Chapter 2
Hypoxemic Respiratory Failure: Evidence, Indications, and Exclusions

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Abbreviations

ARDS	Acute respiratory distress syndrome
ECMO	Extracorporeal membrane oxygenation
PaO_2	Partial pressure of oxygen in arterial blood
FiO_2	Fraction of inspired oxygen
$ECCO_2R$	extracorporeal carbon dioxide removal
LFPPV	Low-frequency positive-pressure ventilation
PCIRV	Pressure-control inverse ratio ventilation
PEEP	Positive end-expiratory pressure
APACHE	Acute physiology and chronic health evaluation
SOFA	Sequential organ failure assessment
BMI	Body mass index
Q_s/Q_t	Shunt fraction

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Evidence

ECMO is increasingly being used for patients with the acute respiratory distress syndrome (ARDS), particularly in cases of severe ARDS in which life-threatening hypoxemia or hypercapnia persists despite maximal conventional mechanical ventilatory support [1, 2]. In addition, ECMO is used in some patients in whom life-threatening gas exchange abnormalities are sufficiently improved with the use of positive-pressure ventilation, but only at the expense of generating excessively high inspiratory airway pressures. ECMO in this setting facilitates lung-protective ventilation and minimizes ventilator-associated lung injury. Despite the increasing use of ECMO in ARDS, high-level evidence supporting its benefit for this indication is lacking. The first successful use of ECMO for severe post-traumatic hypoxemic respiratory failure was in 1971 by Dr. J.D. Hill and colleagues. The patient received venoarterial extracorporeal support with a Bramson membrane lung for 75 h and survived [3]. This success prompted others to attempt the institution of ECMO support for severe hypoxemic respiratory failure, with reports of approximately 150 cases performed from the original Hill report through 1974, though mortality was 85–90 % [4–6]. In 1979, Warren Zapol and colleagues published the results of a multicenter, randomized, controlled trial of mechanical ventilation supplemented with venoarterial ECMO versus conventional mechanical ventilation alone, according to the standard of care at that time, as a therapy for severe acute hypoxemic respiratory failure [7]. Ninety subjects were randomized to conventional mechanical ventilation alone or mechanical ventilation and ECMO, with slow and fast entry criteria utilized for enrollment based on a combination of severity and duration of hypoxemia, resulting in a maximum PaO_2 to FiO_2 ratio of 83. Subjects with prolonged mechanical ventilation (greater than 21 days), evidence of left atrial hypertension (pulmonary capillary wedge pressure greater than 25), and chronic or irreversible diseases were excluded. The trial demonstrated no significant difference in survival (9.5 % in the ECMO group, 8.3 % in the control group, Table 2.1), with high rates of infectious and bleeding complications. The low rate of survival in the

Table 2.1 Demographics and outcomes of prospective randomized trials of ECLS for ARDS

Study	Year	No. of pts.	PaO_2:FIO_2	Modality	ECMO survival (%)	Non-ECMO survival (%)
Zapol et al. [7]	1979	90	<83	$ECCO_2R$	9.5[a]	8.3
Morris et al. [12]	1994	40	63	$ECCO_2R$	33[a]	42
Peek et al. [33]	2009	180	75	ECMO	63[b, c]	47

ECLS extracorporeal life support, *ECMO* extracorporeal membrane oxygenation, *ARDS* acute respiratory distress syndrome, *$ECCO_2R$* extracorporeal carbon dioxide removal, *PaO_2* partial pressure of arterial oxygen, *FIO_2* fraction of inspired oxygen

[a]No statistically significant difference in survival between groups

[b]22/90 patients (24 %) within ECMO referral group did not receive ECMO

[c]Relative risk of death or severe disability 0.69 (95 % CI 0.05–0.97, $p=0.03$) compared to non-ECMO group

control group also highlights the high severity of illness in the study population and the different standard of care for mechanical ventilation in ARDS at that time.

In the late 1970s and into the 1980s, Gattinoni and colleagues in Italy, among others, began experimenting with the use of extracorporeal support in animals, and then in humans with severe forms of ARDS. The concept involved using venovenous extracorporeal support at low blood flow rates principally to remove CO_2, a technique known as extracorporeal CO_2 removal or $ECCO_2R$. By removing CO_2 directly from the blood, they could ventilate the subjects at lower airway pressures and respiratory rates—what they termed "low-frequency positive-pressure ventilation" (LFPPV) while providing passive oxygenation through the endotracheal tube [8–11]. The goal was to provide what Gattinoni referred to as "pulmonary rest," the precursor to low-volume, low-pressure ventilation strategies [11]. Results of a prospective, uncontrolled study of 43 subjects treated with a LFPPV-$ECCO_2R$ strategy for severe respiratory failure (average PaO_2 to FIO_2 ratio of 67) demonstrated a survival of 49 %, despite an anticipated survival of less than 10 % based on similar inclusion and exclusion criteria to those used in the trial by Zapol [9].

Prompted by a significantly higher survival than prior studies of subjects with severe ARDS, a lack of randomization or control group in the Gattinoni study, and the hypothesis that ventilator-associated lung injury plays a critical role in mortality in ARDS, Morris and colleagues at the University of Utah evaluated the role of LFPPV-$ECCO_2R$ in a prospective, randomized, controlled trial of subjects with severe ARDS [12]. Forty subjects were randomized between 1987 and 1991 to receive either conventional mechanical ventilation or a strategy of pressure-control inverse ratio ventilation (PCIRV), followed by LFPPV-$ECCO_2R$ if PCIRV was unable to maintain adequate PaO_2 or pH. Entry criteria were similar to those used by Zapol and Gattinoni. Oxygenation was markedly impaired, with an average PaO_2 to FIO_2 ratio of 63. The results demonstrated no difference in mortality between groups, with a survival of 42 % in the control group and 33 % in the PCIRV plus LFPPV-$ECCO_2R$ group. Hemorrhage with high rates of transfusion led to $ECCO_2R$ discontinuation in seven (37 %) of the subjects in the experimental group, and four subjects (21 %) developed clot within the extracorporeal circuit. Although the authors concluded there was no role for $ECCO_2R$ as a therapy for ARDS, there were several notable limitations of this trial. The intervention group received two different experimental treatment modalities (inverse ratio ventilation and $ECCO_2R$), worldwide experience with extracorporeal techniques was limited prior to study initiation, and the intervention arm was exposed to notably high airway pressures despite extracorporeal support. Additionally, survival among those in the control group was higher than in the previous studies, highlighting the differences in patient characteristics, therapeutic interventions, or protocols for respiratory care between this study and previously published data. Furthermore, while all of these studies used uniform entry criteria that facilitate comparisons between trials, these criteria may not reflect best practice for the initiation of extracorporeal support.

Starting in the 1980s, there were multiple non-randomized, observational studies evaluating ECLS for severe ARDS, several of which are listed in Table 2.2 [9, 13–22]. The studies listed are expectedly heterogeneous in their demographics,

Table 2.2 Demographics and outcomes of observational ECMO trials for acute respiratory failure

Study	Year	No. of pts.	PaO_2:FIO_2	Indication	Modality	Survival (%)
Gattinoni et al. [9]	1986	43	67	ARDS	$ECCO_2R$	49
Wagner et al. [13]	1990	76	–	ARDS	$ECCO_2R$	50
Brunet et al. [14]	1993	23	84	ARDS	$ECCO_2R$	52
Manert et al. [15]	1996	21	54	ARDS	ECMO	81
Kolla et al. [16]	1997	100	56	Severe ARF[a]	ECMO	54
Peek et al. [17]	1997	50	65	Severe ARF	ECMO	66
Lewandowski et al. [18]	1997	49	67	ARDS	ECMO	55
Linden et al. [19]	2000	17	46	ARDS	ECMO	76
Bartlett et al. [20]	2000	86	55	ARDS	ECMO	61
Davies et al. [21]	2009	68	56	ARDS/H1N1	ECMO	75
Freed et al. [25]	2010	6	61	ARDS/H1N1	ECMO	67
Roch et al. [24]	2010	9	52	ARDS/H1N1	ECMO	56
Schmid et al. [22]	2011	176	77	ARDS	ECMO	56

ECMO extracorporeal membrane oxygenation, *PaO_2* partial pressure of arterial oxygen, *FIO_2* fraction of inspired oxygen, *ARDS* acute respiratory distress syndrome, *$ECCO_2R$* extracorporeal carbon dioxide removal, *H1N1* denotes the 2009 novel influenza A(H1N1) virus, *ARF* acute respiratory failure

[a]Defined as shunt fraction >30 %, compliance <0.5 mL/cm H_2O/kg; life-threatening anatomic airway obstruction, refractory status asthmaticus, or uncorrectable hypercapnia with pH < 7.0 and end-inspiratory pressure >45 mmHg

however they all included subjects with marked impairment in oxygenation that would meet the most recent definition of severe ARDS [1].

Among these studies is the Australia-New Zealand experience with ECMO, published by Davies and colleagues, during the influenza A(H1N1) outbreak in 2009 [21]. Sixty-eight subjects were treated with ECMO for ARDS in 15 specialist ICUs that provided ECMO support during the study period. All cases were confirmed or strongly suspected to be a result of influenza A(H1N1), with a high severity of illness as demonstrated by ventilatory parameters: median PaO_2 to FIO_2 ratio of 56, median positive end-expiratory pressure (PEEP) of 18 cm H_2O, median nadir pH of 7.2, and median highest $PaCO_2$ of 69. Survival in this cohort of subjects was 75 % [23]. Similar outcomes were demonstrated in other centers during the influenza pandemic, though with smaller sample sizes (Table 2.2) [9, 13–22, 24, 25].

Contemporaneous with the report by Davies et al., a study with similar demographics and outcomes of subjects with influenza A(H1N1) who were managed without the use of ECMO was reported by Miller et al. in Utah [26]. Among the 47 subjects admitted to the ICU with a confirmed diagnosis of influenza, 30 (64 %) met criteria for ARDS, with a median PaO_2 to FIO_2 ratio of 61 and median PEEP of 22. Multisystem organ failure was common (87 %). None of the subjects with ARDS received so-called "rescue therapies" such as inhaled nitric oxide, prone positioning, inhaled epoprostenol, or high-frequency oscillatory ventilation, although neuromuscular blocking agents were used in 47 % of subjects. Despite a high severity

of illness (median APACHE II score = 25), survival was 73 %. Comparable survival to the Australia-New Zealand cohort raised questions about whether ECMO provides any survival advantage over optimal medical management in cases of severe ARDS related to influenza A(H1N1).

An attempt to reconcile this issue was made by Noah and colleagues from the United Kingdom, who compared ECMO-referred subjects with confirmed or strongly suspected H1N1-related ARDS ($n = 80$) to non-ECMO-referred subjects with H1N1-related ARDS who were enrolled in a separate, concurrent prospective cohort study within the same geographical area and who were potentially eligible for ECMO ($n = 195$) [27]. Only 69 of the 80 subjects referred for ECMO received ECMO (86 %). However, statistical analysis was performed by intention-to-treat principles. Individual, propensity score, and GenMatch matching were used to match subjects from each group on the basis of demographic, physiologic, and comorbidity data that were anticipated a priori to be associated with ECMO use and hospital mortality (prior duration of mechanical ventilation, PaO_2 to FIO_2 ratio, age, SOFA score, body mass index (BMI), pregnancy status, and use of alternative ventilation strategies). After matching for the above variables, the ECMO-referred subjects consistently had a mortality approximately half that of the non-ECMO-referred subjects (24 % vs. 47 % by propensity score matching, RR 0.51, 95 % CI 0.31–0.84, $p = 0.008$). The investigators could not account for differences in ventilatory strategies between groups, nor could they assess the impact of variables not captured in the database of the cohort of non-ECMO-referred subjects, which may have confounded the results of this non-randomized comparison.

Survival rates of subjects receiving extracorporeal support in many of the observational studies in the late 1990s and 2000s were higher (54–81 %) than those reported for subjects with and without extracorporeal support in the earlier randomized trials by Zapol and Morris [15–22, 24, 25]. However, there are inherent flaws in comparing non-randomized studies. Changes in clinical management confound the comparison of survival rates from different eras. This is evident in the decline in mortality rates observed in ARDS over the last decade [28], with mortality of 31 % in the intervention arm of ARMA in 2000 [29], 25 % in the fluid-conservative strategy arm in FACTT in 2006, and 16–18 % in the control arms of ALTA and OMEGA in 2011 [30–32]. Likewise, ECMO technology has evolved significantly since the early randomized trials, with more efficient membranes for gas exchange, the advent of centrifugal pumps, heparin-coated circuits that can tolerate lower levels of anticoagulation resulting in lower bleeding risk, and cannulae that permit single-vessel access with minimal recirculation. Comparisons of non-randomized ECMO studies are also confounded by indication, which is influenced by multiple factors, including but not limited to patient age, disease severity, concomitant medical conditions, concurrent therapies, and physicians' estimation of prognosis.

In an attempt to estimate the effect of ECMO in ARDS using more advanced ECMO technology, and coinciding with increasing usage within the critical care community, the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial was performed [33]. In this prospective, randomized, controlled trial, 180 subjects, age 18–65, with severe but potentially reversible

respiratory failure and a Lung Injury Score (a.k.a. Murray Score, a composite score based on PaO_2 to FIO_2 ratio, PEEP, respiratory system compliance, and radiographic findings [34]) of ≥3.0 or uncompensated hypercapnia (pH < 7.2) despite "optimal conventional management" were randomly assigned to receive ongoing conventional mechanical ventilation at designated treatment centers or be transferred to a single ECMO center at Glenfield Hospital in Leicester for consideration of treatment with venovenous ECMO. Subjects were excluded from the trial if they had contraindications to anticoagulation or if they had been on high pressure (peak inspiratory airway pressure >30 cm H_2O) or high FIO_2 (>0.8) for greater than 7 days. Hemodynamically stable subjects randomized to the ECMO referral arm were initially managed on transfer to Glenfield with a standardized management protocol that included a pressure-restricted ventilation strategy, diuresis to dry weight, transfusion to a hematocrit of 40 %, prone positioning and full nutrition. Those who were hemodynamically unstable or failed to respond to this strategy within 12 h were placed on ECMO. Only 76 % of the subjects referred for ECMO actually received ECMO, however all subjects who received ECMO were managed with a lung-protective ventilation strategy. In total, 93 % of subjects in the ECMO referral arm received treatment with a low-volume, low-pressure strategy at some point in their care. By comparison, because there was no mandate of a lung-protective ventilation strategy in the conventional management group (a low-volume, low-pressure strategy was advised) and perhaps because many of these subjects were difficult to ventilate, only 70 % of those subjects were managed with such a strategy at any time during the study. Subjects were well-matched between groups and the majority were randomized early in ARDS, with 62 % of ECMO subjects and 66 % of conventionally managed subjects having been on high pressure or high FIO_2 for 48 h or less, with an average of 28 h in each group. Average PaO_2 to FIO_2 was approximately 75 in both groups. The primary outcome—death or severe disability by 6 months after randomization—occurred in 37 % of the subjects referred for ECMO, as compared with 53 % of those in the conventional management group, relative risk 0.69 (95 % confidence interval 0.05–0.97, $p = 0.03$).

The results from CESAR, as well as the study by Noah and colleagues, may reasonably support a strategy of transferring patients with severe ARDS to a center capable of performing ECMO as part of a standardized management protocol [35]. However, this trial was not a randomized trial of ECMO as compared with standard-of-care mechanical ventilation. The higher survival in the ECMO-referral group may be accounted for by differences in the care between study groups, most importantly, the discrepancy in the use of a low-volume, low-pressure mechanical ventilation strategy.

To date, there is no prospective randomized trial comparing modern-day ECMO technology and techniques to standard-of-care mechanical ventilation in ARDS. Given that the current body of literature on ECMO in ARDS has been used to justify or dispute the efficacy of ECMO in cases of severe ARDS, there appears to be clinical equipoise to perform another prospective, randomized clinical trial in which subjects randomized to the ECMO arm are guaranteed to receive ECMO and those randomized to the mechanical ventilation arm are managed with a standardized

ventilation protocol [36, 37]. Centers that already offer ECMO and believe in its utility in ARDS may find it difficult to withhold ECMO from subjects who are failing mechanical ventilation alone, and have a need to permit crossover within the study, which may bias results toward the null hypothesis when analyzed by intention to treat. Nonetheless, a carefully designed clinical trial that adequately matches for baseline demographics and potential confounders and adheres to treatment protocols would provide useful additional evidence to help settle the ongoing debate about the role of ECMO in severe ARDS.

Indications

There is no single set of accepted criteria for the initiation of ECMO in ARDS, and the threshold for initiation of ECMO varies considerably across studies and guidelines. The decision to initiate ECMO would ideally be based on a risk–benefit analysis that incorporates the risk of mortality with or without extracorporeal life support while factoring in the risk of complications as a result of its use. Unfortunately, precise data to inform this sort of decision-making do not exist. As risk–benefit analysis improves, thresholds for ECMO initiation will likely change to reflect risk–benefit tradeoffs compared with standard-of-care mechanical ventilation.

The early randomized trials used two sets of criteria to assess the need for ECMO: PaO_2 less than 50 mmHg for 2 h at FIO_2 1.0 and PEEP greater 5 cm H_2O (fast-entry criteria) or PaO_2 less than 50 mmHg for greater than 12 h at FIO_2 greater than 0.6, PEEP greater than 5 cm H_2O, and shunt fraction (Q_s/Q_t) greater than 0.3 despite 48 h of maximal medical therapy (slow-entry criteria) [7, 12]. While these criteria take into account the risks of prolonged hypoxemia and oxygen toxicity, there is no consideration of hypercapnia with resulting acidemia or plateau airway pressures as factors that may influence the decision to initiate ECMO. Furthermore, the specific time and oxygenation cutoffs used for entry criteria have not been independently validated or shown to correlate with mortality. Among the best data available to estimate the prognosis of patients with ARDS without ECMO support comes from the work of the ARDS Definition Task Force [1], which redefined ARDS based on the degree of hypoxemia as a predictor of mortality. Lower PaO_2 to FIO_2 ratio cutoffs correlate with increased mortality (45 % when PaO_2 to FIO_2 is less than 100, vs. 27–32 % in mild to moderate ARDS) and longer duration of mechanical ventilation (9 days in severe ARDS vs. 5–7 days in mild to moderate ARDS). Based on these data, patients with lower ratios of PaO_2 to FIO_2 would seem to benefit the most from aggressive interventions. However, the appropriate cut off for initiating ECMO has yet to be determined. Given the consensus decision by the ARDSnet trial investigators to set a goal PaO_2 of 55–80 mmHg [29], ultimately representing a range of values within which the amount of PEEP or FIO_2 is not deescalated because the patient is presumed to be near the steep portion of the oxyhemoglobin dissociation curve, one may consider a PaO_2 to FIO_2 ratio of 80 as a reasonable cutoff for consideration of ECMO (Table 2.3) [2]. This threshold is similar to the PaO_2 to FIO_2

Table 2.3 Indications and contraindications for ECMO in ARDS

Indications
Severe hypoxemia (e.g. ratio of PaO_2 to $FIO_2 < 80$ despite the application of high levels of PEEP, typically 15–20 cm H_2O), in patients with potentially reversible respiratory failure
Uncompensated hypercapnia with acidemia (pH < 7.15) despite optimal ventilator management
Excessively high end-inspiratory plateau pressure (>35–45 cm of water, according to the patient's body size) despite optimal ventilator management
Relative contraindications
High-pressure ventilation (plateau pressure >30 cm H_2O) for >7 days
High FIO_2 requirements (>0.8) for >7 days
Limited vascular access
Any condition or organ dysfunction that would limit the likelihood of overall benefit from ECMO, such as severe, irreversible brain injury or untreatable metastatic cancer
Any condition that precludes the use of anticoagulation
Thrombotic thrombocytopenic purpura
Absolute contraindications
ECMO as bridge to lung transplantation if transplantation will not be considered

ARDS acute respiratory distress syndrome, *ECMO* extracorporeal membrane oxygenation, *PaO_2* partial pressure of arterial oxygen, *FIO_2* fraction of inspired oxygen, *PEEP* positive end-expiratory pressure, *TTP* thrombotic thrombocytopenic purpura

ratio that was used as part of the slow entry criteria in the early ECMO trials [7, 12], and at the upper limit of many observational studies [15–22, 24, 25]. The PaO_2 to FIO_2 ratio is one component of the Lung Injury Score which uses a combination of physiologic and radiographic characteristics to quantify the extent of lung injury in ARDS [34]. However, because of its non-physiologic component and a lack of data to support its ability to predict survival among patients with the most severe forms of ARDS, it may be less useful as a criterion for initiation of ECMO.

The amount of PEEP that is appropriate to achieve adequate oxygenation in severe ARDS prior to initiation of ECMO has not been well established and varies between patients. There was no difference in survival in several studies of high versus low PEEP strategy in ARDS [38–40]. Nonetheless, many of the studies involving ECMO for ARDS have documented high levels of PEEP to improve oxygenation prior to the initiation of ECMO. It is reasonable to attempt to achieve levels of PEEP up to 15–20 cm H_2O, in conjunction with increases in FIO_2, to reach an adequate level of oxygenation prior to the initiation of ECMO, assuming those levels of PEEP do not significantly compromise the patient's hemodynamic status.

In addition to oxygenation parameters, the ARDSnet protocol specifies a threshold of pH less than 7.15 (usually a result of uncompensated hypercapnia in the setting of poor lung compliance) as the point at which plateau airway pressure targets may be exceeded in order to increase minute ventilation and correct the acidemia. A pH less than 7.15 may therefore be a reasonable threshold to initiate ECMO in attempting to avoid exceeding plateau airway pressure limits that may worsen ventilator-associated lung injury. Along similar lines, a third indication for the ini-

tiation of ECMO is excessively high plateau airway pressures themselves, despite adherence to the best accepted standard of care for ventilator management. Plateau airway pressures exceeding 35 cm H_2O have been shown to correlate with significantly higher incidence of barotrauma [41]. A reasonable range of plateau airway pressures in which to consider ECMO initiation is 35–45 cm H_2O depending on the patient's body habitus [2]. Patients with higher BMI will have higher elastic loads on the chest wall than those with lower BMI, and thus may require higher plateau airway pressures to achieve the same degree of alveolar patency, though the transpulmonary pressure gradient may not be higher.

Exclusions

There are few absolute contraindications for ECMO in severe ARDS. Any condition that precludes the use of anticoagulation is typically considered an absolute contraindication because of the need for systemic anticoagulant therapy to maintain the integrity of the circuit. However, in patients with severe bleeding, anticoagulation may be withheld for significant periods of time with apparent safety [42]. Given the advances in technology, the inability to anticoagulate should perhaps be considered only a relative contraindication to receiving ECMO. Thrombotic thrombocytopenic purpura (TTP) is another disorder that may be problematic because of the high risk of thrombosis (within the patient or the circuit) if platelet transfusion is needed in the setting of life-threatening hemorrhage and thrombocytopenia. While this may not be an absolute contraindication, the likelihood of survival without ECMO would have to be sufficiently low to consider accepting such a high risk.

The theoretical benefit of ECMO for severe cases of ARDS largely relates to lung protection: a decreased need for high-pressure ventilation or toxic fractions of inspired oxygen. Yet, this potential for benefit may be limited if the patient has already been exposed to high airway pressures and inspired oxygen levels such that damage is irreversible. Many clinicians think that patients who have been receiving high-pressure ventilation with plateau pressure exceeding 30 cm H_2O for greater than 7 days are less likely to benefit from ECMO [43–45]. Similarly, prolonged exposure to high fractions of inspired oxygen, which may induce lung inflammation, could nullify any beneficial effect of ECMO support, though this remains an area of controversy [46, 47]. Earlier initiation of ECMO, perhaps for these or other reasons, has been associated with better outcomes in some, but not all, observational studies [18, 45, 48, 49]. Other relative contraindications include limitations in vascular access that would preclude cannula placement and any conditions in which ECMO would be unlikely to alter the patient's overall prognosis, including but not limited to advanced malignancy or severe and irreversible brain injury. Finally, ECMO, when considered as a bridge to lung transplantation, should only be offered if the patient is actually a candidate for transplantation.

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