Development of a Muscle Powered Blood Pump: Fluid Mechanic Considerations

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Abstract

A lack of donor organs for heart transplantation has stimulated research effort into ventricular assistance devices for the past 30 years. Several devices have seen clinical use, but none have delivered sufficient totally implanted support. Skeletal muscle from the patient's own body, conditioned for fatigue resistance, may provide a viable treatment for end stage cardiac failure. However, existing techniques of harnessing muscle power, either directly to the heart or by constructing auxiliary skeletal muscle ventricles, have not achieved effective long-term cardiac assistance. A new concept for utilising the latissimus dorsi muscle for circulatory support has been devised that promises several physiological, mechanical and surgical advantages over current approaches. It is the subject of an application lodged at the European Patent Office by the University of Glasgow.

The potential of the device to promote thrombogenesis needs to be minimised, and it is to this end that the work described in this thesis was initiated.

Prototype artificial ventricles were fabricated in polyurethane and incorporated into a mock circulatory loop. The aim was to identify the best design from four geometrical variations in terms of fluid flow; specifically to characterise stagnation regions, fluid element residence times and high shear stresses. A novel fluid tracer technique was developed, utilising image processing, to produce colour maps of tracer concentration inside a pumping chamber. Three-dimensional fluid flow was characterised with a fluorescent particle tracer method and the aid of animation software. Areas of high shear stress were identified for further examination. These regions were then magnified and shear stress measurements made within them. With a view to future work *in vivo*, the bench model has been used to calibrate a radioactive tracer technique suitable for investigating the flow characteristics of blood in such a device.

The best design was identified and recommendations for further design improvement were made..

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Chapter 0. Overview

0.1 Background

There is a world-wide need for ventricular assistance devices (VADs) for people in end-stage cardiac failure because of the lack of donor organs for transplantation. Existing VADs, and many currently being developed, are not ideal because they require external power supplies, limiting patient mobility, and are a post-operative infection risk.

Conditioned skeletal muscle can provide power at a similar to the heart, indefinitely. Cardiomyolplasty, whereby the heart is wrapped with one of the patient's own conditioned muscles (usually the latissimus dorsi), has been performed upon hundreds of patients world-wide. This procedure does improve the cardiac function in most patients, but the improvements are less than would be expected given the mechanical power available. The muscle provides an extra blood supply and limits hypertrophy, rather than assisting the compression of the heart.

Ventricles have been constructed from conditioned skeletal muscles and shown promising short term results *in vivo*, but the muscles tend to ischemia over a period of time because they cut off their own blood supply when pumping blood.

0.2 The Skeletal Muscle Ventricle

Conditioned skeletal muscle can provide similar levels of power as a healthy human heart, but its structure is intrinsically different. Skeletal muscle can only shorten by a small fraction of its length (around 10%), and peak power development occurs at lesser shortenings. Consequently the Department of Cardiac Surgery at Glasgow Royal Infirmary set out to develop a skeletal muscle powered VAD that more efficiently harnessed the muscle's mechanical output. The proposed device is the subject of a patent application lodged with European patent office.

The department of Cardiac Surgery at Glasgow Royal Infirmary has developed both biological and synthetic artificial heart valves. In particular, work is currently underway to develop the department's polyurethane heart valve into a viable medical product. The work of this thesis represents a natural progression from the polyurethane heart valve development, and utilises the valves in the proposed VAD. The artificial ventricle is also to be constructed from polyurethane.

0.3 Fluid Flow

It is generally accepted that damaged blood elements can initiate the clotting process. If a blood clot (thrombus) forms on a VAD blood contacting surface then it may compromise the VADs

operation. There is also a danger that the thrombus will detach from the surface possibly occluding blood vessels and damaging vital organs, which can be fatal. Blood clotting can be induced by fluid shear stresses and artificial surfaces. Consequently fluid flow studies have been carried out on various blood pumps for the purposes of minimising blood trauma inducing, stagnating and re-circulating regions of flow.

0.4 Brief Overview

The aim of this thesis was to develop methods for analysing the fluid mechanics of a polyurethane pumping chamber, and then to apply them for the purposes of design development.

An experimental rig was constructed to simulate the physiological load upon a VAD, and to actuate it. Polyurethane ventricles were manufactured, by a wax dipping method, and incorporated into four different VAD geometries. A novel fluid tracer method was developed to identify regions of stagnating or re-circulating fluid and to characterise overall residence times of fluid elements within the artificial ventricles. Colour concentration maps of tracer were animated to assist analysis. This method was correlated with the clinical radionuclide tracer method of choice for assessment of ventricular function. The correlation of both methods allows the extension of *in vitro* findings to the experimental *in vivo* situation.

A fluorescent tracer particle method was used to characterise the complex three-dimensional fluid flow in each of the four blood pump designs. Computer animations were constructed from the different sections taken of the fluid flow in each design for a complete pumping cycle. Regions of high shear stress were identified and then shear stress measurements made in these areas.

The optimal design of the four tested was identified, in terms of flow considerations.

Chapter 1. Introduction

1.1 Heart Disease

Heart disease is one of the principal causes of death in the Western world. For a number of patients with heart failure the only long term solution is heart transplantation. Unfortunately the demand for donor hearts far exceeds the available supply and for some patients transplantation is not possible, for medical reasons. Clearly there is a need for another option. One method is to connect a heart assistance device to the circulation to reduce the load upon the recipient's heart. A large variety of devices is discussed here; some have seen clinical usage and others are developmental. These devices are used to keep patients alive until a donor heart can be found and may also allow the heart to rest and recover by itself. Devices have been designed which can be powered by skeletal muscle from the patient's own body or an external source such as electricity. They can be made from components of the patient's own body (such as blood vessels and muscle), artificial materials (such as plastics, metals and cloth) or a combination of the two.

1.2 The Heart

The heart is responsible for supplying the entire body, including itself, with oxygenated blood and transporting de-oxygenated blood to the lungs (1). Essentially it is a muscular pump, consisting of four chambers, the left ventricle and atrium for oxygenated and the right ventricle and atrium for de-oxygenated blood, figure 1.1. Rhythmic contractions of the ventricles pump blood, approximately once per second at rest. Flow through the heart is controlled by passive, unidirectional valves. Oxygenated blood, from the lungs (pulmonary circulation), goes to the left atrium then into the left ventricle through the mitral valve and exits through the aortic valve to the aorta. De-oxygenated blood, from the systemic circulation, goes to the right atrium then into the right ventricle though the tricuspid valve and exits through the pulmonary valve to the pulmonary artery. At the beginning of the ventricular filling phase (diastole) the aortic and pulmonary valves are closed. The heart then dilates and expands reducing the pressure inside each ventricle below that of the corresponding atrium, figure 1.2 (2). This pressure difference opens the inflow valves (mitral and tricuspid) allowing blood to enter and fill the ventricles during diastole, after about 70% of ventricular filling has occurred the atria contract to complete filling of the ventricles. Next the ventricles contract, at the beginning of systole, and the pressure inside them increases above that of the atria so closing the mitral and tricuspid valves. The ventricles continue to contract. Pressure in the left ventricle rises above the diastolic pressure in the aorta (80 mm Hg) and the right

ventricular pressure above the diastolic pressure in the pulmonary artery (10mm Hg). The aortic and pulmonary valves open and blood is ejected from the ventricles (systole). Ejection is rapid at first then slows as emptying progresses until the pressure inside the left ventricle drops below that of the aorta and inside the right ventricle below the pulmonary artery. There is some blood flow against the negative pressure gradient for a short time afterwards due to momentum, then the pulmonary and aortic valves close. The left ventricle pumps oxygenated blood to the whole body and in consequence is thicker walled than the right ventricle, which only has to pump deoxygenated blood to the lungs (the resistance to fluid flow of the body being more than that of the lungs).

The cardiac output of an average healthy adult heart is (1):

Stroke volume (volume each ventricle ejects each cycle)	70 ml per ventricle
Pumping rate	72 beats per minute
Flow rate at rest	5.04 L/min per ventricle.

During exercise the flow rate may reach 35 L/min.

Typical peak ventricle pumping pressures are (3):

Peak left ventricular pressure	120 mm Hg
Peak right ventricular pressure	25 mm Hg

1.3 Malfunction of the Heart

In heart disease the normal operation of the heart is compromised which can result in total heart failure and death. There are many more people requiring heart transplantation than there are donors. In the United States it is estimated, depending upon selection criteria, that 15,000 patients could benefit from a replacement heart annually, while there are only 400 to 1,100 hearts available (4,5). Also, in the USA, heart donor availability is not keeping pace with demand; in 1988 512 patients died while awaiting heart transplantation, in 1989 527 died and in 1990 650 died (6). In the UK there were 259 heart transplants in 1991, 316 in 1992, 297 in 1993 and 310 in 1994 recorded on the national transplant database.

Clearly a solution other than transplantation is required.

It is possible to help some sufferers with a pumping device to assist either the left, right or both ventricles. At present these devices are used to keep a patient alive long enough for heart transplantation to be performed, a procedure known as bridging to transplantation (7-9). Alternatively they may be used for a short time to enable the heart and other vital organs to recover

(9,10). A heart assistance device that is totally implantable, including the power source, and has the potential for permanent long term could improve the quality of life of many people.

1.4 Heart Assistance Devices

A heart assistance device is a pump that aids the heart in its task of circulating blood. They come in many forms and can be connected in a variety of ways: such as from atrium to aorta or ventricle to aorta. They are used to assist either the left, right (uni-ventricular assistance) or both ventricles (bi-ventricular assistance). They can be categorised by power source: muscle powered and non-muscle powered, and produce pulsatile or continuous fluid flow.

1.4.1 Muscle Powered Cardiac Assistance

It would be highly advantageous to use the patient's own skeletal muscle as the power source for cardiac assistance, because it is clearly biocompatible and would require no external, to the body, power source. Early investigations were unsuccessful because skeletal muscle cannot normally produce cardiac levels of power for sustained periods (11).

1.4.1.1 Muscle

Muscle cells have a special ability for generating force and motion, which is an extension of the basic contraction process common to all cells. Muscle cells are generally divided into three types: skeletal, cardiac and smooth (1,3).

Smooth muscle surrounds hollow organs such as blood vessels, intestinal tract, the stomach and air passages to the lungs. It is also present in other organs such as the spleen. Contraction of the smooth muscle surrounding hollow organs can propel the contents through the organ (e.g. intestinal tract), or regulate the flow of contents by varying tube diameter (e.g. arteries). Smooth muscle contraction is not usually under conscious control.

Most skeletal muscle is attached to bones and its contraction is under conscious control. The movements produced by skeletal muscle are primarily related to interactions between the body and the external environment. Skeletal muscle is composed of individual fibres that are arranged in parallel, so that the force developed by a muscle is the sum of that produced by the fibres. Skeletal muscle normally contracts and develops tension only when activated by nervous stimulation. Contraction is described as isometric when a muscle develops tension, but does not change length. When muscle length changes during contraction against a constant force then the contraction is referred to as isotonic.

A skeletal muscle given a single stimulus responds with a single rise and fall in tension called a twitch, figure 1.3 (12). Two twitches separated by a suitable time interval produce the same force records, but if the second stimulus is given before the first twitch has finished then the second twitch reaches a higher peak tension. Bringing the twitches closer together increases this effect, and applying a continuous train of stimulation can yield a constant tension with the stimulation frequency imposing a little ripple, an *unfused tetanus*. Increasing the frequency of the stimulation raises the mean force and reduces the rippling effect until there is no increase in mean force, producing a *tetanic fusion* or *tetanus*. The tetanic fusion occurs at a stimulation frequency of about 50 or 60Hz in mammalian muscle at body temperature.

The passive tension, exerted by an unstimulated muscle, and the tension a muscle develops when stimulated vary with the length of the muscle fibre. There is an optimal length at which a muscle produces maximum tension. In the body, where most skeletal muscles are attached to bones, the relaxed length of muscles is near to the optimal length for force generation.

When a skeletal muscle is subjected to a continuous train of stimuli that produces a maximal tetanic contraction the tension developed eventually declines. This failure of a muscle to maintain tension as a result of previous activity is known as muscle fatigue. Fatigue can also occur if twitches are repeated frequently enough over a period of time. Low frequency twitches can be repeated indefinitely in certain types of skeletal muscle with no signs of fatigue. If a fatigued muscle is allowed to rest then it can recover its ability to contract upon re-stimulation. The recovery depends upon the type of activity undergone by the muscle. A muscle will fatigue rapidly if stimulated at a high frequency, but will also recover rapidly from fatigue.

Three types of muscle fibres can be defined with different mechanical characteristics, table 1.1.

Table 1.1. Characteristics of the three types of skeletal muscle fibres.

	Oxidative slow fibre	Oxidative fast fibre	Glycolytic fast fibre
Speed of contraction	Slow	Fast	Fast
Rate of fatigue	Slow	Intermediate	Fast

Cardiac muscle, as the muscle of the heart, propels blood through the circulatory system by its contraction. Cardiac muscle is generally of the slow fibre type and its fibres are dependent upon a continuous supply of oxygen. The fibres are considerably shorter than those in skeletal muscle. Heart muscle, in a normal healthy human, contracts rhythmically and continuously, and is not affected by fatigue.

Using skeletal muscle to power a cardiac assistance device has not been practicable until recently due to the problem of skeletal muscle fatigue. A skeletal muscle may be required to continuously produce the power, at a similar magnitude to the heart in a resting human, to be of use for cardiac assistance. Salmons and Sreter demonstrated that rabbit skeletal muscle could substantially improve its fatigue resistance after twelve weeks of continuous electrode stimulation, at 10Hz (13). The muscle characteristics were largely transformed from those of fast contracting muscle to the oxidative slow type. A transformed muscle's response to a single stimulation had been slowed and its maximum tetanic tension reduced by more than half. Koller *et al* demonstrated fatigue free operation of sheep latissimus dorsi at 70 contractions per minute after 22 weeks of stimulation (14).

Muscle power can be harnessed directly to the cardiovasculature to provide *direct muscle powered* assistance or, in conjunction with other materials such as plastics, metals and pericardium, to provide *indirect muscle powered* assistance. Devices in both categories are discussed in the following sections.

1.4.1.2 Direct Muscle Powered Assistance

1.4.1.2.1 Myoplasty

Myoplasty means the manipulation of muscle. Myoplasty techniques involve the moving and manipulation of the latissimus dorsi, which is a large isosceles triangle of muscle with a tendon attachment and blood supply at the apex (15). The latissimus dorsi is a large powerful muscle of the back. The side of the muscle opposite the apex (the distal end) is attached to the lower half of the spine and the apex (the origin) is connected to the shoulder. Moving the latissimus dorsi will affect a patient's ability to perform certain movements.

1.4.1.2.2 Cardiomyoplasty

The first successful clinical dynamic cardiomyoplasty was reported in 1985 by Carpentier and Chachques (16) using the latissimus dorsi. The patient was still alive after four months. The left ventricular ejection fraction was 56% without assistance and 69% with the latissimus dorsi being stimulated, as measured with a Tc^{99m} heart scan (the application of this procedure to an artificial pumping chamber is described in chapter 4). In this procedure the muscle is freed from its normal position and the end opposite the tendon attachment is wrapped around the heart while the tendon is attached to an upper rib (17). The muscle is then stimulated in synchrony with the heart by a pacemaker type device that initially trains the skeletal muscle to become fatigue resistant like

cardiac muscle. More than 400 applications of cardiomyolplasty have been made, world-wide, with the majority of patients showing symptomatic improvement, but haemodynamic improvements have not been consistently demonstrated (18).

It is unclear how or if this method assists the heart. It may reinforce the myocardial wall and prevent further dilation of the heart or assist with contraction of the heart (11,19). It is likely that benefits derive from both. A conditioned latissimus dorsi assisting an average, healthy, heart in this configuration would approximately reduce its length by the fraction 0.092, as discussed by Salmons and Jarvis (11). This fraction was reached by calculating the wall stress necessary to oppose a pressure of 120 mm Hg, the corresponding velocity of muscle contraction and then the length of muscle shortening possible during 250msec. For a typically hypertrophied heart an approximate reduction in muscle length of 0.03 would occur because, by Lamé's equation for hoop stress (20), the muscle needs to generate a larger force to compress the heart, thus shortening more slowly. When pressure, $\boldsymbol{P}$, is confined to a cylinder of internal radius $\boldsymbol{R_i}$ and external radius $\boldsymbol{R_o}$ then Lamé's equation for hoop stress, σ_θ, takes the form of equation 1.1, where the stress is measured within the wall at a radius $\boldsymbol{R}$.

$$\sigma_\theta = \frac{\boldsymbol{P}.\boldsymbol{R_i^2}}{\left(\boldsymbol{R_o^2} - \boldsymbol{R_i^2}\right)} \cdot \left(1 + \frac{\boldsymbol{R_o^2}}{\boldsymbol{R^2}}\right) \qquad \text{Equation 1.1}$$

These small reductions in muscle length and hence muscle wrap circumference would yield small improvements in stroke volume. Applying a small displacement to a "short and fat" pumping chamber would, potentially, yield a much larger stroke volume and hence greater cardiac assistance. Also the force generated by skeletal muscle is dependent upon the muscle preload which may be difficult to control in cardiomyoplasty. The initial muscle contraction length will be difficult to optimise because the inner and outer circumferences of the muscle wrap are different.

A hypertrophied heart could be too big to wrap with a latissimus dorsi unless the muscle is used in two sections, bridged with some other material or both latissimus dorsi used. Each solution would involve additional trauma of the muscle and more complex surgery.

A further disadvantage of cardiomyoplasty is the deterioration of the conditioned skeletal muscle, as discussed by Oakley et al (21). They conducted experiments, with sheep latissimus dorsi, to isolate the contributions of electrical stimulation, mobilisation and loss of normal resting tension to muscle damage. Operating the muscles at 80%, as compared to 100%, of their resting lengths was found to be the single most damaging factor. Muscle damage was characterised by less normal fibres, and more connective tissue and fat. The worst damage was observed when all three factors

were combined. Damage was significantly more severe in the distal rather than the proximal parts of the muscles. The distal part of the muscle, furthest from the main blood supply, is wrapped around the heart and when contracting it is likely that it will constrict its own blood supply, resulting in muscle ischemia.

Oakley et al suggested that an undesirable effect of cardiomyoplasty is the displacement of the heart caused by contraction of the latissimus dorsi, because the skeletal muscle is fixed to the skeleton at one end, while the other is relatively free to move (18).

1.4.1.2.3 Aortomyoplasty

Skeletal muscles can, instead, be wrapped around the aorta and stimulated by a pacemaker to contract and provide cardiac assistance by counterpulsation (pumping during diastole) (22). This method has many disadvantages similar to cardiomyoplasty such as skeletal muscle preload control difficulty, possible constriction of muscle blood supply and distortion of the aorta during contraction. A skeletal muscle wrapped around the aorta may well be able to reduce its length by more than a skeletal muscle wrapped around the heart, because the wrap will be of a lesser radius so the muscle could compress the aorta with less force and contract with greater velocity.

The endothelial lining of the aorta could be damaged by the imposition of a non-physiological contraction regime.

1.4.1.3 Indirect Muscle Powered Assistance

Skeletal muscle can be more efficiently harnessed by using artificial materials. These devices have yet to be used clinically, but promising results have been reported in animals.

1.4.1.3.1 Skeletal Muscle Ventricles

Skeletal muscle can be wrapped around a sac or cylinder made of synthetic or biological material, with or without the use of valves to direct circulation, to form an artificial ventricle (23). The ventricle can be manufactured in various geometries by wrapping it around different formers, such as a cylinder, cone or ellipsoid and connected to the circulation. As a sac is being compressed, the heart or aorta is not traumatised by repeated external contraction, however foreign material may be put into contact with blood, increasing the likelihood of coagulation.

Similarly to cardio and aortomyoplasty contraction of the conditioned muscle may constrict its own blood supply, inducing muscle ischaemia, and preload control may be difficult. Badylak *et al* measured reduced muscle blood flow in skeletal muscle ventricles during contraction, constructed from dog rectus abdominus muscle, which was associated with decreased ventricle output (24). Stephenson has directed research work upon skeletal muscle ventricle development for over a decade, and recently reported the survival of 3 dogs for more than two years, with continuously operating skeletal muscle ventricles (25). Of the five non-surviving dogs no deaths were attributable to thromboembolism or ventricle rupture. The ventricles were constructed from conditioned latissimus dorsi muscle and lined with pericardium and connected to the descending thoracic aorta by two conduits. The aorta between the two conduits was closed, directing all descending aortic blood flow through the ventricle with the intention of reducing fluid stagnation regions and, in turn, the potential for thrombosis. No valves were used so, to assist the heart, the muscle was stimulated to contract during diastole to provide counter-pulsation. The same research group has also used a skeletal muscle ventricle to pump blood from the apex of the left ventricle to the descending aorta (26). Valves controlled the direction of fluid flow through the blood pump, while narrowing the aorta just before the connection of the blood pump outlet served to direct blood flow through the skeletal muscle ventricle. Increasing blood flow through the ventricle was done to combat thrombus formation in the pump circuit found in an earlier study, with skeletal muscle ventricles constructed in the same way. Connecting the pump in this way allowed the pressure within it to drop to diastolic levels between contractions, thereby allowing increased blood flow to the muscle reducing ischemia. Lining artificial surfaces inside skeletal muscle ventricles with endothelial cells to circumvent the blood and artificial surface interface problem was also reported by this group (27).

1.4.1.3.2 Skeletal Muscle Power Conversion

Skeletal muscle contraction can be converted to mechanical, electrical or hydraulic power and thus drive a heart assist device. The muscle can be configured to pull along its length and compress a pumping chamber (19). The force generated by the latissimus dorsi could be harnessed *in situ* by compressing a pumping chamber between the muscle and ribcage, but this requires the muscle to apply force perpendicular to its direction of contraction (28). A typically small muscle length reduction would not reduce the pumping chamber volume appreciably.

The force generated by the muscle could be used to produce hydraulic pressure that in turn drives a cardiac assist device. This is a flexible arrangement for placement as various muscles could be

used. The only energy transfer losses would be through fluid friction, compliance of the drive line walls and leakage of fluid. Muscle could be formed into a ventricle and wrapped around a pumping chamber to produce hydraulic pressure to drive a ventricular assistance device (VAD) (29), but this method has similar disadvantages to those ascribed to skeletal muscle ventricles, in the previous section. A better approach would be to use the muscle in a linear configuration, such as actuating a piston which in turn powers a pumping device (30).

Electrical devices not designed with skeletal power in mind could be used, but this approach is inefficient as two power conversions are necessary: mechanical to electrical to mechanical. Waste power as heat may cause problems, such as denaturation of proteins.

1.4.2 Non-Muscle Powered Cardiac Assistance

Non-muscle powered cardiac assistance devices are driven by electricity or fluid pressure (pneumatic, hydraulic). The first successful clinical use was in 1963, as described by DeBakey (31), with an externally driven pneumatic pump. A portable heart assistance device was first implanted in 1991 as reported by Goldsmith (32). Several different non-muscle powered devices are discussed in the following sections.

1.4.2.1 Intra-Aortic Balloon

This is a balloon that may be placed in the descending thoracic aorta via the femoral artery. The balloon is inflated in diastole and deflated during systole thus providing counterpulsatory assistance to the heart typically of 10-20% of cardiac output, and increasing coronary artery perfusion, in this configuration. It is safe, easy to use, cheap and complications are uncommon, but it can displace blood from the aorta back into the left ventricle and put a strain upon the aorta when it inflates. Since the first clinical trials of the intra-aortic balloon pump in the 1960s it has seen major world-wide usage for emergencies and intensive care applications (33,34).

1.4.2.2 Artificial Ventricles

There are many different designs in this category of non-muscle powered assistance. In general the pumps consist of a power source and pumping chamber or ventricle. The ventricles are actuated by fluid pressure (hydraulic or pneumatic) or an electric motor and are either soft, hard or a mixture (for example flexible diaphragm inside a rigid casing). The pumping chambers can be implanted or pump blood outside the body. Patient mobility is always limited to some degree by the need for an external power source.

1.4.2.2.1 Fluid Pressure Driven Pumping Devices

Fluid pressure can be generated by an implanted electric pump to actuate a pumping chamber (35) or supplied via access ports in the skin such as with the Thermo Cardiosystems, pneumatically driven, Heartmate (36). There is a danger of infection through skin access ports and a risk of fluid leaks inside the patient's body. Noise and vibration could well cause patient discomfort.

1.4.2.2.2 Electrical Devices

Power lines can be fed through the skin to an implanted device such as a later version of the Heartmate, from an external battery pack and control system (32,37). Patient mobility will be similar to that provided by the pneumatic Heartmate device with a risk of infection through the skin breach. There will probably be less noise and vibration.

Inductance coils can be used to supply electrical power without breaching the skin. The Pennsylvania State University circulatory support system consists of a flexible blood sac compressed by a rigid plate that is actuated by an electric motor (38). An emergency battery, inductance coil and compliance chamber, which minimises pressure changes in the air space around the motor, are implanted together with the pump. A battery pack is carried by the patient, which can easily be re-charged, thus allowing reasonable patient mobility.

1.4.2.3 Turbine Pumps

One type of turbine pump is designed to be situated in the aorta with an intake tube inserted through the aortic valve into the left ventricle and is consequently less than 1cm in diameter. The drive cable is inserted up the femoral artery (as can be done with the aortic balloon pump). Patient mobility is severely limited due to the external drive line and control system and is intended for the treatment of heart attack sufferers and for post-operative low cardiac output problems (39-43).

Turbine pumps are being developed that have an integral motor and thus require only a power cable attachment that eliminates the risk of drive cable fractures (44,45). Turbine pumps have seen clinical success, although they may well cause a substantial amount of blood trauma as impelling blood through a small turbine at high velocity implies the development of high shear stresses.

A scaled up version of these small turbines consists of a rotary motor inside a metal casing and provides steady ventricular assistance. This device should be cheap to produce and mechanically reliable as it is a simple, continuously operating, design. The likely high shear stresses in the turbine may also cause substantial blood damage (46).

A novel idea is the uni-valved artificial heart that consists of a single oscillating jellyfish valve (47) in a pipe. When the valve moves upstream it acts as a piston in a cylinder and on the downstream return it opens and fluid passes through it. The flow produced is of the same frequency as the vibrations (1-30 Hz) and unidirectional. This design is claimed to be an efficient and simple mechanism (48).

1.4.2.4 Centrifugal Pumps

These pumps consist of a rotating impeller inside a rigid casing. Fluid enters the pump along the axis of impeller rotation, rotational momentum is imparted to it by the impeller and the fluid exits the pump tangential to the impeller rotation (49).

Centrifugal pumps have been used for short term ventricular assistance (50) and progress is being made towards medium term application (51,52). There has been some debate upon the relative merits of pulsatile and non-pulsatile circulatory assistance (53), but there appears to be no difference between the two operating regimes in short term *in vivo* applications (54)

1.4.2.5 Direct Mechanical Ventricular Actuation

Instead of using skeletal muscle to massage the heart, pneumatic polyurethane sacs inside a rigid container have been used to bridge a patient for 56 hours to transplantation (55,56). This method requires the chest to be open, is intended for resuscitation purposes and there is no blood contact with foreign surfaces when pumping.

1.4.2.6 Roller Pump

These pumps are widely used as part of the heart lung machine for cardio-pulmonary bypass during heart surgery. They are used, clinically, for partial circulatory assistance with the pump outside the patient's body (57).

1.5 Medical Therapy

Pharmacological therapy is applied to patients with heart disease, but the effects of these drugs are limited and remain controversial, as reviewed by Neddy (58).

1.6 Coronary Artery Bypass Grafting

Patients with heart disease commonly receive Coronary Artery Bypass Grafts (CABGs). Blood vessels from other parts of the patients' body are removed and used to bypass blocked sections of

vessels supplying the heart with blood. This technique produces successful results with a group of heart disease patients, but not all and there is a problem with blockages forming in the bypass vessels.

1.7 Xenotransplantation

Transplanting hearts from genetically engineered animals is an ongoing research initiative. It is possible that rejection problems could be overcome, although ethical considerations need to be addressed.

1.8 Summary

None of the non-muscle powered devices discussed can provide permanent cardiac assistance with substantial patient mobility; the fundamental limitation being the absence of a long lasting implantable power source. At present the only non-muscle powered systems that come close utilise induction coils to transfer electrical power through the skin. On the muscle powered side cardio and aorto myoplasty, and ventricles formed from wrapped skeletal muscle do not fully utilise the available skeletal muscle power. A viable option may be a device that makes efficient use of a conditioned skeletal muscle in an optimal configuration.

1.9 Ventricular Assist Devices and Blood Clotting

Most VADs will put blood in contact with foreign surfaces or possibly subject it to damaging flow conditions.

Blood inside a test tube will clot because of the air-blood and glass-blood interfaces initiating the clotting chain reaction. Similarly, typical VAD materials, such as polyurethanes, can initiate clotting.

1.9.1 Blood

Blood consists of plasma, red cells (erythrocytes), white cells (leukocytes) and platelets (small granulated bodies) (1). The percentage volume of blood that is erythrocytes is termed the haematocrit. The normal haematocrit for women is 42% and men 47%. An average person contains approximately 5.6 litres of blood. Therefore an average person's heart, at rest, will pump the equivalent of their entire blood volume every minute.

Plasma is mainly water (93% by weight) with various organic and inorganic substances dissolved in it. Erythrocytes are non-nucleated cells of biconcave disk shape, approximately 7μm in diameter.

These red blood cells contain haemoglobin, a red pigment, that gives them their oxygen carrying capacity and colour.

Leukocytes make up less than one per cent of the cells in blood. Their major function is to defend the body against foreign bodies. Platelets are small (nominally 1μm in diameter) compared to red and white blood cells.

1.9.2 Blood Coagulation

The formation of a blood clot in the human body is a complex process. When a blood-transporting vessel is damaged it will, initially, constrict to slow down blood flow and possibly “glue” opposing surfaces together, although this process is only effective in the smaller diameter vessels of the micro-circulation. Blood loss is eventually stopped by two other methods: a platelet plug and blood coagulation (clotting).

Platelets, given the opportunity, will adhere to foreign or rough surfaces and damaged blood vessel walls. The adhesion triggers a change in the platelets and they release chemical agents (e.g. adenosine diphosphate, serotonin) that cause new platelets to adhere to them which, in their turn, release increased concentrations of chemical agents. This positive feedback quickly produces a platelet aggregate or plug. The growth of the platelet aggregate is limited, in the human body, by aggregate inhibitors (prostacyclin) produced by undamaged vessel walls and circulating anti-coagulants (e.g. heparin, plasmin). A blood clot can form around the initial platelet aggregate by the conversion of fibrinogen to fibrin. The conversion is stimulated by the platelet aggregate. This conversion process also stimulates the aggregation of platelets and the formation of thrombi. Thus the rate of growth of a blood clot increases by positive feedback.

The coagulation process described here is somewhat simplified and is in fact a chain of chemical reactions. Each active part of the chain reaction acts only locally and is inhibited in the rest of the circulation (1).

1.9.3 Implications of Clots in Blood Pumps

As reviewed by Sutera it is generally accepted that damaged blood elements (platelets, erythrocytes and leukocytes) can initiate the clotting process (59). If a blood clot, or thrombus, forms on a VAD blood contacting surface then it may compromise the VADs operation. There is also a danger that the thrombus will detach from the surface. A free thrombus in the circulation, known as a thromboembolism, can occlude blood vessels. The occlusion of a blood vessel can damage vital organs, such as the lungs, liver, heart, brain or kidneys which can be fatal.

Even slight damage to blood cells could prevent them from accomplishing their physiological tasks. Sanza *et al* (60) found that a rabbit's spleen will remove erythrocytes from the circulation that have only been slightly damaged (sub lethal damage).

1.9.4 Mechanisms of Blood Element Damage in VADs

The processes in VADs that damage blood elements can be classified as chemical and mechanical.

1.9.4.1 Mechanical Blood Damage

1.9.4.1.1 Squashing and Cavitation

It is possible that blood cells and platelets could be crushed during closure, between the hard surfaces, of mechanical prosthetic heart valves. No VAD described in the literature appears to have two hard surfaces that come into contact when it is pumping.

Gas bubbles will form in a liquid when it flows into a region at a pressure low enough to cause vaporisation. The vapour bubbles are carried with the liquid and in a region of higher pressure they suddenly collapse. This process is known as cavitation. The forces caused by fluid rushing into these cavities create very high local pressures that can cause pitting of nearby solid surfaces (61). It is likely that cavitation in the vicinity of mechanical valves may damage platelets, red and white blood cells (62).

1.9.4.1.2 Fluid Shear Stresses

Fluid is a substance that deforms continuously when subjected to a shear stress (61). Shear force, ***F***, is the force component tangential to a surface, and average shear stress is this force divided by the surface area, ***A***. For a fluid between two close parallel plates, one being stationary and the other moving at a velocity, ***U***:

$$\tau = \frac{F}{A} = \mu \frac{U}{d}$$

where τ is the shear stress, μ is the proportionality factor and ***d*** the distance between the plates. ***U/d*** can be written as ***du/dy*** , the velocity gradient, where ***u*** is local fluid velocity and ***y*** the distance from the stationary plate. The proportionality factor, μ, is the viscosity of the fluid in Newton's law of viscosity for laminar flow:

$$\tau = \mu \frac{du}{dy}$$

In laminar flow, fluid particles move along smooth paths in layers, with adjacent layers gliding smoothly over each other. Fluids are classified as Newtonian, where μ is constant, and non-Newtonian, where there is a non-linear relationship between the applied shear stress and the velocity gradient. The units of viscosity are Pa.s (Pascal seconds). The kinematic viscosity, υ, is

defined as: $\upsilon = \frac{\mu}{\rho}$, where ρ is the density of the fluid.

In turbulent flow, fluid particles move irregularly causing an exchange of momentum from one part of the fluid to another. The fluid particles can range in size from very small (e.g. a few thousand molecules) to very large (an atmospheric gust of a few thousand cubic metres). In turbulent flow energy losses vary as the 1.7 to 2 power of velocity, whereas in laminar flow they vary as the first power of the velocity. For turbulent flow the fluid stresses acting on an element (in three dimensional Cartesian co-ordinates) are: $\sigma_{xy} = \rho u_x u_y$ where σ_{xy} is the Reynolds shear stress on the ***x***-plane in the ***y***-direction, and $\sigma_{xx} = \rho u_x u_x$ where σ_{xx} is the Reynolds normal stress acting in the ***x***-direction on the ***x***-plane.

A more general expression for shear stress is equation 1.1, below.

$$\tau_{ij} = \overline{p}.\delta_{ij} + \mu\left(\frac{\partial \overline{u_i}}{\partial x_j} + \frac{\partial \overline{u_j}}{\partial x_i}\right) - \rho u_i u_j \qquad \text{Equation 1.1.}$$

where : $U_i = \overline{u_i} + u_i$

U_i = Instantaneous velocity in the ***i***th direction.

$\overline{u_i}$ = Mean velocity.

u_i = Varying component of velocity.

τ_{ij} = Component of the stress on a fluid element in the ***i***th direction on the ***j***th plane.

δ_{ij} = Kronecker delta.

$\overline{p}$ = Mean pressure.

The subscripts ***i,j*** are tensor notation and in three dimensional Cartesian co-ordinates can assume the values of ***1,2,3*** representing the ***x,y,z*** co-ordinate system. Hence when ***i=j*** the term $\rho u_i u_j$ is the Reynolds Normal Stress, and when $i \neq j$ it is known as the Reynolds Shear Stress.

In laminar flow with no disturbances and hence no varying velocity components the equation for shear stress is simplified, equation 1.2.

$$\tau_{ij} = \mu\left(\frac{\partial \overline{u_i}}{\partial x_j} + \frac{\partial \overline{u_j}}{\partial x_i}\right)$$ Equation 1.2.

There have been many investigations into the effects of shear stress upon blood in both turbulent and laminar flow conditions. The results of these studies indicate that lethal blood element damage can be related to viscous shear stress magnitude and the time that blood elements are exposed to it (63,64).

The shear stress levels and exposure times that cause platelet and erythrocyte lethal damage can be summarised in two graphs, figures 1.4 and 1.5, as described by Tillman *et al* (64).

By comparison of figures 1.4 and 1.5 erythrocyte damage is the critical factor for short exposure times (<0.01 sec) at 100 - 200 N/m^2. Platelet damage is the critical factor for long exposure times (>0.01 sec) at 10 - 100 N/m^2. There is some disparity in the reported levels of shear stress and exposure time that lead to blood damage. This could in part be explained by the use of different measurement methods and criteria as suggested by Wurzinger *et al* (65). They concluded that platelets exposed to high shear stresses are not directly activated, but because they are damaged secondary biochemical activation is largely a matter of experimental conditions.

1.9.4.1.3 Foreign Surfaces, Stagnation and Re-Circulation Regions

The interaction between blood elements and foreign surfaces is generally considered to be the major cause of blood trauma in VADs (59,66). Designing a VAD that does not produce shear stresses that cause blood damage, outright, is considered to be a soluble engineering problem (67).

The influence of fluid flow upon the initiation of thrombus formation in VADs by foreign surfaces is less well understood. It is likely that minimising the time of contact between blood elements and foreign surfaces will reduce the blood trauma potential of a VAD. Thus regions of stagnant and re-circulating flow are to be avoided.

Affeld *et al* compared platelet deposition models with experimental data (68). They concluded that there is a critical wall shear rate, and therefore shear stress, at which platelet deposition rate on a surface is maximal. Hashimoto *et al* (69) found clot growth at foreign surfaces was greatly inhibited at shear rates above 400 sec^{-1}, with different materials. Folie and McIntire (70) suggested that emboli forming in high flow rate blood vessels would be much smaller than those in the venous

system, and consequently less dangerous. These studies suggest that VAD walls require good wash-out characteristics to prevent platelet aggregation.

Polyurethanes are commonly used in prosthetic medical devices and investigations have been made into their interaction with blood, and surface modification methods to reduce blood element adhesion (71). Another approach to the problem of foreign surfaces is to encourage deposition of selected blood elements and the formation of an endothelial layer (27,72). This approach has been shown to work in the short term by effectively insulating the foreign surface from contact with blood. More work is necessary to determine if the lining will continue to expand, if it can be controlled or whether it can be maintained effectively on a moving surface.

1.10 Summary

Shear stress magnitudes and exposure times to be avoided in VADs are fairly well defined. The influence of fluid flow on the initiation of platelet aggregation by artificial surfaces is less well understood. Re-circulating and stagnating regions of flow should be designed out of a VAD, and surfaces exposed to a blood element aggregate inhibiting shear stress for at least part of a pumping cycle.

1.11 Fluid Dynamic Behaviour of Blood

Blood is essentially cells in plasma that behaves as a Newtonian fluid across a wide range of shear rates (73) (approximately 100 sec^{-1} and above). Plasma is a suspension of protein in an electrolyte solution that is mainly water: a Newtonian fluid. The largest dimension of any particle in plasma is approximately 50nm. The particle size would have to be much larger to affect a deviation from Newtonian behaviour, even in a 5μm capillary. A viscosity of 1.2 mPa.sec is usually quoted for plasma (73).

Red blood cells affect the viscosity of blood and the magnitude of the viscosity change is dependent upon the concentration of red cells, or haematocrit, in tubes of diameter 500μm or larger. At low shear rates blood viscosity increases markedly with decreasing shear rate, and blood has been attributed a yield stress at which it will cease to flow. Tube diameter is also a factor, as in tubes of less than 1mm diameter, at high rates of shear, the viscosity is higher than in larger tubes.

The viscous behaviour of human red blood cell suspensions in plasma, at 25^{o}C, varies with haematocrit as shown in figure 1.6. For a normal human physiology the haematocrit is 42% in females and 47% in males, resulting in a viscosity at high shear rates of around 3 to 5 mPa.sec (74,75).

1.12 Experimental Blood Analogues

Blood is opaque, and most *in-vitro* fluid flow characterisation experiments require an optically clear fluid, so it is desirable to use a transparent blood analogue that simulates the behaviour of blood. Utilising a blood analogue also eliminates the problems of obtaining human blood, anticoagulation and hygiene. Newtonian fluids have been widely used to characterise flow in the vicinity of prosthetic heart valves and inside blood pumps.

Water has been used in VADs for fluid flow characterisation (76,77), but with a room temperature viscosity of 1.0 which does not vary with shear rate it will not, closely, simulate the fluid dynamic behaviour of blood. A commonly used blood analogue, consisting of glycerol (36% by volume) and water, has a viscosity of 3.5 mPa.sec (similar to the viscosity of blood at high shear) and closely matches the density of blood at 37^{O}C (78,79). Mann *et al* compared three fluids in a VAD: glycerol/water, aqueous separan (a non-Newtonian polymer) and bovine blood (80). They found that each fluid produced different flow patterns in the VAD. The rheological properties of the separan analogue fluid were closest to bovine blood, but there were still differences in gross flow phenomenon between the two fluids during parts of the pumping cycle.

The same research group, at Pennsylvania State University, has since developed a blood analogue made from xanthan gum (a food additive), glycerol and water (81). They report a close match between the viscous behaviour of the xanthan gum analogue and porcine blood.

More recently Pohl *et al* compared three of the blood analogues so far described (water, glycerol and xanthan gum) and aqueous Praestol (a polyacrylamide) for *in vitro* heart valve testing (82). They found pressure drop across the valves and valve closing time to be independent of blood analogue, but leakage flow was dependent upon the fluid used. Two of the non-Newtonian fluids assessed exhibited similar viscous behaviour, as a function of shear rate, but yielded widely different values of leakage flow, at different back pressures, with the same valve. This could be because the fluids possess different visco-elastic characteristics. The leakage flows for the water/glycerol analogue were a close match to those measured with blood in a previous study (83). All of the blood analogues discussed so far might not simulate the dynamic behaviour of blood because they are not suspensions of particles in a Newtonian fluid.

Various combinations of particles and fluids have been compared with the viscous behaviour of human blood. A suspension of polystyrene particles in Dextran has been shown to simulate blood reasonably well (84). Calcium chloride is added to control the attraction of the particles, to simulate the interaction and aggregation of red blood cells. The calcium chloride reduces the electro-static

repulsion of the particles and allows the long range Van der Waals forces to come into play. Fukada *et al* suggested that the particles aggregate at low shear rate and disaggregate with increasing shear (85).

The concentration of particles in these particulate suspension blood analogues likely precludes using them for *in vitro* optical flow characterisation.

1.13 Blood Pump Fluid Flow Characterisation Methods

This section is a discussion of fluid flow analysis methods that can be, and have been, applied to blood pumps.

1.13.1 Magnetic Resonance Imaging (MRI)

Fluid flows have been investigated with MRI for several decades (86). The velocities of protons (hydrogen nuclei) are measured by subjecting them to a magnetic field (87). MRI can discern velocity profiles in opaque media, but there is a trade off between spatial resolution and image acquisition time. Another drawback of MRI is the need for expensive hardware and software.

1.13.2 Hot Film/Wire Probes

These probes quantify fluid velocity by measuring the electrical power required to maintain the probe film or wire temperature in a moving fluid. Both types of probe can disturb the fluid flow as they are physically intrusive, although wall mounted hot film probes for measuring wall shear stress may not be(88). The probes need to be calibrated regularly, have a low signal to noise ratio and provide no directional signal (89).

1.13.3 Laser Doppler Velocimetry (LDV)

LDV is a non-intrusive optical method of velocity measurement. The frequency of light scattered from artificial or naturally occurring particles in a fluid is measured. The difference in frequency between the scattered and incident light is called the Doppler frequency. The Doppler frequency is proportional to the velocity of the reflecting particle. Velocity measurements are made at the intersection of two coherent laser beams (89). More than one perpendicular velocity component can be measured by using more laser beam pairs.

The sampling volume, at the laser beam intersection, can be very small giving a good spatial resolution. A fluid volume is interrogated by sampling at many different points. A high sampling

frequency is attainable, and the data can yield time varying information and thereby distinguish between laminar, disturbed and turbulent flow.

The disadvantages of LDV are that there is a large amount of data processing, optical access is required to a refractive index matched medium and a complete picture of the flow field is only slowly formed, hence an instantaneous flow field is unattainable.

1.13.4 Pulsed Doppler Ultrasound Velocimetry

This method uses the same basic principle as LDV, but instead of visible light, ultrasound is used, which allows the method to be applied to opaque fluids. The ultra-sound beam diverges more widely than a laser beam thus limiting the spatial resolution of the technique (80,90).

1.13.4 Flow Visualisation - Particle Methods

Reflective particles will follow fluid flow if they are small enough and of a similar density to the fluid , Agui and Jimenez (91) discussed the motion of seeding particles in a discussion of the performance of particle

tracking. Assuming that the density of the seeding particles is similar to the density of the fluid, the expected difference between the fluid and particle velocities was given as equation 1.3.

$$\left(\frac{\Delta u}{u}\right)^2 \approx 0.018\left(\frac{\Delta\rho}{\rho_f}\right)^2 \frac{d^2\omega_o}{\upsilon} \qquad \text{- Equation 1.3.}$$

$\Delta\boldsymbol{u}$ = velocity difference between the fluid and particle.

$\Delta\rho$ = density difference between the fluid and particle.

$\boldsymbol{u}$ = velocity.

ρ_f = density of the fluid.

ν = viscosity of the fluid

ω_o = lowest turnover rate of the large eddies in the flow (Hz), and can be estimated as the velocity defect of the wake divided by its half width.

$\boldsymbol{d}$ = diameter of the particle.

Clearly if the particle and fluid densities are equal then there is no slip, by equation 1. Differences between fluid and particle velocity could still occur due to dynamic effects such as lift produced by a rotating sphere in irrotational flow.

Illuminating the fluid provides a visual record of particle movement recorded with a video, cine or single exposure camera. The results usually highlight areas of stagnation and vorticity. By using controllable light sources the fluid can be sectioned and fluid movement observed in a defined volume. For instance a two dimensional section of the fluid can be observed by using a laser to create a thin sheet of light.

An instantaneous picture of fluid flow can be obtained, and quantified, given good optical access.

1.13.5 Quantification of Flow Visualisation Results

1.13.5.1 Streaks

If particles move a measurable distance during the exposure time of a camera, while still remaining within the illuminated volume, they will appear as streaks. Velocity fields can be obtained by measuring the length and spatial position of the streaks. There is a directional ambiguity of 180^{o} that can be resolved by pulsing or obscuring the light source during the camera exposure, to produce patterns such as: a dash and a dot (92) or a thin streak with a thick end.

This method can produce an instantaneous, two dimensional, velocity field over a large area of fluid flow. If, in the observed area, particle velocities are different then the slowest will be brightest, as they will reflect more light per unit of distance travelled. This can cause problems such as barely visible fast particles and glare from the slowest.

Another disadvantage of streak measurement is that particles can move out of the illuminated volume during a camera frame. This results in inaccurately low velocity measurements.

1.13.5.2 Particle Tracking Velocimetry (PTV)

PTV overcomes this problem, of particles moving out of the illuminated volume, by measuring the distance between dots, formed by short duration light source pulses. PTV computational algorithms require a minimum of three dots to function, and the order of occurrence must be known (93). The instant of dot image formation can be determined if there is only one light source pulse per frame. The minimum requirement of three dots is satisfied by considering at least three consecutive frames. The order of dot formation can also be defined by applying different intensity light source pulses. The algorithms ‘join up the dots’ by starting with the first pulse dots and searching around them, in an area limited by the maximum velocity, to find all the possible second pulse dots. This process is repeated for the second pulse dots. The search region for the third pulse dot is smaller and projected from the initial velocity vector. A process of elimination yields the set of dots that represents a single particle path.

Ideally there will be a complete set of dots for each particle. In practice this may not happen as particles can enter and leave the volume of illumination during the image exposure, and their paths may only appear as one dot. Some particles may not move very far between pulses and will appear as single bright or blurred dots.

If there are many particles in the fluid then the data processing is computationally intensive.

1.13.5.3 Particle Image Velocimetry (PIV)

PIV is similar to PTV, the difference being that patterns of dots are tracked rather than individual particles. This is done statistically using an auto correlation algorithm (94). Images are divided into rectangles and a mean velocity calculated for each. The algorithm identifies the likeliest match between each rectangle of dots and the rest of the image.

1.13.5.3.1 Directional Ambiguity

Both PIV and PTV have a 180^{O} directional ambiguity, as with measuring particle streaks, that can be resolved by:

- Post processing of the velocity field using some assumptions about the fluid flow, such as the overall direction of movement being from left to right.
- Giving one set of dots a known displacement which is larger than the maximum particle displacement using a rotating mirror in front of the camera. The maximum velocity and hence displacement is found before using the rotating mirror to shift the images.
- Making one set of dots a different colour to the other.
- Using different intensity light pulses.
- Pulsing the light source once per frame and then performing a cross correlation between frames with the auto correlation algorithm.

1.13.5.3.2 Obtaining the Third Velocity Component

In practice both PTV and PIV are usually performed with a laser light source to obtain a sheet of light which essentially yields a two dimensional velocity field. Although a third perpendicular velocity component can be obtained, for example:

- Cenedese *et al* used two different colour lasers to create a light sheet of varying colour through its thickness. A particle's position in the light sheet perpendicular to the plane of view can then be quantified by its colour and the third velocity component calculated (95).

- Coupland *et al* used the three dimensional recording properties of holography to obtain three dimensional spatial data and hence velocities (96).

A disadvantage of most flow visualisation is that only part of a fluid volume can be investigated at a time, although Nishino *et al* illuminated the entire flow field and obtained spatial and velocity information using two cameras viewing from different perspectives (97).

1.13.6 Photochromic Method

Fluid flow is measured by activating colour tracer, present in the originally optically transparent medium, with pulsed laser radiation. The tracer changes colour along the line of the pulsed laser beam and a camera records the displacement of the coloured line. This method is described as having the precision of LDV and the clarity of flow visualisation (98). The method would probably prove difficult to apply to complex three-dimensional fluid flows, such as those in the heart or a blood pump.

1.13.7 Flow Visualisation - Fluid Tracer Methods

By recording the motion of radioactive or optical tracers in fluid flow a representation of fluid movement can be obtained (99). The representation of fluid movement is neither 2D nor 3D, but a projection of 3D fluid motion onto a 2D medium (the camera). A bolus of tracer can be injected before a blood pump inlet and the amount of tracer ejected at the end of each subsequent cycle, measured. Plotting the amount of tracer ejected, from the pump, against time gives an indication of how long blood elements would be exposed to the flow conditions in the pump (100).

1.13.8 Computational Fluid Dynamics (CFD)

Numerical solution of fluid flow is increasingly being used for blood pump design development. The rapid increase in the ratio of computational power to cost is allowing researchers to make full use of commercially available software. The formulation of a realistic model gives the researcher access to all parts of the fluid flow and the effect of design changes can be investigated in the virtual environment (101). Even so the development of complete models of blood pumps, especially those with flexible walls, is extremely time consuming, if not impossible. Simple two-dimensional, steady state, laminar, Newtonian and fixed boundary solutions are now commonplace. Creating models that more closely resemble reality by including, for example, non-Newtonian and turbulent behaviour greatly increases model formulation and computation time. Another drawback is that even a model including all the desired attributes is still an approximation and should be validated.

1.14 Blood Pump Fluid Flow Studies - Experimental

Methods for characterising fluid flow have been discussed. What follows is a description of studies characterising flow in blood pumps, to aid design development and/or check that the flow is desirable.

Clark *et al* applied fluid visualisation and LDV to a blood pump, figure 1.7, as the first phase of a fluid flow investigation (102). Experiments were conducted with Newtonian fluids of water and water/glycerol. Steady flow, with and without valves, and pulsatile flow were examined. The tilting disc valves prevented a region of re-circulation forming on the right side of the chamber, plane A. Velocity measurements indicated possible large shear stresses near the boundaries. The motion of the diaphragm was fluid flow dependent.

Jin and Clark then used a non-Newtonian blood analogue of water/separan/isopropanol (103). The major flow features were found to be two dimensional in nature, by flow visualisation. The prominent flow pattern was a clockwise vortex that formed during filling in plane A. An LDV system produced vector maps of fluid velocities and contour maps of Reynolds normal stresses (RNS's) at different instants during the pumping cycle. The maximum RNS found was 147 N/m^2 occurring for less than 100ms and the maximum Reynolds shear stress (RSS) inferred from this was 74 N/m^2 (RSS=RNS/2). At the time of publication there appeared to be no published results for RNS levels that cause blood damage, but this level of RSS should not cause significant damage to blood. Maximum wall shear stress downstream of the outlet valve was estimated at 24.5 N/m^2. The velocity maps suggested that the VAD walls were well washed during pumping.

Regions of low wall shear stress were identified by observation of flow visualisation particle deposition after 2 hours of pump operation. The areas of deposition were associated with the mechanical valves and the sealing ring between the diaphragm and housing.

Residence times were studied in the pump by recording the paths of single oil particles injected from five different wall positions. The residence times were between 2 and 7 seconds, and more dependent upon stroke volume than pumping rate, suggesting that the VAD should be operated at a high stroke volume to minimise particle residence times. This method is not an overall evaluation of residence times as the particles are only released from a few points.

The results provided a basis for recommendations to be made for improving the pumping chamber geometry to reduce blood damage and the risk of thrombus formation. For example, the sudden

change of geometry between the inflow/outflow pipes and the pumping chamber could be smoothed

Phillips *et al* reported the results of a flow visualisation study of the Penn State sac-type artificial ventricle, figure 1.8 (104), and later applied a one dimensional LDV system (105). The prevalent flow feature was a clockwise vortex. The Penn State program then moved onto an electric pump of similar chamber geometry, figure 1.9.

Tarbell *et al* initially studied fluid flow in an experimental Penn State blood pump, machined from a Plexiglas block, with pulsed Doppler ultrasound velocimetry (90). This technique could only interrogate fluid flow near the walls. A maximum mean wall shear stress of 2.5N/m^2 and a maximum Reynolds normal shear stress of 21.2 N/m^2 were recorded, both of these values are well below known blood damage levels. Regions of low shear were observed during the pumping cycle suggesting that a non-Newtonian blood analogue would be better suited for experimental purposes, rather than the glycerol/water analogue.

Baldwin *et al* mounted hot film probes to measure wall shear stresses at various points in the Penn State pump (88). In this study the maximum wall shear stress near the outlet valve was 270N/m^2 during ejection, and 35N/m^2 around the periphery of the pumping chamber. The difference in magnitude between this result and that quoted by Tarbell *et al* (90) could be because the flush mounted hot film probes directly measured wall shear stresses instead of estimating them by extrapolating the near wall velocity profile, and the previous doppler measurements involved a large measurement volume. An LDV system was used to obtain overall flow patterns and evidence of good wall washing (106). A Newtonian blood analogue of glycerol/aqueous sodium iodide (viscosity=3.8Cp) was used to match the refractive index of the pump Plexiglas (1.49).

Baldwin *et al* described a filtering technique and a method for determining the principal Reynolds stresses from measurements made in pulsatile flows (107). It was suggested that LDV measurements should be viewed with some caution and that turbulent shear stresses may be over-estimated. Reynolds normal stresses and Reynolds shear stresses of 298 and 120N/m^2 were respectively reduced to 41 and 17N/m^2 by the filtering technique. Large variations were observed in transforming from the measured co-ordinates to the principal axes. It was also noted that researchers in this field have not given enough consideration to the number of cycles over which data is averaged and the length of measurement window used to give pseudo-steady flow. In view of these comments it seems likely that a number of the studies could have over-estimated turbulent shear stresses measured in VADs.

This LDV data filtering technique was applied to the Penn State blood pump (67). Turbulent stresses in the pumping chamber and just after the valves were found to be less than 200N/m^2. High Reynolds normal shear stresses of 2000N/m^2 were found in the valve regurgitant jets. The wall shear rate results from the previous wall shear probe study (88) were discussed and it was suggested that the peak wall shear stresses of 30 to 50N/m^2 are more than enough to inhibit the deposition of platelets, but not enough to activate them.

Francischelli *et al* analysed fluid residence times in the Penn State blood pump at different near wall locations with a fibre optic probe and fluorescent dye (108). A bolus of dye was injected and the probe both delivered laser light, to activate the dye, and collected the transmitted light. The 100cc pump was found to expel 95% of the indicator after 5.2 beats and the 70cc pump after 4.1 beats, operating at the same ejection fraction. This was probably because the 70cc pump had an inflow port oriented such that it provided better wall washing than the 100cc. The residence times at the measurement points near the valves were longer than those in the main pumping chamber. This was reportedly due to the re-circulating regions in the minor orifice of the mechanical valves. These re-circulating regions together with the high fluid shear stresses near the valves suggest the possibility of blood damage is high.

All of these results described for the Penn State blood pump suggest that a pumping chamber that produces a single rotating vortex, without stagnation regions, will provide good wall washing and not significantly damage blood in the main pumping chamber. The danger area appears to be the region around the mechanical valves.

Daily *et al* described the development of a scaled down version of the Penn State VAD, for paediatric use (109). Overall qualitative flow visualisation was performed to characterise gross flow patterns and identify stagnation or re-circulation areas. They found the VAD to be more thrombogenic than the adult sized VAD, and concluded that this was because the inner surfaces of the smaller pump were not as well washed and different valves were used. It was found that using bi-leaflet rather than ball and cage valves yielded lesser pressure gradients and energy losses. Analysis determined that the Reynolds number of the flow in the smaller VAD would be lower, leading to greater viscous effects and thinner boundary layers. Consequently blood elements may well remain for longer in the vicinity of these areas of low shear, at blood contacting surfaces, leading to increased clotting. PIV was applied to analyse the fluid flow in more detail, which proved to be highly complex and three-dimensional. The general flow field was similar to that for the adult sized VAD, with a dominant vortex forming during filling in the plane of largest cross-sectional area, figure 1.9. At the start of emptying the flow field changes abruptly as the velocity vectors align themselves towards the inlet.

Shettigar *et al* evaluated bulk residence times of a blood pump (100), figure 1.10. A bolus of tracer was injected before the inlet valve during pumping and the amount ejected during each subsequent beat measured. Radioactive and chemical tracers were used to compare the performance of mechanical and polyurethane valves, and different mechanical valve orientations. The polyurethane tri-leaflet valves produced the shortest residence times, probably due to the lower regurgitation. Directing fluid flow around the outer wall, with a mechanical tilting disk valve, produced the best washout.

Dong *et al* analysed the fluid movement in a centrifugal blood pump with a PIV system. Fluorescent tracer particles excited by the laser light sheet emitted higher wavelength light, thus reducing background optical noise. By controlling particle concentration and magnification of the images, velocities were quantified to within 1% (94). The effects of different blade orientations were evaluated.

Shaffer *et al* also used fluorescent particles for the PIV analysis of flow, in the Novacor VAD (110). Some example images of flow in the vicinity of the inflow valve are presented, together with a velocity field derived from interpolated data.

Affeld *et al* investigated flow in a blood pump by covering the inside surfaces with a shear sensitive paint to find areas of low wall shear stress (111). These areas were found to be comparable with the sites of thrombus formation in the VAD after *in vivo* experiments. Velocities were measured with a novel visualisation camera rotation technique that produced trochoidal particle streaks from which acceleration and turbulent intensity information could be extracted. Affeld *et al* later applied the dye washout method to a nutational pump (77). The velocity field in the nutational pump was analysed in a 5:1 scale model, so that the rotational speed was 1/25 of the original while maintaining the same Reynolds number, by streak length measurement. A maximum shear stress of 63 N/m^2 was calculated.

Nitta *et al* evaluated fluid flow in a sac-type blood pump, figure 1.11, (112). The aqueous soda polyacrylate blood analogue was seeded with large resin particles, and illuminated by the light slit method. Records of particle movement were made with an SLR camera. The streaklines representing particle displacement were quantified via a manual digitisation tablet. A uniform grid of velocity vectors was obtained by interpolation.
The main flow feature was an anti-clockwise vortex formed during filling. Small vortices that formed either side of the inlet during filling were identified as undesirable. Smoothing the connection between the inlet and pumping chamber was suggested as a possible remedy. The experimental validation of this design improvement is described in (113). The pumping chamber geometry was altered to direct flow along the wall by the outlet, thus forming one dominant vortex.
There are several areas for experimental error in this study: the particles are rather large, streak lengths are not accurate because particles can pass through the light sheet during the camera exposure, the flow field is assumed to be mainly two dimensional in the plane of figure 1.11. For instance, it is likely that the small vortices to either side of the inlet are not separate, but are part of a ring vortex.

Orime et al applied flow visualisation to a similar VAD geometry (114). To understand the fluid flow video tapes and pictures were evaluated. The dominant flow feature during filling was a vortex that occupied most of the pumping chamber, while a small vortex was found to one side of the inlet that could aid thrombus formation. The design was modified using clay to direct the inlet flow around the outer walls of the pumping chamber. This modification was shown to yield a filling fluid flow field dominated by a large vortex, with no small vortices, and was incorporated into the design.

Global flow visualisation was applied initially and areas of interest magnified for closer observation.

Sturm *et al* conducted a study of blood pump outflow housings (115). Three sinus shapes were compared by tracer particle flow visualisation, figure 1.12. The modified triple sinus design was found to give the best washing of the valve leaflet facing the sinus.

Shortland *et al* used flow visualisation to characterise fluid flow in two skeletal muscle ventricles (116,117). The blood pump design is a valveless ventricle constructed with conditioned skeletal muscle. The axisymmetric ventricles are shown in figure 1.13. A novel addition to the standard tracer particle flow visualisation method is the use of a liquid crystal shutter, fitted over the CCD video camera lens. The shutter removes movement artefact, due to the two interlaced fields that make up a video frame being slightly out of phase, while retaining the same image resolution. The prevalent flow feature, in each ventricle geometry, is a ring vortex that forms during filling and travels down the ventricle. The effects of filling curve, orifice diameter and ventricle geometry upon ring vortex formation and travel were investigated. It was found that a ring vortex could be encouraged to travel the length of a ventricle, by varying these parameters, so that it washes the walls and entrains all the fluid, i.e. at some point all the fluid is moving.
Shortland et al studied a skeletal muscle ventricle numerical model operating at 1:1 and 1:2 ratios to the cardiac cycle (118). They found that when pumping every other cardiac cycle (1:2 ratio) the ring vortex was able to travel most of the length of the shorter pumping chamber, figure 1.13. To generate vortices that travel the length of the longer ventricle the inlet orifice area could have been reduced, but this may produce damaging flow conditions. Factors included in the model were aortic pressure variation, the visco-elastic properties of the ventricle, the dynamics of the muscle and the mechanical properties of the surrounding tissue. They concluded that to successfully implement a skeletal muscle ventricle the fluid mechanics of each surgical configuration should be fully characterised.

1.15 Blood Pump Fluid Flow Studies - Virtual (CFD)

Tansley *et al* examined the problem of ball occluder heart valve oscillation using a commercial CFD package (119). An axisymmetric, steady flow, Newtonian model was constructed. A modified outflow geometry was found to prevent ball oscillation, in the model.

Peskin and McQueen created a three-dimensional, time varying, numerical model of the heart (120). They modelled the interaction between blood flow and the heart walls by considering the heart as a mesh of elastic/contractile fibres immersed in a fluid. The complicated geometry of the heart, including tri-leaflet valves, was constructed from these fibres. A supercomputer was required to perform the computations.

Kim *et al* modelled steady, Newtonian, fluid flow through a two-dimensional, artificial, blood pump (121). They reported reasonable agreement with published experimental results, although visualisation experiments have shown the flow to be highly three-dimensional.

Bludzuweit adopted a novel approach to analysing the blood damage potential of a centrifugal blood pump (122). A hypothesis of blood damage being dependent upon the amplitude, frequency and cycle number of an oscillating shear stress was presented. Experiments by the Bludzuweit suggested that red blood cell destruction was dependent upon these parameters (amplitude frequency and cycle number).
To apply the theory it was necessary to obtain stress loading histories of individual fluid elements as they pass through a pump. A numerical model of the blood flow through the pump enabled the application of the theory.
Bludzuweit concluded that the practical application of this general blood damage model is hindered by a lack of data for cyclic stress loading of blood, especially when chemical and biological factors are taken into account.

Greg *et al* followed a heuristic design development approach, by which the blood pump design was incrementally changed based upon experience and intuition (123). Flow through the axial turbine pump was modelled numerically for four different geometries. At the fourth iteration most of the undesirable flow behaviour had been eliminated from the model, namely reverse flow and regions of re-circulation.

1.16 Summary

Fluid flow studies have been carried out on various blood pumps for the purposes of minimising blood trauma, stagnating and re-circulating regions of flow. The first step in the fluid dynamic design improvement of blood pumps is usually a qualitative flow visualisation study. Potentially blood traumatising fluid flow can then be identified, for improvement, and examined in more detail, if necessary.

CFD is constantly improving, and has inherent advantages for design improvement as proto-types can be studied in the virtual domain, although care must be taken to ensure that the numerical models approximate reality.

Chapter 2. University Department of Cardiac Surgery SMV Project

There is a need for a completely implantable, short to medium term, heart assistance device, as discussed in chapter 1.

The blood pump device described in this chapter is the subject of an application lodged at the European Patent Office by the University of Glasgow.

2.1 Engineering Design

There are many different methodologies described in the literature that either describe the sequence of activities in a typical design process or prescribe a better sequence, as reviewed by Cross (124). Core to most design process descriptions and prescriptions is the sequence of exploration, generation, evaluation and communication, with feedback loops incorporated accordingly.

The culmination of the process is the communication of a design ready for manufacture before which the design is subject to evaluation against the constraints and criteria of the brief. The design itself arises from the generation of a concept by the designer or design team, usually after the initial exploration of the problem. Feedback is common to most design processes as, for instance, the evaluation may show up fundamental flaws in the problem definition.

The initial formulation of the design problem is very important because it will ultimately effect all subsequent design decisions and will be instrumental in governing the form of the final design.

It is vitally important to be entirely objective throughout the whole design process. Design decisions should always be made against measurable criteria, where possible, and justified accordingly.

The implementation of a design process is usually in response to a need, which is then translated into a problem definition or design brief.

2.2 Need and Environment

There is a need for a VAD that can improve the quality of life of the recipient, as discussed in section 1.3. Conditioned skeletal muscle can be used as a power source, but an effective muscle powered device has yet to be used clinically, as summarised in section 1.8.

2.3 Problem Definition

The problem is to design a self contained muscle powered VAD, capable of providing significant assistance to a failing heart in the short to medium term, either as a bridge to transplant or as a prosthesis in its own right.

A design problem can be broken down into constraints and criteria.

2.3.1 Constraints

Design constraints are characteristics that all design solutions must satisfy. Examples of perceived constraints are given below, most refer to minimum operational requirements, but surgical, manufacture and cost aspects are also addressed.

- Device is powered by conditioned skeletal muscle.
- Implanted device to provide minimal disturbance to host organs and tissue.
- Device to provide suitable cardiac output for significant assistance to a failing heart (e.g. 2 to 3 litres of fluid flow per minute).
- Provide sub-lethal blood pumping conditions during operational lifetime.
- Minimum fatigue life of device (e.g. 1 year).
- Provision for adjustment of device action throughout service life.
- Incorporate back-up and emergency actuation option.
- Cost.

2.3.2 Criteria

Design criteria are used to objectively compare and evaluate the competing design solutions in the optimisation stage and are consistent with the objectives outlined in the analysis of need. Other criteria are used to assess further aspects of the designs such as those issues relating to manufacture, cost, etc. Examples of likely criteria are as follows:

- Power (force, speed) requirements of the device.
- Pumping performance (efficiency, output volume, output pressure, ejection fraction, etc.).
- Blood biocompatibility (mechanical, flow and material interactions).
- Reliability.
- Ease of manufacture.
- Modularity, ease of further development and adaptation.
- Ease of use (implantation/adjustment, i.e. surgical/medical input and monitoring).

- Cost.

There are many ways of utilising criteria to evaluate competing designs, such as those described in chapter 9 of (124) and chapter 9 of (125).

2.4 Proposed Device - 1993

The proposed conditioned skeletal muscle powered VAD is illustrated in figure 2.1, as of the start of the work described in this thesis. The triangular latissimus dorsi is fashioned into a hollow cone with the muscle origin forming the apex and the distal end the open base. The muscle fibres are orientated along the length of the cone so that force is applied along their length, as in the muscles native position. This linear arrangement, as compared to muscle wrap SMVs, avoids energy losses due to force transmission through thick muscle walls, and is less likely to induce ischemia by constricting muscle blood vessels. The adjustable length rod runs along the central axis of the muscle cone and connects the pumping chamber to the muscle cone apex, giving control of muscle cone pre-load stretch so it can be tuned for maximum power output. Controlling the resting muscle tension in cardiomyoplasty or SMV configurations involving wrapped muscle is exceedingly difficult. The hemi-ellipsoidal pumping chamber with two holes in its base, for valved inlet and outlet conduits, is much more rounded than the elongated, conical shapes used in existing SMV's. Intuitively, the shape of the pumping chamber suggests that a high degree of wash-out may be achieved from cycle to cycle, thereby minimising thrombus formation. Ogino *et al* found that increasing VAD compliance improves hydrodynamic performance (126). Undesirably large pressure fluctuations may increase blood trauma while a more compliant artificial ventricle can attenuate them. The proposed device is inherently compliant, so that it may function. Also a large ejection fraction can be achieved by a small change in muscle length. This is important because skeletal muscle power output is maximised for near isometric contraction, and areas of stagnating blood flow are less likely, inside a pumping chamber, operating at a large ejection fraction. An in-extensible 'fly-sheet' draped over the pumping chamber is secured to the open end of the muscle cone. Muscle contraction causes the fly sheet to compress the pumping chamber and expel blood through the outlet conduit. When the muscle relaxes the stiff walled pumping chamber returns to its uncompressed state, drawing blood through the inlet conduit and returning the muscle cone to its resting length. The suggested connection of the device is from the left atrium to the descending thoracic aorta; the latissimus dorsi cone sits in the oblique fissure of the left lung with the proximal muscle apex and central rigid support anchored to the rib, figure 2.2.

From a physiological, mechanical and surgical point of view the proposed approach to cardiac assistance offers many potential advantages over conventional SMV or cardiomyoplasty methods.

It is envisaged that the SMV will deliver cardiac assistance by pumping blood during every other pumping cycle of the patient's heart. Conditioned skeletal muscle contracts slowly enough to limit the muscle shortening that can be accomplished during cardiac systole. It is also possible that residual tension in the muscle after a contraction would interfere with artificial ventricle filling. Professor Carpentier's comment, that cardiac assist from cardiomyoplasty is more effective in some patients when the conditioned muscle is activated in every other cardiac cycle, is mentioned in the discussion by Salmons and Jarvis (11). Anderson *et al* found that switching from muscle stimulation mode II to mode I at 12 weeks appeared to cause a substantial decline in cardiac augmentation, in canine models (127). In mode II the skeletal muscle ventricle is stimulated in a 1:2, 1:3 or 1:4 ratio with the heart, whereas in mode I the muscle is stimulated at a 1:1 or 1:2 ratio. The stimulation mode was changed from II to I at 12 weeks, the decline was noted and the stimulation mode change reversed at 16 weeks. Some recovery in cardiac augmentation was observed after the return to mode II stimulation. The suggested reason for the decrease in cardiac augmentation was that because skeletal muscle is normally perfused during cardiac systole, the conditioned muscle may not be relaxed long enough to allow time for adequate perfusion when operating in every diastole.

In the discussion by Salmons and Jarvis (19) a suggested desirable level of cardiac assistance is 6 l/min (mean flow at rest for an average 70kg human) with a reserve capability of 14 l/min to support activities such as walking up stairs. The power required for these levels of cardiac assistance calculated by multiplying flow rate by the mean systolic pressure (100mm of Hg) is 1.3 and 3 W, respectively. The maximum sustainable power available from a conditioned human latissimus dorsi was estimated as 1.8W, by taking into account the muscle mass losses incurred through conditioning and surgery.

2.4.1 Initial SMV Mechanical Design Development

In a model of the SMV, constructed from a silicon rubber ventricle and a loosely woven fabric fly sheet figure 2.3, the fly-sheet did not compress the ventricle effectively enough to achieve a large ejection fraction (salient design feature 3 in section 2.3). The acute angle between the upper ventricle surface and the base resisted compression. This sharp join is also highly stressed when the pumping chamber is compressed. The ventricle shape was re-designed to address these

problems, figures 2.4 and 2.5, by including a curved transition from base to upper surface. The altered ventricle collapsed much more easily, but the maximum ejection fraction could not be taken above approximately 70%. This ejection fraction was measured while compressing the ventricle against a minimal pressure (100mm of water) so it is likely that the maximum ejection fraction when compressing the ventricle against a higher pressure, say 100mm of Hg, would be lower. Due to the three-dimensional nature of the arrangement, the force exerted by the fly-sheet upon the ventricle is not all directed downwards, some component that acts from the side. This sideways force serves to reinforce the ventricle and resist compression by the fly-sheet. Another problem with this design is that to achieve a 70% ejection fraction parts of the upper ventricle surface contact the quarter toroidal join. This is undesirable because the coming together of two blood contacting surfaces may damage blood elements.

To yield a higher maximum ejection fraction and to address the blood contacting surface collision problem the geometry of the device was altered more radically; the ventricle orientation was changed by 180^{O} and a spring incorporated, figure 2.6. The pumping chamber is now compressed by a plate of possibly variable geometry. Muscle contraction compresses the ventricle and spring, expelling fluid. The muscle then relaxes and the spring returns it and the pumping chamber to their natural shapes.

The following sections describe a generic design process, and its application to the SMV project.

2.5 Design Evaluation

To evaluate designs it is necessary to assimilate information to allow reasoned decisions to be made about the them. An analysis of the nature of this information was completed, both to function as a simple list of requirements and to assist planning of investigations to produce the required data. Information was subdivided into 5 main areas:

1. Mechanical
2. Muscle
3. Surgical
4. Manufacture
5. Regulatory

Some design information can be listed after consultation between relevant personnel, however the remainder will have to be obtained by either experimental investigations, calculations and, more reluctantly, estimation.

Muscle and surgical factors will tend to be of greater initial concern than those in the mechanical category simply because they cannot be ‘designed out’ of consideration; i.e. the design configuration and mode of operation of the final device will largely be dependent on the limiting mechanical performance of the muscle. Manufacture and regulatory considerations at this early stage are of lesser importance, but broad requirements as listed should be borne in mind. A list of information, required to allow design development to continue, was produced:

1. Muscle

- Mechanical characteristics of modified latissimus dorsi muscle.
- Anthropometric muscle data.

2. Surgical

- Size, location, orientation and shape limitations applicable to device.

3. Mechanical

- Start formulation of competing designs based on reformulated problem definition and initial estimates of required parameters.

4. Manufacture

- If manufacturers are not approached at this stage for financial assistance or technical expertise, then minimum considerations for future manufacture should be considered as listed, e.g. ‘design for manufacture’.

5. Regulatory

- Review the regulatory issues that may apply at the present stage, else progress at a more advanced stage may be jeopardised.

The work described in this thesis was initiated to address the mechanical aspects of design development and evaluation, particularly fluid flow and thus pumping chamber geometry.

2.6 Initial Fluid Dynamic Design Constraints and Criteria

The fluid dynamic requirements and desirable features for the SMV are set down in the following sections.

2.6.1 Shear Stress

Blood element exposure time and shear stresses should be kept below those shown in figures 1.4 and 1.5, as discussed in section 1.9.4.1.2.

Platelets in whole blood flowing down a vessel tend to travel near the tube wall and the maximal shear stresses. Table 2.1 shows ranges of wall shear stress in the human body (66). These shear stresses could be considered as ideal and therefore design criteria, excluding the values given for stenotic vessels.

Table 2.1. Typical wall shear rates and shear stresses, assuming the viscosity of whole blood to be 0.0038 Pa.sec.

Blood vessel	Wall shear rate (/sec)	Wall shear stress (N/m^2)
Large arteries	300-800	1.14 - 3.04
Arterioles	500-1,600	1.9 - 6.08
Veins	20-200	0.076 - 0.76
Stenotic vessels	800-10,000	3.4 - 38

2.6.2 Flow stagnation

Regions of fluid re-circulation and stagnation must be avoided within an artificial blood pumping chamber, as discussed in section 1.9.4.1.3. A shear rate of 400 sec^{1} yielded greatly reduced clot growth with different materials, but there were still substantial differences in clotting (up to 50%) between materials at the same shear rate. The curves relating clotting to shear rate for each material combination differed in shape. For example, clotting with stainless steel declined more far more quickly with increasing shear rate than with polytetrafluoroethylene. Thus an optimal value for minimal wall shear rate is likely material dependent.

2.6.3 Residence time

It would be advantageous to minimise the number of pumping cycles that blood elements are resident within the pumping chamber. This will reduce the artificial surface contact time and repeated cyclic exposure of blood elements to flow conditions within the device.

These factors are interrelated; for instance a reduction in shear stress may well introduce stagnation and re-circulation regions, i.e. slowing down the flow may reduce mixing.

2.7 Aims

This thesis addresses the fluid dynamic criteria and constraints through construction of prototype pumping chambers and test apparatus, design and validation of assessment methodologies, application of assessment methods to prototypes.

2.8 Blood Pump Prototypes

Reasoned variations upon the conceptual SMV device are described below.

2.8.1 Pipe Orientation

A logical starting point, and part of the conceptual design, are inlet and outlet pipes connected to the ventricle base at 90^{O}, figure 2.7. This variation will be referred to as B1 from here on.
Angling the pipes at 45^{O} to the base and off setting them from the centre axis, figure 2.8, was chosen as variation B2 with the intention of encouraging vortex formation, in the plane of section A. Previous fluid flow studies of blood pumps, section 1.14, indicate that a vortex occupying most of a blood pumping chamber during filling provides good wall washing, and prevents fluid stagnation areas forming.
Flow through the artificial ventricle is controlled by polyurethane tri-leaflet valves produced in the laboratory (128). The valve bases are seated in sinuses, figure 2.9, that attach to the ends of the pipes in figures 2.7 and 2.8.

2.8.2 Compression Plates

Two variations in compression plate were also chosen for assessment. The first, P1, is flat and the second, P2, has the same dimensions as the upper hemi-ellipsoidal surface of the polyurethane ventricle. Compression of the ventricle by P1 causes it to crumple and wrinkle, whereas P2 compresses it smoothly. Also P2 necessitates no collision of blood contacting surfaces, whereas P1 could induce this when high ejection fractions are developed, i.e. 95%.

The four geometrical variations are shown in figure 2.10 made from combinations of B1 and B2 with P1 and P2.

2.9 Summary

A conceptual design of the Cardiac Surgery SMV has been described. The aim of the work presented in this thesis was to develop techniques for assessing the fluid dynamics of proto-type SMV's and assess four geometric variations of blood pump.

The progression of work is summarised in the next section.

2.10 Synopsis of Subsequent Chapters

Chapter 3

Design and manufacturing of an experimental rig, for actuating blood pump proto-type designs under simulated physiological conditions, and polyurethane artificial ventricles.

Chapter 4

Dye tracer methods for evaluating residence times and identifying stagnating fluid were developed, and compared with a clinically used radionuclide tracer method. The radionuclide tracer method for measuring ejection fraction was validated for possible future *in vivo* use. The production of force, velocity, power and flow rate curves during the pumping cycle of a proto-type blood pump is described.

Chapter 5

The methods described in chapter 4 are applied to the four designs of blood pump. The force, velocity and power requirements for pumping fluid in each design were evaluated together with fluid flow rate curves. The form of the inflow jet in each design is examined.

Chapter 6

The fluid flow patterns in each design are investigated with a flow visualisation technique involving fluorescent tracer particles and computer animations of processed visual data.

Chapter 7

The fluid flow in each design is more closely examined to find areas of high shear rate and consequently shear stress. Magnified views of the fluid flow in likely regions of high shear stress are used for quantification purposes. The problems with extrapolating wall shear stresses from the data are discussed.

Chapter 8

The results for the four designs are compared and discussed with the aim of recommending the best one for future work.

Chapter 3. Experimental Equipment Design and Manufacture

The design and construction of an experimental apparatus for actuating prototype SMVs and simulating the physiological circulation is described in this chapter. The development of a pumping chamber manufacturing technique is also detailed.

3.1 *Superpump* adaptation to linear actuator function

A servo-controlled linear actuator (Vivitro Systems Inc. Superpump - SP3891) was available for use. At one end of the actuator a piston rod protrudes from a hole. A mechanism was required to convey the piston rod movement to a compression plate, and to mount a prototype blood pump.

3.1.1 Design Specification

The mechanism was required to:

- Withstand exposure to water, saline and glycerol.
- Be robust and operate reliably for a reasonable number of pumping cycles (100,000).
- Convey piston rod movement and force to a compression plate or fly-sheet.
- Withstand sideways, perpendicular to the piston rod, such as accidental impacts.
- Incorporate a force transducer.
- Protect the linear actuator.
- Provide attachments for compression plates and fly-sheets.

Desirable qualities were:

- Ease of manufacture and maintenance
- Ease of use, such as fitting and adjusting prototype blood pumps.

A solid model created in a CAD package (AUTOCAD Release 12, AUTODESK Inc.) aided further development of the mechanism.

The finished conceptual design is shown in figure 3.1 as a complete solid model and with a section cut-away.

The linear bearing (LCAN 16-2LS, SKF Engineering Products, 2 Tanners Drive, Milton Keynes, MK14 5BW, UK) slides smoothly along the supporting rod. The upper half of the bearing clamp (not shown) fits over the top of the bearing and is connected to its mirror image, the lower bearing

clamp by threaded rod. The upper half also has the facility for attaching a fly sheet or compression plate. The linear bearing can withstand reasonable sideways force without compromising its operation.

Parts of the mechanism were ordered to specification, while others were produced in the laboratory with the aid of a CNC milling machine (Triac PC with coolant, Denford Machine Tools Ltd., Birds Royd, Brighouse, West Yorkshire, HD6 1NB, UK). The acrylic disk and cylindrical housing provide protection for the force transducer (U4000, Maywood Instruments Ltd., Rankine Road, Danshill West, Basingstoke, RG24 0PP, UK).

Prototype blood pumps can be attached to the supporting rod, via a hole tapped into the top of it.

3.2 Flow circuit

A mock circulatory loop was constructed consisting of a reservoir open to atmospheric pressure and a compliance chamber, figure 3.2. Polyurethane tri-leaflet valves, up and downstream of each ventricle, regulate the direction of flow.

Measurements can be made with electromagnetic flow probes of 26mm diameter and a flow meter (Gould Statham SP2201), connected by rigid tubing, up and down-stream of the ventricle, when physiological saline is used as a fluid. The frequency response of the flow meter and probe is -6db at 50Hz. A pressure transducer (Elcomatic EM721) connected to an Electomatic amplifier (EM722) monitored the compliance chamber.

The stroke length (mm) of the linear actuator directly translates to plate movement, shown as the distance AB on figure 3.2. The actuator can be driven by a sinusoidal waveform generator. Position and velocity signals from the linear actuator and signals from the flow meters are captured by a data acquisition system equipped with an analogue-to-digital board (128). The stroke length and frequency (beats per minute; bpm) of the linear actuator can be monitored continuously.

3.3 Choice of blood analogue

Ideally blood would be used to test a prototype blood pump *in vitro*, but optical fluid flow characterisation techniques require a transparent medium.

Blood analogues of different ratios of xanthan gum, glycerol and water were mixed as described by Brookshier *et al* (81). This analogue exhibits similar behaviour to blood, as discussed in section 1.12.

The ‘normal haematocrit’ ratio of 0.04% xanthan gum, 0.5% NaCl, 40% glycerol in water (by mass) was made and found to be cloudy, such that a 1mWatt HeNe laser beam could only penetrate 5cm

of the fluid. The 'low haematocrit' fluid of 0.0075% xanthan gum was cloudy to a lesser extent with laser penetration of at least 10cm, but with substantial attenuation of the beam. Evidently the xanthan gum was causing fluid opacity. The gum being used was of practical grade quality (Gum xanthan, 11138-66-2, Sigma Chemical Co. PO Box 14508, St Louis, M063178, USA), whereas a purer, analytical grade would be required to make a transparent analogue. During the period of work described in this thesis, the author was unable to obtain analytical grade xanthan gum.

An aqueous solution of Separan (Dow Corning) 0.01875% AP30, 0.05% AP45, 0.01% Magnesium Chloride, 4% isopropranol exhibits similar viscous properties to blood (84). The analogue was transparent and completely penetrable by the 1mW laser beam.

A blood analogue of 36% glycerol (by volume) and water was chosen for fluid flow experiments because it is transparent and its viscosity (3.5 cP), measured in a blood viscometer (Coulter Harkness Viscometer, Coulter Electronics Limited, Coldharbour Lane, Harpenden, Hertfordshire, UK) at room temperature, is similar to that of blood at high shear rates.

3.4 Manufacture of ventricles

Transparent artificial ventricles of hemi-ellipsoidal geometry, figure 2.5, were required for construction of blood pump prototypes.

3.4.1 Initial Attempts at Artificial Ventricle Production

3.4.1.1 Dip moulding

A male mould of standard histological wax (McQuilkin, melting point=40^{O}C) was cast from a female mould, machined from a block of a tough white plastic (acetal copolymer, Stockline Plastics Limited, Glasgow, UK). Polyurethane (Estane 58201 B.F. Goodrich, Belgium) dissolved in DMAC (Dimethylacetamide) was poured over the wax mould to coat it, and left in a dry air circulating vacuum oven for the DMAC to evaporate. The evaporation, at room temperature, required several days and the resulting ventricle was thin-walled and impregnated with air bubbles, figure 3.3. The wax was melted out, but some of it stuck to the ventricle's surface.

3.4.1.2 Rotational Moulding

A female mould was machined from acetal copolymer in two halves, figure 3.4a, so that when connected together it is leak proof. Silicone rubber (Sylgard 184 Silicone Elastomer, Dow Corning, McQuilkin & Co.) was poured into the mould, which was then sealed. The mould is rotated inside an oven for an hour, at 60^{O}C, while the silicone rubber gradually cures on the inside surface. The

silicone rubber remaining un-cured, after the period of rotation, collects at the base of the mould and sets over the next twenty-four hours.

The silicone rubber ventricle is readily extracted from the mould, figure 3.4b, and holes can be cut in the base with a sharp instrument.

Ventricles made by rotational moulding are prone to air bubbles and are not particularly robust, but they are transparent and were used for initial fluid flow experiments.

3.4.2 Towards a polyurethane pumping chamber

Artificial blood pump ventricles have been manufactured by vacuum forming (129), a combination of thermoforming and dip moulding (130) and by dip moulding alone (126,131). The envisaged conceptual SMV design requires a polyurethane ventricle, hence it is better to study fluid flow inside a polyurethane, rather than a silicone rubber, ventricle because the mechanical properties if the materials are different.

The ventricles need to be transparent, for the application of optical flow measurement techniques. A minimal level of durability is required for the purposes of design development. The method of manufacture need not be applicable to high volume production, albeit a repeatable method is desirable.

3.4.2.1 Injection Moulding

Polyurethane softens sufficiently at 180^{O}C to be injected into a mould such as the one shown in figure 3.5. This mould was machined from aluminium, and a hemispherical geometry chosen in the first instance because it was simpler to machine.

Injection was performed with a manually actuated tool in the laboratory and the results were unsatisfactory. The hemispherical shapes were either too thick or of thermally degraded polymer due to frictional heating.

3.4.2.2 Dip Moulding

A large ‘dipping bowl’, of internal diameter 160mm and depth 50mm, was made to order for coating sizeable moulds in polyurethane dissolved in DMAC, figure 3.6. The bowl was made from acetal copolymer which does not dissolve in DMAC. The lid seals to the bowl by a screw thread. Two parallel slots were milled in the lid so it could be turned and a wooden square glued to the base with silicone rubber compound to brace the bowl. A large quantity of polyurethane solution can be kept for several months.

A polyurethane ventricle was made by gluing two halves together, figure 3.7a. The halves were made by dipping a resin (Aluminium liquid, Devcon Ltd. Shannon Industrial Estate, Shannon, Ireland, 10711) mould into polyurethane solution and evaporating the DMAC, figure 3.7b. The disadvantages with this manufacturing method are that the ventricle has a rough, opaque, join around its middle and some of the resin male mould usually adheres to the ventricle inner surfaces.

3.4.2.4 Internal Coating

A problem that became evident with the previous technique is that the faceted moulds produced optical discontinuities at the polyurethane ventricle facet joins in a medium of different refractive index. To address this problem a smooth female mould was machined, in two sections, from acetal copolymer, figure 3.8.

Polyurethane solution was poured into the mould through the holes, in the thin section, and rolled around inside to coat the walls. The excess polyurethane was drained out and the mould put in the air circulating oven at 70^{o}C. The DMAC evaporated completely after 24 hours, and three coats yielded the ventricle in figure 3.9a. The ventricle is smooth and transparent with very few surface anomalies, and when placed in water it is almost completely transparent. Unfortunately there was a weakness along the seam that tore very easily, figure 3.9b. The seam occurs because of the discontinuity at the join of the two mould sections. A six coating ventricle was made which also tore in the same way. An attempt was made to fill the gap with silicone rubber, but polyurethane did not coat this surface. Instead the connecting surfaces of the mould were coated with polyurethane solution to form a gasket, but the ventricle still tore easily.

3.4.2.5 Dip Moulding onto a Wax Mould

A high melting point wax (Shell Micro-Wax HMP, Meade King, Robinson & Co. Ltd., 501 Tower Building, 22 Water Street, Liverpool, L3 1BL, UK) was purchased that solidifies at 84 to 88^{O}C. This is a favourable temperature for dip moulding as polyurethane degrades at about 200^{O}C and DMAC evaporates quickly at 60^{O}C.

A wax male mould, such as in figure 3.8, can be cast from the smooth female mould. The wax decreases in volume during transition from liquid to solid causing cavities and surface defects in the male mould. An extension to the inlet and outlet holes was made to allow molten wax to sink down and keep the mould full, as wax solidifies, figure 3.10. Casting with the extension piece in

place produced a male mould with few cavities, but opening the mould was difficult as the wax plugs tended to stick inside the extension piece.

The formal procedure developed for casting a quality wax mould is:

1. Warm female mould to 100^{O}C.
2. Wipe residual wax off female mould.
3. Clean the mould surfaces with acetone.
4. Spray surfaces, several times, with PTFE lubricant (RS Components 494-736, PO Box 99, Corby, Northants, NN17 9RS, UK).
5. Warm mould to 70^{O}C so the wax solidifies slowly to give a good finish.
6. Pour liquid wax into mould.
7. Monitor the inlet and outlet holes for one hour after casting and pour wax through the holes to keep the mould full.
8. Allow mould to cool overnight and then gently open it to release the wax form.

An air bubble free coating of polyurethane is easily applied to a wax form using the dipping dish. The former is then placed in the air circulating oven at 60^{O}C in orientation A shown in figure 3.11a, for twenty-four hours. Orientating the wax form in this way allows drips to form at the inlet and outlet holes, rather than the upper surface, where they can be easily cut off. Coatings were done in pairs, sequentially, so that DMAC can be evaporated in both orientations A and B, yielding a more symmetrical finish.

The wax is melted out of the inlet and outlet holes at 100^{O}C overnight in an oven. It is important to support the resulting polyurethane ventricle so it does not fall into the wax or deform. Placing it across a glass beaker with a block of acetal copolymer supporting the base is adequate, figure 3.11b.

Not all of the wax drains out of the ventricle and a coating remains on the inside, some of which can be peeled and picked off after immersing the ventricle in cold water. Standard detergent (Teepol D35-490, Philip Harris Scientific) has very little effect upon the wax residue, even when the ventricle is left in water and detergent at 95^{O}C (to melt the wax and possibly help the detergent to bond to it). Concentrated Persil washing up liquid (Lever Brothers Ltd., 3 St James Road, Kingston Upon Thames, Surrey, KT1 2BA, UK) was found to remove the majority of the wax residue. Ultrasonic bathing (XB6 Ultrasonic Bath, Grant Instruments Ltd, 29 Station Road, Shepreth,

Royston, Herts., SG8 6PZ, UK) for six hours in water and Persil detergent completed the wax removal. The first completed polyurethane ventricle is showing figure 3.12.

The base was made thicker by dribbling some polyurethane solution onto it with a spatula and evaporating the DMAC for twenty-four hours; the thickness of the base was not deemed to be critical to function for experimental purposes. Ventricles were made with 2, 4, 6 and 8 upper surface dip coatings. Thickness measurements were made of each ventricle, with a micrometer (pads are of circular cross-section and 3mm diameter), at the positions shown in figure 3.13, and the mean upper surface thicknesses are in table 3.1.

Table 3.1. Mean upper surface thicknesses of polyurethane ventricles manufactured by dip moulding onto a high melting point wax.

Number of Upper surface coatings	Average Thickness (microns)
2	158
4	265
6	337
8	351

Five more 4 upper surface dip coated ventricles were made, as the 4 dip procedure produces a thick enough ventricle for reasonable durability, yet is still transparent.

3.4.3 Repeatability of Manufacture

If the SMV is to eventually become a viable product then some consideration of possible manufacturing methods and their reproducibility is necessary, even at this early stage.

Thickness measurements were made for each of the six 4 dip ventricles. The mean, and the mean plus or minus one standard deviation, of the ventricle wall thicknesses are plotted on figure 3.14. The thickness measurements of the bases are quite variable, but it was decided that the base thickness of the ventricles was not critical at this stage as only a coherent surface was required for attachment to either B1 or B2.

The data for the upper surface thickness measurements were subjected to statistical analysis as they were considered to be the most repeatable. The distribution of each group of data was first examined by creating box plots of the range, quartiles and the mean or median, figure 3.15. None of the distributions appear to be particularly skewed, suggesting that each distribution can be considered as a random sample from a normal population.

A one way ANOVA (Analysis of Variance) was conducted upon the upper surface thickness measurements, of the six 4 dip ventricles, using a software package (SPSS for Windows Release

6.0, SPSS Inc., 444 N. Michigan Avenue, Chicago, Illinois 60611, USA). The Bonferroni (significance level = 0.05) multiple comparison test found significant differences between the first ventricle manufactured and the rest. There is some justification for the first ventricle made being different, as the manufacturing process was not completely formalised at that time. Repeating the one way ANOVA for the other five 4 dip ventricle upper surface measurements yielded a significant difference between the fifth and second ventricles.

The groups of measurements were then compared on a point by point basis between groups with a two-tailed t-test. The population means of the measurements for ventricles 2,3 and 6 were found to be equal at a 95% confidence interval, and for ventricles 4,5 and 6.

In conclusion this method of ventricle manufacture can produce strong transparent ventricles, and has potential as a repeatable method. Possibly mechanical control of the coating procedure or adopting a fixed drying orientation would improve the reproducibility of the process.

3.4.4 Other Avenues for Polyurethane Ventricle Manufacture

The wax mould dipping technique could instead be pursued with a low melting point metal replacing the wax. This could remove the problem of wax deposits on the inner walls of the resultant artificial ventricles and provide a better inner surface finish.

Alternatively for a potentially optically superior ventricle a two part elastomer (MED-4210, Nusil Technology, Carpinteria, CA USA) could be cured as a coating upon a metal mould. The metal could then be melted out. This process was attempted with the high melting point wax, but the elastomer failed to cure upon the wax mould. The elastomer has a lower refractive index than polyurethane, but is mechanically different. Thus the dynamic behaviour of a silicone elastomer would need to be compared with that of a ventricle manufactured from the material envisioned for the final device, which is currently polyurethane.

Another alternative would be to investigate vacuum forming of thermoforming polyurethanes, which has been used to manufacture artificial ventricles and valves (129).

3.6 Four Prototype Blood Pumps

B1 (Base 1 as described in Section 2.8.1) was machined from acetal copolymer. B2 was assembled from an acrylic base with holes angled at 45^{O} and sinuses machined from acetal copolymer. A polyurethane ventricle is attached to B1 with silicone rubber compound (RS 550-230, RS Components, UK), while attachment of a ventricle to B2 required gluing with a solution of polyurethane in DMAC.

P1 (Plate 1 as described in section 2.8.2) was made from an acrylic plate. The dome for P2 was cast in the smooth female mould out of silicone rubber (184 Sylgard) and attached to an acrylic plate with silicone rubber compound.

The four prototype blood pump geometries are shown in figure 3.16.

3.7 Summary

A flow circuit and linear actuator for assessing prototype blood pumps have been described. A transparent Newtonian blood analogue of water and glycerol is the most appropriate for this study. The chosen artificial polyurethane ventricle manufacturing method is to dip high melting point wax formers, cast from a female mould, into polyurethane solution. The wax is then melted out of the ventricles and the residue cleaned off. This production method has some potential as a repeatable process.

Four prototype blood pumps were assessed, made from combinations of straight (B1) and angled (B2) pipes with flat (P1) and domed (P2) compression plates (B1P1, B1P2, B2P1, B2P2).

Chapter 4. Development of Fluid Tracer, Ejection Fraction and Force Measurement Methodologies

4.1 Introduction

The proposed SMV is designed to assist the left ventricle of the failing heart. Devices of this type are commonly known as a ventricular assist devices (VADs). By exposing blood to artificial surfaces and flow conditions, VADs can induce blood clotting as discussed in section 1.9.4. Exposure of blood elements to high levels of shear stress, for a sufficient period of time, results in thrombosis in the vicinity of a VAD. Regions of static or slow moving blood also promote thrombus formation. Blood clotting induced by a VAD is physiologically undesirable as discussed in section 1.9.3.

Regions of stagnant and re-circulating flow can be identified by labelling a bolus of fluid with a tracer and observing its first journey through a VAD. The quantity of tracer in a VAD can then be measured as a function of time to characterise ejection fraction, filling and clearance rate. Shettighar *et al* analysed clearance rates in a VAD using tracers detected by nuclear imaging and chemical methods (100). It was concluded that the VAD cleared faster when fitted with tri-leaflet polyurethane, rather than Bjork Shiley, valves. Clearance rate was improved by orientating the inlet disk valve to direct inflow along the outer ventricle wall. Francishelli *et al* used dye to measure local clearance rates at different positions in the Penn State VAD (108). The results of the study could then be combined with the knowledge of wall (88) and turbulent (132) shear stresses within the VAD. The valve regions were identified as a problem area, as they clear more slowly than the rest of the pumping chamber and possess high wall and turbulent shear stresses.

The mean power required to provide a cardiac assistance of 6l/min is 1.3W, as discussed in section 2.4.1. However this is an ideal calculation assuming 100% efficiency. Measuring the force required to pump fluid in a mock circulatory flow circuit could provide some initial insight into the mechanics of the proposed device.

The aims of this study were to validate the measurement of ejection fraction by radionuclide imaging in artificial pumping chambers; compare two methods of clearance rate assessment of an artificial ventricle; take some preliminary force measurements; and assess the suitability of each method for future work. Clearance rates were assessed with optical and radionuclide tracers.

4.2 Method

Two proto-type, transparent, artificial ventricles, manufactured in our laboratory, were studied. One was constructed from silicone rubber (Sylgard 184 Silicone Elastomer, Dow Corning, McQuilkin & Co.) and the other from polyurethane (Estane 58201 B.F. Goodrich, Belgium). Both ventricles have a hemi-ellipsoidal geometry; external dimensions are shown on figure 1a. The polyurethane ventricle had an average upper surface wall thickness of 0.26mm and the silicone rubber ventricle an average wall thickness of 0.9mm. The ventricles were mounted upon blood pump design B1P1, figure 3.15, for the ejection fraction and tracer experiments. The preliminary force measurements were taken with B2P1.

4.2.1 Flow circuit

Each ventricle was evaluated in the mock circulatory loop, filled with physiological saline, consisting of a reservoir open to atmospheric pressure and a compliance chamber, figure 3.2. A pig tailed catheter (7F, 0.038, 10cm), with its end approximately 5cm before the inlet valve of the artificial ventricle under test, was inserted into the circuit to introduce tracer boli. Measurements were made with the electro-magnetic flow probes, connected by rigid tubing, up and down-stream of the ventricle. The compliance chamber pressure was continuously monitored with the pressure transducer and maintained at an average of 95 mm of Hg, for each experiment, by varying the adjustable circuit resistance. Each ventricle was compressed by a flat plate attached to the servo-controlled linear actuator. The actuator was driven by a sinusoidal waveform generator. The stroke length and frequency (beats per minute; bpm) of the linear actuator was monitored continuously during experiments.

4.2.2 Force Measurement

The force transducer in series with the linear actuator was connected to an SG200 amplifier (Maywood Instruments Ltd.) and the signal monitored continuously during experiments. A static calibration was performed in the laboratory by loading the transducer with known masses. The amplifier incorporated a filter that could be switched in to improve performance in electrically noisy environments or to reduce the effects of high frequency load fluctuations. The natural frequency of oscillation of the compression plate actuating system (linear actuator, force transducer, linear bearing and other components, figure 3.1) was measured 12 times by delivering an impulse of short duration to the compression plate. An example of the signal is shown in figure 4.1. The

natural frequency of vibration was 99Hz ± 3Hz (one standard deviation), thus the filter cut-off frequency was set to 50Hz.

4.2.3 Ejection Fraction Measurement

Ejection fraction is one of the most commonly used indices for assessment of ventricular performance. It is defined as the volume of fluid ejected during one pumping cycle divided by the end diastolic volume of the pumping chamber, expressed as a percentage. This study employed two independent measurements of ejection fraction. The measurements of ejection fraction were performed at a variety of stroke lengths and pumping rates, table 1, to simulate what might be encountered in physiological applications.

Table 1. Pump settings for ejection fraction measurements for polyurethane (P) and silicone rubber (S) ventricles.

Pump Rate (Beats per minute)

Stroke Length (mm)	30	40	50
26.2	P		
20.9	P	P	
19.6		S	
18.3	S	S	
17.0		S	S
15.7	P	S	P
14.4		S	
13.1	S	S	S
11.8	P	S	P
10.5	S	S	S
9.2		S	

4.2.3.1 By radionuclide ventriculography

A standard gamma camera (International General Electric, 25cm field of view mobile gamma camera), with an intrinsic resolution (Full Width at Half Maximum) of approximately 5mm, fitted with a low energy parallel collimator face was positioned approximately 1 cm from the edge of an artificial ventricle. This technique has been correlated against contrast arteriography and the standard deviation of ejection fractions found to be ± 2% (75). Tc-99m (Technetium) of activity ~400 MBq in 1 ml of saline was injected into the flow circuit. The artificial ventricle was then left to pump until the radionuclide distribution equilibrated, when the detected count rate stabilised. The

test conditions of the run were then carefully established in terms of stroke length, pumping rate and pressure. Data was acquired, upon stabilisation of pumping conditions, for 300 seconds, gated (synchronised) to the pump, in listmode. In listmode each detected count is recorded as a point in 2 dimensional space and time (***x,y,t***) together with the synchronisation signal (TTL) from the waveform generator, controlling the linear actuator. The listmode data were then retrospectively reconstructed into 24 frames, representing one ventricular cycle, by summing data from the 300 second record of counts. These frames represent variations in tracer activity in the ventricle during one pumping cycle. Regions of interest were twice drawn around the artificial ventricle on a totalised image (summation of the 24 images representing one cycle), figure 4.2, using standard nuclear medicine software (Maps 10,000 - Link Medical, Marlow, Bucks, UK). Regions were, also, twice drawn to the side of the ventricle to assess background counts. A graph of ventricle volume against time is obtained by totalling the counts within a region of interest and subtracting the background counts, normalised to area, on each of the 24 images, figure 4.3. Four graphs of ventricle volume were obtained from each set of results by different combinations of the two regions of interest with the two background regions. The records of counts were then used to calculate ejection fractions by equation 4.1.

$$EF = \frac{ED - ES}{ED - BG} \qquad \text{Equation 4.1}$$

ED = end diastolic counts = maximum counts over the cycle.

ES = end systolic counts = minimum counts over the cycle.

BG = background counts.

The mean and standard deviation of the four ejection fractions were then calculated.

4.2.3.2 By EM flow meter

Volume flow rate readings from flow probes up and down-stream of an artificial ventricle were recorded by the data acquisition system: instantaneous net flow rate through the ventricle was then found by subtraction, figure 4.4. Thus fluid flow into a ventricle is positive.

Ejection fraction as calculated by equation 1 does not account for any net flow through the ventricle in-between the major filling and emptying phases of pumping. There is some net flow through a ventricle, connected to the mock circulatory loop, between the major pumping phases, figure 4.4. This flow does not show up on a curve of ventricle volume against time, but is evident on a curve of flow rate, through the ventricle, against time. Therefore for a successful comparison of ejection

fraction measured with Tc-99m and EM flow meters it is necessary to convert the net fluid flow rate to ventricle volume by equation 4.2.

$$V(t) = \int_0^t Q(t)dt + V(0)$$ Equation 4.2

V(t) = volume of ventricle as a function of time.

Q(t) = volume flow rate relative to the ventricle.

t = time.

V(0) = volume of the ventricle (unstretched).

Ventricle volume can now be plotted against time over one cycle, figure 4.5.
Table 4.1 shows the settings of stroke length and pumping rate that ejection fractions were measured at, in the silicone rubber and polyurethane ventricles.
The standard deviation of ejection fraction calculated from electro magnetic flow meter readings was derived from 12 repeated sets of data. The 12 sets of data were taken at a pumping rate of 40bpm and a stroke length of 18.3mm. The standard deviation was found to be 0.2% of the mean.

4.2.4 Clearance Curves

Clearance curves, showing the variation of tracer within the polyurethane ventricle against time, were plotted using two tracer methods. Clearance curves were obtained at stroke lengths of 20.9, 18.3, 14.4 and 11.8 mm in combination with pumping rates of 30, 40 and 50 bpm.

4.2.4.1 By radionuclide tracer

To obtain graphs of the volume of radionuclide tracer (in counts) present in a ventricle, versus time, a 1ml bolus of Tc-99m pertechnetate was injected 5cm upstream of the ventricle, via the pig tailed catheter, during stabilised pumping conditions. Detected gamma ray counts were then collected in listmode as for the ejection fraction method described above. Successive images of 2 seconds duration were reconstructed from the listmode file of gamma ray count data. A region of interest was drawn around a totalised image and a region adjacent to it to allow background count correction. The counts contained within each region of interest on each frame were totalled and a clearance curve of counts, background corrected, versus time obtained. Figure 4.6 shows a typical clearance curve of percentage tracer (Tc-99m) present in the pumping chamber against time. The initial high peak is the first pass of the tracer through the pumping chamber. The second peak on

figure 3 is the second pass of a much dispersed bolus through the chamber, after its journey around the closed mock circulatory loop.

4.2.4.2 By Dye tracer

1ml of a visible tracer (Methyl blue histological dye at a concentration of 0.5g in 500ml of experimental fluid) that would not stain the apparatus was injected into the circuit, as described in the above Tc-99m tracer method, during pumping. The transparent ventricle was filmed with a CCD camera (Sony XC-711) and the images recorded on video tape. Images were analysed on a PC equipped with a frame grabber using image analysis software (Microscale TC, Digithurst Ltd, Royston, UK).

Clearance curve by average method: Images were captured in each pumping cycle, at the instant of maximum ventricle volume, after the injection of a dye bolus. The average light intensity (on an 8-bit, 0-255 grey scale) was calculated within a region of interest drawn around the ventricle, figure 4.7, on each captured image. Plotting the average intensities at maximum filling gives a graph of average intensity against time, figure 4.8. The dye bolus causes the ventricle to darken and so the average intensity drops, then rises again as the dye is pumped out of the chamber. Average intensity is not a linear measure of dye concentration within the ventricle. An approximate calibration of the average intensity values can be achieved by assuming an exponential relationship between incident light and transmitted light, as indicated by the Beer-Lambert law (133). Thus the average intensity (grey scale), I_{av}, is approximately related to volume of dye, D, within the ventricle, equation 4.3.

$$I_{av} = const_2 e^{-const_3 D} \qquad \text{Equation 4.3}$$

The constants, $const_3$ and $const_2$, in equation 4.3 were determined experimentally. Calibration images were generated by filming a static ventricle, filled with fluid, in the position of maximum ventricular volume. The uniform concentration of dye within the ventricle was increased incrementally. For each dye concentration the average intensity within a region of interest drawn around the ventricle was calculated. An exponential curve was then fitted to the results using a spreadsheet package (Microsoft EXCEL, version 5). The resulting relationship, figure 4.9, can then be applied to the average light intensity results, such as those in figure 4.8, to give a clearance curve of tracer within the ventricle versus time, figure 4.10.

Analysis by pixel method: The average method, described above, is quick to perform, but an approximation when applied to non-uniform dye concentrations. The amount of dye present in the ventricle could be measured more exactly by calculating the volume of dye at each computer pixel within a region of interest, equation 4.4.

$$L_p = ae^{-bK} \qquad \text{Equation 4.4}$$

K = ml of dye/cm^2. ***a,b*** = constants. L_p = Light intensity at a point on the ventricle, in the field of view.

$$K = c \times l$$

c = average concentration of dye (ml/cm^3) along a line of sight through the light absorbing volume. ***l*** = length of the path that incident light travels to an observer, through the light absorbing volume (path length).

The amount of dye at a pixel can be found by multiplying ***K*** by pixel area. Summing the volume of dye at each pixel over the ventricle gives total dye volume within the ventricle. These two methods of analysis, average and pixel, were applied to images taken at a stroke length of 20.9mm and pumping rate of 30 beats per minute. The pixel analysis images were manipulated so that each pixel represented one square millimetre. The clearance curves produced by each method are shown in figure 4d. As the pixel method is extremely time consuming to apply, and the curves are not substantially different, it was decided to attempt to correlate the average dye method with the Tc-99m method.

4.3 Results

An example graph of force, velocity and displacement against time is shown in figure 4.11. The velocity is derived from the displacement data by equation 4.5.

$$v_i = \frac{d_{i-1} - d_{i+1}}{2.\Delta t} \qquad \text{Equation 4.5}$$

v_i= velocity at point ***i***. d_{i-1} = displacement at point ***i-1***. d_{i+1} = displacement at point ***i+1***. Δt = time interval between points of measurement.

Power can be plotted against time by multiplying the synchronised force and velocity signals, figure 4.12. The maximum power required to compress the ventricle, at a flow rate of 1.98 l/min at 40bpm (18.3mm linear actuator stroke length), was 2.39W.

The average power during compression of the ventricle was 1.208W, over 0.75 seconds. Therefore the energy expended was $1.208 \times 0.75 = 0.906$ J. Force data was collected for the same pumping conditions for B2P1 during 10 different experiments. The standard deviation of average power during ventricular compression was calculated from force transducer readings derived from 10 repeated sets of data. The 10 sets of data were taken at a pumping rate of 40bpm and a stroke length of 18.3mm. The standard deviation was found to be 0.88% of the mean.

Figure 4.13 shows the ejection fractions measured by the Tc-99m tracer method plotted against those measured with the EM flow probes at corresponding flow rates. Least squares linear fits, of near unity gradient, have been fitted to the silicone rubber and polyurethane ventricle data. The standard deviation of the ejection fractions measured by the Tc-99m method was typically $\pm$2% (n=88). The standard deviation of the EM flow meter derived ejection fractions was $\pm$0.2 % (n=12).

To compare the clearance curves measured at 11 different flow rates, by each tracer method, exponentials of the form $y=ae^{bx}$ were fitted to the curves, starting from the first data point chronologically after the maximum. The coefficients of x (the b's) for each method are plotted against each other and a least squares linear fit (r=0.997) made to the data on figure 4.14.

4.4 Discussion

Ejection fractions measured by radionuclide ventriculography have been correlated with EM flow meter measurements, over a range of artificial ventricle pumping conditions. The gradients of the fitted lines on figure 4.13 being 1.02 and 0.94 clearly demonstrate ejection fraction can be confidently measured using Tc-99m tracer.

Equation 1 used to calculate ejection fraction with the Tc-99m method has a right hand side denominator that is computed at the instant of maximum ventricle volume, while the ventricle is pumping. Both the ventricles studied have elastic walls and thus stretch during filling. The differences in geometry, between the stretched and unstretched states, were estimated by filming each ventricle pumping against a pressure of 95 mm of Hg with a CCD camera. Images of each ventricle in its stretched and unstretched states were compared using image analysis software and the radial difference measured. The radial change was found to be approximately 1mm, for the polyurethane ventricle, which would result in a volume difference of approximately 12ml between the stretched and un-stretched states. For the silicone rubber ventricle the radial change was approximately 2mm resulting in a 20ml volume difference. The stretched volumes, for each ventricle, are used in the calculation of ejection fraction from the EM flow meter data to give the

results in figure 4.13. The results in figure 4.13 can be used to calibrate the Tc-99m method for applications where EM flow probes cannot be used, such as *in vivo*.

The clearance curves obtained with the Tc-99m and optical (dye) tracers in a polyurethane ventricle are very similar. The gradient of the line fitted to the comparison of clearance curves, figure 4.14, is 0.91 and suggests that the dye method measures a faster clearance of the ventricle than does the Tc-99m method. This is possibly because there is a tendency to include more than just the ventricle within a region of interest drawn upon a totalised image, figure 4.2, which will yield a slightly slower clearance measurement.

Francishelli *et al* obtained continuous clearance curves of concentration inside a VAD (ventricular Assist Device) using an optical tracer and fibre optic probe (108). The clearance curves were exponential in nature and characterised as such. Shettighar *et al* applied Tc-99m to a VAD, but mainly utilised a chemical tracer and found similar exponential clearance curves (100).

The dye tracer method is more convenient and economical than the Tc-99m method and has a better spatial resolution, while the Tc-99m method can be applied to pumping chambers with no optical access. The major benefit is that the Tc-99m method can be readily applied to implanted blood pumps, to yield *in vivo* data of similar quality to *in vitro* results. The relative geometric independence of radionuclide methods, to quantify ejection fraction, is well recognised, and indeed, is the accepted method of choice for serial assessment of ventricular function in patients. The use and correlation of both methods will allow the extension of *in vitro* findings to the experimental *in vivo* situation.

The energy required for cardiac assistance with an artificial pumping chamber can be estimated by equation 4.6.

$$\boldsymbol{Ej} = \boldsymbol{P}.\Delta\boldsymbol{V} \qquad \text{Equation 4.6}$$

Ej = the energy (Joules) required to compress a pumping chamber, ***P*** = the pressure (Pascals) against which the chamber is working, $\Delta\boldsymbol{V}$ = the change in volume (cubic metres) of the chamber. The energy required to compress the ventricle, mounted upon B2P1, against a pressure of 13243.5Pa (equivalent to 100 mm Hg) with an ejection fraction of 49.5%, and hence stroke volume of 49.5×10^{-6} m^3 (49.5ml) is $13243.5 \times 49.5\times10^{-6}$ = 0.66J, by equation 4.6. There is a difference of 0.246 J between this and the experimental value (0.906 J) possibly because energy is expended stretching the polyurethane ventricle to increase the internal pressure from just above atmospheric

to 100 mm Hg. An approximate calculation of the energy necessary to stretch the ventricle can be made by considering the radial increase of a hemisphere whose volume has been expanded by **12**ml. The value of 12ml is taken from the discussion above upon the volume of the polyurethane ventricle in its stretched and unstretched states. The volume of a hemisphere, of radius ***r***, is:

$\frac{2}{3}\pi r^3$. If the increase in radius, ***r***, of the hemisphere is ***d*** (cm) then equation 4.7 can be solved for ***d***.

$$\left((d+r)^3 - r^3\right)\frac{2}{3} = 15 \qquad \text{Equation 4.7}$$

The real root of this cubic is 0.14 cm found by numerical iteration (Mathcad version 4.0, Mathsoft Inc. 201 Broadway, Cambridge, 02139 USA). The change in circumference of the hemisphere is $2\pi d$=0.0088m. If the upper surface of the ventricle is approximated as a square sheet of polyurethane of 300 micron thickness, and side length 0.09m, then the force, ***F***, required to keep it stretched at 0.0088m can be found by equation 4.8.

$$F = \frac{EeA}{l} \qquad \text{Equation 4.8}$$

E = Young's modulus which will be taken as 7×10^6 Pa for this calculation. ***A*** = cross-sectional area of the polyurethane sheet, and ***l*** = original length of sheet. ***e*** = the extension of the sheet.
The force required is 19.99N and assuming a linear variation of force, from 0 to 19.99N, with extension the work done is $\frac{Fd}{2}$ =0.088 J. Stretching the square sheet in both directions by ***d*** would require 0.18J which is reasonably close to 0.246J; the difference between the experimental and calculated (by equation 4.6) work required to compress the ventricle.
At 0.75 seconds on the graph of force against time, figure 4.11, the reading of the force transducer has only just started to decrease after the completion of ventricular systole. Once the pressure within the ventricle drops below 95mm Hg then the outlet valve closes, but internal ventricular pressure is still above that of the inlet pipe, therefore there is some potential energy stored in the

system. This energy is apparent on figure 4.12 as positive power values after 0.75 seconds because the pressurised ventricle is applying force to the compression plate. The force upon the compression plate due to the pressurised ventricle decreases quickly as the compression plate moves away and ventricle pressure drops, figure 4.11 between 0.75 and 1.0 seconds. Two impulses are delivered to the compression plate after the ventricle pressure has decreased below that of the inlet pipe and filling started, figure 4.11 at about 1.2 and 1.3 seconds. These impulses are due to the transfer of momentum from the in-flowing fluid to the compression plate. One of the salient points of this design of SMV is the use of a spring to return the skeletal muscle to its resting length prior to the next contraction, figure 2.6 and section 2.4. These results indicate that there is some energy available to pre-stretch the muscle. The forces available are of the order of tens of Newtons, while a force of the order of 2N is required to extend a sheep latissimus dorsi muscle, at its resting length, by 10mm (Personal communication from Shortland,A.P. 1997).
It must be noted that these force measurements are made with a proto-type blood pump actuated by a mechanism that is controlled by a sinusoidal displacement signal. Skeletal muscle does not behave as a sinusoidal displacement generator, but instead exhibits complex interrelated force, velocity and displacement characteristics.

4.5 Summary and Conclusions

The Tc-99m method of measuring ejection fraction has been calibrated against electro-magnetic flow probe measurements.
Optical and radionuclide tracer clearance curves have been compared and are in agreement.
The optical tracer technique has a better spatial resolution than the Tc-99m method, but its application is limited to the study of artificial ventricles that permit optical access.
Some preliminary measurements have been made of the force required to compress an artificial ventricle attached to the B2P1 blood pump design.

The application of the methods described in this chapter, to the four blood pump designs, is described in the next chapter.
Part of the work detailed in this chapter forms a published paper and can be found in Appendix A.

Chapter 5. Evaluation of Four Blood Pump Geometries (ejection fraction, force, fluid tracer)

5.1 Introduction

Regions of stagnant and re-circulating flow can be identified by labelling a bolus of fluid with a tracer and observing its first journey through a VAD. Ventricular assistance in the form of a blood pump can improve patient's quality of life and allow the heart to recover (9,134,135). Blood pumps need to be improved beyond what is currently available. A device has yet to see clinical use that can provide long term, totally implanted and non-thrombogenic support.

In vitro experimental work upon the fluid dynamics of heart assistance pumps can lead to design improvements (49,76,103,108,115,117). It is well known that exposing blood elements to high shear stress or artificial surfaces induces blood clotting (59,63,64,136). Minimising the time of exposure to these adverse conditions can reduce the thrombogenicity of blood pumps. Blood element contact with artificial surfaces could well be the major cause of thrombosis in artificial blood pumps (59). Furthermore regions of stagnant or slowly re-circulating blood promote thrombus formation (137,138). Thrombosis in the human body is dangerous and can cause damage to the vital organs.

The aim of this study was to perform an initial investigation of four prototype blood pump geometries by employing optical tracer, ejection fraction and force measurement techniques. The aspects of fluid flow examined were: bulk tracer residence times, 'clearance curves', and areas of re-circulating or stagnating fluid. Clearance curves, produced by a validated method, illustrate the variation of fluid tracer volume inside a pumping chamber with time (139). The analysis of optical data was extended to produce colour maps of tracer concentration with time, to facilitate the investigation of different geometries.

5.2 Methods

The four geometries, as described in section 3.2, were assessed in the mock circulatory loop. The mean pressure in the compliance chamber was maintained at 95 mm of Hg during the experiments. A computer controlled linear actuator applied a sinusoidal displacement to the compression plate, with the amplitude of plate movement defined to be the stroke length. The pumping frequency chosen for this initial evaluation of four blood pump geometries was 30 beats per minute (bpm). Stimulating a conditioned skeletal muscle every other cardiac cycle may well allow better perfusion of the muscle between contractions, as discussed in section 2.3. A pumping rate half that of the average human heart, at rest, is 36 bpm. A pumping rate of 30bpm is more convenient to work with in the laboratory when analysing data and performing flow visualisation studies.

Each design of blood pump was calibrated by plotting linear actuator stroke length against volume flow rate, figure 5.1, calculated from electro-magnetic flow probe data.

5.2.1 Force Measurements

Force readings were collected for each ventricle at flow rates of 2.0 and 1.0 litres/minute at 30bpm, using the system described in section 4.2.2.

5.2.2 Clearance Curves

To produce a clearance curve, 1ml of dye (Methyl blue histological dye at a concentration of 0.5g in 500ml of experimental fluid) was injected 5cm upstream of the inlet valve and the ventricle filmed. The dye bolus was formed during the ejection phase of the blood pump, when the upstream fluid is virtually static, to give consistent bolus size and position. Images from a CCD camera (Sony XC-711) were recorded on video tape. The volume of tracer at the instant of maximum ventricle volume, over consecutive cycles, within the ventricle was measured with image analysis software (Microscale TC, Digithurst Ltd, Royston, UK). The analysis method was calibrated using a set of ten images of known, uniform, dye concentration. Plotting dye concentration against time yielded a clearance curve, for each geometry, at each flow rate. Clearance curves were derived, from optical data, at flow rates of 1.0, 1.55 and 2.1 litres/minute for each geometry and at a flow rate of 2.9 litres/minute for the P1 geometries. For each flow rate the pumping chamber shape was different at the instant of maximum volume during each pumping cycle, because the linear actuator stroke length was different. Therefore calibration images were produced for each geometry and flow rate combination, with the compression plate appropriately displaced.

Ten repeat optical tracer experiments were conducted upon the same pump geometry at a constant flow and pumping rate. Clearance curves were obtained from the ten sets of optical data, figure 5.2. The average standard deviation, from the mean, of each dye volume measurement was 1.8%.

5.2.2 Colour Maps

The optical data, used to produce the clearance curves for each geometry at a flow rate of 2.1 litres/minutes, was further analysed to obtain colour maps of dye concentration. The depth of a polyurethane ventricle as viewed from the orientations shown in figure 2.13 varies. Consequently a raw video image of a ventricle containing a uniform concentration of dye is not a uniform colour. Light incident upon the ventricle will pass directly through it to an observer on the other side. Some of the light will be absorbed by the dye. Therefore at each point on a video image, of the ventricle, the intensity of recorded light is dependent upon the amount of dye encountered by the incident light, and hence the path length, ***l***. This can be represented by Equations 5.1 and 5.2.

$$L_p = ae^{-bK} \qquad \text{Equation 5.1}$$

K = ml of dye/cm^2. ***a,b*** = constants. L_p = Light intensity at a point on the ventricle, in the field of view.

$$K = c \times l \qquad \text{Equation 5.2}$$

c = average concentration of dye ml/cm^3, along a line of sight through the light absorbing volume. ***l*** = length of the path that incident light travels to an observer, through the light absorbing volume (path length, cm).

The processing method for video images is shown on figure 5.3. An image of the ventricle with no dye in it is subtracted from each raw video image to remove background effects. The background corrected images are then cut down so they contain just the ventricle. Next the images are converted from a TIF (Tagged Image Format) graphics file to a raw binary format, where each pixel is equivalent to a square millimetre, using image manipulation software (Photostyler, Autodesk Inc.). Equations 5.1 and 5.2 are then applied to each pixel to calculate the average concentration of dye along the corresponding path length.

5.2.2.1 Determine Constants

To apply equation 5.1 at each pixel the constants (***a,b***) were determined using the calibration images of known, uniform, dye concentration in each geometry. Equation 5.1 was fitted at 100

pixels over the ten calibration images. The 100 pixels formed two horizontal lines across the middle of the ventricle. Tracer concentration was calculated at each point by equation 5.2, using a computer generated grid of path-lengths. The equation defining an ellipsoidal surface is:

$\frac{x^2}{A^2}+\frac{y^2}{B^2}+\frac{z^2}{C^2}=1$. ***A***,***B*** and ***C*** are the major axes of the ellipsoid, and ***x,y,z*** are orthogonal cartesian co-ordinates. If ***(x,y)*** are the planar co-ordinates on a binary format image of a ventricle then ***z*** is the path length at each pixel (parallel light paths were assumed). The maximum error between actual and calculated path length, given the distance between camera lens and objective, at a pixel 5mm from the wall of the ventricle is 2%. The portion of the ventricle, on the image, not part of the hemi-ellipsoid was approximated as a solid of elliptical cross-section with the ends parallel to each other. The path length, ***z***, is calculated by: $\frac{x^2}{A^2}+\frac{z^2}{C^2}=1$. The path lengths are shown on figure 5.4 as a grey scale image, with a linear scale from white (grey value of 255) to black (grey value of 0) corresponding to a scale of 0mm to 56mm path length. A typical calibration image is shown in figure 5.5 after the background effects have been subtracted.

The constants (***a,b***) were thus calculated, by fitting equation 5.1 to a curve of 10 points, 100 times and the mean values obtained. The constants (***a,b***) were checked by applying equation 1a to the calibration images at each pixel. The calibration images were converted to raw binary format and ***K*** found at each 1mm square pixel. Totalling the ***K***'s and multiplying by pixel area yielded a measurement of dye volume within the ventricle. The calculated dye volumes were then compared to the known values and the constants (***a,b***) validated. BASIC programs manipulated the binary graphics files and applied equation 5.1.

The measurement resolution at a pixel is dependent upon the amount of dye present along the path length (***K***). Plotting ***K*** against L_p, by equation 5.1, demonstrates the relationship between measured pixel intensity and the amount of dye along the path length, at that pixel, figure 5.5. Clearly this technique is more sensitive to low amounts of dye.

5.2.2.2 Colour Concentration Maps

K was calculated at each pixel on the experimental images. Multiplying ***K*** at each pixel by the corresponding path length yielded the average concentration of dye, ***c***, along the path length, or line of sight, at each pixel, in ml/cm^3. The dye concentrations were converted to a 0-255 grey scale,

then into a raw binary image and then to a TIF image. Finally the grey scale image is converted to a colour map of dye concentration, for additional clarity, figure 5.3.

The colour map process was applied to the clearance curve results for each geometry, at a 2.1 litre/min flow rate. The colour maps were played in sequence, using animation software (Animator Pro, Autodesk Inc.), to compare the variation of dye concentration in each geometry as a dye bolus enters and subsequently washes out.

5.2.3 Inflow Jet

Consecutive images of the dye bolus entering each geometry were enhanced to better visualise the inflow jet, figure 5.7. The grey balance of the images was altered to expand the range of grey values across the ventricle to the entire 0-255 range, using the image manipulation software. The image brightness information was then compressed (posterised) to eight levels of grey, after blurring the images slightly to reduce optical noise and refine contours. The image processing was automated using the Recorder, a Windows accessory (Microsoft). Enhanced images depicting the dye bolus for a full cycle were animated to compare the inflow jet in each geometry.

The animations of the jet were synchronised by starting each at the frame of the first downward movement of the compression plate. The repeatability of the tracer bolus visualisation of the jet was evaluated by performing five repeat experiments, upon the same pump geometry. The bolus of dye tracer was found to enter the ventricle at the same frame, after the initial downward movement of the compression plate, in each experiment.

The digital freeze frame of the video recorder, that enabled frames to be held while they were captured by the image analysis computer, only worked continuously for two minutes. It took longer than two minutes to capture sufficient video frames for a complete animation. To allow the continuation of the capture process, from the correct frame, a time code generator (Horita, P.O. Box 3993, Mission Viejo, CA 92690) was used to add a time code signal, to the video signal from the CCD camera. The time code signal consists of hours, minute, seconds and video frames (25 per second) that can be displayed on the bottom of the camera images and recorded onto video tape.

5.3 Results

The ejection fractions corresponding to the flow rates of 1.0, 1.55, 2.1 and 2.9 litres/minute, at a pumping rate of 30 beats per minute, were 33.3%, 55.7%, 70% and 96.7% respectively (standard deviation = 0.2%).

The resultant volume flow rate curves for each design are shown on figure 5.8, at a flow rate of 2.1 litres/minute. Ventricular filling starts earlier in the P2 designs.

Figure 5.9 is an example graph of volume flow rate against force for B2P2 at a flow rate of 2.0 litres/minute. The force curve oscillations appear to be slightly out of phase with those on the resultant flow rate curve during ventricular filling (0 to 1 seconds), but in phase during ejection (1 to 2 seconds).

Power is plotted against time for each design on figure 5.10. The power plot from 0 to 1 seconds occurs during ventricular compression, while from 1 to 2 seconds the power values correspond to force applied to the compression plate during ventricular filling.

The energy values necessary to compress the ventricles (from 0 to 1 seconds) on each of the designs during a pumping cycle are shown in table 5.1, at flow rates of 1.0 and 2.0 litres/minute. The work required as calculated by equation 4.6 is 0.44J and 0.88J for 1.0 and 2.0 l/min flow rates, respectively.

Table 5.1. Energy (Joules) required to compress the artificial ventricle on each design derived from experimental data.

		Flow Rate
Pump Geometry		**1.0 litres/minute**	**2.0 litres/minute**
	B1P1	1.25	0.535
	B1P2	1.2	0.524
	B2P1	1.3	0.546
	B2P2	1.109	0.496

5.3.1 Clearance Curves

Figure 5.11 shows the clearance curves plotted on linear axes, for a 1.0 litres/minute flow rate. Percentage tracer, of the maximum inside each geometry after the formation of the dye bolus, is plotted on the y axis to compare clearance curves. The quick filling, within two pumping cycles, is evident. Figures 5.12, 5.13 and 5.14 show the clearance curves for the four geometries (B1P1, B1P2, B2P1, B2P2) at flow rates of 1.0, 1.55 and 2.1 litres/minute. Percentage tracer is plotted on a log scale to better depict the different rates of clearance between the geometries. At each flow rate the order of fastest to slowest clearing geometry is:

B1P2 → B1P1 → B2P2 → B2P1

The clearance curves for the P1 geometries, at a flow rate of 2.9 litres/min, are shown on figure 10. The same order of fastest to slowest clearing geometry prevails

The 100% curves will be referred to in the Discussion.

5.3.2 Colour Maps

The scales of dye concentration against colour are shown for each geometry, figure 5.16a. The variation of dye concentration inside the four geometries, at a flow rate of 2.1 litres/min, is presented on figure 5.16b. Pictorial results for the four geometries are presented in the pattern shown in figure 2.13. The position of inlet and outlet pipes is as shown on figure 2.13.

Cycle 1 depicts the distribution of dye at peak ventricle volume during the cycle that the dye bolus first enters the ventricle. The major concentration of dye in B2P1 is nearer to the lower ventricle wall than in B2P2. The same difference is prevalent to a lesser degree between B1P1 and B1P2. The B1 geometries have a concentration gradient ranging from high at the left side near the inlet, to low concentration on the right, at the outlet. Conversely the B2 geometries have a higher concentration of dye near the outlet and nearer to the compression plates.

At cycle 2 clear fluid, containing no tracer, has entered each geometry. The horizontal gradient of dye concentration, from high to low, is now reversed and is from left to right in the B2 geometries, as dye has washed around to the inlet side of the ventricle. In the B1 geometries clear fluid has entered on the left and the dye moved to the right. The P2 geometries have larger clear areas than the comparable P1s, for example B1P2 compared to B1P1.

At cycle 3 the clearance of dye from left to right in the B1 geometries has continued, while tracer is still more concentrated near the outlet in the B2s. The P1s have high concentrations of dye near the compression plates than do the P2s. This is particularly evident between B2P1 and B2P2, as in B2P1 dye is concentrated along the bottom of the ventricle.

At cycle 4 dye is still concentrated along the bottom of the B2P1 ventricle and near the inlet. There is also a small concentration of dye in B1P1, to the right of the outlet, but this is similar to the pattern seen in B1P2 in cycle 3 and clears in the next cycle.

5.3.3 Jet Images

In figure 5.17 consecutive video images, of 1/25th of a second duration, describe the inlet jet, visualised with dye, as it enters each device starting at T0. The jet heads straight down in the B1

geometries, and in the B2s it angles down and towards the right. The jet impacts the plate earlier at T1 in the P2s and later at T2 in the P1s. Also the jet disperses more in the P2s than in the P1s. The pattern of image presentation and pipe orientation is as described in figure 2.13.

5.4 Discussion

The P2 geometries could only achieve a maximum ejection fraction of 70%, as a larger stroke length would clash the plate and base. The P1s almost completely compress the ventricle and can generate a 96.7% ejection fraction. Hence all four geometries were assessed at ejection fractions of 70%, and below. The P1s were also assessed at 96.7% ejection fraction.

The oscillations of the resultant flow curve, figure 5.9, appear to start during ventricular filling at A. The initiator is probably the rate of filling overtaking the compression plate displacement, thus pressurising the ventricle and stretching it. The rate of filling slows as the ventricle stretches and an impulse is delivered to the compression plate that registers as an oscillation in the force curve at B. The oscillations on both curves appear to die out towards the end of filling. Thus the oscillations on both curves during ejection, from 0 to 1 seconds, may well be due to the ventricle initially being stretched more than necessary and bouncing back.

The oscillations of the resultant flow curves for the P2 designs, figure 5.8, appear to be of a lesser amplitude and start earlier during ventricular filling. This is probably because a larger linear actuator stroke length must be used for the P2 designs, than the P1s, to achieve a flow rate of 2.1 litres/minute. The P2 compression plates return at a higher velocity after compressing the ventricle thus releasing the pressure in the ventricle faster and allowing filling to occur sooner.

Less energy appears to be required to compress the P2 designs to produce flow rates of 1.0 and 2.0 litres/minute, figure 5.10 and table 5.1. The differences between designs are as much as 17% which is substantial given the likely limited power available from a conditioned skeletal muscle.

The results presented in figures 5.8, 5.9, 5.10 and table 5.1 are based upon a sinusoidal displacement curve. It is unlikely that a conditioned latissimus dorsi would behave in such a way given that muscle exhibits complex force, velocity and displacement interrelated behaviour. The current system for operating blood pump proto-types could be developed to monitor the force transducer signal and incorporate the data into a real-time muscle model, such as Hill's (12). The model parameters would need to be established through experimental work and/or from the scientific literature.

Ventricular compression by P2 provides a smooth reversal of curvature due to the meeting of mirror image shapes. It was thought that B2 might induce a rotating vortex during filling, in the plane of section A figure 2.12, which can provide good pumping chamber wall washing (103,106).

5.4.1 Clearance Curves

Although tracer clears fastest from B1P2, at each flow rate, it may have regions of stagnating or re-circulating fluid. There are two extremes of tracer passage through a pumping chamber: Mode (a) - 'Conveyor belt' or '0% mixing', Mode (b) - '100% mixing'.

Mixing occurs when tracer is transferred between fluid elements. In mode (a) tracer enters the pumping chamber then passes through, and out, as a coherent bolus. The clearance curve, in this mode, increases sharply then decreases, at the same rate, because tracer enters and leaves as a coherent volume, figure 5.18a.

In mode (b) tracer is always uniformly mixed (100% mixed) in the ventricle after the filling phase, at maximum ventricle volume during each cycle. Therefore the difference in tracer volume between cycle ***n*** and ***n-1*** is the volume of tracer at ***n-1*** multiplied by ***EF/100***, where ***EF*** is ejection fraction as a percentage.

$$V_t(n)=V_t(n-1)(1-EF/100)$$

$V_t(n)$ - volume of tracer in the ventricle at the ***n***th cycle, at the instant of maximum ventricle volume.

If a volume of tracer, ***T***, enters the ventricle at ***n=0*** then:

$$V_t(0)=T$$

$$V_t(1)= V_t(0)(1-EF/100)=T(1-EF/100)$$

$$V_t(2)= V_t(1)(1-EF/100)=T(1-EF/100)^2$$

$$\therefore\ V_t(n)=T(1-EF/100)^n \qquad \text{Equation 5.3}$$

Equation 5.3 is plotted on figure 5.18a as the mode(b) clearance curve for an ejection fraction of 50%.

In reality a pumping chamber will produce pulsatile flow that is inherently mixing, so mode(a) will not occur, but equally mode(b) will not solely exist as uniform mixing is unlikely to occur. A compromise somewhere between the two modes is more likely. Assuming fluid flow in a chamber is repeatable over pumping cycles then mode(a) would provide the fastest clearance, and mode(b) a chamber that never perfectly clears ($V_t(n)$ tends to ***0*** as ***n*** increases). Mode(b) is plotted on each of

the clearance curve graphs, figures 5.11, 5.12, 5.13, 5.14 and 5.15, starting at the maximum of the curves, and denoted in the legend as 100%. A clearance curve resulting from a combination of mode(a) and mode(b) effects is initially less steep than the 100% mixing curve, but then dips below it as coherent formations of tracer exit the pumping chamber.

The 100% clearance curves are steeper than any for the four geometries at each flow rate. This could, partly, be because not all of the tracer bolus has entered each geometry during the same pumping cycle. Thus tracer will enter before and after the clearance curve maximum delaying ventricle clearance and flattening the clearance curve maximum. This effect can be modelled numerically by adding different clearance curves together. For instance, if half of a bolus enters during cycle 1 then T can be set to 50% at n=1 and equation 5.3 plotted. If the rest of the bolus enters during the next cycle then T can be set to 50% at n=2, equation 5.3 plotted and the two curves added together. The resulting curve has a more rounded maximum and is less steep than the 100% mixing curve. Delayed bolus entry clearance curves with maxima that are similar in shape to those measured experimentally, at each flow rate, are less steep than the B1P2 and B1P1 curves, but are still steeper than the B2P2 and B1P2 curves.

Similar effects could be caused by valve regurgitation, whereby tracer leaves the pumping chamber and then re-enters it. This could happen at both the inlet and outlet valves. The tracer volume involved would be small, but if 3% of the overall tracer volume in the pumping chamber during each cycle leaves then re-enters the model clearance curves decrease almost as slowly as the B2P2 ones.

The valve regurgitation effect is likely to be particularly pronounced for the B2 geometries as tracer does re-circulate back round to the inlet valve side of the pumping chamber over several cycles, as can be seen on the colour tracer maps of dye concentration, figure 5.16b.

Another possible contributing factor towards the experimentally derived clearance curves being less steep than the 100% mixing curve is molecular diffusion of tracer across fluid streamlines.

Equation 5.3 was fitted to the clearance curves (figures 5.11, 5.12, 5.13, 5.14 and 5.15) in a spreadsheet (Microsoft EXCEL, version 5) and the constants, ***EF*** and ***T***, calculated. ***EF*** is apparent ejection fraction and would be equivalent to the actual ejection fraction if 100% mixing of tracer occurred during every pumping cycle. A mixing coefficient is defined as:

$$\textit{mixing coefficient} = \frac{\textit{apparent ejection fraction}}{\textit{actual ejection fraction}} \qquad \text{Equation 5.4}$$

The mixing coefficients for each geometry, at each flow rate, are displayed on table 5.2. The geometry with the highest mixing coefficients (B1P2), at each flow rate, clears fastest. The mixing coefficients are different at each flow rate for each geometry, with no overall trend between flow rate and mixing coefficient, such as better mixing at lower flow rates.

Table 5.2. Mixing coefficients for the four geometries.

Pump Geometry

Pump Geometry	B1P1	B1P2	B2P1	B2P2
2.9	0.657		0.585	
2.1	0653	0.837	0.592	0.607
1.55	0.637	0.881	0.564	0.577
1.0	0.748	0.974	0.57	0.599

Clearance curves were produced for six regions in each geometry, at a flow rate of 2.1 litres/minute. The six regions are defined on figure 5.18b. ***K*** was calculated at each pixel, in each region, by equation 1a, utilising the quantitative image data. Multiplying total ***K*** in each area by pixel area yields dye volume, within that area. The six region clearance curves were found to be of a similar form to figure 5.11. The difference in time to maximum tracer volume between each region was not more than one pumping cycle. Apparent ejection fractions were calculated, by fitting equation 5.3 to the six region clearance curves. The apparent ejection fractions for six regions in each pump geometry are plotted on figure 5.18c. The B2P1 geometry has the lowest apparent ejection fractions in each region, and B1P2 the highest.

Virtually all the apparent ejection fractions are higher than the actual ejection fraction of the entire ventricle, because on this scale of inspection tracer boli maintain some coherent structure resulting in mode(a) effects upon local clearance. There are substantial differences between regions in the same geometry. The standard deviations for the mixing coefficients in each region were calculated from experimental data. The same tracer experiment was repeated five times, at the same flow rate, for the same ventricle. The standard deviations are shown for each region, on the schematic, in figure 5.18b.

An attempt was made to fit equation 5.3 to the variation of dye tracer, with time, at each 1 millimetre square pixel. The apparent ejection fractions were normalised, converted to a grey scale

(0-255) and then to a pseudo colour image. Typical clearance curves, featuring an initial maximum then an exponential decrease, were not found at a large number of pixels, so the resulting images were confused and noisy. Thus at this magnification of tracer behaviour spatial variations of dye concentration dominate a clearance curve.

The B1P2 geometry clears fastest, but it is possible that the high apparent ejection fraction is due to a volume of fluid inside the ventricle that does not interact, or just barely interacts, with the rest of the fluid. This stagnating or re-circulating volume of fluid would reduce the working volume of the ventricle, and increase the apparent ejection fraction.

A more detailed evaluation of tracer residence inside each blood pump geometry must be made.

5.4.2 Colour Maps

Optical data recorded at a flow rate of 2.1 litres/minute were used, to produce colour maps. At this flow rate the ventricles are closest to their natural geometry, figures 2.11 and 2.12, at maximum volume, when pumping. Hence a path length grid could be readily generated from the equation of

an ellipsoid ($\frac{x^2}{A^2} + \frac{y^2}{B^2} + \frac{z^2}{C^2} = 1$).

The order of the geometry that clears fastest to slowest is:

B1P2 $\longrightarrow$ B1P1 $\longrightarrow$ B2P2 $\longrightarrow$ B2P1

which reflects the clearance curve and mixing coefficient results.

Tracer is concentrated near the outlet in the B2 geometries, at the instant of maximum ventricle volume, in the cycle that it enters the ventricle. Some of the tracer is ejected initially. The rest leaves the ventricle after circulating round to the inlet then back to the outlet, over several cycles. Thus the B2s clear more slowly than the B1s.

P1 appears to encourage high tracer concentrations near the bottom of the ventricle, whereas in the P2 geometries tracer is spread more evenly, implying greater mixing and faster clearance. The high concentrations of tracer near P1 that occur over several cycles are potentially areas of concern for thrombus formation, as the same blood elements may well be in contact with the artificial material of the ventricle for a prolonged period.

By this method the B1P2 geometry has no detectable regions of stagnation or re-circulation that are prevalent over pumping cycles.

Evidently there are substantial differences in the flow of tracer through each geometry. Examining the inflow jet provides some insight into the fluid dynamics.

5.4.3 Inflow Jet

Examination of the series of inflow jet images, figure 5.17, shows that P2 encourages the inflow jet to disperse earlier in the pumping cycle, than does P1. The jet is also hitting a convex surface in the P2 geometries, whereas in the P1s it impacts on a concave one. Therefore tracer accumulates near the bottom of the ventricle in the P1s and is better dispersed in the P2s. Thus the P2 geometries clear faster than the P1s.

It can also be seen that tracer spreads towards the right in the B2s, and starts at the left in the B1s.

5.5 Summary and Conclusions

Four geometries of proto-type blood pump, figure 3.15, have been compared utilising fluid tracer techniques, ejection fraction and force measurements.

The resultant flow, force and power curves are different between the designs at the same flow rate. The P2 designs appear to require less energy for operation than the P1s. These results are based upon a sinusoidal displacement curve driving the compression plates. A muscle model could be developed using the current laboratory equipment.

The methodologies described and outlined in this chapter permit an overall picture of fluid flow in each geometry. The rates of clearance for the different geometries have been established, with the likelihood that the fastest clearance will be associated with the least stagnation. Computer analysis of video images permits re-circulating and stagnant flow areas to be visualised.

The B1P2 geometry, of straight pipes and a domed base cleared fastest, no stagnating or re-circulating fluid volumes were detected, and the domed plate provided a smooth compression of the ventricle. A disadvantage of B1P2 is that the domed plate (P2) limits the maximum ejection fraction to 70%. Possibly a less curved compression plate, allowing a higher maximum ejection fraction, would be advantageous if it still retained the advantages of smooth ventricle compression and inflow jet dispersal.

B1 is more of an improvement over B2, than P2 is over P1, in terms of clearance rate and local residence times.

The fluid flow regimes that determine the clearance curves and tracer concentration maps presented in this chapter have since been investigated by fluorescent particle fluid flow visualisation.

Chapter 6. Fluid Flow Visualisation

6.1 Introduction

The methods applied to the four blood pump designs in chapter 5 have provided some insight into the fluid flow regimes in each, such as inlet jet forms, areas of flow re-circulation and stagnation. A more detailed analysis of the fluid flow in each design is necessary to identify regions of high shear stress, correlate flow patterns with the fluid tracer results (residence time and stagnation regions) and see the effect of the geometrical variations between designs for future development work.

VAD fluid flows have been characterised in many previous studies, as discussed in section 1.14, using many of the methods detailed in section 1.13. The flow inside polyurethane ventricles has been studied with flow visualisation (104,112) and laser doppler anenometry (105), while Shortland *et al* performed flow visualisation in a valveless silicone elastomer ventricle (116,117).

Optical methods have seen wide ranging use for the analysis of fluid flows. To obtain a picture of the fluid flow in the polyurethane pumping chambers of each proto-type blood pump design a particle seeding technique was chosen.

6.2 Methods

Tracer particle flow visualisation involves seeding the experimental fluid with particles that are preferably neutrally buoyant, small enough in comparison to the observed area to fully resolve the flow and reflective or responsive enough to light for recording purposes. A volume of fluid is illuminated by a light source and the motion of particles recorded. The frame length of the recording device or the illumination time, whichever is the shorter, governs the recorded length of the tracer particle displacements, known as streaks. The illuminated volume is often a thin plane, yielding a two-dimensional picture of fluid flow. A typical experimental set-up is shown in figure 6.1, with the camera and laser perpendicular to each other. The ventricle is placed inside a viewing tank filled with fluid to reduce the optical distortions due to the different refractive indices of air and ventricle material.

There are many parameters that affect the optical quality of particle flow visualisation images, such as light source, tracer particle size and reflectivity, recording device and the refractive indices of the different mediums through which incident and reflected light travels.

Initial work was conducted with silicone rubber ventricles, described in section 3.4.1.2, but air bubbles in the walls produced many optical effects that obscured particle traces on the images. Polyurethane artificial ventricles were constructed by dipping smooth wax moulds into a solution of polymer and solvent, as described in section 3.4.2.5. The polyurethane ventricles had very few surface defects.

The refractive index of the silicone rubber ventricles is 1.43 (quoted by the supplier). The refractive indices of water and glycerol are approximately 1.33 and 1.47 at room temperature, respectively (140). The refractive index of the polyurethane used for ventricle manufacture was measured by the method of central illumination (141). This method allows the comparison of the refractive index of a material with the media in which it is immersed, and determines if the refractive indices are equal or which one is the greater. Oils of defined refractive index are used as immersion media. The refractive index of the polyurethane was measured as 1.56 and the refractive index of the silicone rubber material was also verified. The blood analogue of water and glycerol has a lower refractive index than the polyurethane. There appear to be no readily available fluids that have a similar viscosity to blood and refractive index similar to the polyurethane, except for some unsuitable solvents. Baldwin et al used an experimental fluid of water, glycerol and sodium iodide to match the refractive index of plexi-glass of 1.49 (132). Unfortunately the amount of sodium iodide required to make enough fluid to fill the mock circulatory loop, and blood pump, was prohibitively expensive. Also even a refractive index of 1.49 is still short of the required 1.56.

The bases of the different proto-type blood pumps designs were sprayed with matt black paint to reduce the number of optical artefacts. Black card was used to line the viewing tank for the same purpose.

Different lasers, a 10mW HeNe (Uniphase model 1135, 1096 Mellon Avenue, Mateca, Ca 95336) and a 5W Argon ion laser (Spectra - Physics model 2010, 1250 W. Middlefield Road, P.O. Box 7013, Mountain View, CA 94039-7013), were experimented with as sources of illumination. Ultimately the Argon laser was used for the bulk of the measurements described in this chapter. The laser beam was directed through a cylindrical lens to diverge the beam into a sheet, then through a concave lens of 1metre focal length to produce a light sheet of approximately 1mm thickness as it passed through the ventricle.

A colour CCD (XC-711P, Sony, Sony House, Middlesex, UK), black and white CCD (FA 87, Grundig Electronics, Mill Road, Rubgy, CV21 1PR, UK) and a 35mm camera were used as recording devices. When the colour CCD camera was operated in colour mode and the signal transmitted to video by a composite cable the images of particles developed horizontal ‘tails’. If the CCD camera

was operated in black and white mode then the tails were not present. The tails may have been caused by the lower frequency response of the system (CCD camera to video recorder) when operated in colour mode as three times as much information must be passed along the same composite cable. The black and white CCD camera was used for the majority of the experimental work because it was more sensitive than the colour camera and of equivalent sensitivity to the 35mm camera using 400ASA film. Flow visualisation images recorded with a 35mm camera and 400 ASA film are shown in figure 6.2. Also using a CCD camera is inherently more convenient as images can be viewed instantly during experiments and more readily captured by a PC, allowing the immediate observation of changes to the flow visualisation system, for the purpose of improved data capture.

A variety of particles were experimented with inside polyurethane ventricles for flow visualisation purposes, with generally poor results. Only large Amberlite XAD2 resin (Rohm and Haas Company, Philadelphia, USA) and copolymer particles (a copolymer of polystyrene 27820, supplied by Fluka Chemicals, Dorset, SP8 4XT, UK) delivered images of any clarity. The polyurethane ventricles produced substantial optical noise, due to light scattering, which obscured certain parts of the flow, even with these particles. Fluorescent particles have been used for flow studies to produce clear images (94). Light is absorbed by the particles and emitted at a different wavelength. A filter placed over the camera lens excludes light from the illuminating source.

The fluorescent particles (45 to 180 μm in diameter) used by Dong *et al* (94) did not provide much improved images as there was still some optical noise from the polyurethane, which appeared to fluoresce slightly. Fluorescent particles were instead manufactured in the laboratory by testing different combinations of particles and histological dyes.

The Amberlite XAD2 particles are sold as absorbents and thus take up Eosin -Y dissolved in water. The particles were wetted with methanol to prevent clumping then covered with distilled water and dye. The product is poured into a funnel lined with normal filter paper and washed a few times with distilled water. The dyed particles are readily scraped off the filter paper. These particles showed up well on flow visualisation images, but there were several problems with them: they are less dense than the chosen blood analogue of glycerol and water, the diameter range of 300 to 700 μm limits the potential flow resolution and possibly their flow following properties. The particles could be sieved down to a size range of 300 to 425 μm that produced very uniform particle streaks on the flow visualisation images. Eosin is a short lived fluorescing dye when used as a stain, but there did not seem to be any reduction in fluorescence after exposing the particles to the 5W argon laser for 30 minutes, at full power.

Some histological dyes, out of the 15 tried, were found to adhere to Amberlite CG420 ion exchange particles (Rohm and Haas Company). When stimulated with the argon laser beam (blue - green) the CG420 particles with Eosin - Y dye attached to them fluoresced strongly at a higher wavelength (green - yellow). The particles are 150 - 80 μm diameter and about half are neutrally buoyant in 40% (by volume) aqueous glycerol. Eosin - Y was applied to the particles as described above, but they did not appear to need as many washes, possibly because the dyes are bonded to the particles rather than absorbed. Some of the fluorescent particles tended to clump together, when added to the solution of dye and water, yielding flow visualisation images with non-uniform particle streak thicknesses. Wetting the particles in methanol to separate them, sucking them into a syringe and then injecting them very quickly into a solution of dye prevented aggregation of the particles. The CG420 particles are no longer available, but strongly basic ion exchange particles of similar size are available (CG50).

The particles were prepared by adding them to a small amount of experimental fluid in a cylinder. This was left for a few hours, during which time some of the particles settled to the bottom, some floated to the top and the desired neutrally buoyant particles remained in the middle. Those particles still in the middle of the cylinder were drawn off and added to the rest of the experimental fluid.

Figure 6.3 shows fluid flow visualised inside B2P1, at the same instant in the pumping cycle, with fluorescent particles (CG420s and Eosin - Y) and the copolymer particles for comparison.

The fluid flow in each design was characterised by taking 8 two-dimensional sections through each ventricle. The *long axis* of the ventricles referred to below is the 45mm axis in figure 2.5, and the *short axis* is labelled as 28mm. Three sections were taken parallel to the long axis of the hemi-ellipsoidal ventricles, figure 6.4a. Section S1 runs down the centre of the ventricle, while S2 and S3 are either side of S1 and split the short axis into 4 equal lengths. The inlet and outlets are offset from the long axis of the ventricle in the B2 designs (angled pipes) and section S2 is on the side of S1 to which they have been offset. Five sections were taken parallel to the short axis, figure 6.4b, such that: S6 splits the long axis in half, S5 bisects the inlet pipe entrance, S7 bisects the outlet pipe exit, S4 is equi-distant between the end of the ventricle and S5, S8 is between S7 and the other end of the ventricle. The laser power used for: S1, 2 and S3 was 1W; S6 was 0.8W; S4, 5, 6 and S8 was 0.4W.

The camera position was changed during the experiments to capture light from the sections after it had travelled through the least possible fluid media, i.e. the camera orientation was changed by

180^{O} after filming sections S4, 5 and S6. Images were recorded upon VHS video tape and captured using a frame grabbing board onto a PC hard disk. Fluid flow was characterised in each design pumping 2.1 litres of fluid per minute at 30bpm. The time code generator was used to insert a time signal onto the video frames as described in section 5.2.3.

The light sheet was positioned relative to the ventricles, to create the eight sections, with a ruler. The blood pumps and camera were levelled with a spirit level. Some of the light sheet was reflected directly back from the glass viewing tank and could be centred upon the incident beam ensuring that the tank was perpendicular to the light sheet. The ventricles were thus aligned with the light sheet as they were first aligned with the viewing tank. The whole rig was supported upon a moveable platform for ease of section selection, through the ventricles. The camera alignment was taken as perpendicular to the light sheet when all the stationary particles in the field of view were in focus.

Each pumping cycle lasted for 2 seconds during which 50 images were recorded at the standard video frame rate. Approximately 2000 images were captured and subsequently processed into animations. The images were cropped using the image grabbing software (Microscale TC, Digithurst Ltd, Royston, UK) macro facility. The grey balance of the images was adjusted automatically for batches of 50 using Photostyler (Autodesk Inc.) and the Windows Recorder accessory (Microsoft).

The image sequences for the eight two-dimensional sections of fluid flow were combined into one animation for each proto-type design using animation software (Animator Pro, Autodesk Inc.). It was easier to identify flow features by viewing an animation rather than static pictures.

Fluid flow was also visualised inside B2P1, in section S1, at flow rates of 1.0, 1.55, 2.1 and 2.9 litres/minute at 30 bpm. The images were combined into a single animation to examine the effects of different flow rates upon fluid flow in the same design.

6.3 Results - Fluid Flow Patterns

Playing the animations of the 8 different two-dimensional sections of fluid flow for each design enables one to characterise the three-dimensional fluid flow in each. The first frame of each animation occurs at the second downwards movement of the compression plate. To describe the salient features of the flow in each design the flow streamlines have been constructed at frames 10, 16, 24 and 40. The raw data are in Appendix B.

The key to flow patterns depicted in figures 6.6, 6.7, 6.8 and 6.9 is shown in figure 6.5. Frame 10 corresponds to the (a) figures, frame 16 to the (b), 24 to the (c) and 40 to the (d).

Some of the images have been horizontally reversed so the three long axis sections are seen as if viewed from the same direction, with the inlet on the left, and the five short axis sections as if viewed from the outlet end of the ventricles.

In the descriptions of fluid flow in each of the designs the left, right, top and bottom of a particular section (S1, 2, 3, 4, 5, 6, 7 and 8) refers to the orientations shown in figures 6.6, 6.7, 6.8 and 6.9.

6.3.1 B1P1

The inlet jet is directed straight down towards the compression plate (P1), figure 6.6a, at frame 10. A ring vortex forms around the jet dominating the left side of sections S1, 2 and 3. The ring vortex has also extended slightly to the right, towards the outlet. Sections S4 and S5 show the inlet jet and ring vortex, while in S6 only the ring vortex is evident. In S7 and S8 the flow exhibits a slight downward movement towards the compression plate as it moves away from the base, and there is some stagnant flow towards the upper right of S1, 2 and S3. The flow is not quite symmetrical along the long axis of the ventricle, although B1P1 was designed to be so. In S2 the right side of the ring vortex, towards the outlet, has more completely formed than in S3. The flow is likely sensitive to small geometrical changes at this stage of the pumping cycle due to the high velocity inlet jet.

The ring vortex has extended to S7 from the inlet, but has distorted and lost most of its energy by frame 16, figure 6.6b. The ring vortex section on the S4 side of the inlet is relatively unchanged from frame 10, with flow between S4 and S6 still dominated by it. However the other half of the ring vortex has distorted slightly and another vortex has been initiated, by shedding, to the upper right of S1. The ring vortex distortion is evident by comparing the diameter of its cross section in S1 with S2 and S3. The flow between S7 and S8 not entrained in the ring vortex consists of many small eddies, and the regions that were stagnant at frame 10 are now experiencing movement.

By frame 24, figure 6.6c, the fluid has generally slowed in all parts of the ventricle while maintaining the same type of motions, such as counter rotating vortex pairs in S2, 3, 5, 7 and 8. The anti-clockwise vortices in S2 and S3 have both moved towards the outlet side of the ventricle to entrain fluid at S8. The slight asymmetry of the flow in B1P1 is clearly shown by the non-symmetrical counter-rotating vortex pairs in S7 and S8.

Virtually all the vortical motion has stopped by frame 40, figure 6.6d, and most of the fluid movement is directed towards the outlet. Between S5 and S8 most of the fluid is heading towards the outlet, while the flow between S4 and S6 is slowly mixing.

6.3.2 B1P2

At frame 10 the inlet jet has again generated a ring vortex that dominates the left hand side of S1, 2 and 3, figure 6.7a. The part of the ring vortex on the outlet side of the ventricle is still travelling towards the right of S1 and has not completely formed as fluid movement is perpendicular to S6 and S7. In S2 and S3 the outlet side of the ring vortex has formed more completely. In S7 and S8 the flow is moving slowly down towards the compression plate with a very slightly vortical motion (not shown). Flow is stagnant between S7 and S8.

By frame 16, figure 6.7b, the ring vortex in S1 has elongated slightly towards P2 as it moves down, although the vortex has slowed its rotation in S2 and S3. The right hand side of the ring vortex has travelled downwards with the movement of P2 and also to outlet side of the ventricle. Fluid is moving to the outlet side of the ventricle down the long axis, S1. Twin counter-rotating vortices are now present in S4, 5, 6 and S7. Virtually none of the fluid in the ventricle is static.

By frame 24, figure 6.7c, all the fluid movement in S1 is now composed of eddies and a general downwards motion, as P2 has just completed its downwards displacement. The left part of the ring vortex in S2 and S3 has all but ceased to rotate, while the right hand side dominates the rest of the sections. All of the sections perpendicular to S1 feature counter-rotating vortical pairs. The counter-rotating vortices in S6 are still present, but squashed up towards B1 and are actually cross-sections of helical fluid motion towards the inlet side of the ventricle. There is some fluid flow that is not symmetrical down the long axis in sections S4, S7 and S8.

At frame 40, figure 6.7d, virtually all the fluid movement is directed towards the outlet, with the remains of counter-rotating vortices slightly present in S5, S6 and S7.

6.3.3 B2P1

The inlet jet is directed across the ventricle at about 45^{O} to the long axis in S1, figure 6.8a. By frame 10 the jet has impacted P1 initiating a ring vortex around itself. Part of the ring has been stretched towards the bottom right of S1. The cross sections of the ring vortex in S2 and S3 are rotating slowly, but slightly faster in S2 which is more influenced by the inflow jet because the inlet and outlet pipes are offset from the long axis towards S2. The counter-rotating vortices in S8 are partly initiated by the sudden movement of the ventricle wall as a portion of it quickly reverses its curvature. The anti-clockwise vortex on the top right of S1 is able to occur because a large wrinkle of the polyurethane ventricle separates it from the deformed edge of the ring vortex evident in S1. The wrinkle prevents the ring vortex travel across the ventricle until about frame 10, and can be seen on figure A3a in Appendix B. The majority of the fluid movement is slow, and there is very little in S4 and S5.

The ring vortex increases in size to dominate the flow in most of the ventricle by frame 16, figure 6.8b. The inlet half of the ring vortex is somewhat slow, and the cross-sections of it on the left of S1, 2 and S3 have the appearance of slow re-circulation regions. The flow fields in S2 and S3 are different because the inflow and outflow pipes are offset from the long axis. The only vortices present are directly related to the inflow jet ring vortex.

The inflow jet has virtually ceased by frame 24, as has most fluid movement in S1, figure 6.8c. There is a vortex in S2 and S3; clockwise in S2 slightly to the right of centre and near P1, anti-clockwise and to the right in S3. The rest of the fluid movement in S3 is towards the inlet, and in S2 the flow is away from the inlet. The flow patterns in S8 and S4 are consistent with an overall circulation of fluid in a plane perpendicular to S4 and S1 around the ventricle.

Fluid movement is mainly towards the outlet by frame 40, figure 6.8d. There is more movement in S2 than S1, and slightly more in S1 compared with S3. The movement on the S3 side is more towards the S2 plane as shown in S6 probably because of the offset outlet pipe. There is very little fluid motion in S4, 5 and S8.

6.3.4 B2P2

The inlet jet has initiated a ring vortex that is offset within the ventricle by frame 10, figure 6.9a. Fluid motion is more vigorous on the side of the ventricle to which the inlet and outlet pipes are offset, S2. In S1 there is a right hand side vortex and an undeveloped left hand vortex, while in S2 and S3 there are two counter-rotating vortices. Two counter-rotating vortices have formed in S4, possibly due to the combined influence of the compression plate (P2) displacement and the inlet

jet. In S5 the offset ring vortex that forms around the inlet jet can be seen quite clearly. There is an apparently slower double vortex motion in S6 because fluid is also moving perpendicular to the section, towards the outlet. Flow is perpendicular to S7 as the ring vortex is extending towards the outlet side of the ventricle. In S8 there is some evidence of slow circulation in a plane perpendicular to S1 and S8.

The left hand side vortex that was forming in S1 at frame 10 has moved down with the descent of P2 at frame 16, figure 6.9b. The right hand side vortex has increased in size to dominate the rest of S1, excluding the inlet jet. The fluid to the top left of S1 corresponding with S4 is almost stagnant. In S3 the right hand side vortex has moved further to the right, while the left vortex has dissipated and flow is now moving back towards the inlet on the left. The fluid common to S8 and S3 is momentarily stationary. In S2 the left vortex has slowed, the right vortex has expanded in size and the inlet jet is still impinging slightly upon the fluid flow shows the end of the ring vortex. In S4 the counter-rotating vortices, that were present previously, have collapsed and circulation of fluid in a plane perpendicular to S1 and S6 back towards the inlet from the outlet side has started. In S5 there is some downwards fluid motion towards the descending compression plate, P2, between the counter-rotating vortices. Counter-rotating vortices are still present in S5, 6 and S7.

Fluid is circulating around the ventricle in a plane perpendicular to S1 and S6 at frame 24, figure 6.9c. The right hand side vortex in S1 is still present, but has slowed. The anti-clockwise vortex in S2 at frame 16 has reversed and now occupies the bottom of S2 near P2. S2 and S3 show flow moving in opposite directions, and examination of S6 suggests that the movement is helical in nature. The overall circulation is also obvious in S8, around the ventricle in a plane perpendicular to S1 and S8.

At frame 40, figure 6.9d, there is a substantial amount of stationary fluid between the left side of the ventricle on S1 and S5. Virtually all fluid motion is directed towards the outlet. There is more fluid movement in S2 than S1, than in S3.

6.3.5 B2P1 at Four Flow Rates

An animation was constructed of section S1 in B2P1 at four flow rates of 1.0, 1.55, 2.1 and 2.9 litres/minute, at 30bpm. The results for frames 10, 16, 24 and 40 are in Appendix B. The overall flow features at each flow rate are quite similar, but occur at different times during the pumping cycle at each flow rate. For instance the ring vortex forms sooner, and travels further, the higher the flow rate. The fluid possess more momentum at higher flow rates thus there is more vortex shedding and mixing of fluid.

6.4 Discussion

In the previous chapter the B1P2 design cleared the fastest and appeared to possess no stagnation or re-circulation regions. The reasons for this in terms of the fluid flow inside the ventricle can now be discussed in the light of the results described in the previous section. In B1P2, as with all the designs, the dominant flow feature during filling is a ring vortex that forms around the inlet jet. The outlet side of the ring vortex, the right of S1, travels across the ventricle to the outlet side entraining all the previously stagnant fluid in its path. Meanwhile the other half of the ring vortex very quickly dominates the rest of the fluid, to the left of S1. A possible cause for concern is the existence of this vortex to the left of the inlet jet in S1 as it may just re-circulate fluid. The colour tracer maps of figure 5.16b show that tracer enters this region then leaves it in the next pumping cycle. The overall mixing of fluid that occurs at frame 24, figure 6.7c, in S1 may well be responsible for clearing out the tracer from this possibly dangerous re-circulation region. Also the vigorous left vortex, in S1, may well eject fluid back into the path of the inlet jet.

The next fastest clearing design was B1P1 in which the ring vortex spreads more quickly across the ventricle to the outlet side. Possibly the fast spread of the ring vortex is detrimental to the clearance of this design as can be seen at frame 24 in S1, S2 and S3, figure 6.6c, where some fluid motion is directed back towards the inlet. Also P1 does not promote such a vigorous and prolonged vortex to the left of the inlet jet in S1, thus not clearing tracer out from this region quite so effectively. This design still clears relatively quickly and all the fluid within the ventricle appears to undergo motion at some point during the pumping cycle.

The jet and consequently fluid tracer are spread to the outlet side of the ventricle during filling in B2P2, but there is some slow re-circulation before ejection back to the inlet side. The tracer that goes to the left of the inlet in S1 experiences either stagnation or slow re-circulation before it is eventually washed out.

The design that exhibited the worst clearing characteristics was B2P1. The region to the left of the inlet in S1 is never particularly involved with the fluid motion of the rest of the ventricle, so any tracer that accumulates in this region resides there for several cycles. The flow is sluggish in all the sections in B2P1, possibly because the inflow jet must pass through a larger body of fluid before it impacts ventricle walls and initiates mixing. The geometry is such that the influence of the inlet jet is initially spread throughout the ventricle rather than affecting one section at a time. The overall circulation of fluid around the ventricle moves dye from near the outlet back to the inlet side across cycles, producing slow clearance times.

The B2 designs cleared more slowly than the B1s because fluid on the left of the ventricle is not effectively cleared out. Clearance of this volume only occurs at about frame 24 when fluid slowly re-circulates around the ventricle in a plane parallel to the base. If the fluid tracer that went to the outlet side was ejected in the next cycle then the clearance rate would be fast, but there would be a region of stagnant fluid to the left of S1.

P2 encourages mixing with B2 and B1. With the B2s the re-circulation parallel to the base happens sooner in the pumping cycle with P2 rather than P1. In the B1s P2 directs the influence of the inlet jet more to the left of the inlet in S1 than does P1, thus preventing fluid tracer from accumulating there.

If the overall re-circulation effect of the B2s were faster then it may well be advantageous, but this may not be possible with this artificial ventricle geometry.

6.5 Summary and Conclusions

The fluid flow patterns that produce the fast clearance of dye tracer from B2P1 have been identified. Regions of high shear rate can be identified from the fluid flow animations and shear stresses within them quantified in the next chapter.

Chapter 7. Shear Stress Evaluation

7.1 Introduction

The three-dimensional fluid flow in each of the four proto-type blood pump geometries has been examined by fluid flow visualisation in chapter 6. In section 1.9.2 the implications of blood clots induced by VADs were discussed and the possible contributory mechanical mechanisms described.

Reported areas for concern are usually in the vicinity of valves that the majority of VADs use to control the direction of fluid flow, as discussed in section 1.14.

Blood damage due to mechanical fluid flow phenomenon is undoubtedly complicated and insufficiently understood, as discussed in section 1.9.4 , but not exceeding physiological flow conditions is likely to be a good indication that the flow in a VAD will not damage blood elements by fluid mechanical means, as discussed in section 2.6.

Another aspect of blood clotting in VADs is the artificial material blood interface. Various authors have suggested that this is the primary initiator of blood clots by prosthetic blood pumping devices. Consequently the fluid tracer methods in chapter 4 were developed to analyse fluid element residence times and identify stagnation areas. The application of the fluid tracer methods to the four designs is described in chapter 5. The deposition of thrombus appears to be greatly inhibited at shear rates of 500 s^{-1} (69,70), but this value is likely material dependent.

To measure shear rate and shear stress it is necessary to quantify fluid velocities both near the wall and within the bulk fluid flow.

Areas of high velocity gradient, and therefore high shear stress, were identified in each of the blood pump proto-types by examination of the fluid flow visualisation animations described in chapter 6.

7.2 Methods

Streak lengths on the fluid flow visualisation animation images, for the four designs, were measured to obtain approximate velocity measurements. The length of a streak is not an exact measure of the displacement of a tracer particle during a video frame. Apart from the errors associated with digitising streaks, tracer particles may only be within a light sheet for part of a video frame and thus any velocity derived from a streak is likely to be an underestimate. Particle displacements can be more accurately measured by pulsing the illuminating source to obtain dots rather than streaks.

For an entire velocity field of sufficient resolution to be generated, from an image of multi-illuminated tracer particles, there must be enough particles visible for at least one velocity measurement to be made in each area of desired smallest resolution. Due to the size and slight blurring of the particles used (because of the refractive index differences between the media) the application of PIV (Particle Image Velocimetry) methods was non-practical. Instead a process of fluid flow analysis, then area selection and magnification was applied. Areas of high shear rate during the pumping cycle were identified, focused upon and velocity measurements made.

It was found that, by examination of the fluid flow visualisation animations, fluid flow associated with inflow jets during filling is the most likely area for high fluid shear stresses to occur. The inflow jets were analysed more closely in each design by taking two perpendicular sections through the jets, both sections were perpendicular to jet direction. The sections were positioned through alignment with the inlet pipe and by ensuring that the highest velocity particles were being recorded. The use of a video camera allowed the measurement of particle displacements on the monitor screen by using the digital freeze frame utility and a ruler or, if necessary, capturing images and performing measurements with the image analysis software.

The laser light sheet was pulsed by chopping the beam with a variable frequency chopper system (model 75157, Oriel instruments, 250 Long Beach Boulevard, Stratford, CT 06497-0872, USA) consisting of an open chopper (77154) and controller (75095). The chopper can be mounted with various chopping wheels of different aperture number, also two wheels can be fitted at the same time to vary aperture angle and therefore the ratio of open to closed.

The CCD camera frame length was set to 1/125 of a second and the light sheet was pulsed 500 times per second, yielding four light sheet pulses per frame. The ratio of pulse length to no illumination was set to 1 in 6. This duty cycle was chosen so that the highest velocity tracer particles appeared as dots at each light pulse, rather than elongated dots, and the distance between the dots was at least several particle diameters. A 12 frame animation was created of the two sections through the inflow jet in each design, and the area and time during the pumping cycle of high shear regions more accurately identified.

The CCD camera field of view was reduced to achieve maximum resolution and hence measurement accuracy in the areas of high shear, by operation of the zoom lens. Tracer particle displacements were measured using the polyline facility of the image analysis software (Microscale TC, Digithurst Ltd, Royston, UK). The scale of the images (mm:pixel) was obtained by recording a ruler at the same distance from the camera as the region of interest would be, in horizontal and vertical positions, to account for any image distortion.

When shear stresses were measured near the wall, by obtaining the velocity of a near wall particle and the distance from the wall perpendicular to its velocity, the position of the wall was found with the image analysis software thresholding facility.

The displacements between dots at different times were measured and velocities calculated from the known time difference between light sheet pulses, by equation 7.1

$$V = \frac{d}{\Delta t} \qquad \text{Equation 7.1}$$

$\boldsymbol{V}$ = mean velocity in the two dimensional plane.

$\boldsymbol{d}$ = displacement.

$\Delta \boldsymbol{t}$ = time between light sheet pulses.

The compression plates in each of the designs do not exceed 5mm/sec, during a pumping cycle, which is equivalent to a displacement of 0.04mm during a 1/125 second frame. When the camera is set at maximum zoom then one pixel is approximately equivalent to 0.1mm, thus the compression plates are pseudo-stationary during a 1/125 second frame.

The measurement of particle velocities from the length of a line drawn between dot centres was validated by measuring steady, developed, flow in a cylindrical pipe, figure 7.1. A Sarns roller pump impels fluid from the compliance chamber to the reservoir, at a point above the level of the water in the reservoir. This arrangement allows a relatively constant head of water to be maintained in the reservoir. The viewing tank is made from transparent acrylic, as is the pipe, and filled with the experimental fluid to reduce optical distortions due to refraction. One side is transparent for viewing and the top is open to a sheet of laser light that illuminates the fluid and particles. The other sides are covered with black card to reduce the number of optical artefacts.

The argon-ion laser output was set at 1W to generate a light sheet of 4.5 mm thickness (± 0.5mm) and 40mm long (so that over the observational area the light sheet is of a constant intensity) via a cylindrical lens.

Images were captured using a colour CCD camera set to B&W (gamma switch) with an exposure time of 1/250 of a second. The images were recorded upon VHS video tape, and later analysed with the image analysis software (Microscale).

The camera was aligned with the pipe by eye and the use of a spirit level. This was checked by recording a piece of graph paper held against the transparent side of the viewing chamber facing the camera. The squares in different parts of the screen were measured with the image analysis software and the graph paper was found to be perpendicular to the camera.

The camera was then focused upon the centre of the pipe by focusing upon the upper and lower horizons of the pipe. Once the pipe and viewing box had been filled with fluid and seeded with particles, the laser was turned on and the stationary particles viewed through the camera and found to be perfectly focused.

The velocity profile, ***V(r)***, in a pipe, of radius ***a***, with a Newtonian fluid, of known viscosity and density, moving down it at a constant rate can be determined by equation 7.1 (142).

$$V(r) = \frac{Q}{2\pi a^2}\left(1 - \frac{r^2}{a^2}\right) \qquad \text{Equation 7.1.}$$

Q = Volume flow rate.

R = radial position from the central axis of the pipe.

The Reynolds number, ***Re***, in a cylindrical pipe is defined by equation 7.2.

$$Re = \frac{U_{av} D \rho}{\mu} \qquad \text{Equation 7.2.}$$

Re = Reynolds number.

U_{av} = Average velocity.

D = Diameter of pipe.

μ = viscosity.

ρ = density.

The ***entry length*** for a cylindrical pipe is an empirical number that, calculated by equation 7.3, defines the distance required for steady laminar flow in a pipe to achieve a fully developed velocity profile, starting from a stationary reservoir (143).

$$entry\ length = 0.03.D.Re \qquad \text{Equation 7.3}$$

For this system ***Re*** = 307.8 and ***D*** = 0.045 m, which implies that the fluid flow was laminar and fully developed, as the entry length is 0.41 metres and fluid measurements were made 1.3 metres downstream of the flow straightener. Fluid velocities derived from streak and dot to dot measurements were made and compared with the theoretical velocity profile, figure 7.2. Quadratics were fitted to the streak and dot data (Mathcad version 4.0, Mathsoft Inc. 201 Broadway, Cambridge, 02139 USA). The streak data produce velocity values that are substantially less than the expected values.

The lower velocity values realised by streak measurement were not due to particles passing out of the light sheet during a video frame, because only the velocity of particles that were visible in frames before and after the frame of measurement were measured. The likely cause of the lower measurements was the difficulty in discerning the length of streak images because the ends were ill-defined. Various manual and automated image processing methods were applied to rectify this problem, but to no avail. Combining 3 successive images of a particle should have yielded an image of a very long streak, but there were gaps between the 3 streaks which accounted for the low velocity measurements. The gap between video frames accounted for a small part of this while the ill-definition of the streaks, possibly due to digitisation, probably accounted for the rest of the gap.

7.3 Results

The following tables (7.1 to 7.7) contain wall shear rate values that were calculated from tracer particle images. S9 is a perpendicular section through the jet parallel to the long axis of the pumping chamber, while S10 is perpendicular to the direction of the jet and S9.

Shear rates were measured in regions of high shear that were identified by examination of the overall fluid flow animations and the animations of the inflow jets. No laminar shear rates, measured away from the walls, were above the lowest of those in the tables below (100 sec^{-1}). The areas in which wall shear measurements were made are shown in figures 7.3 to 7.9 on the zoomed images. For some zoom areas there are no numbers given because no shear rates above 100 sec^{-1} were measured. Also only the highest shear rates were measured in each area and are given in the tables in this chapter.

More measurements were made in areas where the compression plate position was indeterminate to $\pm$0.5mm. Even though the compression plate was pseudo-stationary during a 1/125 second video frame optical effects served to disguise its position. The position of the compression plate was found by thresholding, where all the pixels on an image below a certain grey scale value (8 bit grey scale is from 0 to 255) are coloured in. When the grey scale thresholding limit is adjusted on the zoomed images there is a boundary between the darkness of the viewing tank and the lightness within the ventricle. The polyurethane ventricle walls fluoresce slightly and as such are between the viewing tank and ventricle interior in terms of brightness. Thus as the thresholding limit is increased the viewing tank area is obscured up to the outside ventricle walls, then the ventricle walls are obscured. Increasing the limit any further substantially obscures the flow field, not including the tracer particles, and the position of the internal ventricle walls can be identified.

Even using this thresholding method the position of the internal ventricle wall was sometimes difficult to determine, such as when the P1 compression plate was near enough to the base, such that the ventricle was substantially distorted from its natural geometry, which occurs in area 3 of figure 7.3. Angling the CCD camera at 10^{O} to the horizontal reduced the amount of ventricle wall between the camera and objective. Shear rates could then be measured and the angle of the camera orientation to light sheet plane accounted for.

B1P1

Figure 7.3 shows the areas that were magnified and in which shear rates were measured, in section S1 of B1P1. Measurements were problematic in Area 2 because the plate and particle positions were unclear due to optical distortion, so the camera was aligned at an angle of 10^{O} to the horizontal and Area 3 magnified. The maximum shear rate measured was 1681, table 7.1, corresponding to a shear stress of 5.9N/m^2.

Table 7.1. Shear Rates (sec^{-1}) measured in B1P1 pumping at 2.1 litres/minute in section S9.

Area 1	Area 2	Area 3
617		1420
822		1068
678		1147
1170		1681
946		1418
1125		688
1469		1292
925		
593		

Shear stresses were measured in B1P1 in S5 along the ventricle wall to one side of the jet, figure 7.4. The fluid flow as symmetrical about the jet in this plane. The maximum shear rate was 2754, table 7.2, which is equivalent to a shear stress of 9.6N/m^2.

Table 7.2. Shear Rates (sec^{-1}) measured in B1P1 pumping at 2.1 litres/minute in section S10.

Area 1	Area 2	Area 3	Area 4	Area 5
321	1027	779	1356	
242	904	1777	1458	
227	604	2754		
	915			
	823			
	919			

B1P2

The maximum shear stress for B1P2 in S1 was 20.1N/m^2 and in S5 was 20.3N/m^2. It was not necessary to angle the camera to obtain better images of particles near the compression plate. P2 dents the polyurethane pumping chamber rather than crumpling it, as does P1, thus there is just one ventricle wall thickness between the observer and objective.

Table 7.3. Shear Rates (sec^{-1}) measured in B1P2 pumping at 2.1 litres/minute in section S9.

Area 1	Area 2	Area 3	Area 4	Area 5	Area 6
2711	640	1785	1858	1290	5250
1860	1320	674	2843	2207	1845
2878	554	947	4232	1931	3146
2960	1056		1623	1519	3798
2980			2534		1855
3087			4389		4556
			3042		5417
					5750

Table 7.4. Shear Rates (sec^{-1}) measured in B1P2 pumping at 2.1 litres/minute in section S10.

Area 1	Area 2	Area 3	Area 4	Area 5
1988	1769	2378	1500	4176
	1667	3920	1613	5808
	1968		2250	3136
	2140			
	3166			

B2P1

Observed near wall velocities in B2P1 were all much less than the other designs with no shear rates above 200sec^{-1} measured. 200 sec^{-1} is equivalent to a shear stress of 0.7N/m^2. The light sheet was angled at 45^O to the base of B2P1 so that it bisected the inlet jet in place S5.

Table 7.5. Shear Rates (sec^{-1}) measured in B2P1 pumping at 2.1 litres/minute in section S9.

Area 1	Area 2	Area 3	Area 4
	<200	<100	

B2P2

The maximum shear rate measured in B2P2 was 6094, equivalent to 21.3N/m^2, but this appears to be an anomalous result. The next highest is 3683 in Area3, which is equivalent to 12.9 N/m^2.

Table 7.6. Shear Rates (sec^{-1}) measured in B2P2 pumping at 2.1 litres/minute in section S9.

Area 1	Area 2	Area 3	Area 4
246	405	1430	2089

312	619	1167	2271
427	577	2078	2896
	630	3683	6094
		2517	2288

Table 7.7. Shear Rates (sec^{-1}) measured in B2P2 pumping at 2.1 litres/minute in section S10.

Area 1	Area 2	Area 3	Area 4
909	332	797	799
505	609	2545	1823
662	1548		
1059	1430		
1646	2180		
1038			

7.4 Discussion

The muscle powered blood pump device described in chapter 2 is envisaged to generate a flow rate of between 2 and 3 litres/minute. This is substantially less than the average human heart generates during exercise, consequently damaging shear stresses will be caused by geometry.

The lowest shear stresses, below $7N/m^2$, were measured in the B2P1 geometrical variation. This shear stress is well below any quoted blood damage threshold, as reviewed in section 1.9.4.1.2, almost regardless of exposure time, and is within normal physiological limits, detailed in section 2.6.1.

The low maximum shear rate measured in B2P1 is probably because the inlet jet is directed across the pumping chamber and fluid momentum is dissipated before impact with the wall. From the few flow studies that have been performed to identify shear rates that substantially inhibit clot formation on the walls of a VAD, a value of 400sec-1 ($14N/m^2$) has been published, as described in section 1.9.4.1.3. Therefore it is likely that thrombus formation the vicinity of the inlet jet would be inhibited although judgement of other areas within the pumping chamber must wait for future work.

The next lowest shear stresses were measured in B1P1 and were less than $9.6N/m^2$. This is below the threshold for inducing damage to red blood cells or platelets for exposure times less than 0.1 seconds. These wall shear rates in B1P1, and similarly for the other designs, were measured during a 1/125sec camera exposure. They occurred in only a few areas around the impact site of the inlet jet with the ventricle wall. Therefore it is likely that blood elements were not exposed to these levels of shear stress for more than 0.008 seconds. At this exposure time the limiting shear stress is approximately $300N/m^2$, from figure 1.4.

The maximum shear stress measured in B2P2 was 12.9N/m^2, apart from the possibly anomalous result of 21.3N/m^2.

B1P2 exhibits the highest overall wall shear stresses at 20.3N/m^2.

Jin and Clark reported mean wall shear stresses of 24.5N/m^2 downstream of the outlet valve in a sac-type VAD (103). Their flow rate was 4.05litres/minute.

Tarbell *et al* measured maximum wall shear stresses of 2.5 N/m^2 in the Penn State VAD, pumping at 6.5litres/minute (90). Doppler ultrasound probes, with which the measurements were made, have relatively large measurement volumes so near wall velocity measurements would not have been possible. More recently Baldwin *et al* studied the same VAD at a flow rate of 5.8litres/minute with a hot film wall shear probe (88). Maximum wall shear stresses of 270N/m^2 were measured in the outflow conduit upstream of the valve.

The wall shear stresses for the four designs are within the range of values published in the literature for similar VADs.

To provide some validation of the resulting shear stresses a simple numerical model was constructed using commercial software (Phoenics, Concentration, Heat and Momentum Ltd. Bakery House, 40 high Street, Wimbledon Village, London SW19 5AU), courtesy of the Mechanical Engineering Department of the University of Strathclyde. The geometry of the model is shown in figure 7.10. The steady flow of an axi-symmetric submerged jet impacting a wall was considered, with a uniform velocity profile of 0.8m/sec as the inlet condition. The maximum shear stress was 11N/m^2, at the wall, 20mm from the intersection of the central axis of the jet and the wall. This shear stress is of the same order of magnitude as the results presented in the previous section.

Obtaining near wall shear rate measurements is problematic even with fluorescent particles. When a particle is more than 1mm from a pumping chamber wall the distance is reasonably clear on captured images. An error of 0.1mm results in a $\pm$10% error in shear rate. At distances of 0.1mm from the wall the possible error is substantial. Some of the distances measured to obtain the results in tables 7.1 to 7.7 were of the order of 0.1mm to 0.5mm.

Whenever the ventricle wall position was slightly unclear the shortest distance between the particle velocity vector and wall was measured. The shortest distance between a velocity vector and a ventricle wall was measured when they were not parallel.

Near wall shear stress measurements could be refined with a colour CCD camera to distinguish between polyurethane ventricle fluorescence and tracer particle fluorescence, provided the tracer particles fluoresced at a different wavelength to the ventricle.

7.5 Summary and Conclusions

All of the maximum shear stress were found at the ventricle wall in the vicinity of the submerged jet impact. None of the shear stresses are high enough for long enough to damage platelets or red blood cells, based upon published *in vitro* results.

For design B2P1 the shear stresses were within physiological limits. Measured shear stresses in the other three designs were below that quoted for stenotic vessels.

Given the maximum wall shear rate in B2P1 the wall shear rates are likely too low for effective wall washing to prevent thrombus formation.

Obtaining fluid shear stresses inside a flexible pumping chamber is problematic, especially near the walls. A simple numerical model of a submerged jet impacting a plate provides some validation of the measured shear stresses.

The complete set of results for each design are discussed in the next chapter with the intention of identifying the best design, and the reasons why.

Chapter 8. Conclusions and Further Work Recommendations

8.1 Summary

The fluid flow in four geometrical variations of the proposed skeletal muscle powered blood pump has been investigated. From the clearance curve data, in chapter 5, the order of fastest to slowest clearance was B1P2, B1P1, B2P2, B2P1. The P2 designs (domed compression plate) appear to be slightly more energy efficient and provide a smoother pumping chamber compression than do the P1s (flat compression plate). The P1 designs enable a higher ejection fraction to be achieved, than the P2s.

The fluid flow patterns that influenced the fluid tracer clearance from the four designs were presented in chapter 6, and regions of high shear stress identified. These regions were then examined in more detail in chapter 7 and shear stresses quantified. In design B2P1 the shear stresses were within normal physiological limits, but it is likely that wall shear stresses in the rest of the pumping chamber were too low to provide adequate wall washing. The shear stresses in the other three designs were below established blood damage levels.

The best design, and the best features from the four designs, can be identified based upon this information.

8.2 Identifying the Best Design

The ideas behind the general blood damage model proposed by Bludzuweit (122) could be adapted to the data presented in this thesis, but as stated in the paper there is not enough data available in the public domain to analyse results. Instead the classic methodology for aiding the identification of the optimum design from conflicting criteria and constraints has been adopted.

Categories are defined with corresponding weightings. The designs are then ranked in each category and points awarded for first, second, third, etc. The points for each category are multiplied by the weighting and then totalled for each design. The design with the highest total is not necessarily the best, but this method does help guide the selection of the optimum design. A table is a good forum for presenting this process, table 8.1.

Table 8.1. Points awarded to each design by category

Category	B1P1	B1P2	B2P1	B2P2	Weighting
Clearance	3	4	1	2	3
Shear Stress	2	1	4	3	2
Potential Ejection Fraction	4	2	4	2	1
Smoothness of operation and compression	2	4	2	4	1
Result (rank × weighting)	19	20	17	16	

Clearance rate is given the highest weighting because artificial materials are considered to be the major factor in the thrombogenicity of VADs, as discussed in section 1.9.4.1.3. Shear stress is given the next highest weighting as it can also induce blood clotting.

The B1P2 design has the most points, largely because it clears the fastest. If the characteristics of B1P2 that enable it to clear quickly could be combined with those from the other designs that produce low shear stresses and high potential ejection fraction then a far superior device would result.

The base of B1P2 could be curved so that it provided a pocket for the compression plate to move into, yielding a higher ejection fraction, although the fluid in the pocket may remain unmoving for the majority of a pumping cycle. If the proposed device was built to operate with a consistently high ejection fraction then this would likely not be a problem.

The wall shear stresses associated with the inlet jet could be reduced by placing a larger volume of fluid between the inlet jet and the ventricle wall. One possible way of doing this would be to angle the inflow jet so that it is directed across the ventricle, thus washing out the left side of the pumping chamber, on figure 8.1, as is done in B1P1 and B1P2.

A more radical geometry that is worthy of assessment is a curled tube ventricle, figure 8.2. The advantages of this design are that clearance should be very fast because of the conveyor belt type fluid movement (mode b in section 5.4), but care would have to be taken that there are no small stagnation or re-circulation regions. Also there is more blood contacting surface and it may be difficult to manufacture this form.

One approach is to closely model the form and function of the natural ventricle. MRI studies have been conducted upon human hearts to obtain the fluid flow regime during pumping(144,145). The inlet jet is directed down into the ventricle, thus washing out and mixing all the blood left over from the previous ejection. Also the energy of the inflow jet is dissipated throughout the pumping chamber, thus reducing shear stress, and forming a line vortex that gradually decays. During ejection all of the velocity vectors are directed towards the outlet (aortic valve in the left ventricle).

This fluid flow has many similarities to that found in the four designs, but the twin characteristics of good mixing and inflow jet dispersal are not combined in one design. A possibility that derives from the MRI work is an almost direct copy of the natural ventricle, figure 8.3.

8.3 Recent Relevant Published Work

Electrical storage devices are becoming ever more efficient at storing power in smaller volumes as battery technology improves. Also other technologies such as fuel cells are advancing rapidly, for instance a fuel cell has been developed for medical applications that can provide approximately twice the power storage of the current battery system with the same mass and volume (146). These developments bode well for the future prospects of electrically powered VADs, although there is still some way to go before a completely implanted electrically powered device can be realised.

Recent advances in cloning have sparked controversy over moral implications and the possibilities of replacement organs that are to all intents and purposes a perfect match. These advances in biological engineering may well prove fruitful, provided the moral questions can be answered, and thus address many of the needs that artificial VAD development programs are attempting to meet.

New innovative designs of VAD are still being developed, such as a rotary blood pump based upon the Maillard-Wankel rotary compressor (147). No valves are required which reduces the thrombogenic potential of the device. The pump has a 100% ejection fraction so residence times are minimal and fluid velocities can be kept low to remove the possibility of damaging shear stresses. The problem now being addressed by the development team is the sealing of the gear mechanism.

Lohman highlight various practical problems that had been encountered involving patients supported by VADs (148). Both electrostatic discharge and electromagnetic interference have affected the operation of VADs. A completely implanted muscle powered device involving a pacemaker type muscle stimulator is unlikely to be affected. Reported mechanical problems such as drive-line occlusion (with pneumatic devices), impact damage and temperature extremes will not affect the proposed device described in chapter 2. The third area of concern was classified as chemical, as chemicals have caused stress fractures and cracking of pumps. Both severe and gradual effects were reported. Chemical factors that may need to be considered for the proposed device are those that it could be exposed to during implantation.

8.4 Recommendations for future work.

Commercial computational fluid dynamics software is becoming more advanced and accessible, as is the associated hardware. The development of a numerical model of the proposed device would greatly aid the development process, although it must be developed alongside an experimental model for validation and comparison, as Shortland *et al* have done (120). Then any improved designs should be tested experimentally because of the possibilities of reality dysfunction in numerical models.

Fluid flow in vicinity of valves could be studied by making a base from a plexi-glass block. A holistic view of wall shear stress could be obtained by the dye washout or particle deposition methods. Wall shear stresses could be better measured with flush mounted wall shear probes. However they could only be fitted on the flexible ventricle wall where it is in contact with the rigid compression plate continually during pumping, otherwise the dynamics of the pumping chamber would be changed.

The optical quality of the ventricles could be improved by dipping low melting point metal moulds into polyurethane solution, to obtain a better finish and overcome the wax deposit problem, mentioned in chapter 3. A silicone rubber elastomer could be used which has a refractive index nearer that of water, but the movement of an artificial ventricle constructed from it would need to be evaluated against one made from the polyurethane chosen for the proposed device.

More detailed fluid velocity measurements could be obtained by using smaller fluorescent particles, although this is probably dependent upon improving the optical clarity of the artificial pumping chambers.

It would be very useful to obtain analytical grade xanthan gum for making a non-Newtonian blood analogue, whose shear dependent behaviour would need to be fully characterised.

The signal from the force transducer could be used as the input to the computer controlling the superpump (linear actuator) to model the behaviour of conditioned skeletal muscle. The behaviour of a human fatigue resistance conditioned latissimus dorsi would be needed.

It may be prudent to conduct turbulent flow measurements, although the levels of turbulent stresses that cause blood damage have yet to defined. Conclusions about blood damage drawn from turbulent shear stress studies may need rethinking due to the work of Jones who observed that it is common practice to relate erythrocyte and platelet damage to Reynolds stresses, but Reynolds stresses are not true viscous shear stresses and viscous stresses can be significantly

lower than Reynolds stresses (149). Reynolds stress measurements were linked to viscous shear stresses

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