Artificial lungs: a new inspiration

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An estimated 16 million Americans are afflicted with some degree of chronic obstructive pulmonary disease (COPD), accounting for 100,000 deaths per year. The only current treatment for chronic irreversible pulmonary failure is lung transplantation. Since the widespread success of single and double lung transplantation in the early 1990s, demand for donor lungs has steadily outgrown the supply. Unlike dialysis, which functions as a bridge to renal transplantation, or a ventricular assist device (VAD), which serves as a bridge to cardiac transplantation, no suitable bridge to lung transplantation exists. The current methods for supporting patients with lung disease, however, are not adequate or efficient enough to act as a bridge to transplantation. Although occasionally successful as a bridge to transplant, ECMO requires multiple transfusions and is complex, labor-intensive, time-limited, costly, non-ambulatory and prone to infection. Intravacaval devices, such as the intravascular oxygenator (IVOX) and the intravenous membrane oxygenator (IMO), are surface area limited and currently provide inadequate gas exchange to function as a bridge-to-recovery or transplant. A successful artificial lung could realize a substantial clinical impact as a bridge to lung transplantation, a support device immediately post-lung transplant, and as rescue and/or supplement to mechanical ventilation during the treatment of severe respiratory failure. Perfusion (2002) 17, 253–268.

Introduction

ECMO is the term used to describe prolonged extracorporeal cardiopulmonary bypass (CPB) achieved by extrathoracic vascular cannulation. A modified heart–lung machine is used, most often consisting of a distendable venous blood drainage reservoir, a servo-regulated roller pump, a membrane lung to exchange oxygen and carbon dioxide, and a countercurrent heat exchanger to maintain normal body temperature (Figure 1). The patient must be continuously anticoagulated with heparin to prevent thrombosis within the circuit and potential formation of thromboemboli. Although most ECMO centers are experienced in the treatment of neonatal respiratory failure, institutional expertise and need dictate the availability of pediatric ECMO for respiratory or cardiac support, and adult ECMO for respiratory failure. Since 1989, participating ECMO centers have voluntarily registered all patients with the Neonatal, Pediatric, and Adult ECMO Registry of the Extracorporeal Life Support Organization (ELSO). Information concerning patient demographics, pre-ECMO clinical features, indications, medical and technical complications, and outcomes on ECMO have been collected and updated continuously as new patients receive ECMO support.1

Extracorporeal circulation for respiratory failure was first attempted in newborns in the 1960s.2 Bartlett et al.3 began clinical trials in 1972 and reported the first successful use of ECMO in newborn respiratory failure in 1976. During the initial experience in neonates, ECMO had an overall survival rate of 75–95%.4–6 These results helped to establish the therapeutic effectiveness of ECMO in infants having met criteria predicting greater than 80% mortality. In 1986, Bartlett7 published his first 100 cases of ECMO for neonatal respiratory failure with an overall survival rate of 72%. The collaborative UK ECMO trial8 concluded that ECMO support reduces the risk of death without a concomitant rise in severe disability. ECMO has become the standard treatment for unresponsive severe respiratory failure in neonates, based on successful phase I studies,3 two prospective randomized studies,9,10 and worldwide application in over 20,638 patients with an overall 77% survival rate.1

Pediatric patients with severe parenchymal lung damage and impaired gas exchange may also benefit from extracorporeal support. On average, pediatric patients with unresponsive severe respiratory failure spend about 2 weeks on ECMO, with some survivors receiving ECMO for periods of up to 4–6 weeks before lung recovery.11 Concurrent with the adult collaborative study, ECMO was evaluated in children. Bartlett5 has reported an ECMO survival rate of 30% in children and infants beyond the neonatal period.
with acute respiratory failure (ARF) whose predicted survival rate with conventional therapy was thought to be <10%. Green et al.\textsuperscript{12} reported the results from the Pediatric Critical Care Study Group multicenter analysis of ECMO for pediatric respiratory failure. ECMO was associated with a significant reduction in mortality versus conventional or high-frequency ventilation (74% survival with ECMO versus 53% survival in controls). As of July 2001, ECMO had been used in over 2145 children with respiratory failure, achieving an overall survival rate of 63%.\textsuperscript{1} ECMO has also been used for children needing cardiac support, with a survival rate of 54%.\textsuperscript{1} Patients who would have been excluded from ECMO in the past because of such conditions as immunosuppression following treatment for malignancy, burns, meningococcemia and other diseases are now reported in the literature as ECMO survivors.\textsuperscript{13–16}

**Adult application**

In 1972, Hill et al.\textsuperscript{17} reported the first successful clinical use of ECMO in adults. A number of small patient series soon followed from the United States and Europe.\textsuperscript{18,19} Initially, the overall survival rates were relatively low, but the successes were individually dramatic. A national study of adult ECMO sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the NIH was initiated in 1975 and completed in 1979.\textsuperscript{20} Although 300 patients were to be entered, the study was discontinued after 90 patients, with an approximately 90% mortality in both the control and treatment groups. Following these results, interest in adult ECMO all but ceased. However, in 1986, Gattinoni et al.\textsuperscript{21} reported a 49% survival rate in patients with severe respiratory failure treated with a form of ECMO and several investigators regained enthusiasm. Indications for ECMO, therefore, include acute reversible respiratory or cardiac failure unresponsive to optimal ventilator and pharmacologic management with a predicted mortality rate of \( \geq 80\% \), but from which recovery can be expected within a reasonable period (several days to 3 weeks) of extracorporeal support.

Despite advances in ventilatory support, antibiotic therapy, and critical care, mortality from adult respiratory distress syndrome (ARDS) remains about 50%.\textsuperscript{22–28} Current techniques of ventilatory management are often associated with relatively high inspiratory airway pressures (barotrauma), overdistending normal lung regions (volutrauma), and toxic levels of inspired oxygen, leading to exacerbated lung injury (barotrauma) manifested by progressive deterioration in total lung compliance, functional residual capacity, and arterial blood gases.\textsuperscript{26} Limiting airway pressures to avoid baro/volutrauma of mechanical ventilation is rapidly gaining acceptance. Multiple studies, most notably the recent ARDS Network Trial (NIH/NHLBI NETT), have shown an improvement in survival when utilizing a low tidal volume (LTV=6 ml/kg) ventilator management strategy to reduce lung stretch.\textsuperscript{26,29} The primary goal of ECMO focuses on \( \text{CO}_2 \) removal and \( \text{O}_2 \) exchange with avoidance of high tidal volumes and airway pressures.\textsuperscript{30}

Reversible respiratory failure in adults is difficult to define; therefore, adult criteria for ECMO are controversial.\textsuperscript{20,31,32} Many use a P/F ratio <100, but particular care must be taken to avoid therapy in patients with established pulmonary fibrosis. Bartlett advocates a \( \text{Qp/Qs} > 30 \) as an indication for ECMO. ECMO may also be effective for severe reactive airway disease, since bronchospasm is largely reversible, with most deaths due to complications of mechanical ventilation.\textsuperscript{33,34} Causes of acute respiratory failure supported with ECMO include primary and secondary ARDS of multiple etiologies, and reactive airway disease.\textsuperscript{35} Another disease once considered a contraindication to ECMO was sepsis accompanying respiratory failure. Rich et al.,\textsuperscript{36} however, demonstrated that sepsis or bacteremia was not predictive of survival.

For most adult patients with unresponsive severe respiratory failure, venovenous support is the method of choice, including both extracorporeal \( \text{CO}_2 \) removal (ECCO\( \text{R} \)) and venovenous ECMO (VV ECMO) (Table 1). ECCO\( \text{R} \) emphasizes carbon dioxide removal through low-flow (approximately 1 l) bypass, utilizing low-frequency positive-pressure ventilation (LFPPV) via the natural lungs.\textsuperscript{31,32} With this method, oxygen uptake and \( \text{CO}_2 \) removal are dissociated: oxygenation is accomplished primarily through the lungs, whereas \( \text{CO}_2 \) is cleared through the extracorporeal circuit. Even the most severely injured lungs are capable of oxygen transfer if they...
are not required to provide any ventilatory function. This is the rationale behind ECCO$_2$R and ‘apneic oxygenation’ as developed by Kolobow et al.\textsuperscript{37} andGattinoni et al.\textsuperscript{21} The lungs are inflated to moderate pressures (15 to 20 cm H$_2$O) to maintain functional residual capacity and oxygen concentration is reduced, while CO$_2$ is removed by low-flow partial VV bypass. LFPPV–ECCO$_2$R is performed at an extracorporeal blood flow of 20–30% cardiac output. Vascular access is achieved via combinations of jugular–femoral, femoral–femoral, or saphenous–saphenous veins.

VV ECMO emphasizes oxygenation in addition to CO$_2$ removal, achieved through the use of higher flow rates (~5 l) and a parallel configuration of two oxygenators to increase surface area. Patients with more advanced respiratory failure and high transpulmonary shunt fractions will require the additional oxygen transfer supplied by VV ECMO. In a recent retrospective review of 94 patients, Bartlett’s group concluded that percutaneous cannulation can be utilized for VV ECMO in adults.\textsuperscript{38}  

Venoarterial (VA) extracorporeal support is reserved for patients with cardiovascular instability or failure to maintain an adequate cardiac output during the course of respiratory failure. Disadvantages of VA ECMO include the need for major arterial access, reduced pulmonary blood flow, arterial discharge of emboli, further impairment of left ventricular function by volume overload, and circulatory dependence on an extracorporeal circuit. Advantages include lack of dependence on cardiac function to maintain oxygenation. If cardiac function improves, the patient may be converted from venoarterial to venovenous bypass.

### Venovenous ECMO

VV ECMO has the advantage of maintaining normal pulmonary blood flow and avoiding arterial cannulation with its risk of systemic microemboli. Total support of gas exchange with VV perfusion, returning the perfusate blood into the venous circulation

### Table 1 Comparison of venoarterial and venovenous ECMO

<table>
<thead>
<tr>
<th></th>
<th>Venoarterial ECMO</th>
<th>Venovenous ECMO</th>
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<tbody>
<tr>
<td>Cannulation sites</td>
<td>Internal jugular vein, right atrium, or femoral vein plus right common carotid, axillary, or femoral artery or aorta (directly)</td>
<td>Internal jugular vein alone (double-lumen or single-lumen tidal flow)</td>
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<tr>
<td></td>
<td></td>
<td>Jugular–femoral</td>
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<td></td>
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<td>Femoro-femoral</td>
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<td></td>
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<td>Sapheno-saphenous</td>
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<td></td>
<td></td>
<td>Right atrium (directly)</td>
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<tr>
<td></td>
<td></td>
<td>Gas exchange only</td>
</tr>
<tr>
<td>Organ support</td>
<td>Gas exchange and cardiac output</td>
<td>Cardiac output only</td>
</tr>
<tr>
<td>Systemic perfusion</td>
<td>Circuit flow and cardiac output</td>
<td>Normal pulsatility</td>
</tr>
<tr>
<td>Pulse contour</td>
<td>Reduced pulsatility</td>
<td>Accurate guide to volume status</td>
</tr>
<tr>
<td>CVP</td>
<td>Unreliable</td>
<td>Reliable</td>
</tr>
<tr>
<td>PA pressure</td>
<td>Unreliable</td>
<td>None</td>
</tr>
<tr>
<td>Effect of R→L shunt</td>
<td>Mixed venous into perfusate blood</td>
<td>No effect on flow</td>
</tr>
<tr>
<td>Effect of L→R shunt (PDA)</td>
<td>Pulmonary hyper-perfusion may shunt</td>
<td>Require increased flow usual PDA physiology</td>
</tr>
<tr>
<td>Blood flow for full gas exchange</td>
<td>80–100 ml/kg/h</td>
<td>100–120 ml/kg/h</td>
</tr>
<tr>
<td>Circuit SvO$_2$</td>
<td>Reliable</td>
<td>Unreliable</td>
</tr>
<tr>
<td>Circuit recirculation</td>
<td>None</td>
<td>15–30%</td>
</tr>
<tr>
<td>Arterial PpO$_2$</td>
<td>60–150 Torr</td>
<td>45–80 Torr</td>
</tr>
<tr>
<td>Arterial oxygen saturation</td>
<td>≥95%</td>
<td>80–95%</td>
</tr>
<tr>
<td>Indicators of O$_2$ insufficiency</td>
<td>Mixed venous saturation or pO$_2$</td>
<td>Cerebral venous saturation</td>
</tr>
<tr>
<td></td>
<td>Calculated oxygen consumption</td>
<td>Da-VO$_2$ across the membrane</td>
</tr>
<tr>
<td>Carbon dioxide removal</td>
<td>Sweep gas flow and membrane lung size dependent</td>
<td>Patient PaO$_2$</td>
</tr>
<tr>
<td>Oxygenerator</td>
<td>0.4 or 0.6</td>
<td>0.6 or 0.8</td>
</tr>
<tr>
<td>Ventilator settings</td>
<td>Minimal</td>
<td>Minimal–moderate (dependent on patient size)</td>
</tr>
<tr>
<td>Decrease initial vent settings</td>
<td>Rapidly</td>
<td>Slowly</td>
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through the femoral vein or a modified jugular venous drainage catheter, also has the advantage of avoiding carotid artery ligation.\textsuperscript{39} Bartlett’s group developed a polyurethane double-lumen catheter for single-site cannulation of the internal jugular vein.\textsuperscript{40,41} A tidal flow VV system with a single-lumen catheter\textsuperscript{39} has been developed to aid venous gas exchange. Since the 14F VV double-lumen (DL) catheter became commercially available in 1989, over 2248 neonates have been treated, with an 87% overall survival.\textsuperscript{1} A multicenter retrospective comparison\textsuperscript{41} of VA access to VVDL for newborns with respiratory failure undergoing ECMO was undertaken and in a matched review with no advantage to VV ECMO.

The current practice of waiting until the natural lungs become severely dysfunctional and then having to support cardiopulmonary function almost completely with VA ECMO may give way to the concept of early lung assistance. Single-site cannulation has already become the method of choice in neonates for ECMO. A single-cannula tidal flow VV ECMO system has been developed, which even allows percutaneous access.\textsuperscript{42,43}

Gattinoni and coworkers,\textsuperscript{21} using his modified ECMO technique (LFPPV with extracorporeal carbon dioxide removal [LFPPV–ECCO\textsubscript{2}R]), achieved 49% survival in ARDS. The improvement in survival is also, in part, attributed to better patient selection, VV perfusion, better regulation of anticoagulation, and ventilator management directed toward ‘lung rest’. Bartlett’s experience, initially reported by Anderson \textit{et al.}\textsuperscript{44} in 1993, demonstrated 47% survival in adults with severe respiratory failure. In a retrospective review of 100 adult patients treated by Bartlett’s group, Kolla \textit{et al.}\textsuperscript{33} reported a 54% overall survival. Pre-ECMO variables found to be significant independent predictors of outcome included number of days of mechanical ventilation, P/F ratio, and patient age. Patients with respiratory failure alone had the best prognosis, with a mortality rate of 40%. Rich \textit{et al.}\textsuperscript{34} also retrospectively evaluated Bartlett’s ‘standardized management protocol’ for acute respiratory failure utilizing ‘lung protective’ mechanical ventilation and ECMO in 141 patients. Forty-one patients showed improvement with the initial protocol of ventilator management (83% survival), while 100 patients required ECMO support due to persistent respiratory failure (54% survival). Overall, lung recovery occurred in 67% of the patients with a 62% survival. As of July 2001, 678 adults treated with ECMO have been entered in the ELSO Registry, with an overall survival rate of 56%.\textsuperscript{1}

### Techniques and management

The techniques for ECMO are well described.\textsuperscript{57} All age groups are cannulated with VA access if cardiac support is required for acute hemodynamic compromise (cardiac arrest) or for transport on ECMO. VV access is used in most cases without hemodynamic compromise and is the method of choice for neonates or patients with primary respiratory failure. For VV access in neonates, we prefer the right internal jugular vein for drainage and reinfusion using a double-lumen catheter. For children and adults, we prefer the right internal jugular vein for drainage and the right femoral vein for reinfusion. Rich \textit{et al.},\textsuperscript{58} however, recently compared atrial–femoral and femoral–atrial flow in adult VV ECMO. Femoral–atrial bypass provided higher maximal extracorporeal flow, higher pulmonary arterial mixed venous oxygen saturation, and required less flow to maintain equivalent mixed venous oxygen saturation than atrial–femoral bypass.

In 1981, the first cases of infants with congenital diaphragmatic hernia (CDH) treated with ECMO were reported.\textsuperscript{59} CDH has the lowest survival rate of all categories of neonatal respiratory failure for which ECMO is utilized.\textsuperscript{60–71} The impact on mortality, however, has been institution specific with survival rates ranging from 43% to 87%. Aggregate survival data in the ELSO registry\textsuperscript{1} is 62%.

Although the role of ECMO as a treatment for CDH has been widely accepted, the timing of the surgical repair of the defect in relation to ECMO therapy remains controversial. Operative repair of the defect has been proposed while on ECMO,\textsuperscript{72–76} but survival rates have been variable and as high as 80%\textsuperscript{72,75,77} Delaying repair until the infant is off ECMO is another option in which favorable results have been reported.\textsuperscript{78,79} Unfortunately, the overall mortality rate...
of CDH has remained approximately 50%, even with the increased utilization of ECMO support.\textsuperscript{65,80–83} Evolution of mechanical ventilation techniques, extracorporeal support, use of surfactant, nitric oxide, and different timing of surgical intervention have all contributed to variable survival rates from different institutions.

Complications during ECMO are the rule, not the exception\textsuperscript{84,85} as the management of the patient on ECMO, including patient-related complications, spans the entire field of critical care. We will limit this section to complications unique to ECMO. Cannulae are inserted with great care to avoid vascular damage during insertion, since loss of control of the internal jugular vein can result in massive mediastinal bleeding, and dissection of the carotid artery intima can progress to a lethal aortic dissection. Minor surgical procedures may be required during ECMO; however, they should not be taken lightly due to the risk of bleeding with systemic anticoagulation. Although bleeding may be a significant problem, liberal use of cautery, application of fibrin glue, and a low threshold for re-exploration permit nearly any procedure to be performed.

Occasionally, major surgical procedures are necessary while patients are on ECMO. Evacuation of hemothorax, open lung biopsy, and congenital diaphragmatic hernia repair have been performed during ECMO. Michaels \textit{et al.}\textsuperscript{15} reported on 30 adult trauma patients, of which 19 (63.3%) underwent operative procedures while on ECMO. Procedures on ECMO for ongoing critical care include open reduction and internal fixation, repair of iatrogenic laceration, diagnostic peritoneal lavage, tracheostomy, abscess drainage, and gastrointestinal reconstruction.\textsuperscript{15,86}

ECMO has been reported to allow unrushed, precise reconstruction during complex tracheal surgery and providing brief postoperative support.\textsuperscript{87–91} ECMO also facilitates surgical exposure of the defect and provides postoperative respiratory support to avoid trauma to the fragile tracheal suture lines. Additionally, liver transplantation, lung transplantation, heart transplantation, and evacuation of intracranial hematoma in patients on ECMO have also been performed.

Catastrophic hemodynamic deterioration is unusual while a patient is on VA ECMO. The factors that deserve immediate evaluation when this occurs include venous catheter displacement, inadequate systemic volume status, and the possibility of ECMO circuit failure.

Sepsis is both an indication for and a complication of ECMO. However, according to the ELSO Registry, only 5% of all patients requiring ECMO demonstrate positive blood cultures. This is a remarkably low incidence given the duration of cannulation, the large surface area involved, and frequency of access to the circuit.

Occasionally, a patient’s respiratory status does not improve despite 2–3 weeks of ECMO support. An echocardiogram is repeated to ensure an absence of patent ductus arteriosus (PDA) with predominant left-to-right shunt as well as a congenital heart defect such as total anomalous venous return.

### Cardiac support

ECMO applied to patients with severe cardiac failure was first reported in the 1950s, but it was not commonly used until the 1980s.\textsuperscript{92} Since then, the use of ECMO has been extended to both infants and children after cardiac surgery.\textsuperscript{93–95} There have been over 3000 patients supported with ECMO for myocardial dysfunction, with overall survival of about 39%. ECMO provides greater flexibility in dealing with some forms of complex congenital heart disease in which pulmonary hypertension and hypoxia contribute significantly to the pathophysiology.\textsuperscript{96} The effect of ECMO on the heart includes a decrease in preload, a slight increase in afterload, and a concomitant elevation in left ventricular wall stress. Advantages include support of both right and left ventricles, improvement of systemic oxygenation, and ease of placement. VA cannulation provides the optimal cardiac support when ventricular dysfunction predominates the clinical picture. However, studies have also shown that VV bypass, primarily by improving venous oxygenation, may improve myocardial oxygenation and decrease pulmonary vascular resistance in selected patients, thus providing adequate cardiac recovery and support.\textsuperscript{97}

The majority of patients have received ECMO postoperatively after repair of congenital heart defects.\textsuperscript{84,96,98} In these patients, factors associated with poor survival despite ECMO support include: residual cardiac defect, single ventricle physiology, initiation of ECMO in the operating room, and failure of return of adequate cardiac function to wean from ECMO within 3–7 days. Two changes in the philosophy of cardiac ECMO have occurred with time and experience. Over 100 children have received ECMO either as a bridge to heart transplant or following cardiac transplant. Key points in management of bridge to transplant patients include deciding as early as possible to list patients for transplant and avoiding complications that remove patients from transplant consideration. The second change regarding cardiac ECMO involves patients with sudden cardiac arrest. There are several reports of good survival in patients requiring active cardiopulmonary resuscitation (CPR).
at the time of ECMO cannulation. Overall survival ranged from 41% to 53%. Rapid-deployment ECMO has also been shown to be useful in support of patients who suffer cardiopulmonary arrest.

VA ECMO for cardiac failure may be performed by extrathoracic cannulation (carotid artery and jugular vein, or femoral artery and vein), or more commonly transthoracic cannulation through the median sternotomy incision (the aorta and the right atrium). Carotid-jugular cannulation may best be used in patients who are weaned from CPB in the operating room and develop myocardial dysfunction with cardiogenic shock after operation. Advantages of this approach are a separate incision site remote from the median sternotomy wound and a lower incidence of bleeding from the mediastinal wound. Both of these factors may contribute to a decreased risk of mediastinal infection.

In patients with a cavopulmonary connection (Glenn or Fontan circulation), direct access from the jugular vein to the right atrium is not feasible; therefore, a transthoracic approach is required in these cases. Femoral venoarterial cannulation can be used in certain older children, with placement of intravascular catheters into the inferior vena cava or right atrium through the femoral vein and into the common femoral or iliac artery for arterial return. The venous return with this type of cannulation may be restrictive unless a centrifugal type pump, which provides active venous drainage, is used. The advantage of this peripheral technique includes the minimization of myocardial energy expenditure, is vital to potential myocardial recovery. When left atrial pressures remain elevated despite optimal flow, it is critical to vent the left atrium to the venous drainage system either by direct left atrial cannulation in the OR or transatrial septal cannulation in the cardiac catheterization laboratory.

The most common indication for ECMO in the lung transplant patient is in the immediate postoperative period following primary graft failure (6–20% of recipients) or severe ischemia reperfusion injury. A final role for ECMO in the lung transplant patient is as a supportive measure during a period of late graft dysfunction (lung failure >7 days after transplant).

**Clinical results**

The results of ECMO for pediatric cardiac support reported early survival at 40–44%, with somewhat better survival (43–54%) when the lesion was tetralogy of Fallot, truncus arteriosus, atrioventricular canal, or total anomalous pulmonary venous return. Lower survival rates (14%) have been reported for single ventricle, hypoplastic left heart syndrome, and other malformations requiring a Fontan procedure. Differences in survival rates suggest that the improved survival is associated with a complete biventricular operative repair, while an operation with shunt-dependent pulmonary blood flow is associated with lower overall recovery rates.

ECMO has evolved into several formats, including ECMO (VA and VV), traditional CPB, ECCO₂R, arteriovenous CO₂ removal, and the developing artificial lungs. A comparison of the different extracorporeal treatment modalities is shown in Table 2. The future of extracorporeal support depends on the development of techniques and devices to make the technique less invasive, safer, and simpler in management. The use of the Seldinger wire-guided technique with sequential dilators and placement of large catheters directly or with peel-away sheaths has decreased the incidence of bleeding complications from cannulation sites. Cannulation can be accomplished quickly and easily under a variety of circumstances, including on-ECMO transport and emergency access.

Heparin-bonded oxygenators, pump chambers, and extracorporeal circuits may allow ECMO for days without bleeding, complications, or formation of clots. Heparin-coated circuits allow reduced thrombogenicity and reductions in required systemic heparinization for prolonged support. The future of ECMO also includes laminar flow oxygenators; safe, simple automatic pumps; nonturbulent surfaces to eliminate bleeding complications; advances in respiratory and cardiac care; and new approaches to clinical trials. New applications of ECMO will include emergency room and catheterization laboratory resuscitation in cardiac failure, resuscitation in trauma and hemorrhagic shock, and use as an adjunct to perfusion and temperature control.

**CO₂ removal**

Investigations into ECCO₂R began in the late 1970s. Kolobow and Gattinoni introduced ECCO₂R using a modified form of ECMO with venovenous (VV) perfusion in both animals and humans, where the focus was CO₂ extraction to facilitate a reduction in ventilatory support. Oxygenation was maintained by simple diffusion across the patient’s alveoli, called ‘apneic oxygenation.’ Studies in animals and in humans all showed effectiveness of ECCO₂R in reducing ventilatory requirements.
The alternative use of a simple arteriovenous (AV) shunt for extracorporeal gas exchange significantly reduces the complexity of conventional ECMO yet allows sufficient gas exchange to achieve near total removal of CO₂ produced. It substantially reduces circuit length and eliminates the venous reservoir, emergency bridge, and roller pump, thereby reducing blood element shear stress, minimizing foreign surface interaction, and removing those items that account for the majority of complications with conventional ECMO. Use of fewer circuit components, less intensive monitoring, avoidance of the extracorporeal pump, and elimination of blood transfusion may substantially improve safety compared with conventional ECMO.

Our group has developed a technique of simplified extracorporeal arteriovenous CO₂ removal (AVCO₂R) with a low-resistance membrane gas exchanger to provide lung rest in the setting of severe respiratory failure (Figure 2). Recent developments in computational fluid dynamic design have led to a new generation of low-resistance oxygenators used in this model. Fiber crossing, directional flow, and support structures can be iterated repeatedly using computer-assisted dynamic modeling to target maximal gas exchange at low device resistance. The extremely low resistance of the AVCO₂R gas exchange device (<10 mmHg pressure difference) allows blood flows of as much as 25% of the animal’s cardiac output (>1300 ml/min). Surgical cannulation for vascular access in AVCO₂R is identical to the setup performed in conventional ECMO. However, the prime volume is as low as 200 ml due to fewer circuit components.

During initial animal trials with AVCO₂R, as shunt blood flow (Qb) was increased with sweep gas flow (Qg) held constant at 3 l/min, a proportional increase in CO₂ extraction was seen until Qb reached 1000 ml/min, at which point CO₂ removal plateaued at 112±3 ml/min. Similarly, CO₂ removal increased proportionally with Qg flow when Qb was held constant. The

![Figure 2 Schematic of simple arteriovenous circuit with low-resistance membrane gas exchanger in mechanically ventilated sheep.](image-url)
maximum \( \frac{Q_g}{Q_b} \) ratio was 2:1, and the pressure gradient across the device was <10 mmHg throughout the experiment. Minute ventilation (MV) could be gradually decreased as \( Q_b \) was increased. At maximal \( Q_b (1417 \pm 26 \text{ ml/min}) \), MV was reduced from 6.9±0.8 l/min to 1.3±0.5 l/min (16% baseline) while maintaining normocapnia. At this maximal reduction in ventilator support, changes in \( \text{PaCO}_2 \) were monitored while \( Q_b \) was incrementally diminished. Hypercapnia was observed only at a flow rate of <500 ml/min.

AVCO\(_R\) proved to be capable of removing as much as 96% of the animal’s total \( \text{CO}_2 \) production with a reduction of ventilator support to 16% of baseline MV. These findings are in agreement with Kolobow et al.\(^{37}\) andGattinoni et al.\(^{113}\) who used ECCO\(_R\) in animals and patients with ARDS to achieve adequate arterial oxygenation through ‘apneic oxygenation’ or with minimal ventilation, even when extracorporeal pump flow was as low as 200 ml/min. The utility of such low flow gas exchange may prove vital in situations in which flow is compromised or limited by the clinical status of a critically ill patient. At flows of less than 500 ml/min, moderate hypercapnia (40–70 mmHg) occurred, but it was well tolerated without adverse hemodynamic effects.

To compare pressure/flow characteristics of commercially available percutaneous vascular cannulae, different sizes of percutaneous cannulae were used in vitro at clinically pertinent arterial pressures to allow adequate flow (800–1100 ml/min) yet minimize vessel damage, yielding a family of curves to allow size matching to achieve the desired flow for a targeted \( \text{CO}_2 \) removal.\(^{124}\) Results indicated that blood flow during AVCO\(_R\) depends on three variables: 1) device resistance; 2) the pressure gradient between the arterial and venous systems; and 3) cannula resistance. The effect of venous resistance was minimized by using venous cannulae that were four French sizes larger than their paired arterial cannula. Percutaneous arterial cannulae that are 12F or larger allow sufficient flow for maintaining normocapnia with reserve capacity in adult humans.\(^{125}\)

To evaluate the effect of AVCO\(_R\) on ventilator support requirements during ARDS, an ovine model of severe respiratory failure created by an LD\(_{50}\) smoke inhalation injury was used.\(^{121}\) The effects of sustained AVCO\(_R\) flow on critical hemodynamic variables confirmed that, despite a 20% to 26% cardiac shunt through the AVCO\(_R\) circuit for 7 days, there was no instability in the hemodynamic profile, specifically in the heart rate HR, cardiac output CO, mean arterial pressure MAP, pulmonary artery pressure PAP, or \( Q_b. \)\(^{126}\) The extremely low circuit resistance (pressure gradient <10 mmHg) allows the AVCO\(_R\) circuit to appear as an insignificant component of overall systemic resistance without hemodynamic compromise on initiation of AVCO\(_R\) flow. In addition, the conscious animal, with all autoregulatory mechanisms intact, was able to maintain blood flow to all critical organs (brain, heart, kidney, and mesentery) within 20% of baseline perfusion, despite an AV shunt equal to 25% of the resting CO.\(^{127}\)

AVCO\(_R\) significantly reduces the influence of excessive positive pressure ventilation on hemodynamic variables. By achieving a significant reduction in ventilatory pressures and eliminating hypercapnia, AVCO\(_R\) may attenuate changes in hemodynamics that would otherwise be manifested as the result of increased intrathoracic pressure from mechanical ventilation.\(^{126}\)

AVCO\(_R\), however, does not provide substantial oxygen transfer when the arterial \( \text{PaO}_2 \) level is adequate because inflow to the device is already saturated (>90%) with an \( \text{O}_2 \)-carrying capacity close to maximum. However, there is a small direct transfer (<10%) and some benefit related to the increased AVCO\(_R\) content of the mixed venous blood reaching the pulmonary precapillary bed, which may result in a slight alteration in the normal vasoconstrictive response to local hypoxia with a resultant reduction in the pulmonary shunt.\(^{120}\)

To establish a clinically relevant model of severe respiratory failure in adult sheep, we developed a smoke dose-dependent model of ARDS of predictable severity.\(^{128}\) Percutaneous AVCO\(_R\) allowed reductions in airway pressures and ventilator-dependent days, improved \( \text{PaO}_2/\text{FiO}_2 \), and improvement in survival in a prospective randomized outcomes study of percutaneous AVCO\(_R\) in adult sheep with severe respiratory failure.\(^{129,130}\)

In our initial clinical experience with AVCO\(_R\), feasibility and safety of AVCO\(_R\) was evaluated in a 72-h trial.\(^{131,132}\) Percutaneous AVCO\(_R\) can achieve approximately 70% \( \text{CO}_2 \) removal in adults with ARDS and \( \text{CO}_2 \) retention without hemodynamic compromise or instability. AVCO\(_R\) allows extracorporeal \( \text{CO}_2 \) excretion, control of respiratory acidosis, and may avoid the complications induced by endotracheal intubation with positive-pressure mechanical ventilation.

Controlled clinical trials of AVCO\(_R\) in patients with ARDS, \( \text{CO}_2 \) retention syndromes, and smoke inhalation/cutaneous burn injuries are needed to define the merits and limitations of this treatment to provide optimal gas exchange, limit ventilator induced barotrauma, and ultimately improve survival in patients with severe respiratory failure.

**Paracorporeal artificial lung (PAL)**

An estimated 16 million Americans are afflicted with some degree of chronic obstructive pulmonary disease (COPD), accounting for 100,000 deaths per
The only current treatment for chronic irreversible pulmonary failure is lung transplantation. Lung transplantation has proved successful (75% 1-year, 55% 3-year, and 42% 5-year overall survival) for treating chronic irreversible lung disease in select patient populations.\(^\text{134}\) Since the widespread success of single- and double-lung transplantation in the early 1990s, demand for donor lungs has steadily outgrown the supply.\(^\text{134}\) Median waiting times for a lung transplant have increased during the last decade from less than 200 to over 600 days (almost 2 years!). Only one in four solid organ donors is a suitable lung donor.\(^\text{135}\) Unlike dialysis, which functions as a bridge to renal transplantation, or a ventricular assist device (VAD), which serves as a bridge to cardiac transplantation, no suitable bridge to lung transplantation exists.

The current methods for supporting patients with lung disease, however, are not adequate or efficient enough to act as a bridge to transplantation. Although occasionally successful as a bridge to transplant, ECMO requires multiple transfusions and is complex, labor-intensive, time-limited, costly, nonambulatory and prone to infection.\(^\text{136,137}\) Intravenous devices, such as the intravascular oxygenator (IVOX) and the intravenous membrane oxygenator (IMO), are surface area limited\(^\text{138}\) and currently provide inadequate gas exchange to function as a bridge-to-recovery or transplant.\(^\text{139}\) A new intravenous respiratory support catheter, the Hattler Catheter, is accomplishing substantially greater rates of gas exchange in large animal studies than those of the clinically tested IVOX device.\(^\text{138}\)

Artificial lungs (ALs) attached directly to the pulmonary circulation, utilizing the right heart as the blood pump, have been shown to be capable of fully supporting basal O\(_2\) and CO\(_2\) transfer requirements in pigs and sheep for as long as 7 days.\(^\text{140-142}\) The goal is to design and build ALs that can be perfused entirely by the right ventricle and completely support the metabolic O\(_2\) and CO\(_2\) requirements of an adult. Such a device could realize a substantial clinical impact as a bridge to lung transplantation, as a support device immediately post-lung transplant, and as a rescue and/or supplement to mechanical ventilation during the treatment of severe respiratory failure.

The concept of an artificial lung is not new. Preliminary efforts to design, fabricate, and test prototype implantable artificial lungs have been reported intermittently since 1970.\(^\text{143-147}\) First and foremost, an artificial lung must meet the gas exchange requirements for the patient. Basal gas exchange requirements in an adult average 240 ml/min of O\(_2\) and 200 ml/min CO\(_2\) with a cardiac output of 4 to 6 l/min. During light exercise, these values for O\(_2\) and CO\(_2\) increase to 800 and 700 ml/min, respectively, with a cardiac output of about 8 l/min.\(^\text{148}\) In order to provide efficient gas exchange, virtually all commercially available ‘lungs’ for heart–lung machines utilize the cross-flow principle and are constructed with layers of microporous hollow
fibers. Pressure drop across the fiber bed is only of secondary importance for heart and lung machines since external power (a roller or centrifugal pump) is utilized. ALs, however, are intended to operate with the right ventricle as the pump and must be designed for a very small pressure drop. The MC3 prototype (MC3, Ann Arbor, MI) utilizes radial blood perfusion through a concentrically wound hollow-fiber fabric (Figure 3) and the device reported by Cook et al. uses a relatively thin rectangular bundle of fibers. Both have between 1.5 to 2.5 m² of surface area and generate relatively small pressure drops, in the order of 5 to 10 mmHg for blood flow of 4 to 6 l/m.

Secondly, the AL must be designed to provide minimal blood trauma. Blood activation is minimized in artificial lung designs that have shear stresses between 4 and 8 dyne/cm² and minimal surface area consistent with gas transfer requirements. No blood pump is involved and the fluid shear stresses are very low within the fiber bundles of devices currently under development.

Microporous materials cause a change in surface tension and allow plasma leakage. Thus, microporous materials will not be acceptable for any type of chronic implantation in humans. Research is now directed towards coating the microporous polypropylene fibers with a 1-μm-thick silicone layer or developing a solid silicone hollow-fiber membrane. A recent promising development is that of nitric-oxide-releasing extracorporeal circuits.

The third design issue for the AL is that of hemodynamic compatibility. The design must mimic the high compliance and low resistance of the natural pulmonary circulation to avoid overworking the right heart. One of the complications identified early in the AL design process was right heart failure. Recent mathematical modeling by Boschetti et al. revealed...
that the mode of AL attachment, the location of a compliance chamber, and the fiber bundle resistance within the AL all affect the power needed to pump blood through the AL. The design of the AL should include a compliance component that mimics the compliance of the natural pulmonary circulation.

The fourth design issue for the AL is size and shape of the device. The device configuration would be restricted by the size and shape of available space in the thoracic and/or abdominal cavities.

Beyond the design of the actual device, the mode of attachment plays a role in the success of the AL. The AL can be attached in parallel with the natural lungs, in series with the natural lungs, or in a hybrid combination of the two (Figure 4). There are advantages and disadvantages to each attachment mode and specific disease characteristics may dictate the attachment mode on a case-by-case basis.

In parallel attachment shunts blood from the pulmonary artery (PA) through the AL to the left atrium (LA). A portion of the blood from the right ventricle is shunted through the AL because of high pulmonary resistance, or by using a vascular band on the PA. In fact, if unbanded, this configuration lowers the resistance encountered by the right heart by creating a low-resistance alternative for blood flow. Of the various attachment modes, the in-parallel configuration creates the least amount of stress on the right heart. Thus, it may be best suited for patients who are suffering from pulmonary hypertension. However, there are disadvantages to this attachment mode. First, the lungs have a variety of functions other than gas exchange, including producing, storing, and inactivating various vasoactive and coagulation-modulating molecules, and current ALs make no attempt to mimic these functions. In the parallel attachment mode, the metabolic functions of the lungs are decreased by shunting blood away from the natural pulmonary bed. A decrease in these metabolic functions may result in negative hemodynamic effects. Secondly, the native pulmonary bed serves as a filter for small emboli. The direct shunting of blood from the right ventricle to the left atrium adds the risk of systemic thromboemboli. Finally, if the native lungs have failed, dividing the blood flow between the AL and the natural circulation results in oxygenation of only a portion of the cardiac output with each cycle.

In-series implantation also utilizes an end-to-side anastomosis on the PA as the inlet to the AL. The outlet of the AL, however, is an end-to-side anastomosis to the distal PA. A band on the PA is placed between the two anastomoses in order to divert 100% of the cardiac output through the AL. This configuration creates the greatest stress on the right heart. In-series attachment has the advantage that 100% of the cardiac output is both oxygenated and circulated through the natural pulmonary bed. This attachment mode, thus, may be useful for immediate post-transplant support in a patient who received injured or compromised lungs from donors. The oxygenated blood from the AL may aid in the lung recovery process. Finally, the in series attachment is advantageous in that, if a device fails, a new AL can be attached without the threat of systemic thromboemboli.

Hybrid attachment shunts blood from the proximal PA to the AL, with a split return to the distal PA and the LA. A band would be placed on the PA that could shunt as much as 100% of the cardiac output through the AL. This attachment mode is the best compromise between hemodynamic performance and preservation of some portion of the nonrespiratory functions of the natural lungs.

Beyond AL attachment configuration, there are arguments for both internal (intracorporeal) and external (paracorporeal) placement of the device. Both placements have the advantage of allowing the patient to be ambulatory, a requirement for lung transplant candidates. However, the size and shapes of intracorporeal devices are restricted by the parameters of the body cavities into which they are implanted. Paracorporeal devices have the advantage of being easily accessible for maintenance and change-out if the device fails or when the device has reached its lifespan. Paracorporeal ventricular assist devices are used for many months as bridges to cardiac transplant. Cannula and skin problems seem generally manageable with local wound care and native tissue ingrowth.

A successful artificial lung could realize a substantial clinical impact as a bridge to lung transplantation, a support device immediately post-lung transplant, and as rescue and/or supplement to mechanical ventilation during the treatment of severe respiratory failure.

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