Artificial Lungs
Are We There yet?

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KEYWORDS
- Lung • Circulatory support • Heart failure • Oxygenation

KEY POINTS
- New oxygenator technologies widened the application of extracorporeal life support significantly in the last decade.
- Currently the use is still limited within intensive care units.
- Compared to ventricular assist devices for heart failure, lung replacement technology is lagging behind, not allowing discharge on device.
- Challenges to achieve a true artificial lung for long term use are discussed in this article.

INTRODUCTION

The last decade has seen a change in the clinical use of circulatory support for heart failure. Technical improvements have made it possible to move from a short-term bridge to transplantation to use in chronic therapy. Although it is not a perfect solution, with a high incidence of adverse events, it allows patients to live on chronic support at home for several years. If this scale of expectations is applied to pulmonary support, the answer to the question “Are we there yet?” is “No.”

This article describes the history of pulmonary support, the technical changes, and the clinical indications and discusses the common adverse events. In addition, about it discusses what needs to be improved for pulmonary support to be used as a long-term lung assist device.

HISTORY: DEVELOPMENT OF OXYGENATORS

The development of so-called artificial lungs for clinical use was linked very early with the development of a heart-lung machine for heart surgery. An oxygenator for gas exchange was the limiting factor in the development of these machines. The task was to design a reliable machine to oxygenate and decarboxylate blood. It was preferable for it to be a disposable item to avoid the expensive and time-consuming cleaning and sterilizing processes.

Decarboxylation occurs easily by diffusion, but oxygenation is a difficult task because it requires contact of oxygen with thin layers of blood. For about a century the technical solutions were based on direct contact of oxygen with blood. In 1882 the first experimental so-called bubble oxygenator was developed along with a two-dimensional film oxygenator. After decades of research the first clinical applications using a large stationary screen oxygenator by Gibbon were done in 1953, in which a stable film of blood was exposed to a flow of oxygen. This development was a major change of paradigms in cardiac surgery. After these initial applications the bubble oxygenator emerged as the main choice of design, which was a key step in the development of open heart surgery. It allowed heart surgery programs to be...
established worldwide and was still in use in the 1980s.

It became clear that a limiting factor in the use of extracorporeal gas exchange was blood trauma.6 Unlike the experience with cross-circulation from other humans, mechanical blood trauma became (and still is) an issue: hemolysis was the key factor in limiting the time of use. Additional trauma to blood constituents, like damage to the coagulation system and the induction of an inflammatory response, limited the time of use to several hours and caused severe bleeding events.8

A different idea was that bubbles are harmful to the blood and a system similar to a dialysis membrane, resembling the natural lung, carrying oxygen to the blood and removing CO₂ would be better.9

When the first membrane oxygenators were developed, which improved biocompatibility by avoiding direct air/blood contact and making longer-term use feasible, the application for lung failure was seen immediately and the extracorporeal membrane oxygenation (ECMO) was introduced into clinical practice. However, after some encouraging reports, a clinical trial in 1975 to 1977 revealed disappointing results.10 Therefore the use of ECMO remained controversial.

In the 1980s new designs emerged: the micro-porous hollow fiber membrane and the dense silicone membranes.

When these oxygenators were used for heart surgery the area of the membranes and the transmembranous pressure gradient were substantial, so pumps in the heart-lung machines had to overcome the pressure gradient not only from venous return to arterial outflows but also through oxygenator membranes. In addition, the large foreign surface areas triggered an inflammatory response. Stability of the membranes was also a problem: significant losses of plasma.

Despite these limitations, membrane oxygenators were the technical development that allowed the successful introduction of ECMO for lung failure.11

Closed circuits were designed from components of the heart-lung machine, including a pump and membrane oxygenators.12 Because pressure gradients across these machines were critical, some strategies were designed to allow long-term use.

The pressure gradient consists of the delta of arterial and venous blood pressure in addition to the pressure gradient induced by the circuit tubing, and especially the oxygenator. By using this device for a venovenous approach, the pressure gradient from venous to arterial system was therefore eliminated from the equation.

This simple strategy is still one of the main reasons to prefer a venovenous rather than a venoarterial approach. Second, by using 2 oxygenators in parallel, the overall pressure gradient was significantly reduced. The trade-off is the increase in foreign surface area. It was used in many centers13 because the gain in hemocompatibility was high, especially when greater blood flows were required. In addition, the reliability of oxygenators for long-term use was limited in the 1980s by possible plasma leaks and blood coagulation, so having a second oxygenator in a parallel circle added safety to the system and allowed easy membrane exchange.

With current technology this is no longer required (discussed later).

Silicone membranes seemed to be more stable for long-term use, but their high pressure gradient turned out to be limiting.

This new technology allowed use in patients with acute lung injury and adult respiratory distress syndrome. In addition, it was also used for infants in acute lung failure and in patients after cardiotomy failure.

The predominant indication was respiratory failure despite mechanical ventilation and the aim was to bridge to recovery.

At the same time (1980s) lung transplantation emerged as a clinical reality. However, the experience was limited and the preservation of lungs was still an issue. At that time numerous studies on lung preservation were initiated indicating the need for improvement. The clinical problem was a high incidence of primary graft failure, so even in the early stages ECMO was immediately introduced into lung transplant programs to either bridge to recovery or to early retransplantation.15

Most of the time in primary graft failure the ECMO was used in a venoarterial mode to reduce pulmonary blood flow (with the limitations discussed earlier). Despite reports of success in limited series the overall outcome was so poor that some centers decided not to use this technology.

The next step in the evolution was the introduction of new pump technologies derived from cardiac support and improvements of the tubing surfaces.

However, more important was the introduction of a new membrane type for oxygenators: the polymethylpentene membranes. These membranes became the oxygenators of choice for ECMO therapy around the world. The advantages were the absence of plasma leakage, the 5-fold to 10-fold reduction in pressure (only 11–15 mm Hg at 2.5 L of blood flow), the ease of use, and the safety when operated with a modern centrifugal pump.
These advantages were revolutionary and suggested new applications (Figs. 1 and 2).\textsuperscript{16}

At first it was introduced as a pumpless lung assist device driven by the arterial pressure of the patient. Only a (percutaneous) cannulation in the groin was required to connect the system to the venous and arterial systems. It proved to be effective to eliminate CO\textsubscript{2} and added some oxygenation. Thereby ventilator-induced trauma could be reduced by removing CO\textsubscript{2} with the new system.\textsuperscript{17}

When we used this method as a bridge to transplantation in young recipients with cystic fibrosis, the recipients were mechanically ventilated and the cutoff point for the system was an arterial CO\textsubscript{2} of 100 mm Hg. We learned that such a state could rapidly be reversed by this system.\textsuperscript{18} In addition, so-called septic states with decreased vascular resistance could be reversed by normalizing the CO\textsubscript{2} levels. Thereby most such patients could successfully be transplanted.

The industry moved forward in making this approach usable outside the cardiothoracic units with the development of transcutaneous cannulae and the introduction of this technology to intensivists treating patients with acute lung injury. The aim was to reduce ventilator-induced trauma of the lung by taking away the burden of gas exchange.\textsuperscript{19}

The next step for us was the combination of the modern centrifugal blood pumps with the new oxygenators, which led to the development of miniature ECMO circuits for venovenous or venoarterial application. This step seemed necessary to increase the efficacy of oxygenation and create the least invasive machine for circulatory support. Bulky machines with backup circuits were replaced by simple pump/oxygenator combinations.\textsuperscript{20} These ideas were appreciated by the industry, and an integrated pump/oxygenator unit in 1 small housing became available. This miniaturization process facilitated the use of these devices for transport of patients. Extracorporeal life support centers were able to start therapy at other hospitals and transport patients into their specialized units.\textsuperscript{21} Because of the safety of these new ECMO devices, around-the-clock monitoring by a dedicated perfusionist was no longer required, contributing to the cost-effectiveness of the procedure.

We developed an alternative approach together with the Toronto lung transplant group. In primary pulmonary hypertension a unique pathophysiology exists regarding the cardiac adaptation to the disease. In short, a severe hypertrophy of the right heart to overcome the pulmonary vascular resistance is combined with a volume-depleted left heart caused by reduced cardiac outputs. Right heart failure is usually fast and severe before transplantation, because progress in modern drug therapy has led to very advanced stages of disease when transplant is considered. The use of venoarterial ECMO may relieve the symptoms of right heart failure but further reduces the blood flow to the left ventricle. After transplantation, the full blood flow may lead to left heart failure, which may be confused with primary graft dysfunction. An alternative for such cases is to use the pulmonary artery to left atrium shunt (PA/LA) artificial lung as bridge to transplantation. Driven by the high pressures of the pulmonary artery, an extracorporeal circuit with a pumpless oxygenator can be used to overcome the symptoms. After cannulation of the pulmonary artery and the left atrium, the extracorporeal blood flow bypasses the lung and, after passing through a Polymethylpentene membrane, oxygenator, enters the left atrium. Although blood flow may range from about 1.5 to 2 L/min, it is sufficient to stabilize the circulation.
Bridging patients for several weeks in a nonintubated state to successful lung transplantation was reported from several centers. The connection of an additional extracorporeal circuit leads to higher blood flow to the left atrium, thereby inducing an adaptation of the left heart to volume load before transplantation.

As a further contribution, technical advances in cannulation technology allow safe percutaneous implantation techniques. This development has expanded ECMO use from the realms of cardiac and vascular surgery into intensive care units as well as interventional cardiology. Specialized cannulae designed to allow venovenous ECMO with a single double-lumen catheter have improved the efficacy of this approach.

Use of this technology for respiratory failure outside transplantation gained widespread interest and acceptance during the influenza A (H1N1) pandemic in 2009. The understanding of evolution in technology and its application over the last decade explains why there still is heterogeneity in its application in different centers in the world.

**CANNULATION AND TECHNICAL ASPECTS**

In emergency situations caused by circulatory or acute respiratory failure quick and easy access for ECMO can be achieved by transcutaneous femoral arterial and venous cannulation. Visualization by angiography or sonography may be necessary in some cases for safety and speed. For arterial cannulation the flow to the distal limb needs to be respected. If only partial flow is required a small cannula may help, but in general a distal perfusion catheter is recommended. Control of distal limb perfusion is mandatory after such procedures.

General anesthesia is avoidable in such cases and to cannulate with local anesthesia may be beneficial to avoid mechanical ventilation or circulatory instability. If venoarterial ECMO is used in patients to compensate for hypoxia, femoral cannulation may lead to severe hypoxia of the heart and the brain. Although the lower part of the body is oxygenated by ECMO and retrograde blood flow into the aorta, the upper part of the body may receive deoxygenated blood ejected from the heart into the ascending aorta. Therefore, it is mandatory to monitor proper oxygenation of the upper part of the body. Blood drawn from an arterial line of the right arm, or oxygen saturation measured noninvasively at the right arm or the skull, are used to ensure adequate conditions, especially in sedated patients.

If venoarterial ECMO is considered in nonemergency situations, cannulation of the right subclavian artery may be an option of choice. The advantages are a secure oxygen delivery to the brain and into the aortic root. In addition, for longer-term use and in awake patients, it may be beneficial to avoid arterial groin cannulation to allow for mobilization. Direct cannulation may be cumbersome for the small size of the artery. An end-to-side anastomosis of a short 6-mm to 8-mm vascular graft that is connected to the arterial cannula of the ECMO is preferred by some surgeons. Care must be taken not to cause a hyperperfusion of the right arm by such a procedure.

For venovenous cannulation, 2 options exist. One is the classic placement of the inflow cannula through the femoral vein to the right atrium and the outflow cannula through the jugular vein to the superior vena cava or the upper right atrium. Proper visualization is advisable by echocardiography or angiography. The outflow cannula must be of larger size for effective draining (21–28 Fr). A key factor is to avoid suction events and bad draining for efficacy of the extracorporeal circuit and avoidance of blood trauma. The inflow cannula can be substantially smaller (15–18 Fr). Efficacy of the ECMO is reduced when a substantial amount of blood flow is not drained into the ECMO and bypasses the circuit, which limits the ability to oxygenate the blood.

A newer option is to use double-lumen cannula through the right jugular vein or subclavian vein. Such cannulae are especially designed in a way that the outflow directly flows into the right ventricle and the inflow drains all venous blood returning from the body. This technique was successfully used in acute respiratory distress syndrome and may be of advantage in extubated patients, because it avoids any groin cannulation. However, proper placement and fixation of these large cannulae is the key to adequate support: at the time of placement, echocardiography is required to identify the correct location. Translocation, mostly during mobilization and movements of the patient, may compromise the function, so vigorous fixation may be required.

**INDICATIONS IN LUNG TRANSPLANTATION**

Before ECMO is chosen for any indication, clinicians should consider the underlying disorder and the main objective of the intervention. Is it CO₂ removal, oxygenation deficit, or circulatory failure caused by left or right heart or biventricular failure? Or is it a combination?

The next question concerns the intended time of use. Is it a bridge to recovery, a bridge to transplantation, or just a bridge to decision making? How long might this take?
The third question is about the overall status of the patient. Is there clear information about potential secondary organ failure by hypoxia or circulatory failure? Brain and kidney injury in particular may be the targets of a first assessment. If this is unclear, is a bridge to decision making indicated?

In emergencies, when there is no time for careful assessment, venoarterial ECMO is used by some centers as a first-line treatment of stabilization to allow time for further decision making (discussed earlier). In all other situations, the algorithm of decision making described earlier should apply.

If venoarterial ECMO is chosen, the time horizon of treatment is usually in the range of 1 to 2 weeks. After that, complications associated with blood trauma should be expected. In addition, problems of oxygen delivery to the heart and the brain may occur, which is when femorofemoral cannulation is used and subclavian cannulation should be considered.

In lung transplantation there are 2 major indications for ECMO: respiratory failure and right heart failure. ECMO may be used as bridge to transplantation, during the transplant procedure, or at the transplant, especially in severe primary graft dysfunction.

The main way to bridge patients deteriorating on the waiting list for transplantation is still mechanical ventilation. The success of such intervention depends on the rapid availability of a donor lung. Immobilization because of invasive ventilation leads to rapid decrease in both peripheral and chest musculature. The time to wean patients after lung transplantation is therefore a function of the time on ventilator before transplantation.

This method has been the classic way to use ECMO when patients deteriorate even while being mechanically ventilated. This approach became highly questionable because it involves selecting the patients with the highest risk for transplant. Therefore, a new approach emerged that used ECMO not in addition but as an alternative to mechanical ventilation.

With current technology it seems beneficial not to intubate patients but to use ECMO in awake and ambulatory patients to maintain muscular function and oral feeding and to reduce infections.

As described earlier, the combination of the artificial lung or interventional lung assist (ILA) led to a superior new generation of ECMO circuits outperforming the ILA in the efficacy of oxygenation and allowing circulatory support in the venoarterial mode. The isolated ILA thereby lost its role in lung transplantation. The PA/LA application may remain as one of the last indications.

The use in lung transplantation is now to bridge patients who are extubated with respiratory failure, to support patients in right heart failure, and also to be used during the transplant procedure and be continued thereafter.

Right heart failure requiring mechanical support is a different indication. The main role is to reestablish circulation rather than gas exchange. Therefore, venoarterial support is required. In most cases, partial flow is sufficient to relieve the symptoms of right heart failure. This procedure can be performed with the patient in an awake state using venoarterial ECMO with reduced flows.

Another potential use of ECMO in lung transplantation is during the lung transplant procedure. Different programs have developed, resulting in different opinions about the use of extracorporeal circulation in lung transplantation. When a program was derived from cardiac surgery, it seems natural to use cardiopulmonary bypass in every lung transplant procedure. An approach from thoracic surgeons is generally to do transplants without cardiopulmonary bypass and only call a cardiac surgeon when off-pump transplantation is not feasible. Venoarterial ECMO may be a suitable alternative to the heart-lung machine, especially when it needs to be continued after the transplant procedure. Experience was generated when patients were bridged to transplantation on ECMO. However, the anesthesia management of patients on ECMO is different from patients on conventional heart-lung machines, because meticulous hemostasis is required on ECMO and usually there is substantial concomitant cardiac blood flow. However, ECMO may reduce the cytokine response induced by the heart-lung machine. Because of these different approaches between major lung transplant programs, the use of ECMO in lung transplant procedures remains controversial.

Less controversial is the use of ECMO in severe primary graft dysfunction, because in some cases it represents the only potentially lifesaving alternative, so it should be available in all lung transplant centers. Some major centers prefer the use of venoarterial ECMO, because it reduces the pulmonary blood flow and thereby leads to reduction of lung edema and faster recovery of the graft. Other centers prefer the use of venovenous cannulation, because the overall complication rate is lower and it may be used for prolonged periods of time. Because there is no consensus in this regard, both methods may be used and similar overall outcomes.

An additional strategy for patients with pulmonary hypertension is the use of venoarterial ECMO as a bridge, during the transplantation, and for
gradual weaning after transplantation according to the adaptation of the left heart as assessed by sequential evaluations by echocardiography.\(^{29}\)

It is understandable from the history of extracorporeal gas exchange that, in the years when ECMO was associated with the most severe bleeding complications, neurologic insults, and cannulation problems, it was only indicated when all other measures failed. The new technologies allow a paradigm shift toward earlier indication and as an alternative to mechanical ventilation. It is the opinion of the author that these new principles are underserved and old decision making patterns still exist, leading to inferior results. Therefore, an overall trend for inferior outcomes is observed, leading to controversies about the use in bridging to transplantation.

**FUTURE PERSPECTIVES**

With the current improvements, ECMO therapy has matured and can be used in multiple configurations to support patients with respiratory and circulatory failure. The patterns of ECMO use from the time when ECMO technology evolved are still present. Bad experiences may lead to indications that are too late, leading to inferior outcomes.

The current technology allows the safe use of ECMO for a couple of weeks in venoarterial mode and several weeks in venovenous mode. Maturation of cannulation techniques has led to more percutaneous approaches and greater safety of operation, allowing operation of ECMO without a dedicated perfusionist present. Recent experience with extubated patients has led to a more modern approach and prolonged bridging times.\(^{30}\)

However, the environment of an intensive care unit is still required and hospital discharge on ECMO is not advisable.

The status is comparable with extracorporeal ventricular assist devices, when patients were not allowed to leave the hospital.

What are the limiting factors? Modern oxygenators need to be exchanged within a couple of weeks. One main reason is that perfusion within the oxygenators is not homogeneous, leading to low-flow areas, where blood clotting is likely. In addition, the oxygenators need proper positioning and cannot be turned upside down.

In order to create a real artificial lung, more modifications to oxygenators are required, to allow for position changes, better geometry to extend lifetime, and also to reduce the requirement for anticoagulation. Reliable and automatic regulation of continuous gas flow is an additional essential issue. Cannulation techniques have evolved as a percutaneous approach to be used in the intensive care unit. However, durable long-term conduits still need to be designed.

However, many groups are working to increase the safety of the circuits to achieve an interim step called an ambulatory lung.\(^{31}\)

With current oxygenator technologies, the development of full implantable systems is not feasible. To create an ambulatory artificial lung with extracorporeal components is necessary to allow patients to be discharged on such support systems. Such a system is needed for patients in lung failure who are not eligible for transplants.

When optimization of oxygenators, connection to reliable long-term pumps, regulated sweep gas flows, and suitable cannulae are developed and patients can be discharged, it will be possible to speak of a true artificial lung.

**REFERENCES**

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