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Extracorporeal Membrane Oxygenation for Adults with ARDS-Current Evidence

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Abstract

Acute Respiratory Distress Syndrome (ARDS) is a rapidly progressive form of acute respiratory failure characterized by severe hypoxemia and non-hydrostatic pulmonary edema. Currently, lung protective ventilation strategy is the standard of care for management of ARDS. Despite the best efforts, correction of hypoxemia remains a challenge in these patients. There is significant morbidity and mortality associated with syndrome. ECMO is a form of mechanical system, which can maintain oxygenation even without involvement of lungs and appears ideal for ARDS patients with refractory hypoxemia. It is important for all critical care physicians to understand various aspects of ECMO and the level of evidence of its utility. We performed a literature search through PubMed search engine using key words "ECMO," "Extracorporeal Membrane Oxygenation," "ECCO2R," "Extracorporeal CO2 Removal" AND "ARDS," or "ALI," or "Acute Respiratory Failure," or "Acute Respiratory Distress Syndrome," or "Acute Lung Injury." In this article, we report the summary of the current evidence for utility of ECMO for ARDS. The article also highlights few other aspects of ECMO, which all critical care physicians should know.

Keywords: Extracorporeal membrane oxygenation; ECMO; ARDS; Refractory hypoxemia

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Introduction

The Acute Respiratory Distress Syndrome (ARDS) is a rapidly progressive form of acute respiratory failure characterized by severe hypoxemia and non-hydrostatic pulmonary edema [1]. Although recognized decades ago [2], the lack of a commonly accepted definition of ARDS hindered an accurate study of this condition. For instance, the reported incidence and mortality of ARDS exhibited considerable disagreement among different studies, ranging from 10% to 90% [3]. Thus, in 1994, the American and European Consensus Conference (AECC) criteria for the diagnosis of ARDS were first published [4]. However, it was realized that this definition had its shortcomings. For instance, the term 'acute onset' is not defined and the degree of hypoxemia may vary significantly depending not just on the FiO2, but also with the PEEP levels [5]. It was also observed that the inter-observer agreement in the interpretation of radiological findings was at best modest [6] and the arbitrary cut-off values of Pulmonary capillary Wedge Pressure (PCWP) <18 mmHg was not always discriminative [7]. It was also felt that the terms ARDS and Acute Lung Injury (ALI) represented a spectrum of the same disease and the use of different terminology may not be necessary. Hence, the 'Berlin Definition' was adopted in 2012, which was created by a consensus panel of experts convened in 2011 [8]. The key components of this definition are:

1. Acute, means onset over 1 week or less.
2. Bilateral opacities consistent with pulmonary edema must be present and may be detected on CT or chest radiograph.
3. PO_2/FiO2 ratio <300 mmHg with a minimum of 5 cm H_2O Positive End Expiratory Pressure (PEEP) or Continuous Positive Airway Pressure (CPAP).
4. "Not be fully explained by cardiac failure or fluid overload," in the physician's best estimation using available information-an "objective assessment" (e.g. echocardiogram) should be performed in most cases if there is no clear cause such as trauma or sepsis.

The new definition went on to classify ARDS as mild, moderate, and severe based on the PaO2/FiO2 ratio. Though this definition

too has not been found to be very accurate in autopsy studies [9], it is currently the accepted consensus definition.

ARDS Management

Along with treatment of the underlying cause, appropriate ventilator management is the cornerstone of therapy for best outcome. The goals of mechanical ventilation for ARDS are to minimize iatrogenic lung injury while providing acceptable oxygenation even though there is some retention of carbon dioxide. Currently, lung protective strategy with the use of low tidal volume (4-7 ml/kg of predicted body weight), appropriate (PEEP) with keeping the plateau pressure less than 30 cm of H_2O is the standard of care for ventilation of patients with ARDS. The analyses of mortality from the ARDS Network clinical trials using a consistent disease definition have demonstrated a gradual temporal improvement in survival [10]. However, this syndrome is still associated with a short-term mortality of approximately 45% [11] as well as significant long-term morbidity [12]. Therefore, the role of non-conventional ventilatory techniques is being pursued and evaluated.

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is a form of mechanical system, which is used to provide support to failing lungs or heart. During the management of severe respiratory failure, ECMO draws blood from the venous system, oxygenates it outside of the body, and returns oxygenated blood to systemic circulation without it having to pass through the pulmonary circulation. Similarly, in cases of cardiac arrest or severe cardiac failure, it can be used as an emergency resuscitation tool for gas exchange including oxygenation as well as support to the systemic circulation. ECMO is not a new technique; it has been in clinical practise for the last few decades [13]. However, recently there is a significant increase in use of this technology in various clinical settings [14]. This increase in usage may be attributed to the advancement in technology, which has miniaturised the equipment and simplified the procedures as well as better understanding of its utility in the management of critically ill patients. There is ample medical literature with growing number of publications on the possible expanding role of ECMO [15]. However, due to the complexity of the equipment and the critical illness of the patients suited for its use, there is a high potential for complications. Therefore, it should be used for highly selected patients at designated ECMO centres only. This article will highlight some of the important aspects of this highly complex though potentially life-saving technique.

Understanding of the ECMO System

In simple terms, during ECMO specialized cannulae are used to drain blood from the body, circulated outside by a mechanical pump, passed through a membrane, which oxygenates the blood or removes CO_2 from it and re-infuse into the circulation. In this process, ECMO provides complete or partial rest to the heart and lungs. The machine mainly consists of mechanical pump, oxygenator, circuit, and cannula.

Mechanical pump

There are 2 types of mechanical pumps-the roller pump and the centrifugal pumps. The roller pump is a volume displacement pump, in which rollers attached to the circumference of a rotor compress the flexible tubing against the pump casing. For each half revolution of the pump, a certain amount of blood is pushed to the patient and the flow rate depends on the spinning of the rotor. The major limitation of this type of pump is hemolysis associated with the compression of the tubing. These roller pumps had been the standard for decades, but have mainly been replaced by the novel centrifugal pumps. In the centrifugal pumps, the blood enters along the rotating axis and is propelled outwards and there is no hemolysis [16]. The flow rate depends on the spinning of the impeller as well as the preload and after-load. The problems with the conventional centrifugal pump head include stagnation and heating in the pump head, leading to thrombus at low flows or if the outlet line is occluded, and cavitation and hemolysis when the inlet line is occluded (when the venous line is occluded, the rotor keeps spinning, evacuating blood from the pump head and creating a vacuum in the pump head, which causes cavitation and hemolysis). Hemolysis may be caused by heat generation and thrombus formation in the pump head, stagnant or turbulent blood flow zones in the pump head, oxygenator or other places in the circuit, shear stress caused by high blood flow velocities, excessive suction, and circuit thrombosis.

To overcome these problems, the new pump head designs have incorporated a hole in the center of the rotor, which overcomes the problem of stagnation and thrombosis. The newer pumps feature bearing-less technology; the rotor is levitated into the housing by the magnetic force generated by the motor, hence minimizing friction and improving hemo-compatibility. The risk of thrombus formation is reduced by uniform unidirectional flow and less stagnation, while reduced shearing stress attenuates hemolysis [17].

Oxygenator

The oxygenator is involved in the gas exchange functioning of ECMO. The earlier oxygenators used the silicon and were called as Silicone Rubber Membrane Lungs (SRML). The Kolobow silicone rubber membrane lung was the standard oxygenator used for ECMO applications for the initial years [18]. It was made from a flat reinforced sheet of silicone rubber membrane envelope wrapped around a wire mesh in a spiral coil. Blood and gas flow in counter-current directions within the silicone lung and gas exchange occurs by diffusion across the membrane. Though effective in gas exchange, the silicone lung had a high resistance to flow, which limited the maximum blood flow obtained.

SRML were replaced in 1990s by the Polypropylene Membrane Lungs (PPML), which had lower resistance, easier priming and better gas exchange efficiency. However, PPML were associated with plasma leakages when used for more than 6 hours. The PPML were replaced by hollow fiber Polymethyl Pentene (PMP) membrane lungs, which maintain the superior performance without the problem of plasma leakage [19-21]. The fibres are so

bundled and wound that the gas flows inside of the fibres and the blood flows outside of the fibres in the oxygenator. By making the oxygenators more compact and optimizing the blood flow path, it is possible to decrease the surface area of the membrane and heat exchanger, thus reducing its potential for thrombus formation and inflammatory activation. The limitation of the inflammatory response and the decrease transfusion requirement make these newer oxygenators suitable for long-term use.

The oxygenators also incorporate a heat exchanger, which warms the blood before it returned to the patient. This may also be used to induce hypothermia in post cardiac arrest patients and for re-warming patients with hypothermia. The oxygenator contains a gas blender, which mixes air and oxygen and allows variation the fraction of oxygen delivered to the oxygenator.

In the oxygenator, the extracorporeal venous blood is exposed to fresh gas (or sweep gas) that oxygenates and removes carbon dioxide based on the diffusion gradient. Oxygenation is affected by the fraction of delivered oxygen and the blood flow rate i.e., to increase oxygenation of the venous blood, we can either increase the fraction of oxygen delivered or increase the blood flow. However, the augmentation of oxygenation only occurs up to a certain point after which the time for oxygen transfer becomes too short. Oxygenation is independent of sweep gas flow rate. In contrast, carbon dioxide elimination is dependent on sweep gas flow rate and is independent of blood flow. By increasing the sweep gas flow rate, we reduce the concentration of carbon dioxide in the fresh gas and thereby increase the diffusion gradient allowing greater carbon dioxide elimination [22]. Since CO_2 diffuses faster than oxygen, it transfers approximately 10 times more efficiently than oxygen. Hence, the oxygenator allows distinct control of the oxygenation and CO_2 removal functions by changing the gas and blood flow rates and the fractional O_2 concentration. By comparing the pre- and post-oxygenator blood samples, we expect to find an increase in PaO2 and a decrease in PaCO2. If such a change is not seen, membrane malfunction should be suspected.

Circuit

Currently available circuits used for ECMO are quite blood friendly with complete blood handling surface modification-heparin based and non-heparin bio-passive surfaces. These have reduced the dose of anticoagulation, the daily blood loss, and the systemic hypercoagulability secondary to activation of the coagulation cascade [23].

Cannulae

The initiation of ECMO requires placement of special large bore cannula into the vessels. Most cannulas are made of biocompatible polyurethane, which may be coated with heparin or non-heparin polymers that may reduce platelet activation and the inflammatory response at the blood-cannula interface [24]. While the earlier cannulae used in cardiac surgery patients required surgical placement, now a days, the cannulae can be placed percutaneous by Seldinger technique. Since the flow in the ECMO circuit is dependent on the size of the cannula used, it is imperative to select the best size based in the target vessels and intended flow. Recently, the development of Dual-lumen cannulae to provide venovenous ECMO support via a single jugular venous access has further reduced the number of cannulae needed. However, precise positioning of cannula is imperative for optimal functioning. Using this cannula, ECMO may be provided by using single cannula instead of two. Blood is removed from the patient via one lumen, and then returned via a smaller lumen of this dual lumen cannula. The drainage and return ports are spatially separated to decrease recirculation of blood [25]. Proper positioning of the tip of the cannula is necessary for optimal cannula performance.

Types of ECMO Support

The ECMO can be classified as be veno-venous (VV) or veno-arterial (VA) based on the vessels chosen for insertion of cannulae for drawing and re-infusion of blood.

Veno-venous ECMO

During VV ECMO the blood is extracted from a cannula inserted into a major vein (the inferior vena cava or the superior vena cava). The blood after oxygenation is returned back to a major vein or the right atrium. This implies that the native lung and the membrane lung are in series–the oxygenated blood returned from the membrane lung is perfused in the native lung and the subsequently circulated in the body. This technique supports the lung function but not the cardiac function, and is the most common form of ECMO used in ARDS patients. A unique problem with this technique is that of recirculation-part of the infused oxygenated blood is drained directly by the draining cannula. To circumvent this problem, it is suggested that the blood is drained from the IVC and infused into the right atrium through a cannula inserted into the internal jugular vein [26].

Veno-arterial ECMO

During Veno-arterial (VA) ECMO, the blood is extracted from the RA or a major vein, but is returned to the arterial system (femoral artery, right common carotid, subclavian artery or rarely the axillary artery) instead of venous system. Hence, the native lung and the membrane lung are parallel to each other. This provides both respiratory and hemodynamic support and is used in ARDS patients, who are hemodynamically unstable. However, the risk with VA ECMO is that any embolus from the circuit enters the arterial side and causes systemic embolization. Another unique problem with it is the harlequin syndrome. The oxygenated blood infused into the femoral artery from the ECMO circuit will preferentially perfuse the lower extremities and the abdominal viscera while blood ejected from the heart will selectively perfuse the heart, brain, and upper extremities. This may cause cerebral hypoxia despite good oxygenation of the lower limbs.

Also, VA ECMO patients require vigorous cardiac monitoring-the continuous venous return from the bronchial vessels coupled with the poor unloading of the left ventricle can cause distension and dysfunction of the left ventricle. This reduces the pulsatile blood flow and increases the risk of stasis and clot formation

in the ventricle. When detected, it need to be treated with inotropes especially levosimendan, intra-aortic balloon counter-pulsations, and if these measures fail, then trans-a trial balloon septostomy or insertion of a left ventricular drainage catheter may be required.

Monitoring during ECMO

In addition to the routine monitoring of any ICU patient, the ECMO patient will require frequent assessment of hemodynamic parameters such as cardiac output and end-organ tissue perfusion, and regular monitoring of the functioning of the oxygenator.

Since oxygen delivery to the tissues and CO_2 removal is the primary therapeutic goal of the ECMO, regular assessment of these targets is done. Mixed Venous Oxygen Saturation (SvO2) is a good indicator of the global tissue perfusion and should be regularly assessed. Serum lactate levels can also be monitored for assessing the tissue oxygenation.

For assessing the functioning of the oxygenator, pre- and post-membrane oxygenator pressures and the blood flow may be monitored along with the pO2 and pCO2 levels in the pre and post oxygenator blood samples. An elevated pre-membrane pressure in the setting of a normal post-membrane pressure suggests that there may be clots in the oxygenator, and if accompanied by deterioration in gas exchange, it mandates a change of the oxygenator. In contrast, if both the pre and post membrane pressure are elevated, then the source of increased resistance is located downstream to the oxygenator, perhaps as a clot or kink in the cannula.

Since these patients are receiving heparin, frequent monitoring of anticoagulation (using activated clotting time, point of care aPTT, or viscoelastic test) is required for titration of the dose. Heparin levels and anti-thrombin III levels may also be assessed [27]. Patients also need to be monitored for bleeding, and when detected, appropriate remedial measures instituted. Since platelets are activated by exposure to the foreign surface, it is important to monitor platelet count and function.

In patients with placement of large arterial cannulae, since collateral circulation may be inadequate, the patient should be examined for any evidence of distal ischemia. Ipsilateral distal pulses as well as limb color and warmth should be assessed routinely [22]. In the case of femoral cannulation, dorsalis pedis or posterior tibial distal perfusion cannula can be placed to promote perfusion to the lower extremity.

Indications and contraindications of ECMO

ECMO is an expensive and labor intensive modality of the respiratory support, which is also associated with significant complications. Therefore, the selection of patients, who are most likely to be benefitted with therapy is critical.

According to a consensus conference in France [28], the predictable reversibility of lung lesions and the absence of any other therapeutic limitation are indispensable prerequisites to the use of ECMO. They suggest that the risk-benefit ratio of ECMO in ARDS should be considered unfavourable in cases of 1) hemorrhagic or potentially hemorrhagic intracranial lesions, 2) coma following cardiac arrest, 3) ARDS in which mechanical ventilation exceeds seven days, 4) severe immunosuppression, 5) multiorgan failure syndrome (SOFA > 15).

The Extracorporeal Life Support Organization (ELSO) has published the criteria for the initiation of ECMO for patients with hypoxemic respiratory failure [29]. There are no absolute contraindications of ECMO. However, it is best avoided in certain situations because of expected poor outcome.

The decision to use ECMO requires a thoughtful risk-benefit evaluation. The indications and contraindications of ECMO are summarized in **Table 1.**

ECMO has also been used in a means of cardiac support in patients of cardiogenic shock [30], post cardiotomies shock [31], myocarditis [32], and also as a support in high-risk procedures like PCI in patients of cardiogenic shock, post infarct VSD [33], and acute pulmonary embolism [34]. It has also been used in cardiorespiratory arrest associated with severe accidental hypothermia and in cases of drug intoxication [35,36]. ECMO has also been used as a bridge to heart and lung transplantation [37]. Its use has been extended to organ procurement [38,39] and lung reconditioning by ex vivo lung perfusion [40].

Evidence of ECMO for ARDS

Multiple studies have been published over the last few years, which have described the utility of ECMO for treatment of ARDS. We performed a literature search using PubMed search engine with key words “ECMO,” “Extracorporeal Membrane Oxygenation,” “ECCO2R,” “Extracorporeal CO_2 Removal” AND “ARDS,” or “ALI,” or “Acute Respiratory Failure,” or “Acute Respiratory Distress Syndrome,” or “Acute Lung Injury.” Our search results found 573 studies. We excluded the studies with sample size of less than 20. We found that the majority of the studies are retrospective or non-randomized prospective recruiting variable number of patients **(Tables 2 and 3)**. There were only four randomized control trials (RCTs). These RCTs are summarized in **Table 4**.

A. **Retrospective studies:** There are multiple retrospective studies with variable number of patients treated with ECMO for ARDS of various aetiologies, which have been published over last few years. **Table 2** has summarized the salient features of these studies.

B. **Prospective studies:** There are few prospectively conducted studies, which have reported various outcomes related to ECMO. The important features of these studies have been shown in **Table 3**.

C. **Randomized controlled trials:** It is important to assess the results of RCT for critical appraisal of utility of ECMO in clinical practice. We found only four RCT reporting the impact that ECMO has in ARDS. RCTs have reported various clinically significant outcome parameters such as mortality at various time intervals, length of hospital stay, survival at discharge, complications, the cost of the therapy, etc.

Table 1 Indications and contraindications of ECMO.

Indications	Contraindications
a) ECLS should be considered when the risk of mortality is 50% or greater (PaO2FiO2<150 on FiO2 >90% and/or Murray score 2-3) b) Indicated when the risk of mortality is 80% or greater (PaO2/FiO2<100 on FiO2 >90% and/or Murray score 3-4 despite best care for 4-6 h) c) Retention of CO_2 during mechanical ventilation despite high Pplat (>30 cm of H2O) d) Severe air leak syndrome e) To avoid intubation in a patient on lung transplant list f) Sudden cardio-respiratory collapse	a) Patients on echanical ventilation for >7days with high requirements (FiO2 >90%, Pplat >35 cm of H_2O) b) Immunocompromised state (polymorphonuclear counts <400/mm^3) c) Recent or expanding intracranial hemorrhage d) Non recoverable underlying condition such as advanced malignancies, major brain injury e) No age is contraindication, more risk with advanced age

Table 2 Summary of retrospective studies.

Author, year of publication (Reference)	Patient population	Results and remarks
Kon et al., 2015 [41]	N=55 (11 patients requiring ECMO for more than 3 weeks) Pneumonia 23 (Bacterial-14, viral-9); sepsis 6; trauma 8; others 18	8 (73%) patients receiving long-term and 25 (57%) patients receiving short-term ECMO support survived to 30 days and hospital discharge.
Tsai et al., 2015 [42]	N=90 (only 45 treated with ECMO) Infection 30; Pulmonary Haemorrhage 5; Acute pancreatitis 2; others 8	ECMO therapy had higher hospital survival rates and significantly lower 6-month mortality rates.
Chiu et al., 2015 [43]	N=65 Pneumonia (bacterial-21, H1N1-8); Lung contusion 10; sepsis 10; others 16	Hospital survival rate was 47.7%. Younger age, shorter duration of mechanical ventilation, and lower organ dysfunction scores before ECMO initiation had favorable outcome.
Wu et al., 2014 [44]	N=20 Post-trauma ARDS	16 patients were weaned off 14 survived. Major hemorrhages-7 (3 were lethal).
Hsiao et al., 2014 [45]	N=81 patients Pneumonia 40; sepsis 11; trauma 15; post-operative 7; others 8	The overall mortality=55.5%. Risk factor for hospital mortality - APACHE II score, mean arterial pressure, platelet count, and urine output on day 1 of ECMO support.
Roch et al., 2014 [46]	N=85 Community acquired pneumonia 56 (H1N1-20); nosocomial pneumonia 12; acute pancreatitis 5; others 12	Forty-eight patients died at the hospital (56%).
Lindskov et al., 2013 [47]	N=124 Pneumonia 79 (bacterial-54, viral-25); trauma 18; sepsis 15; others 12	Weaning from ECMO=97 (78%) Survival to hospital discharge=88 (71%) Risk factors for mortality-high SAPS-II, SOFA and Murray scores
Weber-Carstens et al., 2013 [48]	N=116 H1N1disease 61 received ECMO	The overall mortality was 38% (44 of 116 patients) Mortality among patients on ECMO was 54% (33 of 61 patients).
Michaels et al., 2013 [49]	N=36 Pneumonia 21 (H1N1-16, bacterial-5); sepsis 3; others 12	Successful weaning=67% Survival to hospital discharge=60%
Ma et al., 2012 [50]	N=56 Pneumonia 37 (Infective- 30, aspiration-7); abdominal sepsis 9; post-operative 5; others 5	Successful weaning=27 (48%) Survival to hospital discharge=7 (13%)
Noah et al., 2011 [51]	N=80 (69 treated with ECMO) H1N1 disease 69	The hospital mortality rate were lesser (23.7%) among ECMO-referred patients compared to non-ECMO-referred patients (52.5%)
Patroniti et al., 2011 [52]	N=60 H1N1disease 49; others 11	Overall survival to hospital discharge with ECMO was 68%. Survival of patients receiving ECMO within 7 days of mechanical ventilation was 77%.
Muellenbach et al., 2008 [53]	N=22 Post trauma 11; pneumonia 6; aspiration 4; exacerbation of COPD 1	The overall mortality rate was 27%.
Hemmila et al., 2004 [54]	N=405 (255 ECMO for ARDS) Pneumonia 132 (bacterial-79, viral-33, aspiration-13, fungal/ atypical-7); vasculitis/BOOP 6; trauma 32; sepsis/ septic shock 22; cardiac surgery 16; lung transplant 16; others 31	Successful weaning=67% Survival to hospital discharge=52%
Bein et al. 2004 [55]	N=30 Trauma, pneumonia or post-surgery	Overall mortality=50%
Frenckner et al., 2002 [56]	N=38 Pneumonia/sepsis 23; trauma 2; pulmonary embolism 2; aspiration 3; others 8	Overall survival=66%
Mols et al., 2001 [57]	N=245 (62 treated with ECMO)	Survival rate was 55% in ECMO patients and 61% in non-ECMO patients.

Table 3 Summary of prospective studies.

Authors, year of publication (Reference)	Patient population	Results and comments
Seo et al., 2015 [58]	N=69 (postoperative) Cardio-thoracic Surgery 22; liver transplantation 32; Others 15	35 (50.7%) died on ECMO 34 (49.3%) were successfully weaned from ECMO. 21 (30.4%) died after weaning from ECMO. Hospital survival after ECMO was 18.8%.
Pappalardo et al., 2013 [59]	N=60 H1N1	The survival rate in patients treated with ECMO=68 %
Pham et al., 2013 [60]	N =123 H1N1 ARDS	ICU mortality was 44/123 patients (36%; 95% CI, 27–44%). Mortality was comparable between the two matched cohorts (odds ratio, 1.48; 95% CI, 0.68-3.23; p=0.32).
Haneya et al., (2012) [61]	N=22	Weaning from ECMO=16 (72.7%) Survival to hospital discharge=15 (68.2%)
Davies et al., 2009 [62]	N=68 H1N1 ARDS	ICU survival=48/68 (71%) Survival to hospital discharge=32/46 (69%) (2 were still receiving ECMO)
Zimmermann et al., 2009 [63]	N=51 "Multiple aetiologies"	The hospital mortality rate was 49%.
Mols et al., 2000 [64]	N=245 (62 received ECMO) Pneumonia 36; trauma 15; sepsis 5; others 6	The survival rate was 55% in ECMO patients and 61% in non-ECMO patients.
Lewandowski et al., 1997 [65]	N=183 (49 received ECMO) Pneumonia 18; polytrauma 13; aspiration 7; sepsis 5; others 6	The overall survival rate=75%. Survival rates non ECMO group=89% Survival rates ECMO group=55%

Table 4 Summary of RCTs reporting mortality.

Authors, year of publication [Ref]	Time interval	Mortality		Risk ratio (95% CI)
		ECMO	Control	
Zapol et al., 1979 [13]	6 months	38/42 (91%)	44/48 (92%)	0.99 (0.87 to 1.12)
Morris et al., 1994 [66]	30 days	14/21 (66%)	11/19 (57%)	1.15 (0.71 to 1.88)
Peek et al., 2009 [67]	Within 6 months	33/90 (37%)	45/90 (50%)	0.73 (0.52 to 1.03)
Bein et al., 2013 [68]	In-hospital	7/40 (17.5%)	6/39 (15.4%)	1.14 (0.42 to 3.08)

Table 5 Summary of RCTs reporting survival too discharge.

Authors, year of publication [Ref]	Survival to Discharge		p-value
	ECMO	Control	
Zapol WM et al., 1979 [13]	-	-	Not Reported
Morris AH et al., 1994 [66]	7/21 (33%)	8/19 (42%)	0.8
Peek GJ et al., 2009 [67]	-	-	Not Reported
Bein et al., 2013 [68]	33/40 (82.5%)	33/39 (84.6%)	1.0

Mortality at various time intervals

Mortality is one the most important outcome parameter in ICU setting. Any intervention, which can reduce the mortality among these patients, is always desired. Authors have reported rates of all-cause mortality at day-30, 60, and 90 and at six months **(Table 4)**.

The study by Peek et al. was the only RCT, which showed a significant difference in mortality (absolute difference of 15%). However, this study actually compared the referral to the ECMO center rather than ECMO itself. Of the 90 patients in the ECMO referral group, 68 (75%) patients actually received ECMO. This trial recommended the transfer of participants with severe, but potentially reversible respiratory failure to a center with an ECMO-based management protocol. Strong evidence in support of ECMO is still currently lacking. When we look at the survival to hospital discharge, the results are not very encouraging.

The outcome in the ECMO group is showing some improvement in the last decade, but it is not significantly better than that in control group. Some of the improvement in outcome with ECMO may be attributed to better understanding of the disease, use of lung protective ventilation (in the early studies, the ARDS group did not receive lung protective ventilation) and modern advanced equipment with relatively less risks of complications.

Survival to discharge

Survival to discharge has been reported by two studies at different time intervals. The data suggest that there is difference in survival to discharge when ECMO was compared to control group **(Table 5)**.

Duration of hospital stay

While assessing any new intervention for critically ill patients in ICU, it is important to assess its impacts on the duration of hospital stay, and consequently the cost and other complications. Amongst the 4 RCT, three provided data on the length of hospital stay **(Table 6)**.

The study by Peek et al. has reported the duration of hospital stay for ECMO patients, which was almost double as compared to the controls.

It is equally necessary to analyze whether the ECMO group is at risks for adverse events, disability, and how cost effective the technique.

Disability

Data regarding disability is reported by two RCTs **(Table 7)**. The parameters used for assessment of disability were different for both the studies. The largest RCT showed that the disability free survival was better with ECMO compared to control group.

Adverse outcomes and transfusion

One of the major factors limiting the wide acceptance of the technique is the risk of adverse events. All the RCT have mentioned the adverse events **(Table 8)**.

Studies have shown an increased requirement of transfusion and adverse events in the ECMO group (especially bleeding manifestations in the early RCT compared to the RCT done in

Table 6 Summary of RCTs reporting duration of hospital stay.

Authors, year of publication [Ref]	Length of stay (in days)		p-value
	ECMO	Control	
Zapol et al., 1979 [13]	Not Reported	Not Reported	Not Reported
Morris et al., 1994 [66]	26.9 ± 4.9	28.8 ± 5.7	0.09
Peek et al., 2009 [67]	35 (15.6 to 74.0)	17.0 (4.8 to 45.3)	Not Reported
Bein et al., 2013 [68]	46.7 ± 33	35.1± 17	0.113

Table 7 Summary of RCTs reporting data regarding disability.

Authors, year of publication [Ref]	Assessment	Results
Zapol et al., 1979 [13]	Pulmonary function test	No participants had limitations in their daily activities six months after discharge
Morris et al., 1994 [66]	-	Not Reported
Peek et al., 2009 [67]	EQ-5D survey *	ECMO Group- 57/90 (63%) Control Group - 41/87 (47%)# RR= 0.69, 95% CI 0.05 to 0.97; P value=0.03
Bein et al., 2013 [68]	-	Not Reported

*Assessed "severe disability" at six months - determined by the first two items of the EQ-5D survey - Mobility and personal care
Three participants in the control group had unknown disability status.

Table 8 Summary of RCTs reporting adverse events associated with ECMO.

Authors, year of publication [Ref]	Incidence of Adverse events	Requirement of Transfusion
Zapol et al., 1979 [13]	1. ECMO group had lower blood platelet and white blood cell concentrations 2. Septicaemia (20%) and Pneumothorax (45%) were similar in both groups.	Greater blood/plasma infusion reported with 1 to 2.5 liters
Morris et al., 1994 [66]	**Intervention group:** 34 major complications 16 non-CNS haemorrhage **Control group:** 19 major complications 0 non-CNS haemorrhage	Transfusion of packed red blood cells (RBCs) exceeded 0.8 L/d in 10 participants, leading to bypass disconnection in seven participants in the intervention group
Peek et al., 2009 [67]	2 serious adverse events - death (due to mechanical failure of oxygen supply during ambulance transport), and vessel perforation during cannulation (non-fatal), one each in ECMO group	Not reported
Bein et al., 2013 [68]	Total 3 (7.5%) adverse events- 1-transient ischemia of lower limb 2-false aneurysm	Number of RBC units transfused in initial 10 days: ECMO 3.7 ± 2.4 units Control 1.5 ± 1.3 units p < 0.05

Table 9 Summary of RCTs reporting the cost of ECMO.

Authors, year of publication [Ref]	Country	Hospital costs for participants		Comments
		ECMO	Control	
Zapol et al., 1979 [13]	-	-	-	Not Reported
Morris et al., 1994 [66]*	USA	USD 120,800	USD 97,200	
Peek et al., 2009 [67]#	UK	GBP 73,979	GBP 33,435	The lifetime predicted cost utility of GBP 19,000 per QALY in the ECMO group - cost-effective.
Bein T et al., 2013 (68)	-	-	-	Not Reported

*Cost calculations excluded expenses for research staff members and the senior clinical physician (on-call for the initial years of the trial) as well as costs of extracorporeal equipment and disposals.
#QALYs were calculated from UK tariff values and were based on EQ-5D survey results.

Table 10 Summary of RCTs reporting the Health Related quality of life.

Authors, year of publication [Ref]	Method of Assessment	Results
Zapol et al., 1979 [13]	Not Reported	Not Reported
Morris et al., 1994 [66]	Not Reported	Not Reported
Peek et al., 2009 [67]*	Short Form (SF)-36 and EQ-5D surveys at 6 months	No difference between ECMO and control group
Bein et al., 2013 [68]	Not Reported	Not Reported

*17 participants EQ-5D data was missing.

the last decade). With the newer machines, better cannulae, and advanced ECMO circuits, the risks of complications have reduced. It is necessary to factor this when deciding to commence ECMO.

Cost effectiveness

Cost is an important issue in deciding the utility of any intervention. The cost analysis has been reported only by two studies **(Table 9)**. Though the cost analysis in the initial study excluded the cost of the equipment, the cost in the ECMO group was higher. The recent study from UK also confirmed the increased cost in the ECMO group compared to the control group. In the reported cost analysis, sometimes cost related to manpower is neglected; therefore, the actual cost may be higher than the reported one [66-68].

Health related quality of life

Most studies have not reported the results regarding the impact of ECMO on the health related quality of life. The only study, which addressed this question found no significant difference between the groups **(Table 10)**.

Future studies

Currently, the evidence in support of ECMO is not very strong and further studies are required. There are currently randomized controlled trials underway to provide us with further evidence. One of the RCT under way is the EOLIA trial [69]. The trial is trying VV ECMO in severe ARDS. It is currently recruiting patients. The other large trial is the SUPERNOVA [70], which is studying the role of ECCO2R in moderate to severe ARDS. The results of these trials will likely provide concrete evidence, make us wiser and allow us to effectively use this tool in treating ARDS patients.

Complications

Due to its complexity and infirmity of the patients most suited for this intervention, ECMO has a high potential of complications. The hazards of ECMO technique can be classified into circuit related complications and patient-related complications. The ECMO circuit may have thrombi at almost any point because of the blood-surface interactions. They may embolize and have potentially devastating consequences. Hence, appropriate use of anticoagulation and regular scrutiny of the ECMO circuit is needed. Virtually any component of the circuit can fracture causing blood loss. Also, because the pumps can generate negative pressures, there is a risk of air embolism.

The patient related complications include complications due to cannulation, due to anticoagulation, and those due to underlying disease. Bleeding and thrombotic complications remain a leading cause of morbidity and mortality in patients on ECMO [71]. During vascular access, there may be injury to the posterior wall causing compartmental syndromes [72] or hematomas [73]. Guide wires and dilators can also cause arterial dissection. The arterial cannulation is associated with risks of distal ischemia. Bleeding is common due to systemic anticoagulation and platelet dysfunction. It may manifest as bleeding from the cannulation site or GI or airway bleeding. Even routine procedures like suctioning and urinary catheter placements can trigger bleeding. Neurological complications include intracranial hemorrhage, infarction, myoclonus, and seizures [74]. These patients are also at increased risk of nosocomial infections.

Conclusion

While assessing the outcome of ECMO, it is important to realize that ECMO is not a cure; it is only a life support system that allows time for diagnosis and treatment of the condition that initially caused heart or lung failure. ECMO controls gas exchange and perfusion, it stabilizes the patient physiologically, reduces the risk of iatrogenic injury (eg. VILI) and buys time for the clinician to manage the patient. However, its use is not without risks and imposes a heavy economic burden on the treating facility. Its use needs to be decided on a case by case basis after due

consideration of the indications and contraindications and the expected outcome. The data from the ESLO registry accessed in March [75] (https://www.elso.org/Registry/Statistics.aspx) showed that over 73,000 had been treated with ECMO and in the following years it is likely that ECMO is going to be an integral part of the intensivist's armamentarium in treating critically ill patients.

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