Review Article

Adjunctive therapies during veno-venous extracorporeal membrane oxygenation

Federico Pappalardo[1], Andrea Montisci[2]

[1]Department of Anesthesia and Intensive Care and Vita-Salute San Raffaele University, Milan, Italy; [2]Department of Anesthesia and Intensive Care, Cardiothoracic Center, Istituto Clinico Sant'Ambrogio, Gruppo Ospedaliero San Donato, University and Research Hospitals, Milan, Italy

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Federico Pappalardo, MD, Prof. Department of Anesthesia and Intensive Care and Vita-Salute San Raffaele University, Via Olgettina 60, 20132 Milan, Italy. Email: pappalardo.federico@hsr.it.

Abstract: Veno-venous extracorporeal membrane oxygenation (VV ECMO) restores gas exchanges in severely hypoxemic patients. The need for adjunctive therapies usually originates either from refractory hypoxemia during ECMO (defined as the persistence of low blood oxygen levels despite extracorporeal support) or from the attempt to give a specific therapy for acute respiratory distress syndrome (ARDS). In this review, therapeutic strategies to treat refractory and persistent hypoxemia during ECMO are evaluated. In the second part, therapies that can be added on top of VV ECMO to address inflammation and altered vascular permeability in ARDS are examined. The therapies currently available often allow for an effective treatment of hypoxemia during ECMO. ARDS is still lacking a specific therapy, with low-grade evidence sustaining the majority of currently used drugs.

Keywords: Veno-venous extracorporeal membrane oxygenation (VV ECMO); acute respiratory distress syndrome (ARDS); hypoxemia

Submitted Sep 22, 2017. Accepted for publication Sep 26, 2017.
doi: 10.21037/jtd.2017.10.08
View this article at: http://dx.doi.org/10.21037/jtd.2017.10.08

Introduction

Veno-venous extracorporeal membrane oxygenation (VV ECMO) ensures the restoration of respiratory exchanges in patients suffering from acute lung injury (1). However, it is quite common that patients, despite extracorporeal support, remain extremely hypoxemic (2). This event should trigger the attempt to guarantee an improvement in oxygenation with therapeutic measures on top of VV ECMO. Moreover, when the need of VV ECMO is dictated by acute respiratory distress syndrome (ARDS), some adjunctive therapies can be added to address the underlying pathophysiological mechanism of systemic inflammation, excessive fibro-proliferation and altered vascular permeability (3). For the purpose of this review, we will refer to adjunctive therapies as all pharmacological or non-pharmacological strategies employed to address clinical issues during the course of extracorporeal support. For each of these, the current evidence will be summarized.

Refractory hypoxemia

Refractory hypoxemia can be defined as the persistence of low levels of blood oxygen content during VV ECMO, which are considered inadequate to match the patient's metabolic needs (2). The current knowledge about the safe arterial oxygen partial pressure in the blood (paO_2) does not allow neither the determination of a threshold triggering interventions nor the value at which the brain is injured (4-8). Therefore, the decision about the need to start adjunctive or rescue therapies on top of VV ECMO is often left to the clinician judgement, arising from a global

evaluation of the single patient and his comorbidities. Hypoxemia during VV ECMO occurs as a consequence of phenomena that are partly intrinsic to the veno-venous bypass partly to the underlying lung damage such as: mixture between blood oxygenated by ECMO and patient's own blood, high recirculating fraction, intrapulmonary shunt (9). Adjustment of ECMO flow and reduction of recirculating fraction are usually the first measures undertaken to increase the oxygen content in the blood. Available strategies to improve peripheral oxygenation can be classified as follows: (I) increase of ECMO flow; (II) reduction of the recirculation fraction; (III) increase of blood oxygen-carrying capacity; (IV) reduction of oxygen consumption; (V) manipulation of native cardiac output (CO) and intrapulmonary shunt; (VI) switch to veno-arterial (VA) ECMO or hybrid configurations (2). We have evaluated only measures not directly involving the management of extracorporeal support, such as regulation of ECMO flow, the reduction of recirculation fraction or the management of mechanical ventilation. Comprehensive reviews on mechanical ventilation and management of refractory hypoxemia during VV ECMO are referenced (2,10).

Increase of blood oxygen-carrying capacity

The frequency of bleeding complications makes ECMO one of the most blood-expensive settings (11). The number of packed red blood cell transfused has been related to patients' mortality and morbidity (12). These acquisitions drove the attempt to lower the transfusional threshold, while optimizing anticoagulation therapy with the aim to reduce bleeding complications (13). ELSO guidelines state that, during respiratory ECMO, the hemoglobin level should be maintained at 12–14 g/dL (14), owing to the fact that the lower is the hemoglobin level, the higher should be ECMO blood flow to ensure the oxygen delivery. In recent years, many studies showed that good outcomes can be achieved by using a lower than usual threshold for blood transfusion (15,16), provided that this strategy was accompanied by a concomitant blood conservation technique, as reinfusion of circuit blood at the moment of decannulation and by a rigorous titration of anticoagulation (17). To the best of our knowledge, there are no clinical trials with a head-to-head comparison of liberal (around 10 g/dL) versus restrictive (around 7 g/dL) hemoglobin levels triggering red blood cells transfusions in adult patients.

In conclusion, some considerations should be made: firstly, the increase in haematocrit is the first and more effective physiologic mechanism adopted when human subjects are exposed to hypobaric hypoxia (18); in second instance, oxygen delivery during ECMO is closely linked to hemoglobin levels (19); thirdly, the administration of fluids instead of packed red blood cells to treat hypovolemia can lead to fluid overload, which is a significant concern in ARDS patients (20); lastly, the concept of theoretical and transfusion threshold itself could be questioned, as it does not take into account many variables affecting the specific clinical situation (age, comorbidities, concomitant cardiac dysfunction etc.).

Reduction of oxygen consumption: sedation, neuromuscular blocking agents and therapeutic hypothermia (TH)

Deep sedation and neuromuscular blockade (NMB) are widely used in the first phase of ECMO support, until stabilisation occurs. The ACURASYS study randomised 340 patients to receive, within 48 hours from the onset of ARDS, the neuromuscular blocker cisatracurium besylate or placebo for 48 hours. The study showed an improvement of adjusted 90-day survival and a decrease of the length of mechanical ventilation in the treatment arm (21). A meta-analysis, including three RCT comparing NMB versus placebo in ARDS, concluded that a short-term infusion of cisatracurium is associated with a reduced 28-days, intensive care unit (ICU) and in-hospital mortality, without increasing the risk of ICU-acquired weakness (22). The reduction of peripheral and brain metabolic demand during sedation and the suppression of the work of breathing during NMB administration have not been associated, to the best of our knowledge, to better outcomes in ECMO patients. The deliberate and controlled lowering of body temperature above 36 ℃ is termed TH (23). Many factors, as the speed of induction and rewarming and the duration of TH influence the physiologic response (23). The pathophysiologic rationale is the reduction of oxygen consumption of the whole body and the cerebral protective effects. To date, no studies have explored the effect of mild (34–35.9 ℃) TH in ECMO patients. Only anecdotal are the experience of TH in ARDS patients (24-26). TH usually requires sedation to reduce the unpleasant effect of induction and to prevent shivering, which induces a sudden and considerable increase in metabolic rate. On these premises, TH does not seem to offer significant advantage out of selected cases in the first phase of support.

In conclusion, the benefits of sedation, prolonged

neuromuscular blocking, and TH are all linked to the need to reduce oxygen consumption and, as regard to NMB, even to allow for a safer mechanical ventilation. Each expected beneficial effect from therapies requiring prolonged sedation out the first phase of stabilization should be weighted with the advantages of an "awake" ECMO strategy, with an early weaning from mechanical ventilation, oral feeding and active physiotherapy (27-29).

Manipulation of intrapulmonary shunt

Seminal studies highlighted the role of CO in determining intrapulmonary shunt, and the consequent possibility to reduce with mechanical [high tidal volumes and high positive end expiratory pressure (PEEP)] and pharmacological modulators the degree of shunt, improving arterial oxygenation (30,31). An emerging technique to reduce the intrapulmonary shunt is the infusion of esmolol, a cardio-selective beta-1 blocker agent, characterized by an ultra-short half-life that allows for a quickly modulation and recovery from its effect (32). The rationale underlying the infusion of esmolol is that, by reducing CO, esmolol increases the ratio between ECMO flow and patient's CO and, in doing so, prevents the need for dangerous ECMO flow increases during hyper dynamic phases of shock (2); moreover, as stated above, the reduction of CO is a well-known mechanism of intrapulmonary shunt reduction, that is a paramount mechanism of hypoxemia in patients with ARDS (33). Clinical data about the use of esmolol in ECMO patients are limited. A case series of three ARDS patients treated with esmolol for refractory hypoxemia during VV ECMO revealed the feasibility of this strategy to augment the paO_2 reducing CO and thereby ameliorating the match between CO and pump flow, without a significant reduction of oxygen delivery (33). More specifically, three patients with ARDS and refractory hypoxemia despite protective mechanical ventilation and high flows of VV ECMO, with a hemodynamic profile characterized by high CO (>7 L/min), were treated with a continuous infusion of esmolol at a dosage of 50–80 mcg/kg/min. Hemodynamic evaluation during the first 12 hours demonstrated a significant reduction of CO and heart rate (HR) and a significant improvement of peripheral oxygenation, as demonstrated by the increase of paO_2. Furthermore, calculated oxygen delivery (DO_2) did not significantly vary during the treatment. The absence of metabolic acidosis and the decreasing trend of blood lactates during the treatment further confirm the absence of peripheral hypoperfusion because of reduced CO. A possible objection to this approach could be the risk of CO reduction and, consequently, of the peripheral oxygen delivery. However, this technique does no entail the situations of low CO states, which should be strictly monitored and diagnosed by means of markers of tissue hypoxia, such as lactates or metabolic acidosis. Furthermore, the association between esmolol and inotropes, even if limited to sparse reports and experimental studies, could be not lacking a pharmacological and physiologic rationale (34-36). Beta-blockers administration may have other advantages. Myocardial dysfunction is often present in the shocked septic patient, with an incidence of reduced left ventricular ejection fraction ranging from 24% to 50% of affected patients, and there are also consistent findings regarding impaired left ventricular diastolic function and right ventricular dysfunction (37). Chronic therapy with beta-blockers seems to have a protective effect in patient with septic shock (38), and the treatment with esmolol of septic shocked patients on vasopressor therapy has been associated with a strong mortality reduction, even if the latter study was not powered to infer on mortality (39). However, although increasing evidence suggests the possible beneficial role of β-blockers in sepsis, the topic is still controversial.

Prone positioning

In patients under mechanical ventilation suffering from ARDS, the use of prone positioning is a well-known system to improve peripheral oxygenation, whose physiologic effects are related to changes in the stiffness of the whole chest wall, redistribution of regional alveolar inflation from dependent to non-dependent regions, relief of the heart pressure on the lungs (3). The PROSEVA trials (RCTs) and meta-analyses established that prone positioning is effective when long sessions are used (duration of more than 12 hours) and in more severe subgroups of ARDS (40). The RCT assigned 466 patients with severe ARDS to prone-positioning session of at least 16 hours daily or supine positioning. The prone group had a significant lower 28-day and 90-day mortality, with an incidence of complications that did not differ between the two groups (41). Guervilly *et al.* (42) reported the outcomes of series of patients turned to prone positioning during VV ECMO therapy. Fifteen ARDS patients were turned into prone position, without major complications, if they had severe hypoxemia (paO_2/FiO_2 ratio below 70) despite maximal oxygenation, injurious ventilation parameters with plateau pressure exceeding

32 cmH_2O, or failure of attempt to wean from ECMO after at least 10 days on ECMO support. The main findings of the study are significant improvement in paO_2/FiO_2 ratio at 6 and 12 hours after reversal. The improvement in oxygenation persisted 1 and 6 hours after being turned back to the supine position. Positive results were reported even in the study of Kimmoun *et al.* (43). Before this experience, the combined treatment of VV ECMO and prone positioning has been reported only in small case series and in a retrospective study involving few patients, without control group (44). Prone positioning has demonstrated its safety if performed by trained personnel (45). A recent review on complications observed during prone positioning of patients on VV ECMO did not report catastrophic complications as cannula dislodgement or major bleeding (46). Analogously, prone positioning requires sedation and the harm of prolonged deep sedation should be kept in mind.

Pharmacological specific treatment of ARDS

The absence of sound evidence about specific pharmacological treatments of ARDS makes this disease substantially orphan of effective therapies (47,48). Indeed, even if the knowledge of pathophysiology of ARDS has enormously increased in the last years (1), the attempts to hit the suggested targets have been disappointing. Statins, corticosteroids, inhaled nitric oxide (iNO), beta-agonists and drugs influencing vascular permeability will be evaluated below.

Statins

The discovery of pleiotropic effects of statins (49,50) and the results of meta-analyses studies highlighting their positive effect on outcomes of septic patients (51,52) prompted RCTs, with the aim to establish the effects of statins on sepsis and ARDS. The HARP RCT (53) enrolled 60 ARDS patients, randomized to receive simvastatin at the dose of 80 mg/die or placebo until mechanical ventilation cessation or up to 14 days. The authors found no significant differences in mortality, but reported an improvement in oxygenation, pulmonary mechanics and non-pulmonary organ failure.

These positive results have not been confirmed by larger subsequent trials. Indeed, the HARP-2 trial (54), in which 540 patients have been randomized to receive simvastatin or placebo for a maximum of 28 days. In this trial, no differences in 28-days mortality, mechanical ventilation free days and non-pulmonary organ failure were reported in the two groups. Similar results reported the more recent trial in which rosuvastatin or placebo was tested in a population of 745 patients (55). The study was prematurely terminated before reaching the target of 1,000 patients because of the absence of any mortality benefits in 60-days mortality and mechanical ventilation free days and because of the concern about an increase of hepatic and/or renal failure incidence in the treatment arm. The results of the one-year follow-up of the 275 survived patients registered the high burden in terms of cumulative mortality of ARDS together with the physical and mental impairments in survived patients, but no effect of rosuvastatin was noted on these outcomes (56). To overcome the risk of these trials to be underpowered to infer on mortality, an individual patients data meta-analysis was recently conducted (57). The authors included 1,755 patients from six critical trials on statins and sepsis/ARDS. No significant effects on 28-days mortality and mechanical ventilation free days were reported. At the same time, even if treated patients had an increased incidence of raised creatinine or transaminases levels, no difference in serious adverse events was observed between the two groups. Considering the overall results of the above-mentioned studies, it emerged that statins therapy in critically ill patients is essentially safe, but the lack of positive results in terms of mortality reduction does not recommend their routine use as an adjunctive therapy in ARDS patients. However, many issues remain unclear: statins are not homogenous from the pharmacokinetics point of view, and it is not known whether this could have influenced the results of some trials; the effective dose, if any, in this category of patients is unknown; the fragility inherent to all clinical trials in critically ill patients could have contributed to negative results (58); finally, ARDS is a heterogeneous disease, whose phenotype characterization is at an early phase (59). Therefore, the identification of subgroups of patients who could take advantage from statins could be the object of future studies.

In conclusion, experts' opinions are divergent (60-63) about the fate of statins in ARDS patients.

Corticosteroids

Two main reasons justify the use of corticosteroids in critically ill patients: their powerful anti-inflammatory effects and the high prevalence of cortico-adrenal insufficiency in critically ill patients (64). Corticosteroids are widely prescribed in ECMO patients (65); however,

three trials (66-68) did not demonstrate any mortality reduction in treated patients, but all of these studies reported improvements in secondary endpoints, as mechanical ventilation free days, ICU free days, pulmonary and end-organs function. These trials enrolled relatively small numbers of patients, with the risk that difference in mortality could have been not identified. To overcome this risk, Meduri *et al.* (69) conducted an individual patients-data meta-analysis, showing reduced in-hospital mortality in patients treated with low dose corticosteroids. The effect was more pronounced for the subgroup in which corticosteroids were started within 14 days from the onset of ARDS. On the basis of these results, low dose corticosteroids (equivalent to methylprednisolone 1 mg/kg/day) could be considered during VV ECMO for ARDS.

Beta-agonist

Beta-2 agonists are a class of drugs that, beyond its well-known bronchodilator effect, promote sodium and water reabsorption, have anti-inflammatory properties and reduce endothelial permeability (48). This complex pharmacological profile suggested the potential benefits in patients with ARDS. The first small RCT, BALTI-1 (70), showed that patients treated with intravenous salbutamol had, at the end of a 7-day treatment, a reduced extravascular lung water index (EVLWI). Nevertheless, two subsequent larger RCTs with intravenous or inhaled beta-2 agonists reported no effects on mortality and a decreased mechanical ventilation and organ failure free days (71,72). Moreover, in the group treated with beta agonists, the incidence of arrhythmia causing the withdrawal of treatment was higher. In light of these results, confirmed in a recent meta-analysis (73), administration of beta-2 agonists should be avoided.

Alteration of vascular permeability

Alveolar fluid clearance is impaired in ARDS (74) and is associated with increased morbidity and mortality (75). The identification of amiloride-sensitive epithelial sodium channel (EnAC) offered a potential target to address this alteration. The synthetic peptide AP301 is able to enhance the activity of EnAC, promoting sodium and water re-absorption from the alveoli. A preliminary proof-of-concept randomized trial employed aerosolized AP301, demonstrating no improvement in EVLWI, paO_2/FiO_2 ratio, airway pressures, Murray Lung Injury Score nor 28-days mortality (76). However, restricting the analysis to more severe case (SOFA score >11), a reduction of EVLWI and airway pressures were observed. The authors did not report serious adverse events in the experimental arm compared to placebo. Further studies are needed to clarify the potential role of AP301.

Nitric oxide

iNO is a gas, delivered in the mixture of respiratory gases that the patient breathes. iNO reaches the ventilated alveoli and, through a mechanism mediated by guanylate cyclase, relaxes the pulmonary vessels, reduces pulmonary vascular resistance, right ventricular afterload and the degree of intrapulmonary shunt (77). iNO is able to increase the paO_2, but this effect is transient and more pronounced in the first 24 hours of administration (77). Many trials failed in demonstrating that iNO could improve survival of treated patients (78-80); moreover, no significant benefits in surrogate outcomes have been registered. A recent study (81) and a meta-analysis (82) raised the concern about nephrotoxicity of iNO, with unclear mechanism but probably involving lung-kidney cross-talk and metabolites action. Two recent meta-analyses, on the basis of aforementioned studies, do not recommend its routine use in ARDS patients (82,83). Therefore, the administration of iNO as an adjunctive therapy during VV ECMO should derive from hemodynamic rather than respiratory needs. The favourable effect of iNO in reducing right ventricle afterload could be useful in the significant percentage of patients suffering from concomitant right ventricular failure (84). If pulmonary hypertension takes place and determines right ventricular failure and left ventricular underfilling secondary to leftward interventricular septal shift, the administration of iNO could be beneficial (85).

Conclusions

ARDS is a broad category in which many heterogeneous diseases produce similar clinical expressions in their final phase. The definition itself lacks specificity. The characterization of subphenotypes of ARDS is a promising field, but still in its nascent phase. If subgroups of patients with different characteristics were identified, it is conceivable that more specific new or already available therapies could find their definitive role. Nowadays, few drugs or procedures reached enough evidence to be used

routinely as adjunctive therapies for a VV ECMO patient. At the same time, we must be aware that the organisation of trials with an adequate power to infer on mortality in this field is challenging. Contrarily, if the clinical need to adjunctive therapies arises from refractory hypoxemia during VV ECMO, the therapeutic panel is wider.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017;377:562-72.
2. Montisci A, Maj G, Zangrillo A, et al. Management of refractory hypoxemia during venovenous extracorporeal membrane oxygenation for ARDS. ASAIO J 2015;61:227-36.
3. Moerer O, Tonetti T, Quintel M. Rescue therapies for acute respiratory distress syndrome: what to try first? Curr Opin Crit Care 2017;23:52-9.
4. Henig NR, Pierson DJ. Mechanisms of hypoxemia. Respir Care Clin N Am 2000;6:501-21.
5. Abdelsalam M, Cheifetz IM. Goal-Directed Therapy for Severely Hypoxic Patients With Acute Respiratory Distress Syndrome: Permissive Hypoxemia. Respir Care 2010;55:1483-90.
6. Mikkelsen ME, Anderson B, Christie JD, et al. Can We Optimize Long-Term Outcomes in Acute Respiratory Distress Syndrome by Targeting Normoxemia? Ann Am Thorac Soc 2014;11:613-8.
7. Mikkelsen ME, Christie JD, Lanken PN, et al. The Adult Respiratory Distress Syndrome Cognitive Outcomes Study: Long-Term Neuropsychological Function in Survivors of Acute Lung Injury. Am J Respir Crit Care Med 2012;185:1307-15.
8. Hopkins RO, Gale SD, Weaver LK. Brain atrophy and cognitive impairment in survivors of acute respiratory distress syndrome. Brain Inj 2006;20:263-71.
9. Levy B, Taccone FS, Guarracino F. Recent developments in the management of persistent hypoxemia under veno-venous ECMO.Intensive Care Med 2015;41:508-10.
10. Schmidt M, Pellegrino V, Combes A, et al. Mechanical ventilation during extracorporeal membrane oxygenation. Crit Care 2014;18:203.
11. Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. Ann Thorac Surg 2014;97:610-6.
12. Smith A, Hardison D, Bridges B, et al. Red blood cell transfusion volume and mortality among patients receiving extracorporeal membrane oxygenation. Perfusion 2013;28:54-60.
13. Martucci G, Panarello G, Occhipinti G, et al. Anticoagulation and transfusions management in veno-venous extracorporeal membrane oxygenation for acute respiratory distress syndrome: assessment of factors associated with transfusion requirements and mortality. J Intensive Care Med 2017;885066617706339.
14. This I, Care I, Book TR, et al. Extracorporeal Life Support Organization (ELSO) General Guidelines for all ECLS Cases. ELSO Guideline 2009:1-24.
15. Agerstrand CL, Burkart KM, Abrams DC, et al. Blood conservation in extracorporeal membrane oxygenation for acute respiratory distress syndrome. Ann Thorac Surg 2015;99:590-5.
16. Voelker MT, Busch T, Bercker S, et al. Restrictive transfusion practice during extracorporeal membrane oxygenation therapy for severe acute respiratory distress syndrome. Artif Organs 2015;39:374-8.
17. Fan E, Gattinoni L, Combes A, et al. Venovenous extracorporeal membrane oxygenation for acute respiratory failure: A clinical review from an international group of experts. Intensive Care Med 2016;42:712-24.
18. Grocott MP, Martin DS, Levett DZ, et al. Arterial blood gases and oxygen content in climbers on Mount Everest. N Engl J Med 360:140-9.
19. 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;39:838-46.
20. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564-75.
21. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.

22. Alhazzani W, Alshahrani M, Jaeschke R, et al. Neuromuscular blocking agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. Crit Care 2013;17:R43.
23. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 2009;37:S186-202.
24. Hayek AJ, White HD, Ghamande S, et al. Is therapeutic hypothermia for acute respiratory distress syndrome the future? J Intensive Care Med 2017;32:460-4.
25. Villar J, Slutsky AS. Effects of induced hypothermia in patients with septic adult respiratory distress syndrome. Resuscitation 1993;26:183-92.
26. Stub D, Bernard S, Pellegrino V, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). Resuscitation 2015;86:88-94.
27. Yeo HJ, Cho WH, Kim D. Awake extracorporeal membrane oxygenation in patients with severe postoperative acute respiratory distress syndrome. J Thorac Dis 2016;8:37-42.
28. Langer T, Santini A, Bottino N, et al. "Awake" extracorporeal membrane oxygenation (ECMO): pathophysiology, technical considerations, and clinical pioneering. Crit Care 2016;20:150.
29. Biscotti M, Gannon WD, Agerstrand C, et al. Awake extracorporeal membrane oxygenation as bridge to lung transplantation: a 9-year experience. Ann Thorac Surg 2017;104:412-9.
30. Lynch JP, Mhyre JG, Dantzker DR. Influence of cardiac output on intrapulmonary shunt. J Appl Physiol 1979;46:315-21.
31. Dantzker DR, Lynch JP, Weg JG. Depression of cardiac output is a mechanism of shunt reduction in the therapy of acute respiratory failure. Chest 1980;77:636-42.
32. Wiest DB, Haney JS. Clinical pharmacokinetics and therapeutic efficacy of esmolol. Clin Pharmacokinet 2012;51:347-56.
33. Guarracino F, Zangrillo A, Ruggeri L, et al. β-Blockers to optimize peripheral oxygenation during extracorporeal membrane oxygenation: a case series. J Cardiothorac Vasc Anesth 2012;26:58-63.
34. Lu J, Shen Y, Liu LJ, et al. Combining Epinephrine and Esmolol Attenuates Excessive Autophagy and Mitophagy in Rat Cardiomyocytes After Cardiac Arrest. J Cardiovasc Pharmacol 2015;66:449-56.
35. Suzuki T, Morisaki H, Serita R, et al. Infusion of the beta-adrenergic blocker esmolol attenuates myocardial dysfunction in septic rats. Crit Care Med 2005;33:2294-301.
36. Zhang Q, Li C. Combination of epinephrine with esmolol attenuates post-resuscitation myocardial dysfunction in a porcine model of cardiac arrest. PLoS One 2013;8:e82677.
37. Rudiger A, Singer M. The heart in sepsis: from basic mechanisms to clinical management. Curr Vasc Pharmacol 2013;11:187-95.
38. Macchia A, Romero M, Comignani PD, et al. Previous prescription of β-blockers is associated with reduced mortality among patients hospitalized in intensive care units for sepsis. Crit Care Med 2012;40:2768-72.
39. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA 2013;310:1683-91.
40. Bloomfield R, Noble DW, Sudlow A. Prone position for acute respiratory failure in adults. Cochrane Database Syst Rev 2015;(11):CD008095.
41. Guérin C, Reignier J, Richard JC, et al. Prone Positioning in Severe Acute Respiratory Distress Syndrome. N Engl J Med 2013;368:2159-68.
42. Guervilly C, Hraiech S, Gariboldi V, et al. Prone positioning during veno-venous extracorporeal membrane oxygenation for severe acute respiratory distress syndrome in adults. Minerva Anestesiol 2014;80:307-13.
43. Kimmoun A, Roche S, Bridey C, et al. Prolonged prone positioning under VV-ECMO is safe and improves oxygenation and respiratory compliance. Ann Intensive Care 2015;5:35.
44. Otterspoor LC, Smit FH, van Laar TJ, et al. Prolonged use of extracorporeal membrane oxygenation combined with prone positioning in patients with acute respiratory distress syndrome and invasive Aspergillosis. Perfusion 2012;27:335-7.
45. Culbreth RE, Goodfellow LT. Complications of Prone Positioning During Extracorporeal Membrane Oxygenation for Respiratory Failure: A Systematic Review. Respir Care 2016;61:249-54.
46. Vaquer S, de Haro C, Peruga P, et al. Systematic review and meta-analysis of complications and mortality of veno-venous extracorporeal membrane oxygenation for refractory acute respiratory distress syndrome. Ann Intensive Care 2017;7:51.
47. Artigas A, Camprubí-Rimblas M, Tantinyà N, et al. Inhalation therapies in acute respiratory distress syndrome. Ann Transl Med 2017;5:293.
48. Spieth PM, Zhang H. Pharmacological therapies for

acute respiratory distress syndrome. Curr Opin Crit Care 2014;20:113-21.
49. Blum A, Shamburek R. The pleiotropic effects of statins on endothelial function, vascular inflammation, immunomodulation and thrombogenesis. Atherosclerosis 2009;203:325-30.
50. Neurauter G, Wirleitner B, Laich A, et al. Atorvastatin suppresses interferon-gamma -induced neopterin formation and tryptophan degradation in human peripheral blood mononuclear cells and in monocytic cell lines. Clin Exp Immunol 2003;131:264-7.
51. Ou SY, Chu H, Chao PW, et al. Effect of the use of low and high potency statins and sepsis outcomes. Intensive Care Med 2014;40:1509-17.
52. Wan YD, Sun TW, Kan QC, et al. Effect of statin therapy on mortality from infection and sepsis: a meta-analysis of randomized and observational studies. Crit Care 2014;18:R71.
53. Craig TR, Duffy MJ, Shyamsundar M, et al. A randomized clinical trial of hydroxymethylglutaryl- coenzyme a reductase inhibition for acute lung injury (The HARP Study). Am J Respir Crit Care Med 2011;183:620-6.
54. McAuley DF, Laffey JG, O'Kane CM, et al. Simvastatin in the acute respiratory distress syndrome. N Engl J Med 2014;371:1695-703.
55. National Heart, Lung, and Blood Institute ARDS Clinical Trials Network, Truwit JD, Bernard GR,et al. Rosuvastatin for Sepsis-Associated Acute Respiratory Distress Syndrome. N Engl J Med 2014;370:2191-200.
56. Dinglas VD, Hopkins RO, Wozniak AW, et al. One-year outcomes of rosuvastatin versus placebo in sepsis-associated acute respiratory distress syndrome: prospective follow-up of SAILS randomised trial. Thorax 2016;71:401-10.
57. Nagendran M, McAuley DF, Kruger PS, et al. Statin therapy for acute respiratory distress syndrome: an individual patient data meta-analysis of randomised clinical trials. Intensive Care Med 2017;43:663-71.
58. Ridgeon EE, Young PJ, Bellomo R, et al. The Fragility Index in Multicenter Randomized Controlled Critical Care Trials. Crit Care Med 2016;44:1278-84.
59. Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med 2014;2:611-20.
60. Grimaldi D, Durand A, Gleeson J, et al. Failure of statins in ARDS: the quest for the Holy Grail continues. Minerva Anestesiol 2016;82:1230-4.
61. Kruger PS, Terblanche M. Statins in patients with sepsis and ARDS: is it over? No. Intensive Care Med 2017;43:675-6.
62. Alhazzani W, Truwit J. Statins in patients with sepsis and ARDS: is it over? Yes. Intensive Care Med 2017;43:672-4.
63. McAuley D, Charles PE, Papazian L. Statins in patients with sepsis and ARDS: is it over? We are not sure. Intensive Care Med 2017;43:677-9.
64. Briegel J, Bein T, Möhnle P. Update on low-dose corticosteroids. Curr Opin Anaesthesiol 2017;30:186-91.
65. Lamontagne F, Quiroz Martinez H, Adhikari NK, et al. Corticosteroid use in the intensive care unit: a survey of intensivists. Can J Anaesth 2013;60:652-9.
66. Tongyoo S, Permpikul C, Mongkolpun W, et al. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. Crit Care 2016;20:329.
67. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest 2007;131:954-63.
68. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006;354:1671-84.
69. Meduri GU, Bridges L, Shih MC, et al. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med 2016;42:829-40.
70. Perkins GD, McAuley DF, Thickett DR, et al. The beta-agonist lung injury trial (BALTI): a randomized placebo-controlled clinical trial. Am J Respir Crit Care Med 2006;173:281-7.
71. Gates S, Perkins G, Lamb SE, et al. Beta-agonist lung injury trial-2 (BALTI-2): a multicentre, randomised, double-blind, placebo-controlled trial and economic evaluation of intravenous infusion of salbutamol versus placebo in patients with acute respiratory distress syndrome. Health Technol Assess 2013;17:v-vi,1-87.
72. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Matthay MA, Brower RG, et al. Randomized, placebo-controlled clinical trial of an aerosolized β_2-agonist for treatment of acute lung injury. Am J Respir Crit Care Med 2011;184:561-8.
73. Singh B, Tiwari AK, Singh K, et al. β2 agonist for the treatment of acute lung injury: a systematic review and meta-analysis. Respir Care 2014;59:288-96.
74. Matthay MA, Ware LB, Zimmerman GA. The

acute respiratory distress syndrome. J Clin Invest 2012;122:2731-40.
75. Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;163:1376-83.
76. Krenn K, Lucas R, Croizé A, et al. Inhaled AP301 for treatment of pulmonary edema in mechanically ventilated patients with acute respiratory distress syndrome: a phase IIa randomized placebo-controlled trial. Crit Care 2017;21:194.
77. Bhatraju P, Crawford J, Hall M, et al. Inhaled nitric oxide: Current clinical concepts. Nitric Oxide 2015;50:114-28.
78. Troncy E, Collett JP, Shapiro S, et al. Inhaled nitric oxide in acute respiratory distress syndrome: a pilot randomized controlled study. Am J Respir Crit Care Med 1998;157:1483-8.
79. Michael JR, Barton RG, Saffle JR, et al. Inhaled nitric oxide versus conventional therapy: effect on oxygenation in ARDS. Am J Respir Crit Care Med 1998;157:1372-80.
80. Taylor RW, Zimmerman JL, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. JAMA 2004;291:1603-9.
81. Ruan SY, Wu HY, Lin HH, et al. Inhaled nitric oxide and the risk of renal dysfunction in patients with acute respiratory distress syndrome: a propensity-matched cohort study. Crit Care 2016;20:389.
82. Ruan SY, Huang TM, Wu HY, et al. Inhaled nitric oxide therapy and risk of renal dysfunction: a systematic review and meta-analysis of randomized trials. Crit Care 2015;19:137.
83. Gebistorf F, Karam O, Wetterslev J, et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev 2016;(6):CD002787.
84. Vieillard-Baron A, Price LC, Matthay MA. Acute cor pulmonale in ARDS. Intensive Care Med 2013;39:1836-8.
85. Bhorade S, Christenson J, O'Connor M, et al. Response to inhaled nitric oxide in patients with acute right heart syndrome. Am J Respir Crit Care Med 1999;159:571-9.

Cite this article as: Pappalardo F, Montisci A. Adjunctive therapies during veno-venous extracorporeal membrane oxygenation. J Thorac Dis 2018;10(Suppl 5):S683-S691. doi: 10.21037/jtd.2017.10.08

