LECTURES 4-5: ARTIFICIAL HEARTS

4.1. Artificial Heart

The heart's primary function is to pump blood to all parts of the body, bringing nutrients and oxygen to the tissues and removing waste products. When the body is at rest, it needs a certain amount of blood to achieve this function. During exercise or times when, greater demands are placed on the body; more blood is required. To meet these variable demands, the heartbeat increases or decreases, and blood vessels dilate to deliver more blood or constrict during times when less blood is required.

The heart’s structure has four chambers with one-way flaps called valves (Figure 1). The atria are the upper chambers and they receive blood that is being returned to the heart. The right atrium receives blood with little oxygen because the blood has already circulated throughout the body delivering oxygen and nutrients. The left atrium fills with newly oxygenated blood returning from the lungs. When the atria contract, they push the blood through valves (tricuspid and mitral) into the relaxed ventricles.

When the ventricles contract, the right ventricle pumps blood through the pulmonary valve into the lungs. The left ventricle pumps blood through the aortic valve to the body, including the heart (through coronary arteries). This continuous cycle of synchronized contractions is driven by the heart's electrical system.

The artificial heart is typically used to bridge the time to heart transplantation, or to permanently replace the heart in case heart transplantation is impossible. Numerous devices have been developed for mechanical circulatory support in patients with end-stage heart failure. Ventricular assist devices (VADs) are in routine use as a bridge to

transplantation, bridge to recovery, and long-term chronic support. The latest generation includes axial and centrifugal flow blood pumps.

Currently, one total artificial heart (TAH, i.e. AbioCor™) is being used under the Humanitarian Device Exemption in the USA.

The next generation TAH (i.e. AbioCor II) is being developed. It is smaller in size and therefore suitable for more patients.

In Europe, the ACcor TAH and the MiniACcor TAH are currently being developed. These devices have been tested in animal studies and circulatory mock loops.

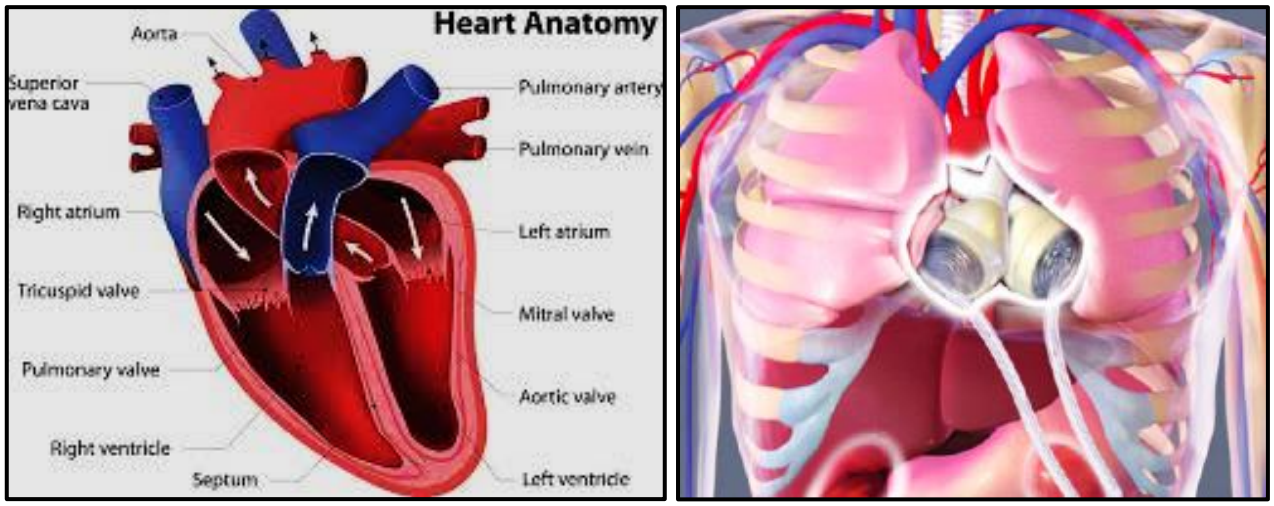

FIGURE 1: Anatomical position of the SynCardia TAH and its pneumatic drivelines. The drivelines enter the patient along the left midclavicular line, approximately 5cm below the costal margin. The TAH lies in the mediastinum attached to the atria, pulmonary artery and the aorta.

When a person is diagnosed with heart failure, it means that the heart is not working as efficiently as it should. Heart failure may be reversible, and people may live for many years after the diagnosis is made. Heart failure may occur suddenly, or it may develop gradually.

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When heart function deteriorates over years, one or more conditions may exist. The strength of muscle contractions may be reduced, and the ability of the heart chambers to fill with blood may be limited by mechanical problems, resulting in less blood to pump out to tissues in the body.

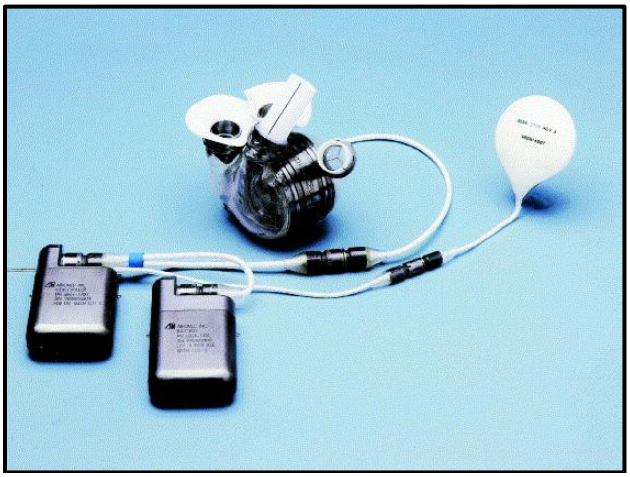
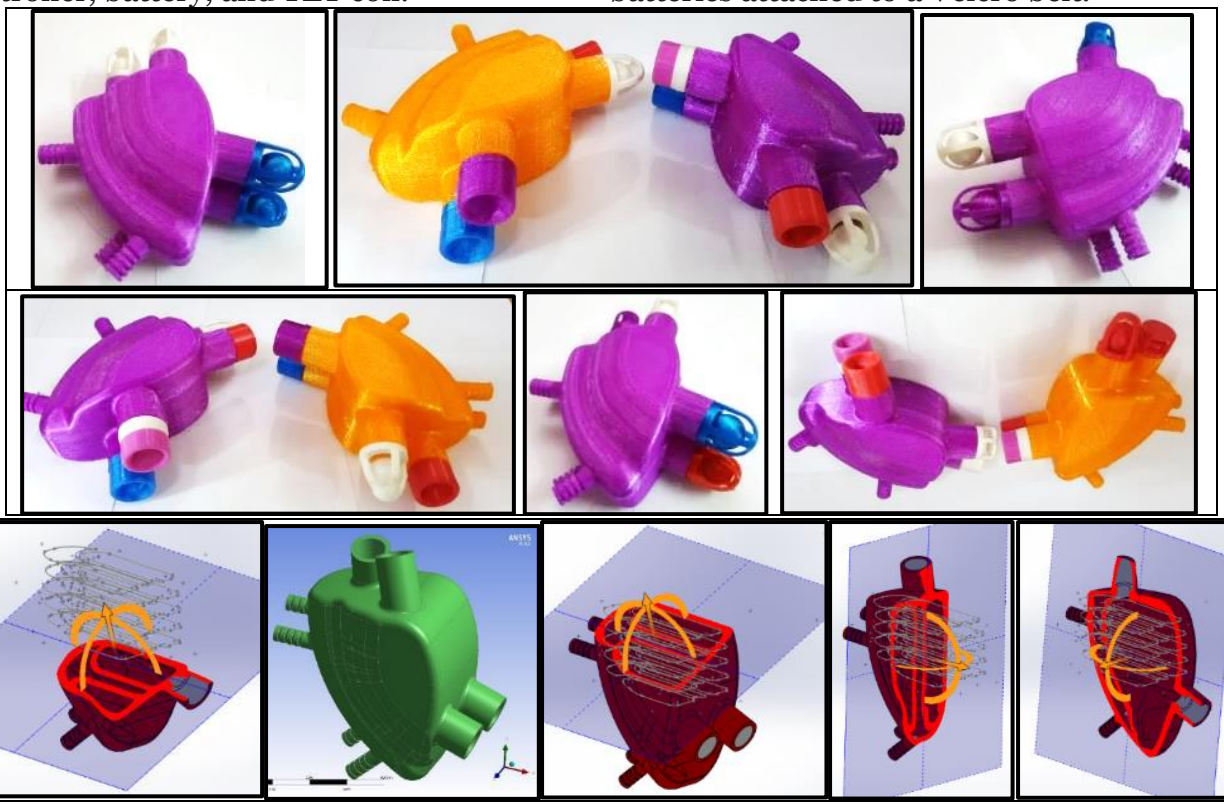


Figure 2. Internal components of the AbioCor IRH include the thoracic unit, controller, battery, and TET coil.

Figure 3. External components displaying the portable TET module and external batteries attached to a Velcro belt.



Conversely, the pumping chambers may enlarge and fill with too much blood when the heart muscle is not strong enough to pump out all the blood it receives. In addition, as the architecture of the heart changes as it enlarges, regurgitation of the mitral valve may develop, making the heart failure even worse.

When a patient is diagnosed as having heart failure, the first treatment is often by means of drugs. The applied types of drugs depend on the type of heart disease and include diuretics (influences blood volume and thus the heart's workload) and drugs that influence the pumping action by either strengthening the heart's pumping action or stimulation of vasodilatation.

In other cases, surgery may be the best treatment of choice. When heart failure is due to valvular disease, surgical implantation of an artificial heart valve or valve repair may alleviate the problem. Surgery may also be helpful in correcting congenital heart defects that can lead to heart failure.

Coronary artery bypass graft surgery and catheterization using a balloon to flatten fatty deposits (called angioplasty) are among the therapeutic techniques used to prevent and treat heart failure caused by occluded, or blocked, arteries.

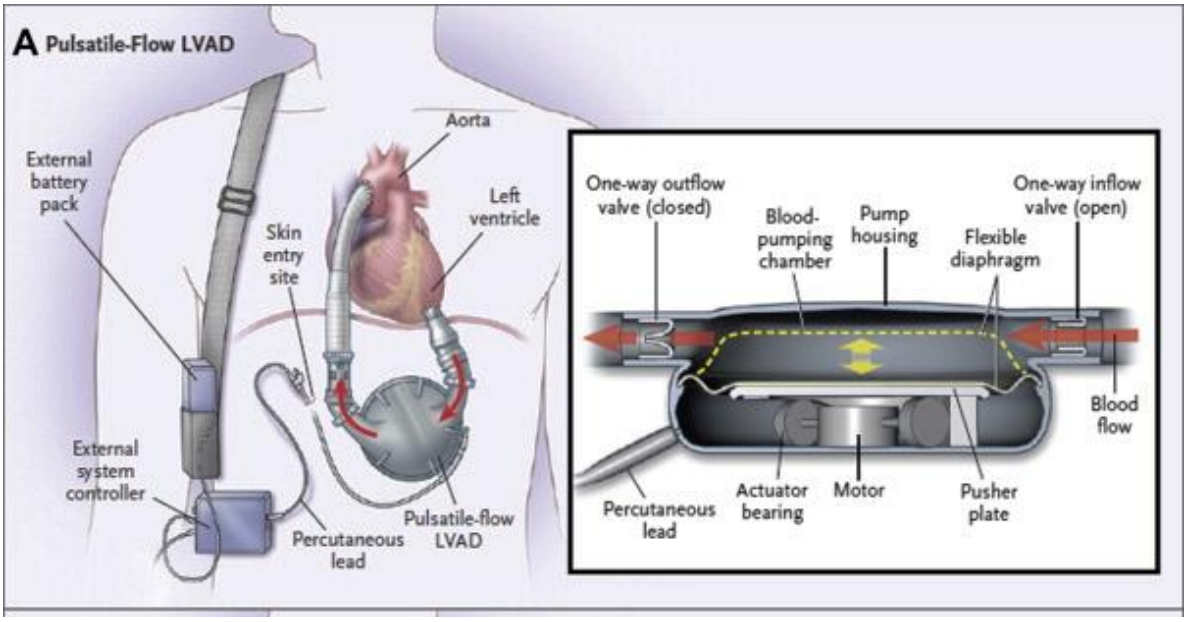
In recent years, the placement of a stent - either a bare metal stent or a drug eluting stent – after angioplasty has become a procedure of choice. Heart transplants are a last resort in treating severe heart failure caused by diseased heart muscle.

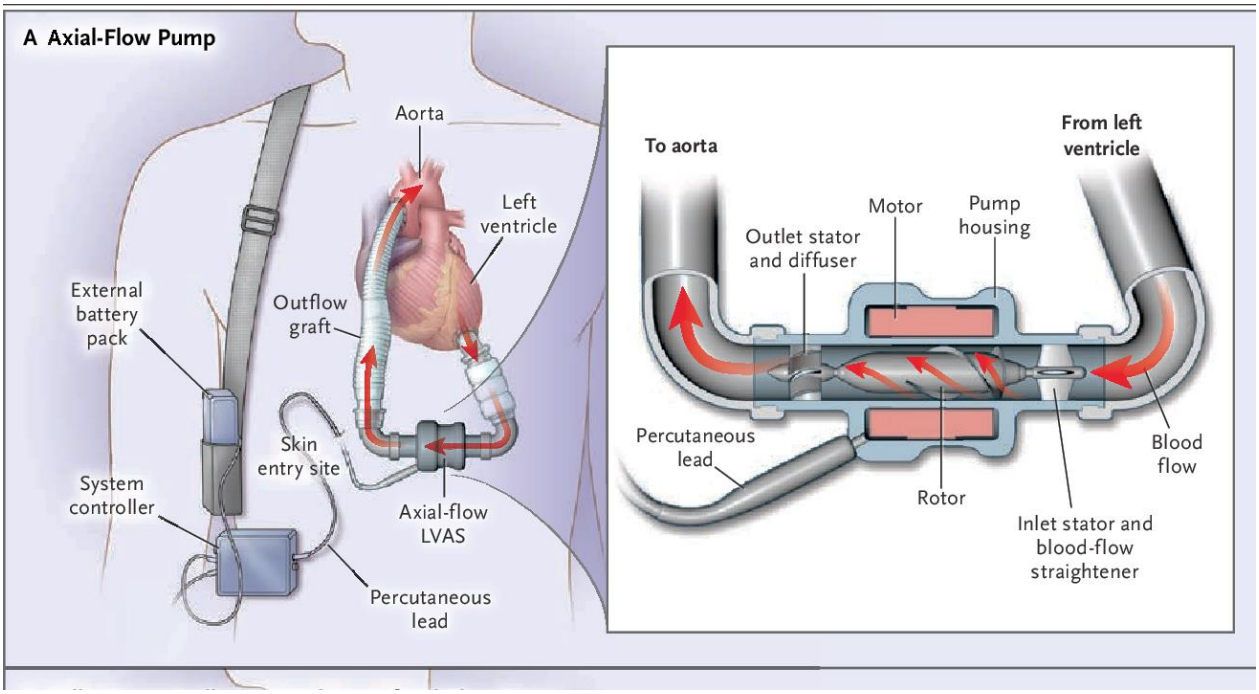
4.2. Types of Heart Blood Pumps

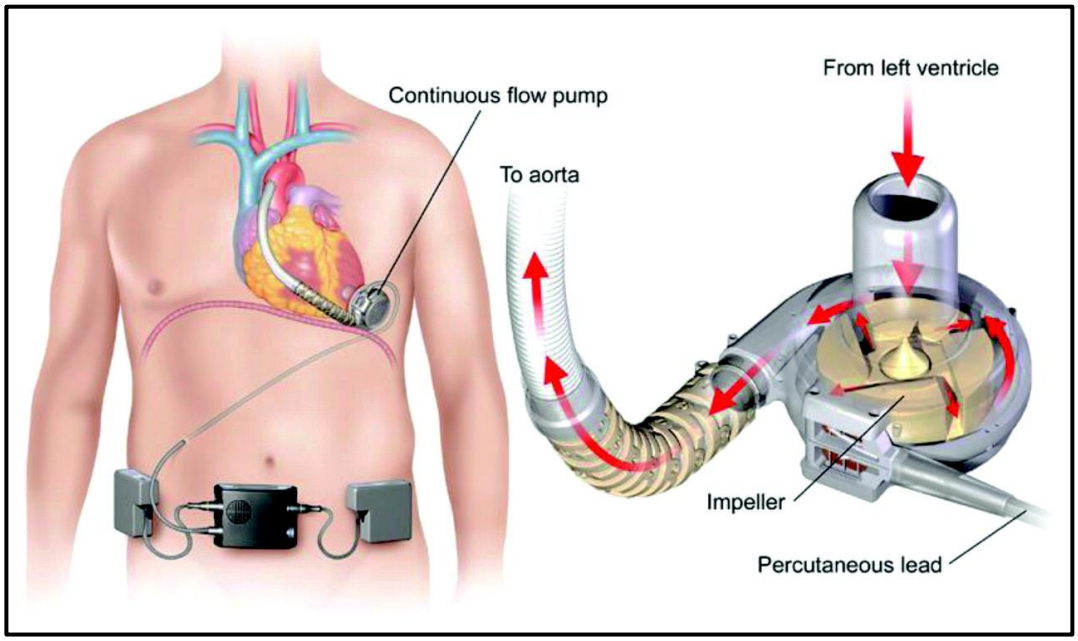
Blood pumps can be classified in two main categories:

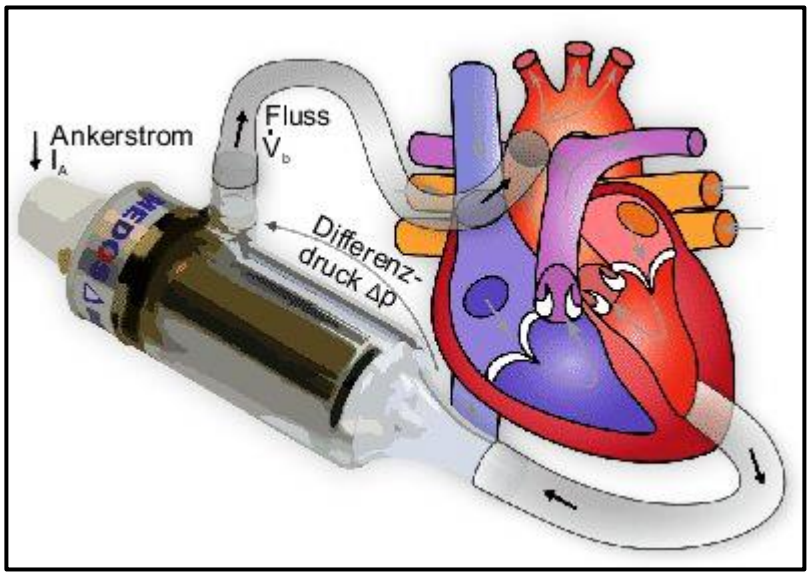
- o Displacement (or pulsatile flow) devices or,
- o Rotary (or continuous flow) devices, which are sub-classified in:
  - Axial flow blood pumps,

- Centrifugal or radial flow blood pumps,
- Diagonal flow blood pumps or mixed flow systems (mainly used as extracorporeal devices for cardiopulmonary bypass systems).









Rotary Diagonal blood flow pump

There are differences in the configuration of the blood pumps in terms of the position of the pump (extracorporeal, paracorporeal or intracorporeal), implantation position (intra-abdominal, intraperitoneal, or preperitoneal pocket), method of driving the mechanism (pneumatically, electrically, magnetically driven), type of power source (wall-mounted, console-based or battery packs), positioning of the cannulae and leads

delivering the power, valve structure, and the nature of the internal surfaces of the devices. Intracorporeal blood pumps are either connected by percutaneous leads through the patient's skin or totally implanted.

In considering pump design theory, axial flow blood pumps generate high flows at low pressure differences, whereas centrifugal flow pumps are capable of producing higher pressures at lower flows. Diagonal flow pumps tend to have the capability of high-generated pressures and high flow rates. Axial flow blood pumps, although far more compact than centrifugal pumps, operate at much higher rotational speeds to produce the desired head pressure and flow. Because of their small size and tubular configuration, axial pumps require less time to implant, thereby decreasing the costs and invasiveness of the procedure.

Centrifugal pumps typically weigh more than axial flow pumps, and this may lead to patient discomfort after installation. In addition, axial flow blood pumps generally consume less power, which allow for more compact and lighter power supply components and eventually implantable batteries.

4.3 Total artificial heart (TAH)

Until recently, only pneumatic total artificial hearts (TAHs) with extracorporeal driving systems have been clinically used including prominent examples such as the Jarvik 7™ of Jarvik Heart, Inc. (New York, USA) and its successor the CardioWest™ temporary TAH of SynCardia Systems, Inc. (Tucson, AZ, USA). These systems have been used for patient with end-stage heart failure. Since July 2001, several patients have been implanted with a different type of TAH, a fully implantable prosthetic device.

4.3.1 AbioCor™ TAH and AbioCor II

Equipped with an internal motor, the AbioCor™ TAH is able to move blood through the lungs and the rest of the body, simulating the rhythm of the heartbeat. The AbioCor™ TAH consists of both external and internal components. The internal components are the thoracic unit or pump, rechargeable battery, controller and TET coil (Figure 2). The thoracic unit consist of an energy converter and two pumping chambers that function as left and right ventricles. The energy converter is situated between the ventricles and contains a high-efficiency miniature centrifugal pump driven by a brushless DC motor.

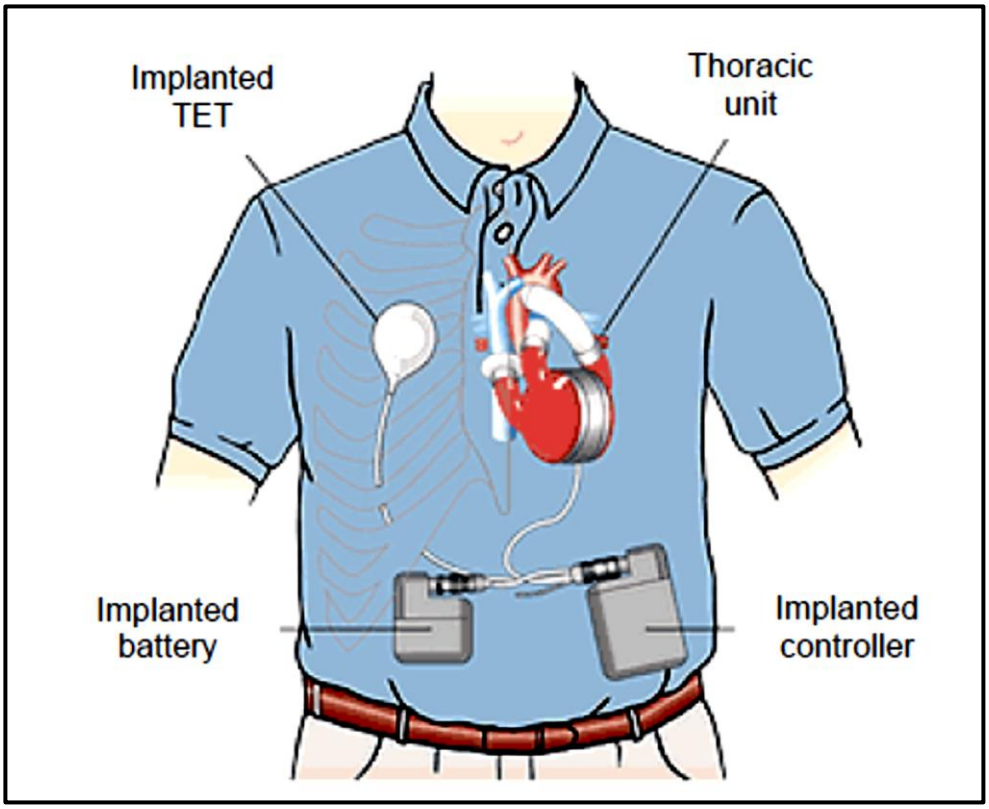


Figure 2 Internal components of the AbioCor™ TAH. Reprinted with permission from Abiomed, Inc.

This centrifugal pump operates unidirectionally to pressurize a low-viscosity fluid. A two RIVM report Implanted battery; Thoracic unit; Implanted controller; Implanted

TET position switching valve is used to alternate the direction of hydraulic flow between left and right pumping chambers. This results in an alternate left and right systole. The rate of the switching valve determines the beat rate of the device. There is a one-to-one correspondence between blood and hydraulic fluid displacement. The displacement of hydraulic fluid to one side results in the creation of a negative pressure in the opposite ventricle. Thus, the device is considered an active fill device.

The internal controller, placed abdominally, drives the energy converter in the thoracic unit, monitors the implanted components, and transmits device performance data to a bedside console by means of radiofrequency telemetry. These radiofrequency transmissions from the internal controller to the external console convey information, including continuous real-time telemetry of hydraulic pressure waveforms, system operating parameters, battery status, component temperature, and alarm information. This information is stored for later retrieval and analysis.

The internal rechargeable battery, also placed abdominally, is lithium ion based and functions as an emergency or backup power source. It is continually recharged by external power received through the internal TET coil and can provide up to 20 minutes of operation while disconnected from the main power source. The internal TET coil receives high-frequency power that is transmitted across the skin from the external TET coil. The internal TET coil system electronics covert this oscillating current to a DC that is used to power the thoracic unit and to recharge the internal batteries.

The four external components consist of an external TET coil, batteries, a TET module, and a bedside console. The bedside console is used during implantation, recovery, and when the patient is in his/her primary residence. The bedside console provides clinicians with a graphic user interface for control and monitoring the implanted system through radiofrequency communication. The console can be configured to operate

in different modes for implantation, recovery, and home monitoring. In addition, the console can be remotely monitored when connected to a telephone jack through a laptop computer.

Technical data AbioCor™ TAH are: weight ~900 g, beat rate 75-150 beats per minute, flow rate 4-8 l/min, rotational speed of centrifugal pump 3000-10,000 rpm. The AbioCor II is smaller (35% reduction in size) and therefore able to fit significantly more of the adult population, and designed with a goal of five-year reliability.

Abiomed, Inc. intends to submit for an FDA Investigational Device Exemption in 2006 in order to begin clinical investigations with a purpose of seeking premarket approval by 2008.

The AbioCor II TAH

4.3.2 ACcor TAH

The ACcor TAH of the Helmholtz-Institute for Biomedical Engineering, Aachen University of Technology (Germany), is being developed primarily for BTT and finally for use as a permanent heart replacement system. It consists of three main components: two diaphragms pump chambers, replacing the explanted ventricles functionally and

anatomically, with inlet and outlet valves, and the electromechanical energy converter. The inlets of the pump chambers are connected to the natural atria while the outlets are connected to the aorta and the pulmonary artery, respectively.

The energy converter consists of a brushless electronically commutated synchro motor and two reduction and hypocycloid gear units which transform the unidirectional rotational movement of the motor into translatory pusher plate excursions. Four acute animal tests in calves have been performed in cooperation with the university hospitals in Vienna (Austria) and Aachen (Germany). The ACcor TAH is capable of providing full circulation for 8.5 hours with a flow of 4-8 l/min.

A 20% smaller sized version of the ACcor TAH, the MiniACcor has been designed, manufactured and assembled. The MiniACcor pump unit is extensively tested within circulatory mock loops. The pump delivers flows between 4 to 7 l/min at aortic pressures of 80 to 140 mmHg at different pump rates.

3.4 Paediatric blood pumps

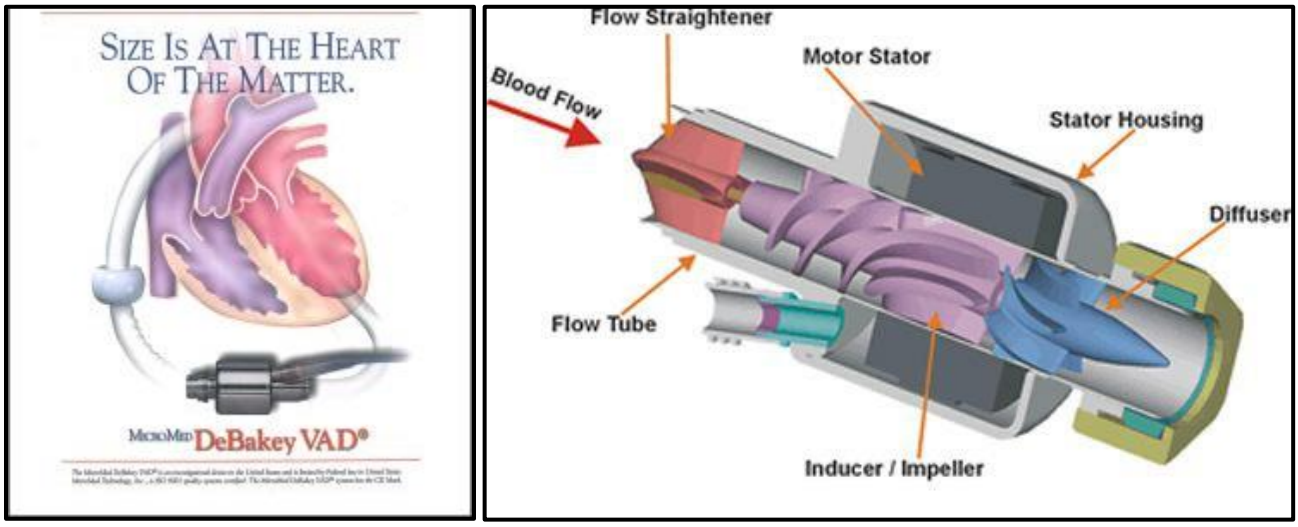
In early stages, hear failure in children is treated pharmacologically as in adults. As the disease severity increases, definitive therapy of heart failure in children consists of heart transplantation. Because sudden death in children awaiting heart transplantation is rare, the majority of deaths in this population are due to progressive heart and multi-organ failure and are therefore, at least in theory, amenable to salvage therapy with mechanical circulatory support, whereas for children, the choices are limited.

There is substantially less experience with paediatric VADs, including extracorporeal membrane oxygenation (a technique best preserved for short-term support and often associated with a high rate of complications). Options for longer-term support are the Thoratec pneumatic VAD (Thoratec Corporation, Pleasanton, CA, USA) , the

EXCOR® Pediatric (Berlin Heart AG, Berlin, Germany), and the MEDOS/HIA System (MEDOS Medizintechnik AG, Stolberg, Germany). These devices are Para corporeal VAD systems employing pneumatically driven, thin membrane pumps to provide pulsatile flow and are available in a variety of pump sizes suitable for pediatric support.

3.4.1 DeBakey VAD® Child

The DeBakey VAD® Child of MicroMed Technology, Inc. (Houston, TX, USA) is a miniaturized version of the DeBakey VAD®. The pediatric version employs the same axial flow pump used in the adult system with design modifications aimed at reducing the lateral space requirements for device implantation. These design modifications include a shortened inflow cannula with a more acute angle for the inflow tubing, a shortened plastic outflow graft protector, and reduced size of the flow probe on the outflow graft. Under the current Humanitarian Device Exemption programmed of the FDA the DeBakey VAD® Child is used to provide temporary left ventricular support as a BTT for children from 5 to 16 years of age with a body surface area >0.7 m^2 and <1.5 m^2 and is designed to be implantable is this size range.



4.4.2 MVAD ventricular assist device

The MVAD of HeartWare Ltd (Sydney, NSW, Australia) is expected to serve as the basis for the development of a paediatric VAD. The size of the MVAD™ is approximately one third the size of the HVAD™, one of the smallest third generation pumps under development as a BTT. Minimally invasive techniques are used to implant the MVAD™ as intravascular device. Currently, the MVAD™ is available for animal studies as a prototype. Animal studies commenced in August 2005. The first human clinical investigations are expected within approximately two years.

FIGURE: Size comparison of the MVAD PumpVThe HeartWare HVAD Pump (right) weighs 160 g compared with the MVAD Pump (left), which weighs 78 g.

4.4 Cell/tissue-based approach for function recovery

Despite recent advances in medical and device therapy for heart failure, the incidence, hospitalization, and mortality rates continue to rise. The possibility of using cell-based therapies for people suffering an acute myocardial infarction, advanced coronary artery disease and chronic heart failure has made enormous advances in moving

towards clinically applicable treatment options. Moreover, cell therapy of the heart seems to be the most abundantly practiced cell therapy in the clinic throughout the world.

There are several mechanisms of action used, or claimed to be used, as a principle for the current cardiac cell therapy approaches. The classic idea is that delivery of the appropriate stem cells would repair a damaged heart via active myocardial regeneration resulting from trans-differentiation of administered stem cells. Stem cells, regardless of origin, have the remarkable potential to develop into many different cell types in the body.

When a stem cell divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialized function, such as the beating cells of the heart. Stem cells may also stimulate heart repair through paracrine signaling actions. Stem cells are known to release angiogenic ligands, protect cardiomyocytes from apoptotic cell death, induce proliferation of endogenous cardiomyocytes, and may recruit resident cardiac stem cells.

Furthermore, stem cells are known to stimulate neovascularization which also results in an enhancement of the self-repair mechanism of the heart by allowing fast recruitment of systemically available stem cells and by preventing further cell death due to the new blood supply routes.

4.4.1 Cell source

The cell source of the applied cells is one of the major variables among the different cardiac cell therapies. One of the most promising and also controversial cell sources are embryonic stem cells, which are totipotent cells (able to differentiate in many cell types) derived from the inner cell mass of blastocysts. In theory, infinite numbers of cardiomyocytes could be obtained from human embryonic stem cell clones. The use of

embryonic stem cells *in vitro* differentiated to cardiomyocytes has shown to improve cardiac function in several rodent models.

The use of resident adult cardiac stem cells is thought to represent a therapeutic target that, if enhanced, could induce cardiac self-repair by mediating mechanisms of repair and replacement. Intriguingly, cardiac stem cells can be clonally expanded from human myocardial biopsies. An easily accessible source of cardiac stem cells is the auricle of the heart. This appendix of the heart contains many stem cells and can easily be missed since it has no direct role in the primary function of the heart.

Bone marrow mononuclear cells are used since these cells have been demonstrated to home to infarcted myocardium after reinfusion. These cells include hematopoietic stem cells that are involved in the process of neovascularization and mesenchymal stem cells that have the potential to differentiate into many cell types including cardiomyocyte-like cells. In many cases, mesenchymal stem cells are isolated from the bone marrow and culture expanded before they are applied to the patient.

4.4.2 Cell delivery

In general, the cells to be applied can be delivered in three ways:

I) Direct injection into the heart,

II) Infusion into the blood stream also referred to as transvascular approaches, and

III) Delivered as 3-dimensional patches.

I) Direct injection into the hart

Direct injection is often based on the delivery of cells that are aimed to function as cardiomyocytes (e.g., mesenchymal stem cells or myoblasts/satellite cells). The cells can either be injected into the target area by open heart surgery or via a catheter-based approach, such as via the coronary artery supplying an infracted zone or across the aortic

valve in the endocardial surface. A catheter-based delivery is less invasive and minimizes the recovery period of the patient.

II) Transvacuolar approaches

Transvacuolar strategies are especially suited for the treatment of recently infarcted and reperfused myocardium when chemo-attractants and cell adhesion molecules are highly expressed. Infusion can be performed either through the coronary artery or through intravenous infusion.

However, the cells are also reported to home to other non-cardiac organs and the clinical applicability appears to be suboptimal.

III) 3-dimensional patches

The last group comprises the use of 3-dimensional cultured patches. These can be created by combining cultured cells with substrate materials, which offers the advantage that the scaffold materials can be shaped in any 3-dimensional form on both a macroscopic and microscopic level. Researchers have created engineered heart tissue by using neonatal rat heart cells, which is a mixed population of heart cells including cardiac myocytes, fibroblasts, smooth muscle cells, endothelial cells and macrophages. The cells are combined with collagen I and Matrigel, reconstituted in circular molds and subjected to mechanical strain. Under these conditions, cardiac organoids developed spontaneously and show contractile as well as electrophysiological properties of working myocardium. This results in large (thickness/diameter, 1-4 mm/15 mm), force-generating engineered heart tissue.

This engineered heart tissue has demonstrated to form thick cardiac muscle layers when implanted on myocardial infarcts in immune-suppressed rats.

The potential future production of contractile patches for human use is illustrated in Figure 3. A biodegradable polymer invented at MIT, called biorubber, is pierced by using a laser to pierce to create a fine network of channels. Each piece is a rectangle roughly 1 cm2 in area and up to 3 mm thick. Subsequently, the bio rubber is seeded with the three major cell types of a heart: cardiomyocytes, endothelial cells, and fibroblasts (e.g. by using adult stem cells derived from fat tissue). As the cardiomyocytes beat, they adhere to and tug on one another, helping them to communicate electrically and to secrete the growth hormones they need to survive. To be strong enough to replace dead heart tissue in people who have had heart attacks, the contractile patches must be at least 5 mm thick. However, currently the patches reach only a thickness of approximately 1-2 mm.

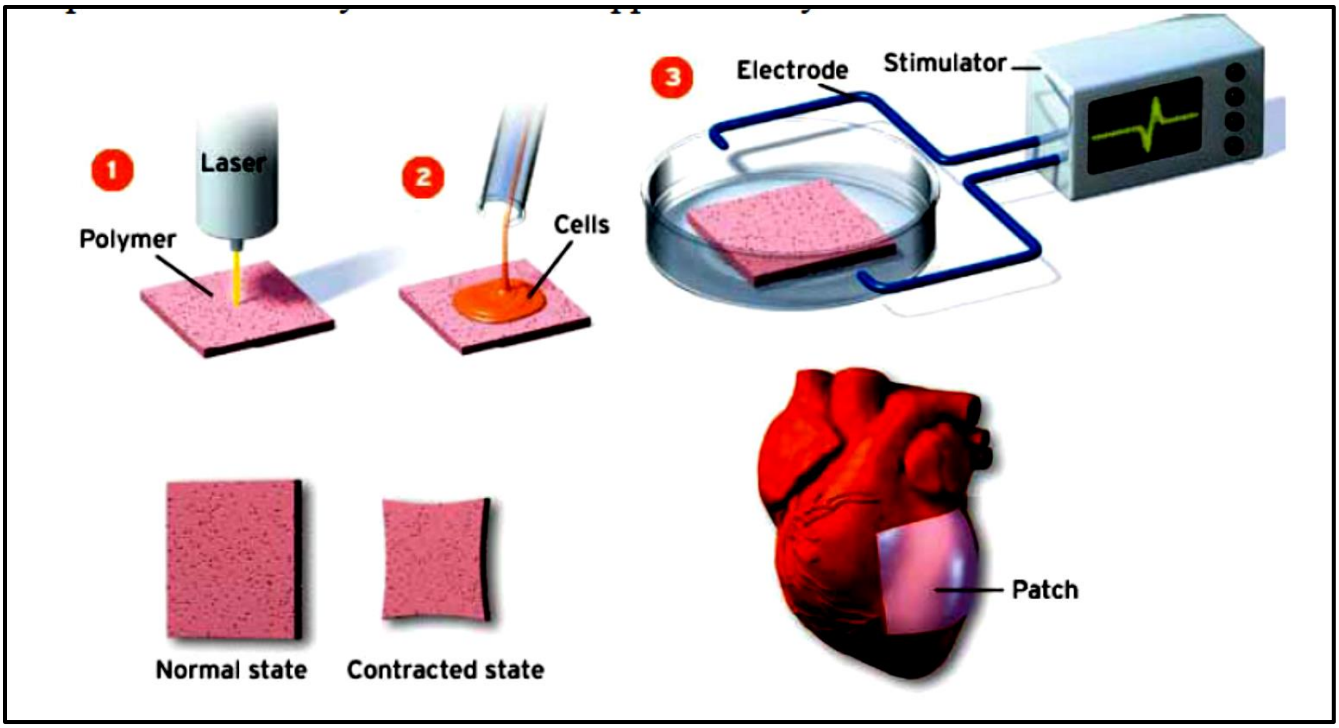


Figure 3 Engineered heart patches as in development at the Massachusetts Institute of Technology. 1) A thin square of biodegradable polymer is perforated with a laser to form a fine network of channels. 2) The polymer patch is seeded with the three types of heart cells. 3) The patch is stimulated with electric current. 4) When mature, the patch beats like a piece of living heart. 5) Once a way is found to increase the thickness of the experimental patches, they will be strong enough to be grafted onto human hearts