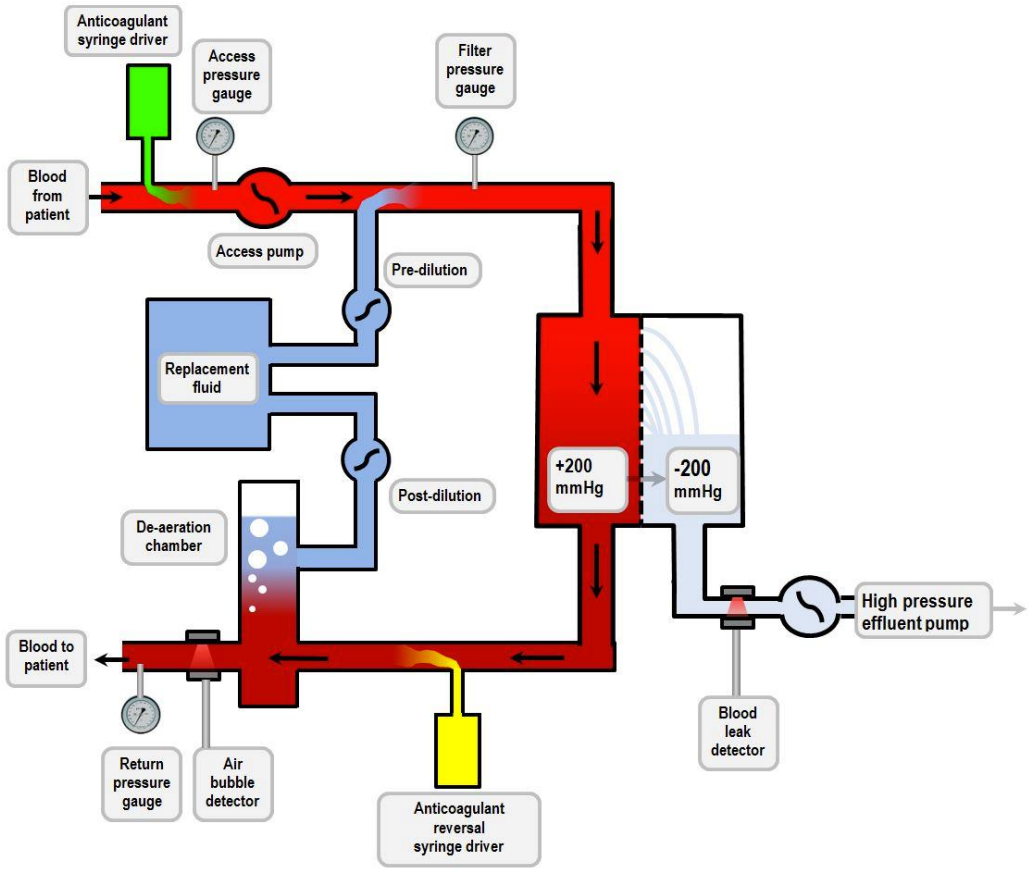

Figure 2 – Diagram of CVVHF circuit, where blood is filtered via convection. Solvent and solutes are both forced from a high pressure in the blood compartment, to a low pressure in effluent circuit. The transmembrane pressure determines rate of ultrafiltrate production. CVVHF machines have pumps, air detectors, and pressure monitors throughout the circuit. Additional fluid can be added pre or post filter. Anticoagulation and fluids can be added at various points. Haemodiafiltration uses the same circuit plus dialysate solution (seen in figure 1) as it combines convection and diffusion (Yartsev 2016).

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CONFLICTS OF INTEREST

Dr Martin on the board of editors for the British Journal of Hospital Medicine.
Dr Dessain has no conflicts of interest.