LECTURES 6-7: ARTIFICIAL LUNG

6.1 Introduction

The natural lung represents a remarkable organ for gas exchange. The lung's principal function is to transport oxygen from the atmosphere into the bloodstream, and to excrete carbon dioxide from the bloodstream into the atmosphere.

This exchange of gases is accomplished in the mosaic of specialized cells that form millions of tiny, exceptionally thin-walled air sacs called alveoli. The alveoli of the lung, the tiny gas sacs at the termini of all the branching airways of the lung, offer intimate contact between inspired gas and blood flowing through capillaries in the lung.

The O_2 and CO_2 diffusing capacities of the lungs are proportional to the gas exchange area of the alveolar-capillary membrane and to the inverse of the diffusion distance across the alveolar-capillary membrane into blood. The substantial gas exchange capacity of the lung stems from an alveolar-capillary area comparable to a tennis court surface, 100–150 m^2, packaged compactly with a high surface area to blood volume ratio of approximately 300 cm^{-1} and a diffusion distance between gas and blood phases of no more than about 1 μm.

The natural lung can provide gas exchange ranging from resting levels for both O_2 and CO_2 (about 200–250 ml/min in average adults) to 10–20 times that under exercise conditions, and it does so use room air as its oxygen supply gas.

Moreover, the lungs have a variety of functions other than gas exchange, including several metabolic functions. These functions include producing, storing and inactivating various vasoactive and coagulation modulating molecules. The native pulmonary bed also

has the property to act as a filter to prevent clot and other debris from entering the systemic circulation causing stroke. In addition to respiratory functions the lungs also:

- influence the concentration of biologically active substances and drugs used in medicine in arterial blood
- regulate the hydrogen ion concentration in the blood
- serve as a physical layer of soft, shock-absorbent protection for the heart, which the lungs flank and nearly enclose.

The most important diseases of the lung which may necessitate organ transplantation or artificial organ support are cancer, acute respiratory distress syndrome (ARDS) and cystic

fibrosis.

6.2 Artificial Lungs

The developing of an artificial lung that approaches the gas exchange powers of the natural lung is a significant engineering challenge. Current hollow fiber blood oxygenators, as used in cardiopulmonary bypass, have membrane areas ranging from 1 to 4 m^2 that are packaged much less compactly than in the natural lung, with a surface area to blood volume ratio 10 times less than in the natural lung.

The effective distance that gas diffuses between blood and gas flow pathways in artificial lungs are approximately 10–30 μm, an order of magnitude greater than in the natural lung. Thus, even with using 100% oxygen gas, artificial lungs currently used or under development aim at gas exchange levels that can only support resting metabolic needs in patients.

Regarding the cell-based solutions, several approaches are being developed worldwide. These can be divided into the following categories:

I) Targeted activation or administration of endogenous stem cells,

II) Creation of pulmonary tissue constructs in vitro,

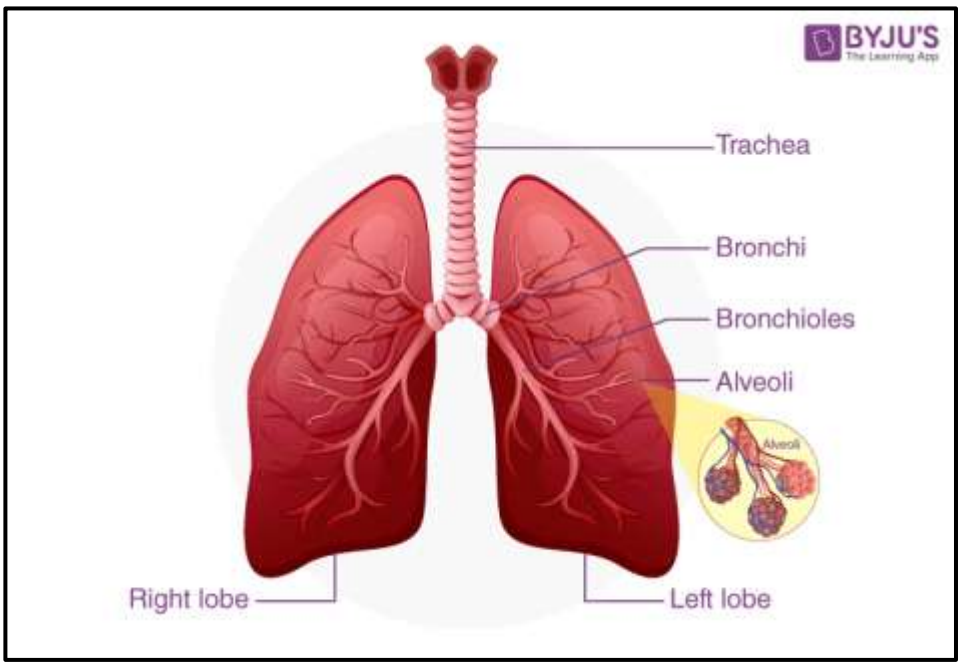
III) Biohybrid lung that combines a medical device with living cells.

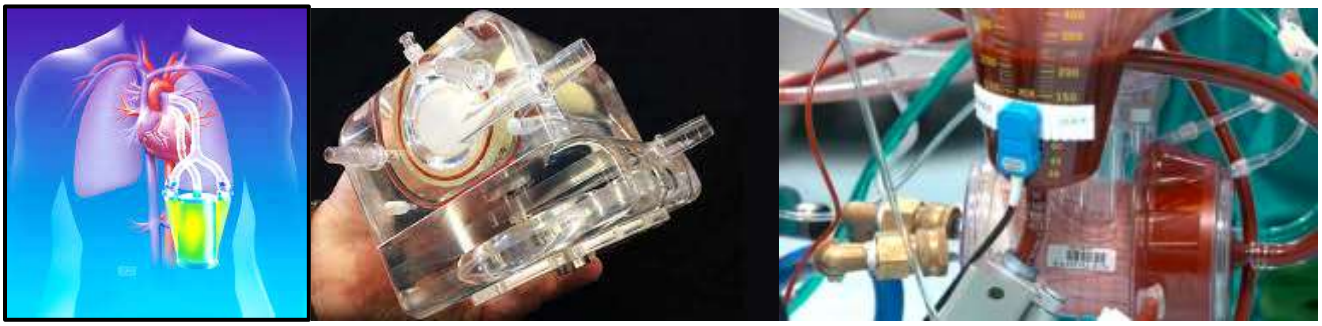
All of these approaches are still in the research phase.

The challenge of biocompatibility inherent in making microvascular-scale blood channels with an extensive blood contact area, that is non-thrombogenic and non-inflammatory, may require the use of endothelial cells, perhaps genetically engineered for enhanced performance or for the robustness required in the application.

Significant advances in tissue engineering, biomaterials, microfabrication, and bioengineering will all need to be harnessed for the technological development of future artificial lungs.

Artificial lungs that allow patients any significant level of increased metabolic activity is not on the immediate horizon.





6.3 Medical device-based approach for function recovery

Artificial lungs are medical devices designed to take over or supplement the respiratory function of the lung: oxygenating the blood and removing carbon dioxide. They are aimed to provide the following benefits over mechanical ventilation:

- Elimination of sedation allows the patient to stay alert, eat and communicate
- Elimination of ventilator associated pneumonia eliminates dangerous complications, and should reduce cost of care and length of stay in the ICU.
- Avoidance of intubation allows the patient to eat, speak and prevents tracheal injury and sinus infection.
- Reduction in weaning failure (from ventilator support) should reduce length of stay in the ICU and potential mortality.
- Reduction in tracheostomies will reduce an invasive surgical procedure to the larynx
- Reduced lung injury may reduce the incidence of death.

The artificial lungs used clinically today are mainly extracorporeal membrane blood oxygenators (ECMO), primarily used in operations requiring cardiopulmonary bypass, but also used less frequently for support of patients with respiratory failure. The ECMO circuit, that includes pumps, reservoirs, heat exchangers and long lines of tubing presents a high priming volume and entails a risk of hemolysis, clotting and plasma leakage due to the blood contact surface.

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The growing incidence of lung disease associated with the ageing population has encouraged work toward next generation artificial lungs that may be used to successfully treat patients with a variety of respiratory failures. Next generation artificial lungs include:

- intravascular approaches (respiratory catheters placed within the vena cava)
- paracorporeal approaches (wearable devices that will be attached directly to patients)
- intrathoracic approaches (devices placed within the thoracic or abdominal cavities).

6.4 State of development

Intravascular oxygenator

Intravascular artificial lungs have been studied and are being developed as a less expensive, less personnel intensive alternative to respiratory support with traditional extracorporeal artificial lungs. Anatomical and physiological constraints of device placement in major blood vessels of the human body impose significant challenges in developing intravascular artificial lungs. Most of the intravascular devices that have been developed are intended for insertion through a peripheral vein (femoral or jugular) and placement in the vena cava, the largest blood vessel in the body through which blood returns to the heart.

The adult human inferior vena cava ranges on average from 2.2 cm to 3.3 cm in diameter and the superior vena cava ranges from 1.5 cm to 2.2 cm. Intravascular artificial lungs must be compact for insertion, yet possess sufficient membrane area to achieve adequate respiratory support. The primary objective of intravascular artificial lungs is to supplement the gas exchange of a failing lung, but not completely replace it. Respiratory support at 40–60% of the body's resting metabolic needs has generally been considered an appropriate target for intravascular artificial lungs.

Intravascular oxygenation (IVOX)

The concept of intravascular oxygenation (IVOX) was introduced by Mortensen and Berry, who investigated the possibility of achieving gas exchange by introducing a bundle of hollow fibers into a blood vessel. The early IVOX was designed to be inserted through the femoral or the jugular vein and to occupy the vena cava for gas exchange.

Compared with extracorporeal oxygenation IVOX presents a smaller blood contact surface, reduces the size of the insertion, reduces the risk of infection and surgical operation time, and sets the priming volume to zero. No blood tubes and heat exchangers are required in the system. The clinical trials on Mortensen's IVOX system demonstrated a rather low oxygen transfer, corresponding to only 20 - 30% of the whole-body requirement and proved to have no effect on the mortality in ARDS patients. This low transfer rate is ascribed to blood flowing parallel to the fibers, causing an increased boundary layer thickness that hinders gas exchange.

Two modified systems to improve the blood flow around the fibers are under development; the Hattler catheter and HIMOX.

Hattler catheter

The Hattler catheter uses technology similar to Mortensen's IVOX system (see Figure 1). It is also an intravascular gas exchange device implanted into the vena cava or right atrium, but the ± 800 hollow fibers that are woven into a fabric, surround a small pulsatile balloon. The balloon is rapidly pulsating at a rate of up to 300 'beats' per minute, creating convective currents around the hollow fibers which allows for enhanced oxygenation of the blood and removal of carbon dioxide. In this way about 50% of the patient's oxygen needs can be provided by the oxygenator.

The Hattler catheter is still under development. An email communication with Alung Technologies Inc. learned that the device is still at a pre-clinical stage.

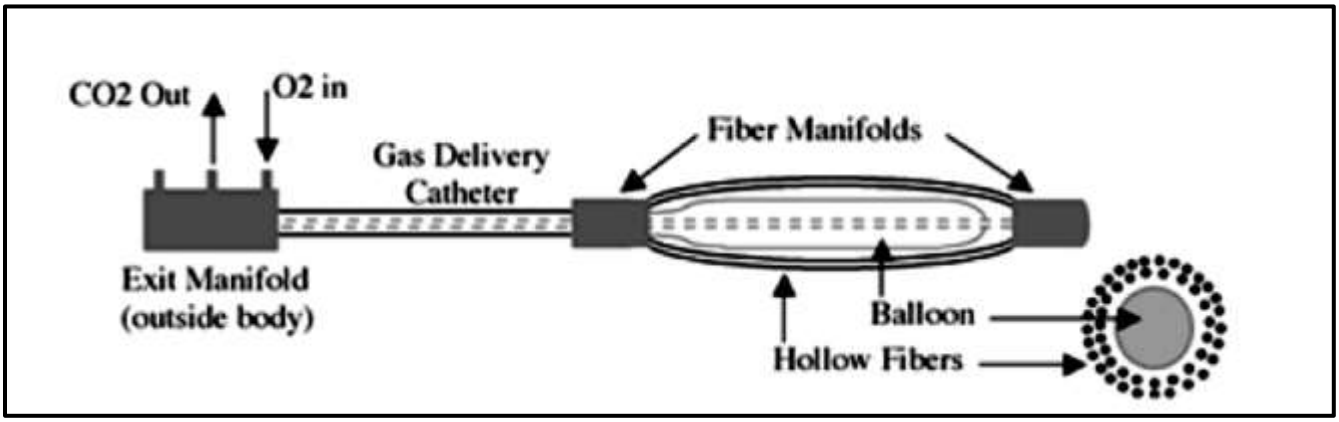

Figure 1: Hattler catheter, including pulsatile balloon.

Highly integrated intravascular membrane oxygenator (HIMOX)

Researchers from the Department of Cardiovascular Engineering of the Helmholtz-Institute for Biomechanical Engineering at the RWTH in Aachen, Germany are working on an improved IVOX device, which they named the highly integrated intravascular membrane oxygenator (HIMOX). This device has improved fiber configuration for better flow and gas exchange properties so that the efficiency is independent from the anatomical and fluid dynamic conditions in the venous system (see Figure 2).

Core of the HIMOX are several serially connected tubular shaped hollow fiber bundles. The bundles are mounted on a central catheter, which guides them during insertion through the vena femoralis into the vena cava and serves as pipeline for gas removal. However, high fiber density presents a detrimental side effect as it increases the blood pressure drop across the fibers. For this reason, a micro axial pump is integrated in the HIMOX.

Technical issues like the controlled twisting and compressing of the fiber bundles in the vena cava have not been addressed jet. Also, micro axial blood pump is still under development by the university. It is unlikely that the HIMOX will be available for clinical testing with a few years.

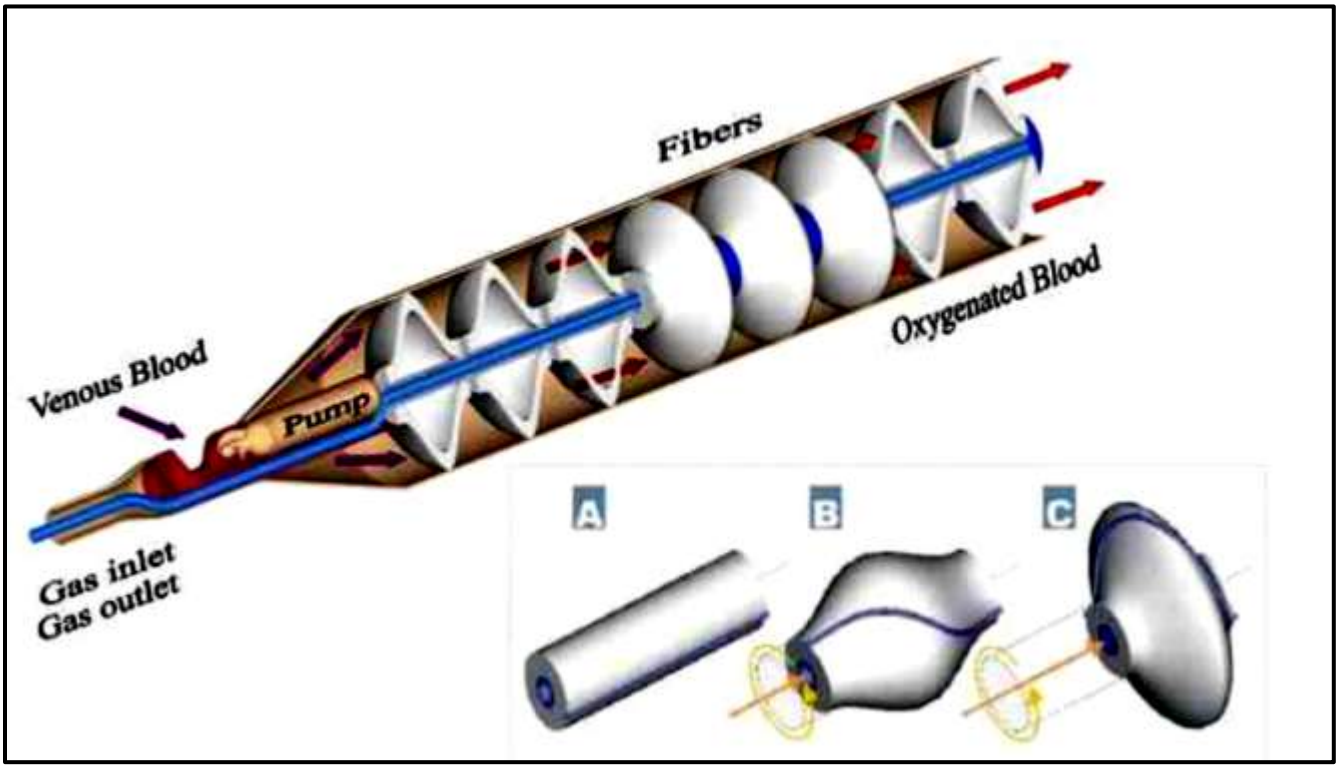

Figure 2: Construction of HIMOX

Pumpless extracorporeal lung assist (pECLA)

With the extra corporeal membrane oxygenators that are used in heart-lung machines a blood pump is necessary to overcome the flow resistance of cannulae and oxygenators and to achieve sufficient blood flow. Using newly designed oxygenators with reduced pressure drop, the difference between arterial and venous blood pressure is sufficient to achieve adequate extracorporeal blood flow.

The heart pumps blood through the pumpless lung assist device via a femo-femoral shunt created by percutaneous arterial and venous cannulation with high-flow cannulae. The low impedance of the lung assist device avoids the use of an artificial blood pump.

Advantages of an interventional lung assist (ILA) are avoidance of all pump related complications, reduced blood contacting surfaces and simplified clinical management. Disadvantages are the indirect control of blood flow which is the result of the arterio-venous pressure gradient, the low oxygen transfer capacity since arterial already

oxygenated blood is flowing into the device, the arterial cannulation which might impose local problems to the cannulated vessel and distal blood flow, and the arterio-venous shunt perfusion up to 25% of cardiac output which needs to be achieved by the left ventricle. Indications for ILA are not formally established in well controlled clinical trials but patients with severe acute respiratory failure and severe hypercapnia seem to benefit best.

Novalung

The safety and feasibility of the first commercially available pumpless lung assist device, Novalung interventional lung assist (ILA) has been shown in more than 150 clinical applications (see Figure 4). In the vast majority of patients treated with ILA, this treatment modality has been an adjunct to mechanical ventilation that allowed optimized lung protective ventilation (to minimize ventilator-associated lung injury, and to ameliorate and eliminate the inflammatory process that is enhanced by mechanical ventilation), thus giving the lung time to heal. However, in a few cases, interventional lung assist has been employed without mechanical ventilation in the awake, nonsedated patient. The application is based on a low resistance lung assist device designed for pulsatile blood flow with tight diffusion membranes and a protein matrix coating. The gas exchange surface amounts to 1.3 m^2.

It allows complete removal of arterial CO_2 and significant oxygenation of the blood. Pressure gradient across the device and cannula is sufficiently low to omit a blood pump. Nevertheless, the blood gas exchange capacity, especially the oxygenation capacity, of ILA is limited in comparison with pump-driven ECMO for two reasons. First, the flow through the artificial lung membrane is restricted. Because with ECMO flow rates of 4–6 L·min-1 can be achieved, physically ILA will never be equally effective.

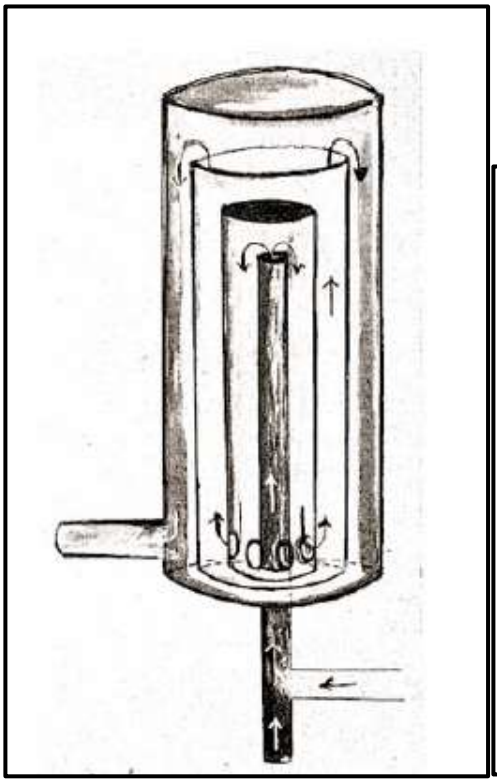

Figure 4: Pumpless oxygenator

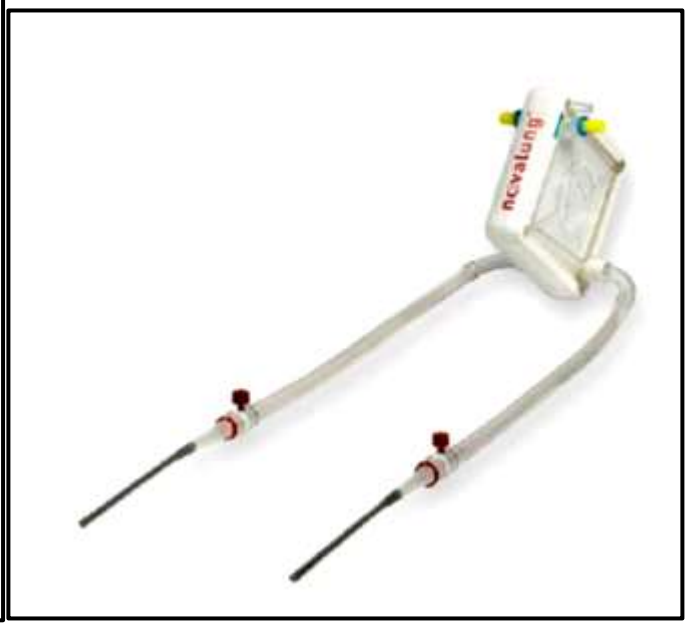

Figure 5: Nova lung interventional lung assist device

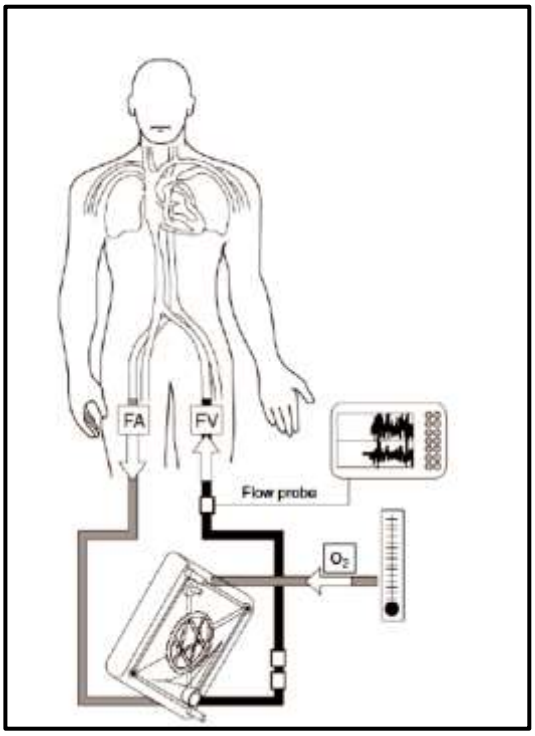

Figure 6: Application of the Novalung

Total artificial lung (TAL)

Several research groups are developing total artificial lung (TAL) devices for treating chronic respiratory failure, primarily as bridge-to-lung transplant devices. Whereas implantable total artificial lungs that can be placed in the thoracic or abdominal cavities may be an ultimate goal, the initial implementation and testing of TALs appears to favor paracorporeal applications, with the TAL external to but immediately attached to the patient. The attachment mode of the TAL is an important design consideration, and in-series, in-parallel, and hybrid configurations have been studied. The in-series configuration connects the artificial lung to the proximal pulmonary artery, diverting all the cardiac output through the device and returning it to the distal pulmonary artery immediately upstream of the natural lungs. Although this mode enables the natural lung to be an effective embolic filter, the mechanical load on the right heart increases because it must provide the pumping energy for blood flow through both the natural and the artificial lung.

The in-parallel configuration attaches the artificial lung between the pulmonary artery and the left atrium so that only a fraction of the blood flow diverts through the artificial lung. The fraction of blood flow through the artificial lung depends on its impedance relative to that of the natural lung. The in-parallel configuration has the clear advantage that the right heart workload is reduced, but only a fraction of total cardiac output receives respiratory support from the artificial lung and that fraction is not exposed to the metabolic and filtering functions of the natural lung. The hybrid configuration attaches the inlet of the artificial lung to the proximal pulmonary artery, and uses a split return to the distal pulmonary artery (and natural lung) and to the left atrium.

The hybrid configuration allows all the cardiac output to flow through the artificial lung with less resistance than the in-series configuration, and also allows greater flow through the natural lung than the in-parallel configuration. Patients with a weak or failing

right ventricle would require either the in-parallel or hybrid configurations because of the reduced power required for adequate perfusion of the artificial lung and natural lung.

BioLung

The first total artificial lung, the BioLung (MC3 Inc.) has undergone intensive bench testing and animal trials. This device could eventually help lung transplant candidates stay alive and mobile for six months or more outside the hospital, and allow them to stay healthy enough to remain at the top of the transplant list. It may also prove suitable for patients with end-stage COPD, pulmonary fibrosis or cystic fibrosis. The BioLung was shown to produce better survival and less lung injury than a conventional ventilator in five-day tests on damaged sheep lungs. The device prototype is well tolerated in series with the normal sheep pulmonary circulation.

This type of device will initially be used in a paracorporeal fashion, i.e., with grafts connected to an extracorporeal artificial lung. This allows safe and rapid nonsurgical exchange, while an implanted artificial lung would require surgery to replace the device.

Therefore, the treatment intervals will not necessarily be limited by the durability of the individual device. Artificial lungs will initially require an extracorporeal oxygen source such as a concentrator or a tank.

Chronic Artificial Lung

A paracorporeal total artificial lung for chronic respiratory support (Chronic Artificial Lung, or CAL) is under development at the University of Maryland as a continuation of earlier work at the University of Pittsburgh (see Figure 8).

The CAL is intended as a bridge-to-transplant device with the goal of 21-day support of basal metabolic needs using a device less than 0.5 m2 in fiber membrane area. The CAL uses active mixing from a rapidly rotating disc made of microporous hollow fiber membranes that enhance gas exchange by increasing blood flow velocity past fiber

surfaces and reducing diffusional boundary layers. The disc rotates within a housing and the centrifugal motion imparted to blood enables the CAL to pump blood (which may reduce the impact of the CAL on the right heart in its intended in-series attachment mode). The motor controller directing disc rotation can generate pulsatile or nonpulsatile flow.

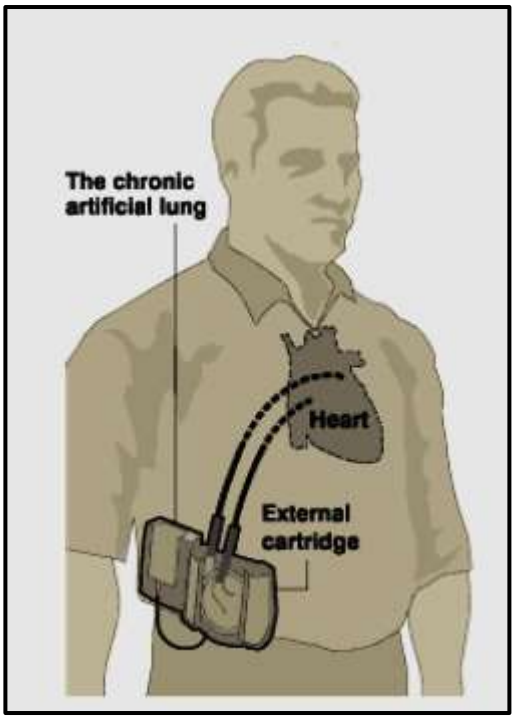

Figure 8: Chronic artificial lung

The CAL generated 5 l/min flow against a 100 mm Hg pressure head at 1600 rpm during steady flow in bench tests using bovine blood, but adding pulsatility to the flow decreased pumping. Published data are lacking but the gas exchange efficiency of the CAL appears promising, with 550 ml/min/ m2 and 450 ml/min/ m2 reported for O2 and CO2 exchange efficiencies, respectively, in scaled-down prototypes.

Portable artificial lung for conscious patients

In June 2006 the Swansea University reported that researchers are working on a new artificial lung. The device, a blood/air mass exchanger, integrates with the body's respiratory system and is designed to breathe for conscious, mobile patients whose lungs

are damaged or diseased. As a portable device, it will allow patients to recover outside Intensive Care Units and offers them a better quality of life.

The device differs from current extracorporeal life-support systems in that it uses only natural air (rather than bottled or piped oxygen). It is also integrated with the natural respiratory control system so that transfer rates of oxygen and carbon dioxide respond naturally to physical activity. In this way, patients can maintain a high level of physical fitness whilst their lungs recover, or they await lung transplant. Variants of the device range from an easily reversible fully external device to a prosthetic lung. The emphasis throughout is on a fully portable device that allows patients mobility unconnected to piped gases or complex intrusive monitoring.

Hexmo is a miniaturized extracorporeal membrane oxygenator (see Figures 9 and 10). The integration of a small rotary blood pump into the centre of the oxygenator reduces the amount of tubing and connectors in the system. Blood is convectively warmed by the pump motor housing; thus, the use of a heat-exchanger can be avoided.

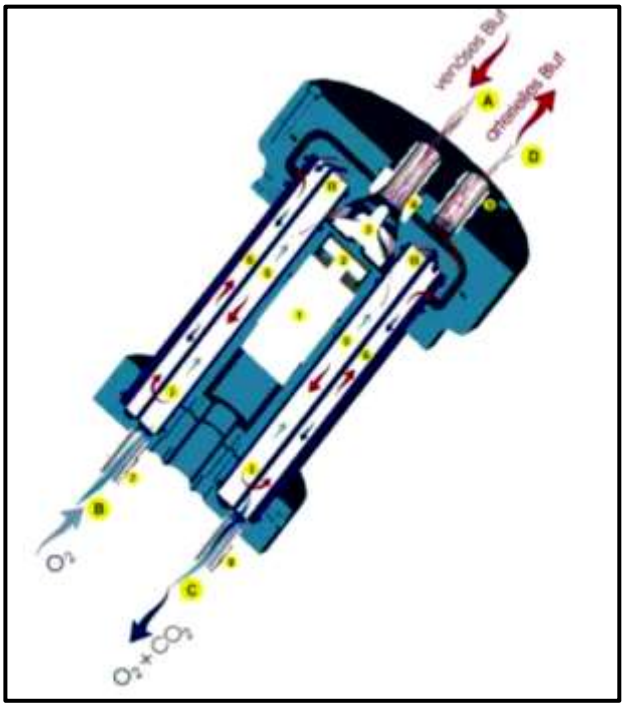

Figure 9: Hexmo construction

In clinical use the double lumen cannula can be introduced minimally invasively via the femoral vein into the inferior vena cava. venous blood enters the cannula in the liver region. After passing the oxygenator, oxygenated blood flows back to the cardiovascular system close to the right atrium. HEXMO presents an oxygenation system that opens the way to mobile application, emergency use and cost reduction.

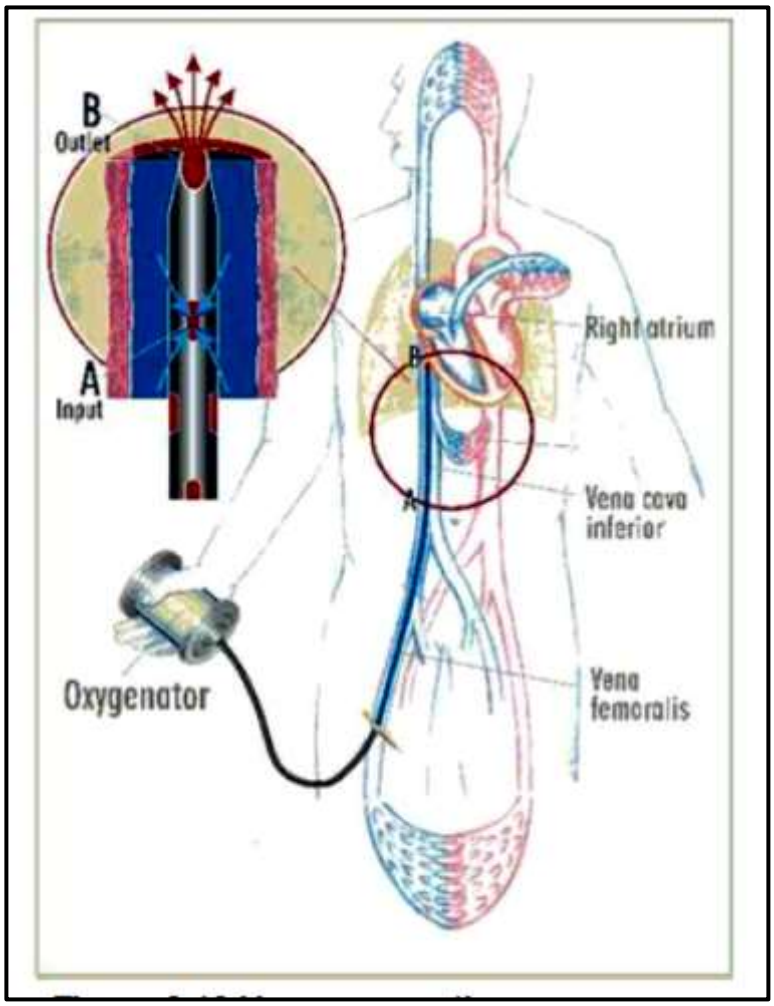

Figure 10: Hexmo operation

Developments in materials

Membrane permeance can play an important role when coated or composite hollow fiber membranes are used to prevent plasma wetting in artificial lungs, a process in which blood plasma infiltrates the microporous walls of hollow fibers.

Composite hollow fibers incorporate a thin nonporous polymer layer as a true membrane or ‘skin’ on the microporous fiber surface. The true membrane blocks infiltration of plasma into pores and is a key functional requirement of artificial lungs for longer-term respiratory support.

Composite hollow fiber membranes are made either by coating an existing microporous fiber with a thin nonporous polymer (a true composite hollow fiber) or by modifying the fabrication of the microporous fiber itself to seal off pores at the surface (an asymmetric hollow fiber). The nonporous polymer skin that prevents plasma wetting also diminishes membrane permeance because a nonporous polymer can present an impediment to gas diffusion.

Material induced activation of blood could theoretically be reduced through the addition of coatings to the surfaces of the artificial lung, that release nitric oxide. Physiologically, nitric oxide acts as a local inhibitor of platelet adhesion and activation. Such a surface may be required for artificial lungs, as it may prevent lack of platelets, platelet dysfunction, and clot formation that has complicated the use of extracorporeal circuits for many years. The university of Michigan is working on polymers that contain tiny silica particles that release low levels of nitric oxide gas.