REVIEW ARTICLE

Extracorporeal Pulmonary Support in Severe Pulmonary Failure in Adults

A Treatment Rediscovered

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SUMMARY

Background: Severe, acute respiratory failure in adults still carries a high mortality. In recent years, improved pulmonary support techniques have been used increasingly alongside conventional treatment. About 1000 such treatments are performed in Germany annually, and the number is rising rapidly. The two types of systems currently in use involve venovenous extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide elimination.

Methods: The underlying principles, technical implementation, efficacy, and adverse effects of the new techniques are summarized in the light of a selective review of the literature, supplemented by the authors' personal experience. Recommendations are given for clinical use.

Results: Currently, only limited high-quality data (from prospective randomized trials) are available to support the use of either of these techniques in adults. Veno-venous ECMO systems can effectively secure gas exchange in patients with severe respiratory failure, with experienced centers reporting survival rates from 63% to 75%. Either pump-free arteriovenous systems or low-flow ECMO systems can be used for extracorporeal carbon dioxide elimination. Complications can be serious or life-threatening and must, therefore, be rapidly recognized and treated: these include vascular injury during cannulation, venous thrombosis in a cannulated vessel, an increased hemorrhagic tendency, and thrombocytopenia.

Conclusion: Modern miniaturized pulmonary support systems enable protective mechanical ventilation with low tidal volumes, reduce ventilator-associated lung injury, and can improve survival rates in critically ill patients with a manageable adverse effect profile.

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Severe acute pulmonary failure can be caused by various serious acute illnesses, such as pneumonia, aspiration, fulminant sepsis, necrotizing pancreatitis, and multiple trauma. If damage is bilateral, acute pulmonary failure is referred to internationally as acute respiratory distress syndrome (ARDS) (*Box 1*). Despite the capabilities of modern intensive medicine, ARDS still has a high mortality rate. A study in the USA only a few years ago found an incidence of ARDS of 58.7 cases per 100 000 people per year; the mortality rate was 41.1% (1). Severe cases, older patients, and those with concomitant illnesses exhibit a higher mortality rate, sometimes exceeding 80% (2–4). When vital gas exchange can only be ensured using aggressive, non-protective mechanical ventilation, the prognosis worsens (2, 5) because aggressive ventilation itself leads to progressive, ventilation-induced lung injury (6).

Extracorporeal gas exchange methods for patients with severe pulmonary failure were first developed in the 1970s (7). Serious complications and severe hemorrhaging limited their use at the time; randomized trials were unable to demonstrate a survival advantage for extracorporeal membrane oxygenation (ECMO) (8, 9). Thanks to major technical developments since then, modern ECMO machines are incomparably superior to the first machines developed in the 1970s. In recent years the H1N1 influenza A pandemic has led to a rediscovery of extracorporeal pulmonary support all over the world. In Germany, venovenous (VV) ECMO has been introduced in more than 50 hospitals; interventional lung assist (iLA), a carbon dioxide removal procedure, is even more widely used.

This article provides an overview of modern extracorporeal pulmonary support systems and when their use is indicated. It analyses their clinical efficacy on the basis of our own experience and a selective search of the literature and describes the procedures' risks and limitations.

Principle and technical implementation

Modern ECMO systems are notable for the compact design of all their individual components. The two main types are pump-driven (VV ECMO) and pumpless (iLA). For severe hypoxemic pulmonary failure,

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BOX 1

Acute respiratory distress syndrome (ARDS):

- Definition according to the 1994 American–European Consensus Conference (AECC) (38):
 - Acute onset
 - Bilateral infiltrates on chest X-ray
 - No evidence of left atrial hypertension or PCWP <18 mm Hg
 - $\text{PaO}_2/\text{FiO}_2 \leq 200$ mm Hg (ALI: $\text{PaO}_2/\text{FiO}_2 \leq 300$ mm Hg)
- 2012 Berlin definition (39)
 - Acute onset: trigger event in the last week
 - Bilateral infiltrates (chest X-ray or CT)
 - No evidence of cardiac pulmonary edema or fluid overload (echocardiogram)
 - Mild ARDS:
 - $200 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mm Hg}$, PEEP ≥ 5 cm H_2O
 - Moderate ARDS:
 - $100 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mm Hg}$, PEEP ≥ 5 cm H_2O
 - Severe ARDS:
 - $\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mm Hg}$, PEEP ≥ 5 cm H_2O

PCWP: pulmonary capillary wedge pressure; PaO_2 : partial pressure of oxygen; FiO_2 : fraction of inspired oxygen; ALI: Acute lung injury; PEEP: positive end-expiratory pressure

the priority is to improve oxygenation; this requires high bloodflow and therefore correspondingly large cannula diameters. For severe respiratory acidosis, when the priority is to remove carbon dioxide, lower bloodflow is sufficient; either low-flow ECMO with smaller cannulas and membrane surface areas or iLA may be used. Thus the pumpless iLA procedure is particularly suited to carbon dioxide removal, whereas VV ECMO effectively increases both oxygen transfer and carbon dioxide removal (*Table*).

The current standard technical equipment for VV ECMO is a centrifugal or axial pump, a plasma-resistant polymethylpentene diffusion membrane

oxygenator, and antithrombotic coating for all components, usually heparin-based (*Figure 1*). For conventional cannulation, a long, 21–23 Fr. (French) cannula is usually implanted through the right femoral vein using the Seldinger technique, and venous blood flows through this to the oxygenator. The return line is usually the right internal jugular vein, into which a shorter, 15–19 Fr. cannula is inserted. Alternatively, a double-lumen cannula can be used instead of two separate cannulas. Double-lumen cannulas were developed for implantation into the right internal jugular vein and have the significant advantage that patients can be mobilized while receiving ECMO support. Their disadvantages are their high cost and more difficult cannulation technique. Unfractionated heparin is used as systemic anticoagulation therapy, with a target aPTT (activated partial thromboplastin time) usually 1.5 times normal value, sometimes lower for patients prone to bleeding.

In essence, iLA is an artificial arteriovenous shunt with an intercalated gas exchange module (*Figure 2*). Because iLA is pumpless, the driving force for bloodflow through the system is the mean arterial pressure. A femoral artery is usually used as the afferent vessel, and the contralateral femoral vein is selected as the efferent vessel. After determining the vascular cross-section using ultrasound, the Seldinger technique is used to implant the arterial cannula, the size of which is chosen in order to maintain sufficient perfusion of the leg. 15 Fr. cannulas are usually used in arteries today.

The oxygenator has a gas exchange surface area of 1.3 m^2 with low flow resistance; anticoagulation with a target aPTT of around 50 seconds is usually sufficient.

Pump-driven extracorporeal membrane oxygenation

Indication

VV ECMO is usually indicated in cases of life-threatening hypoxemia ($\text{PaO}_2/\text{FiO}_2 < 80$ mm Hg) despite optimized mechanical ventilation (in line with ARDSNet [10]) and optimum supportive treatment

TABLE

Extracorporeal pulmonary and circulatory support systems

Procedure	Principle	Indication
iLA (interventional lung assist)	Arteriovenous shunt with intercalated gas exchange membrane; pumpless, i.e. bloodflow is generated by the difference in pressure between arteries and veins	Extracorporeal carbon dioxide removal in patients without shock syndrome, in order to treat severe respiratory acidosis
VV ECMO (venovenous extracorporeal membrane oxygenation)	Pump-driven procedure: Venous blood from the inferior vena cava is enriched with oxygen using a membrane oxygenator; at the same time, carbon dioxide is removed. Return flow usually through a second cannula in the superior vena cava	Severe hypoxemic respiratory failure, to ensure vital gas exchange; also suitable for carbon dioxide removal alone at lower bloodflows (low-flow ECMO)
VA ECMO (venoarterial extracorporeal membrane oxygenation; also VA ECLS: venoarterial extracorporeal life support)	A pump-driven procedure in which venous blood, usually from the inferior vena cava, is pumped into the arterial circulation following oxygenation, especially to support systemic perfusion	Refractory cardiogenic shock, right heart failure, in-hospital resuscitation

Figure 1: Examples of miniaturized modern extracorporeal membrane oxygenation units
a) the Cardiohelp system b) Deltastream DP3/Hilite 7000LT

(negative fluid balance, prone positioning if possible). For some patients, ECMO is used as a rescue procedure, when gas exchange cannot be ensured using conventional methods and progressive hemodynamic instability develops. For other patients, essential gas exchange can only be achieved using aggressive, non-protective ventilation (inspiratory pressure >32 cm H₂O, FiO₂ >0.9 , tidal volume >8 mL/kg predicted body weight). Early use of extracorporeal support should be discussed in these cases, because there is a risk of further critical deterioration caused by an increase in ventilation-induced lung injury (11–13).

Contraindications

The main contraindications for this procedure are an untreatable underlying illness and cardiogenic shock. For the latter, venoarterial extracorporeal life support (ECLS) may be considered. When indicating ECMO, it is important to remember that it is not a causal treatment but one that temporarily stabilizes gas transfer, allows protective ventilation, and helps gain time that may be needed in order for the lungs to heal. Terminal lung disease with no prospect of lung transplantation in the near future is therefore another contraindication. A history of long-term ventilation and concomitant illnesses such as cirrhosis of the liver or chronic terminal kidney failure considerably worsen the prognosis and must also be taken into account when indicating treatment. If there are serious arguments against anticoagulation therapy, longer-term extracorporeal pulmonary support either is impossible or must be considered carefully (*Box 2*).

Pumpless extracorporeal support

Indications and contraindications

The indication for iLA is severe respiratory acidosis (pH <7.20) that poses a risk to vital functions and cannot be managed using conventional therapy. The

Figure 2: Interventional lung assist for carbon dioxide removal

system's oxygen transfer capacity is physically limited and achieves no more than 10% to 15% of total oxygen consumption (14). Severe hypoxemia is therefore a contraindication for iLA; ECMO is indicated instead. Other contraindications are limited cardiac pump function and advanced peripheral atherosclerotic disease.

The efficacy of modern pulmonary support devices

Venovenous extracorporeal membrane oxygenation

Modern pump-driven pulmonary support methods provide highly effective extracorporeal oxygen and carbon

BOX 2

Indication for VV ECMO treatment (University Medical Center Regensburg)

1. Potentially treatable underlying illness or possibility of lung transplantation in the near future

2. Rescue indication:

Life-threatening hypoxemic pulmonary failure ($\text{PaO}_2/\text{FiO}_2 < 65$ mm Hg, $\text{PIP} > 35$ cm H_2O , arterial pH < 7.25) and progressive hemodynamic instability

3. Non-rescue indication (consider ECMO early on in treatment):

Vital gas exchange only achievable using aggressive, nonprotective ventilation ($\text{PIP} > 32$ cm H_2O , $\text{FiO}_2 > 0.9$, $\text{TV} > 6$ mL/kg BW_{pred}) despite optimization of all conventional treatment options, no improvement within 12 to 24 hours

4: Rule out contraindications:

- Cardiogenic shock
- Terminal pulmonary disease with no prospect of transplantation in the near future
- Cirrhosis of the liver > Child class A (relative)
- Terminal kidney failure (relative)
- Age > 75 years (relative)

VV ECMO: venovenous extracorporeal membrane oxygenation; PaO_2 : partial pressure of oxygen; FiO_2 : fraction of inspired oxygen; PIP: positive inspiratory pressure; TV: tidal volume; BW_{pred} : predicted body weight in kg

dioxide transfer. Evaluation of our own patient data shows that beginning ECMO achieves an immediate improvement in oxygenation and resolution of hypercapnia (Figure 3). The intensiveness of ventilation can then be reduced: Tidal volume was reduced from 7.0 (6.0 to 8.4) mL/kg predicted body weight before ECMO to 4.1 (3.4 to 5.4) mL/kg on day 1 ($p < 0.001$) (Figure 3). Peak inspiratory pressure and inspired oxygen concentration were substantially decreased within one day. In most cases, swift hemodynamic stabilization occurred at the same time.

A total of 266 adult patients (age 48 ± 17 years) with severe pulmonary failure were treated with VV ECMO at University Medical Center Regensburg between January 2006 and July 2012. Of these, 186 (70%) were successfully weaned off ECMO; 80 (30%) died during ECMO treatment, mostly as a result of multiorgan failure. Of the patients who were successfully weaned off ECMO, 28 (11%) died before being discharged from the hospital. 158 patients (59%) survived and were discharged. The average time on ECMO was 12 ± 10 days.

Mortality rates over time show a trend towards improved survival; the survival rate was 73% in 2011 (Figure 4). This is the result of increasing experience with extracorporeal pulmonary support methods. The surviving patients were younger, had lower sequential organ failure assessment (SOFA) scores, suffered from kidney failure less frequently, and had lower respiratory minute volumes before ECMO (15).

Several case series describing the outcomes of modern ECMO methods in adult patients have been published in recent years. Many centers worldwide introduced ECMO systems for cases of fulminant pulmonary failure during the H1N1 influenza A pandemic. Reported survival rates of 75% in the first publi-

cation from Australia (16) were confirmed by other centers (survival rates 68% to 71%) (17–19).

In comparison, survival rates of 52% to 63% were achieved with first-generation ECMO systems according to some publications of larger case series (more than 30 patients) (20–25). The registry of the Extracorporeal Life Support Organization (ELSO) from 1986 to 2006 (1473 patients, mean age 34 years) gives a survival rate of 50% (26).

The CESAR trial, which was published in 2009, is to date the only randomized controlled trial in adults using newer ECMO systems (27). 180 patients with severe pulmonary failure were allocated to the ECMO group or a control group that received conventional ventilation. Patients were recruited who had lung injury scores above 3.0 or uncompensated hypercapnia with pH below 7.2. The primary endpoint, death or severe disability at six months, was observed in 37% of patients in the ECMO group and 53% of patients in the control group ($p = 0.03$). This was the first time an advantage had been shown for ECMO treatment in adult patients. However, there were shortcomings in the design of the study: One of the criticisms made is that 22 of the 90 patients allocated to the ECMO group did not receive ECMO because they either improved swiftly or died. In addition, the patients in the control group were treated as judged best in the individual participating hospitals, and as a result only 70% of them received protective ventilation. All patients in the ECMO group were transported to Leicester, UK for treatment, leading to a bias resulting from referral to a specialized center.

Interventional lung assist

The pumpless iLA procedure is currently used in intensive medicine for patients who present severe respiratory

acidosis. The largest number of cases reported on to date, 90 patients with ARDS, was published by Bein et al. in 2006 (28). iLA removed a mean of 50% of the CO₂ produced, causing pH to return to normal levels swiftly. In parallel to this, a slight improvement in PaO₂ was observed. The rate of survival to discharge from hospital was 41.2%. Smaller case series and case studies describe the use of iLA for brain injury (29), for status asthmaticus (30), and as bridging to lung transplantation (31). An initial prospective randomized multicenter trial (XtraVent) was recently completed. It compared conventional protective ventilation to extracorporeal carbon dioxide removal in combination with very small tidal volumes. Its results in terms of duration of ventilation and mortality rate must be awaited before iLA can be evaluated more precisely.

Adverse effects and risks

Despite size reductions and optimized design, extracorporeal pulmonary support systems remain invasive procedures with possibly life-threatening complications and are used for critically ill patients. The literature contains few reliable data on complication rates; an overview taken from the ELSO registry is reproduced in Brodie et al. (11).

Specifically, it is important to distinguish between cannula-related vascular complications and risks of ECMO that are either technical or have systemic effects on patients (Box 3).

Cannula insertion can result in vascular injuries that may cause severe bleeding, and arterial cannulation (iLA) can cause peripheral ischemia. The introduction of smaller cannulas has significantly reduced the incidence of leg ischemia, which is now around 8% (32). The frequency of venous thrombosis in the vessel into which the cannula is inserted is not known precisely; however, the risk is not inconsiderable and in our experience is more than 10%.

Technical problems observed in the past, such as plasma leakage or tube rupture, have now almost completely disappeared. For some patients, particularly those receiving longer-term treatment, the oxygenator needs to be changed as a result of progressive thrombosis. In our own patient population, this was the case in 27% of patients. If increasing hemolysis is observed, the system must be examined for complications such as partial thrombosis of the oxygenator or a thrombus in the pump head.

As a result of modern systems' better biocompatibility, the intensiveness of systemic anticoagulation treatment can be reduced. As a result, fatal bleeding complications are very rare. Nevertheless, patients receiving ECMO are often more prone to bleeding, so individually-tailored anticoagulation must be very closely monitored. A drop in platelet count is also often seen during ECMO treatment. The extent to which heparin-induced thrombocytopenia is more frequent, and whether systemic activation of coagulation and inflammation cascades is induced, are questions currently under discussion.

FIGURE 3

Oxygenation (PaO₂/FiO₂), PaCO₂, and tidal volumes (in relation to predicted body weight) before (gray), during (olive green), and after (blue) ECMO (*¹p < 0.05, *²p < 0.001, always in relation to previous value); PaO₂: partial pressure of oxygen; FiO₂: fraction of inspired oxygen; PaCO₂: partial pressure of carbon dioxide; ECMO: extracorporeal membrane oxygenation

Discussion

The rediscovery of ECMO resulted in particular from fundamental technical developments in membrane oxygenators and pump systems and the consequent improvement in biotolerability. Thanks to this, modern systems' efficacy and complication rates are significantly superior to those of first-generation ECMO systems. Compact design with low foreign surface areas, gas exchange fibers that cannot be penetrated by plasma, and flow-optimized blood pumps with good long-term function substantially reduce blood cell

Survival, death after weaning off ECMO, and death during ECMO treatment

University Medical Center Regensburg 2006 to July 2012 (n = 266); ECMO, extracorporeal membrane oxygenation

FIGURE 4

BOX 3

Risks and complications

- **Vascular:**
 - Vascular injury, bleeding
 - Venous: thrombosis, embolism
 - Arterial: ischemia, compartment syndrome, embolism
- **Mechanical:**
 - Coagulation in system, oxygenator thrombosis
 - Hemolysis
 - Disconnection, cannula dislocation
 - Infection
- **Systemic:**
 - Platelet depletion
 - Bleeding
 - Possible activation of coagulation and inflammation cascades
 - Possible increased risk of heparin-induced thrombocytopenia

trauma, allowing long-term use of ECMO for several weeks.

Modern oxygenators have excellent gas transfer, so patients' oxygenation can be ensured quickly. At the same time, carbon dioxide is removed effectively, making it possible to reduce the respiratory minute ventilation of patients' native lungs immediately. With a bloodflow of 2.8 L/min ECMO accounts for more than 50% of oxygen consumption and approximately two-thirds of carbon dioxide removal (33). If necessary, ECMO can supply a higher proportion of required oxygen, more than 80%, using a higher bloodflow, although this may be accompanied by more complications.

Extracorporeal pulmonary support techniques are some of the treatment options available for severe pulmonary failure in specialized centers. While on the one hand the procedure's efficacy in gas transfer is well documented, on the other hand it is important never to forget that it can cause potentially serious complications. Technical or clinical problems may be acutely life-threatening, so experience and interdisciplinary collaboration are essential. In Germany, more than 50 hospitals have formed an ARDS network in order to optimize ARDS treatment together and facilitate access to information on up-to-date availability of ECMO treatment places online (34) (in German).

Scientific literature on the use of modern pulmonary support systems for adults does not yet provide sufficient information to assess their value with certainty. Only one randomized trial has been published; there are no Cochrane reviews on the subject. Although the CESAR trial showed better survival with no severe disability in the ECMO group (27), its results have been questioned, as is discussed above. Another randomized trial (the EOLIA trial) was recently begun in France. In 2011 a British matched-pair analysis was published showing that ECMO halved the mortality rate for severe H1N1 influenza A infection (23.7% versus 52.5%) (19). In this case, too, patients were transported to specialized centers. This shows that for critically unstable patients an ECMO system should be implanted in the referring hospital by an experienced mobile team (>100 patients in our own patient population), if this is necessary to ensure patients are fit for transport.

Extracorporeal techniques are increasingly used in intensive care medicine to treat hypercapnic pulmonary failure. iLA is currently the most popular procedure in Germany. Low-flow VV ECMO systems with smaller cannulas and gas exchange modules are becoming established as an alternative. For selected patient groups with high mortality risk following intubation, extracorporeal procedures are used on an individual basis to avoid invasive ventilation (35–37). There is no evidence as yet that extracorporeal carbon dioxide removal improves survival rates or reduces the duration of ventilation.

Summary

VV ECMO can swiftly ensure gas transfer in patients suffering from severe pulmonary failure with life-threatening hypoxia. Protective ventilation with small tidal volumes, reduced ventilation pressure and adapted inspired oxygen concentration made possible by the use of ECMO is of great importance. This can limit ventilation-induced lung injury and have a positive effect on patient survival.

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Conflict of interest statement

PD Dr. Müller has received reimbursement of travel expenses and lecture fees from Maquet Cardiopulmonary, Rastatt, Germany.

Prof. Bein has received fees for consultancy on the Advisory Board and lecture fees from Novalung, Heilbronn, Germany.

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KEY MESSAGES

- Modern extracorporeal membrane oxygenation (ECMO) systems can ensure vital gas exchange swiftly and effectively in cases of severe pulmonary failure.
- Extracorporeal gas exchange techniques allow for protective ventilation, reducing the risk of ventilation-induced lung injury.
- As a result of fundamental technical improvements made in recent years, intensive anticoagulation is no longer necessary. Bleeding complications are therefore far rarer than they were with first-generation ECMO systems.
- Critically ill, unstable patients can be transported to a specialized center using portable, miniaturized ECMO systems.
- Because extracorporeal pulmonary support is a bridging procedure rather than a causal treatment, the underlying illness must be potentially treatable, and indication of the procedure must be targeted.

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