Abstract - Many diseases affect the respiratory system and may cause lung failure. With this in mind and the lack of lung donors, researchers and scientists have developed devices that can replace the natural lung. So far they have only developed temporary devices. These either assist the respiratory system during an operation or afterwards and can only be used for a short period of time. Here, we shall discuss the functioning, performance and principle of operation of the artificial lungs. Respiratory assist devices, partially or totally, perform the function of the lungs. Besides the common usage in Cardiopulmonary Bypass procedures, auxiliary lungs could play a role in palliative treatment of wet-lung syndrome following shock, hyaline membrane disease, and organ transplant procedures. No one unit or even one design would be suitable for all cases. The multiplicity of applications undoubtedly would require a variety of units. Respiratory assist devices should perform its function without traumatizing the blood and should be efficient, reliable, safe, inexpensive, and easy to use. In addition, some gross design features might include low priming volume, low head loss, and minimum surface area. The function of the artificial lung is to supply oxygen as well as to remove carbon dioxide. Artificial lungs, used in clinical cardiopulmonary bypass, are traditionally referred to as blood oxygenators, bubble oxygenators, disk oxygenators, or membrane oxygenators.

Keywords – Respiratory Assist Device; Cardiopulmonary Bypass; Blood Oxygenators; (bubble, disk or membrane); Respiratory System; Lung.

INTRODUCTION

In these days many people have problems with diseases that affect their respiratory system, in especially with their donors. With these in mind the scientists have developed devices that can help or replace the natural lung. These devices help our respiratory system during an operation or afterwards, but can only be used for a recuperation time. In this article, we talk about the function, components and advances of the artificial lung.

These devices help, partially or totally, the respiratory system to perform the function of the lungs. The purpose of the artificial lung is to oxygenate the blood.

Description of the Respiratory System

We live because we breathe. Inhaled breath brings life-sustaining oxygen into our body. Oxygen is the fuel that makes our body function. Every minute we breathe in about 13 pints of air. Our lungs are essentially 2500 km of airways, through which oxygen is delivered to all parts of the body from the lungs, and carbon dioxide exhaled from the lungs is sent out into the atmosphere.

Air has a long journey to the lungs: past the windpipe, the vocal cords, to the lower ribs that meet in the center of our chest. From there, the windpipe branches off into the left lung and the right lung. Inside the lung, bronchi connect with tiny air sacs called alveoli. If spread out that, all the air sacs in our lungs would cover about a third of a regular tennis court.

Inhaled oxygen goes into the alveoli, through the lung’s capillaries and into the body’s arteries for delivering oxygen to all parts of the body. On the way, the carbon dioxide-filled blood releases into the alveoli and begins the journey back through our chest cavity, larynx, diaphragm, trachea, nose and mouth, and out into the air.

When our lungs diaphragm expand, oxygen is pulled in. When our lungs contract, carbon dioxide is released from the lungs. The red blood cells are the conductors of this air exchange. Breathing is automatic for this highly intricate system [42].

HISTORICAL DEVELOPMENTS

Recent Historical Developments of the Artificial Lung

Acute respiratory distress syndrome (ARDS) affected about 200,000 Americans in 2001. As many as half of those people died, often because the ventilators used to treat them caused permanent, irreversible lung damage.
ARDS is characterized by a rapid and progressive breakdown of the lungs that impairs its ability to take in oxygen. It is usually associated with the failure of other organs as well and is generally caused by trauma, infection, severe pneumonia, or shock.

Brack Hattler, MD, PhD, tells WebMD that he and his colleagues have been working on their device for 14 years and were ready to begin human testing in Europe sometime in 2001.

Hattler brought a group of transplant experts up to speed on the latest artificial lung technology for presentation at the meeting of International Society for Heart and Lung Transplantation in Vancouver, British Columbia.

A professor of surgery at the University of Pittsburgh, Hattler says the U.S. Department of Defence first asked him to work on developing a "temporary lung" during the days leading up to the Gulf War as they were worried that Iraqi forces led would use chemical weapons against allied forces. Those toxic chemicals could cause severe lung injuries, but not permanent ones. If the lungs were given a breather and allowed to recover, Hattler says, "The damage could be reversed."

This kind of damage is very similar to what is seen in patients with ARDS. Currently patients who have this type of injury are put on a ventilator, which mechanically supplies oxygen and forces the lungs to breathe. Unfortunately, both actions may cause permanent damage.

So the goal was to develop a device that could be "easily used and could replace the lungs for a brief period of about 5 to 14 days," Hattler says. So he with his team developed a device to be placed inside a vein in the leg to supply oxygen to the blood.

"What we are doing is intercepting the blood before it arrives in the lungs," says Hattler, "We can add oxygen and remove carbon dioxide while letting the lungs rest".

He explains that external controls regulate the amount of oxygen supplied as well as the rate at which carbon dioxide is suctioned out of the blood. Hattler says that although this device is the first major breakthrough in artificial lung technology, yet it is based on earlier technology.

Several years ago a venture capital company introduced the concept with IVOX: A device that supplies oxygen to the veins. Lyle Mockros, PhD, Professor of Biomedical Engineering at North-western University in Chicago, informs that the product was actually tested in humans, but was eventually abandoned when the developers ran out of money.

Mockros says his group at North-western, as well as a third team at the University of Michigan, are concentrating their efforts on developing a more permanent artificial lung that could be used on longer-term while a patient waits to get a lung transplant. Current work is focused on devices that are wearable and are attached to the patient.

Physicians have been trying to adapt the heart-lung machine for use as an artificial lung for people with severely damaged lungs, such as people with severe emphysema, Mockros says, but efforts have not been successful.
The difficulty in developing a successful artificial lung is that the lungs have a large surface area and devices that mimic them also have a large surface area. When blood passes over a large artificial area, it can be damaged in a way that causes the formation of blood clots. Designers seek to overcome this risk by giving patients powerful anticlotting drugs, but those can lead to unintended bleeding.

Hattler's device is much smaller, so the surface area is less, and the anticlotting drug heparin has actually been built into the device. This approach reduces the risk for clot formation, Hattler says. If Hattler's device (Figures 2 and 3) is successful in human studies, Mockros says it will be a major advance in the world of artificial lungs [38].

Lessons learned from Intravascular Oxygenator

Intravascular Oxygenation (IO), based on implantation of a membrane oxygenator within the vena cava, is a promising alternative to extracorporeal oxygenation for treating patients with Acute Respiratory Distress Syndrome (ARDS). Compared to extracorporeal oxygenation, IO has a smaller blood-contact surface, reduces the size and the depth of the insertion as well as the risk of infection, and sets the priming volume to zero. The main effort is to increase fiber surface and flow, enhancing gas transfer, without impairing venous return to the heart. HIMOX (High Integrated Intravascular Membrane Oxygenator) presents a new compact fiber arrangement associated with high total gas exchange (Figure 4). A micro axial pump is integrated into the oxygenator within a deformable casing, in order to compensate for flow resistance and to avoid blood stagnation (Figure 5). Key features of HIMOX are several bundles of gas permeable fibers, which can slide on a catheter, assuming two main configurations: Bundles lie parallel to the catheter during insertion, making the oxygenator long and narrow. HIMOX fits into the small insertion of the femoral vein. Bundles are compressed and twisted within the vena cava. Due to compression, fibers spread outwards, making the oxygenator short and wide. The spreaded and twisted configuration allows to fill the volume in the vena cava, maximizing implantable fiber surface. Moreover, the fibers assume a tightly packed cross flow configuration, enhancing blood mixing [11].
Figure 4. Anatomical position of the HIMOX [11].

Figure 5. Top: Three dimensional view representation of the intravascular oxygenator HIMOX [11].

Figure 6. Single Membrane [3].
Figure 7. A single fiber bundle fixed within a casing [11].

PRINCIPLES OF OPERATION

An Artificial Lung Prepared with Culture System

Crafted from fibers of polyethylene, the same plastic found in everything from garbage bags to containers for leftovers, the catheter rests in the vena cava, the main channel for blood on its way back to the heart. To maximize gas exchange, the fibers surround a balloon that can inflate up to 300 times a minute. The entire bundle (Figures 6 and 7) is threaded up a leg artery into the chest and is hooked up to a computer monitor that would be located at a patient's bedside [39].

1. Principal materials used

This section emphasizes methods of production of an artificial lung system comprising of an endothelial cell layer, an epithelial cell layer and an artificial microporous membrane. Endothelial cell layer can include microvascular endothelial cell line, human lung endothelial cell line, human liver endothelial cell line and human umbilical cord cell line. However, there are many non-human endothelial cells available to study on non-human pathogens. Human epithelial cells refer to a type of cell which forms on the outer surface of the body and lines organs, cavities and mucosal surfaces. Such cells can comprise the human endometrial carcinoma cell line, the human cervical carcinoma cell line, the human lung carcinoma cell line and the human larynx carcinoma cell line as well as primary epithelial cell cultures, among others.

The system consists of two cell layers (specifically, an endothelial layer and an alveolar epithelial layer) oriented to either side of and in direct contact with a membrane (an artificial microporous membrane). Here, we shall emphasize on methods for constructing an artificial organ with culture system and on the presence of chemical and pathogens substances inside the artificial system [39].

2. Principles of operation and background of an artificial lung prepared with culture system

Tuberculosis has brought a new focus to study pulmonary illnesses. In specific, tuberculosis (Mycobacterium tuberculosis) infects two billions people worldwide and causes more than three million deaths annually. The recent proliferation of tuberculosis in the U. S. with an evident increase in incidence of multidrug resistant strains is in part due to increases in acquired or re-activated disease in patients infected with the HIV virus. Better understanding of pathogenic mechanisms is needed to search for improved methods of prevention and control.

Researches have found that intracellular growth occurs within cultured human lung endothelial cells. This proves that even a few organisms inhaled into alveolar tissue could multiply to a much significantly before penetrating the epithelial cells, lining the alveolar spaces, and into the blood stream. Alveolar epithelial cells, our cells which form on the outer surface of the alveolar sacs in the lungs. Such alveolar cells include primary lung pneumocytes, human lung carcinoma cell line, human larynx and lung carcinoma cell line.

This artificial system can be used in other applications but specifically to the artificial lung application. The system requires incorporation of an endothelial and alveolar epithelial cell layers on a microporous membrane to study the process of attachment and passage that happens when the pulmonary pathogen agent or foreign substance makes its way from the alveolar surface, through the epithelial cells and into the circulatory system.

The objective of the initial investigation was to attempt to culture a layer of epithelial cells directly over a layer of endothelial tissue. The initial study indicated that the epithelial cells outgrew the endothelial cells. This problem was overcome by establishing a layer of endothelial cells on an artificial microporous membrane suspended in a tissue culture. It was expected that nutrients in the fluid medium would remain accessible to the endothelial cells even after the epithelial cell layer was formed on top of it.

It was believed that the greater exposure to nutrients might prevent the underlying endothelial cell layer from being starved and killed by the epithelial cells.
However, researchers were amazed with the unexpected fact that upon addition of epithelial cells to the layer of endothelial cells growing on the membrane, the endothelial cells migrated through the pores of the membrane and grew into a layer of cells on the opposite side of it, successfully establishing stable layers of two different cell types very close to each other.

An artificial microporous membrane could have a thickness of between 10 and 200 microns with a preferable thickness range of 15 and 30 microns with uniform pores within the membrane. Diameter may range between 0.45 and 10 microns, preferably with a diameter of 3 microns. This membrane can be composed partially or totally of a synthetic material or can comprise of a naturally occurring material in a molecular or ultrastructural arrangement not normally found in nature.

Synthetic materials used in membranes are fluoropolymer, polycarbonate, polyester, nitrocellulose, cellulose, acetate, polycarbonate and polystyrene among others. The membrane is usually coated with biocompatible material on one or both sides to facilitate attachment of cells to the membrane surfaces. These materials could be collagen, laminin, proteoglycan or vitronectin among others.

This specific artificial lung system can be effectively used for the study of the attachment and invasion factors contributing to Mycobacterium tuberculosis pathogenesis and leads itself to similar studies with other pathologic agents. Epidemic, mutants and sporadic cases can also be examined as they pass through these artificial system to investigate which genes are turned on or off in reaction to environmental changes and changes in the requirements for bacteria survival.

3. Function, composition, and significance of an artificial lung prepared with culture tissue

The technology of this type of artificial lung system is obtained compressing an endothelial tissue layer, an alveolar epithelial tissue layer and an artificial microporous membrane, having pores therein, disposed between with the endothelial cell later and alveolar epithelial cell layer and in direct contact with each other such that the membrane has an endothelial side and epithelial side. This artificial system is contained in a vessel compressing an upper chamber into which the epithelial side faces and containing the alveolar epithelial cell layer, and a lower chamber into which the endothelial side faces and containing the endothelial cells. For tissue culture, the vessels can be made in the form of tubes, bottles, chambers, flasks, vials or tissue culture.

The membrane can be supported above the bottom of the vessel at any distance from the bottom of the vessel as long as the membrane can be covered by a fluid medium within the vessel and a sufficient amount of space exists between the endothelial cell layers and the bottom of the vessel to allow nutrients in the fluid medium to contact the endothelial cell layer. The artificial microporous membrane can be supported a distance from of the vessel by number of ways:

- Use of a plastic frame.
- Suspension of the membrane in a vessel.
- Use of gel or wire baskets.

The conditions under which the endothelial cells form a confluent layer of cells on the epithelial side of the membrane can comprise maintaining the endothelial basal medium with about 7.0% fetal bovine serum at 37ºC in about 5.0% carbon dioxide for eight days. The other physiologically balanced medium can be used, providing it contains adequate growth factors for endothelial cells.

The fetal bovine serum concentration can range from 0 to 20% in the medium. The cells can be effectively incubated at a temperature of 25ºC to 42ºC and a CO2 concentration of 2% to 8%. The endothelial cells can be cultured from six to ten days prior to the addition of the epithelial cells.

A “basement membrane material” means a porous extra cellular matrix which functions as a support structure in a manner similar to the way basement membrane material functions as a support structure in whole organs. The artificial lung system can further include a layer of basement membrane material in direct contact with the epithelial side of the membrane and with the alveolar epithelial cell layer. This basement membrane material is included during construction of artificial lung organ system and is place in direct contact with the apical surface of the membrane prior to addition of the endothelial cells. The “apical surface” is the side of the membrane that faces away from the bottom of the vessel.

When the system is completed, the apical surface will coincide with the epithelial side. After that, the endothelial cells then establish a confluent monolayer on the surface of the basement membrane material and subsequently migrate through both the basement membrane material and membrane to the basal surface of the membrane upon addition of the epithelial cells to the apical surface.

The basal surface is the side of the membrane which faces the bottom of the vessel. It coincides with the endothelial side when the artificial lung is completed. Thus, the basement membrane material coats the membrane but does not block the migration of endothelial cells, pathogens or other chemical substances through the pores of the membrane.

The biocompatible materials described herein can form the present basement membrane. The material type includes an extra cellular matrix composed of laminin, collagen, fibronectin or any combination.

This cellular matrix material is recommended for the elaboration of almost any type of human organ. Nevertheless, some system could require more specific...
studies to identify the most adequate material to include in a particular type of artificial organ.

Studies using artificial lung system prototypes could and have been used as models to evaluate the effects of various extra cellular matrix material on the integrity of the cell layers, the ability of pathogens and chemical substances to pass through the system as well as the effects of various extra cellular matrix materials on the mechanisms of transport of pathogens and chemical substances through the system.

In the artificial lung system, alveolar macrophages can be present in the upper chamber and can either be suspended in liquid medium above the alveolar epithelial cell layer or in contact with the alveolar epithelial cells of the alveolar epithelial cell layer.

The existence of alveolar macrophages on the epithelial side of the membrane more closely mimics the environment within the living lung, in which alveolar macrophages are present within the alveolar sacs. Therefore, the construction of the artificial lung can include placing alveolar macrophages in the upper chamber containing the alveolar epithelial cells after establishing the artificial lung.

Usually, the alveolar macrophages can be obtained from the alveolar fluid obtained by alveolar lavage. One way of doing this is by placing a tube into the lung and the alveoli can be sprayed with sterile saline which can then be suctioned from the lung as alveolar lavage fluid. Then the alveolar macrophages can be separated from other cells and particulate materials in the alveolar lavage fluid by techniques for separation of macrophages.

**The Importance of an Artificial Lung Model**

For the purpose of mimicking more closely the environment of living alveolar sacs, the construction of artificial lung systems can include placing alveolar fluid into upper chamber after establishment of the artificial lung system. The alveolar fluid is a highly viscous solution comprising secreted surfactants, saline and other serum proteins (Table 1). In artificial lung system, white blood cells can be present in the lower chamber, either suspended in liquid medium around the endothelial cell layer or in contact with the endothelial cells of the endothelial cell layer.

Chemical agents and toxins which can be introduced to an artificial lung system can include tar, nicotine, coal dust, asbestos, and oxygen radicals among others. These chemical compounds can be introduced into artificial lung system on either the epithelial or endothelial side, depending on where a given substance would be known to interact with lung tissue in the body. The effects of toxic oxygen radicals, which would enter the alveolar sacs through inhalation, can be studied by introducing these molecules into the artificial lung system on the epithelial side of the membrane.

### Table 1. Alveolar fluid characteristics [43].

<table>
<thead>
<tr>
<th>Structure</th>
<th>Alveoli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relations</td>
<td>Component of lungs, works-with capillaries.</td>
</tr>
<tr>
<td>Behavior</td>
<td>Gas passes from high concentration to low across semi-permeable membrane.</td>
</tr>
<tr>
<td>Property</td>
<td>Elastic, semi permeable.</td>
</tr>
<tr>
<td>Function</td>
<td>Gas exchange.</td>
</tr>
</tbody>
</table>

Alternatively, the affects of nitrous oxide, which is produced by white blood cells, can be studied by introducing this compound on both the epithelial and the endothelial sides of the membrane. An example of a substance whose affects would be studied by being added to the endothelial side of the membrane is red blood cells, which would be present in the in vivo environment in blood vessels lined with endothelial cells.

Thus, construction of the artificial lung system can further include placing white blood cells in the lower chamber containing the endothelial cells, after establishment of the artificial lung system. To provide an even more physiologically accurate model of the environment of the living lung, the upper chamber can contain no or a minimal amount of fluid medium. The humidity in the upper chamber can be maintained at a level which keeps the epithelial cells healthy and or mimics the internal environment of the alveolar sac.

This is done, because the epithelial cells lining the alveolar sacs of the lungs are not normally submerged in fluid in a healthy physiological state. Pathogens and other chemical substances in solid, liquid or gaseous state can be introduced into the upper chamber and the affects of these agents on the artificial lung system under these conditions can be determined.

The construction of the artificial organ system or artificial lung system can further include placing a means for maintaining movement of fluid medium in the lower chamber after establishment of the artificial lung. Such means can include a magnetic stir bar and a flow chamber, among others. For example, a magnetic stir bar can be placed on the bottom of the lower chamber of the artificial lung system mimics the movement of blood through the blood vessels. Thus, the effects of substances which can be present in the blood can be studied by introducing these substances into the artificial lung system by placing them into the medium which is moving in or through the lower chamber. As an example, we have that red blood cells which have abnormal shapes, such as sickled red blood cells, can be added to the system to study the interactions of these cells with the cell layers of the artificial organ system.

An additional asset of this artificial lung system is its potential adaptability for the study of a wide variety of organisms. Several epithelial cell lines have been used in
the system which has been used to show differences between a virulent and an avirulent strain of the influenza bacteria biogroup aegyptius. It is routine, for any organism to be studied, to construct an artificial organ system, as described herein, using physiologically relevant epithelial and endothelial cell lines. The endothelial layer can be a different vascular line, such as human umbilical vein cells, even more relevant to the pathogenesis of a given organism.

An artificial organ system is a useful way to screen chemicals (including drugs, medicaments or chemical toxins, among others) to determine the movement of these substances through the artificial system. Such studies can also provide useful information on the effectiveness of applications such as drug treatments and vaccines whose mechanism of action involves blocking the binding of certain pathogens to host cells. In the artificial lung system, such chemicals can be, for example, antibiotics, antiviral drugs, or drugs to treat lung diseases such as cystic fibrosis, asbestos, etc., as well as vaccine and lytic peptide therapeutics against lung and upper respiratory pathogens, among others.

The chemicals of interest can be detected on the endothelial side of the membrane, either in the contact with the endothelial cells or in the liquid medium in the lower chamber, or within the artificial organ system by methods well known. For example, immunofluorescent and immunohistochemical reagents can be applied to the cells of the artificial organ system to identify and locate the presence of various substances added to the artificial organ system.

Hattler Respiratory Catheter

The idea for an artificial lung developed in 1984 when Brack Hattler had two patients rushed into the ER with severe damage to their lungs, their only hope of survival was artificial lungs. Despite Hattler’s efforts both patients died a few days later. After that day, Hattler’s has dedicated himself to developing an artificial lung. This artificial lung would be targeted toward patients with acute respiratory distress syndrome, pneumonia, chronic lung disease, patients in need of organ transplants, and patients in intensive care units. The standard care today is the extracorporeal membrane oxygenators, which can be bulky and expensive, and causes life-threatening complications in more than half of its users. The IMO (Intravenous or Implantable Membrane Oxygenator) device has been designed to oxygenate the blood before it gets to the lungs, which allows the lung to rest and recover. The IMO device is to be only used for patients that have a chance to reverse their respiratory problems.

IMO consists of about 1000 hollow fiber membranes over the span of several feet in length. Oxygen enters through an external tube and flows through the fibers under vacuum. The oxygen in the fibers diffuses through tiny pores in the fiber wall into the blood. At the same time carbon dioxide diffuses out of the fibers and exist through a second tube. The central balloon pulses about 300 times a minutes to move the fibers and mix the blood. As this balloon inflates and deflates blood is drawn across the fibers. This provides little impedance to the blood flow returning to the heart. The IMO device is implanted through the vein in the leg, using percutaneous insertion (as done for angioplasty catheters and intra-aortic balloon pumps). The device is then positioned into the Vena Cava. An advantage of the IMO device is that it allows the lungs to do very little work, therefore letting the lungs rest and heal. When compared to ventilators that make the lungs work twice as hard due to the constant expanding and compressing to oxygenate the blood. This device is expected to benefit up to 700,000 patients a year. The patients will range from people with serious respiratory damage, acute emphysema, and severe asthma to victims of drowning and fire accidents to chemical weapons. The commercial product may be available in 2004 [15].

Intravenous membrane oxygenator

Artificial lungs have been undergoing development since the 1980s. The Intravenous Oxygenator (IVOX) was the first to be implanted in humans. IVOX could not provide adequate gas exchange. IVOX was only able to provide 30% of the basal gas exchange requirements in the best case, while at least 50% was required for IVOX to be deemed clinically useful.
A second generation ILAD, the Hattler Respiratory Catheter, was developed by Dr. Brack Hattler, University of Pittsburgh, USA. The Hattler Catheter can provide 50% of the gas exchange requirements. There are limitations of the amount of gas exchange that these types of devices can provide as there is a limited volume of intravascular space in which the device resides [20].

**Hollow fiber membrane**

The Intravenous Membrane Oxygenator (IMO) has been undergoing research development in the Artificial Lung Laboratory at the University of Pittsburgh under prior grants from the Army Medical Research and Material Command. The IMO promises to augment incomplete respiration in soldiers and civilians suffering from acute respiratory failure, such as that which might arise from inhalation of chemical or biological agents, direct projectile damage to the lungs, or indirect lung compromise from other injuries. The IMO is an artificial lung catheter that is inserted through the femoral vein in the leg and placed within the vena cava. The end of the catheter contains a bundle of hollow fiber membranes (Figure 9) connected through gas pathways in the shank of the catheter to an external O2 source. Oxygen diffuses through the permeable hollow fibers of the IMO into blood and CO2 diffuses out of the blood into the fibers and is removed from the exit gas pathway of the device. A balloon within the fiber bundle, pulsed with helium gas through another gas pathway, mixes the blood effectively over the fiber surfaces to improve the rate of gas exchange. The IMO has reached an advanced stage of research development in the laboratory, has gone through substantial prototype evolution and performance improvements, and has been tested extensively in the bench and in animal implants. The purpose and scope of the work done over the past year in the NTEC program was to finalize the IMO catheter performance and design specifications (i.e. to complete technology development on the IMO) in preparation for technology transfer and the formal product development that would lead to human clinical trials.

Technology development of the Intravenous Membrane Oxygenator (IMO) was completed during the NTEC Year 1 grant program (Figure 9). The principal tasks involved were finalizing the gas exchange specification for the IMO for clinical use, optimizing the gas pathways of the IMO and fiber selection to minimize insertion size, and developing biocompatible coatings to prevent plasma wetting and to minimize thrombus formation. The IMO was prepared for technology transfer to a medical device company which is continuing with the formal product development of the IMO required to gain FDA approval to begin human clinical trials. Once available for human clinical use the IMO will be an attractive alternative therapy for acute respiratory failure (ARF) associated with battlefield trauma and will be of great benefit in military and civilian applications. ARF arises from a variety of insults which leave the lungs unable to maintain adequate gas exchange. Respiratory failure and death usually follow unless the lungs are rested and allowed to recover from the insult. Respiratory failure can occur in soldiers in combat and noncombat situations suffering from trauma, shock, infections, smoke inhalation, or exposed to chemical agents injurious to the lungs. Likewise, the civilian population is not immune from chemical or biological attack, and in the event of such attack the need for pulmonary support for a large number of victims will exist in an emergency setting. Researches expect that the IMO will become a key medical device deployed in these situations [21].

**Figure 9.** Inserted Intravenous Membrane Oxygenator device [21].
Hollow Fiber Membrane Permeability Analysis

The fundamental gas exchange element of the IMO is the hollow fiber membrane (HFM). The capacity of the IMO to deliver oxygen and remove carbon dioxide from venous blood flow is determined by the resistance to gas flux of the HFM wall and of the blood phase flowing over the exterior of the fiber surface. Typically, in extracorporeal oxygenators the dominant mass transfer resistance is that of the blood phase, and the HFM wall resistance is assumed to be negligible. However, an intravenous oxygenator must reside within the vena cava and not restrict blood flow returning to the heart, thus the total fiber surface area is constrained to be approximately 4-6 times less than that of conventional extracorporeal devices. Thus design strategies for meeting gas transfer requirements in intravenous oxygenators rely on mechanisms for reducing blood-side mass transfer resistance. The natural result of a significant reduction in the blood-side mass transfer resistance is to increase the effect of the fiber wall resistance on overall device permeability.

Because of the greater potential effect that the HFM (Figure 10) permeability has on the gas transfer performance of an IVMO, selection of an appropriate fiber is critical. Not only must the fiber permeability be greater than the desired device permeability so as not to limit gas transfer performance, but it must also remain stable for extended periods of time. Contemporary extracorporeal membrane oxygenators are predominantly comprised of microporous-walled hollow fiber membranes which provide greater diffusional capability than "true" membrane fiber constructions. However, after several hours of use, the performance of microporous oxygenators deteriorates due to fiber wetting and subsequent serum leakage through the pores and into the gas flow path. Strategies to resist or block wetting include using fibers with markedly reduced pore size, or alternatively, using a composite fiber consisting of a thin nonporous (true) membrane layered over or sandwiched within a standard microporous wall. In both cases, the very strategies meant to resist fluid wetting also diminish fiber wall permeability. This is especially so in composite fibers, where the nonporous polymer layer can represent an appreciable impediment to diffusion [13].

Figure 10. Hollow Fiber Membrane [13].

To evaluate HFM permeability, a simple apparatus and methodology was developed for measuring HFM permeability in a gas-liquid environment (Figure 11). This procedure has the capability of studying a variety of fiber types in any liquid of interest, such as blood. The central component of the measurement procedure is a diffusion chamber which consists of a parallel arrangement of hollow fiber membranes submerged in a stirred liquid bath of fixed volume (300 cc). The apparatus and methodology developed to make these measurements requires relatively small liquid volumes, and so would lend itself well to fiber permeability studies in blood serum, plasma, or anticoagulated whole blood.

The methodology for extracting membrane permeability from the measurement of the overall system permeability is based on isolating the effect of the liquid side mass transfer resistance from the membrane resistance. This is done by measuring the system permeability at increasing levels of liquid side mixing which results in reduced liquid side resistance. Membrane permeability can then be determined by extrapolating the system permeability, $K$, to infinite mixing where the liquid side resistance is effectively zero, and the system permeability is equal to the membrane permeability, i.e. $K = K_m$.

A detailed analysis of the validity of the measurements obtained with the diffusion chamber is described in an article entitled, "Gas Permeability of hollow fiber membranes in a gas-liquid system" (Journal Membrane Science, Volume 117, 1996) and "A novel method for
measuring hollow fiber membrane permeability in a gas-liquid system" (American Society of Artificial Internal Organs, ASAIO Journal, Volume 42, 1996). The diffusion chamber is currently being used to compare the permeabilities and wetting characteristics of uncoated microporous HFMs versus the same fiber coated with an ultrathin nonporous polymer layer fabricated by Bend Research. Contrary to intuition, it has been found that in a gas-liquid environment, a coated fiber can have greater oxygen permeability than the same fiber, uncoated. The result is exciting for intravenous oxygenation because it means that a fiber which is resistant to wetting can be used without compromising the overall permeability of the device [13].

**Intrathoracic artificial lung**

Researchers at Northwestern University are developing an artificial lung that can be implanted inside the chest cavity and attached directly to the artery connecting the heart to the lung. The researchers have succeeded in preserving lung function in an animal model for 24 hours with the new device, intended primarily as a "bridge to transplant" for patients awaiting lung transplants and as a treatment for acute lung failure.

The implantable artificial lung contains a bundle of fibers that exchange oxygen for carbon dioxide. The "lung" is attached directly to the main pulmonary artery on the right side of the heart and returns the oxygenated blood to the left atrium of the heart. It can be adjusted so that a portion of the blood continues to circulate through the impaired natural lungs.

It marks the first 24-hour use of an implanted artificial lung in an animal model to date, according to Lyle F. Mockros, Professor of Biomedical Engineering at Northwestern University. He has coauthored a report published in the September-October issue of the American Society of Artificial Internal Organs Journal. "The development of a successful, implantable artificial lung will increase the therapeutic options for children and adults with severe lung disease". According to Robert Bartlett, Professor of Surgery at the University of Michigan and a leading authority on the development of artificial lungs, there is very good cooperation among the five groups to develop an implantable artificial lung. There groups are at: Penn State Medical Center; the University of Pittsburgh; in Salt Lake City; University of Michigan and North Western University.

The new device is called an implantable, intrathoracic artificial lung, or ITAL. It consists of a bundle of fibers with tiny holes that allow oxygen to move into the bloodstream and carbon dioxide to move back into the fibers. The devices are being implanted by Carl L. Backer, M.D., assistant professor of surgery. Keith E. Cook, a graduate student in biomedical engineering and lead author of the journal article, was primarily responsible for designing the new ITAL, which is smaller and more compliant than previous designs. The new device has a much higher oxygen and carbon dioxide delivery rate, providing for the first time the full gas-transfer requirements for a person at rest, he added. The artificial lung research is considered particularly urgent now because of the current success of lung transplant operations. Thousands of additional patients could benefit from lung transplants who do not have appropriately matched donor lungs available, and they die while waiting. An estimated 13.4 million Americans have some form of chronic lung disease, with about 75,000 deaths per year. The only current treatment for end-stage lung failure is lung transplantation. An additional 150,000 Americans acquire acute respiratory distress syndrome each year, with a mortality rate of over 50 percent [40].

**VENTILATOR THERAPY**

The acute respiratory distress syndrome (ARDS) continues as a contributor to the morbidity and mortality of patients in intensive care units throughout the world, imparting tremendous human and financial costs. During the last 10 years there has been a decline in ARDS mortality without a clear explanation. The American-European Consensus Committee on ARDS was formed to re-evaluate the standards for the ICU care of patients with acute lung injury (ALI), with regard to ventilatory strategies, the more promising pharmacologic agents, and the definition and quantification of pathologic features of ALI that require resolution. It was felt that the definition of strategies for the clinical design and coordination of studies between centers and continents was becoming increasingly important to facilitate the study of various new therapies for ARDS.

Despite advances in supportive care, the mortality rate in patients with the acute respiratory distress syndrome (ARDS) is widely considered to have remained high, and generally in excess of 50%. Large multicenter prospective controlled randomized trials are needed to provide definitive answers concerning the efficacy of new and existing therapies. These trials generally must address two considerations: Basic research that links the proposed new treatment to important pathophysiologic components of ARDS; and The risk-benefit ratio of the treatment to be tested. It may be naïve to assume that any single therapy will be a "magic” bullet to treat all aspects of ARDS.

This second American European Consensus Conference on ARDS [18] was organized in an attempt to analyze the pathophysiologic mechanisms of lung damage as they relate to mechanical ventilation strategies and to promising agents which may ultimately be shown to have utility in the treatment or prevention of acute lung injury (ALI) and ARDS. In addition, the increasing costs of care associated with only marginally perceived additional benefits of novel therapies prompted the Consensus Committee to re-evaluate the current treatment of ALI/ARDS. In order to analyze the recovery from ALI, an attempt was made to define the clinical and pathologic features of ALI that
require resolution and how these should be defined and quantified. The members of the Consensus Committee were divided into subcommittees, each of which was charged with discussing and developing a position paper on at least one aspect of the problem. These position papers were presented to the entire Committee for comments and discussion. When the Committee reached agreement, specific modifications were made to the position papers. The following subcommittee reports is a result of this consensus process: [ARDS Report #1333]

Although ARDS has previously been considered a problem of diffuse lung injury and a generalized increase of tissue recoil, it now appears that the radiographic, densitometric, and mechanical consequences of ARDS are heterogeneous. In severe cases, the inflation capacity of the lungs may be less than one third of normal. The compliance and fragility of tissues comprising the aerated compartment in ARDS are likely to bemoore functionally normal than previously envisioned, especially in the earliest phase of this disease. Computed values for airway and tissue resistance are elevated in ARDS, an observation that is perhaps best explained by the reduced number of patent airways. The refractory hypoxemia of ALI can be enhanced by supplementing inspired O2 and by raising mean and end-expiratory alveolar pressures. Each of these interventions, however, has associated risks and benefits. Animal studies have shown that high fractions of inspired O2 and high cycling pressures are potentially injurious, especially when applied over extended periods superimposed on pre-existing damage, or combined with other injurious agents. Widely held objectives of ventilation in the setting of ALI have given priority to normalizing arterial blood gases and avoiding depression of cardiac output. Until recently respiratory system pressures in humans have been monitored but not tightly constrained. Flow-controlled, volume-cycled ventilation, using tidal volumes of 10-15 ml/kg, has previously been the standard of practice in the management of ARDS and most other problems of adult ventilatory support. Mean airway pressure, as a clinically measurable reflection of mean alveolar pressure, relates fundamentally to oxygen exchange, cardiovascular performance, and fluid retention under conditions of passive inflation. Positive end-expiratory pressure (PEEP) has been used to increase end-expiratory transalveolar pressure and volume, and thereby to improve gas exchange. The alveolar pressure that determines aerated volume at end-expiration is the sum of deliberately applied PEEP and that which may arise by dynamic hyperinflation (auto or intrinsic PEEP).

The latter may often be significant in ALI/ARDS due to high minute ventilation, the use of extended inspiratory time fractions, and the elevated resistance of the native airway, endotracheal tube, and exhalation valve. All forms of barotrauma described in the pediatric literature, including interstitial emphysema, tension cysts, systemic gas embolism, and damage similar to bronchopulmonary dysplasia, have now been recognized in patients with ARDS. In experimental animals, the choice of ventilatory pattern influences the morphology of normal and previously injured tissue. From these animal studies, it is suspected that excessive regional volumes are damaging, whether produced by positive or negative pressure.

Ventilatory patterns that apply high transalveolar stretching forces cause or extend tissue edema and damage in experimental animals. Recent work strongly suggests that regional overdistention is commonly produced in patients with ARDS by static airway pressures greater than 30 cm H2O, a pressure level known to cause damage in sheep when sustained for more than a few hours. Although excessive tidal volume must be avoided, animal studies suggest that periodic inflations with a relatively large and sustained volume may be needed to avoid collapse of unstable lung units when very small tidal volumes (< 4-5 ml/kg) are used. Judging from the substantial delay to peak incidence of pneumothorax, the lung appears to be able to withstand exposure to somewhat higher forces in the earliest phase of human ARDS without radiographically evident barotraumas. Later in the course of illness the strong collagen infrastructure of the lung degrades unevenly, so that similar pressures are more likely to result in overt alveolar disruption (e.g., pneumothorax, pneumomediastinum, gas cyst formation). Animal studies indicate that failure to preserve a certain minimum end-expiratory transalveolar pressure in the early phase of ARDS may intensify pre-existing alveolar damage, especially when high tidal volumes are used. Indeed, the shear forces associated with tidal collapse and reinflation of injured alveolar tissues may be responsible for an important component of ventilator-induced lung damage. The end-expiratory pressure required to avert widespread alveolar collapse varies with the hydrostatic forces applied to the lung. Consequently, a higher pressure is required in patients to prevent atelectasis in dependent regions than in the regions more superior.

Gravitational factors, therefore, help to explain the strikingly dependent distribution of radiographic infiltrates shortly following the onset of lung injury, as well as reversal of these infiltrates and improved arterial oxygenation in the prone position. In experimental animal studies, total PEEP sufficient to place the tidal volume above the initial low compliance region of the static pressure-volume relationship of the respiratory system (Pflex) appears to attenuate the severe hemorrhagic edema otherwise induced by high ventilating pressures. Stress failure of the pulmonary capillaries with resulting pressures that exceed 40-90 mm Hg, depending on animal species. Although the relationship of this observation to the hemorrhagic edema of experimental (ventilator-induced) lung injury remains unclear, transcapillary mechanical forces of comparable magnitude may be generated in ARDS when high tidal volumes and peak static tidal pressures are used. High vascular pressures and blood flows may also be important determinants of lung injury. Certain adjuncts to conventional ventilation, such as nitric oxide inhalation tracheal gas insufflation, and perfluorocarbon-associated (partial liquid) ventilation,
currently show promise to improve transpulmonary gas exchange; other approaches, such as surfactant administration and inhaled prostacyclin may eventually prove beneficial.

Controversies detailed clinical information is not available for guidance regarding the maximally safe peak and mean alveolar pressures that can be applied for extended periods without inducing alveolar damage or retarding healing. Although failure to preserve a certain minimum end-expiratory transalveolar pressure has been shown experimentally to intensify pre-existing alveolar damage this phenomenon has not yet been clearly demonstrated in humans.

Consequently, expert opinion differs on whether applying the least PEEP that accomplishes adequate gas exchange or the guarantee of some minimal value of end-expiratory alveolar pressure is the best course to follow within the first few days of the disease process. Periodic application of sustained high inflating pressures to recruit unstable lung units continues to be advocated by some highly knowledgeable investigators, especially when small tidal volumes are used, as in high frequency ventilation. The appropriate tidal volume to use undoubtedly varies with the level of PEEP. There is no consensus regarding the contribution of vascular pressures, position changes, infection, inspired oxygen concentration, and other clinical variables on the incidence and intensity of ventilatorinduced lung injury. Allowing Pace, to rise to supernormal values (permissive hypercapnia) appears to be an effective strategy for limiting the need for ventilatory pressure. The full effects of hypercapnia on such important variables as gas exchange, cardiovascular dynamics, and tissue edema have yet to be determined in this setting.

Elevated fraction of inspired oxygen (FIO and high ventilatory pressures are often required to achieve near complete saturation of arterial blood with oxygen. The conditions (if any) under which arterial O2 saturation can be allowed to fall to subnormal values without unacceptable clinical consequences have not yet been delineated. There is no clear consensus regarding the most appropriate indicator of regional or global adequacy/inadequacy of O2 delivery (dysoxia) for routine clinical use. The combinations of O2 concentration and exposure duration that produce significant lung damage have not been firmly established in the setting of ARDS, and may well vary with disease severity and individual susceptibility. Similarly, although a considerable body of experimental data has been accumulated, detailed information is not yet available regarding which ventilation pressures and patterns of ventilation are safe to apply for extended periods. In the absence of definitive data obtained in a clinical context, some knowledgeable practitioners increase lung volume, whereas others prefer to use higher inspired fractions of O2 rather than increase peak, mean, and end-expiratory airway pressures. Although absolute agreement was not reached, the majority of the consensus conferences believe that limiting airway pressure takes precedence over limiting FIO.

A very recent prospective randomized study from a single institution indicates improved lung mechanics, gas exchange, and respiratory mortality by following a strategy emphasizing ventilation with reduced alveolar pressure and tidal volume. Yet, one well-conducted prospective comparison of a modern approach that included inverse ratio ventilation and extrapulmonary CO2 removal (when necessary) to a more conventional strategy was unable to detect a significant outcome difference between them. Most clinicians recognize the need to control maximum alveolar pressure and are cognizant of a connection between mean alveolar pressure and arterial O2 tension; however, there is no uniformity of opinion regarding the best mode and method of ventilatory support. Specifically, whether different methods for achieving a similar mean airway pressure (such as high-level PEEP) and inverse ratio ventilation differ with respect to risks and benefits has not been adequately examined.

The extent to which spontaneous (versus controlled) ventilation should be encouraged has also been an area of uncertainty. There is renewed interest in high-frequency ventilation applied at an appropriate mean lung volume as a ventilatory strategy for ARDS, but the basis of this enthusiasm remains primarily theoretical and experimental at this time. Several recent studies have addressed the topic of risk and benefit for manipulation of oxygen delivery. Because mechanical ventilation can benefit or impair O2 delivery, such observations may hold implications for its implementation [6].

HOW ARTIFICIAL LUNGS WORK

Artificial lungs or lung assist devices have the potential to benefit about 150,000 patients annually who have acute respiratory problems. Lung replacement is one of the possible treatments, but there are not enough natural lung donors. The Intravenous Membrane Oxygenator (IMO) device is an "engineered" device that performs the main function of the natural lung (blood oxygenation and carbon dioxide removal) but operates differently than the natural lung. The IMO is an intracorporeal device implanted within the vena cava that consists of hundred of hollow fiber membranes and an inflating-deflating balloon to generate a secondary flow across the fiber in order to enhance the oxygen transfer rates. The design of IMO devices was optimized by performing Direct Numerical Simulations (DNS) of oxygen transfer and hemodynamics, to reduce the costly time-consuming experimental design cycle. Specifically, the objective was to obtain a better understanding of the basic mechanisms responsible for mass transfer enhancement induced by cross-pulsating flow, quantify the effect of the frequency and amplitude of the balloon pulsation on the efficiency of the oxygenation and carbon dioxide removal, and quantify the risk of blood damage and coagulation. A computational model of the IMO device was developed and performed large scale DNS...
of the conservation of mass, momentum and species equations with a stationary and a pulsating balloon [5].

**Artificial Lung**

Artificial lungs are in an era of prototypes. The work on production of an artificial lung is summarized by Dr. Griffith of the University of Pittsburgh, Pennsylvania. The goal is to develop an artificial device that could maintain respiratory function while allowing time for damaged lungs to recover. At present, extracorporeal membrane oxygenation (ECMO) is the only modality available when an individual cannot be sustained by traditional mechanical ventilation. Two types of devices are currently under development: Paracorporeal devices are designed to provide total support of oxygen and carbon dioxide exchange. This type of device will be used for a prolonged time period to sustain patients waiting for transplantation. Intracorporeal devices are aimed at providing partial support for a shorter period of time for patients with acute respiratory failure. However, progress in developing an artificial lung has been slow due to difficulties in engineering problems and limitation of required materials. Gas exchange across a membrane, achieving adequate surface area, and blood perfusion/mixture are additional obstacles to development of a practical artificial device. In contrast to ECMO, improved features of the new devices include agitated blood flow and gas flow at right angles to blood flow both of which enhance gas exchange.

A device under development at the University of Pittsburgh and the McGowan Center for Artificial Organ Development is the Pitt Artificial Lung. This device utilizes active mixing and pumping to increase the amount of gas exchange within the system. Biocompatibility, blood clots, and fiber endurance pose ongoing challenges.

Another device under development, at the University of Pittsburgh, is the Hattler Respiratory Catheter. This intracorporeal respiratory assist device is inserted through a vein in the leg and positioned in the vena cava, the major vein returning blood to the heart. It consists of hollow fiber porous membranes that allow for exchange of oxygen and carbon dioxide removal. An updated design modification allows for inflation at a rate of 300 beats/minute, thereby enhancing blood mixing to allow for more efficient oxygenation. Gas exchange in cows has been supported for as long as 8 hours. It is anticipated that the temporary device will be approved for clinical trials in approximately 1 year; testing of permanent devices will occur in 2 to 3 years.

Significant research still needs to be done to develop the "ideal" bioartificial lung. One interesting prospect is creation of a bioartificial fiber that would dissolve. This could be seeded with respiratory cells developed in a bioreactor.

In an artificial lung, replacing the gas transfer function of the natural organ implies that blood circulation can be sustained by mechanical pumps for extended periods of time to achieve a continuous, rather than a batch process, and that venous blood can be arterialized in that device by exposure to a gas mixture of appropriate composition. The external gas supply to an artificial lung does not pose particular problems, since pressurized gas mixtures are readily available. Similarly the components of blood which provide its gas-carrying capacity are well identified and can be adapted to the task at hand.

In clinical practice, it is important to minimize the amount of donor blood needed to fill the extracorporeal circuit, or priming volume. Therefore a heart-lung machine is generally filled with an electrolyte or plasma expander solution (with or without donor blood), resulting in hemodilution upon mixing of the contents of the extracorporeal and intracorporeal blood circuits. The critical aspects for the operation of an artificial lung are blood distribution to the exchanger, diffusion resistances in the blood mass transfer boundary layer, and stability of the gas exchange process. Artificial lungs are expected to perform within acceptable limits of safety and effectiveness. The most common clinical situation in which an artificial lung is needed is typically of short duration, with resting or basal metabolism in anesthetized patients.

An artificial lung designed to replace the gas exchange function of the natural organ during cardiac surgery must meet specifications which are far less demanding than the range of capability of the mammalian lung would suggest. Nonetheless, these specifications must embrace all metabolic situations which a patient undergoes in cardiopulmonary bypass [15].

**Artificial Lungs: Direct contact type**

This class of artificial lung is employed in the majority of open-heart surgical procedures, and may be further classified accordingly to the mode of presentation of the blood to the ventilating gas. The sub-types are bubble, film and disc. In the film type, a thin layer of blood flows over a solid surface, which is situated within the gas phase. This thin-film effect is also achieved in the disc oxygenator by continuously forming a blood layer on a series of circular discs pick up blood from are reservoir in which they are partially immersed. The film of blood formed on the remaining disc area is exposed to the ventilating gas. Although the film and disc units have been widely used in the past, they have been superseded by more easily operated bubble systems.

**Artificial Lung: Indirect-contact type-membrane**

All membrane oxygenators in clinical use at present have sheet-membrane geometries as opposed to tubular configurations. The membrane materials employed are
homogeneous polymers (e.g., silicone rubber) with or without fabric reinforcement, or polymer with micropores (e.g., polytetrafluoroethylene). Devices with pure laminar flow are fluid-limited in performance for existing membrane materials. However, laminar-flow units are preferred for clinical use since they are generally easier to operate than systems which employ convective mixing to enhance performance. The descriptions of several clinical membrane oxygenators, which are principally fluid-limited in performance, are given followed by a discussion of two experimental devices with convectively mixed blood flow.

a. Pneumatic Delivery System

The existing pneumatic delivery system is being thoroughly studied to assess its functionality in a scaled-up device (Figure 12). The delivery system has three main functions: to supply oxygen to the fiber bundle; to remove the oxygen and carbon dioxide exhaust gases from the fiber bundle; and to allow the delivery of an oscillating flow of helium to actuate the balloon. For maximal oxygen exchange, the pressure losses before the fiber bundle should be minimized. Any loss of pressure before the fiber bundle will detract from the driving gradient for oxygen exchange. The pressure losses after the fiber bundle should also be as small as possible to reduce the load on the driving system. To ensure full filling and emptying of the balloon, a low resistance helium pathway is required.

The pneumatic delivery system performs well in the prototypes currently being tested. However, several problems are likely to arise when the device is resized for human use. The length of the fiber bundle will be doubled, thus adding length to the oxygen delivery pathway and increasing the pressure losses before the fiber bundle. Also, the size of the balloon will be increased from 30 to 70 cc. At a given beat rate, the flow rate of helium required to fill a 70 cc. balloon will be 2.3 times larger than the flow rate required to fill the 30 cc. balloons. In order for the drive system now in use to provide helium at this rate, the resistance of the helium pathway may need to be reduced.

Testing of the device has shown that the drive system being used to power the balloon fails to fully inflate and deflate the balloon above a beat rate of 180 beats per minute. Therefore, the resistance of the helium pathway must be decreased if a larger balloon is to be pulsed effectively.

It is likely that the concentric tube design now in use will be replaced by a multilumen catheter. Preliminary calculations have indicated that a multilumen catheter would both improve the pneumatic performance of the delivery system and ease the manufacture and assembly of the device [22].

b. Drive System for a balloon

Throughout the development of the IMO, balloon inflation and deflation was controlled with an intra-aortic balloon pump (IABP) console. This console was designed to pulse the balloon at the same rate as the human heart beat (around 80 beats per minute), however gas exchange in the IMO improves as the beat rate increases and maximizes at approximately 150 beats per minute. Unfortunately, the IABP console cannot completely fill and empty the balloon at higher beat rates, necessitating the development of an improved drive system for the IMO [23].

Figure 12. Predicted performance of the system in a scaled-up device [22].

Figure 13. Pneumatic pathway [23].
The main goal of the drive system is to fill and empty the balloon as quickly as possible. This will require both a high pressure reservoir and a vacuum reservoir, each connected to the balloon via a solenoid valve. The balloon is filled by opening the valve to the high pressure reservoir, and emptied by opening the valve to the low pressure reservoir (Figure 13). The balloon pulsation rate is limited by the amount of time it takes to fill and empty the balloon. If the pulsation rate is too high, the balloon will not inflate and deflate completely, and the subsequent decrease in blood mixing will result in inadequate oxygenation. The amount of time required depends on the driving pressure (the pressures in the high pressure and vacuum reservoirs) and the pressure drop across the system. Because it is possible to apply several atmospheres of positive pressure but only draw one atmosphere of vacuum, emptying the balloon will take longer than filling it and will become a limiting factor of the balloon pulsation rate. The ultimate goal of the drive system to fill and empty the balloon quickly enough that oxygenation is not limited by the balloon pulsation rate.

GAS EXCHANGE

During respiration, air becomes saturated with water vapor by the time it enters the alveolar sac. In the alveolus, it also mixes with carbon dioxide (Figure 14).

At the alveolar membrane, each gas diffuses in the direction of decreasing the partial pressure of that gas. In other words, oxygen diffuses towards the blood and is taken up by hemoglobin, and carbon dioxide diffuses towards the alveolus and mixes with the air. No "active process" is involved. Oxygen simply diffuses through the membrane and plasma, and is taken up by the red blood cells.

Although the diffusion occurs very rapidly, the gases do not have time to totally equilibrate. There will be a small pressure difference across the alveolar membrane for each gas. That is, oxygen partial pressure will be somewhat higher in the alveolus than in the blood, and carbon dioxide pressure will be slightly higher in the blood than in the alveolus. In the case of oxygen, this pressure difference is calculated for the lung as a whole as, "arterial-alveolar (Aa) gradient."

About 2% of the blood flow through the lungs bypasses the pulmonary capillaries. This blood is not oxygenated, and forms a "physiologic shunt." Because of this blood that bypasses the alveoli, arterial blood will always contain less oxygen pressure than blood that has equilibrated with the oxygen in the lung alveoli. This "shunt" becomes part of the calculated "Aa gradient."

As blood circulates through the body, an opposite change occurs in the capillaries of the systemic circulation. Oxygen diffuses from the area of higher pressure — the blood — into the lower pressure of the cells. Carbon dioxide diffuses from the cells into the blood [16].
Gas Exchange and Respiratory Surface

As mentioned, a major function of the circulatory system is to transport oxygen and carbon dioxide to and away from cells. In humans, the gas exchange organ system is the respiratory or breathing system (Figure 15).

The actual respiratory surface is on the alveoli inside the lungs. An average adult has about 600 million alveoli, giving a total surface area of about 100m², so the area is huge. The walls of the alveoli are composed of a single layer of flattened epithelial cells, as are the walls of the capillaries, so gases need to diffuse through just two thin cells (Figure 16). Water diffuses from the alveoli cells into the alveoli so that they are constantly moist. Oxygen dissolves in this water before diffusing through the cells into the blood, where it is taken up by haemoglobin in the red blood cells. The water also contains a soapy surfactant which reduces its surface tension and stops the alveoli from collapsing. The alveoli also contain phagocyte cells to kill any bacteria that have not been trapped by the mucus [24].

Figure 16. The alveoli diagram [24].

Table 2. Physical properties of air, oxygen and carbon dioxide [30, 31, 32].

<table>
<thead>
<tr>
<th>Property</th>
<th>MW</th>
<th>Density</th>
<th>Specific volume</th>
<th>Specific gravity</th>
<th>pH</th>
<th>Surface tension</th>
<th>Relative viscosity</th>
<th>Gas constant</th>
<th>Specific heat</th>
<th>Colloid osmotic pressure</th>
<th>Average volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air at STP</td>
<td>28</td>
<td>0.0012</td>
<td>869 g/cm³</td>
<td>0.0016</td>
<td>NA</td>
<td>NA</td>
<td>0.019</td>
<td>289 J/kg.K</td>
<td>1004 g-cal</td>
<td>0</td>
<td>mm Hg</td>
</tr>
<tr>
<td>Oxygen</td>
<td>32</td>
<td>0.0014</td>
<td>714 g/cm³</td>
<td>0.0014</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>260 J/kg.K</td>
<td>909 J/kg.K</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CO₂</td>
<td>44</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>189 J/kg.K</td>
<td>840 J/kg.K</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
The steep concentration gradient across the respiratory surface is maintained in two ways: by blood flow on one side and by air flow on the other side. This means oxygen can always diffuse down its concentration gradient from the air to the blood, while at the same time carbon dioxide can diffuse down its concentration gradient from the blood to the air. The flow of air in and out of the alveoli is called ventilation and has two stages: inspiration (or inhalation) and expiration (or exhalation) as shown in figure 16. Lungs are not muscular and cannot ventilate themselves, but instead the whole thorax moves and changes size, due to the action of two sets of muscles: the intercostal muscles and the diaphragm.

These movements are transmitted to the lungs via the pleural sac surrounding each lung. The outer membrane is attached to the thorax and the inner membrane is attached to the lungs. Between the membranes is the pleural fluid, which is incompressible, so if the thorax moves, the lungs move too. The alveoli are elastic and collapse if not held stretched by the thorax (as happens in stab wounds or deliberately to rest a lung) [24]. The property of the air, oxygen and carbon dioxide are show in table 2.

VENTILATION RESISTANCE

Ventilation Modes

Since the advent of respirators, clinicians have devised a variety of strategies to ventilate the lungs based on patient conditions. For instance, some patients need a respirator to completely take over the task of ventilating their lungs. In this case, the ventilator operates in mandatory mode and delivers mandatory breaths. On the other hand, some patients are able to initiate a breath and breathe on their own, but may need oxygen-enriched air flow or slightly elevated airway pressure. When a ventilator assists a patient who is capable of cemanding breath, the ventilator delivers spontaneous breaths and operates in spontaneous mode. In many cases, it is first necessary to treat the patient with mandatory ventilation and as the patient's condition improves spontaneous ventilation is introduced; it is used primarily to wean the patient from mandatory breathing [29].

RESPIRATORY MECHANICS [41]

The main objective is to investigate the mechanical properties of the airways and respiratory tissues. Our current projects are focused on the study of the upper airway collapsibility in sleep apnea, and on respiratory mechanics monitoring in patients subjected to non-invasive mechanical ventilation. The clinical aims of this research are to achieve better non-invasive diagnostic techniques of these diseases and to optimize their treatment by means of ventilatory support.

Assessing the mechanical properties of the respiratory system during non-invasive ventilation and during sleep is particularly challenging since only methods that are non-invasive and that do not require patient cooperation can be used. We investigate respiratory mechanics by combining conventional techniques with novel approaches such as the Forced Oscillation Technique (FOT). Depending on the hypothesis to be tested, the studies are carried out on animals, on healthy subjects or on patients with different respiratory diseases. Data interpretation is carried out by means of models featuring respiratory mechanics including parameters of pathophysiologic interest.

Non-invasive mechanical ventilation is commonly applied in patients requiring artificial breathing support owing to acute or chronic respiratory failure. Our approach to assess respiratory mechanics in obstructive and restrictive patients subjected to non-invasive mechanical ventilation is focused on the application of FOT. We have recently shown that FOT provides a reliable estimation of the respiratory system resistance in patients subjected to ventilatory support through a nasal/face mask, and that this technique is easily simplified by application of the forced oscillation by means of the ventilator.

Sleep apnea is a highly prevalent disease characterized by recurrent upper airway closure during sleep. Our lab has shown that FOT allows an easy characterization of the degree of airway obstruction along the breathing cycle during sleep, and that the technique is helpful in diagnosing sleep apnea and in titrating the treatment with continuous positive airway pressure (CPAP). We analyze and optimize the methods for the assessment of sleep disturbances by means of simplified sensors (pulse oximeters, thermistors, nasal prongs). We also develop methods for evaluating the performance of automatic CPAP devices.

FOT is a method for non-invasively assessing respiratory mechanics without patient cooperation. FOT is based on the application of a small pressure oscillation (~1 cm H₂O) at the mouth while the patient is spontaneously breathing. The oscillation pressure is generated by a loudspeaker-in-box assembly. Pressure and flow are measured at the patient's airway opening by means of a pressure sensor and a pneumotachograph. A low resistance leak open to the atmosphere is placed in the proximity of the patient to reduce the dead space during the measurement. The FOT device includes the circuitry required to drive the loudspeaker and record the signals. The oscillatory resistance and reactance of the patient's respiratory system are derived by Fourier analysis of the pressure and flow signals recorded at the airway opening. As forced oscillation can be applied at different frequencies, patient mechanics can be assessed over a wide frequency band, which is of particular interest to investigate the mechanical properties of the respiratory system with models featuring airways and tissue viscoelasticity. Given that FOT measurements do not require patient cooperation, the technique is suitable for assessing respiratory mechanics during normal breathing in infants, children and the elderly or in special clinical applications such as mechanical ventilation and sleep monitoring [41].
Table 3. Normal Respiratory Mechanics Values [26].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adult</th>
<th>Neonatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Rate</td>
<td>10-15 breaths/minute</td>
<td>30-40 breaths/minute</td>
</tr>
<tr>
<td>Tidal Volume</td>
<td>7-10 ml/Kg</td>
<td>5-7 ml/Kg</td>
</tr>
<tr>
<td>Minute Ventilation</td>
<td>5-10 liters/min.</td>
<td>200-300 ml/Kg/min.</td>
</tr>
<tr>
<td>Dynamic Compliance</td>
<td>25-50 ml/cm H₂O</td>
<td>1-2 ml/cm H₂O/Kg</td>
</tr>
<tr>
<td>Airway Resistance</td>
<td>2-5 cm H₂O/L/S</td>
<td>25-50 cm H₂O/L/S</td>
</tr>
<tr>
<td>Work of Breathing (Insp.)</td>
<td>0.3-0.6 joules/liter</td>
<td>1.2-2.1 joules/liter</td>
</tr>
<tr>
<td>Intrinsic PEEP</td>
<td>0 cm H₂O</td>
<td>2-3 cm H₂O</td>
</tr>
<tr>
<td>Respiratory Drive PO.1</td>
<td>2-4 cm H₂O</td>
<td>0.7-1.5 cm H₂O</td>
</tr>
</tbody>
</table>

Respiratory Mechanics Products

Mechanical ventilators deliver gas at a pressure and flow which results in a change in patient lung volume. Before waveform graphics became integral components of ventilator systems, ventilator monitoring was restricted to reading the ventilator’s controls, digital monitors and mechanical gauges as well as physical assessments. Detailed analysis of the patient/ventilator interface was, therefore, impossible. Technological advances now permit continuous Respiratory Mechanics monitoring, including graphic display of gas flow, volume, and airway pressure. Output waveforms are useful tools to study the characteristics of ventilator operation and provide a graphic display of the various modes of ventilation. Waveform analysis can be used to optimize mechanical ventilatory support and analyze ventilator incidents and alarm conditions. Using this technology, it is now possible to shape the form of ventilatory support to improve patient-ventilator synchrony, reduce work of breathing, and calculate a variety of physiologic parameters related to Respiratory Mechanics.

There are several products available to assist the medical device manufacturer in adding Respiratory Mechanics monitoring to ventilators or stand alone monitors.

Figure 17. Respiratory Mechanics Module [25].

Figure 18. EZFlow Sensors [25].
CPT's OEM Respiratory Mechanics system is a small, low power and fully digital system that is available with or without a purge (Figure 18 to 20).

The system utilizes a proprietary smart connector which interfaces to the disposable EZ-Flow flow sensor. This chassis mount connector tells the system that a sensor is properly placed, identifies the type of sensor and maintains tubing polarity.

- The module is based upon a Philips 80C51 XA 16 bit microprocessor.
- Pressures are measured by two piezoresistive bridge based differential pressure transducers: 5" H2O and 5 psi ranges. These transducers are internally compensated for temperature, but additional compensation is made from a digital temperature device on the board, placed between the transducers.
- The system utilizes a 24 bit A/D converter to interface transducer output to the microprocessor.
- Power regulation on the board allows for input voltages to range from 4V - 9V. The purge system consumes approximately 1000mW.
- Bi-directional RS232 serial communication is used to interface to the module. The specific protocol is available upon request.
- Clearance above the board can be no less than 0.6 inch; below board clearance needed is 0.4 inch.
- The purge system is for long term, continuous monitoring - purgeless for less than four house of monitoring. The purge function maintains pressure line patency.

The Respiratory Mechanics Module is available for evaluation and product development by purchasing our Respiratory Mechanics Evaluation Kit [25]. Negative and positive pressure ventilators are shown in figures 21 and 22.

**CARDIOPULMONARY BYPASS**

To repair most cardiac defects, the cardiothoracic surgeon requires a bloodless, motionless field in which to work. To achieve this, the motion of the heart and lungs must be stopped.

For this to occur, there needs to be a means for blood to circulate throughout the body, delivering the nutrients and oxygen necessary for life, while the heart and lungs are not functioning. This is made possible through a process known as cardiopulmonary bypass (CPB).

Tubing made of clear polyvinyl chloride (PVC) contains the patients' blood as it is diverted from the body. Large bore catheters (called cannula) are placed in the right side of the heart, allowing the desaturated blood from the body to enter the cardiopulmonary bypass circuit.

The PVC tubing runs through a mechanical pump that can be regulated to the proper cardiac output for a given patient.

For example, a 5-year-old child has a much smaller cardiac output than an adult does; thus the pump must run at a higher rate for the adult patient than the child. More PVC tubing delivers blood from the mechanical pump to a gas exchange device called an oxygenator, or artificial lung.

The oxygenator performs the same job as the lungs: oxygenation of the blood as well as removal of carbon dioxide.

This re-oxygenated blood is then returned to the body via another cannula placed in the aorta. In this way, cardiopulmonary bypass permits the patients' blood to bypass the heart and lungs, achieving the desired bloodless, motionless operative field and still supplying all the other organs of the body with a constant supply of oxygen and nutrient-rich blood.

The sum total of the mechanical pump, oxygenator, cannula and PVC tubing is often referred to as the heart-lung machine, or simply "the pump." When a patient is being supported by a heart-lung machine, the patient is said to be "on bypass" or "on the pump." Conversely, when a patient is taken off of this support, it is termed "off bypass" or "off the pump" [35].
Figure 21. A simplified illustration of negative – pressure ventilator [29].

Figure 22. A simplified diagram of the functional block of a positive – pressure ventilator [29].

Cardiopulmonary bypass risks

Although the origins of cardiopulmonary bypass can be traced back to the 19th century, the field has developed rapidly in the last 50 years.

The first attempt to use a heart-lung machine for total cardiopulmonary bypass was carried out at the University of Minnesota in 1951. Since that time, cardiopulmonary bypass has become a standard, widely used, low-risk procedure.

It is necessary to recognize some adverse effects may be seen when the circulation of the body is taken over artificially.

Cardiopulmonary bypass has a very wide range of effects on the body. All organ systems are affected by cardiopulmonary bypass, mainly the heart, lungs, brain and kidneys.

These effects can range from mild to severe based on how sick the patient is before surgery, the length of time that a patient is supported by cardiopulmonary bypass and the complexity of the operation being performed.

The function of the heart may be compromised to a degree after bypass surgery. Some patients have subtle neurologic changes after bypass surgery. The occurrence of stroke or seizures during or after bypass remains low, but is a possibility.

The kidney may experience damage ranging from decreased urine output to complete renal failure. Areas of the lung may fail to fully expand after bypass. This condition is known as atelectasis.

During cardiopulmonary bypass, the patients' blood makes contact with the foreign surfaces that make up the heart-lung machine, causing the patients' inflammatory system to be activated. Research has shown that this response can be damaging to certain tissues in the body. Due to the extra fluid volume needed to fill the cardiopulmonary bypass circuit, the patients' blood volume is diluted. This may require transfusion of blood products to the patient while on cardiopulmonary bypass and blood clotting abnormalities during the post-operative period.

The risk of serious complications related to being placed on cardiopulmonary support depends on the age of the patient, how ill they are at the time of the operation and the complexity of the surgery to be performed.

In most cases the risk is below one percent, but in higher complexity situations, it may be as high as 10 percent to 20 percent [35].

AEROSOL DELIVERY OF DRUGS

For both lung and systemic diseases, aerosol delivery of drugs into the lungs can often offer substantial advantages over other routes of administration. In the intensive care unit, however, the artificial airway can be a substantial barrier to aerosol delivery, so clinicians must pay careful attention to the ventilator pattern, the delivery gas humidity/density, the device characteristics, and the circuit/tube properties. When those are optimized, aerosol delivery from a nebulizer or metered-dose inhaler and through an endotracheal tube can begin to approach that seen in a nonintubated patient. Novel approaches, such as generating the aerosol within the airway, offer the opportunity to greatly increase deposition efficiency and focal drug targeting in intubated patients.

Medication delivery into the airways of intubated patients can offer substantial advantages over parenteral or oral administration routes. For medications targeted at lung diseases, a higher therapeutic index can be achieved with drugs delivered directly to the site of intended action, with
little or no systemic exposure. The lung can also be a useful portal for medications designed for systemic targets, because drugs that can easily pass through the alveolar-capillary interface (eg, insulin) can be exposed to a large lung surface area in contact with the entire cardiac output.

Effective aerosolized medication delivery into the lungs of intubated patients depends on many of the same factors important in nonintubated patients: efficient device output, small particle size, low-velocity gas flow, large inspired volume, and breath-hold at end inspiration. The intubated patient, however, offers additional challenges: the artificial airway is a different geometry than the natural airway; the aerosol delivery system is generally attached to the ventilator circuit in which heat, humidification, and bias gas flows may be present; pressure gradients down the airways are different than during spontaneous breathing; and the required mechanical ventilatory pattern may not be ideal for aerosol delivery [6].

**BIOFLUID DYNAMICS**

The Immersed Boundary (IB) method is a computational technique that was introduced by Peskin in the early 1970s as a method for studying a particular biofluid dynamics problem, namely the coupled motion of the blood filling the ventricles of the heart, the muscles of the heart wall, and the leaflets of the cardiac valves. Since that time, the method has been extended and applied to a wide variety of biofluid dynamics problems. Among others, these include platelet aggregation during blood clotting, swimming of aquatic flagellates, motion of the basilar membrane in the inner ear, the formation of bacterial biofilms, fluid motion in the afferent arterioles of the kidney, and pumping by ciliated arrays of tentacles on marine organisms. What these problems have in common with the heart problem is that they involve the motion of a viscous incompressible fluid, the motion of one or more deformable elastic objects immersed in the fluid, and/or the motion of one or more deformable elastic surfaces that bound the fluid. Because the objects or surfaces are deformable and elastic, their motion is coupled to the fluid motion, i.e., the motion of each affects the other. These, in fact, are features of essentially all biofluid dynamics problems. This situation is different from the traditional engineering fluid dynamics problem which involves fluid motion through or around a rigid object of specified geometry.

The immersed boundary (IB) method has proved itself to be well suited for studying biofluid dynamics problems on scales ranging from subcellular to organ-size to organism-size. It has been used to look at hydrodynamic interactions among multiple organisms moving in the same fluid. The IB method deals primarily with time-dependent problems, and it takes into account both fluid viscosity and fluid inertia. In designing the original IB method, Peskin realized the advantages of describing the fluid variables and the immersed objects in different ways. The fluid variables (velocity, pressure, force density) are described in what is known as an Eulerian manner. One focuses on each point in space and asks how a quantity, like the fluid velocity, changes with time at that point in space. The objects are described in what is called a Lagrangian manner. Each material point on an object is tagged with a unique label, and one then tracks how the location of the material point with a given label changes as time advances and the system evolves. The state of the system at any time is given by the fluid velocity and pressure fields, and by the locations of the Lagrangian points which constitute the immersed objects. The essence of how the Immersed Boundary method computes the change in the system over a short time interval (or timestep) is as follows.

From the Lagrangian description of each immersed object, it is straight forward to determine how much the object has been stretched and deformed at the beginning of the timestep, and from this to calculate the elastic forces generated within the object. Since the object is in direct contact with the fluid, these forces affect the fluid motion. To calculate the effect of these forces on the fluid, they are transmitted from the elastic objects to the fluid which immediately surrounds them, and thus contribute to the force density term in the fluid dynamics equations which drives the fluid motion. In fact, within the IB method, the fluid dynamics equations are solved everywhere (including inside the elastic objects) and the only way that the fluid 'feels' the presence of the elastic objects is through the force density just described. Contributions to the fluid force density from the immersed objects are localized to regions immediately adjacent to the objects, and it in this way that the geometry of the objects makes itself felt. Once the fluid force density is known, the partial differential equations which describe the fluid motion are solved to determine the new fluid velocity and pressure at each point of space. Finally, the fact that there is 'no-slip' between a point of a viscous fluid and a point of an object immediately adjacent to it gives an equation of motion for each immersed boundary point: The velocity of the immersed boundary point is just the velocity of the fluid at the same location. The immersed boundary point location is therefore changed by an amount equal to this velocity multiplied by the duration of the time step.

With IB method, despite the existence of irregular immersed boundaries, the fluid dynamics equations are solved on a regular finite difference grid. This allows an IB code to utilize fast numerical techniques to calculate the fluid velocities. By contrast, for the competing finite element method, a regular grid cannot be used to update the fluid velocities, and therefore, fast numerical solvers cannot be used. Furthermore, the motion of the immersed boundary would require that the shape of the finite elements change from one timestep to the next, and accuracy considerations would require that the entire domain be regridded periodically. The irregular grids require cumbersome data structures and the regridding is expensive. Similar drawbacks hold for finite difference methods which use boundary-fitted coordinates [7].
Laminar Flow Between Two Parallel Plates

First of all, let us consider a two-dimensional (plane) incompressible steady-state flow of viscous fluid (water) between two parallel stationary plates spaced at a distance of $2h = 0.001$ m (Figure 23). At the channel inlet, the water has standard ambient temperature (293.2 K) and a uniform inlet velocity profile of 0.1 m/s (entrance disturbances are neglected). The inlet pressure is not known beforehand, since it will be obtained from the calculation in accordance with the specified channel exit pressure of 1 atm and the 0.023 m channel length. (The fluid passes through the channel due to the pressure gradient.)

$$u(y) = -\frac{1}{2\mu} \frac{dP}{dx} (h^2 - y^2)$$

Where $\mu$= Fluid dynamic viscosity, $h$ = Half height of the channel, $dP/dx$ = the longitudinal pressure gradient along the channel, which is defined as:

$$\frac{dP}{dx} = -\frac{3\mu u_{average}}{h^2}$$

The Solid Works model is shown in Fig.18 for the 2D calculation. The boundary conditions are specified as mentioned above and the initial conditions coincide with the inlet boundary conditions. The results of the calculation are presented in Figures 25 and 26.

Since the Reynolds number based on the channel height is equal to about $Re=100$, the flow is laminar. Therefore, in accordance with well-known theory, after some entrance length the flow profile $u(y)$ becomes fully developed and invariable.

Figure 23. Flow between two parallel plates [9].

Figure 24. The solid works model for calculation 2D flow between two parallel plates [9].

Figure 25. The longitudinal pressure change along the channel [9].

The calculations have been performed at the result resolution levels of 3 and 5 for determining their influence on the obtained results (the result resolution level specified by the user in FloWorks 2001 governs the computational mesh and convergence criteria). Figure 19 shows that after some entrance length of about 0.002 m the pressure gradient governing the channel pressure loss becomes constant, nearly the same as predicted theoretically. It is seen that the calculations performed at result resolution levels 3 and 5 yield practically the same results.

Figure 26 reveals that the fluid velocity profile at the channel exit obtained from the calculation performed at result resolution level 5 is fairly close to the theoretical one, whereas the result resolution level 3 results are not so accurate [9].
Flow through straight tubes

The membrane-limited process is CO₂-limited and the fluid-limited process is O₂-limited. The corresponding CO₂ curves are relatively close to each other. The fluid-limited CO₂ process is five times less efficient than the membrane-limited process. The gas transfer efficiency could be improved by inducing mixing in the fluid phase. One way of gently mixing the blood is to induce laminar secondary circulations by coiling the tubes and thereby inducing circulation centrifugal forces.

Axial flow through space between concentric round tubes

Blood flowing axially in the annular space between concentric cylinders will be more easily oxygenated than the same flow through a straight tube. The annular geometry provides more gas exchange surface per unit blood volume than the corresponding tube and a resulting decrease in necessary diffusion times.

In a study of blood-gas exchange in an annular geometry, we assume oxygen atmospheres outside the outer tube and inside the inner tube. Figure 27 shows the changes of saturation and \( P_{CO_2} \) as a function of the dimensionless length, \( DL/gq \).

The results depend on the gap ratio, \( Rg \) (the ratio of diameter of the outer surface of the inner membrane to the inner surface of the outer membrane).

These results are useful in the testing of auxiliary lungs designs of sheet material wrapped on large porous cylinders, where case the gap ratios will usually be quite large. Improved gas transfer is thus easily achieved by inducing a technique in which the outer surface of the annulus is rotated. The outer surface rotation superimposes a shear field on the axial flow field, strong enough, the shear field causes the red cells to rotate and thereby generate local transverse convection.

TRANSPORT AND EXCHANGE OF OXYGEN AND CARBON DIOXIDE

In vertebrates, oxygen is carried by hemoglobin located in the erythrocytes (red blood cells) and stored in muscle tissue by myoglobin. Hemoglobin consists of four protein subunits, each containing a non-protein heme group. Oxygen binds to the heme. (There are some exceptions to the presence of hemoglobin or similar molecules in vertebrate blood - the Antarctic Icefish has NO respiratory pigment at all.) Oxygen binds to the Iron. This causes the Iron atom to move closer to the plane of the porphyrin ring. The pulls a histidine closer to heme plane moves the alpha helical segment containing the histidine towards an adjacent helix. This movement pushes a tyrosine which moves the C-terminal (the end of the protein chain with the COO⁻). In hemoglobin, the C-terminal forms an ionic bond with a positively charged residual group on an adjacent subunit, holding the subunits together. Movement of the C-terminal therefore affects the shape of the adjacent subunit and its ability to bind oxygen. Binding of oxygen to hemoglobin is cooperative. Binding of an oxygen molecule to one of the four subunits results in shape changes in the other three subunits, increasing the affinity of these other subunits for oxygen.
Carbon monoxide (CO) binds to the heme/iron group in place of oxygen, thus preventing normal oxygen binding to hemoglobin. Oxygenated hemoglobin is bright red in color and deoxygenated blood is more of muddy dark red color. (Deoxygenated blood is NOT blue, one of the great myths! The blue color of some veins is due to the tissue, not the hemoglobin. Carboxyhemoglobin (CO bound to hemoglobin) is bright red, because the hemoglobin has mistaken the CO for O₂. In cyanide poisoning, the cyanide blocks cellular respiration by binding to cytochrome oxidase in the electron transport chain. The blood also looks bright red because oxygen isn't being used by the peripheral tissues. Oxygen transport can be understood by looking at the binding curves for oxygen to hemoglobin and myosin.

When hemoglobin is bound to CO or there is less hemoglobin present, as in anemia, the maximum capacity of the blood to bind oxygen is reduced (Oxygen binding curves with CO present) [8].

**Carbon dioxide transport in humans**

The carbon dioxide gas is transported through the blood stream by conversion to carbonic acid, which dissociates to hydrogen ion and bicarbonate. The hydrogen ion binds to hemoglobin, and is transported to the lungs. In this case, hemoglobin is acting as a buffer for the acid, but also is acting as an effective “transportation vehicle” for ferrying carbon dioxide to the lungs.

Hemoglobin and bicarbonate act as buffers for the acid produced by metabolism, effectively transporting this acid to the lungs for elimination. Read more about buffers in the “acid-base” section.

As carbon dioxide is formed in the cells (due to aerobic metabolism), it diffuses into the blood plasma. As it enters the red blood cells (which contain carbonic anhydrase) it’s quickly converted to H₂CO₃, which breaks down to H⁺ and HCO₃⁻. About two-thirds of the HCO₃⁻ will diffuse out into the plasma (and is replaced by chloride in the red cell). Only small amounts of carbon dioxide remain dissolved or attached to other compounds. About 30 ml of CO₂ gas are contained in each 100 ml of arterial blood, almost all as HCO₃⁻. As the blood goes through the capillaries, it picks up about 5 ml of additional CO₂. With this addition of acidic CO₂, the pH drops from 7.4 to 7.36. On reaching lungs, the process is reversed, and 5 ml of CO₂ is converted back from H⁺ and HCO₃⁻ and discharged into the alveoli.

At rest, about 200 ml of CO₂ is produced and excreted through the lungs. Over 24 hours, this is the equivalent of 12,500 milliequivalents of acid produced by metabolism and eliminated through CO₂.

Carbon dioxide reacts with water to form carbonic acid that then dissociates into H⁺ and bicarbonate. This reaction can be catalyzed by the enzyme Carbonic Anhydrase that speeds up the conversion by as much as ten million times. Carbonic anhydrase is found inside the red blood cells but not in the blood plasma.

\[
CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \\
HCO_3^- \rightleftharpoons H^+ + CO_3^{2-}
\]

Carbon dioxide diffuses from tissues into the blood plasma and then into red blood cells. Some of the CO₂ binds to amino groups on hemoglobin, but most is converted into bicarbonate. These reactions are reversed in the lungs. Why are the reactions reversed in the lungs?

Bicarbonate transport across the red blood cell membrane involves simultaneous transport of chloride in the opposite direction. This transport, by Band III protein channels, is known as the chloride shift.

Oxygen releases to the peripheral tissues results in binding of hydrogen ions to hemoglobin. Lowering of H⁺ concentrations results in the equilibrium of bicarbonate and carbon dioxide to shift towards more bicarbonate [36].

**Oxygen Transport**

Hemoglobin is a molecule composed of four subunits. Each subunit is a protein chain attached to a porphyrin ring containing one iron atom. As each iron atom can bind one oxygen (O₂) molecule, hemoglobin can carry one, two, three, or four oxygen molecules.

Normal blood contains about 15-16 grams hemoglobin per 100 ml. Each gram of hemoglobin can carry about 1.34 ml of gaseous oxygen. Fully saturated arterial blood will therefore contain about 20 ml of oxygen per 100 cc. The volume of oxygen in the blood is referred to as the O₂ content. Because O₂ content is dependent on the hemoglobin concentration, it doesn’t provide a good measure of lung function. The partial pressure of oxygen (PaO₂), as measured in arterial blood, does provide an accurate picture of gas exchange in the lung.

The relative amount of oxygen in the blood compared to the carrying capacity of the hemoglobin is called the oxygen saturation, and is expressed as a percentage. It’s directly proportional to the PaO₂ — the partial pressure of oxygen. The hemoglobin in arterial blood is only about 97% saturated with oxygen because of venous blood that passes directly through the lung (physiologic shunt). Venous blood is about 75% saturated [36]. Oxygen saturation curve is shown in figure 28.

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Balloon Pulsation Dynamics

Balloon motion significantly enhances the oxygen exchange performance of the IMO device by providing active mixing. Inflation and deflation of the balloon is driven by an Intra-Aortic Balloon Pump (IABP), which delivers helium through a long, narrow catheter to the balloon. The catheter must also supply oxygen to and exhaust carbon dioxide from the fibers, meaning that only a fraction of the catheter's lumen is available for helium flow. There is an upper limit to pulsation frequency, which depends upon the mechanics of the delivery catheter (the physical size of the helium pathway), the power of the drive system, and ultimately the fragility of red blood cells (pumping too fast in vivo could lead to the destruction of red blood cells) [19].

![Oxygen saturation curve](image)

**Figure 28.** Oxygen saturation curve [19].

EFFECT OF ATMOSPHERIC PRESSURE

Low pressure

Because it is practically impossible to breath a normal density air at a low atmospheric pressure without immediate barotraumas, we will group these two in one essay [34].

Acclimatization

The effect of the low pressure on the human body depends on the temperature, because cold air is denser than warm air. For individuals that are borne and raised at altitudes of 13000 ft. the acclimatization to even higher altitudes (17000 to 19000 ft.) is easier. In these:

- The tissue contains more mitochondria and oxidative enzymes.
- The Oxygen-Hemoglobin dissociation curve shifts to the right, making the Oxygen-Hemoglobin bond more labile.
- The Oxygen carrying capacity is increased due to increased red blood cell mass, even when the partial arterial Oxygen pressure is around 40 mm of Hg.
- The chest vital capacity is higher in relation to total body mass.
- There is a large pulmonary capillary bed.
- Pulmonary arterial pressure is higher than the sea lever counterparts.
- And there is physiologic hypertrophy of the right ventricle that maintains increased PA pressures despite lower pulmonary vascular resistance.
- Their work capacity at 17000 only goes down to 87%, when for non-acclimatized individuals it cab go down bellow 50%.

For the non-acclimatized individuals, these altitudes produce a chronic excessively high hematocrit and sharp elevation of PA pressure with right ventricle dilatation as a consequence of hypoxic pulmonary vaso-constriction and increased respiratory and Herat rate. Congestive Herat failure and death often occur. The body temperature and metabolism are not affected directly by low pressure. It has been found however in the acclimatized individual a moderate increase of oxygen consumption due to the increased ability of the tissue to utilize oxygen having more presence of oxidative enzymes [34].

Decompression Sickness

Can occur in non-pressurized airplane climbs of 30,000 feet where the dissolved gasses in tissue begin to bubble, but ascents slower than 5 minutes rarely cause the problem. This condition occurs more readily in divers subjected to high pressures.

Surprisingly short-lived sudden decompressions to atmospheric pressure equivalent to 50,000 ft. cause no obvious harm in experimental animals or humans. When the pressure is lowered to 63,000 ft. equivalent, 2.5% of the weights evaporate from the body fluids before death occurs.

All cavities in the body at moderate altitudes can adjust, as gas escapes to the outside through the various physiologic communications (e.g. Eustachian tubes). Expansion of intestinal gas some times poses a challenge to the fast climber.
In general, the symptoms are Light-headedness, nausea, reduced working capacity, confusion, pain, congestive heart failure and death [34].

**High Pressure**

This essay is in essence about the effects of diving on human physiology. The pressure under sea water increases by one atmosphere every 33 ft.

Air density is directly proportional to atmospheric pressure, the effect of density alone is to increase resistance in the small airways increasing the work of breathing with moderate increase in respiratory rate of 5 to 10% mostly it affects not the rate but the inspiratory effort. Low density mixtures with helium are used for facilitating ventilation of lungs with narrow airways.

For a diver without scuba, the underwater pressure can reduce the capacity of his chest by virtue of compression of the air contained in his lungs(The squeeze) that was originally inhaled at atmospheric pressure, restriction gas exchange with the blood, and mechanically “caving in the chest” compressing vena cava with subsequent cardiovascular collapse.

Scuba divers with good equipment can dive much longer; for the ones on 100% oxygen toxicity is an issue after 12 hours of use with injury to the respiratory mucosa.

When the partial pressure of inspired oxygen rises above 1500 mm Hg. the oxygen dissolved in the blood (not in ox hemoglobin), causes toxicity (e.g. convulsions, and coma at 3 atmospheres after one hour).

If diving with compressed air at more than 150 ft. Nitrogen narcosis becomes an issue, first behaving as “laughing gas” producing joviality, and later at 200 ft. acting as a general anesthetic.

When significant amounts of nitrogen are dissolved in blood, as an example, at 200 ft. the nitrogen saturation can be up to 7 liters of dissolved gas in a diver, the subsequent resurfacing can materialize the gas creating bubbles which can generate pain, air embolism and death, requiring a slow stage by stage decompression. If breath is also held, the rapid resurfacing can materialize the gas creating bubbles which can generate pain, air embolism and death, requiring a slow stage by stage decompression. If breath is also held, the rapid resurfacing can materialize the gas creating bubbles which can generate pain, air embolism and death, requiring a slow stage by stage decompression. If breath is also held, the rapid resurfacing can materialize the gas creating bubbles which can generate pain, air embolism and death, requiring a slow stage by stage decompression. 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**Important observation**

Arterial pressure is measured as a comparative difference from the environment pressure (e.g. blood pressure is said to be 120/80 mm Hg: above atmospheric pressure). The net effect of external pressure changes is to increase or reduce the absolute values of the internal pressures accordingly, but not the relative values of physiological parameters, unless a particular physiologic function is affected as in extreme cold or traumatic injury to the vascular system [34].

**RECENT INVESTIGATIONS**

**Improved Artificial Lungs for Respiratory Support**

Dr. William J. Federspiel is developing next generation artificial lung devices for treatment of patients with respiratory failure. The artificial lungs under development are composed of bundles of hollow fiber membranes fabricated into various modules and catheters that can be perfused with blood intracorporeally or extracorporeally. The hollow fiber membranes are manifolided to gas pathways that allow oxygen gas to flow through the insides of the hollow fibers, thus driving the diffusion of oxygen into the bloodstream and of carbon dioxide outside of the blood stream. Artificial lungs are traditionally mass transfer devices limited due to diffusional boundary layers that arise on the fiber surfaces. His specific potential projects include research and development on: 1. A balloon pulsed respiratory catheter; 2. A self-pumping extracorporeal emergency respiratory support lung; 3. Biohybrid microfabricated artificial lung modules; 4. Hollow fibers with bioactive and mechanically active coatings, and 5. Aspects of control and monitoring consoles for artificial lungs [37].

**A Lung Technology: A Breath of Fresh Air**

While life-supporting, ventilators can damage a person’s lungs, throat and sinuses, cause pneumonia and create a dependency on the machine. Weaning can actually more than double the time the patient is connected to the artificial device. Unfortunately, clinical experience at medical centers across the country shows that the longer a patient is connected to a mechanical ventilator, the greater their chances of dying. So it is a great challenge [37].

**The Hattler Catheter—A New Way to Oxygenate Blood**

Dr. Brack Hattler and Dr. William Federspiel are working with $9 million grants from US Department of Defence and additional investments of $3.6 million from Angels and Innovation Works. A Lung Technologies has developed the Hattler™ Catheter — a more gentle, equally effective and less costly way of delivering oxygen to the bloodstream and transporting carbon dioxide back out.

With an experienced management team in place, the company is working to move the Hattler Catheter through clinical trials, FDA approvals and into ICUs and emergency rooms across the country and around the world [12].

**The Market Need**

Every year, approximately 400,000 patients in the U.S. alone (one million worldwide) require mechanical ventilation as a result of acute respiratory failure, chronic obstructive pulmonary disease, asthma or congestive heart failure. At an
average length of stay of 11 days and a cost of $5,000 per patient, the total cost to provide ventilation each year $2.2 billion. The cost of lengthy ICU stays due to ventilator-induced complications is even greater—driving the total ICU costs into the tens of thousands of dollars per patient [12].

**Hospital Economics**

At a price of $4,000, the Hattler Catheter will reduce costs to the hospital, as well as reducing ICU stays by up to half the time. The combination of lower device cost, plus reduced ICU time could result in savings of up to $15,000-$25,000 per patient. At the same time, because the reimbursement rate for a large organ catheter is higher than that for a ventilator, hospitals stand to increase revenues through the use of the Hattler Catheter [12].

**Growth Prospects**

There are more than 10,000 ICUs worldwide. The larger ones maintain an average monthly patient load of about 20. A-Lung Company plans to penetrate 300 ICUs worldwide by 2009, treating an average of ten patients per month, which would generate sales of $109 million, three years after product launch in the U.S.

During the same period, employment is projected to increase from the current 10 full-time and five part-time employees to 15-20 full-time employees in 2005 and 300 in 2009 [12].

**Management and Advisors**

The critical care in developing the Hattler Catheter has carried through to development of its management and product development team, board of directors and medical advisory board. The founders recruited Nick Kuhn, a bioscience executive from San Diego with extensive experience in the respiratory care market, to lead the company. Kuhn says the medical advisory board represents ‘the top people in the field from key critical care centers across the U.S.’

“The more start-ups I’m involved in, the more I realize just how important the people are,” Kuhn says. “Our management team and board are all seasoned people who have done this before. They’ve manufactured sterile medical devices, they’ve taken companies through clinical trials, they’ve raised money in the public markets.”

As the company continues its quest to pull the plug on mechanical ventilators and the suffering they can impose, hundreds of thousands of patients around the world will continue to hold their breath, a task that ALung hopes to make a little easier [12].

**Feasibility of a pumpless extracorporeal respiratory assist device**

University of Pittsburgh – Medical Center is evaluating the efficacy and feasibility of a pumpless respiratory assist device for its capacity for carbon dioxide removal.

In five adult pigs the left femoral vein and artery were cannulated with a 20F cannula and connected to a low-pressure hollow-fiber artificial lung. After obtaining baseline values of mean arterial pressure, cardiac output, and blood flow across the artificial lung, the mean arterial pressure was reduced 20% and 40% relative to baseline; in a second phase, it was raised 20% and 40%. Cardiac output and artificial lung flow were simultaneously recorded. The carbon dioxide removal capacity of the artificial lung was determined by gradually increasing the arterial partial carbon dioxide tension of the animal.

An increase of 10 mm Hg in mean arterial pressure resulted in an increase of flow of 0.14 L/min. The mean pressure drop across the artificial lung was measured at 17.9 mm Hg. The shunt flow over the artificial lung varied between 14 and 25% of the cardiac output of the animal. Depending on inlet conditions, carbon dioxide removal by the artificial lung was between 62.22 mL/L/min and 104.25 mL/L/min.

A pumpless respiratory assist device can remove a significant proportion of the metabolic carbon dioxide production. However, adequate mean arterial pressure is mandatory to maintain sufficient flow across the device. The technique seems attractive because of its simplicity and can be used in acute lung injury in conjunction of apneic oxygenation for prolonged respiratory support [10].

**Development of Cardiopulmonary Bypass System for Long-term Use**

Researches at University of Pittsburgh are also investing the possibility of and develop therapeutic options of cardiopulmonary support with a heart-lung assist device, such as percutaneous cardiopulmonary support and extracorporeal membrane oxygenation in treating patients with life-threatening circulatory and/or respiratory failure.

An integrated artificial heart-lung device has been developed as a long-term cardiopulmonary support system in respect of antithrombogenecity and durability. In particular, integration of a blood pump and artificial lung, employment of a special hollow fiber membrane, and heparin bonding surface treatment displaying excellent thromboresistance, provides several advantages including the marked reduction in the size of the apparatus and the preservation of the gas exchange function within a sufficient level. The possibility of therapeutic options has been investigated from the viewpoint of native lung metabolism [10].
MC3 Pulmonary Assist device Company: Background and Mission

MC3 is a research and development company with over 10 years experience developing technologies to treat cardiopulmonary disease. MC3 develops novel ideas from conception through to the prototype and testing stages. MC3 performs contract device testing for medical device companies, and collaborates with academicians to develop ideas from the university setting to marketable product.

Technology:

MC3 has four core technologies under patent protection: BioLung®, a pulmonary assist device (Figure 29) to bridge patients to lung transplantation or recovery; Nitric oxide generating materials to enhance biocompatibility of blood contact surfaces, such as vascular grafts and stents; M-Pump, a novel roller pump with inherent pressure limitations and proprietary control strategies for automatic control of a heart/lung machine to regulate patient gas exchange [16].

MC3 plans to significantly increase its efforts surrounding nitric oxide generating materials. Research with these materials has shown potential benefits for use in stents, prosthetic vascular grafts, and several other medical devices.

CONCLUSIONS

In this project we had the opportunity to learn about an artificial lung. We know that the future of artificial lung systems will rely on the development of advance new materials. We believe that the development of artificial lung systems using live tissues is difficult due to the complexity and the complication of dealing with live tissue instead of just inert materials.

As long as medicine keeps developing smaller artificial lung design and more plasma like solutions, the future seems full of hope and we expect that in the future, a fully functional lung system may be developed.

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GLOSSARY

Active sing - Sings in which there is energy input to achieve high shear rates.

Advancing front theory - A type of exchanger theory addressing the limitation of oxygen transport in a blood film through a fully saturated boundary layer leading to a front where the hemoglobin in flowing blood reacts with the dissolved oxygen.

Alveoli - Respiratory airway terminals where most gas exchange with the pulmonary circulation takes place.

Alveolar epithelial cell - A human or non-human cell which forms the outer surface of the alveolar sacs in the lungs. Such alveolar cells include primary lung pneumocytes, human lung carcinoma cell line, and human larynx and lung carcinoma cell line.

Alveolar fluid - A highly viscous solution comprising secreted surfactants, saline and other serum proteins.

Annular conduit - Pipe or channel for conveying fluids that is shaped like a ring.

Apical surface - Is the side of the membrane that faces away from the bottom of the vessel. When the system is completed the apical surface will coincide with the epithelial side.

Arterialization - A gas exchange process whereby oxygen and carbon dioxide concentrations in venous blood are changed to levels characteristic of arterial blood.

Artificial lung - A device which allows for continuous exchange of oxygen and carbon dioxide between circulating blood and a controlled gas atmosphere.

Axial flow - Flow in the direction of an axis of a capillary.

Basal surface - Is the side of the membrane which faces the bottom of the vessel. It will coincide with the endothelial side when the artificial lung is completed.

Basement Membrane Material - A porous extracellular matrix which function as a support structure in a manner
similar to the way basement membrane material functions as a support structure in whole organs.

**Bloodborne** - A substance that can be transported throughout the blood.

**Blood oxygenator** - Synonymous with artificial lung, with the accent placed on oxygen transport, which is the most critical aspect of natural lung replacement, since the body oxygen reserves are very limited. Depending upon the physical process used for blood-gas transfer, artificial lung are classified as: bubble oxygenator, stationary or rotating film oxygenators, and membrane oxygenator.

**Boundary layer** - The film of blood adjacent to a permeable membrane, which, by reason of local fluid dynamics, is not renewed at the same rate as blood in the core of the flow path, thereby creating an additional diffusion barrier between the blood and the gas phase.

**Bubble oxygenator** - Blood-gas transfer device in which a large exchange surface is obtained by the dispersion of oxygen bubbles in a venous blood steam, followed by coalescence of the foam and venting of excess gas (concurrent blood and gas flow) or by spreading of venous blood over a continuously renewed column of generated by bubbling oxygen at the bottom of a reservoir (counterconcurrent blood and gas flow).

**Bypass** - Derivation or rerouting of blood around an organ or body part, to diminish its blood supply, to abolish local circulation for the duration of a surgical intervention. Or to increase blood flow permanently beyond an obstruction. The qualifier used with the word bypass designates the organ so isolated (e.g., left ventricular bypass, coronary artery bypass).

**Carotid artery** - Two main arteries (passageway carrying blood from the heart to other parts of the body) that carry blood to the brain.

**Catheter** - A long hollow cylinder designed to be introduced in a body canal to infuse or withdraw materials into or out of the body.

**Congenital diaphragmatic hernia** - The protrusion of part of the stomach through an opening in the diaphragm.

**Continuous positive airway pressure** - A spontaneous ventilation mode in which the ventilator maintains a constant positive pressure, near or below positive end expiratory pressure level, in the patient’s airway while the patient breathes at will.

**Coronary artery bypass graft (CABG)** - The construction of new blood conduits between the aorta (or the major arteries) and segments of coronary arteries beyond lesions which partially or totally obstruct the lumen of those vessels, for the purpose of providing an increased blood supply to regions of the myocardium made ischemic by those lesions.

**Dead space** - The portion of the respiratory system that does not take part in gas exchange with the blood.

**Diffusion** - The process whereby a material moves from a region of higher concentration to a region of lower concentration.

**Diffusivity** - A quantity ascertained for a given substance by dividing its thermal conductivity by the product of its specific heat and density.

**Drive and Control Console** - A central control panel of the Pneumatic Delivery System. Transducer: a device that converts one form of energy into another.

**ECMO** (*Extracorporeal Membrane Oxygenator*) - A device that using membranes oxygenate directly the blood stream.

**Electrolyte** - A chemical compound that ionizes when dissolved or molten to produces an electrically conductive medium.

**Endothelial cell layer a human** - or other cell type which lines the blood and lymphatic vessels and various other body cavities.

**Epithelial cell layer** - A human or other type of cell which forms the outer surface of the body and lines organs, cavities and mucosal surfaces.

**Expiration** - The breathing process whereby air is expelled from the mouth and nose.

**Extracorporeal** - Outside the body.

**Extracorporeal circulation** - An artificial maintenance of blood circulation by means of pumps located outside of the body, with blood fed through catheters advanced in an appropriate blood vessel and returning the blood to another blood vessel.

**Fiber membranes** - A thin, pliable layer of tissue covering surfaces or separating or connecting regions, structures, or organs of an animal or a plant made up of filaments constituting the extracellular matrix of connective tissue.

**Film oxygenator** - Blood–gas transfer device in which a large exchange surface is obtained by spreading venous blood in a thin film over a stationary or moving physical support in an oxygen-rich atmosphere.

**Fluid-limited case** - Assumes that the membrane is infinitely permeable and the process involves only the gas transfer to the blood.
**Functional residual capacity** - The lung volume at rest without breathing.

**Heart-lung bypass** - Synonymous with cardiopulmonary bypass.

**Heart-lung machine** - A mechanical system capable of pumping venous blood around the heart and the lungs, and arterIALIZing it in an appropriate gas exchange unit.

**Hemodilution** - Temporary reduction in blood erythrocyte concentration (and consequently hemoglobin content, hematocrit, oxygen-carrying capacity, and viscosity) resulting from mixing with the erythrocyte-free poor content of the liquid used to prime an extracorporeal circuit.

**Hemolysis** - The destruction of red blood cells with liberation of hemoglobin in surroundings plasma caused by mechanical damage of the erythrocyte membrane.

**Hemodialysis access** - Arterial-venous connection surgically placed to provide a large amount of blood flow for hemodialysis. These are often loops of PTEE placed in the arm.

**Hollow fiber** - A capillary tube of polymeric material produced by spinning a melt or dissolved polymer through an annular orifice.

**IABP** - Intra-aortic balloon pump.

**I:E ratio** - The ratio of normalized expiratory interval of a mandatory breath. Both intervals are normalized with respect to the inspiratory period. Hence, the normalized inspiratory period is always unity.

**IMO** - Intravenous Membrane Oxygenator.

**Inspiration** - The breathing process whereby air is taken into the mouth and nose.

**Laminar flow** - Nonturbulent flow of a viscous fluid in layers near a boundary for Reynolds number <2000.

**Mass spectrometer** - A device that identifies relative concentrations of gases by means of mass-to-charge ratios of gas ions.

**Mandatory mode** - A mode of mechanically ventilating the lungs where the ventilator controls all breath delivery parameters such as tidal volume, respiration rate, flow waveform, etc.

**Meconium aspiration syndrome** - Breathing in of meconium (a newborn's first stool) by a fetus or newborn, which can block air passages and interfere with lung expansion.

**Membrane-limited case** - Assumes that the gas dispersion in the blood phase is infinitely fast and that the process is limited by the gas transfer time through the membrane.

**Membrane lung or Membrane Oxygenator** - Blood-gas transfer device in which the blood compartment is shielded from the gas phase by a porous or solid, hydrophobic polymer membrane permeable to gases but not to liquids (in particular blood plasma).

**Metabolism** - The sum of the chemical reactions occurring within a living body including build up (anabolism) or breakdown (catabolism) of chemical substance.

**Neointimal hyperplasia** - Fibroblast and smooth-muscle cell growth covering a vascular graft on the inside surface.

**Oscilloscope** - An electronic instrument that produces an instantaneous trace on the screen of a cathode-ray tube corresponding to oscillations of voltage and current.

**Oxygenation** - The process of providing or combining or treating with oxygen.

**Oxygenation boundary layer** - Stationary or slowly moving blood layer adjacent to a gas-permeable membrane, which progressively develops along the blood path and, once enriched with oxygen diffusing through the membrane, effectively becomes a barrier to oxygen transport perpendicular to the direction of flow.

**Patient circuit** - A set of tubes connecting the patient airway to the outlet of a respirator.

**Plasmatic** - The clear, yellowish fluid portion of blood, lymph, or intramuscular fluid in which cells are suspended. It differs from serum in that it contains fibrin and other soluble clotting elements.

**Passive sing** - Sings for which no energy is needed except that required for steady blood flow.

**Pannus** - Neointimal hyperplasia tissue ingrowth at the anastomoses.

**Partial pressure** - The pressure that a gas would exert if it were the only constituent.

**Perfusion** - A technique for keeping an organ or body part alive, though severed from its normal blood circulation, by introducing blood under pressured into the appropriate feeder artery.

**Perfusionist** - The operator of the heart-lung machine during cardiac surgery or respiratory assist procedures.

**Pleura** - The membrane surrounding the lung.
Pneumatic Delivery System - A group of physiologically or anatomically complementary organs or parts with cavities for which the transport of air is controlled.

Pneumotach - A measuring device for airflow.

Positive end expiratory pressure - A therapist-selected pressure level for the patient airway at the end of expiration in either mandatory or spontaneous breathing.

Pressure controlled ventilation - A mandatory mode of ventilation where during the inspiration phase of each breath, a constant pressure is applied to the patient’s airway independent of the patient’s airway resistance and/or compliance respiratory mechanics.

Pressure support - A spontaneous breath delivery mode during which the ventilator applies a positive pressure greater than positive end expiratory pressure to the patient’s airway during expiration.

Pressure support level - Refers to the pressure level, above positive end expiratory pressure, that the ventilator maintains during the spontaneous inspiration.

Priming volume - The volume of the liquid blood, plasma, synthetic plasma expanders, or electrolyte solutions) needed to fill all components of an extracorporeal circuit (oxygenator, heat exchanger, blood pumps, filters, tubing, and catheters) so as to avoid exsanguination once the intracorporeal and extracorporeal circulation systems are joined.

Pulmonary circulation - Blood flow from the right cardiac ventricle that perfuses the lung and is in intimate contact with alveolar membranes for effective gas exchange.

Pulmonary pathogen - an organism that causes a illness or a pathological syndrome in the lungs or that can spread to other organs and internal body regions via the lungs. Examples of these diseases are tuberculosis, pneumonia and influenza, among others.

Pulmonary hypertension - A disorder in which the blood pressure in the arteries supplying the lungs is abnormally high.

Pump-oxygenator - Equipment used to circulate blood through an extracorporeal circuit by means of mechanical blood pumps and to arterialize mixed venous blood by means of a gas exchange device. In most embodiments, the pump-oxygenator also serves to control blood temperature by means of a heat exchanger, typically incorporated in the gas exchange device. Synonymous with heart-lung machine.

Pulsation rate membranous structure- in a hollow organ or passage, as in an artery or vein, that folds or closes to prevent the return flow of the body fluid passing through it.

Respiratory quotient - The ratio of carbon dioxide produced by tissues or eliminated by the lungs to oxygen consumed by tissues or taken in through the lungs.

Spontaneous mode - A ventilation mode in which the patient initiates and breathes from the ventilator-supplied gas.

Secondary flow - Any type of fluid motion, steady or periodic, in which the fluid is moving in a direction different from that of the primary flow. Secondary flow systems may be continuous in distribution, occupying the entire flow path, or comprise local elements that produce periodic remixing of the fluid.

Solenoid valve - a current-carrying coil of wire that acts like a magnet when a current passes through.

Stenosis - Tissue ingrowths into vessel causing a narrow lumen and reduction of the blood flow.

Thermal conductivity - the total amount of heat simultaneously passing through a plate of unit area and thickness in unit time, when its opposite surfaces maintain one degree difference or temperature.

Total body perfusion - Maintenance of blood circulation through the arterial and venous system by means of a positive displacement pump introducing blood into an artery under pressure and collecting it from a vein for continuous recirculation.

Tubular conduit - a pipe or channel for conveying fluids, such as water, or blood, shaped like a tube.

Vascular graft - Tube replacement of an artery or vein segment.

Vascular reconstruction - Reconstruction of an artery or vein after trauma, surgery, or blockage of blood flow from disease.

Vena cava - It is the principal vein returning blood to the heart.

Ventilation - Airflow of the lungs.

Volume controlled ventilation – a mandatory mode of ventilation where the volume of each breath is set by the therapist and the ventilator delivers that volume to the patient’s airway resistance and/or compliance respiratory mechanics.