Lung Transplantation

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29

The artificial lung

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Introduction

Over the last 50 years, we have seen remarkable progress in the area of cardiac support as it pertains to artificial organs. Artificial hearts and ventricular assist devices have changed the way we think about end-stage chronic heart failure. Yet the area of the artificial lung has lingered behind many of these accomplishments, not because the need was not recognized but because a full understanding of the engineering problems and the unique material requirements had not reached a level of development to be fully evident. This has changed, and at the centre of this progress has been a close collaboration between the clinician-scientist and the engineer. Here, the underlying concepts that are fundamental to gas exchange in blood have been instrumental in guiding research and in defining the haemodynamic impact on the host as it pertains to both extra- and intracorporeal artificial lung devices [1]. An overview of how this change has occurred and where it appears to be leading us is the subject of this chapter.

Background

Artificial lung technology can be broadly classified into current and next generation (Figure 29.1). What is presently available to clinicians derives from the pioneering work of John Gibbon and his contemporaries who, in the 1950s, developed the early prototypes of the heart–lung machine [2–5]. The goal of these pioneers was to support the heart and the lungs during heart surgery, and the objectives in the design of their oxygenators predicted many of the parameters for artificial lungs under current development. As Galletti and Brecher enumerated, the 'ideal' oxygenator must achieve the following [6]:

1 Oxygenation of venous by blood safely and efficiently bringing blood into close proximity to the oxygen source. The barrier posed by large diffusion distances must be overcome while providing oxygenation over a wide range of venous inlet conditions.
2 Carbon dioxide must be safely and efficiently eliminated to avoid both arterial hyper- and hypocapnia.
3 The oxygenator must avoid high shear stress, turbulence, and incompatible surfaces so as to minimize damage to blood cells, platelets and proteins.
4 The oxygenator must be able to perform its functions with a small priming volume.
5 The oxygenator must be easy and safe to operate, minimizing especially the possibility of air embolism.

These design objectives and early work evolved over the ensuing 40 years to the cardiopulmonary bypass circuits that we use today, with an excessive area of external, synthetic material exposed to the blood through tubes and cannulas, heat exchangers, and several square metres of membrane surface area in the oxygenator – overall a very bioactive environment conducive to the activation of the complement and coagulation cascades along with a host of inflammatory mediators. A goal, therefore, to improving any support systems in the future includes a means of reducing synthetic material interactions by reducing the bulk of material to which the blood is exposed. Next generation technology takes into consideration this fact and attempts to reduce the synthetic material exposed to blood whether in a paracorporeal or intracorporeal configuration.

ECMO

Although support of the lungs was integral to cardiopulmonary bypass during heart surgery, the emphasis was not on the lungs or on any form of targeted lung disease.

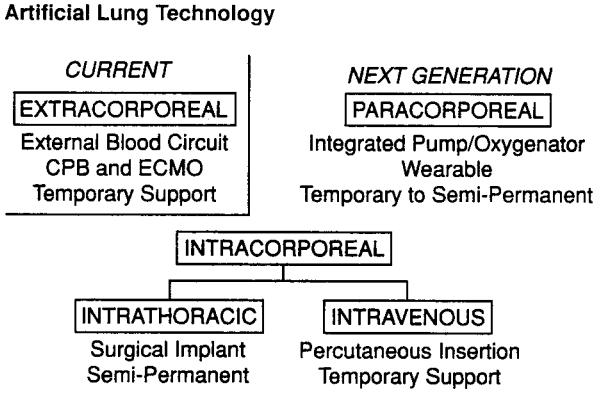

Figure 29.1 Artificial lung technology: current and next generation. CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation.

ECMO For Respiratory Failure (U. of Michigan Experience)

	Numbers	Mortality
Neonates	586	12%
Children	132	30%
Adults	146	44%

Figure 29.2 Recent results from the University of Michigan experience with extracorporeal membrane oxygenation.

Therefore, as attention turned to the lungs, a natural extension of cardiopulmonary bypass for heart surgery was extracorporeal membrane oxygenation (ECMO), which used the same approach and equipment but concentrated on support of the lungs. In spite of the fact that early trials with ECMO in the 1970s were not encouraging and had mortality rates as high as 80–90% in adult patients with the acute respiratory distress syndrome (ARDS), interest in extracorporeal lung support has continued [7,8]. More recent trials by experienced clinicians such as the Michigan group have lowered this mortality in the adult to 40–50% (Figure 29.2) [9]. This is still a challenge to be further improved upon but clearly a great deal has been learned since the early trials of ECMO that could be applied to the concept of an artificial lung.

Artificial lungs

Artificial lung development can be categorized broadly into devices that are intended as implantable or paracorporeal for prolonged and total support, and intravenous devices

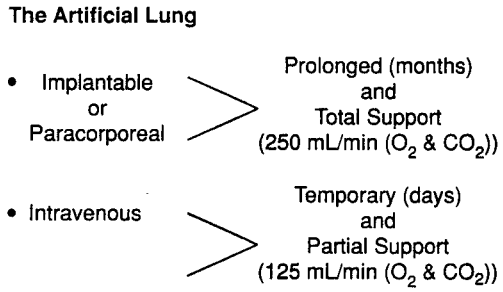

Figure 29.3 Artificial lung development.

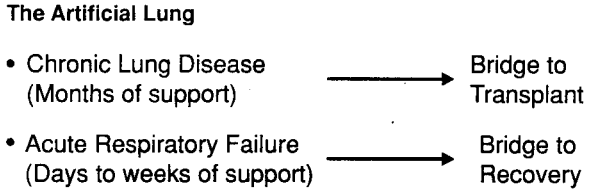

Figure 29.4 The artificial lung as a bridge to transplant or to recovery.

that will provide only temporary and partial support for the lung (Figure 29.3). At present, both implantable and paracorporeal devices would function as a bridge to transplant, whereas intravenous devices that provide only partial support can be used only in the setting where the natural lungs should recover either from a reversible disease or from an acute exacerbation of a chronic lung condition.

Whether one is considering total or partial support, the metabolic requirements for basal gas exchange are different. Total and prolonged support is usually conceptualized in the setting of chronic irreversible lung disease and the invasiveness involved with its implementation makes it less attractive as a temporary support measure (Figure 29.4). Partial support as a bridge to recovery, however, depends on the fact that, even with severe acute respiratory failure, there are areas of the lung that retain relatively normal architecture and compliance [10]. These areas can be accessed for their contribution to gas exchange along with what would in addition be provided by a partial support device. The extent to which partial support assists in gas exchange would enhance the ability to proportionally reduce tidal volumes and peak inspiratory pressures while managing the ventilator in the patient with acute respiratory failure. A 22% reduction in mortality was recently reported in ARDS patients treated with low tidal volume ventilation (6 mL/kg) when compared with the increased death rate with higher tidal volumes (12 mL/kg) [11]. The gas exchange goal of partial support of the lungs is also different from that of total support. Partial support attempts only to

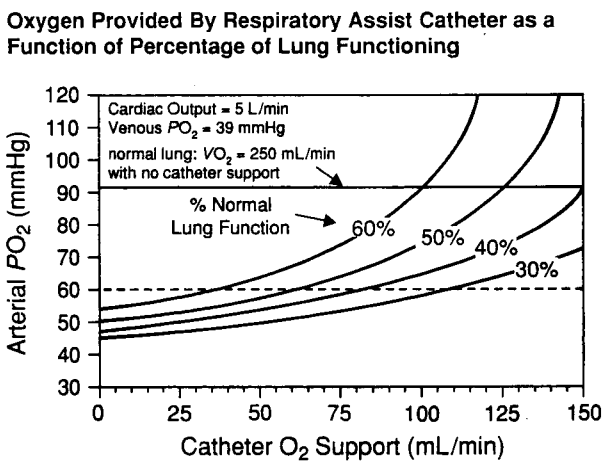

Figure 29.5 The amount of oxygen that a respiratory assist catheter positioned in the venous system would have to add to an adult patient with a normal hematocrit, cardiac output, and venous PCO_2 39 mmHg (1 mmHg ≈ 133.3 Pa) as determined by the amount of residual lung still functional.

supplement, in the case of oxygen, by adding enough O_2 to the patient's blood to raise the pressure of oxygen (PO_2) to 60 mmHg (8 kPa) or a saturation of 90% or greater. Adding 100–125 mL O_2/min to the patient represented graphically in Figure 29.5 would be life sustaining, even though only 30% of the patient's lung is functional.

Basic principles for artificial lungs

Before considering examples of artificial lungs that are at various stages of development, it is important to remember several principles of gas exchange, for both O_2 and CO_2, as they would apply to any artificial lung. An in-depth review of these concepts and the theoretical basis behind them can be found in a recent review [1]. The more important of these principles are summarized here:

1 Positioned within the bloodstream, microporous hollow fibre membranes, the working component for gas exchange of any artificial lung, function by diffusion gradients determined by the partial pressures of O_2 and CO_2 on either side of the hollow fibre membrane wall. The gas flow in the lumen of these hydrophobic hollow fibres is 100% oxygen, here represented as 760 mmHg (101 kPa) at sea level (Figure 29.6), which allows oxygen to enter the blood. The concentration of carbon dioxide within the blood promotes entry into the fibres and removal with the exhaust gas. These hollow fibres are usually coated with a micrometre thick or thinner layer of a silicon polymer that prevents plasma from leaking into the fibre

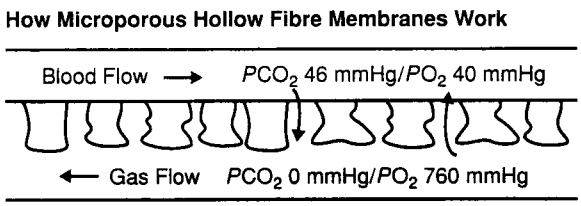

Figure 29.6 Diffusion gradients for O_2 and CO_2 as established by blood flow on one side of the wall of a hollow fibre membrane and gas flow on the opposite side. Oxygen diffuses into the blood and CO_2 into the hollow fibre membrane lumen.

after prolonged use. In addition, heparin is bonded to the fibre lumen surface to enhance thrombo-resistance and in general promote a reduced reactive response engendered by any artificial surface.

2 Gas transfer for oxygen and carbon dioxide from the hollow fibre lumen of an artificial lung to the blood and vice versa is determined at both the membrane level and the blood level by permeability coefficients (K) for each gas, which take into account how the gas diffuses initially in its gaseous (K_g) environment, when it encounters the membrane (K_m) and finally when it reaches the liquid–blood barrier (K_l). The mass transfer for oxygen (KO_2) can therefore be expressed as: $KO_2 = K_g + K_m + K_l$. Diffusion of a gas in a gaseous environment is essentially unimpeded, and therefore the only two components of the equation that are of practical importance would be diffusion through the hollow fibre membrane wall (K_m) and diffusion on the liquid side (blood side) of the fibres (K_l). Thus liquid-side and membrane gas permeabilities dictate overall gas exchange and represent serial transport processes with the micrometre thin liquid boundary layer (K_l) adjacent to the fibre wall representing the predominant resistance to gas diffusion.

3 Agitated blood flow as provided by a pulsating balloon leads to improved gas exchange when compared to unagitated flow because it enhances the permeability coefficient (K) for oxygen and carbon dioxide, especially as it relates to its effect in improving permeability at the liquid boundary layer (K_l).

4 Fibres woven into constrained fibre mats (as compared to free fibres) enforce a precise spacing between fibres, increasing the uniformity and reproducibility of balloon-generated blood flow through the hollow fibre membrane fabrics and eliminating the potential for fibres to clump together once exposed to blood.

5 Finally, the gas exchange can be improved if the blood flows at right angles to the hollow fibres, a condition known as cross-flow, which is significantly more efficient

Design Specifications for an Implantable Artificial Lung

- Capable of transferring > 200 mL/min of O_2 and CO_2
- Minimal shunting
- Blood-side pressure loss < 15 mmHg at blood flow rates of 4–6 L/min
- Low gas-side pressures to avoid gas embolism
- Compliant housing chamber
- Size and configuration to fit in hemithorax
- Thromboresistant and otherwise biocompatible
- Reliability and durability to function at least 2–3 months

Figure 29.7 Specifications for an implantable artificial lung designed for total support.

at O_2–CO_2 transfer than parallel flow, where the blood flow is parallel to the fibres.

Keeping these principles in mind, design specifications for an implantable total artificial lung are listed in Figure 29.7 [12]. Most of these specifications are obvious, such as biocompatibility, gas transfer requirements, size, and function for two to three months. Other specifications require comment such as blood-side pressure loss, which must be as low as possible to avoid failure of the right ventricle as it provides inflow to the oxygenator. Also, the need for a compliant chamber as part of the oxygenator is important when one remembers that the natural lungs work under conditions of low resistance and high compliance. Both of these conditions are favourable to the right ventricle, and compliance allows red cells to be distributed to the pulmonary capillaries both in the systolic and diastolic phases of the cardiac cycle.

Next-generation artificial lungs

Artificial lung technology for the next generation has proponents for both paracorporeal and intracorporeal implementation (Figure 29.8). The paracorporeal approach involves invasively sewing grafts onto the right atrium and pulmonary artery or the right atrium and aorta, bringing these grafts through the chest wall and attaching them to an integrated pump oxygenator (Figure 29.9). Paracorporeal devices are intended to be tethered by very short grafts to the patient and to be wearable. In reality, they are simplified forms of ECMO or $ECCO_2R$ (extracorporeal carbon dioxide removal). The oxygenator, however, is smaller and more efficient, and there is less synthetic material exposed to the blood. A paracorporeal device that is being developed at the University of Pittsburgh has a rotating disk of hollow fibres that spins and propels the blood while oxygenating and removing CO_2 (Figure 29.10). The ability

Artificial Lung Technology

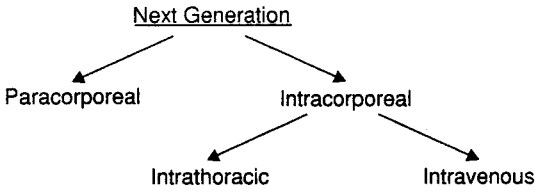

Figure 29.8 Next generation artificial lung technology.

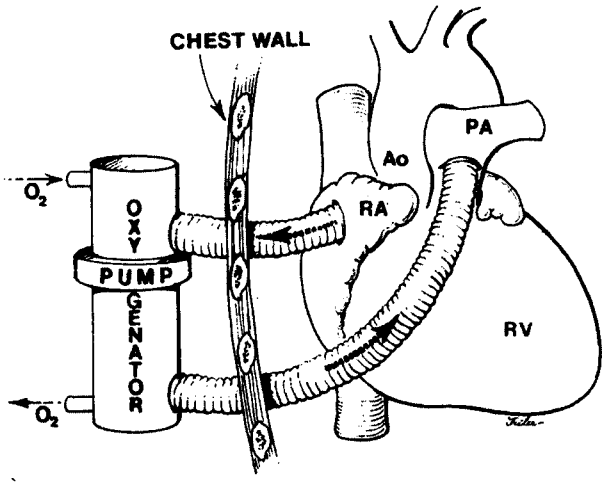

Figure 29.9 Paracorporeal configuration for total pulmonary support. The integrated pump-oxygenator is tethered to the chest wall. PA, pulmonary artery; RV, right ventricle; RA, right atrium; AO, aorta.

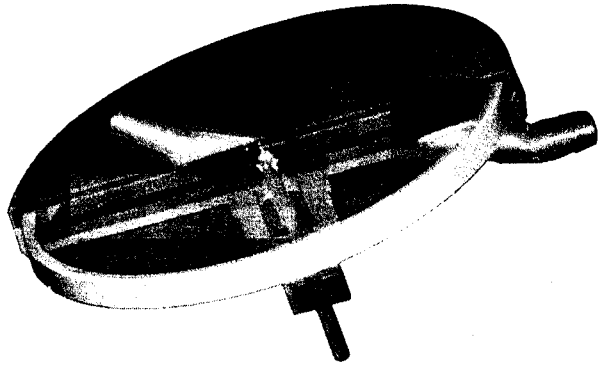

Figure 29.10 A spinning disk oxygenator that both oxygenates and propels blood, being developed as a paracorporeal device.

to have access to the oxygenator should it fail is attractive. Also, it becomes clear that, with a paracorporeal approach, one is following down the same path that cardiac ventricular assist devices did years ago. A paracorporeal