

CHAPTER 2

HEART DISEASE AND ARTIFICIAL HEART VALVES

2.1 Introduction

Each implant of a heart valve prosthesis is associated with some complications. Either the recipient requires anticoagulation therapy for their lifetime or the prosthesis requires surgically replacement after a certain amount of time. This issue is a balance of relieving the haemodynamic burden of a faulty natural valve and the inherent imperfections of a prosthesis. Unfortunately, there is no prosthesis to date used to replace an abnormal cardiac valve that performs as a normal functioning heart valve. This chapter describes the major problems associated with the implantation of cardiac valve prostheses. The performance of an implant and the use of reliable detection methods of valve insufficiency are vital for the patient. The most common non-invasive techniques used to evaluate valve function are also discussed.

2.2 Anatomy

The heart is situated in the middle of the chest with its long axis oriented from the left upper abdominal quadrant to the right shoulder. The weight and size of the heart depends on age, sex, weight, and general nutrition. The adult male human heart weighs approximately 325 grams and the female heart weighs approximately 275 grams.

The heart consists of four chambers: two atria and two ventricles (Figure 2.1). The atria receive blood from the body via the major veins. The superior and inferior vena cava delivers oxygen-depleted blood from the body to the right atria, while the pulmonary vein delivers freshly re-oxygenated blood from the lungs to the left atria. Blood passes from the atria to the ventricles through the atrioventricular valves. Blood from the right atria flows to the right ventricle, which then pumps the oxygen depleted blood to the lungs to be re-oxygenated. Blood from the left atria passes through the mitral valve, into the left ventricle, which then pumps the blood through the aortic valve with an average mean flow rate of 5 l/min to the rest of the body.

Two types of valves exist in the human heart: bicuspid and tricuspid. The main function of both types of valves is to regulate blood flow through the heart and the valves generally serve three sub-functions: (a) prevent regurgitation of blood from one chamber to another, (b) permit rapid flow without imposing resistance on that flow, and (c) withstand high-pressure loads.

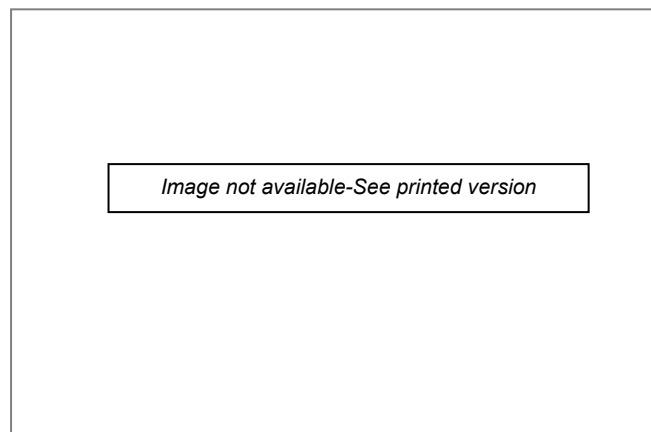


Figure 2.1
Cross-section of a human heart with directions of blood-flow

(Figure obtained from www.heartlab.rii.on.ca)

Basic valve anatomy:

The sequence of events producing a heartbeat is known as the cardiac cycle. During the cycle, each of the four chambers goes through a contraction, called the systole, and a relaxation, called the diastole. In the first phase of the cycle both atria contract, the right first, followed almost instantly by the left atria. This contraction fills the relaxed ventricles with blood. When the ventricles contract, blood is expelled to the lungs and the rest of the body. As they do so, the atria relax and are filled once again by the veins. This cycle lasts, on an average, six-sevenths of a second.

The pressure created by the heart's contraction varies from point to point in the heart and great vessels. Blood returning from the right atrium through veins is under a relatively low pressure of 1 – 2 mmHg. The right ventricle, which delivers blood to the lungs, boosts the pressure to about 20 mmHg during systole. Blood returning from the lungs to the left atrium is once again at a low pressure, rising with contraction to 3-4 mmHg. The left ventricle delivers blood to the body with considerable force. It raises the pressure to about 120 mmHg with contraction, the same as the pressure in the arteries of the body. Between beats, the flow of blood into the capillaries lowers the pressure in the arteries to about 80 mmHg.

The four valves function in the following manners:

- The mitral valve is located between the left atrium and the left ventricle. It is the only valve with two flaps (cusps).
- The tricuspid valve is located on the right side of the heart, between the right atrium and right ventricle. It is made up of three cusps.
- The aortic valve is located on the left side of the heart and opens to allow blood to leave the heart from the left ventricle into the aorta, which is the main artery of the body. It closes to prevent blood from flowing back into the left ventricle.
- The pulmonary valve is situated on the right side of the heart, between the right ventricle and pulmonary artery. It allows blood to exit the heart and enter the lungs via the pulmonary artery. It closes to prevent blood from flowing back into the right ventricle.

Although all four valves have similar tissue structure and function, the aortic valve best demonstrates the principles. Aortic valve cusps open against the aortic wall during systole and close rapidly and completely under minimal reverse pressure, rendering the closed valve fully competent throughout diastole. As these cusps cycle, there are substantial and repetitive changes in size and shape. In particular, the aortic valve cusps have nearly 50% greater area in diastole than systole. This requires complex and cyclical structural rearrangements (Sauren et al., 1980).

The heart valves have a highly layered complex structure and highly specialized, functionally adapted cells and extra cellular matrix (ECM) (Schoen, 1997). A cross-sectional view of a heart valve cusp is shown in Figure 2.2.

The layers are:

- The *ventricularis*, facing the inflow surface is predominantly collagenous with radially aligned elastic fibers.
- The centrally located *spongiosa* is composed of loosely arranged collagen and glycosaminoglycans (GAG's)
- The *fibrosa*, facing the outflow surface is composed predominantly of circumferentially aligned, densely packed collagen fibers. They are largely arranged parallel to the cuspal free edge (Hoffman-Kim, 2002).

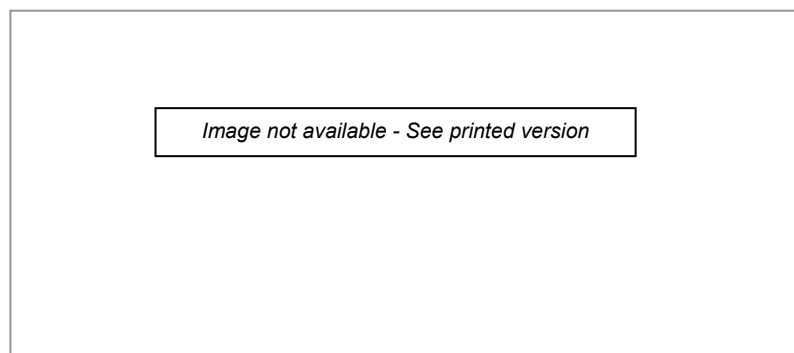


Figure 2.2

Composition of an aortic cusp

(Figure adapted from: Hoffman-Kim D, 2002)

Interstitial cells populate the matrix of heart valves and express a variety of phenotypes. A proportion of these express smooth muscle alpha actin (Taylor et al., 2000). Of the three different layers, the fibrosa provides the primary strength. The spongiosa appears to lubricate relative movement between the two fibrous layers and dissipate energy by acting as a shock absorber during closure. The elastin of the ventricularis enables the cusps to decrease surface area when the valve is open but stretch to form a large coaptation area when backpressure is applied. Interstitial cells maintain the extracellular matrix. Sufficiently thin to be perfused from the heart's blood, normal human aortic (and other) valve cusps are predominantly avascular. Although the pressure differential across the closed valve induces a large load on the cusps, the fibrous network within the cusps effectively transfers the resultant stresses to the aortic wall and annulus, a ring of tissue that surrounds and supports the aortic orifice (Schoen, 1997).

2.3 Valvular Heart Disease (VHD)

As described in the previous section, four valves control blood flow to and from the body through the heart i.e. the aortic valve, the pulmonary valve, the tricuspid valve, and the mitral valve. Patients with VHD have a malfunction of one or more of these valves. Each of these valves may malfunction because of a birth defect, infection, disease, or trauma. When the malfunction reaches a level of severity so that it interferes with blood flow, an individual will have heart palpitations, fainting spells, and/or difficulty breathing. These symptoms may progressively worsen and can result in death, unless the damaged valve is replaced (Cheitlin, 1991). There are several types of VHDs with distinct symptoms and treatments. These are:

- Mitral valve prolapse (displacement)
- Mitral valve insufficiency (regurgitation)
- Mitral valve stenosis (narrowing)
- Aortic valve insufficiency
- Aortic valve stenosis
- Tricuspid valve insufficiency
- Tricuspid valve stenosis
- Pulmonary valve stenosis
- Pulmonary valve insufficiency

VHD is a non-specific, all-encompassing term for various diseases affecting the heart valves and can be classified into two general categories: congenital and acquired. Congenital VHD is present from birth, and occurs in about 0.6% of non-premature live births. It can be caused by chromosomal abnormalities, such as trisomy 18 or trisomy 21 (Down's syndrome). In most cases, the causes of congenital valvular disease are unknown. Acquired VHD is more common than congenital VHD. Acquired VHD is generally caused by a disease or injury to the heart, which affects the individual at some point in their lifetime. An autoimmune disorder related to a streptococcus bacterium, acute rheumatic fever, may cause valvular stenosis due to calcification of the

valves. Other causes of VHD include tumors that develop in the heart muscle, injury to the chest and systemic lupus erythematosus (SLE), an autoimmune disease.

From a social, medical and financial point of view, cardiovascular disease and VHD in particular, has a global impact. According to the American Heart Foundation cardiovascular diseases cause 12 million deaths per year worldwide. This accounts for almost 50% of all deaths in the world. 300,000 procedures for heart valve repair or replacement are performed per year and finally, heart valves are currently a \$260 billion industry in the US alone.²

Two different ways of treatment of VHD are currently possible: medical, with drug therapy or surgical, with valve repair or replacement. There are two main types of faulty valve that may or may not require valvular replacement surgery. These involve valves that do not close properly and leak blood into another quadrant of the heart (regurgitation) or valves that are calcified and don't open properly (stenosis). Valvular regurgitation cause the heart to work less efficiently because it has to pump some blood twice, and usually results in an enlargement of the heart chambers because there is more blood to pump. However, in severe cases the heart is not strong enough to compensate for the efficiency loss and it results in congestive heart failure. Valvular stenosis is a cause of high blood pressure in the heart because blood builds up behind the closed valve and forces the cardiac muscle to work harder to pump blood through the heart. The heart usually compensates by growing a thicker layer of muscle. By disrupting the flow and pressure dynamics of the entire cardiac cycle, valvular disease can ultimately cause secondary heart failure. In extreme VHD cases, valvular replacement surgery has become a viable option.

² www.americanheart.org

2.4 Detection of VHD

In general, detection methods for VHD can be divided into invasive and non-invasive techniques. Noninvasive imaging techniques have been used increasingly during the past decade for the evaluation of VHD and currently these techniques have almost completely replaced invasive detection methods for the diagnosis and assessment of the severity of VHD (Cheitlin, 1991). This section discusses different non-invasive techniques and their role in the assessment of valvular disease. A brief overview is presented on the X-ray principle followed by Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). Echocardiography is the most common technique used for detection of VHD and its relevance to different valvular complications, both native and prosthetic is also discussed. Each of the techniques discussed possess specific features concerning working-principles, visualisation-quality, and accuracy.

Methods:

Cardiac auscultation, using a stethoscope, to distinguish sounds recognized as a sign of health or of disease, remains the most widely used primary method of screening for VHD. From the evaluation of the auscultation procedure the physician can recommend a secondary detection method in order to assess the valvular disorder in detail. Several non-invasive techniques are available to diagnose VHD without the help of an invasive technique. However, combinations of both types of techniques can be a useful help to obtain a detailed diagnosis of the suspected VHD (Cheitlin et al., 1997). Examples of these combinations are: catheterisation (invasive), echocardiography (non-invasive) and the use of angiocardigraphy i.e. use of x-rays following the injection of a radiopaque substance. Preferably the detection of VHD is not performed as a semi-invasive investigation and can be avoided in selected cases. Each of the techniques discussed in this section are based on different principles and each has different advantages and disadvantages. Moreover, some of these techniques are also useful for determining the performance of implanted prosthetic heart valves or TEHV-replacements.

2.4.1 X-Ray Principle

X-ray technology was invented by accident when in 1895 a German physicist, Wilhelm Roentgen, discovered X-rays while experimenting with electron beams in a gas discharge tube. Roentgen's remarkable discovery precipitated one of the most important advancements in the history of human imaging. With X-rays broken bones, cavities and swallowed objects may be detected with extraordinary ease. Modified X-ray procedures may also be used to examine softer tissue, such as the lungs, blood vessels or the intestines.

The chest X-ray provides information about the size and configuration of the heart and great vessels, as well as pulmonary vasculature, and pleural effusions. Cardiac chamber dilation, rather than wall thickening is generally perceived as an alteration in cardiac silhouette. Although current X-ray methods are not directly used for the detection of VHD, it's able to detect abnormalities in the heart and great vessels and assist in the assessment of valvular disease. The working principle is the base for the computed tomography-scanning technique that is particularly useful in the detection and assessment of valvular diseases.

2.4.2 Computed Tomography (CT)

Computed Tomography (CT) is based on the X-ray principle i.e. as x-rays pass through the body they are absorbed or attenuated (weakened) at differing levels creating a matrix or profile of X-ray beams of different strength.

CT imaging, also known as "CAT scanning" (Computed Axial Tomography), was developed in 1973 when the X-ray-based CT was introduced by Hounsfield. This technique is currently available at over 30,000 locations throughout the world. CAT scans take the idea of conventional X-ray imaging to a new level. Instead of finding the outline of bones and organs, a CAT scan provides a full three-dimensional computer model of a patient's internal organs. CT has been the basis for interventional work such as CT guided biopsy and minimally invasive therapy. The obtained images are also used

as a basis for radiotherapy, cancer treatment planning, and to determine how a tumor is responding to treatment. The image provided with this technique provides both good soft tissue resolution (contrast) as well as high spatial resolution using radiation. For this reason, CT-scanning is contraindicated to assess valvular abnormalities on patients during pregnancy.³

2.4.3 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) has rapidly gained acceptance as an accurate, reproducible, non-invasive method for optimal assessment of structural and functional parameters in patients with VHD. Due to the development of newer and faster techniques its clinical role is gradually expanding, making detection of valvular disease simpler and clearer without moving the patient. MRI is based on the principles of Nuclear Magnetic Resonance (NMR), a spectroscopic technique used to obtain microscopic chemical and physical information about molecules. MRI began as a tomographic imaging technique that produced an image of the NMR signal in a thin slice through the human body. MRI has advanced beyond a tomographic imaging technique into a volume imaging technique.

Paul Lauterbur first demonstrated MRI in small test tube samples in 1973. He used a back projection technique similar to that used in CT. Since then several improvements have been made, bringing the images of the scans closer to real-time. Finally, in 1987 a technique called echo-planar imaging was used to perform real-time movie imaging of a single cardiac cycle (Chapman et al., 1987). In that same year Charles Dumoulin introduced Magnetic Resonance Angiography (MRA) that allowed the imaging of flowing blood without the use of contrast agents.

MRI for the detection of Valvular Heart Disease.

Exact visualization of valve morphology is possible with the cross-sectional imaging modalities, using MRI and CT. These techniques may be used, if other non-invasive

³ www.imaginis.com/radiotherapy

imaging modalities, such as echocardiography (section 2.4.4) fail or provide only limited information. The main advantages of MRI compared to CT in the diagnosis of VHD, are the absence of radiation exposure and the possibility of quantitative evaluation of valve function using flow measurements. Furthermore, MRI has the capability to detect the presence of stenotic and regurgitant lesions. However, MRI instrumentation is substantially more expensive and not as widely available. A major restriction associated with this technique is that it cannot be used in patients with any metallic prosthetic devices such as pacemakers or stents.

2.4.4 Echocardiography

Echocardiography uses ultrasound to image the heart and great vessels. It is widely regarded as *the* technique of choice for evaluation of suspected VHD. An ultrasonic transducer transmits and receives the ultrasound waves. It is placed on the patients' chest wall and moved around to view different heart structures. Ultrasound waves are reflected only when they reach the edge of two structures with different densities. The reflected waves produce a moving image of the edges of heart structures.

Echocardiography is used for the determination of a wide range of heart related problems but, in particular, diseases that affect heart valves i.e. presence of aneurysms, clots, tumors and vegetations (bacterial growths) on valves. In **Appendix A1** an overview is presented on how echocardiography may be used to determine and assess common valvular diseases, both within native or implanted prosthetic heart valves (Cheitlin et al., 1997). In general, echocardiography can be divided into four sub-techniques:

- M-mode
- TEE (Trans Esophageal Echocardiography)
- 2-D
- Doppler

Each of these techniques is derived from the same principle: the "Doppler effect," defined as a measured change in the frequency of sound or light waves caused by the

motion of the source or the observer. The sub-technique M-mode is a one-dimensional view of a small section of the heart as it moves while a 2-D echocardiogram produces a moving two-dimensional slice of the heart. Doppler ultrasound is used to evaluate the velocity and turbulence of blood flow in the heart. The trans esophageal echocardiography (TEE) approach uses a special ultrasound transducer that is inserted in a patient's esophagus. With this technique it is possible to image the heart from a different orientation not seen through the conventional chest-wall approach. Unlike trans thoracic echocardiography (TTE), where the transducer is placed on the patient's chest, TEE positions the transducer behind the heart. In general, echocardiography often provides a definitive diagnosis and may use the need for catheterisation in some cases.

Echocardiography and prostheses

The clinical use of different types of prostheses are associated with different risks. Therefore, evaluations should be tailored to the patient's clinical situation and type of prosthesis. However, the evaluation of an implanted prosthetic heart valve is difficult even in the best of circumstances. In some patients with known prosthetic valve dysfunction, re-evaluation is indicated even in the absence of a changing clinical situation. "In some cases re-operation may be dictated by echocardiographic findings alone" (Cheitlin et al., 1997). Figure 2.3 shows how the 2-D echocardiography-technique visualizes a bioprosthetic aortic valve *in vivo*.

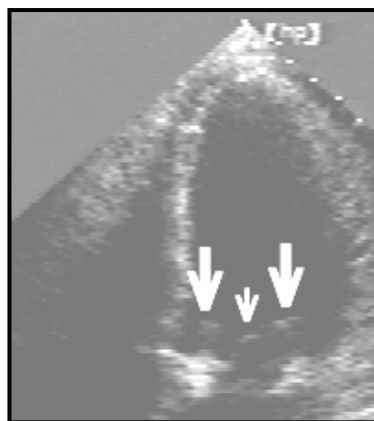


Figure 2.3

Bioprosthetic aortic valve in vivo: white arrows represent struts of valve

(Figure obtained from: www2.umdnj.edu/~shindler/prosthetic_valves.html)

Murmurs

Heart murmurs are produced by turbulent blood flow and are an indication of stenotic/regurgitant valve disease or acquired/congenital cardiovascular defects (Cheitlin et al., 1997). In valvular and other congenital forms of heart disease, a murmur is usually the major evidence of the abnormality, although some haemodynamically significant regurgitant lesions may be silent. In patients with ambiguous clinical findings, the echocardiogram is the preferred test because it may provide a definitive diagnosis. In some patients the Doppler echocardiogram is the only non-invasive method capable of identifying the cause of a heart murmur. In the evaluation of heart murmurs, the purpose of performing a Doppler echocardiogram is to:

- Define the primary lesion and its etiology and judge its severity.
- Define haemodynamics.
- Detect coexisting abnormalities.
- Detect lesions secondary to the primary lesion.
- Evaluate cardiac size and function.
- Establish a reference point for future observations.
- Re-evaluate the patient after an intervention.

As valuable as echocardiography may be, the basic cardiovascular evaluation is still the most appropriate method to screen for cardiac disease and will usually establish the clinical diagnosis. "Echocardiography should not be used to replace the cardiovascular examination but can be helpful in determining the etiology and severity of lesions, particularly in paediatric or elderly patients" (Cheitlin et al., 1997).

2.4.5 Discussion

The first line of diagnostic intervention in the determination of a VHD is still and will continue to be cardiac auscultation. By using a stethoscope, systolic clicks may easily be defined and from here a visualisation technique for further examination can be recommended.

By reviewing the available visualisation techniques it was concluded that the best and most common method currently used is echocardiography. This technique makes it possible to detect a wide range of heart valve and heart valve-related diseases (Cheitlin et al., 1997). Newer techniques such as CT and MRI may eventually replace this technique because of superior image quality, unrestricted viewing angles and the possibility of making 3D reconstructions from 2D images. In comparison to CT-scanning, MRI has the advantage that it is not limited to the axial plane. Current limitations of MRI are that it can not visualize implanted metallic prosthetic heart valves because of their magnetic field. Another restriction is the cost of an MRI apparatus, which is not comparable to the cost of an echocardiography apparatus.

Although CT and MRI evaluation of patients with VHD is almost never performed as a first line of diagnostic intervention, their performance does provide important morphologic and physiologic information concerning the etiology and status of the valvular dysfunction. Evaluation of the heart chambers and aortic artery size as well as ventricular wall thickness provide the basis for diagnosing and analysing the severity of VHD. For assessment of stenosis severity, measurement of trans-valvular pressure gradient is an appropriate measure and MRI may not confer any benefits over echocardiography.

Ultra fast CT and MRI generate high-resolution cardiac images. Ultra fast CT requires intravenous injection of X-ray contrast media while MRI does not. However, it is widely accepted that both technologies can be used to evaluate a wide range of features. These include: cardiac chamber and aortic vessel dimensions, intracardiac and extracardiac masses, ventricular hypertrophy, left ventricular mass, congenital heart disease, regional and global left ventricular function and right ventricular function.

Specifically, MRI is highly useful for detection and semi-quantitation of valvular regurgitation while ultra fast CT is not. Another major disadvantage with CT is that radiation can harm foetal tissue. Although both techniques can detect aortic and mitral valve stenosis and assess coronary artery bypass graft status, ultra fast CT is the preferred method.

A summary of the advantages and disadvantages of currently available non-invasive techniques for the assessment of valvular disease is presented in Table 2.1.

Table 2.1
Non-invasive techniques for the assessment of VHD

Technique	Advantages	Disadvantages
Stethoscope	<ul style="list-style-type: none"> • Quick • Cheap 	<ul style="list-style-type: none"> • Not accurate • No visualisation
CT-scan	<ul style="list-style-type: none"> • 3D visualisation • High contrast 	<ul style="list-style-type: none"> • Limited to one plane • Use of radiation
MRI-scan	<ul style="list-style-type: none"> • No radiation • No contrast agent • Quantitative measurements 	<ul style="list-style-type: none"> • No prosthetic valves • Expensive
Echocardiography	<ul style="list-style-type: none"> • Wide range of VHD • Cheap 	<ul style="list-style-type: none"> • No 3D visualisation • Not very accurate

2.5 Problems with artificial heart valves

Current available heart valve substitutes can be divided into two groups - mechanical and biological. The mechanical replacements may further be subdivided depending on the type of occluder, while the type of tissue is used to classify the biological substitutes. This section provides a brief overview of the currently used replacements (Table 2.2). Each type of replacement used in cardiovascular surgery is something of a compromise. The problems associated with the clinical use of mechanical and biological prostheses are compared and discussed in this chapter. Ideal replacement valve requirements are reviewed and discussed in the last part of this section (section 2.5.4). In general, assessment of the haemodynamic performance of both types of heart valve substitutes are based on three main criteria;

- The replacement should function efficiently and present a minimum load to the heart.
- The substitute should be durable and maintain its efficiency for the patient's lifespan.
- The replacement should *not* cause damage to molecular or cellular blood components or stimulate blood clotting.

Table 2.2

Overview of heart valve substitutes

Mechanical Valves	Tissue Valves
<ul style="list-style-type: none">• Ball Valves• Disk Valves	<ul style="list-style-type: none">• Animal Tissue Valves (Xenografts)
<ul style="list-style-type: none">• Single Leaflet Disk Valves• Bileaflet Disk Valves	<ul style="list-style-type: none">• Human Tissue Valves (Homografts, Autografts, Ross Procedure)

2.5.1 Mechanical Valves

Many prosthetic heart valves have been implanted worldwide during the last decades. Although these valves have undergone many improvements, the ideal mechanical heart valve has not yet been developed (Ellis et al., 1998). As stated in the introduction chapter, problems associated with mechanical prosthetic heart valves include thrombosis, haemolysis, tissue overgrowth, infection (endocarditis) and excessive pressure gradients (Wright and Temple 1971; Magilligan et al., 1980). The problems with most of the existing heart valves are well documented in the literature and alternative designs have been suggested and hydro-dynamically examined by many researchers (Chadran and Cabell, 1984). An overview of the evolution of the mechanical heart valve is presented in **Appendix A2**. In this section, an overview of the literature is presented on how two of the most common complications, thrombosis and haemolysis, are related to the clinical use of mechanical valve prostheses.

Thrombosis:

All clinically used mechanical valves have one main problem in common i.e. the increased risk of blood clotting. It has been suggested that the locally altered fluid mechanics increase shear-stresses and strongly influence the creation of blood clots. When blood clots occur in the heart, there is a high risk of a heart attack (Caro et al., 1978). More recent evidence indicates that a major proportion of shear stresses are associated with thrombosis occurring in altered flow fields, such as an atherosclerotic plaque in a stenosis (DeWood et al., 1980). Furthermore, several studies have suggested that rupture of an arterial plaque initiates thrombus formation (Alpert, 1989). The initial cause of plaque disruption is still unknown. It is known, however, that the endothelium has an abnormal response when exposed to turbulent flow. It is also believed that turbulent flow contributes to the activation and deposition of platelets that contribute to blood clotting. Furthermore, some investigators have suggested that haemodynamic forces have the potential to activate endothelial cells, which in turn are able to accommodate changing physiological conditions (Gimbrone et al., 1989). Therefore it has been hypothesised that a major cause of thrombosis may be directly associated with mechanical heart valves. As a result, to prevent blood clots, mechanical valve recipients must take anti-coagulant drugs (eg. sodium warfarin) for their lifetime. This effectively

turns patients into borderline haemophiliacs. The anti-coagulant used may also cause birth defects in the first trimester of foetal development, and rendering mechanical valves unsuitable for women of childbearing age. Another problem with most mechanical valves is that they have a gap between the disc edge and the housing's inside wall to prevent jamming between the disc and the housing. The size of this gap is a determinant of the regurgitation during the closed phase of the valve cycle. These leakage gaps may lead to increased haemolysis due to the high shear stresses with the gap flow and within the turbulent mixing region of the backflow jet (Knott et al., 1988). It has been reported that the leakage jet velocities are three to five times higher than the peak forward flow velocities.

Haemolysis

Destruction of red blood cells (RBCs) is a condition associated with the clinical use of mechanical heart valves. An erythrocyte (RBC) consists of flexible membrane and haemoglobin, which endows blood with its large capacity for carrying oxygen. The RBC is capable of extreme distortion and is able to deform into an infinite variety of shapes without stretching its membrane. However, with very severe deformation as occurs when RBCs are exposed to a high shear stress, the membrane will become tense and stretched, lose its flexibility and may consequently rupture. The RBC loses its haemoglobin, through the ruptured membrane, a process known as haemolysis.

Haemolysis occurs in intensely turbulent flow such as the downstream area of a mechanical heart valve. Several experiments have been conducted to investigate the magnitude and duration of the produced shear stresses required to haemolyse RBCs. Shear stresses in the range of 1500 to 4000 dynes/cm² have been shown to cause lethal damage to RBCs (Blackshear et al, 1965; Sallam and Wang, 1984). Lower levels of RBC destruction, are possible if the total exposure time is low. Sublethal damage can reduce both the elasticity of the RBC membrane and the lifetime of the RBC itself. Chronic conditions can be a precursor to anaemia (deficiency of RBCs) and therefore shear stresses as low as 500 dynes/cm² may be clinically important. Bulk forward-flow velocity and turbulent shear stress studies have been used extensively to investigate valves (Figure 2.4). While improvements in valve design have been introduced to

reduce turbulence or alter flow-velocity contours, most of these changes have produced insignificant differences in currently used mechanical heart valves. Leakage patterns of mechanical heart valves have been studied as these patterns relate to hinge mechanisms and to haemolysis. Very high backflow with turbulent stresses in the order of 9000 dynes/cm² have been documented in a variety of tilting-disc designs, well above values believed to cause RBC damage. From a haemodynamic point of view, leakage through mechanical valves during the closure phase is substantially more important than that observed in forward flow (Knott et al., 1988; Ellis et al., 1998). For future valve designs, an understanding of the influence of the leakage gap and hinge dimensions is crucial to the improvement of haemodynamic performance and minimization of haemolysis and/or thromboembolic events.

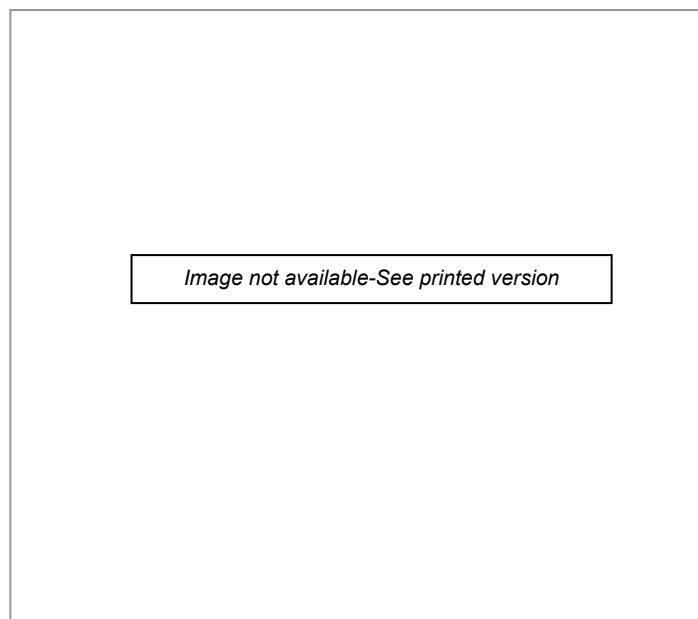


Figure 2.4
Hypothetical shear fields and red cell path lines through a bi-leaflet heart valve

(Figure from: http://www.ctdigest.com/May99/2_rev2/2_rev2.html.)

2.5.2 Biological Valves

Bio-prosthetic valve leaflets are fabricated from a combination of chemically treated xenogenic tissue and/or synthetic materials. The valve-frames are usually flexible in the axial direction but effectively rigid in the plane of the sewing ring in order to maintain position. The type of tissue is used to classify tissue valves and this originates from either animal or human tissue. The type of tissue used can be either valve tissue or non-valve tissue. Human tissue valves, transplanted from another person are called homografts, while autografts are valves transferred from one position to another within the same patient. The most common autograft procedure involves transferring the pulmonary valve to the aortic position, called the Ross Procedure (Ross, 1967). In general, tissue valves have better haemodynamic performance than mechanical replacements, although their limited durability is a major drawback (Borttolotti et al., 1987). In this section the problems related to the clinical use of three types of tissue valves are discussed A. Homografts, B. Autografts and C. Xenografts.

- A. Homografts/Allografts: Homografts or Allografts are human tissue valves. After death, the valve is removed treated with antibiotics and transplanted into the recipient. There are usually no problems with rejection of the valve and patients do not require any type of immunosuppressive therapy. Homograft valves are donated by the donor family and then preserved in liquid nitrogen (cryopreserved) until needed. These valves tend to have exceptionally good haemodynamic profiles, a low incidence of thromboembolic complications and do not require chronic anticoagulation (Borttolotti et al., 1987). Such valves are especially efficacious for replacing those excised because of endocarditis (O'Brien et al., 1987; Tuna et al., 1990). Cryopreserved allografts are unable to grow, remodel, or exhibit active metabolic functions and their usual degeneration cannot be attributed to immunologic responses. As with heart transplants, homograft availability is limited by a lack of suitable donors.

- B. Autografts (Ross Procedure): Autografts are valves taken from the same patient in which the valve is implanted. The most common autograft procedure is the Ross procedure developed by Donald Ross in the sixties and has become widely accepted (Ross, 1967). The Ross procedure is used in patients with diseased aortic valves. The abnormal aortic valve is removed and the patient's own pulmonary valve is transplanted to the aortic position. A homologous pulmonary valve is then used to replace the patient's pulmonary valve (Figure 2.5). The main advantage of the Ross procedure is that the patient receives a living valve in the aortic position. The hope is that in children, the valve will continue to grow as the child grows older. Other potential benefits are better haemodynamics (there is essentially no pressure drop across the valve) and better durability.

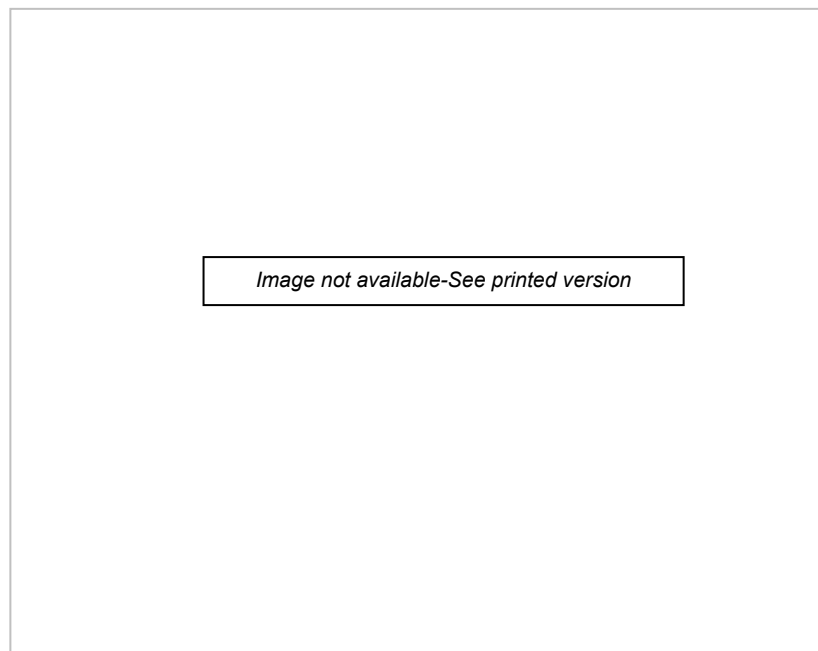


Figure. 2.5
Schematic of the Ross procedure

(Figure adapted from: Kouchoukos et al., 1994)

However, it remains unclear whether the durability of valves implanted by the Ross procedure is better when compared to porcine or pericardial valves (David et al., 1996). The Ross-procedure is a technically difficult procedure for a surgeon and involves considerable skill and time. The pulmonary valve must be sculpted to fit the aortic root and the pulmonary homograft must similarly be shaped to fit the pulmonary root. Special measurements must be made to fit the transplanted pulmonary valve into the aortic root. There are many potential complications in less skilled hands; the most common one is leakage of the valve after the procedure. However, many patients have small amounts of aortic regurgitation and some have moderate or even severe amounts and require a second operation for valve replacement. Other potential complications include stenosis of the coronary artery, right-sided endocarditis (since a prosthetic valve has now been implanted in the pulmonary position) as well as the usual complications of valve replacement (David et al., 1996).

- C. Animal Tissue Valves (Heterografts, Xenografts)

Animal tissue valves are called xenografts from the Latin prefix "Xeno-" for foreign or heterografts. Xenografts may be of valve tissue, typically porcine valve tissue, or they can be of non-valve tissue, eg. bovine pericardium. The term heterograft has the same meaning but the prefix comes from a different root, "hetero-" meaning "different".

All three types of tissue valves discussed are sterilised with glutaraldehyde before human use and maintain a low rate of thromboembolism without anticoagulation. Stroke and bleeding problems rarely occur with these types of valves. However, valve failure with structural dysfunction due to progressive tissue deterioration (including calcification and non-calcific damage) is a serious disadvantage that undermines the attractiveness of tissue valve substitutes (Schoen et al., 1992). Moreover, the calcification-process in bio-prosthetic valves is accelerated in children and young adults. The degradation mechanisms of bio-prosthetic valves are progressive and the rate of failure is time dependent. They usually need replacement within ten to fifteen years or sooner in younger patients. Bovine pericardial valves suffer from poor

durability, and usually perform significantly worse than porcine xenografts (Hammermeister et al., 1993). There is also a concern for the transmission of prion diseases i.e. BSE (cattle) and scrapie (sheep). There are currently no tests available for the diseases and the diseases are uniformly fatal. The long-term mortality of patients with tissue valves replacements do not differ significantly compared to those with implanted mechanical valves. Comparison between mechanical valves and bio-prostheses from *in vivo* trials such as the Edinburgh trial and the Veteran trial demonstrated that the mechanical-valve and bio-prostheses groups did not differ for long-term mortality or total valve-related complications. Other important complications, including valve infection (endocarditis) and non-structural dysfunction, affect both tissue and mechanical valves (Schoen and Levy, 1999).

2.5.3 Mechanical versus Biological

Most of the clinically used valves are not yet ideal, but patients with implanted valves can lead a relatively normal life. During the past three decades more than 80 different prosthetic valves have been trialled and currently about 20 of these are still in clinical use. A twelve-year comparative study of mechanical vs. bio-prosthetic valves found that approximately one third of all heart valve replacement recipients had prosthesis-related problems within 10 years of surgery (Bloomfield et al., 1991). Despite all the research and development efforts, there are still no ideal manufactured valves, particularly when comparing the haemodynamic performance. **Appendix A3** summarizes the respective advantages and disadvantages of mechanical valves, homografts, xenografts, and bioprosthetic valves.

2.5.4 Discussion: The ideal Replacement

Heart valve prostheses have been used successfully for the treatment of VHD, and it cannot be disputed that hundreds of thousands of lives have been saved and extended by their use. However, many currently used heart valve replacements are associated with problems directly related to the design of the valve. Therefore, it may be useful to describe some of the design goals for an ideal repair material or replacement valve. The design goals for an ideal valve replacement may be divided into basic design goals and other desirable characteristics as shown in Table 2.3.

Table 2.3
Ideal requirements for heart valve substitutes

Basic design goals	<ul style="list-style-type: none">• Prompt and complete closure• Non-obstructive• Non-thrombogenic• Non-haemolytic• Last the lifetime of a patient• Chemically inert• Infection resistant
Other desirable characteristics	<ul style="list-style-type: none">• Repair of cumulative injury• Provide ongoing remodeling• Grow in maturing recipients• Tissue engineered• Not annoying to the patient (noise free)

The ultimate valvular replacement would be a device that incorporates the basic design goals with the other desirable characteristics. Reviewing the points presented in Table 2.3, it is apparent that biomedical engineers will need to focus on a biological substitute, to meet demands such as self-repair and growth. Besides these demands, limited

durability of currently used biological replacements in general presents a major drawback for clinical use (Borttolotti et al., 1987). Furthermore, all current biological heart valve substitutes are unable to grow, repair, or remodel within the recipient (Mitchell et al., 1998). This universal limitation is most detrimental to young patients in need of heart valve replacements because successive surgery is required to replace the implanted valves that cannot grow with the child (O'Brien et al., 1999). One solution that may meet all of these requirements is to grow an identical copy of a healthy valve with cells from the recipient. Using this strategy, many different fields that include design, engineering, biology and medicine need to be combined as a 'multidisciplinary' approach.