Artificial Organs

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Gerald E. Miller

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Gerald E. Miller
Virginia Commonwealth University

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ABSTRACT

The replacement or augmentation of failing human organs with artificial devices and systems has been an important element in health care for several decades. Such devices as kidney dialysis to augment failing kidneys, artificial heart valves to replace failing human valves, cardiac pacemakers to reestablish normal cardiac rhythm, and heart assist devices to augment a weakened human heart have assisted millions of patients in the previous 50 years and offers lifesaving technology for tens of thousands of patients each year. Significant advances in these biomedical technologies have continually occurred during this period, saving numerous lives with cutting edge technologies. Each of these artificial organ systems will be described in detail in separate sections of this lecture.

KEYWORDS

Artificial heart and ventricular assist, Artificial heart valve, Cardiac pacemaker, Dialysis, Human heart and heart surgery, Human kidney

Contents

CHAPTER 1

Artificial Heart Valves

The replacement or augmentation of failing human organs with artificial devices and systems has been an important element in health care for several decades. Such devices as kidney dialysis to augment failing kidneys, artificial heart valves to replace failing human valves, cardiac pacemakers to reestablish normal cardiac rhythm, and heart assist devices to augment a weakened human heart have assisted millions of patients in the previous 50 years and offers lifesaving technology for tens of thousands of patients each year. Significant advances in these biomedical technologies have continually occurred during this period, saving numerous lives with cutting edge technologies. Each of these artificial organ systems will be described in detail in separate sections below.

1.1 CARDIAC ANATOMY AND PATHOPHYSIOLOGY

The human heart consists of two pumping chambers (ventricles) and two filling chambers (atria). The heart is a pulsatile pump, operating via muscular contraction of both the ventricles and atria, and is designed to produce positive displacement of blood through two circulatory systems. The right ventricle pumps blood into the pulmonary circulation, where blood becomes oxygenated and the left ventricle pumps into the systemic circulation that allows oxygenated blood to reach tissues throughout the body, where oxygen is transported to these tissues.

In order for blood to flow in the proper direction from each of the ventricles as well as from each atrium to the associated ventricle, the heart contains heart valves to prevent backflow of blood. The atrioventricular valves (between the atria and the ventricles) prevent backflow into the atria when the ventricles contract during systole. The outflow valves (from each ventricle) are designed to prevent backflow during ventricular diastole. The human heart valves are shown in Figure 1, with the bileaflet mitral valve located between the left atrium and the left ventricle and the trileaflet aortic valve located between the left ventricle and the aorta (outflow tract). The trileaflet tricuspid valve is located between the right atrium and the right ventricle, while the trileaflet pulmonary valve is located between the right ventricle and the pulmonary artery. Each of these valves consists of an annulus from which valve leaflets project into the orifice opening. There are no valves located between the atria and the respective veins feeding blood into the atria. Thus, there is no valve from the vena cava to the right atrium, nor a valve from

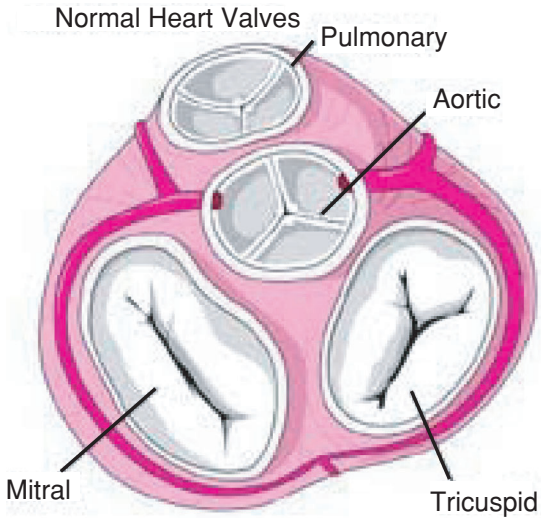


FIGURE 1: Human heart valves.

the pulmonary vein to the left atrium. All heart valves operate by means of a pressure gradient, moving in the direction of decreasing pressure at all times, whether toward the open or closed position.

Human heart valves are designed to close in an overlapping fashion with the valve leaflets abutting over each other in a fashion noted in Figure 2. The leaflets overlap to ensure adequate

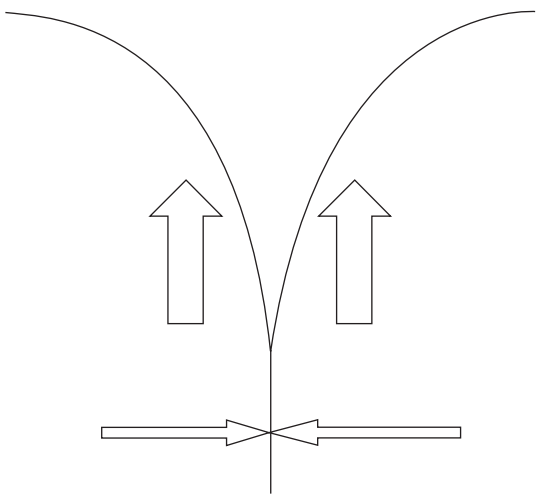


FIGURE 2: Human valve closure with overlapping valve leaflets showing pressure gradient acting upward against closed valve and lateral frictional force created by overlap of leaflets.

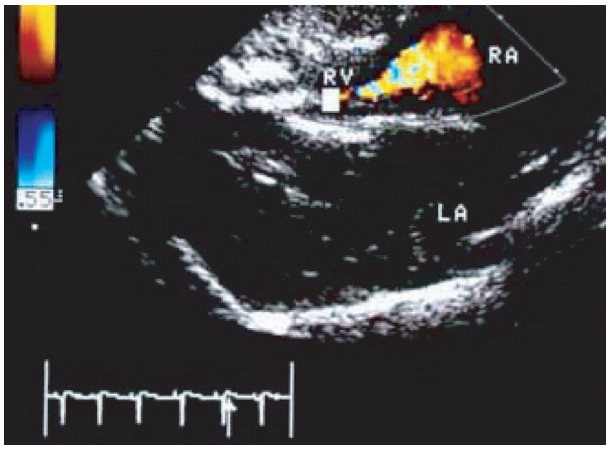


FIGURE 3: Doppler ultrasound image of a heart indicating jetting from the right ventricle toward the right atrium, resulting from reversing flow across the tricuspid valve.

valve closure with the vertical forces created by a pressure gradient across the valve being transferred (in part) to lateral (friction) forces. Thus, each valve leaflet is actually longer than one half of the radius of the valve orifice, which provides sufficient length for the leaflet overlap.

There are two potential sources of heart valve failure, each of which requires years to develop. One such mechanism is valve *stenosis* or narrowing of the valve orifice (best seen with the valve in an open position). Valve stenosis is often related to atherosclerosis and creates a narrowed outflow area. This not only reduces the area for blood flow, but also creates an added pressure drop due to the existence of a contraction in the flow pathway. This situation may be diagnosed with an echocardiogram that uses 2-D ultrasound and a Doppler flow probe. However, symptoms of such a narrowing would not normally appear until the orifice is significantly reduced (up to a 50% reduction in area). With the reduced area, it is possible that the flow across the valve orifice may become turbulent, which can also be visualized with Doppler ultrasound or even with the aid of a stethoscope. A color Doppler profile of a heart is shown in Figure 3.

Another source of valve failure is via weakening of the valve leaflets. In such a case, the leaflets begin to bulge upwards with a portion of the overlapping leaflets protruding above the valve orifice. Such an occurrence is termed valve *prolapse*. In the extreme case, the leaflets bulge so far that the overlap of the valve leaflets during closure is in jeopardy. If a gap appears between the leaflets in the (purportedly) closed position, there is a regurgitation of the blood backwards from its normal intended path (see Figure 3). Since the gap between the leaflets is initially small, the backflow is typically turbulent, which can be easily heard via a stethoscope or imaged via Doppler ultrasound. The sounds heard are called heart murmurs. In advanced heart valve failure from either mechanism, the use of a stethoscope followed by ultrasound (as needed) may

indicate a need to replace the failing valve. The mitral valve and the aortic valve (both in the left heart) are the most prevalent valves to be replaced. This is not unusual as the left heart experiences greater pressures than the right heart.

1.2 PROSTHETIC HEART VALVES

As with any implantable device, issues related to biocompatibility, longevity, and function of replacement heart valves are important. Artificial heart valves have been clinically available for over 50 years with early designs consisting of either a caged ball or a tilting disk (within a caged or strut assembly). Early successful designs of each type include the Starr Edwards ball valve and the Bjork Shiley tilting disk valve. The ball valve, as seen in Figure 4, consists of a silastic or silicone rubber ball encased within a stainless steel cage and annular ring. The metallic ring (used for strength) was covered with a Dacron sewing ring. All materials are biocompatible with ample animal and clinical trials in support of these choices. The sewing ring allows attachment of the valve to the surrounding tissue of the original valve annulus.

The ball valve had an important advantage, at the time, in that it is structurally strong and durable. However, it closes with considerable force that can cause hemolysis and thrombosis, as seen in Figure 5. In addition, the ball acts as a central occluder with the valve in the open position, thus producing a greater pressure drop across the open valve that reduces the downstream

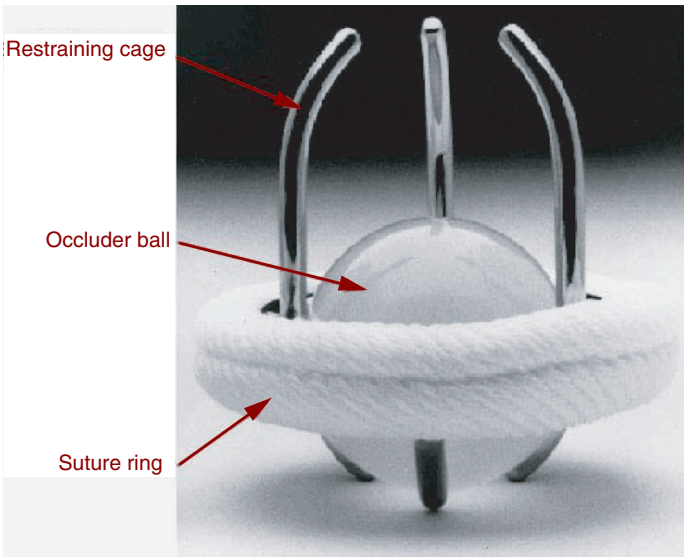


FIGURE 4: Prosthetic ball valve in the closed position showing with the ball sitting in the dacron-covered annular ring and the upper cage protecting the ball in the open position.

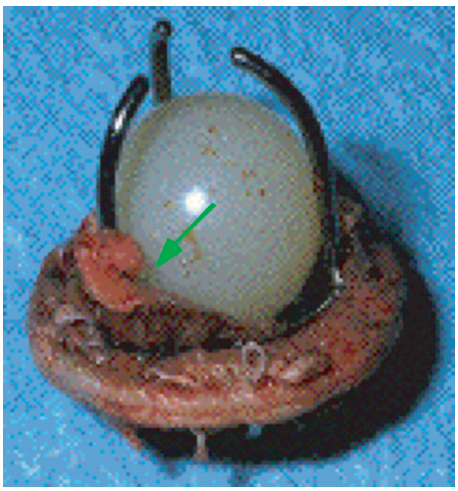


FIGURE 5: Thrombus formation at the seat of a ball valve as a result of the closing force of the ball against its seat.

pressure available to propel blood through a circulation. This type of valve also has a large vertical profile that makes implantation, particularly in the mitral position, somewhat difficult for many patients whose anatomical space is limited.

The tilting disk valve, as seen in Figure 6, opens to 60° as constrained by a stainless steel strut. The disk is constructed of pyrolytic carbon, given the trade name pyrolite.

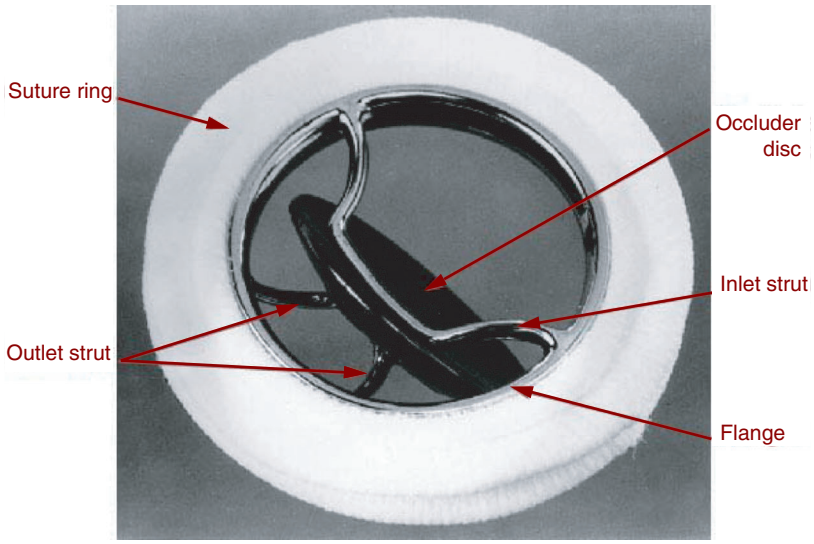


FIGURE 6: Tilting disk valve in the open position.

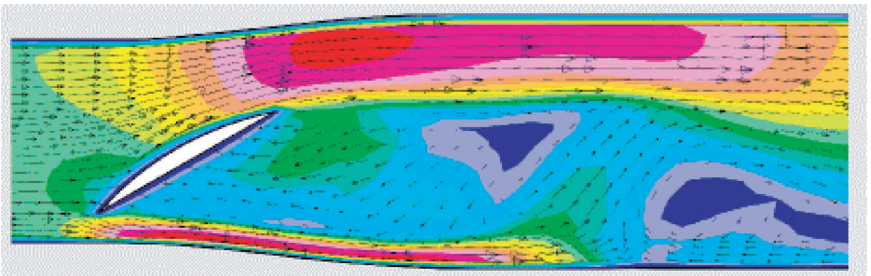


FIGURE 7: Flow patterns around a tilting disk valve generated by computational methods. Note the reversal of the velocity vector behind the tilted disk and the higher velocities at the periphery.

The tilting disk valve has an open profile that offers blood flow around the tilted disk as well as to the outer sides, which are between the disk and the blood chamber or artery. As such, it is far less of a central occluder to blood flow than the ball valve and has a smaller pressure drop across the open valve, which is also advantageous. This valve only opens to 60° due to the stainless steel strut assembly. The valve is not actually affixed to the struts. A flow pattern across the open valve is shown in Figure 7, which indicates a partial central occluder (the tilted disk) as well as peripheral flow around the disk. There is a bit of recirculation behind the disk and the peripheral flow is at relatively high velocities as compared to the central region. As is the case with most flow images, the red (or dark gray) colors in the image refer to higher velocities, the yellow (or lighter gray) refer to moderate velocities, the green (or lighter gray) refer to small velocities, and the blue (or very light gray) refer to extremely small (near zero) velocities. Arrows within the flow field indicate individual vector lines of fluid particles within the flow field.

Many modern prosthetic heart valves are bileaflet in nature as shown in Figure 8.

The bileaflet valves open to 80° and pivot via pins that connect to the valve leaflets and protrude into slots within the annular ring. The ring is composed of either stainless steel or titanium, often with a pyrolytic carbon coating. There is a dacron sewing ring attached to the

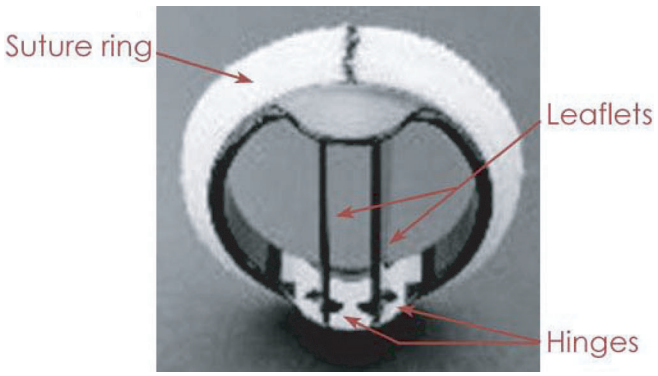


FIGURE 8: Bileaflet valve showing flanges where leaflet pins pivot within annular ring.

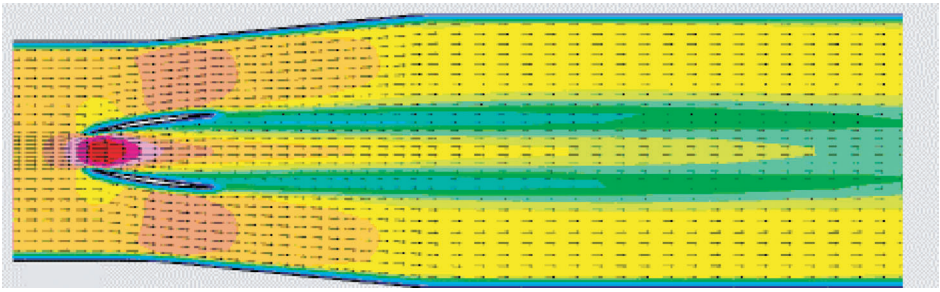


FIGURE 9: Flow through an open bileaflet valve with a large central flow region as well as a large peripheral flow region. Trailing edge vortices are seen emanating from the tips of the leaflet edges.

metal substrate for ease in attachment to the valve orifice. The leaflets are often composed of pyrolytic carbon for strength and durability. With two leaflets, the closing force is less than that of a single tilting disk valve, and certainly far less than that of a ball valve. As the pin assembly can be a site for thrombus formation, such valves normally have a washout zone near the pins to flush that area and avoid stagnant blood leading to thrombus formation. As such, this valve has mild regurgitation as a design element. Figure 9 depicts flow across an open bileaflet valve, indicating far more central flow than the tilting (monoleaflet) valve. There is no central occluder in the bileaflet valve as there was (partially) with the tilting (monoleaflet valve). Thus, there is a greater central flow region in this type of valve.

Ideally, prosthetic heart valves require low levels of hemolysis (red cell destruction), low levels of thrombosis, and a long life span (20–30 years). Most patients must receive anticoagulants indefinitely to deter thrombosis. Pyrolytic carbon and silicon rubber as valve or ball materials have been shown to be relatively antithrombogenic and their surfaces are often covered with proteins over time. Dacron polyester is sometimes used for valve leaflets. Such a material is more flexible than the pyrolite leaflets and thus closes with far less force and less hemolysis. However, such flexible leaflets also take longer to open and close, as they flex during the leaflet movement. An undue delay in valve closure produces a slight backflow, not unlike that of a natural human valve, which produces the incisura (dip) in the aortic pressure waveform. However, too much delay can adversely affect net forward flow, thus reducing net cardiac output.

Bioprosthetic valves, often a preferred alternative, are composed of natural valves from a pig, which has a cardiovascular system most similar to humans. These valves must be "treated" with glutaraldehyde to resist antigenicity or rejection of a foreign substance. As such, these biological valves are stiffer than natural heart valves due to the treatment process. In some cases, the bioprosthetic valve has a dacron sewing ring attached along its base and may even have a stiffening ring of stainless steel attached along its base as well. In some cases, dacron is attached along the outer face of the leaflets to provide greater strength to the leaflets. This does not

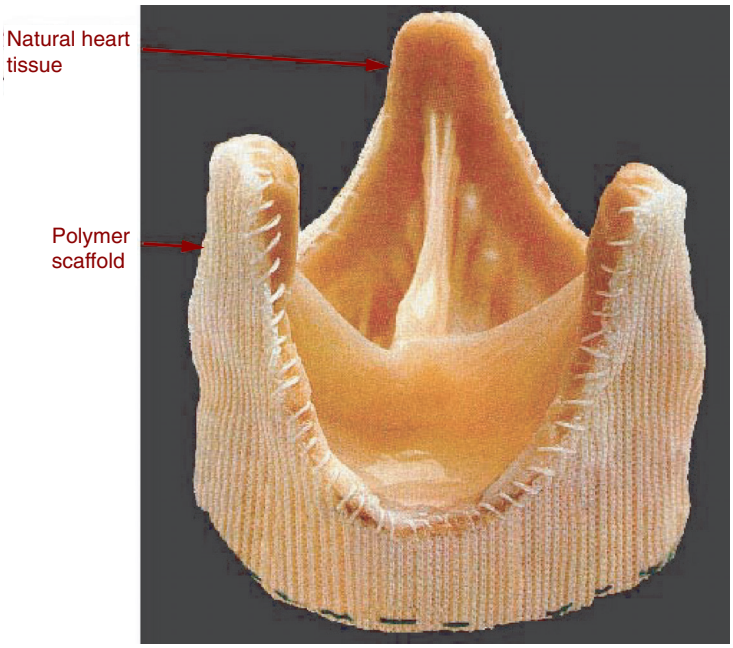


FIGURE 10: Bioprosthetic (pig) valve with dacron along the base and outer edges of the leaflets.

significantly add to the stiffness of the leaflets as compared to the glutaraldehyde treatment. Figure 10 depicts a bioprosthetic valve with a dacron covering.

Surgical implantation of prosthetic heart valves has evolved into an efficient and rapid procedure. The orifice diameter of the patient is evaluated with the aid of pulse echo ultrasound,

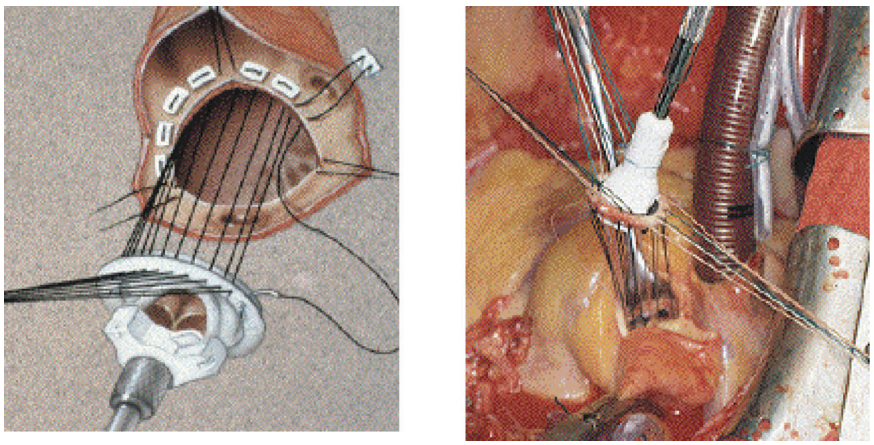


FIGURE 11: Prosthetic heart valve within valve holder with sutures preplaced within sewing ring and valve orifice.

the 2-D version often called echocardiography. The appropriately sized prosthetic valve is then placed into a valve holder and sutures are threaded through the sewing ring of the valve. The patient is placed on cardiopulmonary bypass (heart–lung machine) and the original valve is removed. The prosthetic valve is then placed into the orifice by one surgeon and another continually sews the sutures around the valve orifice using the curved needle attached to the sutures. The valve holder is then lowered into place, and the holder eventually depressed to release the valve—and the empty holder is then removed. The orifice is checked for potential leaks and additional sutures are placed on site as needed. The patient is then removed from bypass and the incision site closed as is the chest incision. The entire procedure often is completed within 1 h and the patient is normally on cardiopulmonary bypass for as little as 15 min. Figure 11 depicts a prosthetic heart valve within a valve holder with sutures in place.

1.3 EVALUATION OF PROSTHETIC VALVES

The performance and efficacy of prosthetic heart valves are normally evaluated by means of pressure gradients across the open valve, long-term durability, and prevalence of adverse physiological conditions such as calcification, stenosis, thrombosis, or hemolysis. Pressure gradients can be determined via direct pressure sensors or via Doppler ultrasound (indirect determination by means of flow/pressure relationship). Thrombosis, hemolysis, and calcification are determined via direct biochemical measures or via imaging modalities such as ultrasound. Such determinations are on mechanical test beds or blood flow loops in mock circulatory systems, or with animal models. Computer modeling techniques are also employed to evaluate valve performance using computational fluid dynamics. An excellent review of the fluid mechanics of prosthetic heart valves was produced by Yoganathan *et al.* (2004). Other groups involved with the evaluation of prosthetic and bioprosthetic heart valves include Labrosse *et al.* (2005), Jamieson *et al.* (2005), Medart *et al.* (2005), Pierrakos *et al.* (2004), Malouf *et al.* (2005), Goetze *et al.* (2004), Wu C *et al.* (2004), and Wu Y *et al.* (2004).

CHAPTER 2

Artificial Heart and Cardiac Assist Devices

2.1 CARDIAC ANATOMY AND PATHOPHYSIOLOGY

As was described above in the section dealing with heart valves, the human heart consists of two ventricles responsible for ejection of blood and two atria responsible for holding and filling the ventricles. The left heart pumps blood into the systemic circulation and the right heart into the pulmonary circulation. Figure 12 depicts the heart with all four chambers.

According to the National Center for Chronic Disease Prevention, 950 000 Americans die each year due to cardiovascular disease with over 61 million Americans suffering from this disease and over 6 million hospitalizations each year as a result. Major causes of cardiac-related pathologies include atherosclerosis in either the aorta or in coronary vessels such as depicted in Figure 13.

In many cases, coronary artery blockages and/or blockages in the aorta can be alleviated via surgery to remove the blockage, either through mechanical "reaming," via laser ablation, or via balloon catheter expansion. Often, stents are placed in a coronary vessel after removal of the blockage. In those instances where the blockage cannot be removed by such means, more extensive surgery can be performed to bypass the blockage with transplanted veins or via artificial vessels composed of biomedical polymers. This procedure is termed coronary artery bypass grafts or CABGs.

Often after such surgery, the patient's repaired heart is too weak to fully support the blood pumping requirements of the systemic circulation and will require some period of reduced load in order to recover. In other cases, the repaired heart cannot ever function at a normal level of 5 L/min at 95% oxygen saturation with a mean pressure of 100 mmHg. In still other cases, the heart cannot be adequately repaired and functions at a reduced level on a permanent basis. One approach to the latter cases would be to seek a heart transplant. However, given the vast number of potential cases in need of such a transplant and the inherent need for appropriate blood typing and tissue typing, there are insufficient numbers of donor hearts. The United Network for Organ Sharing notes that donor hearts number 2000–3000 per year with the stated need at least tenfold greater.

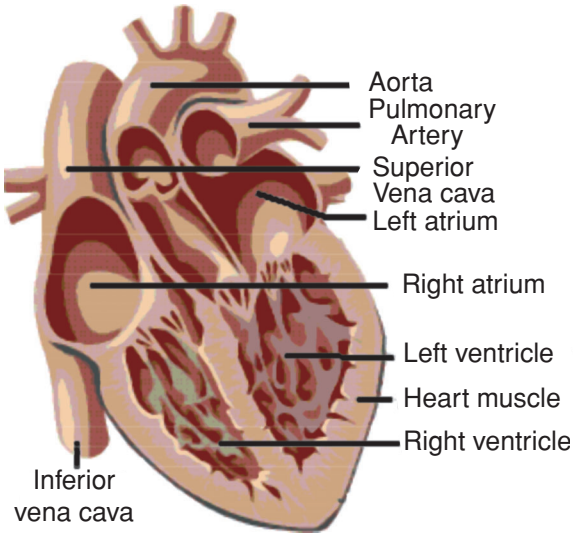


FIGURE 12: The human heart with four chambers: two atria and two ventricles.

As such, a stopgap mechanism is to employ a mechanical assist pumping system, called a ventricular assist device or VAD. This can be utilized in true "assist" mode for those patients recovering from open heart surgery and whose heart will recover full function within a few days. In those other cases where the patient's heart will not completely recover, or where surgical

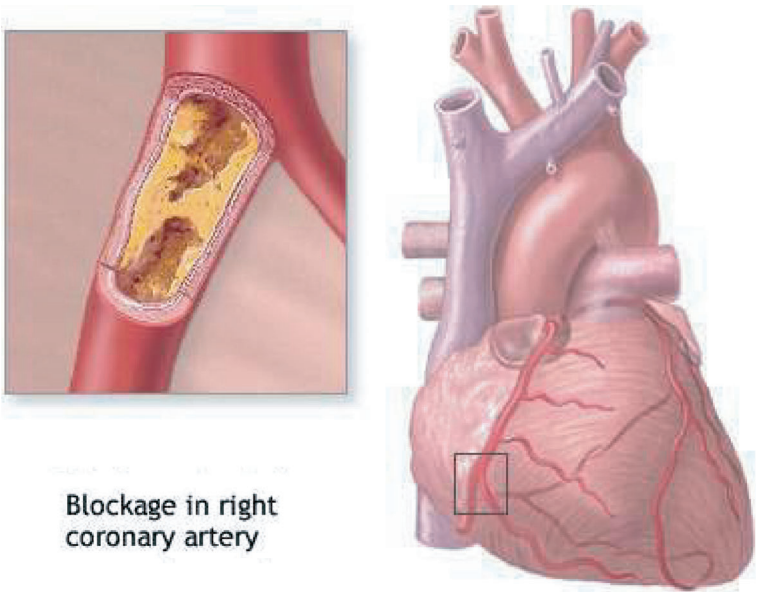


FIGURE 13: Coronary artery blockage with inset showing blockage and larger view showing location within the heart musculature.

intervention would not be beneficial, then this device can be utilized for a longer period until such time as a donor matching heart becomes available. In such cases, the device is termed as a "bridge to transplant." In the first two cases, the natural heart might pump as little as 2–3 L/min with the artificial heart pumping the remainder. When the left heart is being assisted, the device is termed an LVAD (left ventricular assist device). When the right heart is to be assisted, the device is termed an RVAD. For those cases where both hearts are being assisted, two devices are used in biventricular assist mode (BiVAD). In still other cases, when the patient's own heart cannot function even partially at the above level, it may be necessary to completely replace the failing heart with two pumps acting in tandem as a total artificial heart for end-stage heart failure.

2.2 HEART ASSIST TECHNOLOGY

Artificial hearts and heart assist devices have been in development and analysis for decades. The original pneumatically powered design, as typified by the Jarvik-3 and the Jarvik-7 pumps, consisted of a polycarbonate case surrounding a flexible polyurethane sac. The space between the two allowed high pressure air, designated as "systolic drive pressure" to collapse the blood containing sac and caused systolic ejection. A small vacuum pressure, designated as "diastolic pressure" pulled the sac toward the casing and caused diastolic filling. Artificial heart valves were employed for each artificial ventricle to prevent backflow during either portion of the cardiac cycle in a fashion similar to the natural heart. This sac type pump acted in a fashion similar to the natural heart in that it was inflow and inlet pressure sensitive (designated as preload sensitive), but not affected by the load against which the heart pumps (designated as not being afterload sensitive). The Jarvik pump is shown in Figure 14, with the air lines from the outer casing which are then connected to a drive system that provides the alternating high and low pressure to the blood sac. The two pressures, the systolic duration, and beat frequency can all be controlled and varied from a drive console.

Although pneumatically driven pumps are still utilized clinically, many original such designs have now incorporated electrically powered cam drive systems that move a piston/diaphragm arrangement to eject blood during systole and then, when the piston is pulled back toward the drive unit, initiates diastolic filling. Such blood pumps are still pulsatile and thus need valves to eliminate backflow and regurgitation. A biventricular device of this type is shown in Figure 15, with no pneumatic air lines emanating from the pump as was the case for the sac-type design.

Power for the electrically operated LVADs or BiVADs is achieved with external, rechargeable batteries as is shown in Figure 16. Transcutaneous energy transmission occurs via a pair of coils—one placed over the skin and one placed below the skin, the latter attached to the VAD. The VAD is connected to the apex (base) of the left ventricle (or to the base of both ventricles in biventricular support) with the aid of an inlet cannula. This orientation allows gravity to

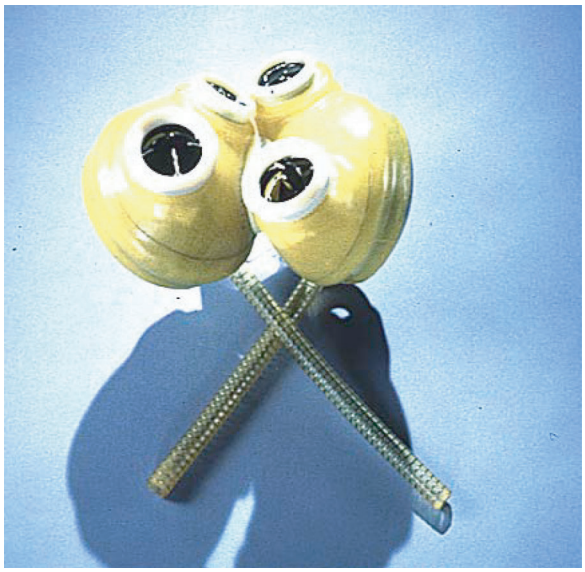


FIGURE 14: The Jarvik-7 pneumatically driven artificial heart showing two ventricles and the air lines which lead to the spacing between the outer casing and the inner flexible blood sac.

assist emptying of the ventricle into the device, which offloads the ventricle in part. The VAD then pumps a portion of the cardiac output through a cannula that connects to the aorta via an end-to-side anastomosis.

Unlike the pneumatically driven blood pumps, where the air from the pneumatic drive unit is vented to the atmosphere, the electrically driven pumps are normally closed systems.

FIGURE 15: Biventricular electrically operated pusher plate design for a blood pump with four valves similar to that of the natural heart.

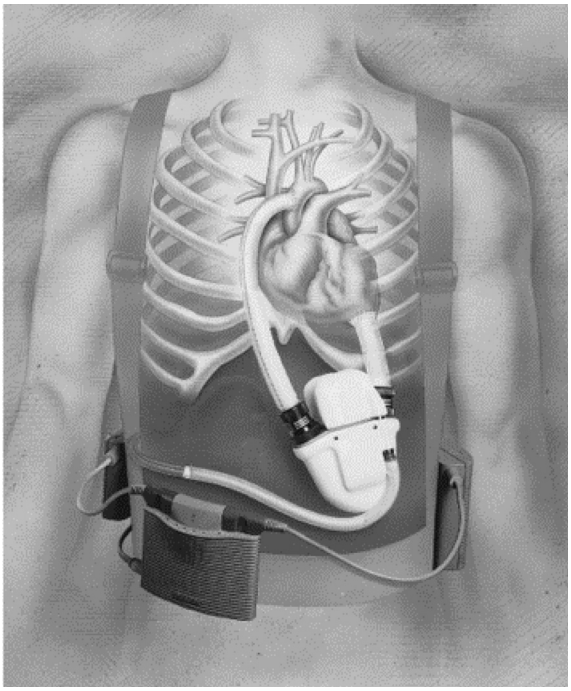


FIGURE 16: Novacor electrically powered LVAD with external battery pack and connecting cannula from apex of left ventricle and to aorta.

As such, when the diaphragm moves back toward the internal drive system, there can be a period where the air within the drive chamber is compressed, resulting in an increase in local pressure. As the diaphragm moves away from the drive unit (during systole), the air in this chamber becomes rarified and the pressure is reduced. Rather than exist with changing pressures within the drive system, early versions of electrically powered pumps contained a flexible sac, a compliance chamber, whereby the excess air in the drive system is shunted to the compliance chamber, thus maintaining a relatively constant pressure within the pump drive chamber. As the diaphragm moves forward during systole, the air is shunted from the compliance chamber into the drive chamber of the pump and vice versa during diastole. Later versions of electrically operated pumps utilize a venting system to avoid the need for a compliance chamber, which is an added component that takes up space and adds to the complications of the device operation.

The use of positive displacement pumps, such as the sac or pusher plate blood pumps, offers several advantages. These include the use of pulsatile flow similar to that of the natural heart as well as an insensitivity to afterload—i.e., the device can pump against any reasonable load, even a hypertensive load. Issues with such pumps include the sensitivity to preload and

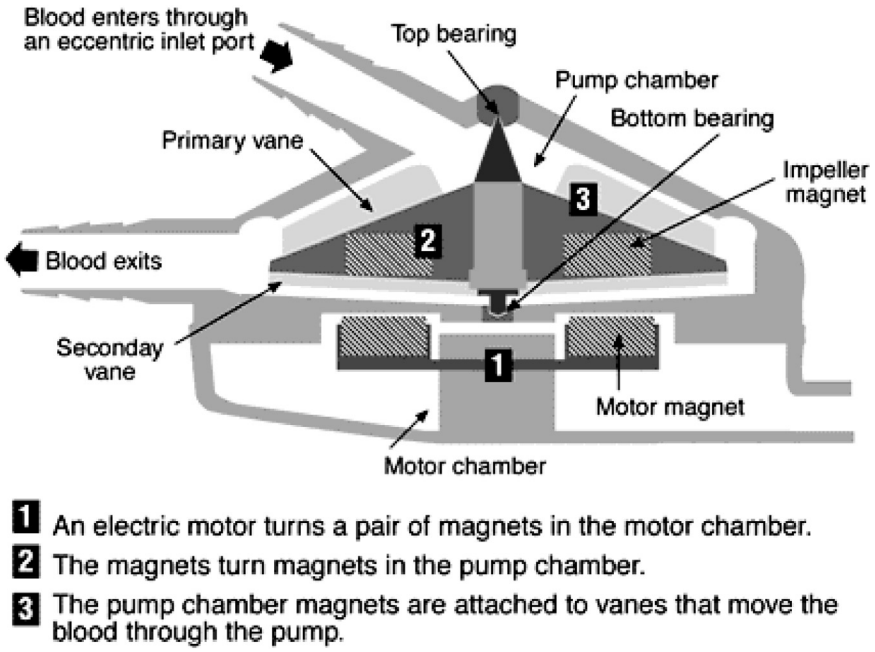


FIGURE 17: Centrifugal blood pump with inlet at top center and outlet at bottom left. Spinning rotor produces increased pressure at the periphery.

problems associated with artificial heart valves such as calcification, hemolysis, thrombosis, and mechanical failure. It was these issues that initiated the later use of rotary blood pumps as assist and/or bridge to transplant devices. Such rotary devices often require less power than their positive displacement counterparts and do not utilize valves, as they produce steady flow. Such rotary blood pumps are configured as either a centrifugal pump or as an axial pump.

The centrifugal blood pump is configured with an inlet to the pump from the top center and an outlet radially at the periphery. This arrangement is not unlike a tornado in flow design and the flow of such a device is similar—low pressure and velocity in the center with higher pressure and velocity at the periphery. Centrifugal pumps are electrically powered and utilize magnets to spin the rotor and, oftentimes, suspend the drive assembly as seen in Figure 17.

Another centrifugal design was produced by Medtronic and consists of nested cones as seen in Figure 18. Still another centrifugal design consists of a series of parallel disks spinning about an axis in unison as seen in Figure 19.

Centrifugal blood pumps have several advantages including a lack of valve-related problems, a relatively lower power drain (than positive displacement pumps), and an ability to pump at higher rates by spinning the rotor faster. Without a displacing drive chamber, there is no need

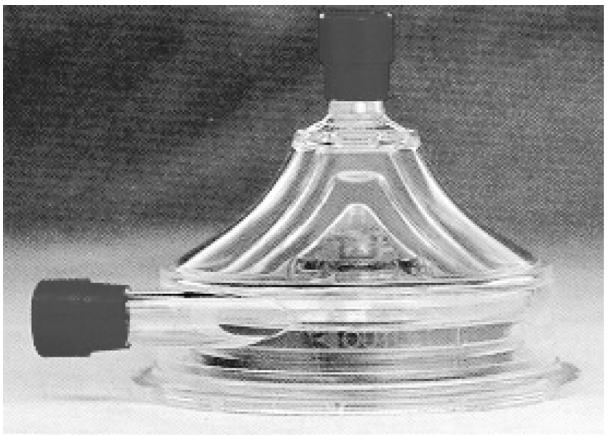


FIGURE 18: Medtronic BP-80 centrifugal blood pump with nested cones and magnetic drive.

for a compliance chamber as there is for some positive displacement pumps. The centrifugal pumps are placed below the left ventricle in a fashion similar to the positive displacement pumps with the outlet cannula extending toward the aorta as is the case for the pulsatile pump connections. Centrifugal pumps are sized similar to their pulsatile analogs and usually can produce 5–7 L/min with an increase in pressure of 100 mmHg at rotation rates of 1500–3000 rpms. Drawbacks to such pumping systems include the use of steady flow rather than pulsatile flow, as well as being significantly affected by afterload. In fact, it is possible for such pumps to spin, but produce no forward flow, if the outlet pressure generated by the pump is lower than the afterload pressure. This is known as "deadheading" and can be remedied by spinning the rotor faster to increase the outlet pressure of the pump.

The other versions of rotary pumps are the smaller axial flow pumps. Unlike the centrifugal pumps, the axial flow pumps have their inlet forward and their outlet directly behind, much as a jet engine is configured. One advantage of such an arrangement is that the flow is more stable in the flow-through arrangement. In addition, the axial pumps, being smaller than their centrifugal counterparts, can be fitted within the base of the ventricle, thus eliminating the inlet cannula. This type of pump can also be placed within the aorta to allow for flow through the device from the left ventricle, and on toward the remainder of the systemic circulation with an added pressure and flow generated from the pump. As such pumps are smaller and have lesser blood contacting area, they require higher rotation rates than their centrifugal counterparts—often reaching 15 000–25 000 rpms. It was originally thought that such rotation rates would produce harmful shearing stresses to blood elements. However, the extremely short exposure time of blood within the device allows only partial deformation of blood elements without permanent damage occurring. A typical axial flow pump is shown in Figure 20.

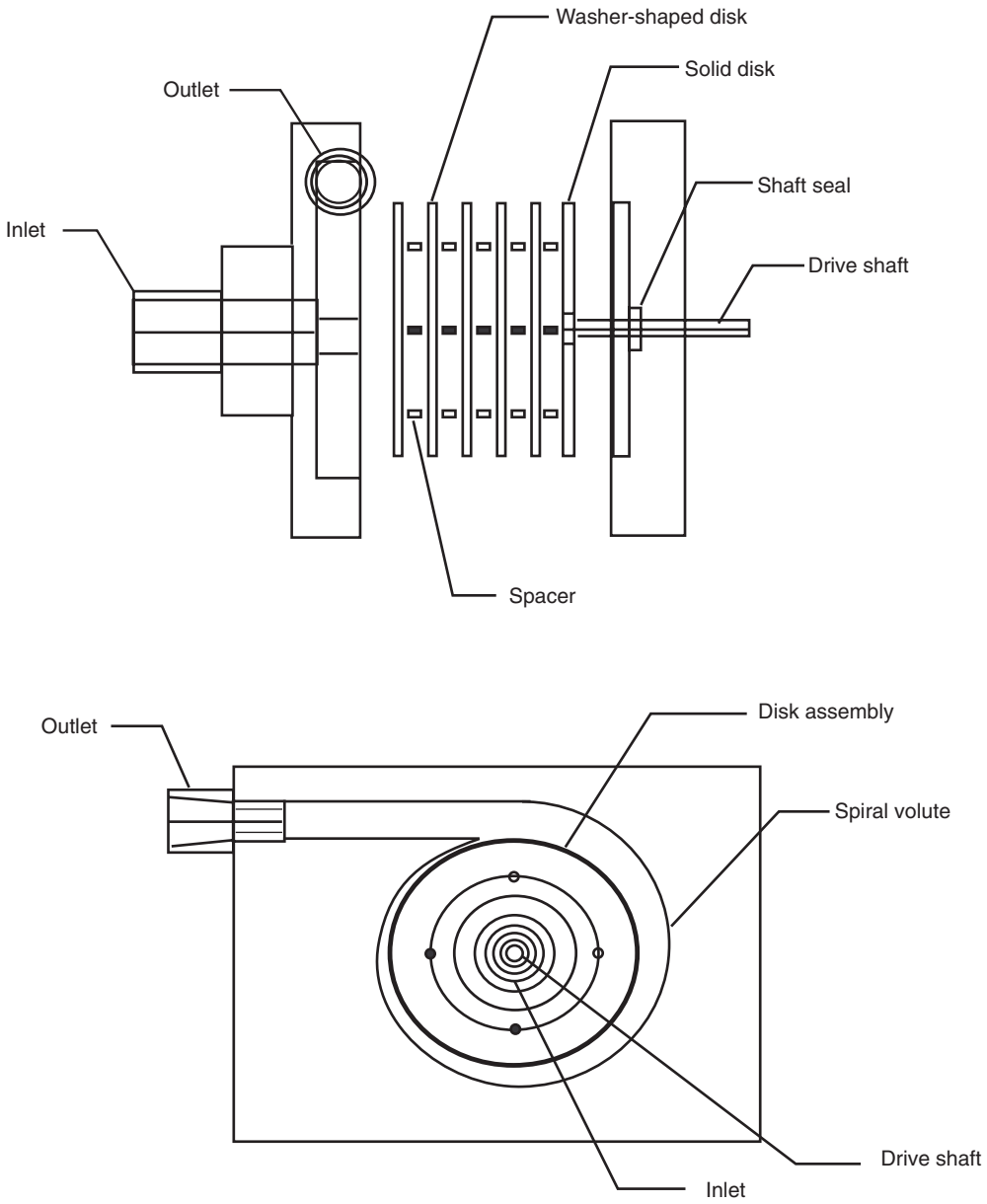


FIGURE 19: Multiple disk centrifugal blood pump based upon the Tesla Turbine design.

The axial flow pump is not only magnetically driven, but requires magnetic suspension. The rotor is magnetically suspended inside the stator, often with blood immersed bearings. A front and rear diffuser are utilized to direct blood flow toward the space between the rotor and the stator. As with their centrifugal pump counterparts, axial flow pumps are preload

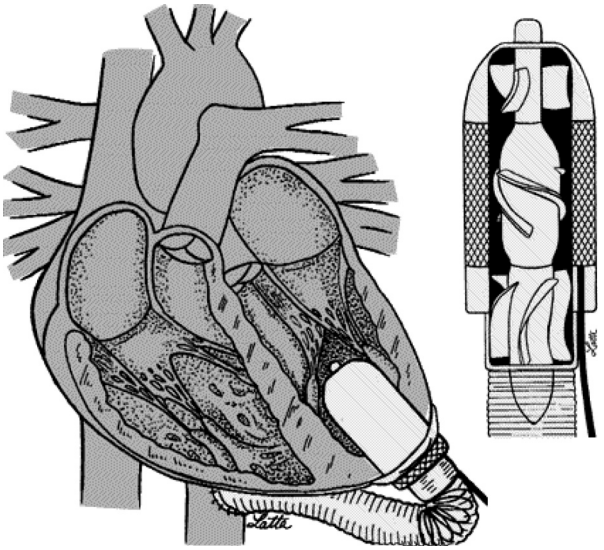


FIGURE 20: Axial flow blood pump configured within the base of the left ventricle. Flow through the device is completely axial with forward and rear diffusers to direct flow to the outer sections between the rotor and the stator.

insensitive and afterload sensitive. As such, they are relatively unaffected by inlet conditions. Axial flow pumps, being smaller in size, do not normally produce flow rates as large as centrifugal pumps, and are not normally utilized for long-term bridge-to-transplant support. However, being of a more compact size, it is far easier to configure such pumps than the larger centrifugal versions.

2.3 EVALUATION OF BLOOD PUMPS

Blood pumps are usually evaluated either experimentally on the bench (designated *in vitro*) or in animal models (*in vivo*) or in clinical studies (*in situ*). There are also computational models using finite element techniques, collectively termed "computational fluid dynamics." Experimental studies *in vitro* (on the bench) employ a mock circulatory system that mimics the human circulation in terms of the physical load against which the device must pump blood. In the bench top study, a blood analog is often employed consisting of a glycerin–water mixture. A mock circulatory system is shown in Figure 21 and consists of a compliance element simulating aortic compliance, a resistor simulating peripheral resistance, and a venous reservoir or compliance element simulating either venous inlet pressure or venous compliance.

Experimental studies of the fluid mechanics within blood pumps and inside the attached cannula (both input and output cannulae) can be typically conducted by laser Doppler anemometry (LDA) and/or particle image velocimetry. Both techniques require that the test fluid is transparent and that the associated flow field is within a transparent section. Collectively,

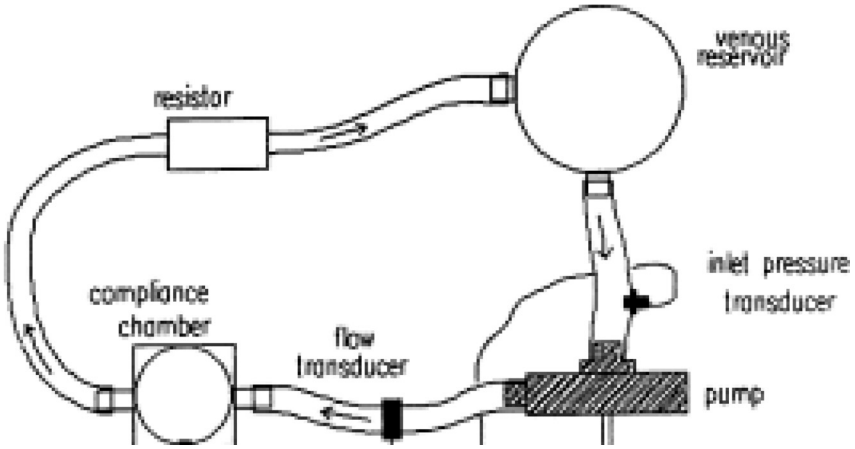


FIGURE 21: Mock circulatory system for *in vitro* testing of blood pumps.

this field is known as *flow visualization*. A particle image velocimetry (PIV) system requires the use of neutrally buoyant particles that are fluorescent so as to be easily illuminated by a dual laser system. A PIV system employs a CCD camera and dual lasers to illuminate the particles at two time intervals closely spaced (within 30 ms) with the tracks between particles calculated by the supporting computer. A typical PIV system is shown in Figure 22.

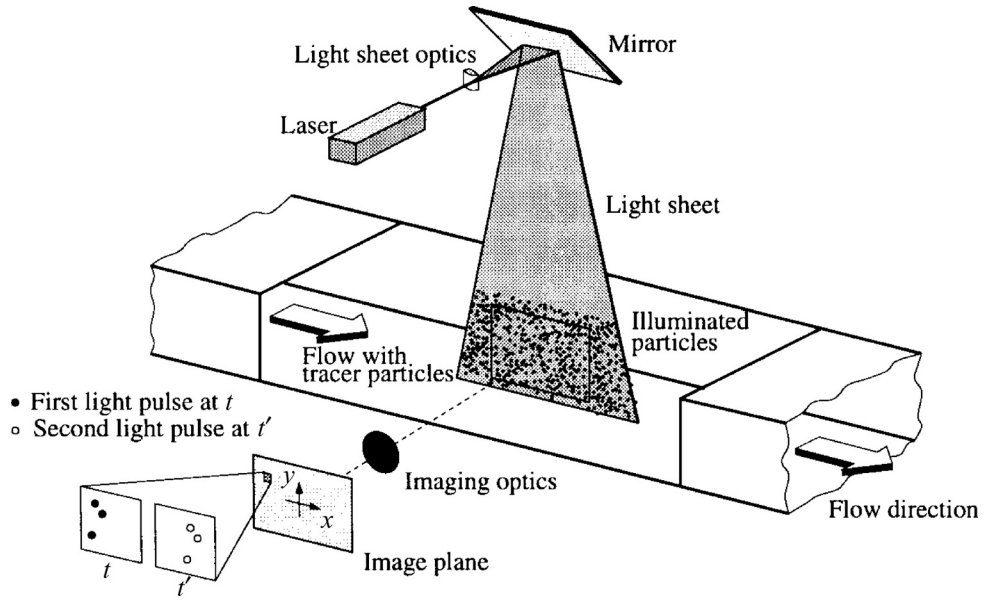


FIGURE 22: Typical PIV system with laser-illuminated particles within the flow field.

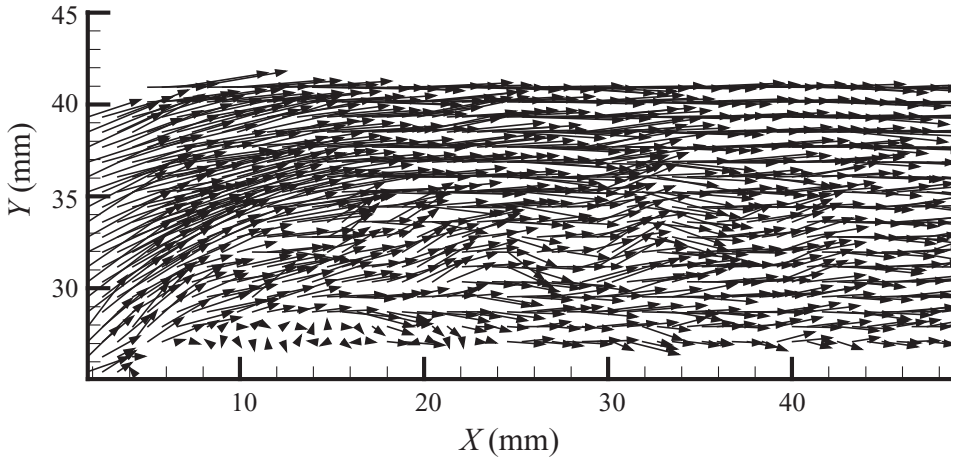


FIGURE 23: PIV vector mapping (snapshot) of particles within a flow field at one instance in time (over a 30-ms interval).

A snapshot of the fluid dynamics of the flow field generated by PIV-illuminated particles is shown in Figure 23. Such snapshots are generated 30 or more times per second and 100 of such images can be averaged to produce a flow profile indicating overall flow trends. Such an average flow profile is shown in Figure 24.

In addition to flow visualization techniques, such as LDA or PIV, it is common to measure volume flow rate with either a Doppler ultrasound flow sensor or an electromagnetic

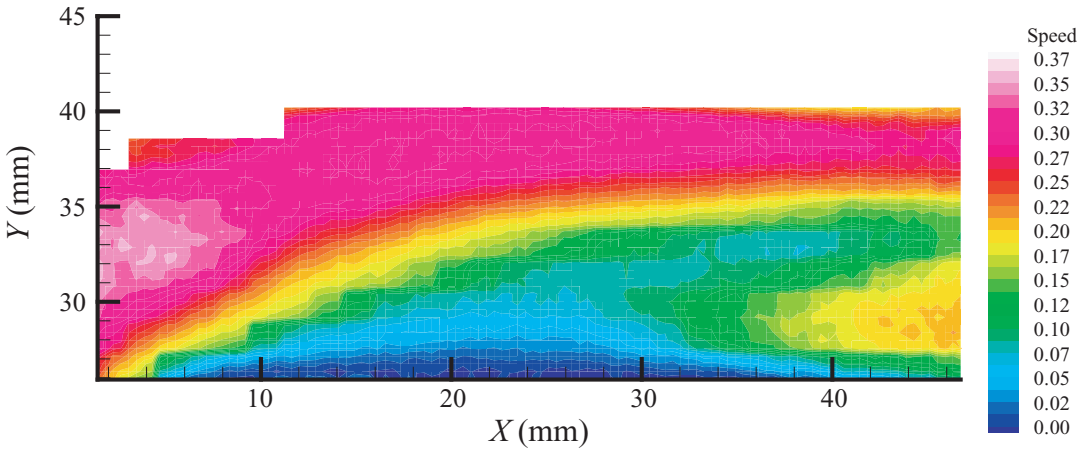
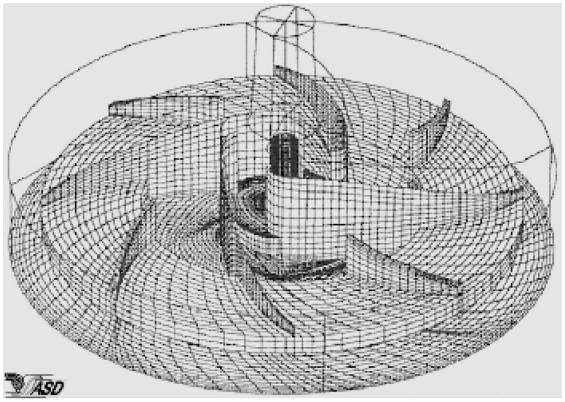


FIGURE 24: Time averaged (contour) plots from sequential vector plots of a PIV-measured flow field. Blue zone indicates low velocity (near lower wall) and red zone indicates higher velocity at outer (top) wall. Slight reversal of flow in yellow is seen at the far right.



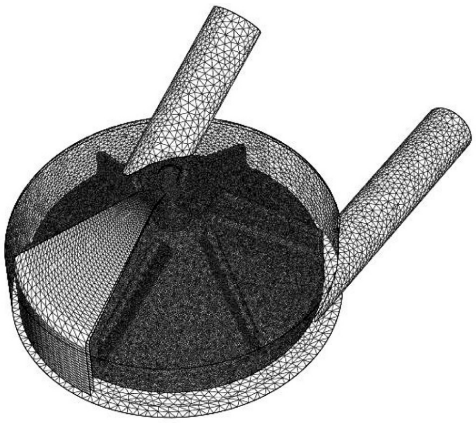


FIGURE 25: Grids generated by computational fluid mechanics algorithms to represent flow boundaries and computational accuracy steps.

flow sensor. It is also common to measure pressure within the flow field at several locations including at the inlet to the pump, at the outlet to the pump, within the compliance chamber of the mock circulatory system, and within the pumping chamber itself. Standard dome-type pressure transducers or solid-state transducers are employed. The former are less expensive, but have a limited frequency response of 100 Hz while the latter are more sensitive and accurate, can be mounted flush within a flow field conduit, but are also far more expensive and fragile.

In many cases, it may be appropriate to model the flow field by computational methods, particularly when a variety of configurations must be examined. The use of computational fluid mechanics (CFD) is often advantageous as a means of verifying experimental data as well as a method of avoiding the need to make expensive *in vitro* experiments with numerous physical configurations. Computational modeling employs the development of digital grids that depict the physical boundaries of the flow field within which the pressure–flow relationships can be analyzed. A typical grid pattern generated within a centrifugal pump is shown in Figure 25.

CFD algorithms can then generate simulated flow field information consisting of pressure and/or velocity fields within the physical grid framework as seen in Figure 26. It is possible to superimpose PIV or other flow visualization techniques onto the grid system as well.

Blood pumps are also evaluated in terms of pressure flow relations as well as for the potential for hemolysis. A typical pressure–flow relationship for a centrifugal LVAD is shown in Figure 27, which indicates a family of curves for various rpms of the pump. The data indicate that the flow is reduced at increasing afterload pressures, which is typical of centrifugal pumps. Similar performance curves of pressure versus flow are typically utilized for all LVAD designs including positive displacement pumps. Alterations in design of the pumps are often based upon the performance results noted in this figure. Hemolysis data is shown in Figure 28 and

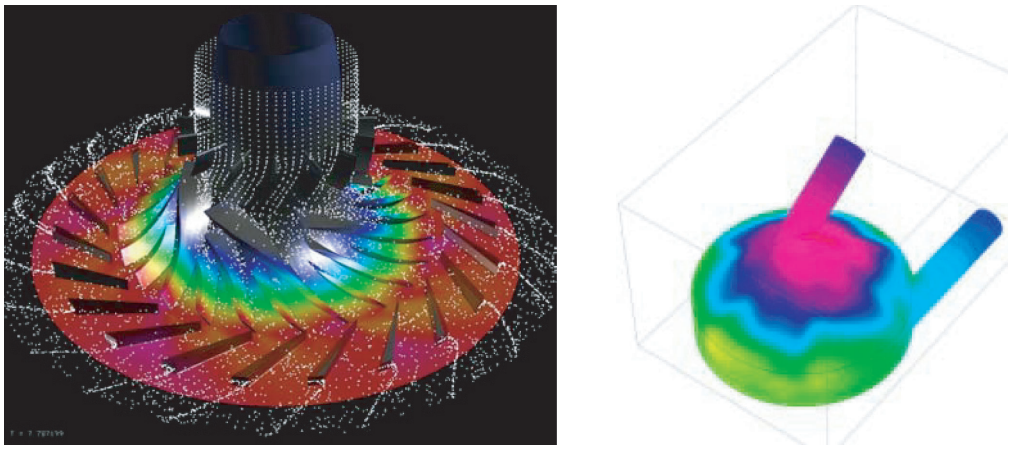


FIGURE 26: CFD-generated flow fields within designated grid system. Left figure indicates flow field data within the device while right figure indicates stress data on walls of the device.

is generated with the pump attached to a modified mock circulatory system with whole blood used within the circulation. Hemolysis can be evaluated as either measured evidence of plasma free hemoglobin or by an index of hemolysis which is based in part on a relative scale of plasma free hemoglobin.

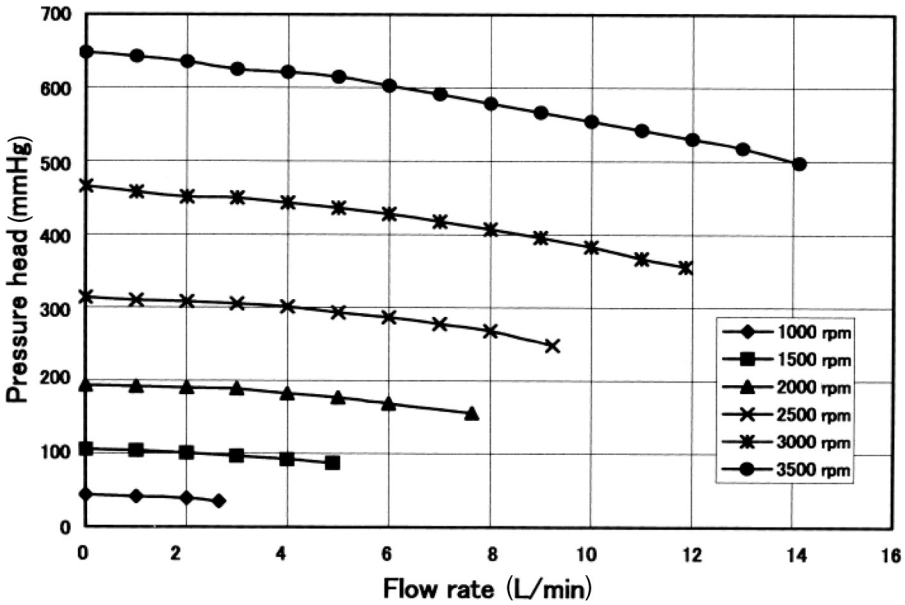


FIGURE 27: Performance curves for a centrifugal blood pump indicating pressure–flow relationships for varying pump rpms. Flow is reduced at increasing pressures (afterloads).

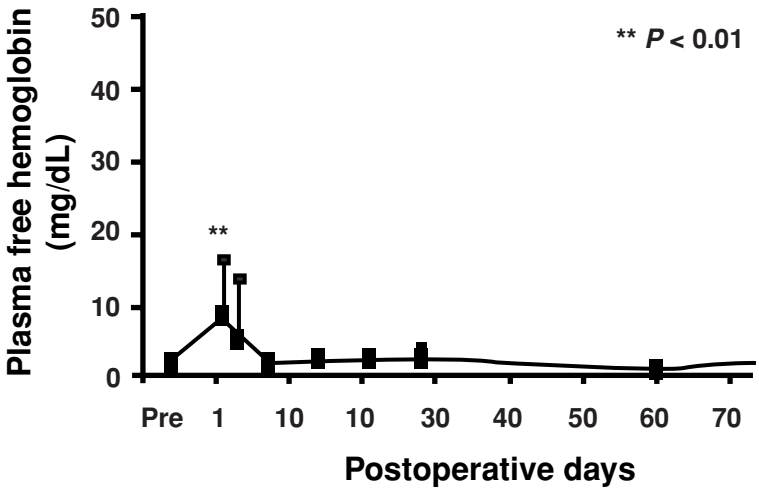


FIGURE 28: Hemolysis data for an LVAD showing levels of plasma free hemoglobin postoperative (postimplantation of pump). After an initial spike, the hemolysis data is quite low, which is typical of many LVAD designs.

Studies of the efficacies of various VAD technologies have been conducted by numerous investigators over the previous 50 years. Of late, several investigators have analyzed the role of ventricular assist devices as either a bridge to transplantation or as a long-term destination therapy including Mehra (2004), Birks *et al.* (2004), Westaby (2004), Kherani *et al.* (2004), Stevenson and Rose (2003), Matsuda and Matsumiya (2003), and Wheeldon (2003), among others. Additionally, there have been significant developments in the use of ventricular assist technology for use in pediatric applications as noted by Reinhartz *et al.* (2002), Duncan (2002), Deiwick *et al.* (2005), and Throckmorton *et al.* (2002). Biventricular support by means of mechanical devices has been studied by Samuels (2004).

The role of steady flow as generated by centrifugal and axial flow blood pumps has been debated for many years. Saito (2004), Mesana (2004), Myers *et al.* (2003), Ichikawa and Nose (2002), among others have examined this issue.

The status of using ventricular and circulatory assist devices was examined by a working group of the National, Heart, Lung, and Blood Institute as reported by Reinlib *et al.* (2003). The United Network for Organ Sharing (UNOS) has examined issues related to the use of ventricular assist technology as it pertains to the selection of patients for heart transplants. Does the use of the VAD lessen the patient's urgent need for a transplant, thus lowering their status "in line" while waiting for a transplant? Or does it increase their needs? Morgan *et al.* (2004) report on the latest findings from UNOS on that topic. Deng and Naka (2002) provide an overview of the state of the art for mechanical circulatory support as do Nemeh and Smedira (2003).

Velocity measurements within ventricular assist devices via flow visualization techniques have been reported by Yamane *et al*. (2004), Tsukiya *et al*. (2002), Manning and Miller (2002), Day *et al*. (2002), Wu *et al*. (1999), Mulder *et al*. (1997), Kerrigan *et al*. (1996), and Miller *et al*. (1995). Computational fluid dynamics (CFD) techniques have been employed by numerous investigators to analyze various design configurations of circulatory assist devices including Song *et al*. (2004a,b), Okamoto *et al*. (2003), Curtas *et al*. (2002), Anderson *et al*. (2000), and Pinotti and Rosa (1995), among others.

CHAPTER 3

Cardiac Pacemakers

3.1 CARDIAC ELECTROPHYSIOLOGY

The heart weighs between 7 and 15 ounces (200–425 g) and is a little larger than the size of your fist. By the end of a long life, a person's heart may have beat (expanded and contracted) more than 3.5 billion times. In fact, each day, the average heart beats 100 000 times, pumping about 2000 gallons (7571 L) of blood. Electrical impulses from your heart muscle (the myocardium) cause your heart to contract, and are created by the movement of ions (principally potassium) across membranes in a fashion called depolarization of cells. This depolarization is propagated along pathways as the ion transport continues. This electrical signal begins in the sinoatrial (SA) node, located at the top of the right atrium. The SA node is sometimes called the heart's "natural pacemaker" with the average heart beat occurring 72 beats/min. An electrical impulse from this natural pacemaker travels through the muscle fibers of the atria and ventricles, causing them to contract. Although the SA node sends electrical impulses at a certain rate, your heart rate may still change depending on physical demands, stress, or hormonal factors. The initiating electrical signal from the SA node travels down a preferred pathway of specialized conducting myocardial tissue toward the atrioventricular (AV) node, which is the electrical connecting point from the atria to the ventricles. After a slight transmission delay (designed to allow the atria to contract and fill the ventricles before the ventricles contract), the specialized conduction pathway continues into the ventricles. There are two bundles of fibers, called the left and right bundle branches of His, culminating in purkinje fibers, that promote rapid transmission of electrical current through both ventricles. The electrical pathways are shown in Figure 29.

3.2 THE ELECTROCARDIOGRAM

The waves of depolarization that spread through the heart during each cardiac cycle generate electrical currents, which in turn spread through the body's interstitial fluids and eventually up to the body's surface. Recording electrodes, placed on the surface of the skin on opposite sides of the heart, are used to detect such electrical potentials. These signals are filtered, amplified, and recorded as a measure of the underlying cardiac electrical activity. The record that results from this procedure is termed an electrocardiogram (ECG or EKG). An ECG is an important

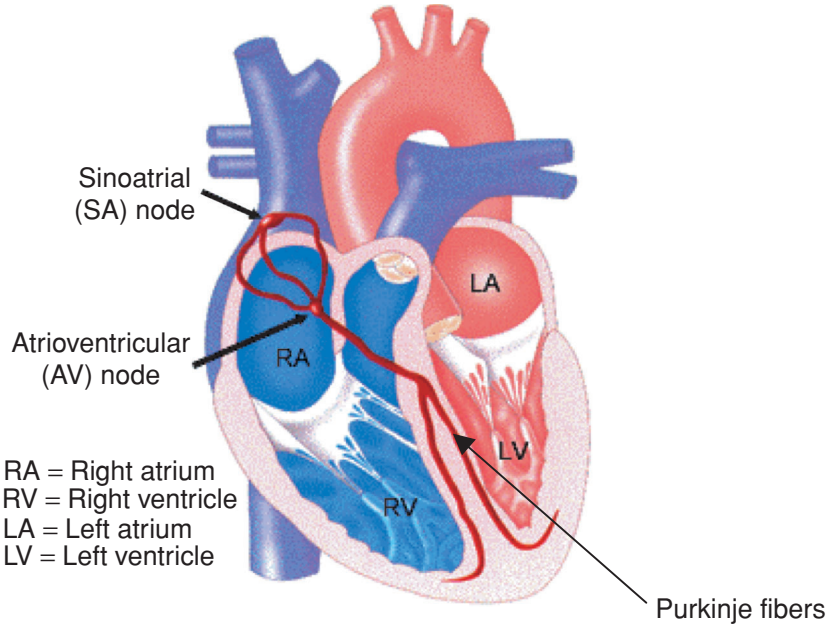


FIGURE 29: Electrical excitatory pathways in the heart.

diagnostic tool to determine whether any cardiac malfunction may have an underlying electrical reason. A typical ECG waveform is seen in Figure 30. The normal ECG consists of three basic features: a P wave, a QRS complex, and a T wave. On some patient waveforms, the QRS complex is seen as three separate waves.

The electrical currents produced as the atrial muscle cells depolarize prior to contraction generate the P wave. This is followed in time by the QRS complex and results from currents

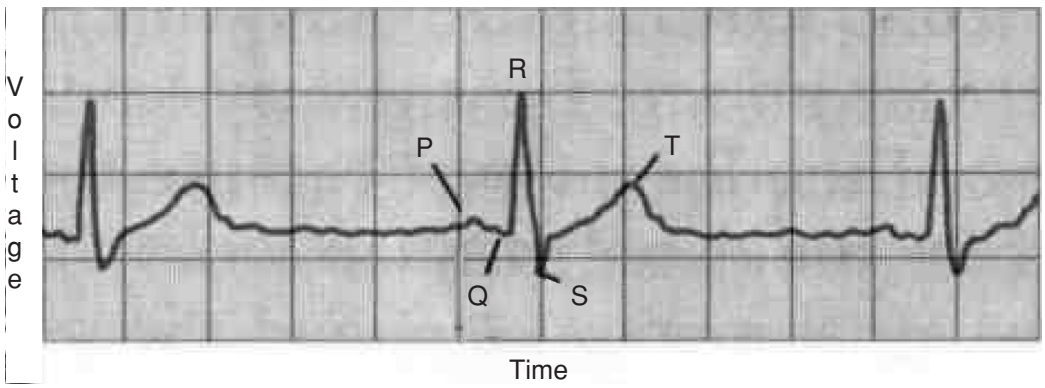


FIGURE 30: Typical ECG showing P, QRS, and T waves.

generated as the ventricles depolarize prior to their contraction. There is a slight time delay between these waves resulting from the delay produced at the AV node, as stated above. Thus, both the P wave and the QRS complex represent depolarization waves. Following ventricular contraction, the ventricle muscle cells repolarize (reverse polarity and reverse ionic transport), and these reversing electrical currents produce the T wave that typically occurs 0.25–0.35 s following ventricular depolarization.

Repolarization of the atria is masked by the QRS complex, and is thus not normally seen on the standard ECG. The intervals between these waves and the width and shape of these waves on the ECG are useful diagnostic measures of cardiac function, as is the overall frequency of the cardiac cycle. The interval between the beginning of the P wave and the beginning of the QRS complex is designated by the PQ interval. Since the Q wave is often absent, it is sometimes termed the PR interval and represents the duration of time (normally about 0.16 s) between the onset of atrial contraction and the onset of ventricular contraction. In patients with certain heart diseases including scarred and/or inflamed tissue, this may lead to a lengthening of the PR interval because more time is required for the depolarization wave to spread through the atrial myocardium and the AV node. The time required for the generation of the QRS complex is termed the QRS duration and represents the amount of time needed for ventricular depolarization. The QT interval extends from the beginning of the QRS complex to the end of the T wave and represents the time required for ventricular contraction and repolarization. Typically, the normal QT interval lasts for approximately 0.35 s. The ST interval represents the time required for the ventricles to repolarize and extends from the S wave to the end of the T wave.

The term *tachycardia* denotes an overall fast heart rate, typically at more than 100 beats/min. Tachycardia may result from fever, from stimulation of cardiac sympathetic nerves, from certain hormones or drugs, or by weakening of the heart muscle itself. When the myocardium is unable to pump blood effectively, homeostatic reflexes are activated that subsequently increase the heart rate. The term *bradycardia* denotes a slow heart rate of less than 60 beats/min and is a condition common to athletes, whose enlarged hearts pump a greater stroke volume per heart beat than that of a nonathlete. In addition, bradycardia may also result from decreased body temperature, due to certain drugs, or via stimulation of the heart by its parasympathetic nerve fibers originating from the vagus nerve. Bradycardia may also occur in patients with atherosclerotic lesions of the carotid sinus region of the carotid arteries. The term *arrythmia* refers to any electrical abnormality in the ECG including rate-related conditions as well as conduction delays or even complete blockages.

The SA node is the natural pacemaker of the heart, providing a stimulating source that initiates the electrical depolarization cycle at approximately 72 beats/min. Should there be a *block* of the excitation wave between the SA node and the AV node, then the origin of the excitation for the remainder of the heart becomes the AV node, whose normal rhythmic rate is slower than

that of the SA node (approximately 55 beats/min). The remainder of the excitatory pathway (AV node to purkinje fibers) remains intact. Should there be a partial or total block between the AV node and the purkinje fibers, then alternate excitatory sources within the ventricular muscle assume the excitatory role, albeit at a much lower rate (30 beats/min). These are readily evident in the ECG waveforms as a reduced heart rate, as widening of the waves within the ECG, and/or as changes in the shape of the waves.

Premature contractions can occur within a normal rhythmic cardiac excitation (called sinus rhythm) due to altered excitatory events within an atrium or a ventricle. Premature atrial contractions (PACs or PABs for premature atrial beats) are atrial beats that occur too early due to an abnormal electrical signal. Often, things such as caffeine, alcohol, medications (especially decongestants), certain medical conditions such as hyperthyroidism, anemia, and hypertension, and stress can trigger PACs. Some people may feel a fluttering in their hearts when experiencing PACs, whereas others have no symptoms. PACs are benign and may require no treatment. Premature ventricular contractions (PVCs or PVBs for premature ventricular beats) are early ventricular contractions that occur when the ventricles contract out of sequence with normal heart rhythm. Though they are generally benign and usually do not require treatment, PVCs may result in more serious arrhythmias in those with heart disease or a history of tachycardia. For these people, antiarrhythmic drugs and an implantable cardioverter defibrillator (ICD) may be prescribed. PVCs most often occur spontaneously; however, like PACs, they can also be triggered by caffeine, alcohol, medications (especially decongestants), certain medical conditions such as hyperthyroidism, anemia, and hypertension, and stress. PACs and PVCs are readily observed as added waves within the ECG. An *ectopic* or premature atrial beat produces an added P wave within the standard ECG waveform. A PVC produces an added R wave or QRS segment within the normal ECG waveform. Repeated PAC or PCV events may indicate a serious condition that will require intervention.

Fibrillation is caused when the heart muscle begins to quiver, or fibrillate, continually and cannot contract normally. When a heart is in a state of fibrillation, there is no synchronization between the atria and the ventricles, nor any standard heart beat/contraction. This may cause the patient to experience a racing sensation—and sometimes discomfort in the chest—and/or to feel light-headed or faint. Ventricular fibrillation (VF or V Fib) is a life-threatening arrhythmia that necessitates immediate treatment with an external defibrillator, an internal defibrillator (ICD), antiarrhythmic drugs, or VT ablation. Fibrillation is easily recognized on the ECG waveform as a loss of the QRS segment replaced by a noisy, lower amplitude signal. Atrial fibrillation (AF or A Fib) is a very fast, uncontrolled atrial heart rate caused by rapidly fired signals. During an episode of AF, the atrial heart rate may exceed 350 beats/min. Not all of these beats reach the ventricles, so the ventricular rate is not this high. However, the ventricular rate is often higher than normal and can also be erratic, exceeding 100 beats/min. Sometimes an impulse will circle the atria, triggering atrial flutter, which is similar to AF. Alone, AF is rarely serious, but if a

patient has high blood pressure, valvular disease, or heart muscle damage, AF can increase the risk of stroke or heart failure.

There are several treatments for AF, including medication, ablation, and an electrical therapy called cardioversion. Electrical cardioversion converts the heart rate back to normal sinus rhythm through the use of a controlled electrical shock that excites all the heart cells at once, allowing the SA node to resume its role as the heart's natural pacemaker. If medication and electrical cardioversion do not improve the AF, the physician may recommend cardiac ablation to prevent conduction of abnormal electrical impulses from the atria to the ventricles, with implantation of a permanent pacemaker to control heart rate. Ventricular fibrillation (VF) is a chaotic heart rate resulting from multiple areas of the ventricles attempting to control the heart's rhythm. Ventricular fibrillation can occur spontaneously (generally caused by heart disease) or when ventricular tachycardia has persisted too long. When the ventricles fibrillate, they cannot contract normally, hence, they cannot effectively pump blood. The instant VF begins, effective blood pumping stops. VF quickly becomes more erratic, resulting in sudden cardiac arrest or sudden cardiac death. This arrhythmia must be corrected immediately via a shock from an external defibrillator or an internal device (ICD). The defibrillator can stop the chaotic electrical activity and restores normal rhythm by depolarizing the entire heart with the idea that normal sinus rhythm will be restored if the SA node fires first and initiates the normal excitation process.

3.3 CARDIAC PACEMAKER

An artificial cardiac pacemaker is an implantable device that produces an excitatory wave at an appropriate site within the heart: a) at the SA node to replace a failing natural SA node (or correct atrial fibrillation) and generate a normal sinus rhythm, b) at the AV node where a malfunctioning AV node exists, or c) within one or both ventricles to continue excitation beyond a partial or total heart block (or to correct ventricular fibrillation). A cardiac pacemaker consists of 1) an electrical device, the pulse generator, which produces the excitatory signal, 2) the wires, called the leads, which connect the pulse generator to the cardiac tissues, 3) a battery system (housed within the pulse generator) to power the pulse generator, and 4) a programmable segment (also housed within the pulse generator) to evaluate the heart excitatory function and send the appropriate excitatory segment from the pulse generator. A schematic diagram of a cardiac pacemaker and the leads is shown in Figure 31.

The batteries within the pulse generator "can" are typically lithium iodide and have a life span of approximately 10–12 years. The pulse generator casing is typically titanium which is welded and hermetically sealed. An epoxy top is attached from which the leads are attached to the pulse generator. This allows for changes in the leads without disrupting the pulse generator case. A typical pulse generator is small in size, often less than an ounce in weight, less than two inches wide, and a quarter-inch thin. Thus, the device is roughly the size of two silver dollars stacked on top of one another. Once implanted in the upper chest, just below the skin

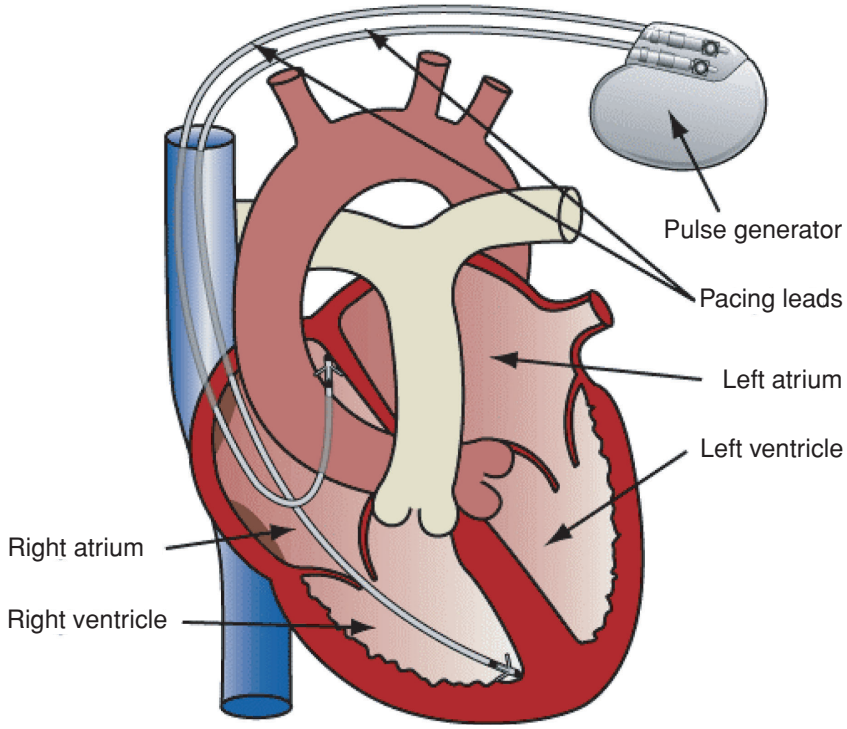


FIGURE 31: Schematic diagram of an implantable cardiac pacemaker.

near the collarbone, the pacemaker's presence is nearly invisible to the eye. When the batteries have become depleted, the entire pulse generator case is replaced. The surgical implantation procedure will be explained in more detail below. A pulse generator is seen in Figure 32, with the leads connected to the "can" seen in Figure 33.

FIGURE 32: Typical pacemaker pulse generator with epoxy top for connection to leads.

FIGURE 33: Pulse generator with leads attached.

The pacing lead, which connects to the pulse generator header, is a flexible insulated wire with an electrode tip. This tip, which can be inserted through a vein into the heart, carries impulses from the pulse generator to the heart, stimulating the heart to beat. It also carries information from the heart back to the pulse generator, which the physician accesses via a special programmer or into the pulse generator circuit embedded program. Leads that are inserted via a vein into the heart have tines on the end as shown in Figure 34 or have a screw end, which can be threaded into the cardiac muscle as shown in Figure 35.

FIGURE 34: Pacemaker lead with tines on end for embedding into heart tissue.

FIGURE 35: Pacemaker lead with screw end for implantation into heart tissue.

The leads shown in Figures 34 and 35 are both designated as endocardial or transvenous leads. The tined lead shown in Figure 34 is a passive fixation device where the tines become lodged in the trabeculae (fibrous meshwork) of the heart. The helix or screw-ended lead shown in Figure 35 is an active fixation device that extends into the endocardial tissue (interior surface of the heart). Such a lead can be positioned anywhere in the heart chamber. The other category of lead is the myocardial or epicardial lead which is secured to the outer surface of the heart as shown in Figure 36. Such leads are connected to cardiac tissue via sutures or screwed into tissue as was the case with the endocardial lead.

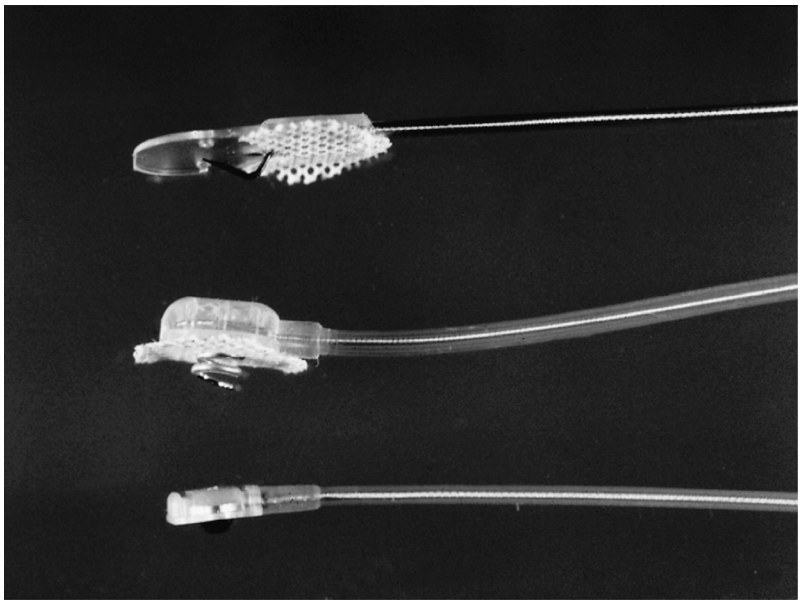


FIGURE 36: Myocardial pacemaker leads which are sewn into exterior cardiac tissue via sutures or screwed into the exterior surface.

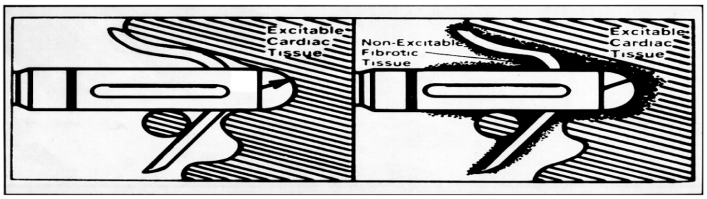


FIGURE 37: Fibrous capsule surrounding a tined lead as a result of an inflammatory response.

Once leads have been implanted, there is often a tissue reaction that creates a fibrotic capsule around the lead, as shown in Figure 37. Such a capsule can increase the resistance to the stimulating pulse to cardiac tissue, which would require an increase in the amplitude of the original pulse from the pacemaker. This would deplete the batteries at a rate faster than normal. In order to avoid such a circumstance, some leads contain a steroid that eludes into the surrounding tissue to reduce the onset of an inflammatory response. This is seen in Figure 38.

Leads can be either unipolar or bipolar. Unipolar leads, as shown in Figure 39, are single leads inside of an insulating sheath, which send the impulse signal from the pulse generator with the returning electrical signal traveling through the tissues to the pacemaker. The unipolar lead normally has a smaller diameter than the bipolar lead and exhibits a greater tendency for pacing artifacts on the surface EKG, since the returning electrical signal travels through tissue.

The bipolar lead, as shown in Figure 40, is a coaxial lead with a larger overall diameter. The returning signal (after stimulating cardiac muscle) pathway is through the second embedded lead, rather than through tissues. As a result, the bipolar lead has a lower susceptibility to affect

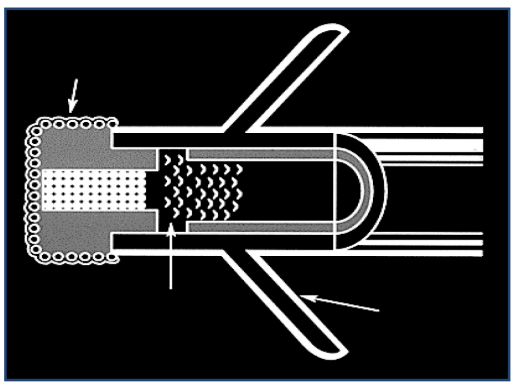


FIGURE 38: Steroid eluding lead designed to deter inflammatory response and fibrous capsule formation.

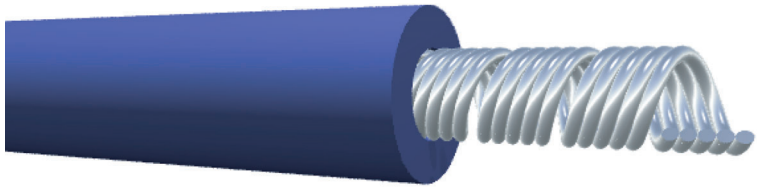


FIGURE 39: Unipolar pacemaker lead.

the EKG and is less susceptible to external interference, such as from ambient electromagnetic "noise."

The insulation on pacemaker leads is either silicone or polyurethane. Silicone is inert, biocompatible, biostable, repairable with medical adhesive, and has a long and successful history in biomedical applications. Polyurethane is also biocompatible, but additionally has a higher tear strength, lower friction coefficient, and a smaller required thickness.

Pacemaker systems that are fixed rate often utilize a single lead that is placed in the atrium (if there is an SA nodal problem) or the ventricle for AV nodal or bundle branch problems. For circumstances where there is a need for a demand style pacemaker, there must be two leads placed within the heart as seen in Figure 41.

The sensing electrode is placed within the atrium to sense any variation in normal sinus rhythm, such as what might occur during exercise of increased heart activity. The stimulating electrode might be placed within the ventricle and the rate of stimulation is dependent on the sensed SA nodal rate. Modern demand pacemakers thus have four main functions:

- Stimulate cardiac depolarization
- Sense intrinsic cardiac function
- Respond to increased metabolic demand by providing rate responsive pacing
- Provide diagnostic information stored by the pacemaker.

The output of the pacemaker, which stimulates cardiac tissue, can be visualized on the surface EKG as is seen in Figure 42.

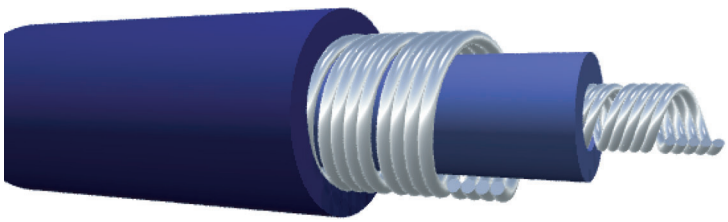


FIGURE 40: Bipolar pacemaker lead.

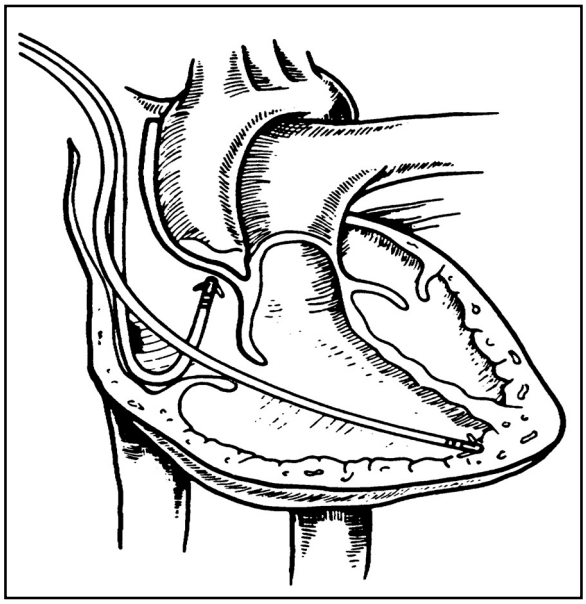


FIGURE 41: Demand style pacemaker with two leads: one for sensing and one for stimulation.

A typical stimulating pulse from the pulse generator must be large enough to cause depolarization (i.e., to "capture" the heart) and must be sufficient to provide an appropriate pacing safety margin. The pulse width must be long enough for depolarization to disperse to the surrounding tissue. As such, pulse generation waveforms are typically evaluated on a strength duration curve as noted in Figure 43.

Once a pacemaker elicits a stimulating pulse and the heart muscle depolarizes, there exists a refractory period whereby another stimulating pulse would not elicit further depolarization.

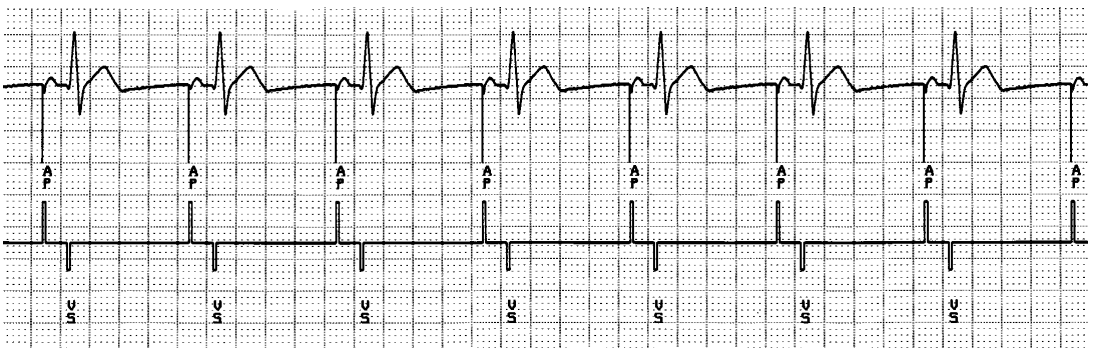


FIGURE 42: Surface EKG with pacemaker stimulation pulses noted within the EKG waveform as well as on the axis below.

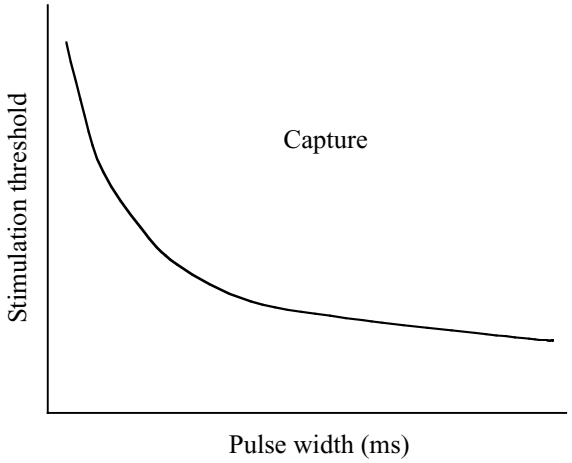


FIGURE 43: Strength–duration curve to evaluate the required necessary stimulating pulse to achieve "capture," i.e., produce a depolarization.

This same refractory period exists during normal cardiac electrical stimulation, such that any ectopic wave would not elicit a second depolarization. Repolarization would normally need to occur before a second pulse would produce another depolarizing wavefront. As was noted above, modern pacemakers often employ a sensing electrode in one heart chamber and a second stimulating electrode in another chamber. A system of classification has been established for pacemakers which is used to describe the various parameters that can be incorporated into modern pacemakers, as seen in Figure 44.

Referring to this classification system, a VOO pacemaker (see chart) stimulates the ventricle with no atrial or ventricular sensing (nor any response to sensing). This would be a fixed rate pacemaker that stimulated the ventricle regardless of the patient's intrinsic cardiac

CHAMBER PACED	CHAMBER SENSED	RESPONSE TO SENSING	PROGRAM FUNCTION	FUNCTION
V: Ventricle	V: Ventricle	T: Triggered	P: Simple	P: Pace
A: Atrium	A: Atrium	I: Inhibited	M: Multi	S: Shock
D: Dual	D: Dual	D: Dual	C: Communicating	D: Dual
O: None	O: None	O: None	R: Rate modulate	O: None
S: Single	S: Single	O: None		

FIGURE 44: Pacemaker classification system.

electrophysiology. A VVI pacemaker (see chart) senses ventricular electrical activity and paces the ventricle if there is a lack of normal intrinsic activity sensed. If normal ventricular excitatory pulses are sensed, then the pacemaker output is inhibited (the I) in the pacemaker classification. A VVIR pacemaker is identical to the VVI pacemaker except for the added "R" term indicating program function (R = rate). This pacemaker changes the stimulation rate of firing when the intrinsic ventricular stimulation warrants it. Similarly, a VAIR pacemaker senses atrial activity and stimulates the ventricles. The pacemaker pulse rate is affected by the atrial activity. If the patient's metabolic activity alters the SA nodal firing rate, then the pacemaker senses this and increases the ventricular firing rate. If there is a normal sinus rhythm, then the pacemaker output is inhibited. Similarly, a VDIR pacemaker senses intrinsic activity in both chambers with the pacemaker capable of delivering a variable rate.

Originally, pacemakers of the 1950s were external devices with the leads implanted into the heart. The first transistorized, wearable, battery powered pacemaker developed by Wilson Greatbach in 1957, and the first totally implanted pacemaker was in 1960. The battery life was approximately 18 months. In the mid-1960s, transvenous leads were developed that could be introduced through a vein, rather than require opening the chest to attach the lead. Original designs for pacemakers incorporated a fixed rate. In the mid-1960s, the first "demand" pacemakers were developed that sensed when there was a missed beat and then initiated a pulse to excite the cardiac muscle, while being inactive during normal sinus rhythm. The screw tip and tined leads were developed in the 1970s, and in 1975, the longer lasting lithium iodide battery was developed to replace the mercury–zinc battery. At that same time, the titanium case and epoxy top was developed, which better shielded the pacemaker from outside electromagnetic disturbances, such as a microwave oven. In that same time span, the first programmable pacemakers were developed as were the first dual chamber pacemakers. In the 1990s, the pacemakers became smaller with advances in batteries and in microelectronics. To date, over 2 million cardiac pacemakers have been successfully implanted.

3.4 PACEMAKER IMPLANTATION

A schematic diagram depicting the surgical implantation of a cardiac pacemaker is shown in Figure 45. The pacemaker pulse generator with its epoxy top is implanted just below one of the collarbones. The leads are then inserted through a vein leading to the heart or via minimally invasive surgery to affix them to the exterior of the heart.

The use of the easily accessible site below the collarbone allows the pulse generator with its battery pack to be easily replaced once the batteries have become depleted. By using a local anesthetic, a small opening in the skin and underlying thin tissues can be created in order to remove the pulse generator. Since the leads are connected to the epoxy top of the pulse generator by means of a force fit, then the leads can be easily removed and snapped

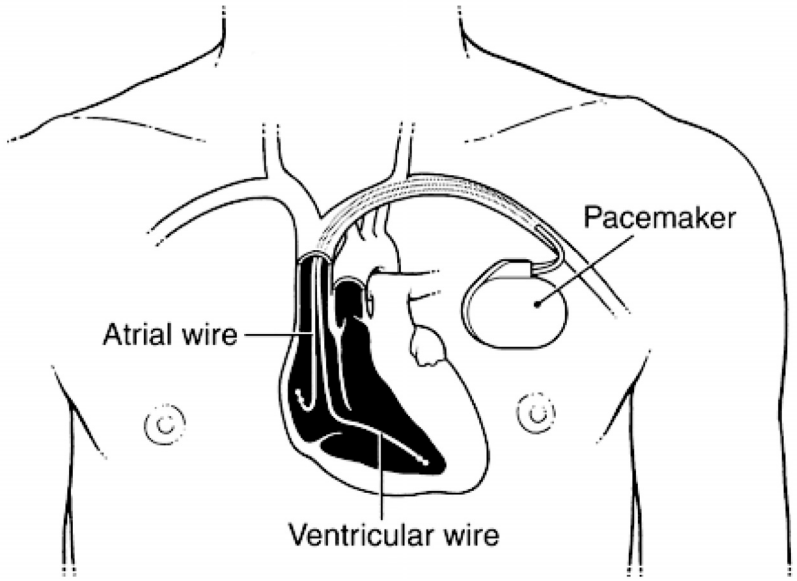


FIGURE 45: Implantation of a cardiac pacemaker pulse generator below a collarbone with the leads threaded through a nearby vein toward the heart.

into the replacement pulse generator (and battery pack) within the new epoxy top associated with the new generator. The time "off" of pacing is thus extremely short—the time it takes to pull the lead(s) out of one epoxy top and into another. The new pulse generator is then placed in the site of the old unit, and the small incision is then closed. The entire replacement procedure often takes as little as 30 min from open to close. As the modern batteries for cardiac pacemakers can last as long as 12 years, replacement of the pulse generator is infrequent.

3.5 CARDIOVERTER

If the patient is susceptible to ventricular fibrillation, then a standard cardiac pacemaker may not be able to reestablish sinus rhythm. As with the case when an individual suffers a "heart attack," where VF occurs, it is necessary to convert the patient by completely depolarizing the entire heart by means of a defibrillator. Most individuals are familiar with external defibrillators that use large paddles and a large current density to provide an overwhelming depolarization to the heart. The premise is that when the heart then completely repolarizes, that the SA node will fire before any other site within the heart and reestablish sinus rhythm. The large paddles and large current density are necessary for external defibrillation, as the skin and exterior tissues provide a large resistance to electrical current flow.

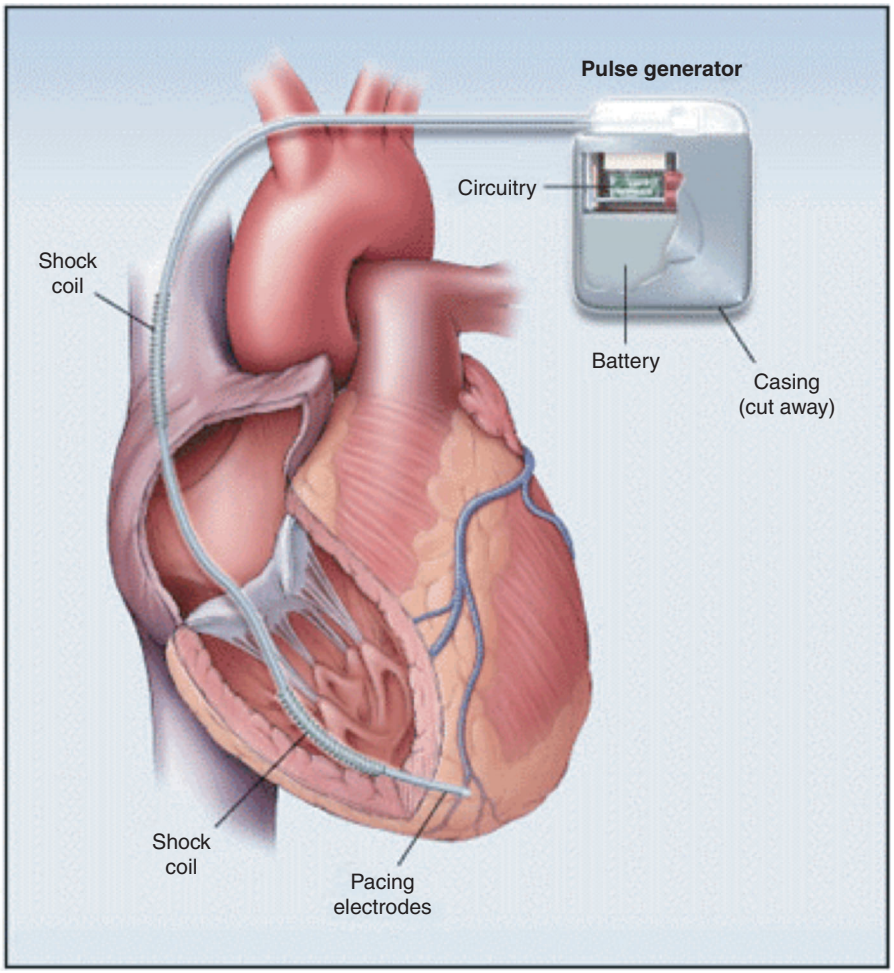


FIGURE 46: Dual pacemaker and cardioverter within the same case. Note the shocking coil which surrounds the pacing lead.

However, if the defibrillator were placed deeper within the body, then the amount of current necessary to defibrillate the heart is far less. As a result, the device is far smaller. For those patients who may require defibrillation on a regular enough basis, an implantable version can be placed in the same site as a cardiac pacemaker—below the collarbone with the leads threaded through a vein toward the heart. For those patients who require frequent cardiac pacing, but are also less frequently susceptible to ventricular fibrillation, then a combination unit of pacemaker and implantable cardioversion device (ICD) is implanted as shown in Figure 46. This device is sometimes called an implantable cardiac defibrillator (ICD).

The shocking coil for the cardioverter (defibrillator) unit (within the same housing as the pacemaker) surrounds the pacemaker lead. Should the pacer sensing electrodes detect ventricular fibrillation and the normal pacing protocol does not reestablish sinus rhythm, then the cardioverter fires to completely depolarize the heart. The pacemaker portion of the housing is electrically decoupled and insulated from the cardioverter during this process so as to avoid damage to the pacemaker circuitry.

Studies regarding the development of cardiac pacemakers have been ongoing for several decades. More recent studies include a discussion of permanent transvenous pacing by Petrie (2005), a discussion regarding appropriate selection of a pacemaker by Ellenbogen and Wood (2005), a discussion regarding the use of single chamber versus dual chamber pacing by Toff *et al.* (2005), an update on implantable pacemakers by Woodruff and Prudente (2005), and indications and recommendations for pacemaker therapy by Gregoratos (2005).

Several studies have examined the role of interfering external factors that may adversely affect a cardiac pacemaker. Of particular note has been the effect of an MRI on pacemaker activity as reported by Irnich *et al.* (2005), Vahlhaus (2005), and Del Ojo *et al.* (2005). Other external factors recently examined regarding interference with pacemaker performance included electromagnetic fields of high voltage lines by Scholten *et al.* (2005), and electromagnetic interference from induction ovens by Hirose *et al.* (2005).

Clinical issues that may adversely affect pacemaker performance include dislodged and/or fibrosed leads as discussed by Khan *et al.* (2005), Shimada *et al.* (2002), and Cutler *et al.* (1997). Issues associated with the use of implantable cardioverter defibrillators were examined by Nazarian *et al.* (2005), Gersh (2004), Sanders *et al.* (2005), Alter *et al.* (2005), Bryant *et al.* (2005), and Silver (2005).

The use of implantable cardiac pacemakers has proven to be an extremely successful "artificial organ" with millions of patients successfully treated. The later use of implantable defibrillators and dual pacemaker/defibrillators has also been successful, albeit with far less cases to date than with pacemakers alone.

CHAPTER 4

Dialysis

The human kidneys are responsible for continually cleansing blood of metabolic waste products (such as urea, uric acid, creatinine), excess ions, and excess water. The resultant filtrate is then transported to the ureter to be removed as urine. Approximately 20% of the blood supply is routed to the kidneys at any time in order to provide a continual means of removing potentially toxic materials from the blood. The water removal from the kidneys serves as a secondary means of controlling blood pressure, as total blood volume is a factor in venous return, cardiac output, and thus arterial pressure. There are two kidneys, each consisting of a network of millions of individual mass transfer elements called *nephrons*. Transport occurs across the surface of the nephron. As is the case with the lungs, which have similar elements called alveoli, the nephrons provide a means of greatly expanding the surface area available for mass transfer within a constrained volume. The theory is similar to that of a single large sphere as compared to millions of smaller spheres within the same volume. The net surface area of the large sphere is much smaller than that of the combined surface area of the numerous small spheres. Thus, mass transfer of metabolic waste products occurs by branching blood into smaller and smaller channels until the actual mass transfer occurs at the small end point—the nephron. Again, this is similar to the trachea branching into the bronchi and eventually to the alveoli in the lungs.

4.1 THE NEPHRON AND MASS TRANSFER

The kidney and its most elemental mass transfer unit, the nephron, are shown in Figure 47. Unlike most organs within the human body, the kidneys are supplied with blood directly from an arteriole, which branches from the renal artery. The use of an arteriole allows for control of the source hydrostatic pressure to each nephron (by means of vasoconstriction or vasodilation) and provides a constant source of pressure to each mass transfer unit.

The nephron consists of the glomerulus, a relatively porous membrane with pores diameters of 50 Å and pore lengths of 500 Å. These pore diameters allow a large amount of fluid to enter into the nephron tubule system, while excluding (by size) such blood elements as cells, large proteins, large sugars, etc. The glomerular filtration rate (GFR), the amount of fluid flow through all of these membranes, equals 125–150 mL/min. As the total blood flow to the kidneys

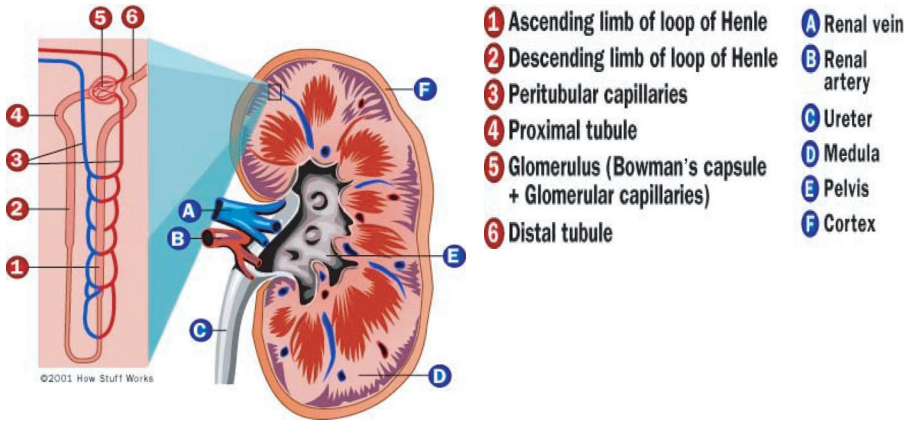


FIGURE 47: The human kidney and the nephron (shown in detail to the left).

equals 1000–1200 mL/min (20–25% of total blood flow), and plasma (the liquid portion of blood) represents approximately one half of the renal blood flow (for a hematocrit of 45% plus white cells and platelets), then the GFR represents approximately 25% of plasma renal flow (150 of 600 mL/min). This means that 25% of the liquid portion of the blood is leaving the blood as it travels into the tubules of the nephron. Luckily, only about 1–2 mL/min eventually finds its way to the ureter, which indicates that the remainder is returned to the blood supply. This occurs through reabsorption of the filtrate into blood vessels that parallel each nephron, the *vasa recta* or *peritubular capillaries* as is seen in Figure 47. The glomerular filtration rate is controlled by a hydrostatic pressure gradient as well as an osmotic pressure gradient (from the blood side to the filtrate side across the glomerulus). The hydrostatic pressure gradient is a relatively large 50 mmHg (for so short of a "pore" length) and the reverse osmotic pressure gradient is 25 mmHg. The osmotic pressure gradient is reversed from the hydrostatic pressure gradient since cells and large proteins on the blood side do not travel across the pores, and exert an osmotic pressure from the filtrate side to the blood side. The net 25 mmHg pressure gradient that pushed fluid across the glomerulus is still quite large and results in a significant transport of fluid as was described above.

The filtrate (the name of the fluid once it enters the tubules of the nephron) then follows the tubule pathway from the proximal tubule, through the loop of Henle, then through the distal tubule and the collecting duct, eventually ending in the ureter. Along the way, through a combination of concentration-driven passive diffusion as well as active transport, positive ions are transported across the tubules into the surrounding extracellular fluid. Negative ions follow the same pathway, primarily by means of a charge balance as well as passive diffusion. Water follows along the same pathway by means of a concentration-driven osmosis. All of these constituents are then absorbed by the vasa recta to return to the blood supply.

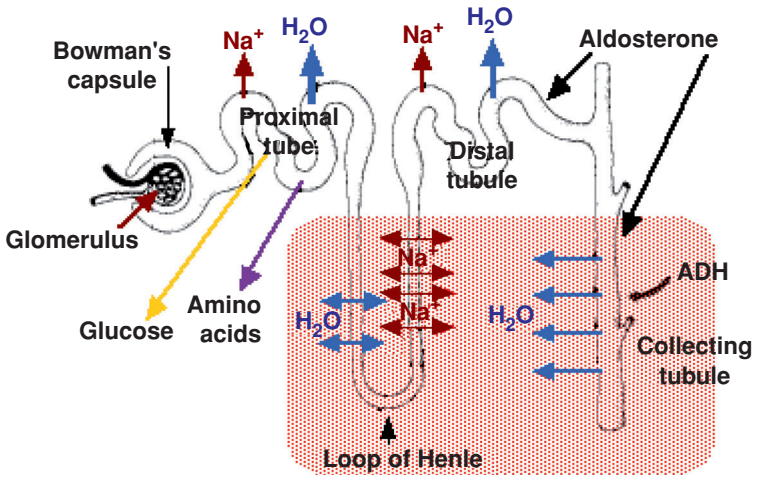


FIGURE 48: Movement of ions and water across the tubule system of the nephron as controlled by the hormones: aldosterone and ADH.

The loop of Henle operates by a countercurrent mechanism whereby the downward and upward sections are both contributing to the extracellular osmolarity, which is very high at the bottom of each loop and lessens toward the top of each loop. This occurs as ions are transported in both directions within each section of the loop, with most of the ion transport out of the loop at the bottom and into the loop at the top. The counter current mechanism allows the ascending loop to return fluid (and ions) into the descending loop and eventually into the extracellular fluid at the bottom of both loops. This fluid and ion mixture eventually finds its way back to the vasa recta.

The entire process of fluid flow and mass transfer across the glomerulus and through the tubule system is designed to transport a significant amount of fluid into the tubules with the bulk of it returning to the vasa recta. This process allows for selective retention of water and ions inside the tubules as controlled by hormones, which in turn allows for selective concentration of urine as is seen in Figure 48.

This approach—moving alot of fluid into the tubules to allow for a variable amount to be returned, cannot be duplicated by means of dialysis—the artificial cleansing of blood. Dialysis utilizes a standard transport of ions, metabolic wastes and water across a semipermeable membrane with this fluid mixture traveling across the membrane by means of simple diffusion, and not returning to the blood, as it does in the natural kidney.

4.2 DIALYSIS PROCEDURE AND THE DIALYSIS SYSTEM

Dialysis is the artificial cleansing of blood to remove the same components as those removed by the natural kidney: metabolic waste products such as urea, ureic acid, and creatinine; excess ions; and excess water. This is accomplished by means of concentration gradient-driven diffusion for

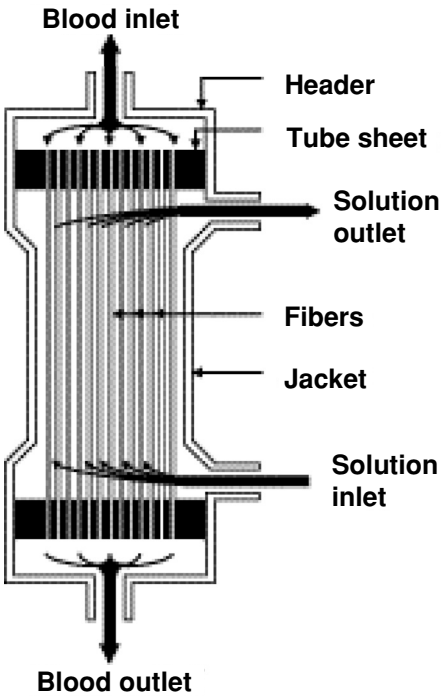


FIGURE 49: Capillary tube dialysis cartridge.

the first two components and by a pressure gradient for water. This process occurs within a capillary tube dialysis cartridge as is shown in Figure 49.

The cartridge is a polycarbonate canister containing 11 000 minute capillary tubes, each with pores small enough to allow transport of the three major blood components listed above, while too small to allow blood cells, large proteins, etc. to cross. In this fashion, the capillary tube pores are not unlike the glomerulus pores in the natural kidney nephron. The cartridge has upper and lower ports for blood to enter and exit the canister. Surrounding the capillary tubes is a fluid, called *dialysate*, which bathes the capillary tubes as serves as the recipient of the wastes, ions, and excess water which leaves the blood from within the capillary tubes. The dialysate is pumped from one side port of the cartridge and leaves from the other side port. The capillary tubes are typically composed of cellulose, which has been proven to be a biocompatible material. At the top and bottom of the capillary tube pack is a polyurethane "potting" section which appears to be a yellowish mass. In fact, this compound serves to briefly pool the incoming blood from the large inlet port so that it can more readily enter the minute capillary tubes. The reverse is true at the bottom of the capillary tubes where the blood enters the potting compound and then into the large outlet port. Dialysis cartridges come in many sizes and are matched to the size of the patient—from children to large adults as can be seen in Figure 50.

FIGURE 50: Capillary tube dialysis cartridges.

Dialysate is similar to clean blood, in that it has no waste products and has the normal level of ions. The typical dialysate mixture consists of the following normal level of blood ions:

NaCl	5.8 g/L	Na	132 meq/L
$NaHO_3$	4.5 g/L	K	2.0 meq/L
KCl	0.15 g/L	Cl	105 meq/L
$CaCl_2$	0.18 g/L	HCO_3	33 meq/L
$MgCl_2$	0.15 g/L	Ca	2.5 meq/L
Glucose	2.0 g/L	Mg	1.5 meq/L

The glucose is used to provide an osmotic gradient to assist in water transport from blood to dialysate. Blood with a high concentration of wastes and ions enters into the top of the dialysis cartridge with clean dialysate entering in the side port nearby. Along the length of the dialysis cartridge, simple diffusion takes place with wastes moving from the source of high concentration (blood) to the point of zero/low concentration (dialysate) across the capillary pores. Similarly, ion transport occurs from a high concentration (in the blood) to one of low concentration (in the dialysate). Water is transported from blood to dialysate by means of a concentration gradient of glucose assisted by a pressure gradient. A typical blood flow rate through the capillary tubes (as a whole) is 200 mL/min with the dialysate flow rate at 500 mL/min. The higher flow rate of dialysate ensures that dialysate with newly acquired waste products are quickly dispelled from

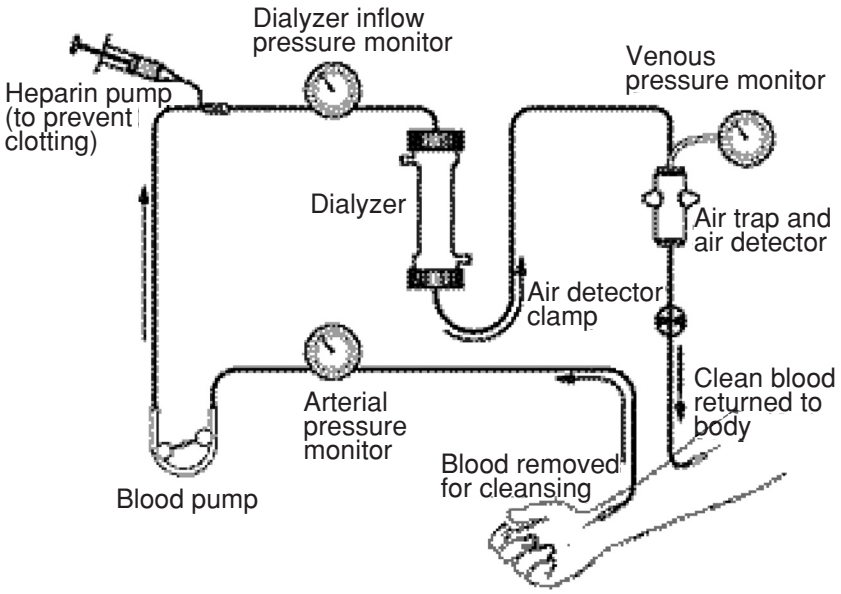


FIGURE 51: Typical dialysis system.

the cartridge and replaced with clean dialysate, thus maintaining a large concentration gradient for mass transfer.

A typical dialysis system is shown in Figure 51. Blood access from the body is connected from needles to tubing, which is routed throughout the machine and into the dialysis cartridge. Blood from the bottom of the dialysis cartridge is then routed through the remainder of the tubing and onwards to return to the body. The dialysis machine consists of various sensors and monitors along with two key elements—a roller pump which pushes blood slowly along a tubing pathway (to avoid stagnation and resultant clotting) and bubble traps to allow any ambient air from remaining in the blood to cause an air embolism.

The dialysis cartridge and tubing set are disposed of following dialysis, although in some dialysis centers, the cartridge itself is cleaned and may be reused. This latter issue will be discussed in more detail in a subsequent section.

Blood is accessed from the radial artery in the forearm and returns to the cephalic vein. Typical chronic dialysis patients undergo dialysis three times per week for 4 h/session. This results in numerous insertions of needles into the forearm. Although the skin becomes tough after time, the underlying blood vessels do not. As a result, chronic dialysis patients often undergo a minor procedure whereby an arteriovenous graft is placed below the skin connecting the radial artery to the cephalic vein as is seen in Figure 52.

The graft not only protects the blood vessels from repeated needle insertions, but also connects the high pressure artery to the low pressure vein—keeping the vein from collapsing.

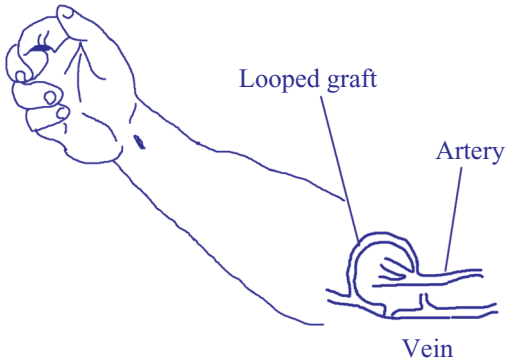


FIGURE 52: Arteriovenous graft in the forearm for chronic dialysis patients.

The pressure gradient from the artery to the vein also provides a gradient to propel blood through the tubing set and the dialysis cartridge. Thus, the roller pump within the dialysis system merely provides a boost for blood flow rather than having to provide the sole means of blood flow through the system.

A typical dialysis tubing set is shown in Figure 53 and includes bubble traps and sufficient tubing to connect from the artery/vein access needles to the dialysis machine, the dialysis cartridge, and back again to the forearm.

A typical dialysis machine is shown in Figure 54 with slots for the dialysis cartridge and bubble traps as well as an embedded roller pump and blood sensors.

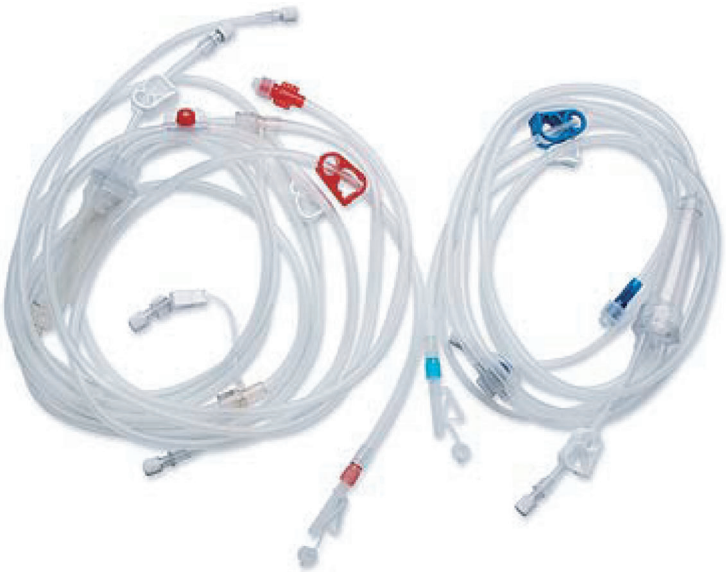


FIGURE 53: Dialysis tubing set for the blood pathway.

FIGURE 54: Dialysis machine.

The left-hand color-coded (blue and red) tubing is for the dialysate (clean and "dirty" ports). The slot to the right of this tubing is for the dialysis cartridge. To the right of the cartridge location is where the bubble traps are inserted. The roller pump is to the right of the bubble traps. At the bottom of the machine are two tubes with a tray below them. A dialysate concentrate jug is placed on the tray and one of the tubes is inserted into the jug. The machine draws dialysate concentrate from the jug, which is mixed with processed/treated water.

A typical dialysis center includes a water treatment room which converts municipal water into that which is clean enough to be used in close contact with blood. This water treatment includes a sediment filter, a water softener section, an ion exchanger section, an ultraviolet light to destroy bacteria, and a reverse osmosis unit which back-pressures water across an extremely fine (small pore) membrane to remove microscopic elements. The resulting treated water is sent to various patient treatment stations and each dialysis machine is connected to the water port via a hose located on the back of the machine. The mixture of treated water and dialysate concentrate is then transported to the dialysis cartridge through the front, color-coded tubing as was seen to the left of Figure 54.

A typical dialysis machine is approximately 60 inches high, 17 inches wide, 22 inches deep, and weights 190 pounds. It is on rollers to allow placement near the patient. The typical front-mounted screen displays the time on dialysis, time remaining, target water loss (in kg), water uptake rate (in kg/h), and blood pressure and/or heart rate.

4.3 HISTORY OF DIALYSIS

Thomas Graham, Professor of Chemistry at Anderson's University in Glasgow, coined the term dialysis in 1861. He noticed that crystalloids were able to diffuse through vegetable parchment coated with albumin (which acted as a semipermeable membrane). He called this "dialysis." Using this method, he was able to extract urea from urine. In 1913, Abel, Rowntree, Turner, and colleague constructed the first artificial kidney. They used hirudin, produced from leeches obtained from Parisian barbers, as an anticoagulant. They passed animal blood from an arterial cannula through celloidin tubes that were contained in a glass "jacket." The glass jacket was filled with saline or artificial serum. They coined the term "artificial kidney." Blood was returned into the vein of the animal via another cannula. The inventors wrote, "this apparatus might be applied to human beings suffering from certain toxic states, especially if due to kidney damage, in the hope of tiding a patient over a dangerous chemical emergency." The apparatus was never used to treat a patient (Robson JS, 1978). George Haas from Germany performed the first successful human dialysis in autumn 1924. The dialysis was performed on a patient with terminal uremia "because this was a condition against which the doctor stands otherwise powerless." The dialysis lasted for 15 min, and no complications occurred.

The first practical human hemodialysis machine was developed by WJ Kolff and H Berk from the Netherlands in 1943. This rotating drum artificial kidney consisted of 30–40 m of cellophane tubing in a stationary 100-L tank. It was Kolff who made clinicians and experimentalists interested in the treatment of uremia, and this machine delivered the effective hemodialysis treatments. This rotating drum machine is seen in Figure 55.

In 1946, Nils Alwall produced the first dialyzer with controllable ultrafiltration. It consisted of 10–11 m of cellophane tubing wrapped around a stationary, vertical drum made of a metal screen—resembling a rotating drum device stood on its end. In 1956, Kolff and Watschinger developed the principles of the Alwall machine to develop the "twin coil" artificial kidney (Figures), a modification of the "pressure cooker" dialyzer developed by Inouye and Engelberg in 1952. The first patients treated by dialysis were all believed to have acute renal failure. The methods in use for getting adequate flows of blood into the machine exhausted veins and arteries very quickly, and only a few dialysis treatments could be undertaken. The development of methods to use blood vessels repeatedly while preserving them made it possible to contemplate keeping a few patients alive for longer periods even though they had permanent

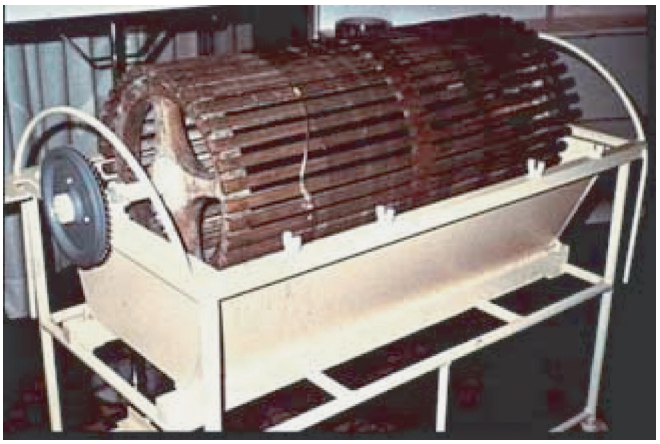


FIGURE 55: Kolff rotating drum dialysis machine—the first practical hemodialysis system.

renal failure. The arteriovenous shunt was the key development. The first substantial program for dialysis of patients with chronic renal failure began in Seattle in the same year.

Home hemodialysis was introduced to overcome the difficulties in providing adequate facilities in hospitals for the increasing number of patients being put forward for treatment. If a relative provided help for the patient, it could be carried out without the use of doctors, nurses or hospital premises, extending the number of patients that could be treated, as well as being better for the patient. However, in 1965, at the American Society of Artificial Internal Organs meeting, reports of home hemodialysis of four patients in Boston and two in Seattle were supplemented by a report of two patients treated at home in London (Shaldon). All reported success and plans to expand their programs.

Today, hundreds of thousands of chronic dialysis patients undergo routine, periodic dialysis three times per week at local dialysis centers located throughout the nation. Dialysis represents one of the most successful organ replacement systems with millions of patients treated successfully for partial or total renal failure. Diabetes and heart disease remain principal causes for renal failure with alcohol and substance abuse also accounting for numerous cases.

4.4 DIALYZER CARTRIDGE REUSE

Many local dialysis centers are privately operated facilities. Although dialysis conducted in hospitals for hospital patients (acute dialysis centers) results in single use of dialysis cartridges, many private facilities reuse cartridges. This entails the rinsing of the cartridge following patient dialysis, after which the cartridge is treated with a sterilant such as formaldehyde, gluteraldehyde, or renalin. Up to four cartridges are placed into a cleaning machine that provides several rinse steps and introduction of the sterilant. The patient's name is written on the cartridge and the cartridge is placed into a bin where it will be stored until that patient needs it for the next session.

The cartridge is then rinsed several times before used for that patient. Although there is a capital expense in purchasing the cleaning machine along with supplies and manpower needed to rinse and sterilize the cartridges, there is a net modest savings rather than purchasing a new cartridge for every patient session. The cartridges cost $10–12 each and the dialysis facility is reimbursed at a set rate for each patient session by insurance, Medicare, or Medicaid. If there is a small net savings, even after expenses associated with cleaning and storing the cartridges, then the dialysis facility would show a large profit, given the number of patient sessions conducted each year. A typical dialysis center might have 20 patient stations. Each patient undergoes dialysis three times per week for 4 h/session. If the center runs an MWF morning, MWF afternoon, T-Th-S morning and T-Th-S afternoon patient cohort, then there are a total of 240 sessions/week (3 sessions for each of 20 stations for each of four patient cohorts). As such, even a modest savings per session adds up to substantial overall savings and profit.

Dialyzer-reuse machines are shown in Figure 56.

Although cost issues are often at the forefront of the rationale to reuse dialyzer cartridges, there has been a considerable debate regarding the efficacy and safety when reusing cartridges. One health-related rationale for the reuse of cartridges is the "first use syndrome" which refers

FIGURE 56: Dialyzer-reuse machines: a four-cartridge system on the left and a single-cartridge unit on the right.

to residual manufacturing byproducts still inside the cartridge when it is unpacked from its wrapping. By reusing cartridges, the uses after the first use no longer suffer from this problem. On the other hand, the health-related arguments against reuse are that a) there is residual sterilant (formaldehyde, etc.) even after rinsing that might harm the patient over time, and b) the clearance of wastes and ions from the dialysis cartridge is reduced over time as blood byproducts clog some of the capillary tubes. Many dialysis cartridges may be reused up to 25 times per patient before the clearance levels fall below 80% of the maximum, which is the standard cutoff before the cartridge must be discarded. The Association for the Advancement of Medical Instrumentation (AAMI) sets standards for cartridge clearance levels. Numerous studies have examined the various factors regarding reuse of dialyzer cartridges including Fan *et al.* (2005), Robinson and Feldman (2005), Szathmary *et al.* (2004), Narsipur (2004), Stragier (2003), Ward and Ouseph (2003), Rahmati *et al.* (2003), and Parks (2002), among others. The issues regarding reuse continue to be debated, although the prevalence of reuse is high among the vast majority of chronic, privately operated dialysis centers.

As dialysis is utilized by hundreds of thousands of patients and the process affects blood chemistry and overall health, there have been numerous studies on the process itself, on disease states that require dialysis, on the various techniques and technologies regarding dialysis. In particular, there are issues associated with cardiovascular disease that impact hemodialysis and vice versa. Studies that have examined this link are numerous and include Familoni *et al.* (2005), Saxena and Panhotra (2005), Di Benedetto *et al.* (2005), Iorio *et al.* (2005), and Ronco and Tetta (2005), among others. Issues associated with blood access and the use of AV fistulas have been studied by Dember *et al.* (2005), Wijnen *et al.* (2005), and Peirce *et al.* (2005), among others. Issues related to blood chemistry and general health considerations have been examined by Panichi *et al.* (2005), Piccoli *et al.* (2005), Prado *et al.* (2005), Gusella *et al.* (2005), Lee *et al.* (2005), and Kiss *et al.* (2005), among others. In addition, there have been studies that have examined the effect of missed dialysis sessions in patient health as well as the desire of patients to quit dialysis including those by Gee (2005), Davison and Jhangri (2005), and Unruh *et al.* (2005), among others.

Dialysis remains a popular and cost-effective means of augmenting reduced kidney function and is a viable alternative to kidney transplantation. The latter approach can be costly and the numbers of available donor kidneys that are properly blood typed, tissue typed, and in a nearby geographic zone are relatively few in number. Although there are continuing issues related to the health of dialysis patients, particularly those with cardiovascular disease, the use of dialysis remains steady and there is no projection that it will decrease in the near future.

The future of dialysis may be in the development of a miniaturized, implantable system. Nissenson *et al.* (2005a,b) at the UCLA Medical School have developed a nanotechnology-based artificial nephron system that employs two membranes operating in series within one very

small cartridge. The first membrane mimics the function of the glomerulus, allowing substances up to the size of albumin (MW 69 000). The second membrane mimics the function of the renal tubules, selectively reclaiming designated solutes, in a manner similar to that of the natural kidney. No dialysate is used in this device. As such, this miniaturized system is closer to that of an actual nephron than to currently employed dialysis systems.

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