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# Acute kidney injury and extracorporeal life support

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## INTRODUCTION

The overall acute kidney injury (AKI) incidence of 7 to 10% in hospitalized patients has increased dramatically over the last several decades at a rate of 13%/year, which is probably related to increasing patient age, a higher comorbidity burden (including chronic kidney disease), and the aggressive nature of many diagnostic tests and treatments utilized in this population[1]. AKI results in an higher mortality rate which, in some series,exceeds 80%[2].

Organ failure, namely cardiac and respiratory, is a major risk factor for the development of AKI. The cross-talk between AKI and cardiorespiratory failure is a consequence of both direct loss of normal organ function and the inflammatory dysregulation associated with each organ failure[3]. Current clinical strategies are focussed on preventive and supportive measures, which for AKI include strict volume control and elimination of uraemic substances by renal replacement treatment (RRT).

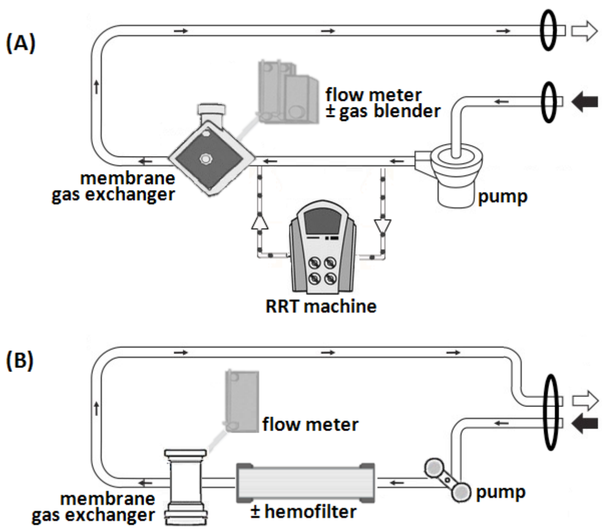
There are many strategies for dealing with cardiorespiratory failure, but the new kid on the block for severe refractory cases is Extraco rporeal Life Support (ECLS), which in the authors' experience has been a game changer in previously almost uniformly fatal situations. This editorial – developed essentially for nephrologists – presents an introduction to ECLS, summarizes AKI epidemiology and pathophysiology in ECLS patients, points out indications for RRT, explains technical aspects of concomitant RRT and ECLS, and discusses the future prospects of these techniques.

### Extracorporeal Life Support (ECLS)

ECLS is a general denomination comprising extracorporeal techniques in which blood is drained by an external pump to a membrane gas exchanger (which has a constant flow of fresh gas controlled by a flow meter and possibly associated gas blender) and then returned to systemic circulation (Figure 1). Centrifugal pumps (which have replaced roller or peristaltic pumps in ECLS) have radial rotating impellers which generate the driving pressure for the blood flow. The blood then interacts in the membrane gas exchanger (e.g., hollow-fibre polymethypentene low-resistance diffusion membranes) with a constant flow of oxygen (sweep-gas flow) which enables gas exchange[4,5].

**Figure 1**

Differences between high flow and low flow ECLS systems. (A) high flow systems (typically used for V-V or V-A ECLS) in which a RRT device can be integrated in the circuit; and (B) low flow system (typically used for ECCO2-R) can be integrated with an inline hemofilter (that can be either downstream or upstream of the gas exchange membrane)



Blood oxygenation and/or $CO_2$ removal are controlled by three features: (1) extracorporeal blood-flow rate, which is controlled mainly by modification of the centrifugal-pump speed; (2) sweep-gas flow rate, which is controlled by the flow meter; and (3) fraction of delivered oxygen in the sweep gas, which is controlled by the gas blender[6].

The different forms of ECLS depend on the pump blood-flow rate and the cannulation site.

**High-flow systems** use large bore cannulas (18-31F) to pump-drain blood at flow rates between 3.0 and 8.0 L/min and include Veno-Arterial ECLS (V-A ECLS) and Veno-Venous ECLS (V-V ECLS).

In V-A ECLS, full cardiorespiratory support is provided by pump-draining blood from a large vein (e.g., the femoral vein) passing it through the membrane gas exchanger and delivering it back to an artery (e.g., the femoral artery)[7]. It has been used, based on observational cohorts[8], in refractory cardiogenic shock (resulting from different aetiologies) after conventional therapies have failed, and in cardiac arrest (extracorporeal cardiopulmonary resuscitation, eCPR).

In V-V ECLS exclusive respiratory support is provided by pump-draining blood from a large vein (e.g., the femoral vein) passing it through the membrane gas exchanger, and returning it back to the right heart via a large vein access (e.g., the internal jugular)[7]. More recently bicaval dual-lumen cannulas (e.g., Avalon™, Maquet, Germany) have been introduced. These are inserted via the right internal jugular vein (only one upper-body cannulation site required) and drain blood from the superior vena cava through one lumen, which is then returned into the right atrium through a second lumen[9]. V-V ECLS has been used (based on observational cohorts[10] and one randomized controlled trial[11]) in refractory but potentially reversible respiratory failure after conventional therapies have failed to improve gas exchange. For nephrologists, it is interesting to notice that haemodynamically unstable patients can easily tolerate an extracorporeal blood flow > 3.0L/min, provided the appropriate large bore cannulas are used to feed the circuit.

While oxygenation necessitates high blood flows, $CO_2$ removal can be accomplished by much lower blood flows due to significant differences in $CO_2$ and oxygen kinetics. Only around 35mL of oxygen can be added to 1 L of venous blood (assuming a SvO2 of 75% and haemoglobin of 10g/dL); thus requiring a blood-flow rate of about 6.0-8.0 L/min to provide the body oxygen requirements of 250mL/min[12]. Additionally, as 1 L of blood contains around 500 mL of $CO_2$ and the $CO_2$ production is about 250 mL/min, a blood flow of 0.5 L/min would theoretically be sufficient to remove all of the $CO_2$ produced. However, in practice, this percentage is much lower (about 25% of total $CO_2$ production) because its efficiency depends on a multitude of variables (e.g., actual blood $CO_2$ content, haemoglobin concentration, exchange performance of the membrane)[12].

**Low-flow systems** use smaller bore dual-lumen cannulas (14-0 Fr) inserted via the right internal jugular (or femoral) vein to pump-drain blood using centrifugal or peristaltic pumps at much lower flows (<1.0 L/min) providing $CO_2$ removal exclusively, and are thus frequently referred as extracorporeal $CO_2$ removal ($ECCO_2$-R) systems[5]. This therapy can be provided by specifically allocated systems (eg, Hemolung®, ALung Technologies, USA; iLA Activve®, Novalung, Germany) or, more recently, integrated into renal-replacement therapy RRT-based systems[13-15]. These have been used (based on observational cohorts) for implementing ultraprotective ventilation strategies[16,17], and for the prevention of intubation in patients with chronic obstructive pulmonary disease[18,19].

## EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF AKI IN ECLS

Single-centre studies have shown that AKI occurs in 70-85% of all ECLS patients. Those with AKI and especially those who require RRT are at high risk of mortality, independent of potentially confounding variables[20,21].

Before ECLS initiation, patients are at high risk of AKI due to their clinical condition and the prevalent use of nephrotoxic medications. Moreover, AKI may be related to several conditions derived from or associated with the extracorporeal therapy; which are haemodynamic, hormonal and/or inflammatory in nature[20].

In patients with circulatory failure, AKI is generally due to the haemodynamic alterations associated with the baseline disease. These patients have increases susceptibility (frequently preexisting chronic kidney disease) and are, prior to ECLS initiation, under mechanical ventilation and high doses of vasopressors[20]. AKI results from an imbalance between factors able to protect renal function (e.g., increase in kidney perfusion obtained through support with V-A ECLS) and factors able to induce kidney injury (e.g., ischaemia-reperfusion damage or systemic inflammation). Moreover, during V-A ECLS, the continuous flow may not be enough to maintain adequate tissue perfusion and oxygen delivery in peripheral organs such as the kidney. The importance of pulsatile perfusion to maintain renal function, mainly preserving cortical blood flow, has been extensively demonstrated[22] requiring an assist rate greater than 80% to keep renal perfusion close to the physiological pulsatile flow. Furthermore, in the more haemodynamically stable patients requiring V-V ECLS, the native pulsatile cardiac output is maintained without impairment of renal perfusion[23].

In both V-A and V-V ECLS the blood shear stress and exposure to artificial surfaces may cause a hypercoagulable state, as well as systemic inflammation. The activation of neutrophils is a pivotal event which causes widespread microvascular injury, capillary leaks and multiorgan dysfunction[24].

The uraemic milieu directly leads to increase in pulmonary vascular permeability and upregulation of lung pro-inflammatory signalling molecules (e.g., IL-6 and IL-10) predisposing to ARDS[3]. This is of specific importance because it may validate the use of $ECCO_2$-R devices integrated into RRT-based systems.

Other potential causes of AKI in ECLS patients are iatrogenic aortic retrograde dissection during cannulation, which can involve renal arteries, and the roller or centrifugal pumps for the extracorporeal circuit which may induce haemolysis / haemoglobinuria, a well-known cause of AKI.

Finally, considering that each additional organ failure has a substantial detrimental effect on patient outcome, the increase in mortality due to the association between ECLS and RRT is not surprising. Lin et al. observed that a higher RIFLE stage at the onset of ECLS was associated with a significant increase in mortality rate for all patients (20% non-AKI, 57.1% for RIFLE-R, 72.2% for RIFLE-I, and 100% for RIFLE-F[21]).Of especial relevance is that of all patients needing RRT for AKI treated with ECLS, almost 50% survivals remain RRT dependent after discharge, leading to chronic kidney disease[25]. The main risk factor for this grim outcome, however, was the level of renal function at the initiation of ECLS.

## ECLS INTEGRATED RRT

### High-flow systems

All modalities of RRT (intermittent therapies, continuous RRT, and hybrid therapies) can be used to support ECLS patients with AKI and there are no comparative studies basing clinical practice on expert opinion and local experience[23]. Continuous RRT is the modality most common utilized because of the frequently associated haemodynamic instability and need for accurate and continuous fluid balances. This last point is extremely important because while the indications for starting RRT are relatively similar to those of non-ECLS patients, fluid overload treatment or prevention is the most frequent indication for RRT. Namely, early start of RRT may provide optimal management of nutrition, medications and blood products without further increasing the fluid overload[26]. This has been associated with improved outcomes by decreasing time on ECLS due to improved fluid management[27].

There are three main method for performing RRT during high-flow ECLS(26): (1) ECLS circuit-independent RRT through a dedicated venous access catheter; (2) inclusion of a RRT device monitor in the ECLS circuit; and (3) introduction of a hemofilter filter into the ECLS (in-line hemofilter).

The high-flow ECLS circuit provides the optimal access for RRT for most ECLS configurations and a separate venous access catheter is not required. However, V-V ECLS configurations using dual-lumen cannulas and V-A ECLS configurations with small return cannulas (≤17 Fr) may not support RRT due to excessive circuit pressures.

While the in-line hemofilter technique (hemofilter typically placed between the pump, which provides the forward flow, and the membrane gas exchanger, which traps clots and air) has the advantages of being relatively simple and inexpensive, most centres are abandoning it because of increased nursing workload, absence of pressure monitoring in the hemofiltration circuit leading to delayed detection of clotting or rupture of the filter, and poor control of net ultrafiltrate volume[23]. Therefore the inclusion of a RRT device in the ECLS platform is becoming the preferred method for performing RRT during high-flow ECLS[28].

The earlier school of thought was to connect the RRT machine to the venous limb of the ECLS circuit. However when using a centrifugal pump, the RRT connection must always be sited on the positive pressure (post-pump) part of the circuit (most current RRT software will accept this highly positive access pressure range after standard start). If a separated membrane gas exchanger and pump system (eg, Rotaflow/PLS platform) is used, the access and return lines for RRT are linked to two connectors between the outlet of the pump head (post-pump) and the gas exchanger (Figure 1A), with the access line proximal (closer to the pump head) and the return line distal (closer to the gas exchanger). Additionally, if an integrated gas exchanger and pump system (e.g., Cardiohelp/HLS platform) is used, the access line should be connected to the gas exchanger inlet port and the return line connected to the post gas exchanger connector.

As systemic anticoagulation in generally used during ECLS, regional anticoagulation of the RRT circuit is usually not employed. During low heparin or heparin-free ECLS situations there is a high risk of clot embolization, which shortens oxygenator lifespan and increases patient complications. The use of regional citrate anticoagulation is feasible, safe and effective during low heparin or heparin-free ECLS situations[29]. The usual blood flow rate on the continuous RRT circuit is 150-250 mL/min and the recommended effluent dose is 20-35 mL/Kg/h (to achieve this delivered dose it is generally necessary to prescribe in the range of 25-30 mL/Kg/h to account for machine downtime), as for other non-ECLS patients[28].

### Low-flow systems

Low-flow systems do not support RRT due to excessive circuit pressures. However, recently, $ECCO_2$-R gas exchange membranes have been integrated into renal-replacement therapy (RRT)-based systems. These systems can be used exclusively for $ECCO_2$-R if the gas exchange membrane is used stand-alone, or for $ECCO_2$-R and RRT if the gas exchange membrane is used coupled with a hemofilter[13-15].

The first of these devices was the Decap® (Hemodec, Italy) which uses a dedicated modified RRT circuit (including associated leak and bubble detectors) and incorporates a gas exchange membrane upstream to the hemofilter. Additionally, the ultrafiltrate from the hemofilter is returned to the bloodstream before the membrane gas exchanger membrane inflow, allowing additional $CO_2$ removal. This device in an initial animal study[30] demonstrated a 20% reduction of total $CO_2$ (while using a flow rate about 5% of the cardiac output) and has been reported in a small clinical study[17] and one case report[31] with promising results.

Since then other systems have hit the market[15] with little success (eg, Abylcap®, Bellco, Italy). More recently a new gas exchange membrane (Prismalung™, Novalung, Germany) which uses the RRT-based platform Prismaflex® (Baxter, USA) has been introduced. This $ECCO_2$-R can be used as stand-alone or with concomitant RRT in combination with a hemofilter (Figure 1B), with the gas exchange membrane dowstream to it. In an initial animal study (using a stand-alone gas exchange membrane) a satisfactory $CO_2$ clearance was obtained (14% reduction of total $CO_2$) demonstrating the applicability of the system[13]. The wide availability of the Prismaflex® platform has generated great enthusiasm but no additional clinical studies are yet available.

## FUTURE PROSPECTS

The Kidney Interventions during Extracorporeal Membrane Oxygenation (KIDMO) group is an international, multidisciplinary collaboration, composed of ECLS experts and nephrologists. This group promoted a change in the ELSO registry data collection forms to better document AKI and RRT, which will help in understanding the true incidence of AKI and its effect on outcomes[20]. Ultimately, prospective multicentre evaluations and intervention trials will be needed to develop strategies to prevent AKI, and optimize RRT in ECLS patients.

$ECCO_2$-R is largely an experimental technique which is not exempt from adverse events (e.g., cannulation and anticoagulation associated bleeding, thrombocytopaenia, intravascular haemolysis) and its future will be modelled by: (1) additional studies validating its cost-effectiveness in the referred indications; and (2) technical developments, enhancing the efficiency of $CO_2$ removal at low blood-flow rates[5].

A number of ongoing studies will provide additional information. A multicentre pilot study (SUPERNOVA; ClinicalTrials.gov NCT02282657) and a multicentre randomized controlled trial (REST; ClinicalTrials.gov NCT02654327) are assessing the safety/feasibility and efficacy of ECCO2-R facilitated ultraprotective ventilation strategies in ARDS patients. A number of ongoing studies (ClinicalTrials.gov. NCT02260583; NCT02107222; NCT02259335) are assessing the efficacy of ECCO2-R strategies in the long-term outcomes of acute hypercapnic respiratory failure patients.

Moreover, promising results have been obtained on the efficiency of $CO_2$ removal by the use electrodialysis (using an electrodialysis cell that regionally modulates blood electrolyte concentration to convert dissolved bicarbonate to $CO_2$ before entering the membrane gas exchanger[32]) and acidification of the extracorporeal blood (using organic acids – lactic or citric acid – that similarly convert dissolved bicarbonate to $CO_2$ before entering the membrane gas exchanger[33]).

## CONCLUSION

ECLS is a form of cardiorespiratory extracorporeal support which is progressively more used in modern critical care. AKI is frequently observed in patients supported with ECLS, related to their prior clinical condition or derived from this specific extracorporeal therapy. Many of these patients will need RRT, which can be safely performed but with issues unique to ECLS which must be carefully addressed. Thus, in the near future nephrologists will be more frequently involved in the care of ECLS patients, as members of the multidisciplinary team, to devise ECLS-specific protocols for the prevention and treatment of AKI (including RRT).

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