CHAPTER 123

Extracorporeal Membrane Oxygenation and Renal Function

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OBJECTIVES

This chapter will:

1. Briefly summarize the definitions and markers of acute kidney injury.
2. Review the recent literature on incidence and outcomes of renal failure in patients supported with extracorporeal membrane oxygenation (ECMO), as well as the literature on the use of renal replacement therapy in ECMO patients.
3. Describe the relationship between ECMO and acute kidney injury, possible risk factors, and related pathophysiology.

EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO) is intended to provide temporary extracorporeal respiratory support by the use of an artificial membrane lung in case of pulmonary failure unresponsive to conventional treatments. ECMO is indicated in case of high mortality risk, provided the underlying pathology is potentially reversible. Indeed, ECMO provides a life support system that enables evaluation, diagnosis, and, possibly, resolution of the most severe acute lung diseases. Although the technique was intended originally to buy time for the lungs to heal,[1] ECMO is now recognized as a powerful tool to allow lung rest and foster recovery by minimizing the invasiveness of mechanical ventilation. In patients with respiratory failure, the common approach is the venovenous VV-ECMO bypass in contrast with the venoarterial VA bypass, which is used in the presence of severe heart failure. Impaired renal function is frequent in all conditions requiring ECMO, and ECMO can affect the renal system. Physiologic, clinical, and technical aspects of VV- and VA-ECMO treatments are described in dedicated chapters of this book. Here, we discuss the effects of VV-ECMO on renal function in adult patients, focusing on the incidence and pathophysiology of renal failure in ECMO patients. A brief description of the techniques available for combined ECMO and renal replacement therapy also is included.

ACUTE KIDNEY INJURY IN EXTRACORPOREAL MEMBRANE OXYGENATION PATIENTS

Acute kidney injury (AKI) identifies a rapid deterioration of kidney function, characterized by reduced glomerular filtration rate (GFR) and urine output yielding increased serum creatinine. The definition of AKI evolved over the years and recently the KDIGO (Kidney Disease: Improving Global Outcomes) task force revisited the original RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) and AKIN (Acute Kidney Injury Network) criteria. All the definitions are based on clinical and physiologic markers (e.g., serum creatinine, electrolytes, and urea nitrogen plus urine output), and the RIFLE and the AKIN criteria, from which the KDIGO definition derived, have been validated in various patient populations including ECMO[2–6] and showed high sensitivity and specificity[2,7–11] and a good capacity to predict clinical outcomes.[4,9,12] However, current physiologic markers for AKI (elevated serum creatinine and decreased urine output) are not adequate for early diagnosis, because

their changes occur late and often are influenced by many other factors (e.g., serum creatinine increases only when GFR declines more than 50%) and, for this reason, other markers are under investigation. Among the other candidates, one of the most sensitive[13] appears to be the neutrophil gelatinase-associated lipocalin (NGAL), but, up to now, neither NGAL nor any of the others proposed biomarkers has replaced serum creatinine (SCr) in AKI definition.

AKI is a common complication in critically ill patients treated with extracorporeal lung support, and it may be associated with worse outcomes. The Extracorporeal Life Support Organization (ELSO) registry defined *renal complications* in ECMO patients by serum creatinine values between 1.5 and 3 mg/dL or higher and/or the need for dialysis. The ELSO reported in 2012 that, among adult patients supported by VV-ECMO for severe respiratory failure, SCr elevation between 1.5 and 3 mg/dL occurred in 18.9% of the cases (survival 37%), whereas in 12.9% of the cases SCr exceeded 3 mg/dL (survival 39%); dialysis was used in 14.2% (survival 39%), hemofiltration in 23.3% (survival 51%) and, finally, continuous arteriovenous hemodialysis (CAVHD) in 12.5% cases (41% survival).[14] Studies using AKIN and RIFLE definitions reported an incidence of renal failure in adult patients with respiratory failure ranging between 34% and 78%[15–17] with resulting mortality up to 80%. Lin et al. reported 78% mortality in patients with AKI versus 20% in non-AKI patients treated with ECMO.[18] Kielstein et al. reported an 87% mortality rate in ARDS patients with AKI requiring RRT treated with ECMO.[19] The use of renal replacement therapy (RRT) in adult patients in published ECMO series ranges between 25% and 68%.[20] Zangrillo et al. reported that renal failure requiring continuous hemofiltration occurred in 52% of the patients[21] treated with ECMO, ranking among the most common complications. Haneya et al., in a retrospective observational study in 262 adult patients with ARDS treated with VV-ECMO, found that 50% of the patients required RRT for renal failure or fluid overload (FO)[17]. The need for RRT in patients receiving ECMO support is associated with increased mortality.[17,18,22] In ECMO patients, the need for RRT may reflect inadequate renal perfusion or direct injury to the kidney either because of the disease process itself or to ECMO-associated side effects (e.g., hemolysis, multiple transfusion).[19,23] Evidence of fluid overload (FO) usually plays a key role in the decision to start RRT in ARDS treated with ECMO, and it is a factor associated with longer ECMO duration and higher mortality.[24] In fact, according to an online survey regarding renal support therapy during ECMO based on 65 international ECMO centers, the predominant indication for RRT was the treatment (43%) or prevention (16%) of FO.[24] Haneya et al. reported that FO was the indication for RRT in 66% of their cohort of ECMO patients and that early RRT application for FO prevention improved the outcome and did not seem to affect mortality.[17]

PATHOPHYSIOLOGY OF ACUTE KIDNEY INJURY IN EXTRACORPOREAL MEMBRANE OXYGENATION PATIENTS

The pathophysiologic mechanisms possibly leading to kidney injury in patients treated with ECMO remain poorly understood and evidences on positive or negative cause/effect interactions between ECMO and AKI lack. Patients receiving ECMO, in fact, are often affected by multiple organ dysfunctions, including renal failure, before the initiation of the extracorporeal treatment. ECMO application, in these cases, can improve oxygenation or perfusion but it also could lead to worsening of renal function. This makes it difficult to identify the ultimate cause of renal failure during ECMO.

TABLE 123.1

Possible Positive and Negative Effects of Extracorporeal Respiratory Support

POSITIVE EFFECTS	NEGATIVE EFFECTS
Allows superprotective ventilation	Foreign surface contact
Minimizes VILI and circulating inflammatory mediators (biotrauma)	↓ Platelet drop
Lower airway pressure	↓ Release of inflammatory mediators
Lower intrathoracic pressure	Risk of bleeding
↓ Improved hemodynamics	Transfusion
Improved kidney function	

VILI, Ventilation-induced lung injury.

Kilburn et al. recently provided an extensive review of the literature treating the complex relationship between ECMO and AKI, possible risks, and benefits and the related pathophysiology.[25] Villa et al.[23] treated the same issue: they schematically grouped the pathophysiologic mechanisms leading to AKI during ECMO in the following:

- *ECMO-independent/patient-related* (pretreatment variables or leading to ECMO initiation, which may cause AKI). Hemodynamic alterations resulting from the baseline disease may lead to low cardiac output and reduced renal perfusion. Aggressive life-sustaining interventions before ECMO initiation in critically ill patients with severe refractory cardiopulmonary insufficiency may increase the risk of AKI resulting from sepsis, ischemia, respiratory failure, cardiac failure, vasopressor requirements, and nephrotoxic agents.[16]
- *ECMO-related (variables directly originating from ECMO therapy, which may cause AKI).* ECMO-related variables include hemodynamic factors, hormonal factors, systemic inflammation related to ECMO, organ cross-talk, and circuit-related factors.

Here, we briefly review only the second type ECMO-related factors. Table 123.1 summarizes positive/negative effects of Extracorporeal Respiratory Support and their relationships.

HEMODYNAMICS

Venovenous ECMO maintains the native pulsatile blood flow, and it has multiple possible advantages on cardiac, pulmonary, and renal function.[16,26] The ECMO circuit is in-series with the natural circulation, and blood is drained from and returned to the venous system. This implies no acute volume changes, with unchanged preload and afterload of the left ventricle.[27] As blood reaches the right heart at a higher-than-normal oxygenation level, this venous "hyperoxia" may contribute to unload the right heart and increase cardiac output by a reversal of hypoxic pulmonary vasoconstriction.[28,29] In addition, the resolution of severe hypercapnia after the institution of VV-ECMO also may contribute to a reduction of pulmonary hypertension and right ventricle (RV) afterload.[30,31]

After ECMO initiation, certain management strategies such as intravenous fluid administration, the use of diuretics, vasopressor therapy, and PEEP may lead to hemodynamic instability, altering continuous renal blood flow with consequent ischemia/reperfusion-associated AKI.[23,25]

Villa et al. pointed out that also the downregulation of hormonal pathways occurring during VA-ECMO may induce

renal failure.[23,32,33] A study on preterm lambs, comparing the endocrinologic response during VA- and VV-ECMO, suggested that VV-ECMO possibly may be less invasive than VA-ECMO for the fetal heart, because atrial natriuretic peptide (ANP), an index of cardiac distress, was lower in VV-ECMO as compared with VA-ECMO.[34]

Fluid balance is another factor determining the incidence of AKI during ECMO as cumulative FO is an independent factor of mortality that may worsen gas exchange, increase the length of stay and the duration of mechanical ventilation in patients on ECMO. The international ELSO guidelines recommend that the goal of fluid management should be to "return the extracellular fluid volume to normal (dry weight) and maintain it there." Moreover if "the diuretic response is not sufficient to achieve negative fluid balance, or if the patient is in overt renal failure, continuous hemofiltration is added to the extracorporeal circuit to maintain fluid and electrolyte balance."[35]

COAGULATION AND SYSTEMIC INFLAMMATION

The contact of the blood with nonbiologic surfaces, sheer stress, and turbulence may trigger the coagulation and inflammatory response pathways. Within 1 minute of starting the extracorporeal support platelets already adhere to the circuit.[36] The initial reaction of blood is based on the interaction between the surface of the extracorporeal circuit and the plasma proteins, producing a monolayer of proteins on the surface of the circuit and oxygenator, which is represented mainly by fibrinogen, albumin, and γ-globulins.[37] The fibrinogen layer in turn triggers platelet adhesion to its receptors. Once adhered to fibrinogen, platelets become activated and undergo a shape change leading to aggregation between them and with leukocytes.

It has been reported that circulating platelet count decreases by 26% during the first 15 minutes of ECMO, and by another 16% in the following hour.[38] The activation and consumption of platelets is a continuous phenomenon throughout the course of extracorporeal support often requiring platelet transfusion.[39] Simultaneously, the coagulation system becomes activated through the contact activation pathway. The inflammatory response during ECMO is rather similar to the activation occurring during systemic inflammation and ARDS.[36] Contact with foreign surfaces activates the complement system through the alternative pathway.[40] Activated complement factors induce the synthesis of cytokines belonging to the subgroups of proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor-alpha (TNF-*a*) and antiinflammatory (IL-10) cytokines.[41–43] Proinflammatory cytokines amplify the response of neutrophils, which adhere to the capillary/venular endothelium and undergo degranulation to produce cytokines, arachidonic acid metabolites, and reactive oxygen species, causing widespread microvascular injury and multiorgan dysfunction.[44] Kidneys are a target of coagulation derangement and inflammation storm induced by ECMO, which may alter their perfusion and function, more or less reversibly.

ORGANS CROSS-TALK

Acute kidney injury often occurs, in the setting of multiorgan failure, in combination with acute lung injury. The combination of the two reaches mortality rates as high as 80%. A model of self-propagating cycle of AKI and acute lung injury has been proposed, in which AKI induces pathophysiologic effects on the lung and ALI, in turn, exacerbates kidney injury. The effects of acute lung injury on AKI are mediated by hypoxia, hypercapnia, positive pressure ventilation, and biotrauma. This leads to reduced renal perfusion, impaired kidneys excretory function, blood-gas disturbances, and inflammation-apoptois.[25,45]

Patients undergoing VV-ECMO with respiratory failure and receiving lung protective ventilation often have suffered prolonged hypercapnia before connection to ECMO, which can alter hemodynamics and renal blood flow significantly.

Finally, invasive mechanical ventilation is a risk factor for acute kidney injury in the critically ill patients.[46] Thus, in patients requiring ECMO, timely initiation may mitigate pre-ECMO risk factors for renal dysfunction.[25] Raised intrathoracic pressure secondary to high PEEP on ECMO may induce renal hypoperfusion and impair the kidneys' excretory function. The more severe the ARDS, the higher is the risk of ventilator-induced lung injury (VILI) and systemic inflammation linked to mechanical ventilation (biotrauma). This induces kidney injury directly by mechanical factors (high intrathoracic pressures) and by the release of inflammatory mediators from the mechanically injured lung. ECMO has the capability of decreasing the need for alveolar ventilation down to levels potentially as low as zero. This effect allows tidal volume and respiratory rate to be tailored to minimize ventilator-induced lung injury to the lowest possible level (superprotective ventilation), and sometimes may allow for complete liberation from ventilator assistance.

RENAL REPLACEMENT THERAPY DURING EXTRACORPOREAL MEMBRANE OXYGENATION

Another chapter in this section extensively reviews renal replacement therapy (RRT) strategies during ECMO. In this paragraph, we briefly underline only the main points for completeness.

As previously told, recent studies report that nearly 50% of the patients treated with ECMO require RRT[17,21] and that RRT in ECMO patients is used as treatment for FO (43%), prevention of FO (16%), supportive treatment of AKI (35%), and to correct electrolyte disturbances (4%).[24]

Several RRT treatments are available during ECMO, including intermittent hemodialysis (IHD), peritoneal dialysis (PD), continuous renal replacement therapies (CRRT), the most commonly used being CRRT.[20] Despite the absence of precise guidelines recommending a particular technique, there are three main modalities of combining CRRT and ECMO:

Classic independent CRRT access requiring an additional vascular access. This is the most commonly used modality when the CRRT had been initiated before ECMO institution, and it has the advantage of no interference with ECMO. However, if the indications for RRT arise during ECMO, introduction of another large venous catheter in a patient receiving high doses of anticoagulation is associated with high risk of multiple complications.

Introduction of an in-line hemofilter in the ECMO circuit. The connection of the dialysis inlet to the ECMO circuit is made after the ECMO pump, before or after the oxygenator,

while the outlet is pre-ECMO pump or to the ECMO bladder. This is a relatively simple and economic technique requiring smaller amounts of priming volumes and no need of an additional external pump. However, in this technique, ultrafiltrate measurement can have significant errors and, if the inlet is after the oxygenator, it decreases ECMO efficiency by recirculation.

Introduction of an external CRRT machine in the ECMO circuit. Different configurations have been reported in literature. Usually, the CRRT inlet is connected to the venous line of the ECMO circuit before the roller pump and the blood then is returned from the CRRT machine to the ECMO circuit before the roller pump (before or directly to the bladder). If a centrifugal pump is used, the inlet of the CRRT machine should be connected after the pump to avoid air entrainment and the blood returned to the venous limb of the ECMO circuit before the pump.[16,20]

Other studies, reporting the combined use of VV-ECMO and CRRT, connected the CRRT machine to the luer port on the outlet of the oxygenator and the blood returned to the luer port on the inlet of the oxygenator.[47,48] Finally, other authors connected the inflow of the CRRT machine to the venous limb of the ECMO circuit before the pump and the outflow to the venous limb of the circuit pre-oxygenator.[49,50] The substantial risks are blood loss during the connection of CRRT to the ECMO circuit because of the high positive pressures and air entrapment in the pump and oxygenator when the connection is made within the negative pressure line.

Details, advantages, and disadvantages of the various techniques are reported in reviews and meta-analysis.[20,51] One of the problems of positioning an external CRRT machine in the ECMO circuit is the access pressure alarms on the CRRT machine. Typically, the default access pressure alarms are set at negative values while the blood presenting at the entry point of the CRRT machine is at pressures close to zero or positive. If these pressures lie outside the default pressures of the machine, the alarm settings may have to be changed or flow restrictors are needed. This solution, however, is not recommended because it increases the risk of thrombosis and hemolysis.[16]

Despite being outside of the purpose of this chapter, we like to mention that, recently, devices combining extracorporeal CO_2 removal ($ECCO_2R$) and renal-replacement technologies have been used successfully for the management of patients suffering from acute respiratory failure.[52] This technique has been used to partially remove carbon dioxide sufficient to buffer the respiratory acidosis associated to low tidal volume ventilation (lower than 6 mL/kg) in the framework of more protective ventilatory settings.[53] Some of these devices use ultrafiltrate recirculation to the inflow of the membrane lung, a technique that did not affect CO_2 removal of an $ECCO_2R$ device[54] providing a suitable modular platform for coupling CO_2 removal therapy with various forms of dialysis and blood purification.

CONCLUSION

Impairment of the renal function is common in patients undergoing ECMO. It can develop before or after ECMO institution, and it can have a significant impact on patient outcome. The interaction between ECMO and renal recovery is a delicate equilibrium with complex, specific pathways. In particular, the use of ECMO in patients with ARDS has major effects on renal function, potentially positive and negative. Between the possible negative effects, we have to consider the systemic coagulation and inflammation caused by the contact with foreign surfaces and the activation of humoral and cellular mechanisms. Hemolysis is another major factor that may alter kidney function during ECMO, even if it can be minimized by the use of modern technology. Nonetheless, positive effects appear very important: they are manly related to (1) the relief of ventilation with high volume and pressure made possible by ECMO, (2) the beneficial effects on right ventricular afterload and preload, and, finally, (3) the reduction of the systemic inflammatory effects of VILI. Moreover, the presence of the ECMO circuit makes the application of CRRT easier and simpler in most occasions.

Key Points

1. Acute kidney injury is a common complication in critically ill patients treated with extracorporeal membrane oxygenation (ECMO) and may be associated with worse outcomes.
2. The need for renal replacement therapy in patients treated with ECMO may reflect inadequate renal perfusion and/or direct injury to the kidney because of the disease process or ECMO-associated side effects.
3. Patients starting ECMO support frequently already have multiple organ dysfunction, including renal failure.
4. It is very difficult to identify the ultimate cause of renal failure developing during ECMO.
5. The presence of the extracorporeal circuit for ECMO provides an easy way to add an additional circuit for renal replacement.

Key References

17. Haneya A, Diez C, Philipp A, et al. Impact of Acute Kidney Injury on Outcome in Patients With Severe Acute Respiratory Failure Receiving Extracorporeal Membrane Oxygenation. *Crit Care Med.* 2015;43:1898-1906.
19. Kielstein JT, Heiden AM, Beutel G, et al. Renal function and survival in 200 patients undergoing ECMO therapy. *Nephrol Dial Transplant.* 2013;28:86-90.
21. Zangrillo A, Landoni G, Biondi-Zoccai G, et al. A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. *Crit Care Resusc.* 2013;15:172-178.
23. Villa G, Katz N, Ronco C. Extracorporeal Membrane Oxygenation and the Kidney. *Cardiorenal Med.* 2015;6:50-60.
25. Kilburn DJ, Shekar K, Fraser JF. The Complex Relationship of Extracorporeal Membrane Oxygenation and Acute Kidney Injury: Causation or Association? *Biomed Res Int.* 2016; 2016:1094296.

A complete reference list can be found online at ExpertConsult.com.

References

1. Zapol WM, Kitz RJ. Buying time with artificial lungs. *N Engl J Med*. 1972;286:657-658.
2. Yan X, Jia S, Meng X, et al. Acute kidney injury in adult postcardiotomy patients with extracorporeal membrane oxygenation: evaluation of the RIFLE classification and the Acute Kidney Injury Network criteria. *Eur J Cardiothorac Surg*. 2010;37:334-338.
3. Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med*. 2007;35:1837-1843, quiz 1852.
4. Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care*. 2006;10:R73.
5. Kuitunen A, Vento A, Suojaranta-Ylinen R, et al. Acute renal failure after cardiac surgery: evaluation of the RIFLE classification. *Ann Thorac Surg*. 2006;81:542-546.
6. Uchino S, Bellomo R, Goldsmith D, et al. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med*. 2006;34:1913-1917.
7. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8:R204-R212.
8. Bagshaw SM. Acute kidney injury: diagnosis and classification of AKI: AKIN or RIFLE? *Nat Rev Nephrol*. 2010;6:71-73.
9. Joannidis M, Metnitz B, Bauer P, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med*. 2009;35:1692-1702.
10. Haase M, Bellomo R, Matalanis G, et al. A comparison of the RIFLE and Acute Kidney Injury Network classifications for cardiac surgery-associated acute kidney injury: a prospective cohort study. *J Thorac Cardiovasc Surg*. 2009;138:1370-1376.
11. Ricci Z, Cruz DN, Ronco C. Classification and staging of acute kidney injury: beyond the RIFLE and AKIN criteria. *Nat Rev Nephrol*. 2011;7:201-208.
12. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. *Kidney Int*. 2008;73:538-546.
13. Kamis F, Yegenaga I, Musul M, et al. Neutrophil gelatinase-associated lipocalin levels during the first 48 hours of intensive care may indicate upcoming acute kidney injury. *J Crit Care*. 2016;34:89-94.
14. Paden ML, Conrad SA, Rycus PT, et al. Extracorporeal Life Support Organization Registry Report 2012. *ASAIO J*. 2013;59:202-210.
15. Kielstein JT, Tolk S, Hafer C, et al. Effect of acute kidney injury requiring extended dialysis on 28 day and 1 year survival of patients undergoing interventional lung assist membrane ventilator treatment. *BMC Nephrol*. 2011;12:15.
16. Askenazi DJ, Selewski DT, Paden ML, et al. Renal replacement therapy in critically ill patients receiving extracorporeal membrane oxygenation. *Clin J Am Soc Nephrol*. 2012;7:1328-1336.
17. Haneya A, Diez C, Philipp A, et al. Impact of Acute Kidney Injury on Outcome in Patients With Severe Acute Respiratory Failure Receiving Extracorporeal Membrane Oxygenation. *Crit Care Med*. 2015;43:1898-1906.
18. Lin CY, Chen YC, Tsai FC, et al. RIFLE classification is predictive of short-term prognosis in critically ill patients with acute renal failure supported by extracorporeal membrane oxygenation. *Nephrol Dial Transplant*. 2006;21:2867-2873.
19. Kielstein JT, Heiden AM, Beutel G, et al. Renal function and survival in 200 patients undergoing ECMO therapy. *Nephrol Dial Transplant*. 2013;28:86-90.
20. Seczynska B, Krolikowski W, Nowak I, et al. Continuous renal replacement therapy during extracorporeal membrane oxygenation in patients treated in medical intensive care unit: technical considerations. *Ther Apher Dial*. 2014;18:523-534.
21. Zangrillo A, Landoni G, Biondi-Zoccai G, et al. A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. *Crit Care Resusc*. 2013;15:172-178.
22. Englberger L, Suri RM, Li Z, et al. Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. *Crit Care*. 2011;15:R16.
23. Villa G, Katz N, Ronco C. Extracorporeal Membrane Oxygenation and the Kidney. *Cardiorenal Med*. 2015;6:50-60.
24. Fleming GM, Askenazi DJ, Bridges BC, et al. A multicenter international survey of renal supportive therapy during ECMO: the Kidney Intervention During Extracorporeal Membrane Oxygenation (KIDMO) group. *ASAIO J*. 2012;58:407-414.
25. Kilburn DJ, Shekar K, Fraser JF. The Complex Relationship of Extracorporeal Membrane Oxygenation and Acute Kidney Injury: Causation or Association? *Biomed Res Int*. 2016;2016:1094296.
26. Haines N, Wang S, Undar A, et al. Clinical outcomes of pulsatile and non-pulsatile mode of perfusion. *J Extra Corpor Technol*. 2009;41:P26-P29.
27. Scaravilli V, Sangalli F, Patroniti N. Basic aspects of physiology during ECMO support. In: Sangalli FP, N, Pesenti A, eds. *ECMO-Extracorporeal Life Support in Adults*. Vol. Italia: pringer-Verlag; 2014:19-36.
28. Sylvester JT, Shimoda LA, Aaronson PI, et al. Hypoxic pulmonary vasoconstriction. *Physiol Rev*. 2012;92:367-520.
29. Stratta C, Lavezzo B, Ballaris MA, et al. Extracorporeal membrane oxygenation rescue therapy in a case of portopulmonary hypertension during liver transplantation: a case report. *Transplant Proc*. 2013;45:2774-2775.
30. Schmidt M, Tachon G, Devilliers C, et al. Blood oxygenation and decarboxylation determinants during venovenous ECMO for respiratory failure in adults. *Intensive Care Med*. 2013;39:838-846.
31. Reis Miranda D, van Thiel R, Brodie D, et al. Right ventricular unloading after initiation of venovenous extracorporeal membrane oxygenation. *Am J Respir Crit Care Med*. 2015;191:346-348.
32. Milting H, EL Banayosy A, Kassner A, et al. The time course of natriuretic hormones as plasma markers of myocardial recovery in heart transplant candidates during ventricular assist device support reveals differences among device types. *J Heart Lung Transplant*. 2001;20:949-955.
33. Thompson LO, Skrabal CA, Loebe M, et al. Plasma neurohormone levels correlate with left ventricular functional and morphological improvement in LVAD patients. *J Surg Res*. 2005;123:25-32.
34. Nomura Y, Kato K, Fujimori K, et al. The endocrinological responses of veno-venous extracorporeal membrane oxygenation on hypoxic fetal lambs. *Fukushima J Med Sci*. 2012;58:9-16.
35. The international ELSO guidelines (Available at: http://www.elso.org/Portals/0/IGD/Archive/FileManager/929122ae88cusersshyerdocumentselsoguidelinesgeneralalleclsversion1.3.pdf).
36. Peek GJ, Firmin RK. The inflammatory and coagulative response to prolonged extracorporeal membrane oxygenation. *ASAIO J*. 1999;45:250-263.
37. Ranucci M. Coagulation, anticoagulation, and inflammatory response. In: Sangalli F, N, Pesenti A, eds. *ECMO-Extracorporeal Life Support in Adults*. Vol. Italia: pringer-Verlag; 2014:77-89.
38. Robinson TM, Kickler TS, Walker LK, et al. Effect of extracorporeal membrane oxygenation on platelets in newborns. *Crit Care Med*. 1993;21:1029-1034.
39. Annich G, Massiccotte M, Lequier L. Blood biomaterial surface interaction during ECLS. In: Organization ELS, ed. *ECMO: Extracorporeal Cardiopulmonary Support in Critical Care*. Vol. 4th ed. United States: 2012:75-84.
40. Chenoweth DE, Cooper SW, Hugli TE, et al. Complement activation during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxins. *N Engl J Med*. 1981;304:497-503.
41. Bruins P, te Velthuis H, Yazdanbakhsh AP, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. *Circulation*. 1997;96:3542-3548.
42. Fischer WH, Jagels MA, Hugli TE. Regulation of IL-6 synthesis in human peripheral blood mononuclear cells by C3a and C3a(desArg). *J Immunol*. 1999;162:453-459.
43. Donnelly RP, Freeman SL, Hayes MP. Inhibition of IL-10 expression by IFN-gamma up-regulates transcription of TNF-alpha in human monocytes. *J Immunol*. 1995;155:1420-1427.
44. McILwain RB, Timpa JG, Kurundkar AR, et al. Plasma concentrations of inflammatory cytokines rise rapidly during

ECMO-related SIRS due to the release of preformed stores in the intestine. *Lab Invest*. 2010;90:128-139.
45. White LE, Hassoun HT. Inflammatory Mechanisms of Organ Crosstalk during Ischemic Acute Kidney Injury. *Int J Nephrol*. 2012;2012:505197.
46. van den Akker JP, Egal M, Groeneveld AB. Invasive mechanical ventilation as a risk factor for acute kidney injury in the critically ill: a systematic review and meta-analysis. *Crit Care*. 2013;17:R98.
47. MacLaren G, Combes A, Bartlett RH. Contemporary extracorporeal membrane oxygenation for adult respiratory failure: life support in the new era. *Intensive Care Med*. 2012;38:210-220.
48. Simons AP, Weerwind PW. Re: How to perform a haemodialysis using the arterial and venous lines of an extracorporeal life support. *Eur J Cardiothorac Surg*. 2011;39:1084-1085.
49. Cianchi G, Bonizzoli M, Pasquini A, et al. Ventilatory and ECMO treatment of H1N1-induced severe respiratory failure: results of an Italian referral ECMO center. *BMC Pulm Med*. 2011;11:2.
50. Yap HJ, Chen YC, Fang JT, et al. Combination of continuous renal replacement therapies (CRRT) and extracorporeal membrane oxygenation (ECMO) for advanced cardiac patients. *Ren Fail*. 2003;25:183-193.
51. Chen H, Yu RG, Yin NN, et al. Combination of extracorporeal membrane oxygenation and continuous renal replacement therapy in critically ill patients: a systematic review. *Crit Care*. 2014;18:675.
52. Terragni PP, Del Sorbo L, Mascia L, et al. Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology*. 2009;111:826-835.
53. Pesenti A, Rossi GP, Pelosi P, et al. Percutaneous extracorporeal CO2 removal in a patient with bullous emphysema with recurrent bilateral pneumothoraces and respiratory failure. *Anesthesiology*. 1990;72:571-573.
54. Scaravilli V, Kreyer S, Linden K, et al. Modular extracorporeal life support: effects of ultrafiltrate recirculation on the performance of an extracorporeal carbon dioxide removal device. *ASAIO J*. 2014;60:335-341.