

Lung Transplantation

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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.

Artificial Lung Technology

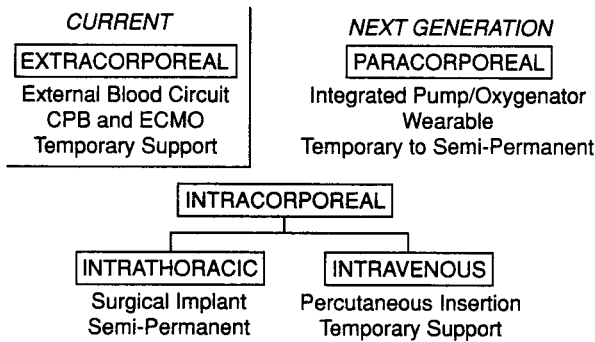


Figure 29.1 Artificial lung technology: current and next generation. CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation.

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

The Artificial Lung

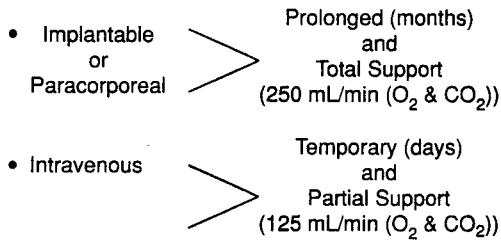


Figure 29.3 Artificial lung development.

The Artificial Lung

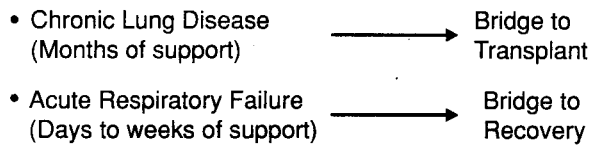


Figure 29.4 The artificial lung as a bridge to transplant or to recovery.

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

Oxygen Provided By Respiratory Assist Catheter as a Function of Percentage of Lung Functioning

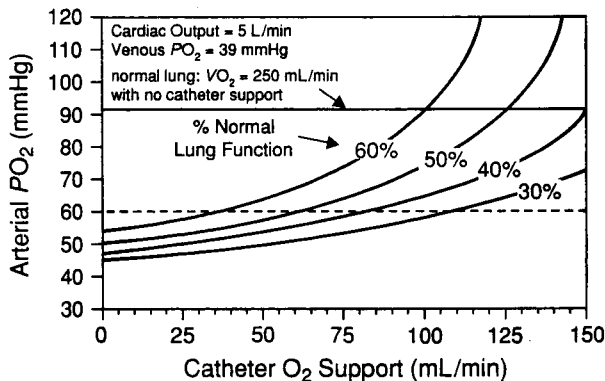


Figure 29.5 The amount of oxygen that a respiratory assist catheter positioned in the venous system would have to add to an adult patient with a normal hematocrit, cardiac output, and venous PCO_2 39 mmHg (1 mmHg \approx 133.3 Pa) as determined by the amount of residual lung still functional.

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

How Microporous Hollow Fibre Membranes Work

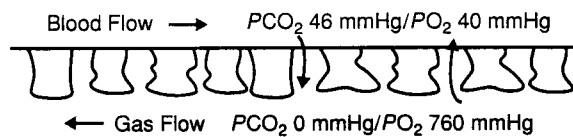


Figure 29.6 Diffusion gradients for O_2 and CO_2 as established by blood flow on one side of the wall of a hollow fibre membrane and gas flow on the opposite side. Oxygen diffuses into the blood and CO_2 into the hollow fibre membrane lumen.

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 (K_{O_2}) can therefore be expressed as: $K_{O_2} = K_g + K_m + K_l$. 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 O₂ and CO₂
- 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 O₂–CO₂ 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 ECCO₂R (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 CO₂ (Figure 29.10). The ability

Artificial Lung Technology

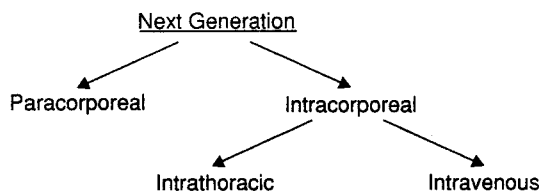
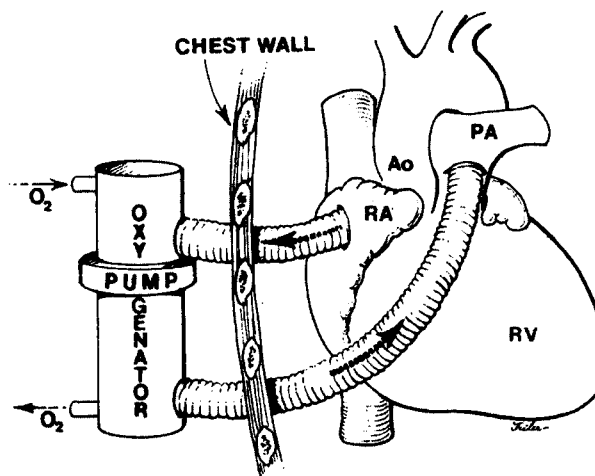


Figure 29.8 Next generation artificial lung technology.



Paracorporeal

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.

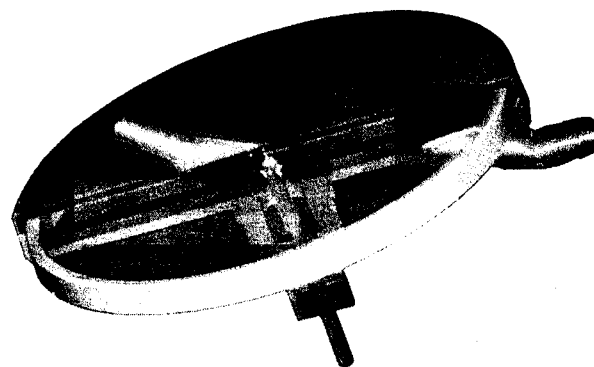


Figure 29.10 A spinning disk oxygenator that both oxygenates and propels blood, being developed as a paracorporeal device.

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

device that is being developed by Tatsumi and colleagues in Japan has been able to provide total gas exchange requirements in goats for five to seven days with the animals ambulatory [13]. The benefits of a paracorporeal device include, therefore, its compact size and its integrated functions.

With intracorporeal or implantable devices, there are two choices – intrathoracic or intravenous (Figure 29.8). The intrathoracic requires a surgical implant, the oxygenator is intended to be internally positioned with oxygen lines exiting the left chest. It is a semi-permanent support as a bridge to transplant, less suitable for temporary support in its present configuration because of the invasiveness involved. Although intended for intracorporeal use, these devices are tested in the research laboratory, with the oxygenator positioned paracorporeally, although connected to the native vasculature as if the device were intrathoracic. Intrathoracic insertion involves placing the device either in series (Figure 29.11) where the right ventricle drives the blood through the oxygenator and then returns it to the distal pulmonary artery with no communication between the proximal and distal pulmonary artery, or the oxygenator can be placed in parallel where blood is returned to the left atrium (Figure 29.12). A third possibility not represented is that blood would be returned from the oxygenator to both the pulmonary artery and the left atrium in a so-called hybrid configuration. A distinct advantage of the hybrid configuration is that, in providing some pulmonary

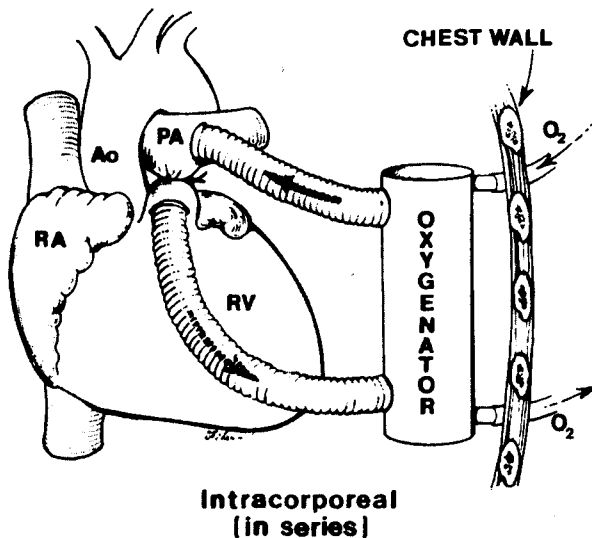


Figure 29.11 Intracorporeal, in series artificial lung. A band between the proximal and distal pulmonary artery assures that all right ventricular output is diverted to the oxygenator. For abbreviations, see Figure 29.9.

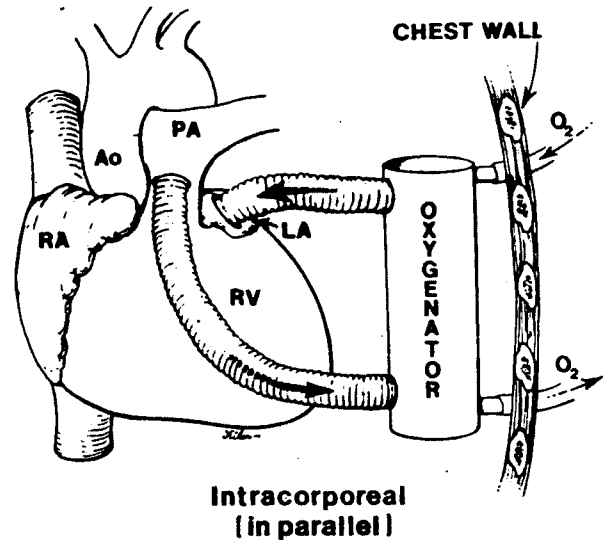


Figure 29.12 Intracorporeal, in parallel, artificial lung. Partial banding of the distal pulmonary artery (not shown) controls the volume of blood diverted to the oxygenator. For abbreviations, see Figure 30.9.

artery flow, it helps to maintain nongas exchange properties of the lung as they pertain to metabolic and hormonal functions.

Two groups have devoted a considerable effort in the development of an intrathoracic lung, the group at the University of Michigan under the leadership of Drs Bartlett, Montoya and Lynch, and the group at Northwestern University under the leadership of Drs Mockros and Vaslef (present address, Duke University Medical Center). An example of the Michigan lung is seen in Figure 29.13, with its contained attachment grafts and, in its most recent configuration, a compliant external housing made of an elastomir, which allows for improved haemodynamics as far as the right ventricle is concerned as it ejects into a compliant chamber before the blood is distributed to the oxygenator [14–18]. Sheep have been totally supported for up to seven days with the Michigan lung with no pump except the right ventricle to drive the blood. These devices are frequently called 'pumpless devices' because there is no artificial blood pump. Mockros et al. have also developed an intracorporeal-intrathoracic lung also with a compliant casing [14, 19–22]. This pumpless artificial lung (Figure 29.14) has been tested mainly in a parallel configuration with a proximal graft sewn to the pulmonary artery that receives the output of the right ventricle and the distal graft sewn to the left atrium. By banding the distal pulmonary artery, the amount of blood directed through the oxygenator can be controlled. Total gas exchange in

Michigan Lung

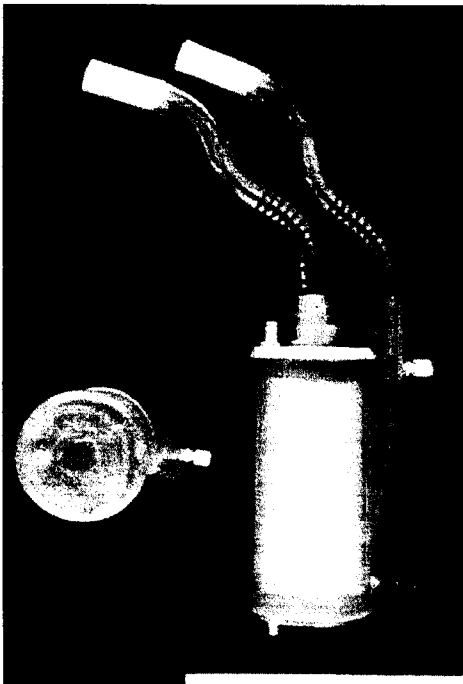


Figure 29.13 The Michigan intracorporeal lung. A compliant external housing can be seen receiving the graft connected to the proximal pulmonary artery (not shown). The tubing and graft exiting the centre of the oxygenator connects to the distal pulmonary artery.

A Thoracic Artificial Lung

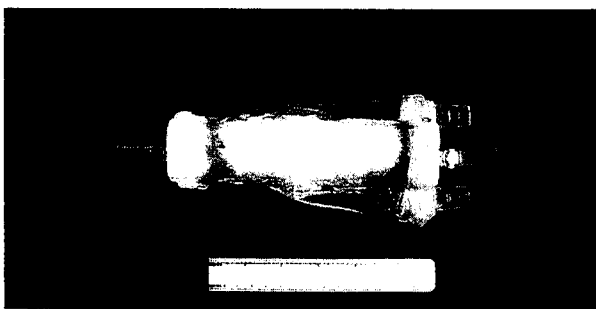


Figure 29.14 The Northwestern intracorporeal lung. This most recent prototype shows very clearly the compliant external layer surrounding the fibre bundle that receives the output of the right ventricle.

The Artificial Lung (Areas of Concern)

	Intracorporeal (Intrathoracic Artificial Lung)	Paracorporeal (Artificial Lung)
Invasiveness	+	+
RV Strain	+	-
Need for Blood Pump	-	+
Blood Trauma	-	+
Blood side Pressure Loss (oxygenator flow)	+	-
Potential for Mechanical failure	-	+
Potential for Oxygenator failure	+	+

Figure 29.15 A comparison of intracorporeal and paracorporeal devices. Intracorporeal devices, although tested in the research laboratory outside the chest, are intended for intrathoracic placement. RV, right ventricular.

pigs has been provided for over 24 hours with the artificial lung providing complete support. So, comparing intrathoracic (implantable) lungs with paracorporeal lungs that are intended as a wearable device outside the body, the following points can be made (Figure 29.15):

- 1 They are both significantly invasive.
- 2 Right ventricular strain is not a concern with a paracorporeal device driven by an external pump.
- 3 Blood trauma over a prolonged period of time is of greater concern with paracorporeal devices because of the higher shear stresses potentially involved with the pump function.
- 4 Blood-side pressure losses are a concern if the right ventricle is the driving force for propelling blood through the oxygenator.

Both paracorporeal and intracorporeal (implantable) devices are being readied for clinical trials in the next three to five years.

Artificial lungs can best be thought of as those that are being developed as bridge to transplant and those that are intended as a bridge to recovery for short-term use in the treatment of reversible, acute respiratory failure. Short-term support with the intracorporeal artificial lung is the only technology that has been tested in humans and occurred when the intravascular oxygenator (IVOX) developed by J. D. Mortensen underwent clinical trials, following its insertion into the human vena cava, in the early 1990s [23] (Figure 29.16). The device consisted of a bundle of microporous hollow fibre membranes through which oxygen was extracted under vacuum. Devices tested clinically ranged in membrane surface area from 0.21 to 0.51 m². The hollow fibre membranes of the IVOX were crimped

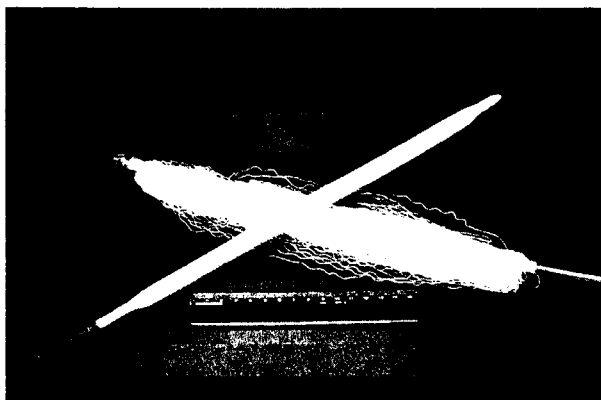


Figure 29.16 The IVOX and the respiratory assist catheter (HC) juxtaposed. The IVOX as seen here was used in clinical trials [23].

along their length in an effort to produce secondary fluid currents around the fibres. Otherwise, the device resided in the central venous system and was dependent upon passive parallel flow past the fibres to promote gas exchange. The fibres were free-floating and, lacking constraint, randomly assumed their position, including the propensity for some fibres to clump together once placed in the venous system. The polypropylene microporous hollow fibre membranes of the IVOX had an ultrathin siloxane coating, permeable to O_2 and CO_2 , but impermeable to water, thus preventing the membrane pores from being subject to plasma leakage. A second coating applied to all components of the IVOX was a covalently bonded heparin derivative intended to increase the thrombo-resistance of the device. The IVOX is the only intracorporeal device to have undergone phase I and phase II human clinical trials in the early 1990s. The phase I trials established the safety for introducing an intravascular oxygenator in humans, and the phase II trial examined the clinical efficacy and gas exchange performance for this device. A total of 160 patients from the USA and Europe was studied. Once entry criteria for acute lung failure were met, patients underwent a right internal jugular or femoral vein cutdown for device implantation. The largest size IVOX ($0.21\text{--}0.51\text{ m}^2$ membrane surface area) was chosen for implantation according to the vena cava size determined by ultrasound and the suitability of the access vein. The IVOX was furled during insertion and guided over a wire into position in the inferior vena cava, right atrium, and superior vena cava, where unfurling occurred to fully expose the hollow fibre membranes to the returning venous blood. Heparinization (activated clotting time $180\text{--}200\text{ s}$) was maintained during use of the device. After activation of the IVOX, attempts were made to reduce the fraction of oxygen in inspired gas ($F_{I}O_2$) and minute ventilation as long as blood gases could

be maintained, with oxygen saturations over 90%. The IVOX trials confirmed earlier animal experiments and proved the feasibility of extended intravenous respiratory gas exchange in severe acute respiratory failure patients [23]. In some patients, peak O_2 and CO_2 transfer rates varying between 40 and 70 mL/min were noted. During IVOX utilization, some clinical trial patients showed improvement in blood gas partial pressures and the ability to reduce the intensity of mechanical ventilation. The IVOX functioned in some patients for weeks without adverse effects. In these severely ill patients with acute respiratory failure, 60% survived to have the device removed, but only 30% improved to a point where mechanical ventilation could be discontinued. These same patients were hospital survivors and were discharged for an average 30% survival rate. Further trials of the IVOX were not pursued because of failure to show improvement in survival compared with historical controls. Food and Drug Administration consideration was not in question because of the lack of concurrent controls and randomization in the clinical trials. Nevertheless, as the first and only trial of a short-term intravenous oxygenator designed for support of the patient while the lungs recover, the IVOX provided valuable evidence that gas exchange (O_2 and CO_2) occurs in humans, but at a level that at the very best met only 30% of patients' needs and was frequently not reproducible. Very significantly, the trial demonstrated that hollow fibre membranes could reside in the human vena cava for prolonged periods without haemodynamic compromise or thrombus formation. Those involved in the clinical trial of the IVOX felt that, in order to be clinically useful, an intravenous respiratory assist device would have to supply 50% of basal metabolic needs (Figure 29.5), be relatively easily insertible, and demonstrate consistent and reproducible gas exchange in patients with acute respiratory failure. These recommendations for improvements have been instrumental in our approach to designing devices dedicated to gas exchange in the venous system.

Gas exchange within the venous system

Our interest in the development of an intravenous hollow fibre membrane lung-assist device, the Hattler Respiratory Support Catheter, or Hattler Catheter (HC)* began

* Also reported in previous publications as the Intravenous Membrane Oxygenator (IMO) for use in intracorporeal membrane oxygenation. The catheter-based device, however, exchanges both oxygen and carbon dioxide. Simply describing it as a membrane oxygenator is not sufficient. It is intended for temporary respiratory support in cases of acute respiratory failure.

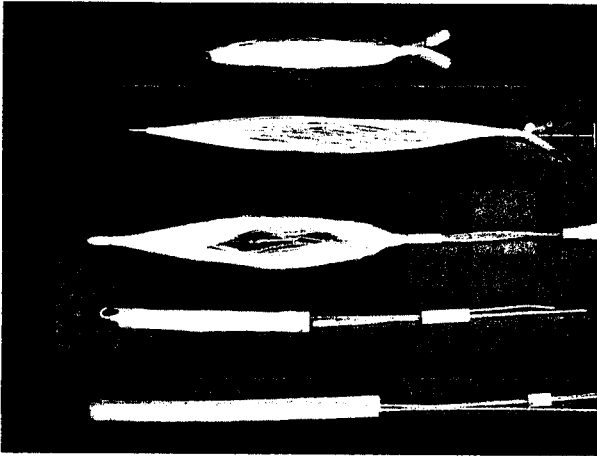


Figure 29.17 An example of various prototypes tested during the development of the respiratory assist catheter (HC). Prototype 'A' was the earliest prototype, tested in 1984.

with early prototype design and animal testing in 1984 [1]. These initial efforts were primitive compared to devices now being tested and involved bulky bundles of hollow fibres through which 100% oxygen would flow (Figure 29.17). Both ends of each hollow fibre were potted into a single proximal manifold so that O_2 and CO_2 exchange would occur as the oxygen traversed the full length of the fibre (Figure 29.17, example A). To avoid gas emboli, oxygen was extracted by vacuum through the fibres. In vivo testing of these devices following surgical placement in the vena cava of dogs revealed that O_2 and CO_2 exchange occurred, but at levels that were not considered of clinical value [1]. It became apparent during these early experiments that passive and undisturbed flow of blood in the vena cava, flow that was largely parallel to the hollow fibres, did not provide adequate gas exchange. Our efforts have evolved, therefore, over the ensuing years in defining conditions that allow for better mixing of the blood with the hollow fibre membrane bundle and in providing cross-flow to the fibres that are represented within the hollow fibre membrane mats [1, 24–40]. The devices on which we have concentrated our efforts have always been intended to be catheter based, and introduced and removed through either the jugular or the femoral vein. Once in the venous system, the goal has been to provide up to 50% of the basal oxygen and carbon dioxide exchange requirements in the adult patient over a 7–10 day interval of support (Figure 29.5). In reality, shorter intervals of support may be of benefit. A recent National Institutes of Health trial has provided evidence that, as early as 48 hours following the institution of a lung protective strategy, an improvement in the pulmonary status of ARDS patients can be seen [11]. Zwischenberger et al.

have confirmed these clinical findings in an ovine smoke inhalation model of acute lung injury [41]. Our goals, therefore, in developing a respiratory assist catheter have been as follows:

- 1 Provision of active mixing of blood at right angles and across the hollow fibre membranes.
- 2 Provision of O_2 and CO_2 exchange at approximately 125 mL/min for both (50% of basal requirements) with the ability of CO_2 exchange to progressively increase with permissive hypercapnea, as is seen with reduced tidal volume ventilation as a lung protective strategy in the therapy of acute respiratory failure.
- 3 The device must maintain its gas exchange functions for 5–10 days in the therapy of patients with reversible acute lung injury.
- 4 The device must be relatively thrombo-resistant and resistant to plasma leakage into the hollow fibres by incorporating a thin polymer coating (less than $1 \mu\text{m}$) to which a heparin molecule is attached. Under these conditions, and with a device that actively moves blood through the fibres, the need for full anticoagulation is decreased.
- 5 The device must be made of constrained hollow fibre mats, thus preventing fibre clumping. Fibres are thus maintained in a consistent configuration regardless of their contained vessel, which enhances reproducible gas exchange for devices of identical membrane surface area.
- 6 The device, although initially requiring a cut-down to directly expose the vein for insertion, should eventually be designed for percutaneous insertion.

The catheter-based device that has been designed to meet these requirements is shown in Figure 29.18. For comparison, the IVOX that was used in the clinical trials in the early 1990s and the respiratory assist catheter (HC) are

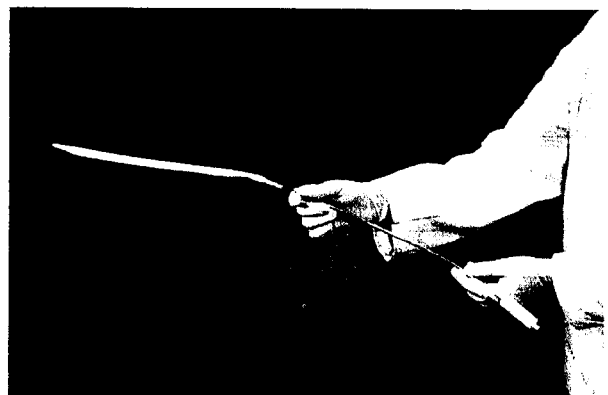


Figure 29.18 The respiratory assist catheter (HC) being held by a technician.

Operational Features of the IMO

- Pulsating balloon within device captures normal vena cava blood flow and drives it across hollow fibre membranes.
- This 'active' mixing leads to more gas transfer (O_2 and CO_2), less required fibre area. Better artificial respiration.
- Constrained fibre bundles are designed not to occupy the entire cross-section of the vena cava.

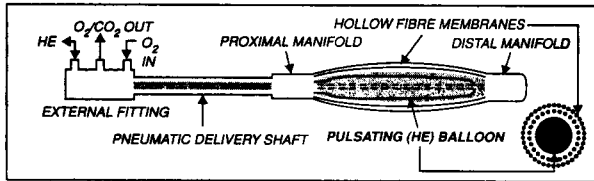


Figure 29.19 The respiratory assist catheter (HC) in position.

Description of IMO

- Insert through femoral or jugular vein
- Resides in superior and inferior vena cava, incorporating right atrium
- Oxygenates venous blood and removes carbon dioxide before blood reaches the lungs

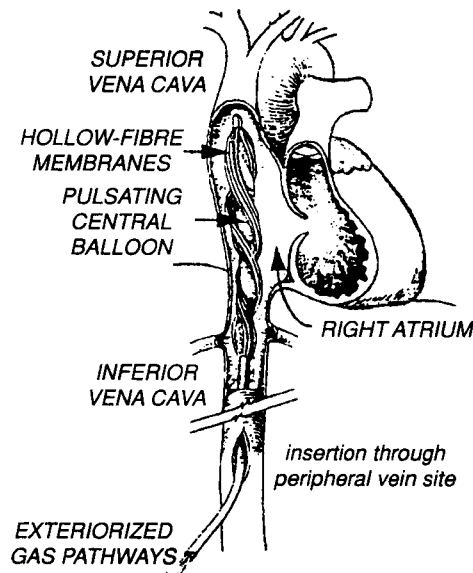


Figure 29.20 Operational features of the respiratory assist catheter (HC or IMO) (see text).

superimposed on each other as seen in Figure 29.16. A schematic of the respiratory assist catheter (HC) that is being readied for clinical trials in Europe in 2004 is shown in Figure 29.19 and how it would sit in a patient in Figure 29.20. Hollow fibre membrane mats surround a central balloon in concentric layers. These hollow fibres are potted into proximal and distal manifolds at each end of the device. The gas exchange component therefore sits at the end of a catheter through which 100% oxygen flows to the proximal manifold and is extracted by vacuum from the distal manifold after traversing down the length of each hollow fibre. A separate port provides helium to the balloon

and is driven by a console capable of completely inflating and deflating the balloon at 300 beats/min or greater. The device is inserted at present through a cut-down on the common femoral or internal jugular vein where it then occupies the inferior vena cava, right atrium, and superior vena cava positions. Biocompatibility of the HC is dependent on reducing sheer stress and the potential for blood clotting and fibrin and cellular deposition on the surface of the hollow fibre membranes. A heparin bond linked to a $<1 \mu\text{m}$ thick siloxane coating covering the pores of the hollow fibre membrane has been used to enhance biocompatibility at the blood-membrane interphase. In addition, we

have demonstrated that nitric oxide as part of the sweep-gas within the hollow fibres markedly diminishes cellular and platelet deposition on the membrane surface [30]. Other than the use of specialized coatings and controlling the composition of the oxygen mixture being vacuumed through the hollow fibres, a general principle applied to the design of the HC has been to minimize shear stress as a means of promoting biocompatibility. Flow in the vena cava is largely laminar where shear stresses occur because adjacent fluid layers travel at different speeds. Fluid in the centre of the stream moves more quickly than fluid near the vessel wall. Therefore shear rate is highest at the wall and lowest at the centre, where friction is minimal. Flow velocity profiles visualized in the laboratory have shown that balloon pulsation not only improves gas exchange but also disrupts the layer of fluid next to the vessel wall (area of high shear stress), therefore reducing overall shear and potential damage to the formed elements of blood (Figure 29.21). Since the HC depends on blood flowing freely around the device where blood is captured and directed towards the fibres by balloon pulsation, very low blood-side pressure drops across the device (2–3 mmHg) have been noted in large animal implants. By reducing the pressure drop, a reduction in shear stress at the same flow rate is noted, which promotes overall biocompatibility.

Once inserted in the venous system, the respiratory assist catheter (HC) occupies the superior and inferior vena cava, spanning the right atrium. Studies in calves have shown that, while carbon dioxide exchange was studied, the average carbon dioxide flux was 305 ± 25 mL/min per m^2 with the device in the right atrium whereas in the inferior vena cava position it was approximately 265 ± 18 mL/min per m^2 . This is not unanticipated, since under these latter

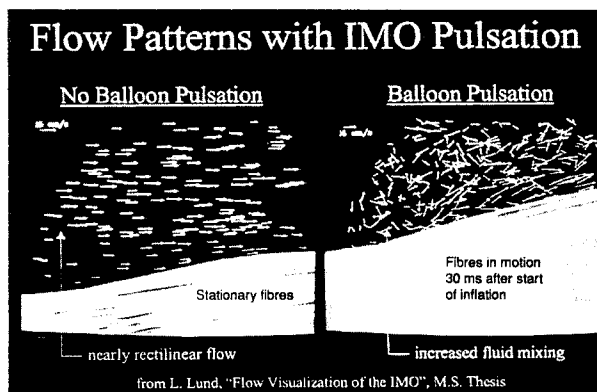


Figure 29.21 The effect of balloon pulsation with a respiratory assist catheter positioned in a flow visualization chamber seeded with fluorescent particles. The computer assigns vectors to each particle's motion.

Ex-Vivo Vena Cava Circuit

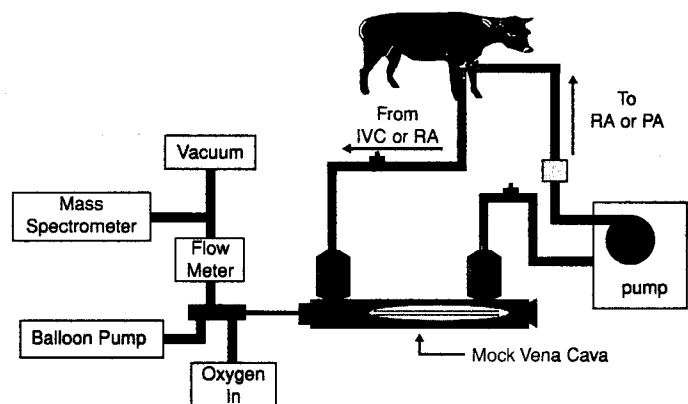


Figure 29.22 Ex vivo circuit for testing the respiratory assist catheter (HC). Blood from the cow's right atrium (RA) fills a mock vena cava where the HC is positioned. Oxygenated blood is then returned to the pulmonary artery (PA). IVC, intravenous catheter.

conditions, blood entering the right atrium from the upper body would not be exposed to the gas exchange fibres, creating a significant shunt fraction with reduced overall gas exchange. With the HC in the desired position, the total hollow fibre membrane surface area that the blood is exposed to is no more than $0.43 m^2$ of membrane surface area. This decreases the magnitude of blood–synthetic material interactions.

In addition to extensive bench-testing, the respiratory assist catheter (HC) has been tested in ex vivo circuits using calves 90–100 kg in weight (Figure 29.22). The HC is positioned in a mock vena cava, which receives blood from the right atrium. The blood, once oxygenated, is pumped back to the pulmonary artery. Continuous gas exchange is measured with a mass spectrometer. Since the IVOX implanted in humans was tested under similar protocols a comparison can be made to the respiratory assist catheter (HC). As seen in Figure 29.23, with no pulsation, the IVOX and respiratory assist catheter (IMO) perform similarly in an ex vivo circuit. However, with balloon pulsation, the respiratory assist catheter significantly increases its gas exchange capability both ex vivo and in vivo following implantation into the calf.

For in vivo testing of the HC over one to five days, we have used calves extensively monitored for haemodynamic and gas exchange parameters. Here the catheter is inserted through the jugular vein. In vivo carbon dioxide removal progressively increases with balloon pulsations up to 300 beats/min (Figure 29.24). Results of short-term implants in cows are seen in Figure 29.25 comparing devices

IMO Gas Exchange Performance

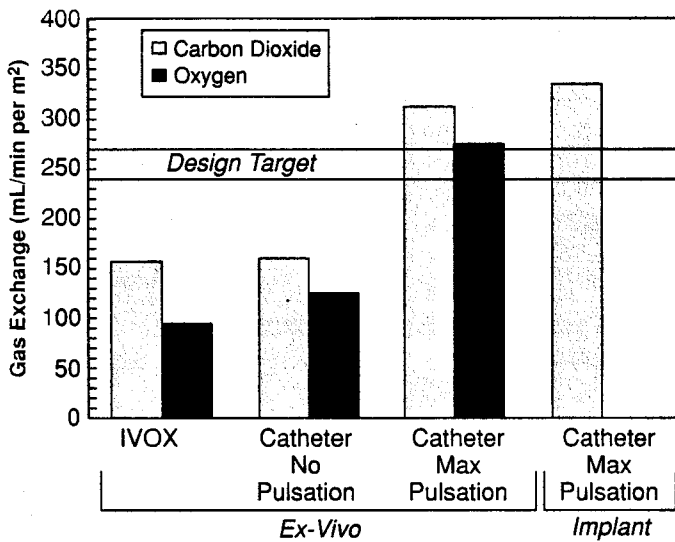


Figure 29.23 O₂ and CO₂ exchange in the cow both ex vivo and in vivo (implant). With no balloon pulsation, the IVOX and the IMO (HC) perform equally. With balloon pulsation (300 beats/min), the HC significantly increases its gas exchange performance both ex vivo and in vivo.

Acute In Vivo Implantation of IMO

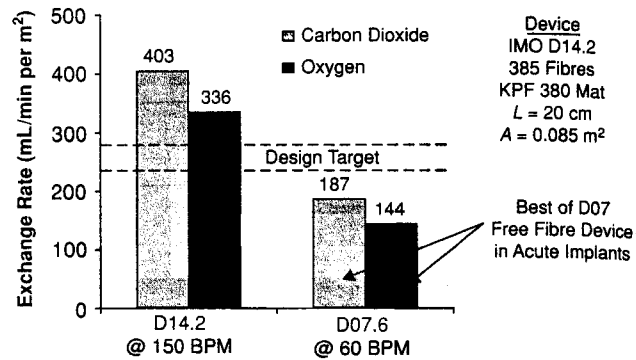


Figure 29.25 In vivo gas exchange performance for two respiratory assist catheters tested in cows. Devices made of fibre mats uniformly perform significantly better than devices made of free floating, non-constrained fibres. *L*, length; *A*, area. BPM, beats/min.

haemodynamics, including cardiac output, mean arterial pressure, pulmonary artery pressure, and venous pressures do not change with positioning of the device in the venous system. This is because the device is chosen purposely not to occupy the entire diameter of its containing vessel (i.e. vena cavae and right atrium). Unimpeded flow around the device is essential in order to allow the pulsating balloon to capture and direct blood towards the fibre mat in a cross-flow configuration. Plasma-free haemoglobin rises early in these chronic experiments but returns to levels of 2–4 mg/dL. Autopsies of these animals showed no distal emboli or end-organ failure.

If permissive hypercapnoea is allowed to occur in the calves, the device will increase its CO₂ output as the PCO₂ rises and the minute ventilation drops, raising the possibility that the device could function effectively in patients as tidal volumes are reduced in the therapy of acute respiratory failure (Figure 29.26). Diseases where temporary support may be beneficial are listed in Table 29.1.

Permissive Hypercapnea in the Calf and CO₂ Exchange Rate With the Hattler Catheter

PCO ₂ (mmHg)	VCO ₂ (mL/min per m ²)	Minute Ventilation (L/min)
50	320–28	20
60	426–32	—
70	480–45	11

Figure 29.26 The respiratory assist catheter (HC) increases its CO₂ output as the PCO₂ rises with decreased minute ventilation.

In Vivo CO₂ Removal vs. Beat Rate

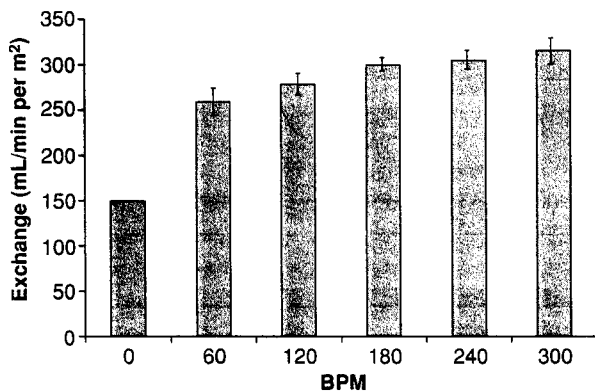


Figure 29.24 In vivo CO₂ gas exchange in the cow as determined by balloon pulsation rate (BPM, beats per minute).

constructed from constrained fibre fabric mats with devices made from free-floating, nonconstrained fibres. Free fibre devices have diminished gas exchange capabilities largely because groups of free floating fibres tend to clump together once in the bloodstream, creating fibres at the centre of the clump that are not exposed to blood.

In chronic experiments carried out over four to five days, gas exchange is maintained constant in the awake and standing animal over this entire time interval [42]. Here,

Table 29.1. Disease states where temporary support of the lungs may be beneficial

Severe acute respiratory failure
Hypercapnic respiratory failure
Medically resistant status asthmaticus
Toxic (chemical) damage to the lungs
In the perioperative lung transplant interval
Persistent pulmonary air leaks
Any setting where reduced ventilation would be beneficial, including patients difficult to wean from the ventilator
Severe reactive pulmonary hypertension with right ventricular failure

Summary

Technology to implement temporary and partial support of the lungs is available today but awaits clinical trials. Technology for chronic (months) and total support of the lungs is being actively investigated with a goal of clinical trials in the next three to five years. Beyond where we are now, the future of artificial lungs will be part of the exciting new field of hybrid organs with genetically engineered stem cells mounted to altered biomaterials (Figure 29.27). This area is with us today in the laboratory and will be part of our future in the care of patients with acute and chronic lung diseases.

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REFERENCES

- Hattler BG, Federspiel WJ. Gas exchange in the venous system: support for the failing lung. In: Vaslef SN, Anderson RW, eds. *The artificial lung*. Landes Bioscience, Austin, TX, 2002.
- Gibbon JH, Kraul CW. An efficient oxygenator for blood. *J Lab Clin Med* 1941; **26**: 1803-1809.
- Gibbon JH. Application of a mechanical heart-lung apparatus to cardiac surgery. *Minn Med* 1954; **37**: 171-180.
- DeWall, Warden HE, Read RC, et al. A simple expendable artificial oxygenator for open heart surgery. *Surg Clin North Am* 1956; **36**: 1025-1034.
- McCaughan JS, Weeder RR, Schuder JC, et al. Evaluation of new non-wettable microporous membranes with high permeability coefficients for possible use in a membrane oxygenator. *J Thorac Cardiovasc Surg* 1969; **40**: 574-581.
- Galletti PM, Brecher GA. Bubble oxygenation and membrane oxygenation. In: Heart-lung bypass: principles and techniques of extracorporeal circulation. Grune and Stratton, New York, 1962: 61-78, 108-120.
- Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure: a randomized prospective study. *JAMA* 1979; **242**: 2193-2196.
- Gattinoni L, Pesenti A, Masheroni D, et al. Low-frequency positive pressure ventilation with extracorporeal CO₂ removal in severe acute respiratory failure. *JAMA* 1986; **256**: 881-886.
- Bartlett RH, Roloff DW, Custer JR, et al. Extracorporeal life support: the University of Michigan experience. *JAMA* 2000; **283**: 904-908.
- Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000; **342**: 1334-1349.
- The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342**: 1301-1308.
- Vaslef SN. Implantable artificial lungs: fantasy or feasibility. *New Surg* 2001; **1**: 116-126.
- Tatsumi E, Takewa Y, Akagi H, et al. Development of an integrated artificial heart-lung device for long-term cardiopulmonary support. *ASAIO J* 1996; **42**: M827-M832.
- Vaslef SN, Anderson RW. Development of an implantable artificial lung. In: Vaslef SN, Anderson RW, eds. *The artificial lung*. Landes Bioscience, Austin, TX, 2001.
- Fazzalari RL, Montoya JP, Bonnell MR, et al. The development of an implantable artificial lung. *ASAIO J* 1994; **40**: M728-M731.
- Fazzalari FL, Bartlett RH, Bonnell MR, et al. An intrapleural lung prosthesis: rationale, design, and testing. *Artif Organs* 1994; **18**: 801-805.

The Future of Artificial Lungs

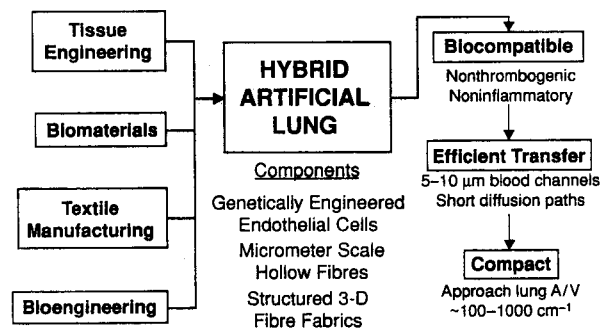


Figure 29.27 The future of artificial lungs will evolve from a close interaction between the life sciences and engineers. 3-D, three dimensional; A/V, area/volume.

- 17 Lynch WR, Montoya JP, Brant DO, et al. Hemodynamic effect of a low-resistance artificial lung in series with the native lungs of sheep. *Ann Thorac Surg* 2000; **69**: 351–356.
- 18 Lynch WR, Hatt JW, Montoya JP, et al. Partial respiratory support with an artificial lung perfused by the right ventricle: chronic studies in an active animal model. *ASAIO J* 2000; **46**: 202.
- 19 Vasleff SN, Mockros LF, Cook KE, et al. Computer-assisted design of an implantable intrathoracic artificial lung. *Artif Org* 1994; **18**: 813–817.
- 20 Boschetti F, Perlman CE, Cook KE, et al. Hemodynamic effects of attachment modes and device design of a thoracic artificial lung. *ASAIO J* 2000; **46**: 42–48.
- 21 Vaslef SN, Cook KE, Leonard RJ, et al. Design and evaluation of a new, low pressure loss, implantable artificial lung. *ASAIO J* 1994; **40**: M522–M526.
- 22 Cook KE, Makarewicz AJ, Backer CL, et al. Testing of an intrathoracic artificial lung in a pig model. *ASAIO J* 1996; **42**: M604–M609.
- 23 Conrad SA, Bagley A, Bagley B, et al. Major findings from the clinical trials of the intravascular oxygenator. *Artif Organs* 1994; **18**: 846–863.
- 24 Hattler BG, Johnson PC, Sawzik PJ, et al. Respiratory dialysis: a new concept in pulmonary support. *ASAIO J* 1992; **38**: M322–M325.
- 25 Reeder GD, Hattler BG, Rawleigh J, et al. Current progress in the development of an intravenous membrane oxygenator. *ASAIO J* 1993; **39**: M461–M465.
- 26 Hattler BG, Reeder GD, Sawzik PJ, et al. Development of an intravenous membrane oxygenator (IMO): enhanced intravenous gas exchange through convective mixing of blood around hollow fibre membranes. *Artif Organs* 1994; **18**: 806–812.
- 27 Hattler BG, Reeder GD, Sawzik PJ, et al. Development of an intravenous membrane oxygenator: a new concept in mechanical support for the failing lung. *J Heart Lung Transplant* 1995; **13**: 1003–1007.
- 28 Federspiel WJ, Hewitt T, Hout MS, et al. Recent progress in engineering the Pittsburgh intravenous membrane oxygenator. *ASAIO J* 1996; **42**: M435–M442.
- 29 Macha M, Federspiel WJ, Lund LW, et al. Acute in vivo studies of the Pittsburgh intravenous membrane oxygenator. *ASAIO J* 1996; **42**: M609–M615.
- 30 Konishi R, Shimizer R, Firestone L, et al. Nitric oxide prevents human platelet adhesion to fiber membranes in whole blood. *ASAIO J* 1996; **42**: M850–M853.
- 31 Lund LW, Federspiel WJ, Hattler BG. Gas permeability of hollow fiber membranes in a gas–liquid system. *J Membr Sci* 1996; **117**: 207–219.
- 32 Lund LW, Hattler BG, Federspiel WJ. Is condensation the cause of plasma leakage in microporous hollow fiber membrane oxygenators? *J Membr Sci* 1998; **147**: 87–93.
- 33 Federspiel WJ, Hattler BG. Sweep gas flowrate and CO₂ exchange in artificial lungs. *Artif Org* 1996; **20**: 1050–1056.
- 34 Hout MS, Hattler BG, Federspiel WJ. Validation of a model for flow-dependent carbon dioxide exchange in artificial lungs. *Artif Organs* 2000; **24**: 114–119.
- 35 Federspiel WJ, Williams JL, Hattler BG. Gas flow dynamics in hollow fiber membranes. *Ann Inst Chem Eng J* 1996; **42**: 2094–2099.
- 36 Hewitt TJ, Hattler BG, Federspiel WJ. A mathematical model of gas exchange in an intravenous membrane oxygenator. *Ann Biomed Eng* 1998; **26**: 166–178.
- 37 Federspiel WJ, Hewitt TJ, Hattler BG. Experimental evaluation of a model for oxygenation exchange in a pulsating intravascular artificial lung. *Ann Biomed Eng* 2000; **28**: 160–167.
- 38 Federspiel WJ, Hout MS, Hewitt TJ, et al. Development of a low flow resistance intravenous oxygenator. *ASAIO J* 1997; **45**: M725–M730.
- 39 Federspiel WJ, Golob JF, Merrill TL, et al. Ex-vivo testing of the intravenous membrane oxygenator (IMO). *ASAIO J* 2000; **46**: 261–267.
- 40 Golob JF, Federspiel WJ, Merrill TL, et al. Acute in-vivo testing of an intravascular respiratory support catheter. *ASAIO J* 2001; **47**: 432–437.
- 41 Jayroe JB, Alpard SK, Donfang W, et al. Hemodynamic stability during arteriovenous carbon dioxide removal for adult respiratory distress syndrome: a prospective randomized outcomes study in adult sheep. *ASAIO J* 2001; **47**: 211–214.
- 42 Hattler BG, Lund LW, Golob J, et al. A respiratory gas exchange catheter: in-vitro and in-vivo tests in large animals. *J Thorac Cardiovasc Surg* 2002; **124**: 520–530.