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EDITORIAL

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Exciting new ECMO technology awaits compelling scientific evidence for widespread use in adults with respiratory failure

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MacLaren et al. [1] discuss the exciting potential offered by extracorporeal support, including extracorporeal membrane oxygenation (ECMO). Many uses of ECMO have recently been discussed. These include a technically advanced means of transporting patients with severe respiratory failure [2] and a treatment for acute respiratory distress syndrome (ARDS) following novel H1N1 influenza infection [3]. Extracorporeal support remains an exciting domain of investigation, development and clinical application. Innovations, such as IVOX, abound among developers and practitioners of extracorporeal support [4]. Dr. Bartlett has been a consistent leader and innovator in this field.

MacLaren et al. [1] make impressive arguments, and their illustrations are clear and compelling. Their Fig. 6 is a striking example of the advances/changes in clinical care. The new extracorporeal circuits they nicely describe are clearly much simpler, easier to use, and appear more safe than those used in the past. Importantly, they appear safer than those used in the two past clinical trials that adhered to accepted experimental standards [5, 6]. This raises legitimate questions about the current value of the results of those two older clinical trials. These legitimate questions should be answered with new clinical trials that adhere to accepted experimental standards. The authors clearly indicate that major advances in both extracorporeal circuitry and clinical care have taken place, since the technology of these two older clinical trials was introduced. I believe it is time for these advances to be matched by similar advances in extracorporeal clinical trials. Rigorous clinical trials with modern technology will likely provide results that answer crucial questions about "in whom, how, and when" extracorporeal support should be applied.

The experimental design of two-group randomized controlled clinical trials has not changed substantially since the older trials were completed [5, 6]. In the absence of credible new clinical trial results, we have no better information to guide decisions about widespread use of extracorporeal support than that provided by the two past clinical trials that adhered to accepted experimental standards [5, 6]. Some clinicians hold strong beliefs in the efficacy of ECMO support for patients with severe ARDS. Dr. MacLaren [7] articulately expressed these beliefs in a recent letter. Such strong beliefs are not new. In 1984 and 1985 Gattinoni et al. [8] reported a dramatic increase in survival with use of low frequency positive pressure ventilation with extracorporeal carbon dioxide removal (LFPPV-ECCO2R) (using veno-venous support). My colleagues and I conducted a randomized controlled clinical trial with the expectation that LFPPV-ECCO2R was likely to be a significant treatment advance (from our published discussion: "...we concluded from published reports that there was about a 0.5 prior probability that LFPPV-ECCO2R was a superior therapy for ARDS" [6]). However, we did not detect a survival advantage of LFPPV_ECCO2R. Gattinoni et al., in a letter to the editor, replied that the LFPPV_ECCO2R technique was not yet optimized and the technique not yet ready for a clinical trial (see letters to the editor in [6]). We asked, in a reply letter, how it could be known that the LFPPV-ECCO2R technique was beneficial (the conclusion of the strong believers) when the technique was not yet adequately evolved to perform a clinical trial? I cite these published exchanges only to indicate that current uncertainty about the role of extracorporeal support is an old one. It will only be resolved by new and properly conducted randomized controlled clinical trials. Such a clinical trial has not yet been done. The recent clinical trial in the UK did not adhere to accepted experimental standards [9, 10]. The uncertainty might also be resolved by spectacular and compelling observational results, e.g., like those observed with the initial treatment of pneumococcal pneumonia with penicillin in the 1940s. However, this is unlikely. We will not likely encounter observational results more compelling that those of Gattinoni et al. [8] in 1984 and 1985 when they reported a 77% survival of patients meeting the 1970s ECMO criteria. Survival of such patients had to that point been consistently 10% in Boston and Salt Lake City centers, two of the original NIH ECMO clinical trial centers [5].

In response to previous publications [11, 12], Dr. MacLaren [7] raised three issues: ECMO must be correctly applied; ECMO must be applied to the appropriate patient; and finally that we need to define when, how, and in whom we can optimally use the technique. I believe MacLaren raised crucial issues that can only be defined with detailed methods for selection of patients, conduct of extracorporeal support, and management of important clinical interventions. Short of this, clinicians cannot know when, how, and in whom to optimally apply ECMO. For example, in the current publication, MacLaren et al. [1] indicate that patient complications continue to occur, uncertainties remain, and that "there are no effective means of confidently predicting recovery or death".

The alternative to credible clinical trial results is to accept at face value the claim of experts that their experience "managing adult patients on ECMO for refractory respiratory failure," or similar expressions, demonstrates, documents, and validates the efficacy of ECMO [7]. Unfortunately, such beliefs, no matter how strongly and sincerely held, are frequently proven to be invalid when formally tested using scientifically rigorous methods [13]. Experience can easily mislead due to the selective emphasis or recollection that characterizes human cognition. Past treatments that were enthusiastically supported and widely disseminated but subsequently shown to be of no value—or even harmful—include avoiding beta blockers in heart failure treatment; insulin for schizophrenia; vitamin K for myocardial infarction; hormone replacement therapy to prevent cardiovascular disease; flecainide for ventricular tachycardia; and immobilizaton of scaphoid bone fractures [14]. More recently we have been exposed to a change in the management of sepsis. Sepsis therapy with drotrecogin alfa (Xigris®) was recently interrupted by withdrawal of the drug by the manufacturer [15].

Noah et al. [3] resumed the ECMO dialog in a recent publication describing retrieval of H1N1 respiratory failure patients for ECMO in the UK. This publication elicited an editorial that echoed arguments raised by others, calling for more compelling data to support the efficacy of ECMO before ECMO is widely propagated for management of severe ARDS [16]. Roger Bone, 25 years ago, discussed some of the issues that made observational studies of extracorporeal support difficult to interpret [17]. These issues are still a problem and they are central to the controversy surrounding extracorporeal support today. I believe extracorporeal support is an exciting and promising technique. I think its clinical applications require a more firm scientific foundation than currently exists. Maclaren et al. have compellingly described the new ECMO technology. I hope this is followed by new and compelling evidence that the new technology has enabled us to reap the promised benefits of extracorporeal support.

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REVIEW

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Contemporary extracorporeal membrane oxygenation for adult respiratory failure: life support in the new era

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Abstract *Background:* Extracorporeal membrane oxygenation (ECMO) has been used in clinical medicine for 40 years but remains controversial therapy, particularly in adult patients with severe respiratory failure. Over the last few years, there have been considerable advances in extracorporeal technology and clinical practice, ushering in a new era of ECMO. Many institutions adopted ECMO as rescue therapy during the recent H1N1 influenza pandemic, reigniting the controversy. *Discussion:* Hollow-fibre oxygenators and Mendler-designed centrifugal pumps have replaced the old silicon oxygenators and roller pumps. The advantages of these novel systems and the principles that underlie their function are outlined. Advances in cannula technology allow greater ease of patient positioning, in some cases facilitating extubation and ambulation on ECMO. Improvements in ECMO circuitry have led to a reduction in heparin and blood product requirements, with consequently fewer complications. Greater understanding of severe acute respiratory distress syndrome has allowed clinicians to successfully support adults on ECMO for months at a time, as a bridge to either recovery or transplantation. *Conclusions:* ECMO is safer, cheaper, and simpler than in previous eras. Both circuit and patient can be cared for by a single trained nurse. Additional prospective studies of ECMO for adult respiratory failure are underway. Contemporary ECMO in awake, potentially ambulant patients to provide short-term support for those with acute, reversible respiratory failure and as a bridge to transplantation in those with irreversible respiratory failure is now ready for widespread evaluation.

Keywords Acute respiratory distress syndrome · Mechanical ventilation · Lung transplantation · H1N1 influenza

Introduction

Extracorporeal membrane oxygenation (ECMO) is the use of a substantially modified cardiopulmonary bypass circuit to provide short-term respiratory (and potentially circulatory) support to critically ill patients. ECMO is established as standard therapy in children with acute respiratory or circulatory failure refractory to conventional management strategies [1–3], but substantial controversy lingers over its use in adult respiratory failure [4–7]. After the first successful case was reported in 1972, a multicentre randomized study of ECMO sponsored by the National Institutes of Health was conducted in the 1970s, showing 90% mortality in both ECMO and conventional care groups [8]. Over the next two decades, ECMO for adult respiratory failure underwent further evaluation. Survival rates of approximately 50% were routinely reported in uncontrolled series [9], but the ECMO system was complicated, cumbersome, and potentially hazardous unless constantly attended to by trained specialists. Bleeding was a common, life-threatening complication. These factors meant that ECMO was rarely used outside a small number of dedicated centres.

There have been relatively recent, substantial technological improvements in ECMO circuitry, principal among them new pump and oxygenator designs. The new ECMO system is simpler, safer, and can be managed by one bedside nurse trained and experienced in circuit management. Major bleeding is much less frequent than in the past. Some of these new-generation devices have been recently approved by the Food and Drug Administration and are now used in parts of North America. Elsewhere in the world, e.g. Europe and Australasia, these devices have been in use for over a decade. These technological advances have been coupled to refinements in the clinical care of ECMO patients. It is now possible to support patients for weeks or even months at a time without any additional complications over and above those of critical illness. Furthermore, the role of ECMO in many of the conditions formerly regarded as contraindications, such as sepsis [10, 11], trauma [12, 13], malignancy [14, 15] and pulmonary haemorrhage [16], has been reappraised in the light of more recent research. All of these changes have ushered in a new era of extracorporeal life support.

The influenza A(H1N1) pandemic in 2009 created a resurgence of interest in ECMO and led many clinicians to incorporate it into their practice [17–19]. This review is written for intensivists experienced at managing critical illness but not necessarily expert in ECMO. Reviews on other indications for ECMO such as adult circulatory failure can be found elsewhere [20, 21], as can critiques of both ECMO research and its role in modern intensive care units (ICU) [6, 7]. This article focusses on contemporary circuit components and overviews the management of adult patients receiving ECMO for respiratory failure.

Circuitry

In venoarterial (VA) ECMO, venous blood is oxygenated and returned to the aorta (usually via the femoral artery) (Fig. 1). This is an effective technique to provide emergency mechanical circulatory support for patients with cardiogenic shock refractory to conventional medical therapies and is considerably cheaper than employing ventricular assist devices (VAD) [21–26]. ECMO has been successfully used as a bridge to myocardial

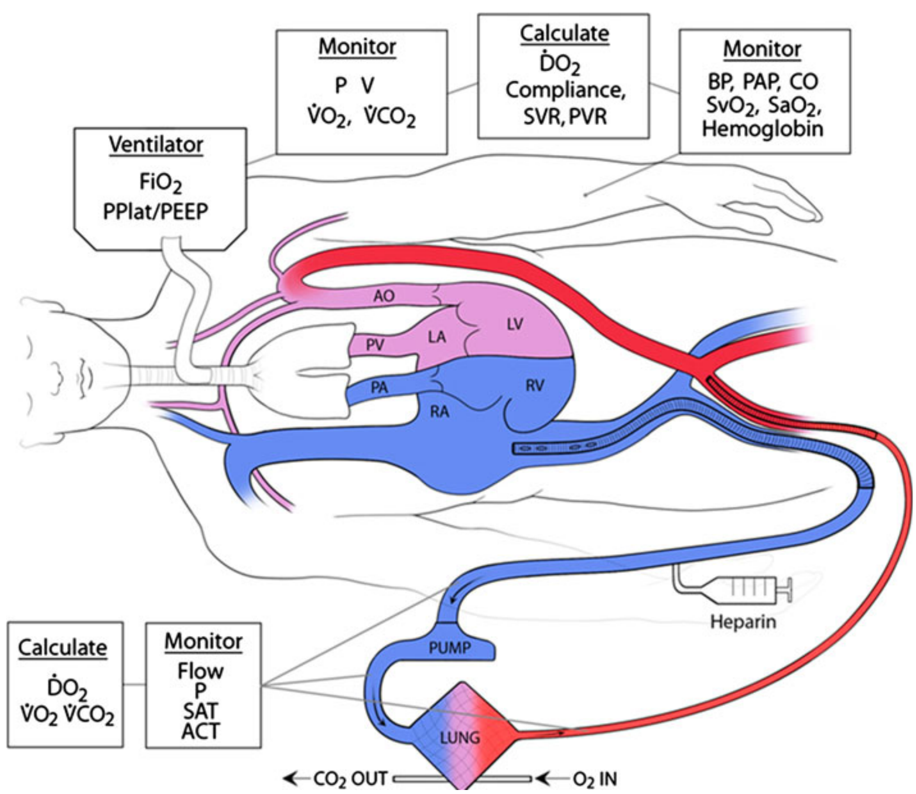

Fig. 1 Venoarterial extracorporeal membrane oxygenation with femoral–femoral access. The pre-pump heparin is optional. *FiO_2* fractional inspired oxygen, *Pplat* plateau airway pressure, *PEEP* positive end-expiratory pressure, *P* pressure, *V* volume, *VO_2* oxygen uptake, *VCO_2* carbon dioxide uptake, *DO_2* oxygen delivery, *SVR* systemic vascular resistance, *PVR* pulmonary vascular resistance, *BP* blood pressure, *PAP* pulmonary artery pressure, *CO* cardiac output, *SvO_2* mixed venous oxygen saturation, *SaO_2* arterial oxygen saturation, *Sat* saturation, *ACT* activated clotting time, *CO_2* carbon dioxide, *O_2* oxygen

recovery, VAD implantation or cardiac transplantation in patients with various aetiologies of severe cardiac failure, e.g. acute myocardial infarction, end-stage dilated cardiomyopathy, viral myocarditis, complications of cardiac surgery or cardiac arrest [21, 22, 26–31].

In venovenous (VV) ECMO, blood is removed from one or both vena cavae via the jugular or femoral veins, pumped through an oxygenator and returned directly into the right atrium, thereby preserving pulmonary blood flow, pulsatile systemic flow, and oxygenation of blood in the left ventricle and aortic root. Except in cases of associated overt cardiac failure or refractory shock, patients with acute respiratory failure should be supported with VV-ECMO (Fig. 2), since VA-ECMO is associated with greater risk of complications, including systemic thromboembolism, limb ischaemia, maldistribution of oxygen and increased left ventricular wall tension. Acute right heart failure secondary to acute respiratory distress syndrome (ARDS) is not an indication per se for VA-ECMO in most cases, since oxygenation of pulmonary artery blood will decrease hypoxia-induced vasoconstriction and pulmonary artery pressure in the hours following VV-ECMO initiation. VV-ECMO also facilitates a substantial reduction in intrathoracic pressure via a reduction in mechanical ventilation, which may also improve right ventricular function.

ECMO circuits have two principal components: the oxygenator and the pump. Additional circuit components include cannulas, tubing and the heat exchanger. Each will be considered in turn.

Modern oxygenators comprise multiple hollow fibres <0.5 mm in diameter coated with polymethylpentene, allowing diffusion of gas but not liquid. As blood runs through the oxygenator, fresh gas flow (‘sweep’) is piped through the inside of the hollow fibres (Fig. 3). Carbon dioxide clearance is more effective than oxygenation because the greater solubility of CO_2 facilitates more rapid diffusion (Fick’s law) and because of the relatively linear shape of the CO_2 dissociation curve, in contrast to the sigmoid shape of the O_2 dissociation curve. Although a minimum rate of fresh gas flow is necessary to oxygenate the blood, increasing the gas flow rate further will not lead to substantial improvement in oxygenation, but merely reduce $PaCO_2$. In order to increase PaO_2, blood flow through the circuit must be increased. The patient’s $PaCO_2$ is principally determined by the rate of fresh gas flow, whereas the main determinant of PaO_2 is blood flow rate through the circuit. Effective CO_2 clearance can be achieved with as little as 10–15 ml/kg/min of blood flow, while effective oxygenation usually requires at least 50–60 ml/kg/min, although this value can be as high as 80–100 ml/kg/min and varies with both the amount of recirculation and total cardiac output.

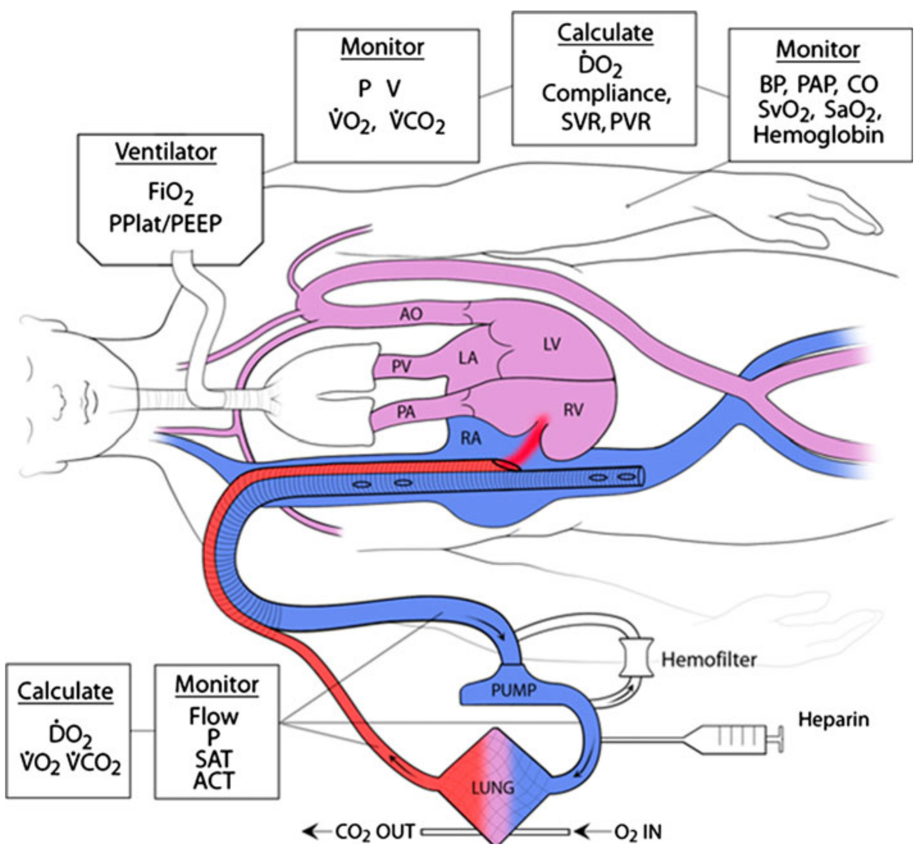

Fig. 2 Venovenous extracorporeal membrane oxygenation with bicaval drainage. The heparin location and in-line haemofilter are optional. *FiO₂* fractional inspired oxygen, *Pplat* plateau airway pressure, *PEEP* positive end-expiratory pressure, *P* pressure, *V* volume, *VO₂* oxygen uptake, *VCO₂* carbon dioxide uptake, *DO₂* oxygen delivery, *SVR* systemic vascular resistance, *PVR* pulmonary vascular resistance, *BP* blood pressure, *PAP* pulmonary artery pressure, *CO* cardiac output, *SvO₂* mixed venous oxygen saturation, *SaO₂* arterial oxygen saturation, *Sat* saturation, *ACT* activated clotting time, *CO₂* carbon dioxide, *O₂* oxygen

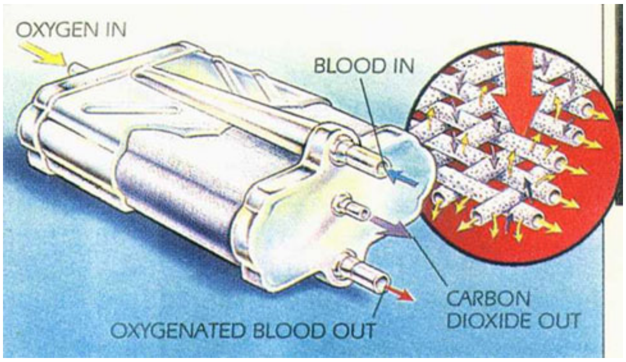

Fig. 3 Diagram of an oxygenator. See text for details

There are a number of advantages to modern hollow-fibre oxygenators over the old silicon membrane oxygenators. They cause less platelet and plasma protein consumption and have more effective gas exchange [32, 33]. Additionally, they offer lower resistance to blood flow and have small priming volumes of <300 ml. The devices are coated with thrombo-resistant coatings. These oxygenators are currently manufactured by a number of companies including Dideco, Maquet, Medos, Novalung and Sorin. Other systems that can effectively function for months without systemic anticoagulation are in development [34]. The low blood flow resistance of these newer oxygenators facilitates the use of centrifugal pumps.

Blood flow through an ECMO circuit is driven by a centrifugal pump, in which a rotating impeller spins on a small bearing or is magnetically suspended (e.g. Rotaflow, Maquet, Hirrlingen, Germany; Revolution, Sorin, Milano, Italy; Centrimag, Levitronix LLC, Waltham, MA). The impeller spins at 2,000–5,000 revolutions per minute (rpm), creating a constrained vortex that suctions blood into the pumphead and propels it out toward the oxygenator (Fig. 4). These pumps are suitable for prolonged perfusion because there is a hole in the centre of the rotor (Mendler design) [35]. This eliminates the stagnation, thrombosis and heat production of earlier centrifugal pumps. These pumps are preload and afterload dependent; i.e. blood flow is affected by both the volume of blood coming into pump as well as the post-pump pressure. Some of the newer pumps also offer the option of providing pulsatile flow (e.g. Deltastream, Medos, Stolberg, Germany), but these are primarily designed to enhance circulatory support on VA-ECMO. Pulsatile flow pumps generate greater surplus haemodynamic energy and thus theoretically better perfusion [36]. However, it is uncertain whether this translates into clinical benefit. It may be helpful in patients on VA-ECMO with combined respiratory and circulatory failure [37], but there is as yet little reason to believe that this mode would be beneficial in VV-ECMO.

Mendler-designed centrifugal pumps have a number of advantages over the older, roller pumps. They have smaller priming volumes of <40 ml, do not require gravity drainage, circuit bridges or venous reservoirs, operate effectively for weeks at a time with very little incidence of technical failure and are much simpler to care for and maintain. The suction created by centrifugal pumps can cause cavitation and haemolysis when the venous line is occluded, so careful attention must be paid to blood volume, venous line patency and maintaining a safe rotation velocity (i.e. rpm) of the pump.

Traditionally, two cannulas of 21–28 Fr size were used for adult VV-ECMO. A third cannula could be inserted as an additional drain to enhance flow if required. Recently a dual-lumen catheter designed by Wang and Zwischenberger is being manufactured by the Avalon company (Avalon Elite, Avalon Laboratories, Rancho Dominguez, CA) [38]. This cannula is inserted via the right internal jugular vein and positioned such that the tip rests in the inferior vena cava [39]. Blood is removed from ports in both vena cavae and returned directly into the right atrium (Fig. 5). The cannulas are currently manufactured in sizes ranging from 16 to 31 Fr. In addition to providing adequate flow and minimizing recirculation, these cannulas have the obvious advantage of facilitating ECMO using a

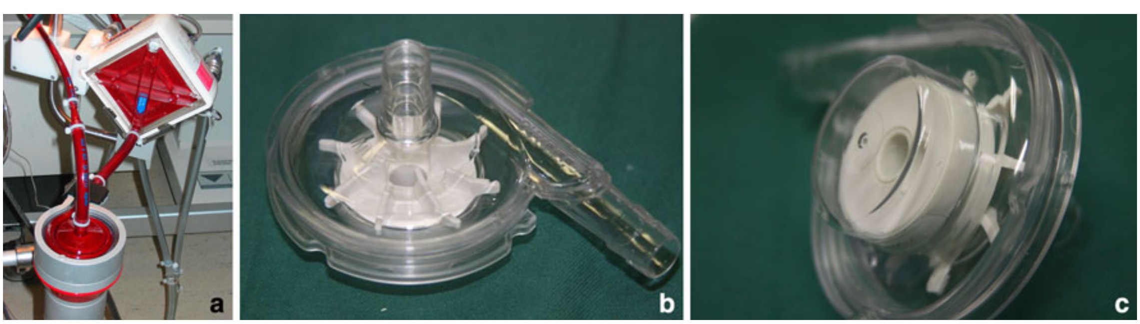

Fig. 4 **a** Centrifugal pump in active use. Blood is suctioned into the top of the pump and propelled toward the oxygenator (Courtesy of Derek Best, with permission). **b** Different centrifugal pump after use, showing Mendler-designed impeller. **c** The base of the same pump, demonstrating the absence of an impeller pin or mounting. This pump is suspended in a magnetic field when in use (Courtesy of Si Guim Goh, with permission)

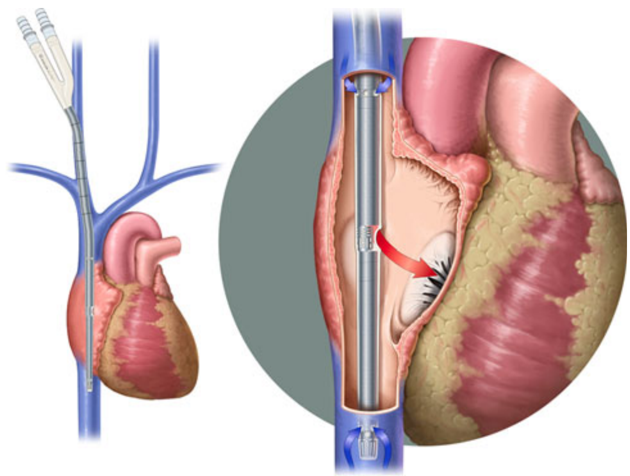

Fig. 5 Diagram of correctly positioned Avalon catheter. See text for details (with permission from Avalon Laboratories)

single access vein, reducing the chances of vascular trauma and permitting easier patient positioning. It is essential to insert them using either image intensification or echocardiography to position them correctly and minimize the risk of atrial or vessel perforation.

The tubing of an ECMO circuit is made of polyvinylchloride, polyurethane or silicone rubber and can be coated with a biocompatible lining to reduce the systemic inflammatory response and risk of thrombosis. Such coatings include poly(2-methoxyethyl acrylate), albumin, heparin or phosphorylcholine. Both coated and uncoated circuits adsorb many drugs, including sedatives and antibiotics [40–42]; for example, fentanyl and morphine availability can be reduced by as much as 65%, depending on the surface coating [43].

Body temperature is maintained by a circulating water bath and compact heat exchanger in the circuit. This is highly effective such that the patient's core temperature usually equals the temperature of the water bath. Consequently, ECMO patients may not become febrile.

Another extracorporeal approach to respiratory failure is selective extracorporeal CO_2 removal (ECCOR) [44, 45]. In ECCOR, CO_2 is removed, the ventilator is turned down to a low rate at low pressure and the patient is dependent on native lung function for oxygenation. The Novalung Company (Hechingen, Germany) produces a membrane lung which can be perfused using a femoral arteriovenous shunt. This provides enough blood flow for CO_2 removal, but not oxygenation [46, 47]. Limb ischaemia has been a problem in some series [48]. Low-flow VV CO_2 removal devices (e.g. Hemodec, Salerno, Italy; iLA activve, Novalung, Hechingen, Germany; Hemolung, ALung, Pittsburgh, PA, USA) may be available in the near future, alleviating the serious limitations of the Novalung device such as limb ischaemia or the risk of systemic embolization.

Patient management

The latest generation of low-resistance oxygenators and pumps has led to a safer, simpler approach to management, sometimes referred to as ECMO II. Until recently, an ECMO specialist with lengthy training in both perfusion and ICU nursing care was required to safely employ ECMO, in addition to a regular ICU nurse. Now ICU nurses with additional training in ECMO technology and management can care for both circuit and patient. The ECMO specialist team provides the education and consultation management as well as overseeing the programme, preparing the circuits and managing cannulation, weaning and decannulation. ECMO II is less expensive than original ECMO. The cost per case is around US $10,000, comparable to many other therapies in modern medicine [49].

The exact indications for VV-ECMO have not been the subject of comprehensive prospective research, although it is recommended that it be considered in situations when patient mortality is predicted to be >80% despite optimal use of less invasive therapy [20, 50]. In principle, it should be used when less invasive therapies fail but before lasting injury occurs, e.g. iatrogenic barotrauma or sustained cerebral hypoxia. Some specific indications for ECMO in adult respiratory failure are listed in Table 1. However, the rate of physiological decline may be more important than the absolute amount of ventilatory support, and it is important that ECMO referrals are made in sufficient time to allow patient assessment, cannulation and, in some instances, transfer to another institution. Ideally, this means discussing individual cases with an ECMO service at the same time as other advanced therapies are being considered or instituted, as well as tailoring the criteria for ECMO referrals to local institutional resources, such as availability of a cannulation team or distance to the nearest referral centre. If transport to another institution is required, a specialized ECMO retrieval team should travel to the referring institution, cannulate and transport the patient back. Outcomes in such instances can be excellent [53].

Contraindications to ECMO are few but include advanced age, severe disability and incurable malignancy. Relative contraindications include uncontrolled coagulopathy, intracranial bleeding and high-pressure positive-pressure ventilation for more than 1 week prior to ECMO [50, 54]. Complications from VV-ECMO include bleeding, venous thromboembolism and infection.

Cannulation is accomplished percutaneously using the Seldinger technique, then unfractionated heparin is started by infusion. A bolus dose (50–75 U/kg) is optional. As newer devices are less thrombogenic, heparin can usually be titrated to maintain activated partial thromboplastin times (APTT) at 1.2–1.8 times normal (measured daily). Alternatively, activated clotting times (ACT) 1.5 times normal (measured hourly) can be targeted. Anticoagulation is one of

Table 1 Indications for ECMO in adult respiratory failure

Title	Year of publication	Indications for ECMO	References
Zapol et al.	1979	PaO_2/FiO_2 ratio <50 for >2 h, or PaO_2/FiO_2 ratio <83 with FiO_2 ≥0.6 and ≥5 cmH_2O PEEP for >12 h, and intrapulmonary shunt >30% of cardiac output when measured at FiO_2 1.0 and ≥5 cmH_2O PEEP	[8]
CESAR	2009	Murray score ≥3.0, or uncompensated hypercapnia with pH <7.20	[4]
EOLIA	Ongoing	Severe ARDS defined according to usual criteria, and meeting one of the three following criteria of severity: (a) PaO_2/FiO_2 ratio <50 with FiO_2 ≥0.8 for >3 h, despite optimization of mechanical ventilation and despite possible recourse to usual adjunctive therapies (NO, recruitment maneuvers, prone position, HFO ventilation, almitrine infusion) (b) PaO_2/FiO_2 ratio <80 with FiO_2 ≥0.8 for >6 h, despite optimization of mechanical ventilation and despite possible recourse to usual adjunctive therapies (NO, recruitment maneuvers, prone position, HFO ventilation, almitrine infusion) (c) pH <7.25 for >6 h (RR increased to 35/min) resulting from MV settings adjusted to keep Pplat ≤32 cmH_2O (first, Vt reduction by steps of 1 ml/kg to 4 ml/kg then PEEP reduction to a minimum of 8 cmH_2O)	[51]
ELSO guidelines	2009	PaO_2/FiO_2 ratio <80 with FiO_2 ≥0.9 and Murray score 3–4, or CO_2 retention with $PaCO_2$ >80 mmHg or inability to achieve adequate ventilation with Pplat ≤30 cmH_2O, or severe air leak syndromes	[52]

CESAR conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure study, *EOLIA* extracorporeal membrane oxygenation for severe acute respiratory distress syndrome trial, *ELSO* extracorporeal life support organization, *PEEP* positive end-expiratory pressure, *ARDS* acute respiratory distress syndrome, *NO* nitric oxide, *HFO* high-frequency oscillation, *RR* respiratory rate, *MV* minute ventilation, *Vt* tidal volume

the most important issues in patients on ECMO and requires frequent review. Detailed guidelines for management of anticoagulation and bleeding are published by the Extracorporeal Life Support Organization (ELSO) and are freely available [50].

Guidelines from ELSO recommend maintaining normal haematocrit in patients on ECMO to enhance tissue oxygen delivery and maximize extracorporeal circuit efficiency [50]. However, some institutions have more restrictive transfusion thresholds and will accept lower haemoglobin levels (e.g. 8–9 g/dL) in patients with SaO_2 >85%, in the absence of bleeding or coronary artery disease. In bleeding patients, coagulation disturbances should be treated with blood product replacement and the platelet count maintained within the low-normal range (e.g. >50–100 × 10^9/L). In patients who have no bleeding diatheses (e.g. hypofibrinogenaemia), the platelet count can be safely monitored unless <20 × 10^9/L. Thromboelastography can be useful in complex cases such as disseminated intravascular coagulation. Plasma free haemoglobin should be measured daily to detect haemolysis. The cause of haemolysis is usually cavitation created by excessive suction from the centrifugal pump. Thrombosis in the circuit can occur and is detected as small clots at connectors and low-flow zones. This can lead to both small emboli (which are not a serious problem during VV access) or haemolysis. If plasma free haemoglobin is consistently >0.5–1.0 g/L, the anticoagulation strategy, cannula position and pump speed should be reviewed and consideration be given to electively changing the circuit.

Circuit flow is maintained at 50–100 ml/kg/min and titrated to achieve SaO_2 >80%. Fresh gas flow is initiated at the same rate as circuit blood flow and then adjusted to maintain $PaCO_2$ in the normal range. Positive-pressure ventilation is reduced to minimize the risk of iatrogenic injury (e.g. inspiratory pressure <25 cmH_2O, PEEP 10–20 cmH_2O, rate 4–6 breaths per minute; or CPAP at 10–20 cmH_2O). In those in whom prolonged respiratory support is anticipated, consideration should be given to early tracheostomy while on ECMO to facilitate patient comfort and ease of care [55, 56].

The ECMO circuit should be monitored several times daily by the medical and nursing team caring for the patient and at least once every 24 h by a perfusionist or other ECMO specialist. Circuit and cannula surveillance is intended to verify the correct functioning of the device and identify evolving complications early, including fibrin deposits or clots on the ECMO membrane; clots in the cannulas or pump; bleeding; signs of inflammation or infection at the cannula insertion sites; unexpected drops in ECMO outflow; or the appearance of clinical or biochemical signs of intravascular haemolysis. If any of these complications occur, a combined multidisciplinary consultation should be conducted to establish the best therapeutic approach [50].

The management of ECMO patients has been transformed in recent times as a direct result of the improvement in circuitry; for example, one of the advantages of the novel, single-lumen ECMO cannulas is the ease of patient positioning. Patients can sit up or out of bed. In more experienced centres, patients awaiting lung transplantation can be extubated and encouraged to ambulate on ECMO (Fig. 6) [57, 58]. This may help prevent deconditioning and improve long-term outcome [59]. The realization that patients can be bridged to transplant awake and ambulatory for months is beginning to influence care of acute lung failure patients. The ECMO centre at Karolinska Institute, Stockholm, has emphasized for years that awake, spontaneous breathing leads to better results in acute disease in children and adults, although this strategy has not been subjected to controlled investigation. In addition to the benefits of spontaneous breathing, awake management may avoid many potential complications of intensive care such as excessive sedation, dependent oedema and pressure sores.

In patients not intended for extubation, light sedation can be administered to ensure comfort and prevent inadvertent dislodging of the ECMO cannulas. As noted above, sedative dosage may be higher than expected because of reduced drug availability and an effective increase in volume of distribution. Muscle relaxation is rarely necessary except in occasional patients with $SaO_2 < 80\%$ despite ECMO, in whom neuromuscular blockers may be helpful early in the course of disease [60].

Patients should be fluid restricted and every attempt made to restore patient dry weight [61, 62]. Diuretic infusions are often used, although extracorporeal ultrafiltration can easily be performed by connecting continuous renal replacement therapy (CRRT) to the ECMO circuit. Post-oxygenator blood is drained into the CRRT circuit and returned pre-oxygenator. The oxygenator functions as an effective bubble trap so the risk of air or clot embolization is minimized.

Fig. 6 Patient on venovenous ECMO awaiting lung transplantation (Courtesy of Charles Hoopes, MD, with permission)

Weaning off VV-ECMO is simple. A weaning trial is conducted when pulmonary function has recovered sufficiently to allow adequate ventilation on modest amounts of positive-pressure ventilation, assessed on the basis of improvements in clinical assessment, lung compliance and radiological appearance. The ventilator is set to moderate levels of mechanical support (e.g. tidal volume 6 ml/kg, plateau pressure <30 cmH_2O, PEEP 5–12 cmH_2O, FiO_2 <0.6) then the fresh gas flow to the oxygenator is switched off while blood flow continues. If the patient remains stable and adequately ventilated after 1–4 h of observation, the ECMO cannulas can be removed. In most instances, this can be done without surgical repair of the vessel but simply by pulling out the cannula and applying pressure for 30 min. As the cannula is removed, the patient should perform a Valsalva maneuver to reduce the chance of air embolism.

Some clinicians may consider withdrawal of support in patients who have minimal improvement in lung function after an arbitrary period of extracorporeal support (e.g. 2–3 weeks) [54, 63]. However, there are no effective means of confidently predicting recovery or death. Alveolar capillary dysplasia in babies is incompatible with life but no comparable disease state exists in adults. Lung recovery may take weeks or months in some conditions, including ARDS, and successful recovery has been reported after >50–100 days of ECMO support [55, 64].

Clinicians providing ECMO should co-ordinate their services at a regional level and collaborate in multicentre research [65]. This regional co-ordination should include at least one centre with high-volume activity which heads a regional or national network of ECMO-capable institutions, with mobile ECMO teams capable of both respiratory and cardiac support. The Extracorporeal Life Support Organization, formed in 1989, provides additional resources to clinicians and maintains a large international registry which now has data on over 45,000 patients supported with ECMO (http://www.elso.med.umich.edu) [9]. All centres providing ECMO to patients should be encouraged to join ELSO and participate in its efforts to answer important research questions, including how to refine patient selection, optimize the timing of ECMO initiation and quantify long-term changes in outcome as ongoing improvements in technology are made. ELSO conducts regular courses in ECMO technique, holds an annual meeting, and publishes both guidelines for patient management and the 'Red Book', the standard reference text of ECMO.

Results of ECMO in the recent H1N1 pandemic

In Australia and New Zealand between June and August 2009, 15 hospitals provided ECMO for refractory influenza A(H1N1)-associated respiratory failure, with existing

ECMO centres helping the others to start [17]. Many of the 201 patients treated in these centres recovered with conventional care. However, 68 of these patients continued to deteriorate despite advanced mechanical ventilatory support (as indicated by median PaO_2/FiO_2 ratio 56, median PEEP 18 cmH_2O and median acute lung injury score 3.8) and were placed on ECMO. Over 80% failed other attempts at rescue therapy including prone positioning, inhaled nitric oxide, prostacyclin and high-frequency oscillatory ventilation. Mortality was 21%. Bleeding was the most frequent complication, and death was attributed to intracranial haemorrhage in six patients [17].

Intensivists elsewhere read about this experience and prepared for the pandemic in the northern hemisphere winter. Established ECMO centres expanded their capabilities, new centres were initiated and regional triage plans were developed [19, 66]; for example, Italy nationally coordinated 14 ECMO centres to manage the pandemic. The Scottish government commissioned an expert working group which subsequently recommended the establishment of a national adult respiratory ECMO centre [66]. ELSO created an H1N1 registry, which ultimately collated data on 256 ECMO cases with a case fatality rate of 34% [67]. Similar results were seen with the French Reseau Européen de Recherche en Ventilation Artificielle (REVA) registry [68, 69].

Firm conclusions regarding the efficacy of contemporary ECMO cannot be drawn from these nonrandomized cohort studies [6, 7]. Nonetheless, the majority of patients survived in most published series and the pandemic caused an international resurgence in ECMO use [9]. A major factor in the rapid mobilization of ECMO during this pandemic was the new oxygenators, pumps and access cannulas. Centrifugal pumps and polymethylpentene-coated oxygenators were universally employed in the largest series [17].

Conclusions

ECMO is more complex and less commonly used than CRRT, but some parallels may be drawn between them. In the 1980s and early 1990s, CRRT was perceived as too specialized for use in many ICUs. However, it has been widely adopted and is now routinely available in most high-income countries [70]. Access is provided by one dual-lumen catheter, and care of both patient and circuit is provided by a critical care nurse without the need for specialized input from a nephrology service. The evolution of extracorporeal circuitry has created a comparable situation with ECMO. Bedside care can be provided by a single trained nurse, and many intensivists perform ECMO cannulation without the aid of specialty surgical services.

A prospective study in adult respiratory failure is currently underway in France, the ECMO for Severe Acute Respiratory Distress Syndrome (EOLIA) trial [51], which may avoid the methodological issues criticized by some in the earlier CESAR study [4]. This study is designed to test the efficacy of early VV-ECMO in ARDS with tight control of mechanical ventilation in the control group, initiation of ECMO prior to transportation to ECMO centres and use of ECMO in every patient randomly assigned to receive it.

Despite the technological advances in extracorporeal respiratory support, chronic artificial respiratory support lags behind comparable developments in circulatory support, where progressive miniaturization and substantial amounts of national funding have created a new world with VADs either as a bridge to transplantation or as possible destination therapy. Nonetheless, the improvements in ECMO technology have allowed some centres to use ambulatory ECMO or other extracorporeal devices to liberate patients from mechanical ventilation and successfully bridge them to lung transplantation [58, 71–74]. Whether it will ever be feasible to safely use fully implantable, miniaturized respiratory devices as destination therapy remains an open question at present [75]. However, the use of contemporary ECMO in awake, potentially ambulant patients to provide both short-term support for those with acute, reversible respiratory failure and a bridge to transplantation in those with irreversible respiratory failure is now ready for widespread evaluation.

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