

What can go wrong with Lungs and how can they be replaced?

A.Subrahmanyam and Paul T Ramesh

Department of Physics, IIT Madras , Chennai 36
Department of Cardiothoracic Surgery, Apollo Hospital, Chennai.

The lungs are a pair of organs in the chest which are primarily responsible for the exchange of oxygen and carbon dioxide between the air we breathe and the blood (the hemoglobin of the red blood cells is responsible for the gas exchange) . The lungs supply oxygen to the tissues and carries back carbon dioxide from tissues. Breathing is an involuntary action initiated by the autonomic nervous system of the brain. Even if we want to stop breathing, the brain does not allow.

At rest, a person breathes about 14 to 16 times per minute. After exercise it could increase to over 60 times per minute. New babies at rest breathe between 40 and 50 times per minute. By age five, it decreases to around 25 times per minute. The total surface area of the alveoli (tiny air sacs in the lungs) is the size of a tennis court.

Respiratory failure is one of the leading causes of both mortality and morbidity world wide. With ever increasing environmental pollution, the first and most important organ being affected and afflicted is the lungs. Advances in the management of end stage lung disease have not paralled the management of end stage heart, liver or renal disease.

As we breathe air in through our nose or mouth, it goes past the **epiglottis** and into the **trachea**. It continues down the trachea through our **vocal cords** in the **larynx** until it reaches the **bronchi**. From the bronchi, air passes into each lung. The air then follows narrower and narrower **bronchioles** until it reaches the **alveoli**.

Within each air sac, the oxygen concentration is high, so oxygen passes or **diffuses** across the alveolar membrane into the **pulmonary capillary**. The oxygen binds to hemoglobin

and the carbon dioxide is released. This is a simple gas kinetics being executed day in and day out (so long as we breathe).

This exchange of gases occurs rapidly (fractions of a second). The carbon dioxide then leaves the alveolus when we exhale and the oxygen-enriched blood returns to the heart. Thus, the purpose of breathing is to keep the oxygen concentration high and the carbon dioxide concentration low in the alveoli so this gas exchange can occur! How sensitive this gas exchange is : if the brain tissues do not receive oxygen for more than four minutes, there is severe danger to life.

What can go wrong with lungs:

There are many common conditions that can affect the lungs. Diseases or conditions of the lung fall mainly into two classes -- those that make breathing harder and those that damage the lungs' ability to exchange carbon dioxide for oxygen.

Diseases or conditions that **influence the mechanics of breathing:**

- **Asthma:** The bronchioles constrict, reducing the size of the airways. This cuts down on the flow of air and makes the respiratory muscles work harder.
- **Emphysema:** The lungs become stiff with fibers and become less elastic, which increases the work of the respiratory muscles.
- **Bronchitis:** The airways become inflamed and narrower, which restricts the flow of air and increases the work of the respiratory muscles
- **Pneumothorax:** Air in the chest cavity equalizes the pressure in the chest cavity with the outside air and causes the lungs to collapse. This is usually caused by trauma or injury.
- **Apnea:** Breathing slows or stops under a variety of conditions. There are many types of apnea, and they are usually caused by problems in the respiratory centers of the brain.

Diseases or conditions that **minimize or prevent gas exchange:**

- **Pulmonary edema:** Fluid between the alveolus and pulmonary capillary builds up, which increases the distance over which gases must exchange and slows down the exchange.
- **Smoke inhalation:** Smoke particles coat the alveoli and prevent the exchange of gases.
- **Carbon monoxide poisoning:** Carbon monoxide binds to hemoglobin more tightly than either oxygen or carbon dioxide, which minimizes the delivery of oxygen to all the tissues of the body, including the brain, the heart and muscles. Carbon monoxide is a common product of poorly vented heaters (space heaters, furnaces, water heaters) and of automobile exhausts. This condition can be fatal if not caught soon after exposure.
- **Pneumonia** is an inflammation of the lungs caused by bacteria, viruses or chemical irritants. It is a serious infection or inflammation in which the air sacs fill with pus and other liquid.
- **Pulmonary hypertension** is a lung disorder in which the blood pressure in the pulmonary artery rises far above normal levels.
- **Pulmonary embolism**, a severe and life-threatening condition, is the blocking of the pulmonary artery by foreign matter such as:
 - a blood clot (thrombus) or pieces of it
 - fat
 - Air
 - tumor tissue
- **Tuberculosis (TB)** is a chronic bacterial infection that usually infects the lungs, although other organs are sometimes involved. TB is primarily an airborne disease.

There is a difference between being infected with the TB bacterium and having active tuberculosis disease.

- **Lung cancer** usually starts in the lining of the bronchi, but can also begin in other areas of the respiratory system, including the trachea, bronchioles, or alveoli.

Lung cancers are believed to develop over a period of many years.

Nearly all lung cancers are carcinomas, a cancer that begins in the lining or covering tissues of an organ.

The tumor cells of each type of lung cancer grow and spread differently, and each type requires different treatment. More than 95 percent of lung cancers belong to the group called **bronchogenic carcinoma**.

One of the sleeping disorders : snoring, is related to breath disorders. Snoring is a fairly common affliction, affecting 40 percent of men and 25 percent of women. If you snore, you make a raspy, rattling, snorting sound while you breathe during sleep. Older people are particularly prone to snoring: About one-third of people ages 55 to 84 snore. Despite its frequency, however, snoring is a sleep disorder that can have serious medical and social consequences.

Chronic Obstructive Pulmonary Disease (COPD) is a long-term lung disease usually caused by smoking. COPD includes a few lung diseases: the most common are **chronic bronchitis** and **emphysema**. Many people with COPD have both of these diseases.

Chronic lung diseases such as pulmonary fibrosis and emphysema afflict a large population. For patients to survive, they require transplantation of a living human lung. However, geographic obstacles and a patient's state of health often impede donor-recipient matches. Those needing a transplant wait an average of two years for a lung; 20 percent die before receiving one.

Can there be a substitute for lungs? This question also can be asked as : can blood be oxygenated and carbon dioxide removed artificially? Can there be artificial lungs? These questions are becoming more relevant with increasing levels of environmental pollution.

It may be noted that the research on lungs has not far advanced as in the case of heart, mainly because, lungs are more complex.

The history :

One of the major advances in medicine is the invention and refinement of artificial circulation, also known as heart-lung bypass. The efforts to bring this concept into reality began in early fifties. Dr. John H. Gibbons Jr. is credited with developing the first clinically successful heart-lung pump. He performed the first successful use of artificial circulation in humans on May 6th, 1953 as he closed a hole between the upper heart chambers in an 18 year old girl. Initially, the machine of Gibbon was massive, complicated, and difficult to manage. At the present state-of-the-art, minimal blood trauma occurs during conventional heart-lung support periods. This allows surgeons to apply this technology freely with excellent overall results. It is now commonplace for surgeons to stop the heart beat even for several hours while the circulation is maintained by modern, commercially available heart-lung support equipment.

The principle of the heart-lung machine (also known as pump-oxygenator or cardiopulmonary bypass) is actually quite simple. Blue blood (low oxygen) withdrawn from the upper heart chambers is drained (by gravity siphon) into a reservoir. From there, the blood is pumped through an artificial lung consisting of polyurethane tubular fibers. The blood flows through the tiny capillary tubes and the oxygen gas is pressurized from outside the fiber. Thus the blood comes into intimate contact with the fine surfaces of the device itself. Oxygen gas is delivered to the interface between the blood and the device, permitting the blood cells to absorb oxygen molecules directly (this is precisely what happens in natural lungs). This device is known as Membrane Oxygenator. Now the blood is red in color, indicating its rich content of oxygen destined to be delivered to the various tissues of the body. Finally, the heart-lung machine actively pumps the red blood back into the patient through a tube connected to the arterial circulation. The heart-lung

circuit is a continuous loop; as the red blood goes into the body, blue blood returns from the body and is drained into the pump completing the circuit.

The present status:

The modern heart-lung machine is actually more sophisticated and versatile than the overview given above. In fact, the pump-oxygenator can do a number of other tasks necessary for safe completion of an open heart operation.

During the period of artificial circulation, the machine is attended to at all times by a specialized technician, called the perfusionist. These individuals are highly trained in all aspects of artificial circulation and the equipment involved. Each heart operation requires a dedicated and trained perfusionist to manage all aspects of the heart-lung machine during the time period of artificial circulation.

An implantable lung could keep patients with serious lung diseases alive long enough for them to beat potentially deadly infections.

The new artificial lung uses tiny hollow fibres to mimic the structure of a human lung, and increase the surface area available for oxygen to pass into the blood.

The resulting device is small enough to allow implantation into the body, where it would be attached to the pulmonary artery, the main blood vessel from the heart to the lungs.

From here, the heart's own pumping power would drive blood through it.

The Artificial Lung Laboratory of the McGowan Center for Artificial Organ Development (Pittsburgh, USA) focus attention to support breathing independent of the lungs . His group is developing next generation artificial lungs or blood oxygenators, including small implantable devices for temporary support and wearable devices for longer-term support: the Hattler Catheter, a unique artificial lung inserted as a venous catheter to provide temporary breathing for patients with acute lung failure. Enhanced

mass transfer is not only a key to implantable oxygenators, where anatomy can impose significant constraints, but is also pertinent to next generation, wearable artificial lungs.

The Total Artificial Lung

The faculty at the Division of Critical Care, Michigan, are working to develop an artificial lung that will “bridge” more patients to transplantation. By stabilizing patients who have diseased lungs, the device will increase opportunities for donor-recipient matches as well as improve transplant survival rates. Researchers estimate that annual lung transplants would subsequently increase from some 1,500 to several thousand.

About the size of a soda can, the device is connected to the heart’s right ventricle. It relies on the heart—not a mechanical pump—to send blood through the lung, where it receives oxygen (and offloads carbon dioxide) as it flows through arrays of microfibers, or membrane oxygenators. Oxygen-rich blood passes from the device into the left atrium and then to the rest of the body.



The natural lung can provide gas exchange ranging from resting levels for both O₂ and CO₂ (about 200–250 ml/min in average adults) to 10–20 times that under exercise conditions, and it does so using room air as its oxygen supply gas. In contrast, current hollow fiber blood oxygenators, as used in cardiopulmonary bypass, have membrane areas ranging from 1 to 4 m² that are packaged much less compactly than in the natural lung, with a surface area to blood volume ratio 10 times less than in the natural lung. The effective distance that gas diffuses between blood and gas flow pathways in artificial lungs is approximately 10–30 mm, an order of magnitude greater than in the natural lung. Thus, even with using 100% oxygen gas, artificial lungs currently used or under development aim at gas exchange levels that can support resting metabolic needs in patients.

Four principal development efforts have tackled the challenge of intravascular artificial lungs since the 1980s. Mortensen and colleagues at CardioPulmonics, Inc. (Salt Lake City, UT) developed the IVOX, the only intravascular artificial lung that has undergone human clinical trials. The IVOX consisted of a bundle of crimped hollow fiber membranes joined at the distal end to the inner lumen of a dual-lumen gas conduit, and at the proximal end to the outer lumen of the gas conduit, which led outside the body to a console for providing sweep gas flow through the fibers. The crimped fibers of the IVOX helped minimize fiber clumping in the vena cava and also helped disturb blood flow and diffusional boundary layers on fiber surfaces to improve overall gas exchange permeance. A total of 160 patients with severe acute respiratory distress were studied in applications that lasted up to 28 days of support. The clinically tested IVOX ranged from 0.21 m² to 0.51 m² in membrane area, and the average rates of O₂ and CO₂ transfer accomplished in the trials ranged from 40 to 70 ml/min, or about 20–30% of baseline metabolic needs. The IVOX demonstrated that intravascular artificial lungs can be implanted within the vena cava and perform for extended periods without significant complications in situ (for example, from blood thrombosis).

The implantable Intrathoracic Artificial Lung (ITAL) under development at Northwestern University focuses on resting the lung in acute respiratory failure and as a bridge-to-lung transplantation in chronic lung failure. Mathematical models were developed to estimate the required surface area for 200 ml/min of oxygen transfer at a blood flow rate of 5 l/min with a pressure drop of less than 15 mm Hg.

The BioLung™ total artificial lung under development at MC3, Inc. (Ann Arbor, MI) and the University of Michigan is intended for complete respiratory support as a bridge to transplant for 1–6 months.

A paracorporeal total artificial lung for chronic respiratory support (Chronic Artificial Lung, or CAL) is under development at the University of Maryland. The CAL is intended as a bridge-to- transplant device with the goal of 21-day support of basal metabolic needs using a device less than 0.5 m² in fiber membrane area. The CAL uses active mixing from a rapidly rotating disc made of microporous hollow fiber membranes that enhance gas exchange by increasing blood flow velocity past fiber surfaces and reducing diffusional boundary layers.

Sri Chitra Tirunal Institute for Medical Sciences and Technology, Trivendrum, India has been awarded NRDC award in 2006 for developing a membrane Oxygenator.

Total Liquid Ventilation

Whereas humans would drown when submerged in water because it can't provide the proper levels of oxygen, there are "breathable fluids"—in fact, though it's counter-intuitive, breathing liquids is easier on the lungs than breathing gases. In TLV, a patient's lungs are completely filled with breathable liquids such as perfluorocarbons (PFCs), which have twice the density of water and the same viscosity, are non-toxic and able to hold high levels of dissolved oxygen and carbon dioxide. The patient is then put on a ventilator, which oxygenates and moves the liquid into and out of the lungs. It's a regimen that has the potential to improve pulmonary function, reduce acute lung inflammation and injury, and facilitate respiration in those who suffer from respiratory ailments such as pneumonia and Acute Respiratory Distress Syndrome (ARDS).

In the 1980s, Bartlett (Michigan) led the team that developed the extracorporeal membrane oxygenation, or ECMO, machine now used in intensive care units worldwide to circulate and oxygenate the blood of desperately ill trauma, burn, infection and organ failure patients. Though his team built the world's most experienced, successful ECMO team, they still realize that ECMO is best for short-term use to get patients through a crisis.

Long-term ECMO use can be risky and costly, as can long-term use of mechanical ventilators, which have been used for decades to help patients whose own lungs are damaged. Half of all patients put on ventilators for acute lung problems die before their crisis is over. And those who survive ventilator or ECMO use have a higher risk of dying before or after a lung transplant.

The emerging concept in oxygenation:

Researchers have been expending considerable efforts to split water into hydrogen and oxygen using photocatalytic action. However, this research is focused to generate enough hydrogen to be used as alternate energy source . Since blood contains about 80% water, it is proposed to split this water by photocatalytic action so that the generated oxygen can be attached to hemoglobin directly. This process eliminates the external oxygen as well as the clogging fibers. The photocatalytic materials being inorganic, this process being simple and efficient, it can be used for a relatively longer times (may be a few years) and it is very cost effective well within the reach of many millions.

The photocatalytic action uses a semiconducting material like Titanium oxide (TiO₂). When a UV light falls on to TiO₂, the light energy generates an electron and a hole (positively charges electron); the former acts as reducing agent and the latter as oxidizing agent. The oxidizing hole converts water first into hydrogen peroxide and then into hydrogen and oxygen (the energy required is about 13.9-16.0 kJ mol⁻¹). The efficiency of the photocatlytic action depends upon the material and the removal of the reducing electron.

Preliminary experiments conducted on the photocatalytic oxygenation of deoxygenated human blood at the Physics Department in IIT Madras (in collaboration with Apollo Hospital) have given positive results. The photocatalyst prepared in the form of thin films have oxygenated the human blood with good efficacy (about 10 ml of oxygen in 100 ml of blood in 120 minutes with a surface area of 14 cm²). Since the oxygen is generated within the blood, the process is highly efficient and thus this process does not demand large areas (as in the case of membrane oxygenators), means the device can be really portable. The efficacy of oxygenation show a very high promise to develop into a small portable device which can come to the rescue of patients with various pulmonary disorders. The important feature of this new concept is that the materials employed are bio-compatible, the oxygenation is instantaneous, quantum efficiency of oxygen production is simple and the device seems to have no limitations on prolonged usage, and the UV light does not seem to damage any of the blood constituents. This new concept now is being accepted worldwide and one more group in MIT, USA also is working on similar lines.

The preliminary analyses on human blood have shown that the photocatalytic process does not damage any of the constituents of the blood. However, efforts are being expended to develop a highly efficient photocatalyst working in the visible light.

(note: The authors have presented the results in the 53rd ASAIO Conference in Chicago during 07-09 June, 2007).