UNIT II - ARTIFICIAL ORGANS

ARTIFICIAL HEART AND LUNG ASSIST DEVICES

A ventricular assist device (VAD) is a mechanical pump that's used to support heart function and blood flow in people who have weakened hearts. The device takes blood from a lower chamber of the heart and helps pump it to the body and vital organs, just as a healthy heart would.

Ventricles are the lower chambers of your heart.

A VAD can help support your heart:

- During or after surgery, until your heart recovers.
- While you're waiting for a heart transplant.
- If you're not eligible for a heart transplant.
    - A VAD has several basic parts. A small tube carries blood out of your heart into a pump. Another tube carries blood from the pump to your blood vessels, which deliver the blood to your body.
    - A VAD also has a power source that connects to a control unit. This unit monitors the VAD's functions. It gives warnings, or alarms, if the power is low or the device isn't working well.
    - Some VADs pump blood like the heart does, with a pumping action. Other VADs keep up a continuous flow of blood. With a continuous flow VAD, you might not have a normal pulse, but your body is getting the blood it needs.
    - Research has shown that, compared with other VADs, continuous flow VADs may decrease hospital stays and complications and improve survival. However, more research is needed.

Types of Ventricular Assist Devices

- The two basic types of VADs are a left ventricular assist device (LVAD) and a right ventricular assist device (RVAD). If both types are used at the same time, they're called a biventricular assist device (BIVAD).
- The LVAD is the most common type of VAD. It helps the left ventricle pump blood to the aorta. The aorta is the main artery that carries oxygen-rich blood from your heart to your body.
- RVADs usually are used only for short-term support of the right ventricle after LVAD surgery or other heart surgery. An RVAD helps the right ventricle pump blood to the pulmonary artery. This is the artery that carries blood from the heart to the lungs to pick up oxygen.
- A BIVAD might be used if both ventricles don't work well enough to meet the body's needs. Another treatment option for this condition is a total artificial heart (TAH). A TAH is a device that replaces the ventricles.
- VADs have two basic designs. A transcutaneous VAD has its pump

An implantable VAD has its pump located inside of the body and its power source located outside of the body. A cable connects the pump to the power source through a small hole in the abdomen. Implantable VADs are used mainly for people who are waiting for heart transplants or as a long-term solution for people who can't have heart transplants. Until recently, VADs were too big to fit in many people's chests, especially women and children. Only people who had large chests could get them. However, recent advances have resulted in smaller, more reliable devices. This now makes treatment with VADs an option for more people. Researchers also have made advances in how well VADs work and how much they improve people's quality of life. In the past, VADs mostly were used for people who had end-stage heart failure. Now VADs also can help people who have earlier stages of heart failure. Children who have heart failure also can be treated with VADs. VADs approved for use in adults sometimes are used in children if the children are large enough for the device. Also, the Food and Drug Administration recently approved a VAD designed for smaller children.

LUNG ASSISTING DEVICES

The Novalung Interventional Lung Assist device is a membrane ventilator that allows for oxygen and carbon dioxide gas exchange to occur by simple diffusion. It has been used in patients with severe acute lung failure due to ARDS, inhalation injury, severe pneumonia, chest injury, foreign body aspiration, and after thoracic surgical interventions. The concept of "protective ventilation" was described decades ago, but with the introduction of extracorporeal ventilation devices such as the Novalung it may reach new dimensions. It potentially helps to avoid or reduce ventilator associated lung injury and remote secondary organ failure, which is related to injurious mechanical ventilation.

Technical aspects of the equipment

The iLA consists of a plastic gas exchange module with diffusion membranes made from polymethylpentene (PMP). These PMP fibers are woven into a complex configuration of hollow fibers. The PMP material is woven to bundles in a low resistance configuration mat arranged in well defined stacks, which provides maximum blood/gas mixing. Gas transfer takes place without the direct contact with blood. In addition, the PMP membrane surface in contact with blood is treated with a heparin coating to provide a biocompatible and non-thrombogenic surface. Blood flows over the exterior surface of the device's fibers; the ventilating gas (commonly O_2) flows inside these fibers. In this way the Novalung iLA mimics the native lung. This allows for the blood exiting the device to have the normal amount of oxygen and carbon dioxide that exits the normal lung. In the arterio-venous portion of this pumpless shunt carbon dioxide exchange is the primary function due to arterial inflow blood, while a veno-venous

attachment, which requires the support of a mechanical pump, additionally allows full oxygenation support.

Clinical use and results

The Novalung has been used in over 1200 patients in Europe to enable advanced protective ventilation. We have recently reported on the successful use of the Novalung iLA as a bridge to lung transplantation in patients with severe ventilation-refractory respiratory acidosis and hypercapnea. The use of the device allows for a safer form of ventilation ('protective ventilation'), because the patients' carbon dioxide levels and pH can be adjusted to normal levels with the device. Extracorporeal life support with the Novalung iLA has been applied up to 32 days at the Hannover Thoracic Transplant and Cardiac Assist Program.

The driving force for this mode is the left ventricular output. In other situations, which include low cardiac output or hypoxic lung failure, a blood pump is required to divert a relatively larger amount of blood from the venous system through the Novalung, which can be returned into the systemic arterial circulation (veno-arterial mode) or the central veins (veno-venous mode), respectively. The optimal extracorporeal circuit design and configuration for circulatory support is determined by the underlying disease state and the treating physician's choice.

ARTIFICIAL HEART VALVE

An **artificial heart valve** is a device implanted in the heart of a patient with valvular heart disease. When one of the four heart valves malfunctions, the medical choice may be to replace the natural valve with an artificial valve. This requires open-heart surgery.

There are three main types of artificial heart valves: the mechanical, the biological, and the tissue engineered valves.

- Mechanical heart valve
    - Percutaneous implantation
        - Stent framed
        - Not framed
    - Sternotomy/Thoracotomy implantation
        - Ball and cage
        - Tilting disk
        - Bi-leaflet
        - Tri-leaflet
- Tissue (biological) heart valves

  - Allograft/isograft
  - Xenograft
- Tissue-Engineered heart valves

MECHANICAL VALVES

Mechanical heart valves (MHV) are prosthetics designed to replicate the function of the natural valves of the human heart. The human heart contains four valves: tricuspid valve, pulmonary valve, mitral valve and aortic valve. Their main purpose is to maintain unimpeded forward flow through the heart and from the heart into the major blood vessels connected to the heart, the pulmonary artery and the aorta. As a result of a number of disease processes, both acquired and congenital, any one of the four heart valves may malfunction and result in either stenosis (impeded forward flow) and/or backward flow (regurgitation). Either process burdens the heart and may lead to serious problems including heart failure. A mechanical heart valve is intended to replace a diseased heart valve with its prosthetic equivalent.

There are two basic types of valves that can be used for valve replacement, mechanical and tissue valves. Modern mechanical valves can last indefinitely (the equivalent of over 50,000 years in an accelerated valve wear tester). However, current mechanical heart valves all require lifelong treatment with anticoagulants (blood thinners), e.g. warfarin, which requires monthly blood tests to monitor. This process of thinning the blood is called anticoagulation. Tissue heart valves, in contrast, do not require the use of anticoagulant drugs due to the improved blood flow dynamics resulting in less red cell damage and hence less clot formation. Their main weakness however, is their limited lifespan. Traditional tissue valves, made of pig heart valves, will last on average 15 years before they require replacement (but typically less in younger patients).

There are three major types of mechanical valves – caged-ball, tilting-disk and bileaflet valve – with many modifications on these designs.

Caged ball valve

The first artificial heart valve was the caged-ball, which utilizes a metal cage to house a silicone elastomer ball. When blood pressure in the chamber of the heart exceeds that of the pressure on the outside of the chamber the ball is pushed against the cage and allows blood to flow. At the completion of the heart's contraction, the pressure inside the chamber drops and is lower than beyond the valve, so the ball moves back against the base of the valve forming a seal.

Tilting-disc valve - Tilting disk valves have a single circular occluder controlled by a metal strut. They are made of a metal ring covered by an ePTFE fabric, into which the suture threads are stitched in order to hold the valve in place. The metal ring holds, by means of two metal supports, a disc which opens and closes as the heart pumps blood through the valve. The disc is usually made of an extremely hard carbon

material (pyrolytic carbon), in order to allow the valve to function for years without wearing out. The Medtronic-Hall model is the most common tilting-disc design in the US. In some models of mechanical valves, the disc is divided into two parts, which open and close as a door.

Bileaflet valve - Bileaflet heart valves consist of two semicircular leaflets that rotate about struts attached to the valve housing. This design was introduced in 1979and while they take care of some of the issues that were seen in the other models, bileaflets are vulnerable to backflow and so they cannot be considered as ideal. Bileaflet valves do, however, provide much more natural blood flow than caged-ball or tilting-disc implants. One of the main advantages of these valves is that they are well tolerated by the body. Only a small amount of blood thinner is needed to be taken by the patient each day in order to prevent clotting of the blood when flowing through the valve. These *bileaflet* valves have the advantage that they have a greater effective opening area (2.4–3.2 square cm c.f. 1.5–2.1 for the single-leaflet valves). Also, they are the least thrombogenic of the artificial valves. Mechanical heart valves are today very reliable and allow the patient to live a normal life. Most mechanical valves last for at least 20 to 30 years

Durability

Mechanical heart valves have been traditionally considered to be more durable in comparison to their bioprosthetic counterparts. The struts and occluders are made out of either pyrolytic carbon or titanium coated with pyrolytic carbon, and the sewing ring cuff is Teflon (PTFE), polyester or Dacron. The major load arises from transvalvular pressure generated at and after valve closure, and in cases where structural failure does happen, it is usually as a result of occluder impact on the components. Impact wear and friction wear dictate the loss of material in MHV. Impact wear usually occurs in the hinge regions of bileaflets, between the occluder and ring in tilting-discs, and between the ball and cage in caged-ball valves. Friction wear occurs between the occluder and strut in tilting-discs, and between the leaflet pivots and hinge cavities in bileaflets. MHV, made out of metal are also susceptible to fatigue failure owing to the polycrystalline characteristic of metals, but this is not an issue with pyrolytic carbon MHV because this material is not crystalline in nature

CARDIAC PACEMAKER

A pacemaker or **artificial pacemaker** is a medical device which uses electrical impulses, delivered by electrodes contracting the heart muscles, to regulate the beating of the heart.

The primary purpose of a pacemaker is to maintain an adequate heart rate, either because the heart's natural pacemaker is not fast enough, or because there is a block in the heart's electrical conduction system. Modern pacemakers are externally programmable and allow a cardiologist to select the optimum pacing modes for individual patients. Some combine a pacemaker and defibrillator in a single implantable

device. Others have multiple electrodes stimulating differing positions within the heart to improve synchronisation of the lower chambers (ventricles) of the heart

A pacemaker is a small, battery-operated device that senses when your heart is beating irregularly or too slowly. It sends a signal to your heart that makes your heart beat at the correct pace.

Most pacemakers have 2 parts:

- The generator contains the battery and the information to control the heartbeat.
- The leads are wires that connect the heart to the generator and carry the electrical messages to the heart.

A pacemaker must be implanted under the skin. This procedure takes about 1 hour in most cases. You will be given a sedative to help you relax. You will be awake during the procedure.

A small incision (cut) is made, most often on the left side of the chest below your collarbone. The pacemaker generator is then placed under the skin at this location. The generator may also be placed in the abdomen, but this is less common.

Using live x-rays to see the area, the doctor puts the leads through the cut, into a vein, and then into the heart. The leads are connected to the generator. The skin is closed with stitches. Most people go home within 1 day of the procedure.

Two kinds of pacemakers -- transcutaneous and transvenous pacemakers -- are used only in medical emergencies. They are not permanent pacemakers

Pacemakers may be used for people who have heart problems that cause their heart to beat too slowly. A slow heartbeat is called bradycardia. Two common problems that cause a slow heartbeat are sinus node disease and heart block.

When your heart beats too slowly, your body and brain may not get enough oxygen. Symptoms may be light-headedness, tiredness, fainting spells, and shortness of breath.

Some pacemakers can be used to stop a heart rate that is too fast (tachycardia) or that is irregular.

Other types of pacemakers can be used in severe heart failure. These are called biventricular pacemakers. They help coordinate the beating of the heart chambers.

Most biventricular pacemakers implanted today can also work as implantable cardioverter defibrillators (ICD), which restore a normal heartbeat.

How does a pacemaker work?

A pacemaker consists of a battery, a computerized generator, and wires with sensors at their tips. (The sensors are called electrodes.) The battery powers the generator, and both are surrounded by a thin metal box. The wires connect the generator to the heart.

A pacemaker helps monitor and control your heartbeat. The electrodes detect your heart's electrical activity and send data through the wires to the computer in the generator.

If your heart rhythm is abnormal, the computer will direct the generator to send electrical pulses to your heart. The pulses travel through the wires to reach your heart.

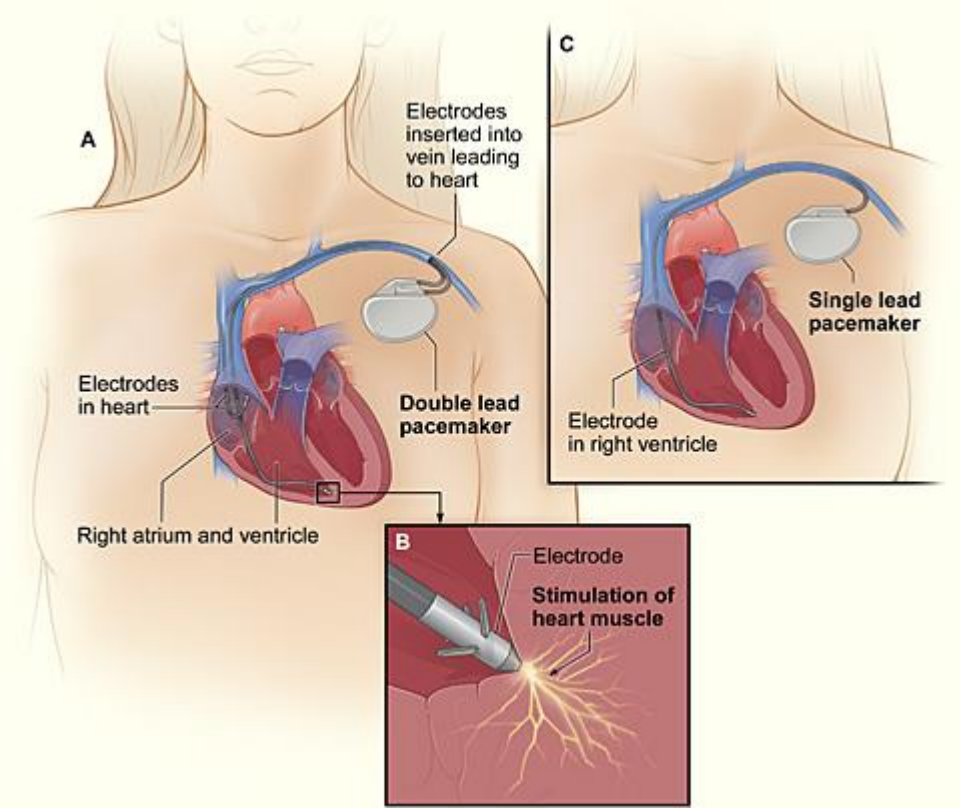
Newer pacemakers can monitor your blood temperature, breathing, and other factors. They also can adjust your heart rate to changes in your activity.

The pacemaker's computer also records your heart's electrical activity and heart rhythm. Your doctor will use these recordings to adjust your pacemaker so it works better for you.

Your doctor can program the pacemaker's computer with an external device. He or she doesn't have to use needles or have direct contact with the pacemaker.

Pacemakers have one to three wires that are each placed in different chambers of the heart.

- The wires in a single-chamber pacemaker usually carry pulses from the generator to the right ventricle (the lower right chamber of your heart).
- The wires in a dual-chamber pacemaker carry pulses from the generator to the right atrium (the upper right chamber of your heart) and the right ventricle. The pulses help coordinate the timing of these two chambers' contractions.
- The wires in a biventricular pacemaker carry pulses from the generator to an atrium and both ventricles. The pulses help coordinate electrical signaling between the two ventricles. This type of pacemaker also is called a cardiac resynchronization therapy (CRT) device.



The image shows a cross-section of a chest with a pacemaker. Figure A shows the location and general size of a double-lead, or dual-chamber, pacemaker in the upper chest. The wires with electrodes are inserted into the heart's right atrium and ventricle through a vein in the upper chest. Figure B shows an electrode electrically stimulating the heart muscle. Figure C shows the location and general size of a single-lead, or single-chamber, pacemaker in the upper chest.

PACEMAKER IMPLANTATION

A pacemaker is implanted to treat bradycardia (an abnormally slow heart rate). Pacemakers can also adjust the heart rate to meet the body's needs, whether during exercise or rest. Implantation of a pacemaker involves positioning leads (thin, insulated wires) in the heart and placing the device in a pocket of skin, usually in the shoulder area. Typically the implant procedure involves only local anesthetics and a sedative, rather than general anesthesia. Most people have a fairly quick recovery after a pacemaker implant.

What Is a Pacemaker?

A pacemaker is a small implantable device that treats abnormal heart rhythms called arrhythmias. Specifically, a pacemaker treats slow arrhythmias called bradycardia. Arrhythmias result from a problem in the heart's electrical system. Electrical signals follow a certain pathway through the heart. It is the movement of these signals that causes your heart to contract.

A pacemaker system has two parts, and each plays a role in treatment. The pacemaker leads are thin, insulated wires that carry electrical signals back and forth between the device and the heart. The leads can sense when the heart is beating too slowly and needs treatment. The pacemaker device, or pulse generator, is quite small, easily fitting in the palm of your hand. It contains computerized parts that run on a battery. The device treats your heart by sending very small amounts of electrical energy to the heart through the leads. Patients usually can't feel the treatment. The pacing system delivers treatment based on what it senses in your heart, even if you don't feel any symptoms. The pacemaker can be implanted below the collarbone on either the right or left side of the body. In some cases the device is implanted in the abdomen. Before confirming where to place the device, you and your doctor will talk about:

- Your age and overall health
- Whether you have had chest surgery
- Your activities and lifestyle

Pacemaker Implantation Procedure

Implanting the Leads: You lie on an exam table and an intravenous (IV) line is put into your arm. The IV delivers fluids and medications during the procedure. The medication makes you relaxed and groggy, but not unconscious. (General anesthesia is usually not needed.) During the procedure, you will be attached to several monitors. Your doctor numbs a small area of skin and inserts the leads through a small incision, usually near the collarbone. The doctor gently steers the leads through the blood vessels and into the heart. The doctor can see where the leads are going by watching a video screen with real-time, moving x-rays (fluoroscopy). Depending on the treatment your heart needs, either one or two leads are implanted in your heart. A pacemaker that uses one lead is called a single-chamber pacemaker. A pacemaker that uses two leads is called a dual-chamber pacemaker. With a dual-chamber pacing system, one lead goes in your top right chamber (the atrium) and the other lead goes in your bottom right chamber (the ventricle).

Testing the Leads and Device: Your doctor connects the implanted leads to the device and tests the system. In this way the doctor makes sure that both parts of the pacemaker system—the leads and the device—work properly. During the testing you may feel your heart beating faster. Implanting the Device: Your doctor places the device just under the skin—usually near your collarbone—and then stitches the incision closed.

What Happens After the Procedure?

The pacemaker implant experience can vary from one person to another. Some people stay in the hospital overnight, while others go home the same day as the procedure. There is usually tenderness at the incision site, just as there is any time you have stitches. However, most people have a fairly quick recovery.

ARTIFICIAL BLOOD

A **blood substitute** (also called **artificial blood** or **blood surrogates**) is a substance used to mimic and fulfill some functions of biological blood. It aims to provide an alternative to blood transfusion, which is transferring blood or blood-based products from one person into another. Thus far, there are no well-accepted *oxygen-carrying* blood substitutes, which is the typical objective of a red blood cell transfusion; however, there are widely available non-blood volume expanders for cases where only volume restoration is required. These are helping doctors and surgeons avoid the risks of disease transmission and immune suppression, address the chronic blood donor shortage, and address the concerns of Jehovah's Witnesses and others who have religious objections to receiving transfused blood.

The main categories of 'oxygen-carrying' blood substitutes being pursued are hemoglobin-based oxygen carriers (HBOC) and perfluorocarbon-based oxygen carriers (PFBOC). Oxygen therapeutics are in clinical trials in the U.S. and Europe, and Hemopure is available in South Africa.

Oxygen-carrying substitutes.

An *oxygen-carrying blood substitute*, sometimes called *artificial haemoglobin*, is an artificially made red blood cell substitute whose main function is to carry oxygen, as does natural hemoglobin. The use of oxygen-carrying blood substitutes is often called oxygen therapeutics to differentiate from true blood substitutes. The initial goal of oxygen carrying blood substitutes is merely to mimic blood's oxygen transport capacity. There is additional longer range research on true artificial red and white blood cells which could theoretically compose a blood substitute with higher fidelity to human blood. Unfortunately, oxygen transport, one function that distinguishes real blood from other volume expanders, has been very difficult to reproduce.

There are two basic approaches to constructing anoxygen therapeutic. The first is perfluorocarbons (PFC), chemical compounds which can carry and release oxygen. The specific PFC usually used is perfluorodecalin. The second is haemoglobin derived from humans, animals, or artificially via recombinant technology, or via stem cell production of red blood cells in vitro.

Advantages over human blood.

Oxygen therapeutics, even if widely available, would not eliminate the use of human blood, which performs various functions besides oxygen transport. However oxygen therapeutics have major advantages over human blood in various situations, especially trauma.

Blood substitutes are useful for the following reasons:

1. Donations are increasing by about 2–3% annually in the United States, but demand is climbing by between 6–8% as an aging population requires more operations that often involve blood transfusion.

2. Although the blood supply in many countries is very safe, this is not the case for all regions of the world. Blood transfusion is the second largest source of new HIV infections in Nigeria. In certain regions of southern Africa, it is believed that as much as 40% of the population has HIV/AIDS, although testing is not financially feasible. A disease-free source of blood substitutes would be incredibly beneficial in these regions.
3. In battlefield scenarios, it is often impossible to administer rapid blood transfusions. Medical care in the armed services would benefit from a safe, easy way to manage blood supply.
4. Great benefit could be derived from the rapid treatment of patients in trauma situations. Because these blood substitutes do not contain any of the antigens that determine blood type, they can be used across all types without immunologic reactions.
5. While it is true that receiving a unit of transfused blood in the US does not carry many risks, with only 10 to 20 deaths per million units, blood substitutes could eventually improve on this. There is no practical way to test for prion-transmitted diseases in donated blood, such as mad cow and Creutzfeld-Jacob disease, and other disease could emerge as problems for the blood supply, including smallpox and SARS.
6. Transfused blood is currently more cost effective, but there are reasons to believe this may change. For example, the cost of blood substitutes may fall as manufacturing becomes refined.
7. Blood substitutes can be stored for much longer than transfusable blood, and can be kept at room temperature. Most haemoglobin-based oxygen carriers in trials today carry a shelf life of between 1 and 3 years,[7] compared to 42 days for donated blood, which needs to be kept refrigerated.
8. Blood substitutes allow for immediate full capacity oxygen transport, as opposed to transfused blood which can require about 24 hours to reach full oxygen transport capacity due to 2,3-diphosphoglycerate depletion. Also, in comparison, natural replenishment of lost red blood cells usually takes months, so an oxygen-carrying blood substitute can perform this function until blood is naturally replenished.
9. Oxygen-carrying blood substitutes also would become an alternative for those patients that refuse blood transfusions for religious or cultural reasons, such as Jehovah's Witnesses.
10. Synthetic oxygen carriers may also show potential for cancer treatment, as their reduced size allows them to diffuse more effectively through poorly vasculated tumour tissue, increasing the effectiveness of treatments like photodynamic therapy and chemotherapy.
11. The U.S. military is one of the greatest proponents of oxygen therapeutics, mainly because of the vital need and benefits in a combat scenario. Since oxygen therapeutics are not yet widely available, the United States Army is experimenting with varieties of dried blood, which take up less room, weigh less and can be used much longer than blood plasma. Saline has to be added

prior to use. These properties make it better for first aid during combat than whole blood or packed red cells.

Risks

Haemoglobin-based blood substitutes may increase the odds of deaths and heart attacks. According to studies of outcomes of transfusions given to trauma patients in 2008, blood substitutes yielded a 30% increase in the risk of death and about a threefold increase in the chance of having a heart attack for the recipients. More than 3,711 patients were tested in sixteen studies using five types of artificial blood. Public Citizen sued the U.S. Food and Drug Administration (FDA) to attain information on the duration of these studies which were found to have been conducted from 1998 until 2007. The FDA permits artificial blood transfusions in the US without informed consent under a special exemption from requirements of informed consent during traumatic care.

ARTIFICIAL SKIN

Artificial skin refers to a collagen scaffold that induces regeneration of skin in mammals. The term was used in the late 1970s and early 1980s to describe a new treatment for massive burns. It was later discovered that treatment of deep skin wounds in adult animals and humans with this scaffold induces regeneration of the dermis. It has been developed commercially under the name IntegraTM and is used in massively burned patients, during plastic surgery of the skin, and in treatment of chronic skin wounds.
The term “artificial skin” sometimes is used to refer to skin-like tissue grown in a laboratory, although this technology is still quite a way away from being viable for use in the medical field. 'Artificial skin' can also refer to flexible semiconductor materials that can sense touch for those with prosthetic limbs,

The skin is the largest organ in the human body. Skin is made up of three layers, the epidermis, dermis and the fat layer, also called the hypodermis. The epidermis is the outer layer of skin that keeps vital fluids in and harmful bacteria out of the body. The dermis is the inner layer of skin that contains blood vessels, nerves, hair follicles, oil, and sweat glands. Severe damage to large areas of skin exposes the human organism to dehydration and infections that can result in death.

Artificial skin is another example of a percutaneous implant, and the problems are similar to those described above. Important for this application is a material which can adhere to a large (burned) surface and thus prevent the loss of fluids, electrolytes, and other biomolecules until the wound has healed.

In one study on wound-covering materials with controlled physicochemical properties, an artificial skin was designed with a crosslinked collagen-polysaccharide (chondroitin 6-sulfate) composite membrane. This was specifically chosen to have controlled porosity (5-150 μm in diameter), flexibility (by varying crosslink density), and moisture flux rate.

Several polymeric materials and reconstituted collagen have also been examined as burn dressings. Among the synthetic ones are the copolymers of vinyl chloride and vinyl acetate as well as polymethyl cyanoacrylate (applied as a fast-polymerizing monomer). The latter polymer and/or its monomer were found to be too brittle and histotoxic for use as a burn dressing. The ingrowth of tissue into the pores of polyvinyl alcohol sponges and woven fabric (nylon and silicone rubber velour) was also attempted without much success. Nylon mesh bonded to a silicone rubber membrane, another design attempt, prevented water evaporation but has not been found to induce fibrovascular growth.

Rapid epithelial layer growth by culturing cells *in vitro* from the skin of the burn patient for covering the wound area may offer a practical solution for less severely burned patients. Implantation of an allogenic fibroblast/polymer construct has proven useful for providing long-term skin replacement. Related to this, temporary tissue engineered replacements are possible alternatives for burns requiring larger area coverage. These can be similar to the synthetic dressing, a nylon mesh and silicone rubber component, but incorporates allogeneic fibroblasts. This temporary covering hopefully will stimulate or allow fibrovascular growth into the wound bed by providing the appropriate matrix proteins and growth factors.

ARTIFICIAL PANCREAS

The **artificial pancreas** is a technology in development to help people with diabetes automatically control their blood glucose level by providing the substitute endocrine functionality of a healthy pancreas.

There are several important exocrine (digestive) and endocrine (hormonal) functions of the pancreas, but it is the lack of insulin production which is the motivation to develop a substitute. While the current state of insulin replacement therapy is appreciated for its life-saving capability, the task of manually managing the blood sugar level with insulin alone is arduous and inadequate.

The goal of the artificial pancreas is two-fold:

1. to improve insulin replacement therapy until glycemic control is practically normal as evident by the avoidance of the complications of hyperglycemia, and
2. to ease the burden of therapy for the insulin-dependent.

Different approaches under consideration include:

- the medical equipment approach—using an insulin pump under closed loop control using real-time data from a continuous blood glucose sensor.
- the bioengineering approach—the development of a bio-artificial pancreas consisting of a biocompatible sheet of encapsulated beta cells. When surgically implanted, the islet sheet will behave as the endocrine pancreas and will be viable for years.

- the gene therapy approach—the therapeutic infection of a diabetic person by a genetically engineered virus which causes a DNA change of intestinal cells to become insulin-producing cells

A biological approach to the artificial pancreas is to implant bioengineered tissue containing islet cells, which would secrete the amount of insulin, amylin, and glucagon needed in response to sensed glucose.

When islet cells have been transplanted via the Edmonton protocol, insulin production (and glycemic control) was restored at the expense of immunosuppression. Encapsulation of the islet cells in a protective coating has been developed to block the immune response to transplanted cells, which relieves the burden of immunosuppression and benefits the longevity of the transplant.

One concept of the bio-artificial pancreas uses encapsulated islet cells to build an *islet sheet* which can be surgically implanted to function as an artificial pancreas.

This islet sheet design consists of:

- an inner mesh of fibers to provide strength for the islet sheet;
- islet cells, encapsulated to avoid triggering a proliferating immune response, adhered to the mesh fibers;
- a semi-permeable protective layer around the sheet, to allow the diffusion of nutrients and secreted hormones;
- a protective coating, to prevent a foreign body response resulting in a fibrotic reaction which walls off the sheet and causes failure of the islet cells.

Islet sheet research is pressing forward with large animal studies at the present, with plans for human clinical trials within a few years.

The pancreas produces three hormones that are important to glycemic control:

- insulin, which lowers blood glucose by converting glucose into glycogen;
- amylin, which slows digestion and slows the rate of glucose entering the bloodstream, and temporarily suppresses release of glucagon;
- and glucagon, which raises blood glucose by converting glycogen into glucose.

Upon digestion of carbohydrates, glucose levels in the blood will begin to rise. As the blood and glucose flow into the pancreas, insulin and amylin are co-secreted by the pancreatic beta cells directly into the bloodstream in response to elevated blood glucose levels. In the presence of glucose these insulin responses are almost exclusively delivered in boluses every 4 to 6 minutes. Insulin causes blood glucose to be removed from the bloodstream and stored in the liver and muscle cells. As the blood sugar goes higher, additional insulin will bring the blood sugar back down in a classic negative feedback loop. As insulin is released from the beta cells, amylin is also released into the bloodstream. Amylin slows gastric emptying, and also inhibits the release of glucagon from the pancreatic alpha cells. The effect of amylin is to spread out the blood glucose peak after eating, reducing the quantity of insulin needed. As the blood

sugar level comes back toward normal, the beta cells will stop spurting insulin and amylin. As the glucose level approaches a low mark, the pancreatic alpha cells will release glucagon directly into the bloodstream. Glucagon causes the liver to release stored glucose back into the bloodstream. Increased glucagon will increase blood glucose levels to produce a positive error in the negative feedback loop. Together, the three endocrine hormones work as a system to maintain the blood glucose level between high and low boundaries. By delivering the insulin in boluses as presented by a non-diabetic pancreas, the goal of an artificial pancreas can be achieved.

When the beta cell produces insulin from proinsulin, a connecting peptide (or C-peptide) is also manufactured and released into the bloodstream. Absence of C-peptide in the blood indicates that insulin has not been released from the pancreas, and this fact confirms the diagnosis of diabetes type 1. C-peptide was believed to be only a by-product of natural insulin production; however, recent studies suggest that C-peptide exerts beneficial therapeutic effects on diabetic nociceptive neuropathy.

In insulin-dependent persons, blood glucose levels have been roughly controlled using insulin alone. The number of grams of carbohydrate is estimated by measuring foods, and the measurement is used to determine the amount of insulin necessary to *cover* the meal. The calculation is based on a simple *open-loop model*: an insulin to carbohydrate ratio (adjusted based on past success) is multiplied by the grams of carbohydrate to calculate the units of insulin needed. That quantity of insulin is then adjusted based on a pre-meal blood glucose measurement (insulin bolus increased for a high blood sugar or insulin bolus delayed and reduced for a low blood sugar). Insulin is injected or infused under the skin, and enters the bloodstream in approximately 15 minutes. After the insulin has acted in the bloodstream, the blood glucose level can be tested again and then adjusted with injection of more insulin, or eating more carbohydrates, until balance is restored. Assuming the design requirement is to truly mimic normal pancreatic delivery of insulin to the liver in order to achieve proper hepatic stimulation, and to cause normal insulin induced functions, until another system is available to deliver portal vein concentrations of insulin, an intravenous infusion device will be needed.

There are notable differences with insulin replacement compared to the function of pancreatic insulin delivery:

1. the insulin dose is predicted based on measured food (where accuracy of measured carbohydrate is difficult) whereas pancreatic insulin is released in proportional response to actual blood glucose levels;
2. pancreatic insulin is released into to the portal vein, where it flows almost directly to the liver, which is the major organ for storing glycogen (50% of insulin produced is used by the liver);
3. pancreatic insulin is pulsatile which helps maintain the insulin sensitivity of hepatic tissues;

4. injected insulin is delivered subcutaneously (under the skin) but not directly to the bloodstream, so there is a delay before injected insulin begins to reduce blood glucose (although this can be compensated by injecting insulin 15 minutes before eating);
5. insulin which is not delivered intravenously cannot achieve normal momentary concentrations in the portal vein which connects the pancreas to the liver;
6. replacement insulin therapy does not include amylin (although Symlin is now available for use), which can reduce the insulin need by 50%;
7. replacement insulin is dosed as a best compromise between aggressive use for lowering the blood sugar when eating but also conservative use to avoid a post-prandial low blood sugar due to excess insulin, whereas pancreatic function releases insulin aggressively and later includes automatic release of glucagon at the end of an insulin cycle to manage the blood sugar level and avoid hypoglycemia.

An insulin pump to infuse a rapid-acting insulin is the first step in simulating the function of the pancreas. The pump can accurately deliver small increments of insulin compared to an injection, and its electronic controls permit shaping a bolus over time to match the insulin profile required for a given situation. The insulin pump is controlled by the pump user to bolus manually based on a recent blood glucose measurement and an estimate of the grams of carbohydrate consumed. This predictive approach is said to be *open-loop.* Once a bolus has been calculated and delivered, the pump continues to deliver its basal rate insulin in the manner that has been programmed into the pump controls based on the predicted insulin requirements of its user.

While insulin replacement is appreciated as a life saving therapy, its practical use in controlling blood glucose levels sufficiently to avoid the long-term complications associated with hyperglycemia is not ideal. Also, it is generally agreed that even with very tight glucose control, there are a significant number of patients who go on to develop all of the life impacting complications of diabetes. Thus, the goal of the Artificial Pancreas should be to normalize carbohydrate and lipid metabolism at a minimum.