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Review

Ambulatory home wearable lung: progress and future directions

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Extracorporeal life support (ECLS) was first implemented as an extension of cardiopulmonary bypass technology. The early use of ECLS in patients with acute respiratory distress syndrome (ARDS) was discouraging, likely due to limitations of technology and understanding of the disease process. However, over the last decade, there has been a rapid expansion in ECLS use. This "rebirth" in 2009 was largely driven by the need for ECLS during the Influenza A subtype H1N1 pandemic and the results of the conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) trial showing improved outcomes in patients with ARDS on ECLS compared to traditional management. Along with the increase in overall use of ECLS, there has been an increase in the number of patients with lung failure who are on long-term support, either awaiting lung recovery or transplantation. Many of these patients are awake, participating in physical rehabilitation, and even ambulating while supported with ECLS. Given the recent advances in patient care, and improvements in ECLS technology, the movement towards home for stable patients supported with ECLS may be on the horizon. Patients supported with ventricular assist devices (VAD) underwent a similar transition towards home in the 1990s, before which they were hospital bound. The road to an ambulatory home wearable lung will likely mirror that pathway. This review will give a brief overview of the transition of VAD patients out of the hospital, the history of ECLS, the current state of ECLS for lung failure, new and upcoming ECLS technology, and hurdles on the road home for ECLS patients.

Keywords

Acute respiratory distress syndrome; Ambulatory devices; End-stage lung disease; Extracorporeal life support; Extracorporeal membrane oxygenation; Respiratory failure

1. Introduction

On July 18, 1963, a 42-year-old man underwent an aortic valve replacement at Baylor College of Medicine. Postoperatively, he developed cardiogenic shock and suffered a cardiac arrest. Given his grim prognosis he was considered for left ventricular bypass, and on July 19 an early version of the DeBakey blood pump was implanted. Unfortunately, his injury was non-recoverable and support was stopped after 4 days [1]. This marked the first clinical use of a left ventricular assist device (LVAD). Over the next several decades various LVADs were developed and used clinically, primarily for short-term support post-cardiotomy and as a bridge to heart transplantation [2]. Patients were bound to intensive care units (ICU) and tethered to bulky consoles.

In the late 1980s, with an eye towards long-term support, electrically-powered implantable devices were developed through the National Heart, Lung, and Blood Institute (NHLBI) program and approved as investigational devices; most notably the Novacor LVAD and the vented electric (VE) HeartMate LVAD [2]. In 1991, a 33-year-old man, who was supported with the VE HeartMate while awaiting heart transplantation at Texas Heart Institute, was allowed to leave the hospital and visit home [3]. He was the first patient with an LVAD to do so. Shortly thereafter, a patient with the same device was formally discharged from the hospital and another patient returned to work while awaiting transplantation [2]. It was quickly noted that these were not exceptional cases. Many patients supported with these devices did not require intensive care monitoring, and by the mid-1990s the potential for LVADs as outpatient therapy became a reality with noted improvement in quality of life [4–6].

With continued advancement in technology and patient care, patients with current LVADs achieve remarkable survival at 1 year (86.6%) and 2 years (79.0%) after implantation [7]. Improvements in devices and the clinical stability of patients with LVADs have, in part, spurred recent revisions to the heart allocation policy put forth by the United Network of Organ Sharing [8, 9], whereby these patients now have a lower priority listing. The potential for comparable outcomes and quality of life to heart transplant patients may exist in the near future with these devices.

Trailing these strides in the care for patients with end-stage heart failure has been the management of patients with end-stage lung disease. The complexity of meeting the needs of oxygenation and/or ventilation for those with end-stage lung disease has posed an additional technological hurdle, as opposed to the pump failure in patients with end-stage heart failure. While some patients are able to get by with home supplemental oxygen, others require hospitalization for more advanced therapies such as mechanical ventilation or extracorporeal life support (ECLS).

The prospect of liberating patients with end-stage lung disease from the hospital; as destination-therapy or while

awaiting transplantation, is an unlikely scenario with mechanical ventilation. However, with ECLS, an ambulatory home wearable lung may be on the horizon. This review will focus on the historical progress of ECLS, its current status, new and upcoming technology, and the clinical path forward that may drive the field towards that goal.

2. History

The first successful use of a pump-blood oxygenator was in 1953 by John Gibbon, Jr. [10]. Blood entered down both sides of vertical screens (1.6 m^2) and was spread into a thin film where gas exchange occurred by direct exposure to an oxygen-rich environment. This and other early oxygenators were limited to a few hours of use due to issues of hemolysis, bleeding, and the risk of arterial gas emboli due to direct contact of blood and gas [11–13]. The need to eliminate the blood-gas interface was clear, and this was the impetus that laid the foundation for ECLS.

Various materials were used as a membrane; including plastic films, ethylcellulose, Dacron and fiberglass, and silicon [14–17]. These were arranged as parallel plates, and by machining capillary channels in the membranes, blood flow could be more carefully controlled [16]. It was a silicone membrane oxygenator of this design that was used by Dr. Hill in 1972 on a 24-year-old man who had severe hypoxic respiratory failure following an automobile accident [18]. The patient was supported for 75 hours until his lung function improved allowing removal of the device.

The National Institute of Health (NIH) set forth a multicenter, randomized trial to evaluate the use of ECLS as a therapy in adults with acute respiratory distress syndrome (ARDS), the results of which were published in 1979 [19]. The trial was flawed as there were four different novel oxygenators used on fewer than 95 patients in nine centers; most of which were new to the technology. With no survival benefit seen (~10% in patients supported either with mechanical ventilation alone or with ECLS), the use of ECLS in the adult population significantly slowed over the next 20 years. However, driven by Dr. Bartlett and colleagues, neonatal use continued based on the successful use of prolonged ECLS for a newborn infant, Esperanza, with severe respiratory failure in 1975 [20]. Publishing their experience on 45 newborns with respiratory failure in 1982, they reported a survival of 55% [21]. He used the spiral coil Kolobow Sci-Med silicone membrane oxygenator, and introduced the surprisingly well-tolerated cannulation of the carotid artery and jugular vein.

Contemporaneously, oxygenator development continued with the adoption of polypropylene hollow-fiber membranes derived from renal dialyzers, where blood flowed through the fibers and gas around the fibers. An oxygenator of this design became first commercially available in 1981 by Terumo Corporation. Due to its efficient gas exchange, small size, and ease of use, it quickly achieved a majority of the market share for short-term use [22, 23]. Modern hollow-fiber oxygenators have blood flowing around the fibers and gas flowing through the fibers; thus providing a larger cross-sectional area for gas exchange, and better mixing of the blood due to the Fahraeus-Lindqvist effect [24, 25]. Together, these changes have resulted in a reduction in the pressure head and the problematic clotting which historically occurred within the fibers [26]. Plasma leakage into the fibers was initially an issue with oxygenator use beyond a few hours. The introduction of polymethylpentene and skinned pores in the early 2000s drastically reduced this complication, leading to the oxygenators most-widely used for ECLS today [27, 28].

Interest in the use of ECLS in adults with respiratory failure was renewed when Dr. Bartlett's group reported a 52% survival among 255 patients supported between 1989 and 2003 [29]. Unlike the early NIH trial, their protocol-driven approach targeted lung-rest ventilator strategies, optimization of oxygen delivery, and minimal anticoagulation; thus shedding light on appropriate management strategies in these patients [30]. This development set the stage for the CESAR trial. The United-Kingdom-based multicenter study randomized adults with ARDS to consideration for ECLS versus conventional treatment, and demonstrated that patients in the ECLS arm had an improved rate of survival without disability compared to those who received conventional treatment (63% versus 47%; $p = 0.03$) [31].

The same year the CESAR trial results were published, H1N1 caused a respiratory viral pandemic. In this setting, the use of ECLS for adult respiratory failure saw a rebirth. The Extracorporeal Life Support Organization (ELSO) registry noted more than double the cases of adult respiratory ECLS in 2009 compared to prior years, leading to the current era of ECLS use [32]. Since then, over the past decade there has been a continued rise in not only the number of cases performed, but also the centers performing ECLS.

3. Current status of ECLS for lung failure

There are three patient populations in which the prospect of home ECLS therapy may become a reality: patients with ARDS awaiting recovery, patients with lung disease awaiting transplantation, and patients not suitable for transplantation but suffering with end-stage disease. Per the ELSO registry, over the last 5 years there have been over 17,000 adult respiratory ECLS cases with a survival of 61% [32]. Along with the rise in overall ECLS runs, there has been an increase of prolonged respiratory ECLS cases [33]. Posluszny *et al.* [34] have defined these prolonged runs as $\geq$14 days, and in recent years, have shown 600 to 900 cases annually in ELSO registry analysis. More than 12% of these ECLS runs were $>$6 weeks long. Overall survival in these long-term patients has been noted to range from 30 to 50% [33, 35]. However, there have been several reports of patients with ARDS who were bridged to recovery or lung transplantation with ECLS runs $>$100 days long [36–41].

The longest case reported is of a seven-year-old with a 30% burn and smoke inhalation who had recovered near normal pulmonary function after 605 days of extracorporeal mem-

brane oxygenation (ECMO). The patient required several modes of ECLS: veno-arterial (VA) ECMO for one week, veno-venous (VV) ECMO for two months, right-atrial-to-pulmonary-artery for 16 months, and extracorporeal CO_2 removal for two months [42]. It appears that lungs can recover from severe injuries if scarring and fibrosis can be mitigated. Consolidated stiff lungs are filled with inflammatory cells. They cannot be forced open until these inflammatory cells are removed. The Karolinska group has documented normalization of a lung over months of poor elasticity without use of high positive end-expiratory pressure (PEEP) and peak pressures [43]. Since there are no adjuvant drugs for fibrosis, we believe the lung needs rest through a safe, long-term support.

The number of ECLS runs for end-stage lung disease patients awaiting transplantation has also been growing over the past 20 years [44–46]. Several of these patients were on ECLS therapy for more than 50 days before undergoing transplantation. Data from all patients indicate that survival with this strategy is equivalent, if not better, when compared to patients who are bridged with mechanical ventilation [47, 48]. Improved outcomes have been noted when patients are liberated from the ventilator and spontaneously breathing, and are able to participate in physical therapy [45, 46, 48]. This offers the opportunity to prevent deconditioning while allowing for physical rehabilitation and improved nutrition. Not only does this improve the rate of successful bridge to transplant, but it also leads to a quicker recovery post-transplantation.

The ability to ambulate patients on ECLS is a stark contrast to the initial use of these devices. Patients were historically bed-bound; not only due to the size of the ECLS circuits, but also due to the presumed critical acuity and fear of catastrophic complications such as device malfunction/damage, bleeding, or dislodgement of cannula. With the reduction in membrane surface area to <2 m^2 and the modern centrifugal pumps, the size, reliability, and hemocompatibility of ECLS systems have dramatically improved. Anticoagulation for ECLS support has primarily been heparin-based; however, direct thrombin inhibitors are increasingly being used [49]. Whereas anticoagulation goals have typically been an activated clotting time of 180–220 seconds, many centers have shifted to a partial thromboplastin time of 1.5–2.5 times the normal range, or an anti-Xa range of 0.3–0.5 U/mL. More recently, there has been a trend towards further reduction of anticoagulation goals, with some centers switching to subcutaneous prophylaxis dosing or even no-heparin regimens in the setting of VV ECMO [50–52]. While the data is limited, these strategies do not seem to have increased thrombotic complications in short-term ECLS runs.

Along with the decreased concern for bleeding, advances in cannulation approaches have made the mobilization of patients more practical; most notably the use of single-site dual-lumen cannula in the case of VV ECMO, or the "sport model" with upper body cannulation in the case of VA ECMO [53, 54]. In late 2008, we learned from C.W. Hoopes (personal communication) that patients could ambulate while supported on ECMO, and we adopted his protocol in 2010 [55]. Since then we have been routinely ambulating patients, even those with femoral cannulas [56, 57]. Still, given the size of the ECLS circuit and need to transport gas tanks with the circuit, mobilization of these patients generally requires multiple healthcare workers to manage both the patient and the equipment [56, 58].

4. New/future technology

Since the early 2000s, the interventional lung assist device (Xenios, Heilbronn, Germany) has been aimed towards the treatment of hypercarbic respiratory failure. This device can either be pumpless in an arterio-venous configuration or pump-assisted for low-flow CO_2 removal. Outside of the ARDS population, a device such as this may be well-suited for patients with chronic obstructive pulmonary disease. It is currently in the process of the being adapted for long-term ambulatory lung assist [59].

Several other ECLS systems with further oxygenation capabilities aimed for wearable ambulatory lung support have been in development. Our group believe that ECMO might provide a platform for recovery, bridge to transplantation, and even satisfactory permanent support of irreversible lung disease. With 22 years of support from the NHLBI and more recent support from a commercial subcontractor, we have been able to translate our laboratory prototypes into a portable console for a wearable pump-lung unit. This device, Breethe OXY-1 system (Abiomed, Danvers, MA, USA), has recently become available for clinical use under 510(k) approval for use up to six hours. The system consists of an integrated pump-oxygenator unit with an oxygen concentrator encased in a mobile console to obviate the need for gas tanks during mobilization. Though human use has just begun, this system had promising 30-day *in-vivo* performance in large animal models [60]. We are anxious to watch its use grow in the ICU, and anticipate its performance to justify approval for long-term use, ambulation, and even a safety study for use at home.

Similar systems that have been under development in parallel are the percutaneous, paracorporeal artificial lung by the University of Kentucky group, and the Paracorporeal Ambulatory Assist Lung by the University of Pittsburgh group [61, 62]. Both of these systems have undergone *in-vivo* large animal model testing with encouraging results. The University of Michigan group has taken another approach with their compliant thoracic artificial lung [63]. This device is used in a pulmonary artery to left atrium configuration to allow the right ventricle to act as the pump for the oxygenator. To date, 14-day *in-vivo* studies have shown good performance with minimal clot formation, and 60-day studies are to follow. The Mobybox ECMO device (Hemovent, Aachen, German) presents yet another approach, as it is fully pneumatically driven requiring no power supply [64]. Seven-day *in-vivo* studies have shown no visible clotting, and the device has

received Conformitè Europëenne (CE) marking to place it on the market in the European Union.

Coating of ECLS blood contacting surfaces is another field of investigation in hopes to further improve biocompatibility. Though some devices on the market do not have any coating, others have phosphorylcholin, or heparin coated surfaces. As of yet, there is no evidence to suggest that this reduces thrombotic complications for long-term support, particularly relevant to an ambulatory lung device. Research efforts have focused on ionically-charged surfaces, biochemical coatings (e.g., albumin, polyethylene glycol, nitric oxide, anticoagulants), and endothelialization of surfaces [59, 65–67]. In future oxygenators, these coatings may markedly reduce or even obviate the need for anticoagulation.

Just as hollow-fiber membranes led to the current era of ECLS systems, the next jump may be in 3D-membranes or microfluidic devices. The 3D-membranes designed based on triply periodic minimal surface geometries can result in oxygen transfer rates 26–69% higher than hollow-fiber membrane designs [68]. Microfluidic devices take a biomimetic approach in the design of channels on the range of 10–20 μm in diameter to allow for more efficient gas exchange [59, 69]. Ambient air is often used as the ventilating gas opposed to oxygen required for current devices [70]. Selvaganapathy's group has reported stackable modules of microfluidic devices with flow rates ranging from 10 to 60 mL/min [71, 72]. This work has been aimed towards assist in pre-term neonates with recent animal work done in a swine model [73]. However, for clinical feasibility, particularly in adult patients, the technology would need to be scaled up (estimated 833 stacked layers for an adult device) which may lead to hemocomplatibilty issues [74–76]. The prospect of 3D-microfluidic topologies may mitigate both of these issues by providing greater surface area for gas-exchange, thus lowering priming volume.

5. Road to home

Following the ELSO annual meeting in 2017, Palmer spoke to our group of his landmark experience with an out-of-hospital ECMO experience [77]. His team had been supporting a 59-year-old woman with idiopathic pulmonary fibrosis for 160 days on VV ECMO as a bridge to transplant. She was emotionally depleted in her long wait and asked to go home for a meal. He engineered a 440 km day-trip from the ICU. He felt the "pasta reprieve" gave her the emotional boost to survive an additional wait of 69 days in the ICU before a donor was located and successful transplantation could be performed. We ask why an ICU is required if a trip home is possible.

Despite the technological strides and clinical advancements over the past 20 years in ECLS devices, there remain challenges that need to be addressed on the path to an ambulatory home wearable lung. These largely consist of cannulation strategies, physiologic requirements for daily activities, device reliability and monitoring, anticoagulation, and outpatient management.

Though centers have been able to ambulate patients who are femorally cannulated, this would likely not be a strategy suitable for discharge. Percutaneous dual-lumen cannula for patients requiring VV ECMO, or an upper body cannulation strategy for those requiring VA-ECMO, would be more preferable. However, even these peripheral cannulation strategies may not be ideal given the care required to keep cannulas tethered in place and the discomfort of a large-bore cannula maintained long-term in a patient's neck. Perhaps conversion to a tunneled central cannulation strategy once patients reach a point of stability would permit the safest strategy, along with providing easier cannula site maintenance when at home. Steuer *et al.* [78] have also suggested the use of grafts sewn to a patient's common iliac veins, which could potentially be suitable for a low-flow CO_2-removal application.

Many patients reach a point of physical therapy and ambulation while supported on ECLS; however, it is likely a more thorough assessment of physiologic requirements would need to occur prior to hospital discharge. Certain patients may prove to have higher requirements than others and pose a greater challenge. In a simulated model, Chicotka and colleagues assessed various ECMO configurations in patients with idiopathic pulmonary fibrosis when at rest and during exercise to the extent where total body oxygen utilization was roughly equivalent to a patient with functional New York Heart Association III symptoms [79]. They found that regardless of the configuration, blood flow and gas flow would likely need to be increased to meet the physiologic requirements of patients. Assessment of device settings required to achieve 3–4 metabolic equivalents for individual patients would need to be done, so that patients may perform daily activities. Furthermore, patients and their caregivers would need to be familiar with changing the device settings during these tasks. Alternatively, the implementation of an autoregulatory ECLS circuit responding to physiologic needs would be needed, such as those demonstrated in animal models by Kopp *et al.* and Conway *et al.* [80, 81].

The ability to monitor ECLS systems to predict component failure or need for maintenance would also be essential. Tracking the device performance in terms of gas exchange and transmembrane pressures against baseline values would help identify worsening efficiency of the device and formation of thrombus, respectively. These could serve as indicators for outpatient assessment or the need for pump-oxygenator exchange before device failure ensues. Having a clinical team, consisting of physicians, nurses, and ECLS specialists, available for patient issues and outpatient assessment and management would be essential for this task.

The appropriate anticoagulation regimen would need to be determined as well. Continuous infusion of an intravenous anticoagulant would require additional care and expertise, and likely be prohibitive to hospital dis-

charge. While prophylactic subcutaneous dosing and no-anticoagulant strategies have been used, the long-term safety of these would need to be assessed. Utilization of a direct-acting oral anticoagulant, or warfarin, could be another option; however, their use in the setting of ECLS remains unproven.

Perhaps the next steps towards evaluation of the safety and feasibility of an at-home ambulatory lung should be to mirror the approach taken with the early generation durable LVADs. The newer integrated pump-oxygenator systems may allow for improvement in ease of care similar to the introduction of the VE HeartMate and the Novacor LVADs. Evaluating adverse events, and the need for physician intervention during the course of ECLS therapy could be the driver for evaluation as outpatient therapy [5]. From there, patient criteria should be set forth to determine eligibility for discharge similar to the VE HeartMate and Novacar bridge trials [82, 83].

6. Conclusions

From its first clinical implementation over 50 years ago, the use of ECLS has expanded to over 450 centers [32]. The technological advances and improvements in clinical care have allowed for the survival of thousands of patients who likely otherwise would have died. With longer duration ECLS runs occurring with increasing frequency, particularly in the setting of bridge to transplant and ARDS, and the performance of physical rehabilitation and ambulation, the next natural step in evolution of the field is the de-escalation in acuity of care from ICUs to floor care to home. Continued advancements in ECLS will likely lead to a similar pathway of LVADs, making the ambulatory home wearable lung an eventual reality.

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AS, MAA, ZJW, and BPG—writing—original review and editing. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

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Conflict of interest

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