EXTRACORPOREAL MEMBRANE OXYGENATION AND CONTINUOUS RENAL REPLACEMENT THERAPY.

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Based on the presentation "CAVH: Filtration on ECMO. Adults (and paeds)." Given at AmSECT 57th International Conference, March 8th, 2019.

Kramer[1] published the first patient series on continuous veno arterial haemofiltration in 1977 based on data from the previous few years. Within a few years of continuous AV haemofiltration being accepted as a treatment for overhydration it was being used with ECMO.

Heiss[2] documented 20 cases of neonates being treated with continuous ultrafiltration on ECMO between June 1981 and December 1986. Heiss also reported no complications or deaths were related to the haemofilter using the circuit design shown in Fig 1.

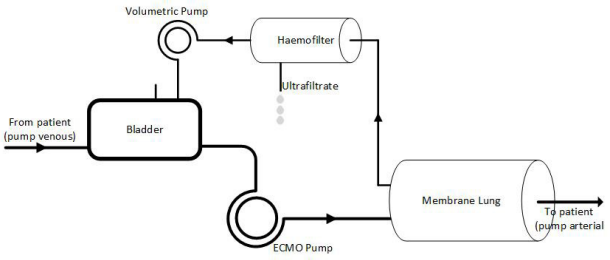

Fig 1.

According to ELSO data[3] from 1990 until 2018, renal replacement therapy used in conjunction with ECMO ranged from 14% to 55% across all patient groups.

Looking specifically in the adult patient population in a number of studies (Table 1.), since 2009 realistically ⅓ to ½ of patient will get concomitant filtration.

Study	Number of Patients	Number / % dependent on RRT
Brogan et al.[4] (2009)	1473	648 / 44%
Yan et al.[5] (2010)	67	30 / 44.8%
Wu et al.[6] (2010)	346	187 / 54%
Lan et al.[7] (2010)	607	301 / 49.6%
Chen et al.[8] (2011)	102	26 / 25%
Lee et al.[9] (2012)	185	76 / 41%
Kielstein et al.[10] (2013)	200	56 / 50.4%
Aubron et al.[11] (2013)	158	88 / 55.7%
Schmidt et al.[12] (2014)	195	103 / 52.8%
Haneya et al.[13] (2015)	262	131 / 50%
Antonucci et al.[14] (2016)	135	63 / 46.7%
Na et al.[15] (2018)	431	170 / 39.4%
Kim et al.[15] (2018)	732	219 / 29.9%
Kaushal et al.[17] (2018)	235	85 / 36.2%

Table 1.

In the paediatric world there is far more variation as demonstrated in a number of studies (Table 2.), and this may be due to the age related problems in adult patients giving a more consistent degree of Acute Kidney Injury (AKI).

Study	Number of Patients	Number / % dependent on RRT
Heiss et al.[2] (1987)	100	20 / 20%
Weber et al.[18] (1998)	55	38 / 69.1%
Hoover et al.[19] (2008)	86	26 / 30.2%
Santiago et al.[20] (2009)	23	19 / 82.6%
Smith et al.[21] (2009)	48	28 / 58.3%
Askenazi et al.[22] (2011 review)	7941	1786 / 22.5%
Paden et al.[23] (2011)	378	154 / 41%
Selewski et al.[24] (2012)	203	57 / 28%
Wolf et al.[25] (2013)	153	59 / 39%
Gupta et al.[26] (2014)	3502	170 / 13.8%
Lou et al.[27] (2014)	207	28 / 13.5%
KIDMO[28] (2016)	832	401 / 48%
Yetimakman et al.[29] (2017)	35	15 / 42.8%

Table 2.

There are four broad ranging but specific indications for filtration documented by Symons et al.30 in the paediatric population but the indications translate into all patient groups requiring continuous renal replacement therapy (CRRT). These are: Acute Renal Insufficiency/AKI; Fluid Overload; Biochemical Imbalance and Fluid Restrictions Limiting Medical Care. There are of course other indications such as poisoning and drug toxicity etc.

AKI:

Definitions of renal insufficiency and AKI indicate that they are often pretty much the same thing. However, the definition of AKI used by ELSO[31] includes the need for renal support therapy or serum creatinine > 1.5 mg/dL when the top end of the normal range is 1.2. Standard classifications for AKI are as follows:

RIFLE Classification Serum Creatinine Criteria

Risk: Increase in serum creatinine ≥1.5 x baseline or decrease in GFR 25%

Injury: Increase in serum creatinine ≥2.0 x baseline or decrease in GFR 50%

Failure: Increase in serum creatinine ≥3.0 x baseline or decrease in GFR 75% or an absolute serum creatinine ≥354µmol/L with an acute rise of at least 44µmol/L

AKIN Classification Serum Creatinine Criteria

Stage 1: Increase in serum creatinine ≥226.2 µmol/L or increase to ≥ 150-199% from baseline.

Stage 2: Increase in serum creatinine 200 – 299% from baseline

Stage 3: Increase in serum creatinine to ≥300% (≥3-fold) from baseline or serum creatinine ≥354 µmol/L with an acute rise of at least 44 µmol/L or initiation of RRT.

KDIGO defines AKI as being present if any of the following three criteria are met: 1. Increase in serum creatinine by at least 0.3 mg/dL (27 µmol/L) within 48 hours, 2. Increase in serum creatininer by at least 1.5 times baseline within the prior 7 days, or 3. Decrease in urine volume to less than 0.5 mL/kg/h for 6 hours.

KDIGO staging of AKI is similar to the RIFLE and AKIN criteria with the addition of inclusion of paediatric patients (<18 years) to KDIGO Stage 3 for those with an estimated GFR of less than 35 mL/min/1.73 m^2 (0.34 mL/s/m^2)

Does it matter if there is AKI before ECMO or after establishment of support? If the patient is already on filtration there are the questions of where does the circuit go and whether to change the filter anticoagulation.

Fluid Overload:

In his neonates Heiss[2] reported commonly seeing a 500gm increase from birth weight. Mobilisation of this third space can cause hypertension and delay the resolution of lung injury due to excess lung water.

In patients undergoing ECMO treatment, large-volume fluid administration is often needed. This is due mainly to disease type and severity. However, maintaining adequate blood flow for ECMO treatment also plays a part. Patients typically are subjected to a systemic inflammatory response within the first few days of ECMO treatment. This systemic response induces vasodilation and fluid loss to the interstitial compartment, resulting in reduced vascular volume. In addition, major conditions associated with patients undergoing ECMO, such as shock and low cardiac output as well as increased capillary leakage related to sepsis-like syndrome, are factors that contribute to fluid overload.

Administration of sufficient amounts of intravenous fluid to maintain a satisfactory extracorporeal blood flow is a critical component in the management of patients commencing ECMO support. Accordingly, 85.9% of the patients maintained a positive CFB. Jenks[32] thirty years later also noted that fluid overload is common.

Kim et al.[16] in their 2018 paper on adult ECMO patients and permissive fluid volume concluded:

- "Mortality risk began to increase significantly when cumulative fluid balance (CFB) was 82.3 ml/kg in the cardiovascular disease group.
- In patients with respiratory diseases, the mortality risk increase was significant for those with CFB levels above 189.6 ml/kg."

Biochemical Imbalance (other than those associated with renal insufficiency):

Serum electrolyte levels are frequently altered during critical illness. Sodium, potassium, phosphorus, calcium, and magnesium are lost in the effluent. Electrolyte levels are strongly determined by the electrolyte composition of the balanced dialysate solution and the efficacy of solute clearance by CRRT. Electrolyte disturbances are common in critically ill children. They may not only be the reason to initiate CVVH but also occur in > 50% of cases during CVVH. So in trying to fix one problem another arises.

Fluid Restriction Limiting Medical Care:

This is more a paediatric or even neonatal issue rather than an adult problem. It occurs when there is limited space to allow provision of parenteral nutrition or other solutions in oliguric patients. CRRT allows volume removal and permits quasi unrestricted feeding. Murphy[33] in her 2017 paper showed that institution of early CRRT in neonates on ECLS allows for administration of greater volumes of parenteral nutrition with improved protein delivery. This study characterizes one benefit of early CRRT initiation in neonates on ECLS and suggests these patients could experience improved nutritional outcomes.

Others:

A variety of toxins and drugs, such as toxic alcohols, lithium, salicylate, valproic acid, and metformin, are dialysable, and the timely use of RRT in cases of poisoning and drug intoxications with these compounds may be able to prevent serious complications. The ability of RRT to remove a particular drug or toxin from the circulation is a function of its size, volume of distribution, and protein binding. Therefore RRT is effective for the removal of smaller, nonprotein-bound molecules. However, because the goal in the treatment of intoxications and overdoses is the rapid clearance of the offending agent, conventional intermittent haemodialysis is generally preferred over CRRT in this setting, but in patients who are hemodynamically unstable combination of CRRT with ECMO is an option.

Types of CRRT/Filtration.

CRRT in non ECMO situations can be implemented with four different techniques (Fig 2.) using veno-veno access, and the choice of technique depends upon patient need and physician preference. Used in conjunction with ECMO, Veno-Venous access is generally replaced by Veno-Arterial access, but the modality of choice still remains based on patient need and physician preference.

Slow Continuous UltraFiltration (SCUF) uses the principle of ultrafiltration purely to remove excess fluid from the body and therefore is used to safely treat fluid overload. For this reason fluids removed are generally not replaced.

Continuous Veno-Venous Haemofiltration (CVVH) uses the same principles as SCUF; that is ultra-filtration. However the filter used in CVVH is different from that used in SCUF as convection to remove solutes is more important, so the size of the pores in the filter is increased thus allowing further molecules to pass into the ultra-filtrate. The fluid that is filtered from the blood is then replaced by a suitable fluid with chemistry similar to normal blood which is applied in either pre or post dilution. As this mode uses convection it is useful in removing molecules of all sizes depending on the size of the filter pores.

Continuous Veno-Venous HaemoDialysis (CVVHD) is driven by diffusion of molecules across a semi-permeable membrane along a concentration gradient. A dialysate with similar chemistry to normal blood is pumped counter-current to the blood through the filter. Any molecules that are in greater concentration in the blood are drawn across into the dialysate and removed from the body. Molecules which are low in the blood are also replaced by the normal levels in the dialysate.

Continuous Veno-Venous HaemoDiaFiltration (CVVHDF) is able to combine ultrafiltration, convection and diffusion to enable the ultimate removal and replacement of solutes and fluids within the blood. Combined to the fluids and molecules removed via convection and ultrafiltration the filter has a dialysate running counter current to blood flow to increase diffusive clearance. Ultrafiltration and convection also help with fluid and solute removal with fluids being either partially or fully replaced.

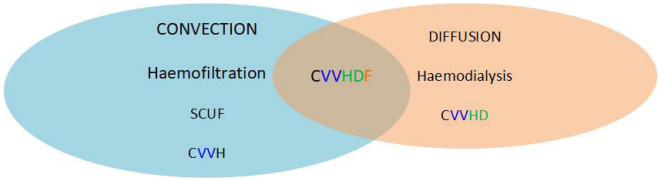

Fig 2. CRRT Techniques

Main Modalities of CRRT/Filtration Access with ECMO:

Separate Vascular Access.

This option requires additional vascular access and is most commonly used, when the filtration had been used prior to introducing ECMO. The advantages of this approach include no interference with either the systemic or the ECMO haemodynamics, and the ultrafiltration is controlled by the CRRT machine.

However, when the indications for filtration arise during ECMO, introducing another large venous catheter in a patient receiving high doses of anticoagulation is associated with the risk of multiple complications. Moreover, any additional vascular access sites should be reserved in case higher output of ECMO is necessary and an additional cannula is required because the blood supply from one inflow cannula is insufficient. This approach does not differ from filtration in patients not treated with ECMO.

Connecting a Filter into the Circuit.

There are several ways to do this depending on the type of circuit used and operator preference. Each method has advantages and disadvantages. Yorgin [34] in 1992 documented methods for circuits incorporating bladders in Fig 3., as did Seczynska et al.[35] in 2014 (Figs 4, 5, 7 -10) .

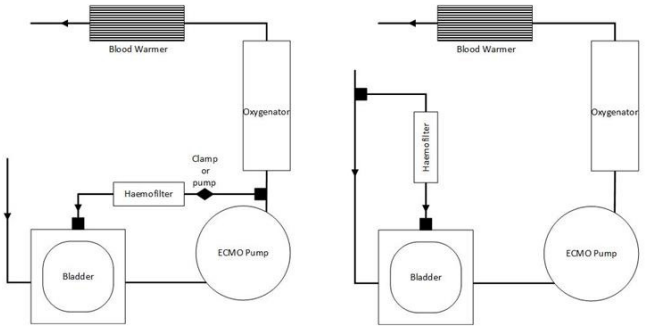

Fig 3.

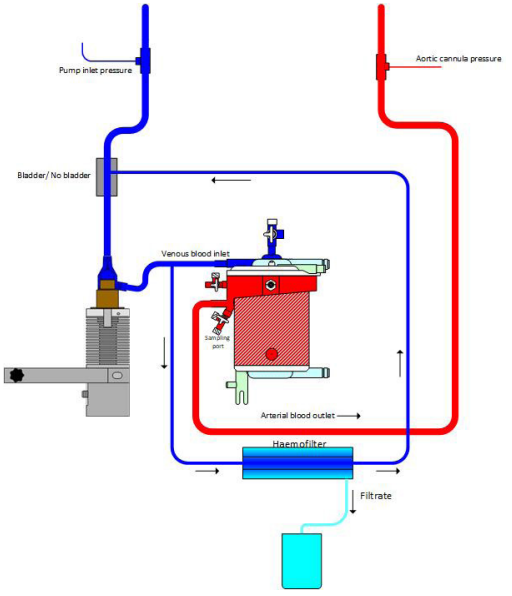

Fig 4.

These are the traditional methods where the filter and filtrate flows may or may not be accurately controlled, and can also be used in circuits without a bladder with the return being connected to the drainage limb from the patient.

Haemofiltration rate is controlled by manipulating the haemofilter transmembrane pressure with adjustable clamps on the filter outlet and inlet.

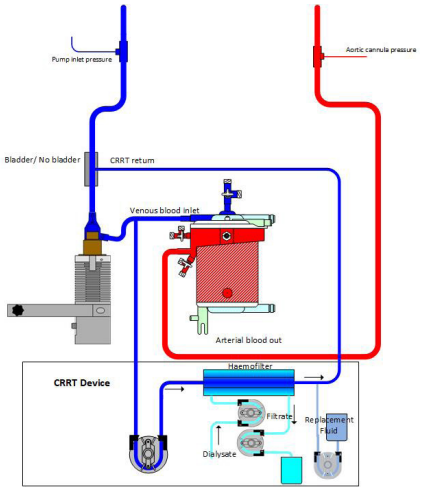

Fig 5.

Using a dedicated CRRT device enables accuracy of flows but the difference in pressure between the ECMO circuit and CRRT circuit and the need for additional connectors may be problematic.

Na[15] connected the inlet line of the CRRT circuit to the port of the post-pump ECMO circuit with an additional pressure control line (inner diameter 1.5 mm, length 30 cm; Hyupsung Medical Co., Gyeonggi-do, South Korea) to manage excessive pressure on the inlet line of the CRRT device transmitted from the positive pressure part of the ECMO circuit. He then modified the connection of the outlet line to the port of the ECMO circuit at the pre-centrifugal pump, adding an additional pressure control line similar to the connection of the inlet line of the CRRT circuit to the ECMO circuit. His findings suggest that the high positive or negative pressure values of the CRRT were attenuated and the lifespan of the CRRT circuit was significantly increased after using the additional lines on both the inlet and outlet lines of the CRRT device connected into the ECMO circuit. Furthermore, the use of multiple lines was not associated with an increase in haemolysis-related complications (Fig 6.)

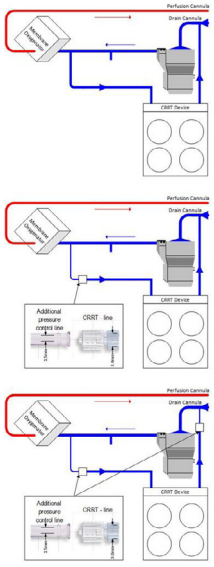

Fig 6.

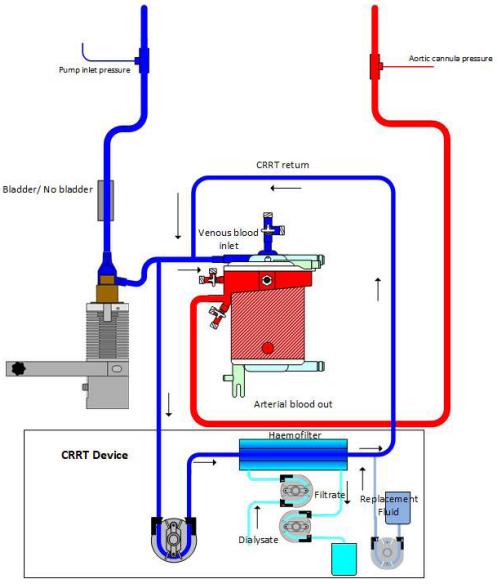

Fig 7.

Positioning both the CRRT inlet and return post-pump and pre-oxygenator still had connector and pressure issues.

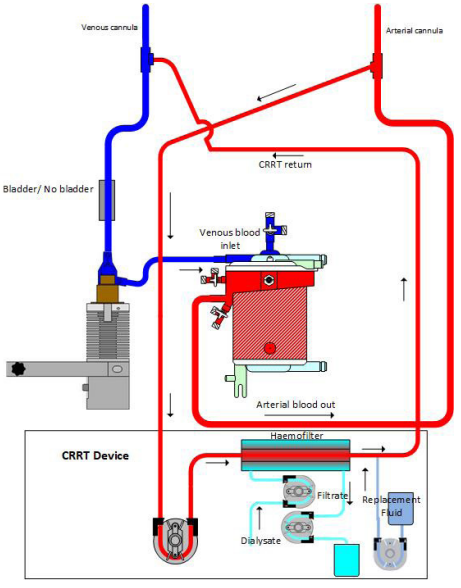

Fig 8.

Rubin[36] demonstrated this technique in 2010 in 21 patients without complication related to the technique. This technique is advantageous if the cannulae have Luer connections built in but adding connectors specifically for CRRT connection makes the ECMO circuit more complicated than it needs to be when an easy solution is to use the integrated ports on the oxygenator.

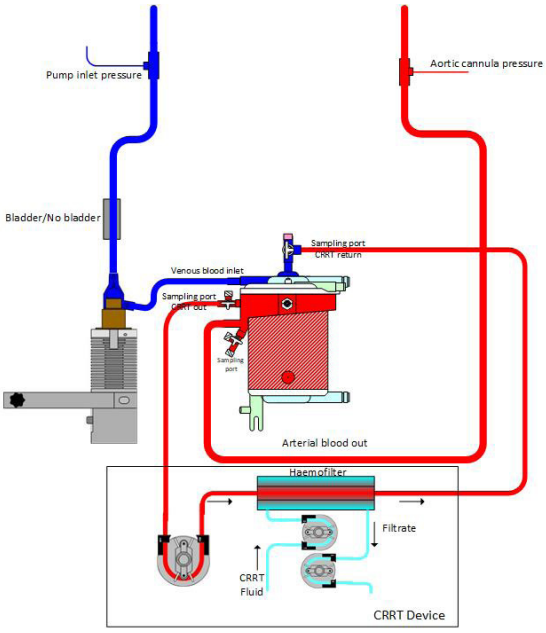

Fig 9.

Using the integrated Luer ports on the oxygenator means that you can monitoring pressure pre-and post-oxygenator on the CRRT device. Additionally the oxygenator works as bubble and clots trap, it prevents air entering the ECMO and CRRT circuits.

The disadvantage is high pressure for access and return lines CRRT, triggering alarms, blocking flow in the CRRT circuit. This is overcome by selecting positive access pressures from the set-up menu of CRRT machine for "arterial" and venous line of the CRRT. There is also a risk of clotting in the circuit associated with stopping the flow in the CRRT, but if three way taps are employed as seen in the diagram, turning the taps when the CRRT is turned off solves the problem.

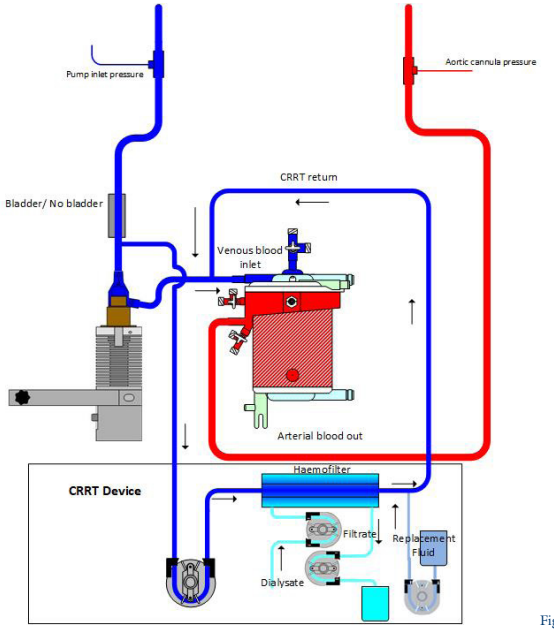

Fig 10.

In this set up the oxygenator also works as gaseous microemboli trap. However, connections with arterial line pre-pump and venous line post-pump can trigger low-pressure haemofilter inlet alarms and high-pressure return alarms in the CRRT circuit, respectively. These can interfere with pressure monitoring within the CRRT device reducing the lifespan of the haemofilter. The large difference in flow and pressure will increase shear stress, activate the clotting cascade and release unwanted cytokines. This can predispose to the potential haemolysis, disseminated intravascular coagulation and increased systemic inflammation.

Complications:

Is the number of potential complications for patients on ECMO with Filtration the sum of complications for those with ECMO alone and Filtration alone? It is more than the sum of the individual parts because the 2 systems interact.

Gaseous microemboli.

The findings from Shank et al.[37] suggest that adding CRRT drawing blood pre-pump and returning post pump pre-oxygenator is unsafe and not advised for clinical use. The centrifugal pump circuit showed significantly more microemboli for most configurations when a bladder was not used. Positions A and B significantly decreased the % of microemboli volume and count returned to the pseudo patient compared to C using a roller pump circuit. This studies results show the cumulative emboli count in the first 30 seconds after a 0.5ml bolus of air is added to the circuit. This is not necessarily representative of embolic activity during routine clinical operation.

The study by Erdoes[38] that showed a significant increase in gaseous micro emboli detected in the cerebral arteries of ICU patients on CVVHD compared to non CVVHD patients measured in 30 minute intervals. There is clearly ongoing microembolic activity attributable to the haemofiltration.

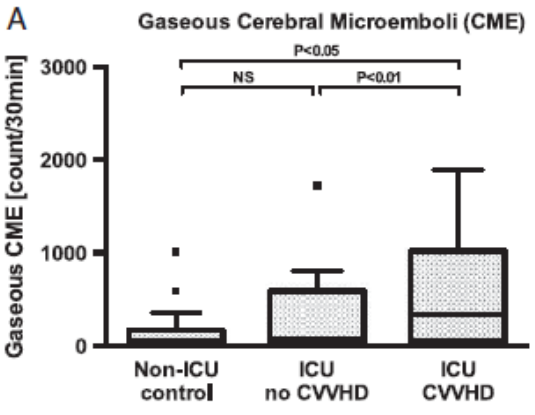

Fig 11.

From data collected for my units 2011 publication on the efficiency of integrated filters in oxygenators[39] we showed an association between microemboli count and initiation of haemofiltration on bypass. You can see that there is an initial burst of emboli but it quickly settles. The total count is half that Shank[37] counted with a bolus of air.

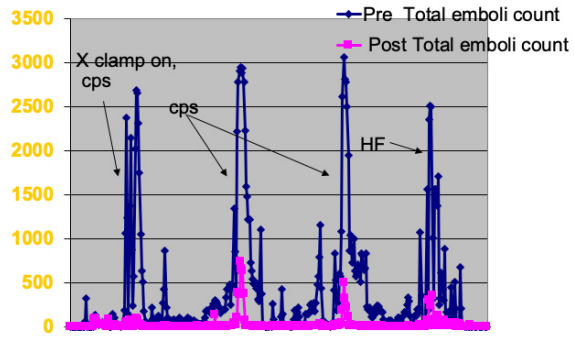

Fig 12.

Fluid Imbalance

In unstable patients with multiple organ failures and fluid overload, although ECMO alone can improve hemodynamic stability by increasing cardiac output via an ECMO pump (VA ECMO) and improved myocardial oxygenation, the presence of volume overload can nullify these advantages. Hence, maintenance of fluid balance is essential in the treatment of critically ill patients supported with ECMO and CRRT. ECMO can have haemodynamic consequences and can interfere with the reliable assessment of volume status. Standard markers of volume assessment like CVP can be unreliable in these patients. Also volume assessment can be made difficult by the myocardial dysfunction attributable to use of ECMO. Many pathways have been proposed for the development of this phenomenon including low ionized calcium at the onset of ECMO, effect of reactive oxygen species, toxic substances related to the ECMO circuit, noxious cytokines involved in inflammation during ECMO on the myocardium, retrograde nonpulsatile blood flow in femorally cannulated patients, particularly, with a history of left ventricular dysfunction, coronary hypoxia due to harlequin syndrome (exclusively seen with use of femoral arterial catheter placement in a VA ECMO configuration), and increase in left ventricular afterload.

To deal with fluid imbalance:

- Use the correct form of filtration.
- Know what your goal is.
- Is the goal compatible with the ECMO circuit?
- Rate of fluid removal?
- What exactly am I removing?
- Do I need to replace some of it?

Biochemical Imbalance

Hypokalemia is present in 5–25% of patients treated with CRRT and is mainly due to inadequate potassium supplementation. CRRT also frequently leads to electrolyte derangements, e.g. hypophosphatemia: the incidence of hypophosphatemia during CRRT varies between 10.9 and 65%; hypomagnesaemia etc., which may lead to complications such as hemolysis and rhabdomyolysis. In CVVH/CVVHD there is a loss of about 0.2 g amino acids/l of ultrafiltrate (up to 10–15 g amino acids per day), and of 5 g and 10 g/day of proteins, depending on CRRT modality and filter type. CRRT may cause significant modifications in the nutritional 'household' by inducing substantial and incompletely quantified losses of macro- and micronutrients. The amino acids glutamic acid, glutamine, cysteine and arginine have sieving coefficients similar to urea. Selenium and folate losses have also been reported by Zappitelli[40] in 2009. These have a potential effect on immune function and DNA synthesis during recovery from critical illness. Vitamins B1, B6, B9, and C are lost in the filtrate and losses should be compensated for in any replacement fluid as required. Trace elements, with the exception of selenium, are not cleared in relevant quantities. Manganese accumulation is of concern because of potential neurotoxicity.

To deal with biochemical imbalance:

- Know what your goal is.
- Use the correct form of filtration.
- What am I removing?
- What is in the dialysate?
- What is in the replacement fluid?
- How do I keep track of this?
- How often do I need to check?

Clotting/Anticoagulation

Clearly anticoagulation is not an issue if 8/15 papers listed in Table 3 do not even give details. If you have an anticoagulated patient there should be no need for regional anticoagulation, although Shum was reporting using citrate in low heparin or heparin free situations.

- Azar[41] 2018 - ECMO heparin
- Chadha[42] 2017 – no data
- Heiss[2]1987 – ECMO heparin
- Hoover[19] 2008 – No data
- Meyer[43] 2001 – No data
- Paden[23] 2011 – No data
- Qinhua[44] 2017- No data
- Rubin[36] 2010 – No data
- Santiago[20] 2009 – ECMO Heparin + 5u/kg/hr for CRRT
- Schmidt[12] 2014 – ECMO (APTT 50-70s)
- Shum[45] 2014 – regional citrate
- Symons[46] 2013 – ECMO heparin
- Tijssen[47] 2017 – No data
- Tsai[48] 2011 – No data
- Yetimakman[29] 2017 – ECMO heparin

Table 3.

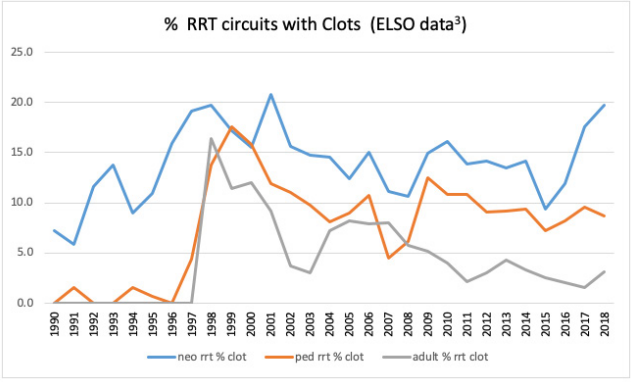

Fig 13.

According to ELSO data up to 2018[3] (Fig 13.) the percentage of clot in RRT circuits on ECMO varies with patient age but somewhere between 5% and 15% could be expected.

Anticoagulation for the CRRT:

The randomised study by Singer[49]used either unfractionated or low molecular weight heparin for anticoagulation of the haemofiltration circuit at 1000 and 600 U/h respectively. Samples were drawn at 1 and 2 h from arterial and venous limbs of the haemofilter circuit for measurement of plasma heparin (as anti-Factor Xa activity), antithrombin III and haematocrit. Ultrafiltrate samples were collected at the same time for measurement of anti-Xa activity. Singer concluded that despite their small sizes, neither unfractionated nor low molecular weight heparins cross the haemofilter membrane into the ultrafiltrate in any measurable quantity. Both heparins were present in plasma at a level suitable for therapeutic anticoagulation.

This is why standard heparin anticoagulation is not an issue and probably why it is not mentioned.

At RCH we use the following protocol which is similar to that of Santiago[19]:

- No heparin prime.
- Heparin 2 units/kg/hr pre-filter:
  - <10kg 20 unit/ml heparin solution (1000 units heparin in 50ml 0.9% NaCl)
  - >10kg 100 unit/ml heparin solution (5000 units heparin in 50ml 0.9% NaCl)
- Deduct the above 2 units/Kg/hr from the total heparin administered to the patient for the ECMO-related anticoagulation.
- Do not measure ACT/aPTT from the haemofiltration circuit.
- Target patient ACT/aPTT as per ECMO anticoagulation protocols.
- If CVVHF is discontinued before ECMO, increase by 2units/Kg/hr the total heparin administered to the patient.

The direct thrombin inhibitors (DTIs) Bivalirudin, Hirudin and Argatroban have been used to maintain CRRT haemofilter patency in small studies[50-54]. However there is a paucity of information regarding DTIs with ECMO and CRRT and in the Pieri[55] and Berei[56] papers anticoagulation for the CRRT circuit was not mentioned. One complication of using Bivalirudin is the degree of elimination through the filter. A study by Koster[57] showed it is dependent on the pore size of the filter.

Conclusion:

Combined use of ECMO and CRRT has numerous benefits. ECMO is an effective means of providing cardiorespiratory support for patients. ECMO support may also prevent myocardial damage that can be caused by inotropic agents or hypoxia, and enhance recovery of myocardial function. Both these factors tend to improve oxygenation and perfusion of organs including the kidneys which in turn may lead to more timely recovery of renal failure. Correction of hypoxia using ECMO generally results in the reduction of lactic acidosis. Adding CRRT (with bicarbonate-based solutions) can manage lactic acidosis avoiding fluid overload and hypocalcaemia in hemodynamically unstable patients. Combining ECMO with CRRT could result in speedy reversal of the metabolic consequences of lactic acidosis[12, 58, 59]. Another major advantage of combining ECMO with CRRT is the management of volume status. Improvement in fluid overload or improving fluid balance has been associated with improved lung function, speedier recovery of left ventricular function, better diastolic compliance, better contractility and less myocardial oedema, and time to weaning from ECMO and ventilator support. In addition to these advantages, starting renal replacement therapy also allows for the administration of required nutrition, medications, and blood products, while avoiding excessive fluid accumulation. It can correct azotaemia, electrolyte imbalance and decrease levels of inflammatory cytokines as well as reduce the effects of SIRS induced by the blood to artificial surface interface attributable to ECMO.

The basics for successful combination of ECMO and CRRT:

- The type of ECMO pump should influence the position of the CRRT device. With a centrifugal pump, the device should be connected after the ECMO pump because of the risk of air entrapment due to the negative pressure generated by centrifugal pumps.
- Regardless of the type of pump, the filtered blood from the CRRT device should be returned prior to the oxygenator to reduce the risk of air or clot being sent to the patient.
- Monitor and maintain desired electrolyte and volume levels.
- Anticoagulation is generally not an issue as standard ECMO anticoagulation protocols should suffice.
- Be aware of possible loss of non-heparin anticoagulant through the filter.
- CRRT/haemofiltration on ECMO has been in use for almost as long as ECMO. Using appropriate protocols it is safe.

References:

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