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From multiple organ support therapy (MOST) to extracorporeal organ support (ECOS) in critically ill patients

The complex nature of the multiple organ dysfunction syndrome (MODS) requires an integrated supportive therapy. Native organs have a continuous crosstalk and have in common in most cases an altered composition of the blood circulating and perfusing them. In this article we describe the concept of extracorporeal organ support (ECOS) for the treatment of combined organ dysfunction in critical illness. ECOS includes all forms of therapies where blood is extracted from the body and processed in different circuits with specific devices and techniques. Simultaneous application of different devices and circuits implies possible interactions among artificial organ support systems with potentially negative consequences. We propose a multidisciplinary effort to combine all these techniques avoiding mistakes and problems and we suggest the creation of a new generation of ECOS equipment with integrated features to avoid artificial organ negative crosstalk.

The management of critically ill patients in the ICU is progressively increasing in complexity (Kadri et al. 2017). Significant advances in care, comorbidity and advanced age of patients have led to a greater severity of illness at admission (Kaukonen et al. 2014). Simultaneous dysfunction of various organs is frequent, leading to the so-called multiple organ dysfunction/failure syndrome (MODS/MOFS) (Ziesmann and Marshall 2017).

The complex nature of multiple organ dysfunction syndrome

Several organ systems are involved in critical illness where initial impairment of one organ function is often followed by dysfunction or damage in other organs. This is especially true in the context of sepsis or other systemic disorders (Ziesmann and Marshall 2017). For example, the effect of acute kidney injury (AKI) on distant organs is now well documented (Kellum and Prowle 2018). This phenomenon may be observed with a primary injury to other single organs followed by secondary damage/dysfunction of other organs (**Figure 1**). The initial sequence of events often results in a vicious circle leading to a continuous negative organ interaction and a progressive worsening of the syndrome (Husain-Syed et al. 2015). This is typically the case in cardiorenal syndrome (CRS) where several bidirectional and temporally related heart–kidney interactions may lead to five different clinical subtypes (Ronco et al. 2008). The syndrome initiation, the primary organ involved and the mechanisms are different in nature: haemodynamic alterations and congestion, iatrogenic effect of interventions, direct toxicity of drugs or contrast media, neuro-hormonal derangements and immune-mediated/inflammatory damage (Husain-Syed et al. 2016). Nevertheless, after a significant organ crosstalk has initiated, the progressive dysfunction of both organs leads to significant worsening of the clinical picture.

> need for next-generation ECOS machines to achieve harmonisation of components, techniques, and operations of multiple extracorporeal therapies

Other conditions may involve acute and chronic lung disease scenarios leading to AKI or accelerated chronic kidney disease (CKD),

and vice versa (Husain-Syed et al. 2016). Some of these interactions include the participation of the heart in an even more complex cardiopulmonary-kidney crosstalk (Husain-Syed et al. 2015).

Critically ill patients may develop liver dysfunction in the context of MODS or may suffer from primary liver disorders. Liver dysfunction may become the trigger for several pathological pathways, eventually involving lungs, kidneys and brain (Siddiqui and Stravitz 2014). Combined liver and kidney dysfunction is common and described by different types of hepatorenal syndrome (HRS) (Fukazawa and Lee 2013). AKI represents a well-known complication of liver disease through different biological pathways and it is associated with increased morbidity and mortality. Renal dysfunction in cirrhosis is often functional in nature and secondary to haemodynamic derangements, cardiac dysfunction and altered plasma composition. Nevertheless, an increasing number of patients with cirrhosis may develop structural damage of the kidneys leading to a progressive deterioration of organ function (Arroyo and Jiménez 2000). In turn, once kidney function deteriorates in liver patients, a progressive worsening of the syndrome is typically observed with unfavourable outcomes.

Gut and kidney may also present reciprocal negative interactions due to primary alterations in host microbiome profile and disruption of gut barrier function leading to systemic inflammation, AKI, progression of CKD with effects on uraemic toxicity and potential increase in cardiovascular risk (Jacobs et al. 2017). On the other hand, the effects of AKI on the increased risk of bleeding and other derangements of the gastrointestinal tract have been described (Doi and Rabb 2016).

All these syndromes are often the result of a mixture of direct organ injury, secondary systemic disorders and altered tissue perfusion in different organ systems. Preexisting organ dysfunction can make the clinical picture worse (Rosenthal et al. 2018). Furthermore, primary and secondary organ injury/dysfunction results from a complex balance between individual susceptibility and exposure (insult) intensity (Agarwal et al. 2016). The interaction between these two factors is particularly evident in the case of sepsis where several organs are affected by an exaggerated and uncontrolled imbalance between the pro- and anti-inflammatory response of the host. The so-called immune-homeostasis is compromised and organ dysfunction is generally the result of altered blood perfusion and metabolism at the tissue and cellular level (Boomer et al. 2011). Although individual characteristics become less important when the intensity of exposure (insult) is overwhelming, the contribution of host response to organ injury may still be significant and precision medicine criteria should be applied for the final treatment strategy (Zieamann and Marshall 2018).

Multiple organ support therapy (MOST)

Critically ill patients with MODS require a complex and articulated therapeutic approach that includes pharmacological strategies (such as antibiotics for infection source control, circulatory and respiratory support, organ-specific drugs, correction of abnormalities of coagulation, electrolyte, acid-base, metabolism) and specific organ support systems. All these interventions should be integrated in a global strategy to support single organs and manage the combined effects of multiple organ crosstalk. In a seminal paper, we described the concept of *multiple organ support therapy* (MOST), identifying the possibility to provide simultaneous and combined support to different failing organ systems (Ronco and Bellomo 2002). MOST includes oxygenation and ventilatory support (invasive and noninvasive mechanical ventilation [MV], venovenous extracorporeal membrane oxygenation [ECMO] and extracorporeal carbon dioxide removal [ECCO$_2$R]), mechanical circulatory support (intra-aortic balloon pump, venoarterial ECMO, percutaneous and surgical ventricular assist devices [VADs] and total artificial heart), renal replacement therapy (RRT) and extracorporeal liver support (molecular adsorbent recirculating system, plasmapheresis and sorbent therapies). All these techniques are currently used in the ICU although very little is known about their interaction with native organs and other artificial organ support systems (Ronco 2006).

Extracorporeal organ support (ECOS)

Extracorporeal blood purification techniques such as haemodialysis or haemofiltration, have been used successfully for several decades to replace renal function in critically ill patients with kidney failure. New applications are today emerging for extracorporeal techniques. The experience with extracorporeal blood therapies in sepsis suggests redefining the spectrum of application, and we are today exploring the concept of *extracorporeal organ support* (ECOS) to describe all forms of therapies where blood is extracted from the body and processed in different circuits with specific devices and techniques (Ranieri et al. 2017). The principle for ECOS is that in MODS failing organs have in common the blood perfusing their tissues, and circulating blood becomes the target for specific treatments.

The idea of using extracorporeal therapies for sepsis came from the occasional observation that septic patients treated with RRT for AKI displayed a rapid and significant improvement in haemodynamics, with a reduced requirement of vasopressor support a few hours after application of the extracorporeal circulation. Further experiments demonstrated that the ultrafiltrate recovered from septic patients

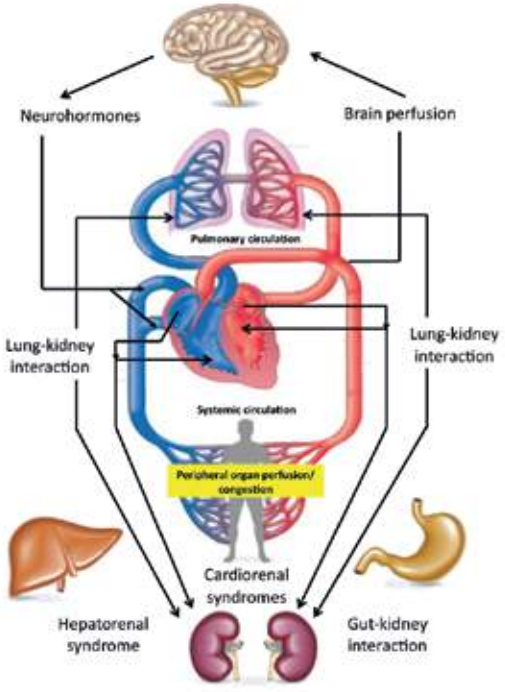

Figure 1. Schematic representation of different native organ interaction and crosstalk. The injury to one organ may result in a secondary damage/dysfunction of other organs whose compromised function activates a vicious circle and a worsening of MODS.

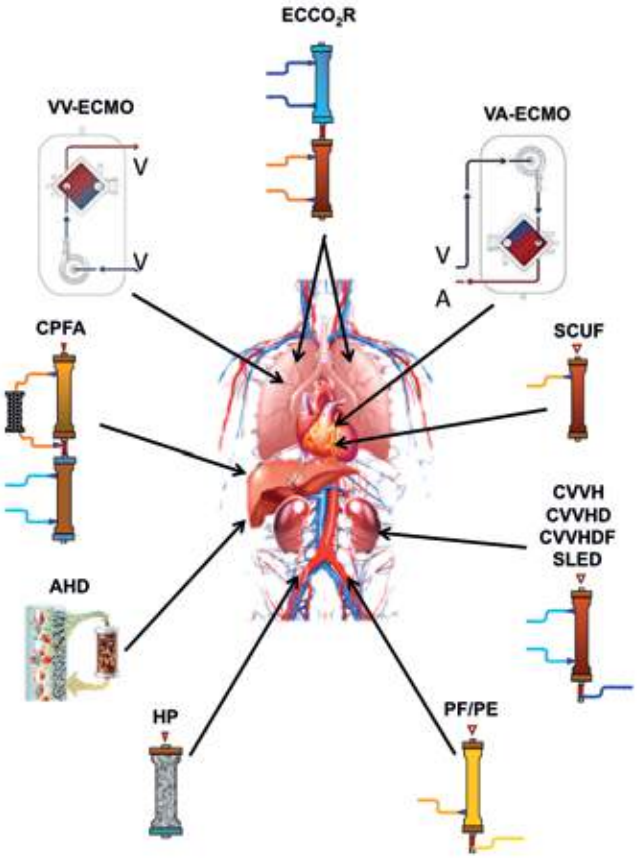

Figure 2. Schematic representation of current ECOS techniques

$ECCO_2R$ extracorporeal CO_2 removal VA-ECMO venous arterial extracorporeal membrane oxygenation SCUF slow continuous ultrafiltration CVVH continuous venovenous haemofiltration, CVVHD continuous venovenous haemodialysis CVVHDF continuous venovenous haemodiafiltration SLED sustained low efficiency haemodialysis PF plasmapheresis PE plasma exchange HP haemoperfusion AHD albumin haemodialysis CPFA continuous plasma filtration adsorption VV-ECMO venovenous extracorporeal membrane oxygenation
Minor modification of these seminal therapies have been reported in the literature but these represent the original concept

treated with haemofiltration and injected in healthy animals produced septic symptoms (Tetta et al. 1998). The improvement in septic manifestations in patients undergoing RRT suggested a possible reduction of circulating chemical mediators eliminated in the ultrafiltrate. The absence of significant variation in circulating levels of cytokines created some conflicting positions (Sieberth and Kierdorf 1999) that will never be resolved until a well-designed and adequately powered trial on extracorporeal therapies in sepsis in the absence of AKI is performed. Still, the question of whether mortality is the correct endpoint for such a study is wide open. Nevertheless, some hypotheses were formulated such as the peak concentration hypothesis (Honoré et al. 2006), based on the idea that a non-selective elimination of the peaks of both pro- and anti-inflammatory mediators might contribute to a restoration of a certain degree of immune-homeostasis and to a reduction of the severe imbalance produced by the exaggerated host response to bacterial invasion. Also, a personalised approach, matching RRT intensity with the risk of albumin and amino acid, catecholamine and antibiotic loss, should be advocated to avoid jeopardising the beneficial effects of extracorporeal therapies (Bagshaw et al. 2016). The culture of this approach comes from the discipline of nephrology. For years, chronic haemodialysis has sustained thousands of lives even though a clear understanding of the molecular basis of uraemia has not been achieved yet. A similar approach can be used for sepsis and multiple organ failure where altered blood composition represents the common ground for damage/dysfunction: whatever component is in excess or defect compared to its physiological concentration in blood, it can be removed or corrected by a specific extracorporeal treatment and device. This is the basis for the application of ECOS in critically ill patients (**Figure 2**).

Kidney support

Kidney support can be provided by different intermittent and continuous blood purification techniques such as intermittent haemodialysis, slow low-efficiency dialysis, continuous venovenous haemofiltration, haemodialysis, haemodiafiltration. These techniques, based on diffusive and/or convective transport of solutes and water transport by ultrafiltration across a semipermeable membrane, allow adequate blood purification, acid-base/electrolyte correction and volume control. In the case of sepsis, such techniques are further expanded with the use of high-volume haemofiltration (HVHF), coupled plasma filtration adsorption (CPFA) and high-cut-off membrane (HCO) applications. The last two techniques are also used when liver dysfunction or rhabdomyolysis are present and large molecular size molecules are to be removed from the circulation. In the case of protein-bound solutes, albumin dialysis (AHD) has also been suggested as well as plasmapheresis (PP) or plasma exchange (PE). A special nomenclature has been created to better define the characteristics of each component of the extracorporeal circuit (Neri et al. 2016) and each specific technique (Villa et al. 2016).

Adsorption

Adsorption has been proposed as a third mechanism for solute removal from the circulation. Sorbents prepared in specific cartridges can be placed in direct contact with blood as in the case of direct haemoperfusion (HP), or used after plasma filtration (PF) from whole blood (PFAD) to avoid direct contact of platelets and white cells with the sorbent particles. After plasma is processed in the sorbent bed, blood is reconstituted and returned to the patient. HP has been used for years in case of acute intoxication, hyperbilirubinaemia and immunoadsorption. Recently, biocompatible sorbent devices have been created for endotoxin removal (polymyxin-B haemoperfusion [PMX-HP - Toray Medical Company]) or cytokine removal (cartridges for HP from Cytosorbents Corporation, Jafron Biomedical or others) in severe sepsis or septic shock.

Heart support

Heart support has been originally achieved removing the excess of fluid in the body by ultrafiltration when diuretics cannot provide adequate diuresis. The spectrum of extracorporeal techniques has today expanded to other options. Venoarterial (VA-ECMO) is used in patients with acute cardiac or circulatory failure to restore end-organ perfusion and organ function, and to bridge either to recovery, to definite cardiac support (e.g. ventricular assist devices, VADs) or heart transplantation. MODS is particularly common in patients requiring cardiac support and use of lung support and RRT may become additionally necessary (Van Dorn et al. 2018). Again VA-ECMO is part of ECOS because blood is processed outside the body while VAD, Total implantable heart, Impella® (Abiomed) or intra-aortic balloon pumps technologies belong to the MOST category but not to ECOS.

Lung support

Lung support in the context of ECOS has been traditionally identified with venovenous (VV)-ECMO. VV-ECMO is mostly used for correction of hypoxaemia refractory to lung-protective ventilation and prone position in patients with severe acute respiratory distress syndrome. The experience coming again from haemodialysis brought into clinical practice however the possibility to achieve partial lung support with a certain removal of CO_2 from the circulation. This concept of "respiratory dialysis" has further evolved to a system where a small oxygenator is placed in series with a CVVH circuit (Romagnoli et al. 2016). The technique called $ECCO_2R$ is used as an alternative or supplement to mechanical ventilation for correction of hypercapnia, but not for blood oxygenation since the blood flows through the circuit are relatively low (350-450 ml/min). Recently, RRT in conjunction with $ECCO_2R$ has been advocated to allow "super-protective" MV settings, and reduction of vasopressor demands in patients with ARDS experiencing AKI (Allardet-Servent et al. 2015). In some cases, $ECCO_2R$ can also allow continuation of noninvasive MV, thus avoiding invasive MV.

Liver support

Liver support can be provided by albumin dialysis, plasma filtration/adsorption, plasma exchange and haemoperfusion. Not only removal of bilirubin and other protein-bound toxins can be achieved by these techniques, but also significant reduction of ammonium level can be observed during treatment. The Molecular Adsorbent Recirculating System MARS® (Gambro®), Prometheus® therapy system (Fresenius Medical) and other equipment based on cascade filtration and dialysis with albumin-based dialysate and sorbents are today available for this purpose (Faybik and Krenn 2013).

Native and artificial organ crosstalk

There is a clear need to explore crosstalk and interactions between different organ systems in the critically ill patient. The literature on complex syndromes with multiorgan involvement emphasises the need for multidisciplinary management. In these conditions, the level of multiple organ dysfunction makes MOST highly recommended or even mandatory. Frequently however, patients who display clear indication for ECMO and are undergoing such a complex therapy, may require further organ support with the addition of RRT, liver support, haemoperfusion for detoxification, or cardiac support. In these circumstances, extracorporeal support and organ replacement may become safer and more uniform if different functions are combined in a fully integrated hardware. Fluid balance, solute removal, CO_2 removal, aromatic amino acid removal, electrolyte and acid base equilibration, blood detoxification and oxygenation should be considered a continuum, where the artificial organ crosstalk is constant. Variations in CO_2 must consider the use of buffers in dialysis or the application of citrate as anticoagulant for an adequate equilibrium of acid-base. The future is likely to see the introduction of a unified hardware with special circuitry that will allow performance of all different organ support therapies on demand, simply escalating or de-escalating the complexity of the system. Thus, from ECMO and RRT, a patient may be progressively moved to $ECCO_2R$ and intermittent haemodialysis and, finally, even be discharged with organ support including chronic haemodialysis and respiratory dialysis in case of non-recovery or progression towards chronic illness.

Next generation ECOS equipment

If MOST is applied and especially in the context of multipurpose ECOS, artificial organ crosstalk should be considered by a multidisciplinary task force to avoid negative interactions and unwanted side effects. An integrated monitoring of patients, chemistry and machine parameters will offer the basis for "smart" biofeedback leading to correction in prescription and delivery of extracorporeal organ support (Ricci et al. 2017).

We strongly advocate the need for next generation ECOS machines to achieve harmonisation of components, techniques and operations of multiple extracorporeal therapies. We suggest the possibility to perform simultaneous multiple functions and techniques optimising artificial organ crosstalk while avoiding unwanted side effects or operational drawbacks due to poor integration of prescription and delivery parameters. Further studies are needed to establish the ideal timing of interventions, to find out whether early implementation impacts organ recovery and optimises resource utilisation, and to identify the patient groups that can be expected to benefit from long-term organ support. ■

Conflict of interest

Claudio Ronco declares he has no conflict of interest. Zaccaria Ricci declares he has no conflict of interest. Faeq Husain-Syed declares he has no conflict of interest.

Abbreviations

AHD albumin dialysis
AKI acute kidney injury
CKD chronic kidney disease
CPFA coupled plasma filtration adsorption
$ECCO_2R$ extracorporeal carbon dioxide removal
ECMO extracorporeal membrane oxygenation
ECOS extracorporeal organ support
HCO high-cut-off membrane
HP haemoperfusion
HRS hepatorenal syndrome
HVHF high volume haemofiltration
MODS/MOFS Multiple Organ Dysfunction/Failure Syndrome
MOST multiple organ support therapy
MV mechanical ventilation
PE plasma exchange
PF plasma filtration
PFAD plasma filtration adsorption dialysis
PP plasmapheresis
RRT renal replacement therapy
VAD ventricular assist device

References

For full references, please email editorial@icu-management.org or visit https://iii.hm/hwx