CONTROLLED PULSATILE ARCHITECTURE IN CARDIOPULMONARY BYPASS : IN-VITRO AND CLINICAL STUDIES

by

T. Gourlay BSc (Hons)

A thesis submitted in accordance with the regulations governing the award of the Degree of Doctor of Philosophy in Bioengineering.

Bioengineering Unit
University of Strathclyde
Glasgow, United Kingdom

October, 1997

" If a man begin with certainties, he shall end in doubts,

but if he will be content to begin with doubts,

he shall end in certainties. "

Francis Bacon (1561-1626)

The Advancement of Learning

I dedicate this work to my family and friends who have tolerated my insufferably bad disposition during its preparation.

ACKNOWLEDGEMENTS

There are many people, without whose assistance, this work could not have been completed. I am indebted to Prof. KM. Taylor of the Dept. Of Cardiothoracic Surgery, Hammersmith Hospital and Prof JM. Courtney of the Bioengineering Unit, Strathclyde University, for their guidance, patience and encouragement during the preparation of this work. I would also like to thank my friend John Brannan from the Department of Cardiac Surgery for his invaluable assistance at the proof reading stage. I acknowledge the help and assistance of many others including; Sue Tebbutt for her help with the biochemical assays, Dr. McGregor for help with the statistical analysis and Suzanne for acting as reference manager. I also thank all on the 5th floor of the MRC building for helping me to maintain a sense of humour throughout. In addition I would like to thank all at the Bioengineering Unit for helping when needed and finally to Mr. Suzuki for providing me with a distraction whenever required.

I wish to thank all of my friends and family for their support and undying patience throughout this course of study.

ABSTRACT

The clinical effects of pulsatile cardiopulmonary bypass (CPB) has been the focus of study for some time. In an effort to establish which aspects of pulse architecture are responsible for these clinical benefits, it is necessary to describe, in hydrodynamic terms, the pulse flow and pressure patterns, or architecture. A model of the human systemic circulation was designed and constructed for this purpose and two pulsatile perfusion pumps were studied, one was a roller pump, the other a new ventricular pump. It was anticipated that the ventricular mechanism would offer a higher degree of control of pulse architecture. Both systems were found to offer a high degree of output control and as anticipated the ventricular system offered better control of output architecture than the roller pump. In all aspects of the study of output architecture the ventricular pump was more powerful than the roller pump. However it was found that the ventricular pump was associated with the generation of significantly more microbubbles and this precluded its use in the clinical study. Having established four different architectures with the roller mechanism, one of which was non-pulsatile, the clinical study proceeded with this pump alone. The pulsatile groups as a whole, were found to offer metabolic and haemodynamic advantages over the non-pulsatile group. There were no differences between the various groups in terms of measures of organ damage during CPB. The non-pulsatile flow group had the highest level of nitric oxide activity, which appeared not to be related to any haemodynamic effect, but to a reperfusion or hypo-perfusion phenomenon. The differences between the pulsatile flow groups were in general not significant. The difficulty in achieving statistical significance between the pulsatile flow groups was thought to be related to the very small differences between the groups in terms of the magnitude of the parameters which contribute to the architecture. The methodology developed in this study can help to establish which aspects of pulse architecture are of importance during clinical CPB. This may not be possible however until the microbubble generation problems associated with the use of the ventricular mechanism has been solved.

CONTENTS LIST

CHAPTER 1

INTRODUCTION

CHAPTER 1: INTRODUCTION.

1.1 CARDIOPULMONARY BYPASS.

Cardiopulmonary bypass (CPB) was first used clinically in the 1950's (Gibbon, 1954). Since then, it has evolved significantly and its use has become more widespread. Clinical CPB is carried out in almost every country of the world on patients undergoing open heart surgery. Simply put, the CPB system performs the function of the heart and lungs whilst the heart is being repaired. Without this technique, open heart surgery would not be possible. The CPB system is complex and consists of many parts, but there are two major components which supply the vital functions, the blood oxygenator which performs the function of the lungs, and the arterial pump which performs the function of the heart during the operation.

The blood oxygenator has gone through many design changes since its first use. This device has evolved from a rotating disc oxygenator, through bubble oxygenator designs to the current membrane oxygenators, which are in widespread use and of which there are many different configurations (Bethune, 1986; Converse Peirce, 1986). These design changes reflect the technological evolution over the decades and were driven by a desire for compatibility, performance and ease of use. Other devices have evolved in parallel with the oxygenators. Arterial-line filtration was developed very early on to remove microemboli generated from within the CPB circuitry (Patterson and Kessler, 1969). Cardiotomy suction and filtration systems have evolved to process the blood lost at the operative site. These developments have been carried out in an effort to offer the patient a more adequate and safer perfusion during open heart surgery.

In contrast to the oxygenator, the second major component, the blood pump, has changed very little. The roller pump employed by Gibbon (1954) in his first cardiac procedure is still the mechanism most frequently used today to perform the pumping function in place of the isolated heart. The Hammersmith team led by Melrose (1955) performed their first open heart surgical procedure with a rotating disc oxygenator and a roller pump (fig 1.1).

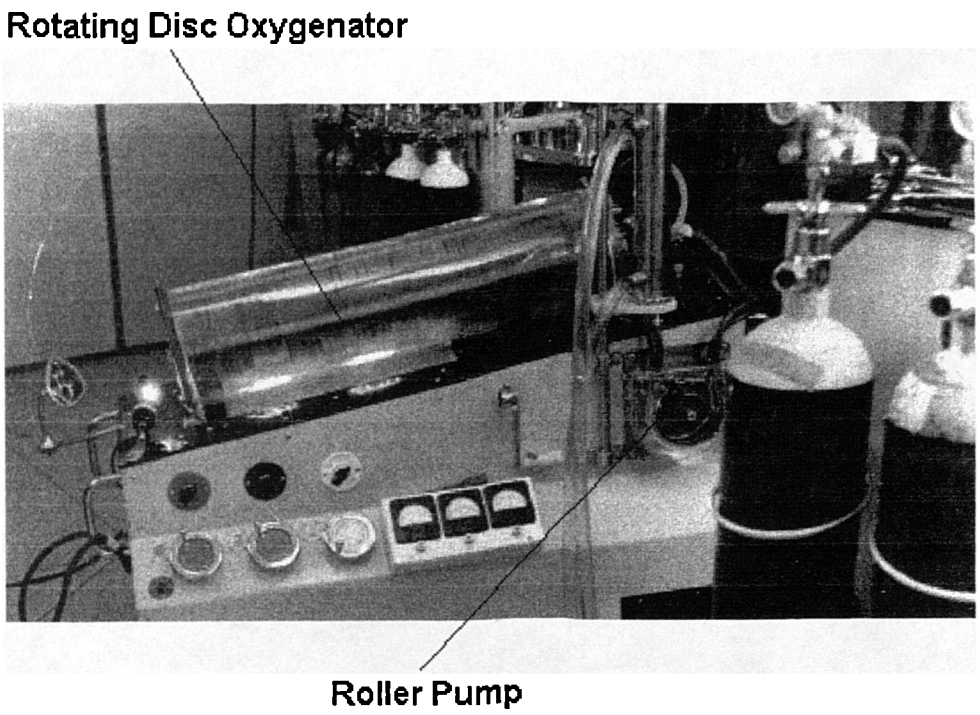


Figure 1.1 Melrose rotating disc pump/oxygenator (circa 1960) in the operating theatre at Hammersmith hospital where it was developed. The roller pump which provided the blood flow to the patient can be seen on the right of the console below the oxygenator.

The technology has changed and advanced over the years, but the original roller pump concept, which has its origins before the development of CPB (DeBakey et al,

1934), remains, to this day, the most widely used pumping mechanism for cardiac surgical applications (fig 1.2).

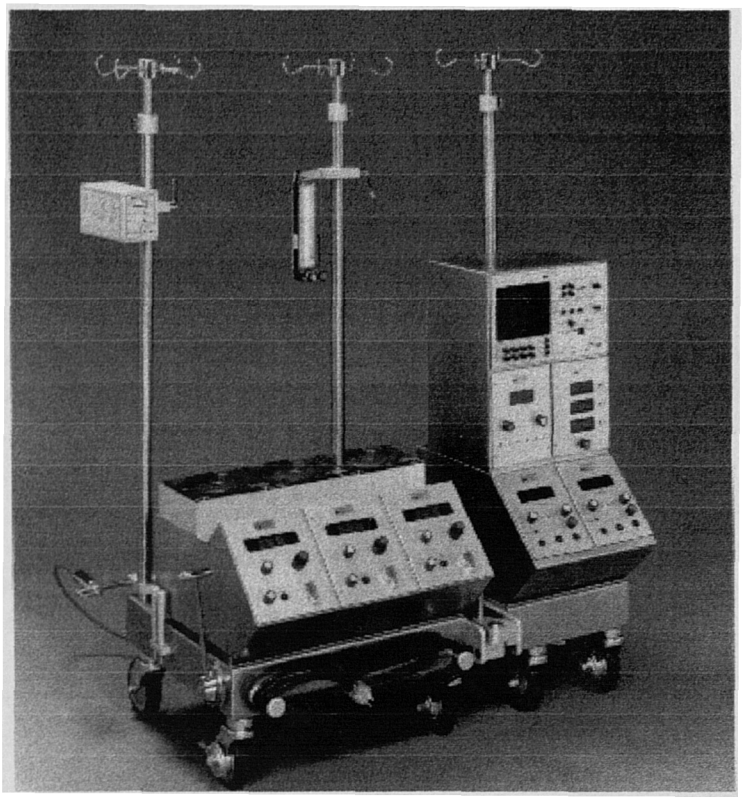


Figure 1.2 Stockert pump console showing a battery of roller pumps which act as arterial and suction pumps.

1.2 PULSATILE AND NON-PULSATILE CPB.

The heart provides a pulsatile flow to the body, and since very early in the development of CPB, the issue of whether or not the arterial pump should provide a pulsatile blood flow has been the foçus of controversy (Many et al, 1968). Even before the advent of CPB, there was significant interest in the physiological importance of the pulse. Long (1946) described a "pulsating perfusion apparatus" for

research use a decade before the first clinical CPB procedure. Work on de-pulsing the blood flow to isolated organs in an effort to study the effects of non-pulsatile blood flow pre-date this. Hooker (1910) described just such an experimental procedure. The advent of clinical CPB promoted the development of apparatus designed to provide pulsatile blood flow during this procedure. The roller pump was a part of this development. Jacobs et al (1969) described a roller pump modified to deliver pulsatile blood flow during CPB. Interest continued in this field and in the 1970's, the first commercially available pulsatile pump was offered to the cardiac surgical community by the Stockert company. This pump was the basis of many of the early studies which looked at the pulsatile blood flow issue and remains in clinical use today, relatively unchanged from its original design. Early clinical studies which used this pump pointed to a reduction in patient morbidity and mortality when pulsatile blood flow was employed during CPB (Taylor et al, 1983).

Many investigators have challenged the findings of researchers who show improved organ function during CPB with pulsatile blood flow. Frater et al (1980) could find no difference between pulsatile and non-pulsatile groups during and after CPB in a study focused on haemodynamics and hormone secretion. At the heart of these disagreements may be the question of what constitutes pulsatile flow. Most of the clinical papers published on the subject simply describe the flow regime employed as being either pulsatile or not. Some believe that there must be a more complex description to what is a very complex issue (Wright, 1994) and that the many factors which describe the shape of the pulse wave may, in combination or individually, be responsible for the perceived benefits of pulsatile CPB. The elimination of one aspect of this pulse architecture may render the pulse ineffective.

Roller pump-generated pulsatile flow remains controversial (Hornick and Taylor, 1997), but most manufacturers of pumps now offer a pulsatile blood pump option for perfusion pump consoles (fig 1.3), confirming the persistent interest in this flow modality and the confirmed belief on the part of some users in the clinical benefits offered by pulsatile blood flow.

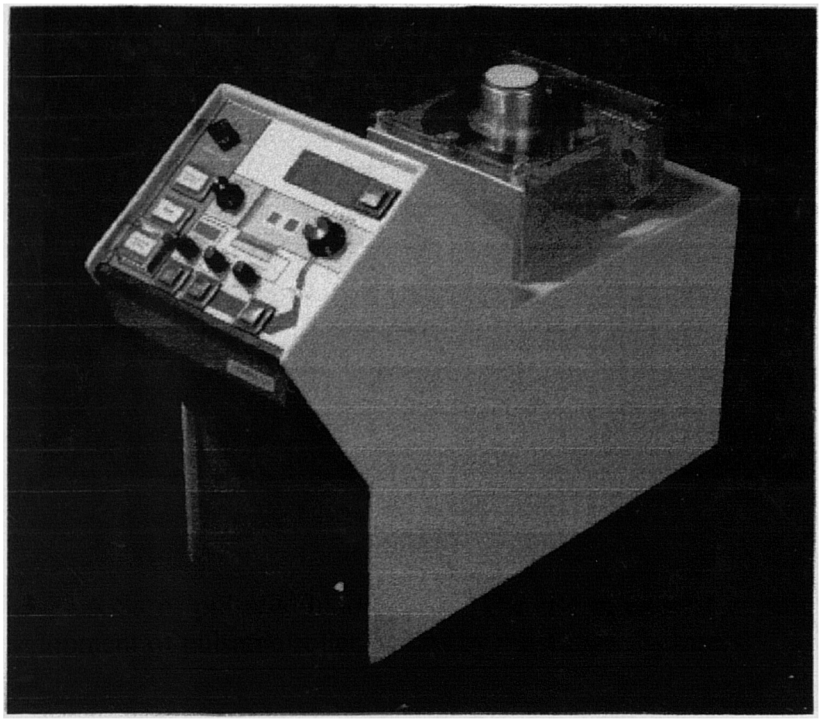


Figure 1.3 A Sarns pulsatile blood pump. The rise in interest in pulsatile CPB led to the development of pulsatile roller pumps by most manufacturers.

1.3 CONTROLLED PULSE ARCHITECTURE.

Pulse architecture refers to the many factors which combine to describe a pulsatile flow regime. The factors which will be employed in this study for this purpose are described in table 1.1.

Aspects of Pulse Architecture Employed for this Study
1. $dp/dt_{(max.)}$
2. Pressure amplitude
3. Pressure frequency
4. Mean pressure
5. Pulsatile hydraulic power
6 Mean hydraulic power

Table 1.1 Aspects of pulse architecture employed to describe the flow regimes in both aspects of this study.

The factors relating to pulse pressure used to describe pulsatile architecture are shown in figure 1.4.

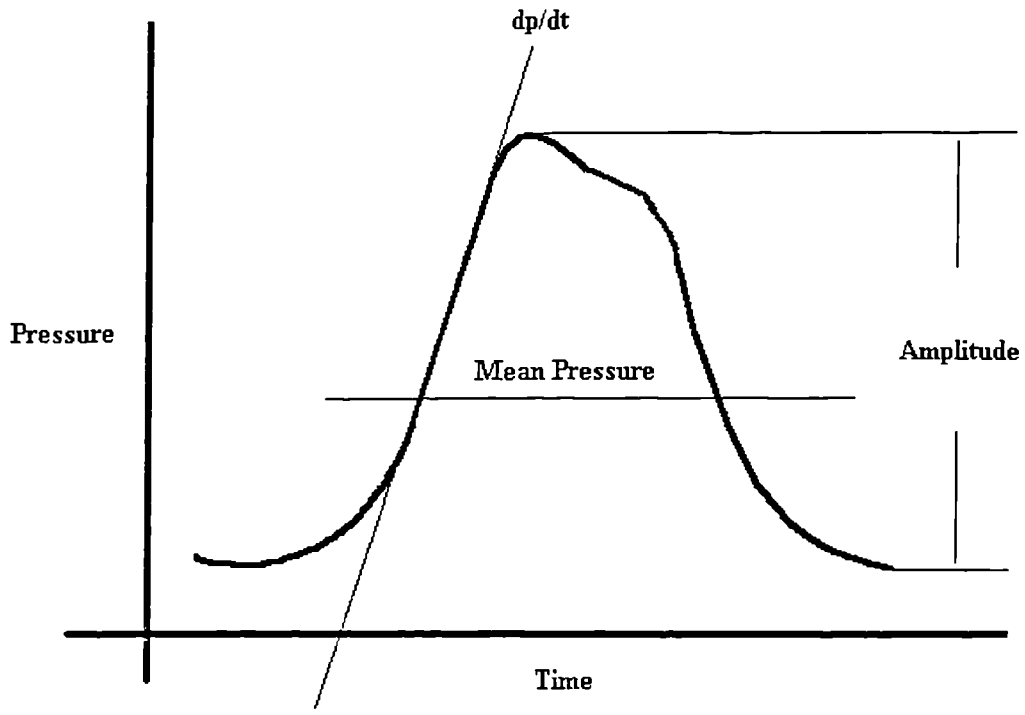


Figure 1.4 Single pressure waveform showing the factors relating to pressure which are involved in describing pulsatile architecture in this study.

In addition to the factors described in figure 1.4, pulse frequency and hydraulic power measurements derived from flow and pressure measurements are employed in describing the pulse architecture referred to in this work. Clinically, all measurements are made in the exposed aorta of the patient to eliminate reflections associated with the block nature of many of the components employed in the CPB circuit.

Controlled pulse architecture refers to knowledge of the effect of changing the control parameters of the pump on the architectural profile of the blood flow and pressure in the patient. This can only be established in the laboratory environment where the resistive and compliant loads can be controlled (Westerhof 1971). To carry out these tests, a model of the human circulatory system has been built, incorporating loads of physiological magnitude and function.

1.4 CONSTRUCTING A MODEL OF THE HUMAN SYSTEMIC CIRCULATION FOR FLOW STUDIES.

There are many methods available for modelling the circulation. These vary from extremely complex electrical analogues of the circulation requiring mainframe computers to carry out the analysis to simple paper calculations of the effect of a simple intervention on one aspect of pulse or flow architecture (Noordergraaf et al, 1960). However, a physical model of the circulatory system is required for assessing blood pumps and such a model must mimic, in as far as possible , the resistance and compliance which will be encountered by the pump in the clinical setting. Physical models have been designed for testing beating hearts (Westerhof, 1971) and for assessing the hydraulic power delivery of extracorporeal blood pumps (Wright, 1988).

Typically, these models consist of three main components; a characteristic resistance, a peripheral resistance and a compliance chamber. Such a model will be employed in assessing the output architecture of the perfusion pumps intended for use in the clinical aspect of this study.

1.5 THE GENERATION OF PULSATILE BLOOD FLOW.

In addition to the roller pump, there are other ways of generating pulsatile blood flow. Alternative systems include ventricular pumps, compression plate pumps and centrifugal pumps. Of these, only the centrifugal pump is in widespread clinical use and this is generally only employed in the non-pulsatile mode of operation (Nose' 1993). Compression plate pumps and ventricular pumps have been designed for clinical use, but, with a few exceptions such systems remain in the realm of research tools for non-clinical use (Sanderson et al, 1973). Ventricular pumps and compression plate pumps have both been associated with considerably greater pulsatility, measured by hydraulic power output, than roller pump mechanisms (Wright, 1988), but their clinical use has been hampered by a number of problems, ranging from material compatibility to difficulty with placement of the systems within the normal clinical perfusion circuit. The safe compatibility of the pulsatile pump system with the normal perfusion system is of paramount importance if such a device is to be employed clinically. Previous studies (Gourlay et al, 1987) have highlighted the potential problems associated with the combination of pulsatile blood flow and devices present in the arterial line of the perfusion circuit. The assessment of safety in terms of compatibility with other perfusion devices will play an important part in this study.

At the beginning this work, a new pulsatile ventricular pump was made available to the author for clinical use. This device is called the True Pulsatile Pump (TPP) and is manufactured in Israel by the Galram Corporation. The device has been employed in clinical studies in Israel with good results, although nothing has been published on its use. This ventricular system offers a physiological alternative to the pulsatile roller pump which has been described as less than optimal in terms of pulsatile blood flow generation (Wright, 1989). Both systems were employed in these studies.

1.6 PRE-CLINICAL STUDIES.

The pre-clinical studies were carried out in two phases. Firstly, the output architecture of the two pump systems will be studied with regard to the main control options available on each system. This will give an understanding of the effect of each control parameter on the overall output architecture. Those aspects of output architecture described in table 1.1 were measured in the model circulation. This process has been carried out previously by this group (Gourlay, 1987), but the characterization of the pulse architecture as a whole was not a part of these previous studies. Once the output architecture associated with a combination of control profiles has been established, a number of profiles were selected for clinical application. These would reflect, as far as is safely possible, the range of architecture control available with each pump system. Prior to clinical use, the safety of each system will be assessed with regard to output architecture and compatibility with other perfusion devices employed clinically. The compatibility of the pumps with membrane oxygenators was assessed with particular attention to the generation of gaseous microemboli, said to be associated with the combination of pulsatile flow and arterial line oxygenators

(Pearson, 1983, Gourlay et al, 1987). In addition, the haemocompatibility of the systems and the pulse architecture profiles were investigated to measure whether any adverse effect on blood cells is associated with any particular system or profile. The high shear rates associated with high output pulsatile systems may breach safety levels in terms of the generation of haemolysis and the aggregation and activation of blood cell species (Wright, 1986).

Once the pulse architecture groups have been identified and the safety has been established, the devices will be employed in a clinical study of the effects of this architecture control.

1.7 CLINICAL STUDIES.

One aim of the clinical study is to assess the pulse architecture of the two pump systems in the clinical setting and to establish whether the profiles exhibited clinically match those generated in the laboratory model. The prime aim of these studies, however, is to assess whether there is any clinical benefit associated with any particular architecture group or with any particular aspect of the pulse profile. Patients undergoing routine coronary bypass procedures were used for this study with a number of clearly defined exclusion criteria. The factors selected for study represent a number of mechanisms said to be affected by the presence of pulsatile flow. These cover damage to vital organs, haemodynamic effects, metabolic processes and outcome parameters, all reported to be sensitive to pulsatile blood flow in the clinical setting (Taylor, 1995). The selection of these parameters was based upon a number of factors, not least the financial cost of assays and technology required for measurement

purposes. However, the protocol was designed to cover as broad a spectrum of responses to pulsatile blood flow as possible in a study of limited size, with particular attention being paid to the operative period.

1.8 THESIS OBJECTIVES.

Considering the nature of the pump systems selected and the information to be derived from the study, the thesis objectives are as follows:

(i) To develop a model of the human systemic circulation with which pulsatile blood pumps can be evaluated.

(ii) Using the model circulation, to establish the level of control offered by each system in terms of pulse architecture measured in the model.

(iii) To assess the safety of each system in-vitro with regard to compatibility with other CPB components.

(iv) To assess whether the pulse architecture measured clinically is similar to that measured in the model circulation.

(v) To investigate, using the tools available, whether there is any particular advantage to be gained from the application of any of the selected architecture profiles in the clinical setting.

CHAPTER 2

PULSATILE BLOOD FLOW AND PULSATILE CARDIOPULMONARY BYPASS

CHAPTER 2 PULSATILE BLOOD FLOW AND PULSATILE CARDIOPULMONARY BYPASS

2.1 INTRODUCTION

The application of cardiopulmonary bypass (CPB) in the clinical treatment of cardiac anomalies dates back to 1953, when a team led by Gibbon performed the first cardiac repair procedure supported by a "pump oxygenator"(Gibbon, 1954). Gibbon's tremendous achievement in performing the first clinical CPB-supported heart operation came at the end of almost two decades of research. He had performed his first pump oxygenator supported procedure on an animal in 1937 (Gibbon 1937) . In the years since Gibbon's first clinical procedure, both the surgical and cardiopulmonary support techniques and technologies have evolved to such an extent that long-term cardiopulmonary assist procedures, complex surgical repairs and, latterly, heart and lung transplantation are performed routinely throughout the world. Successful support of the pulmonary and circulatory systems in order that a heart operation can be performed was the result of decades of research and development activity in several associated spheres. The focus of this review, the pumping system, is only one aspect of the technological development which was required prior to successful clinical application of CPB and does not take into account developments such as anti-coagulation, without which supported circulation would be almost impossible. The development of the pump for CPB progressed to the present day, shadowed by the question of whether the blood flow should be pulsatile like the heart, which presents complex engineering problems, or non-pulsatile, which may offer advantages in terms of simplicity from an engineering point of view.

The question of whether or not to pulse during CPB has been the subject of debate since the first application of this technique. The application of CPB offers researchers a unique opportunity to study the physiological role of the pulse under

controlled conditions. Indeed, the quest for understanding of the physiological importance of the pulse itself pre-dates clinical CPB by several thousand years. Hypocrates (460-377 BC) described the pulse as the force which is created by the meeting of two opposing streams of blood. The driving force for these blood streams, the heart merited no mention. The ancient physicians produced many theories explaining the presence of the pulse. Praxagoras (c 340 BC) surmised that the pulse was the result of bubbles bursting in the arteries as part of the process by which the body "rid itself of humors". Progress in the understanding of the circulatory system was being made by this time. Praxagoras also demonstrated that the circulatory system consisted of both veins and arteries and that each had a different role to play. Aristotle (384-322 BC) noted that "the blood of animals throbs within their veins" and possibly more significantly that "The veins pulsate as a whole synchronously and successively inasmuch as they depend on the heart. It keeps moving, and so do they". Aristotle, therefore, noticed, at last, the relationship between the movement of the heart and the pulsatile nature of the motion of the blood vessels. The presence and physiological significance of the pulse as such were now established; however, these great physicians still had no real understanding of the true physiological significance of the pulse or the processes which depend upon its presence. Galen (130 - 200) believed that the arteries contained air and took part in the respiration process, drawing air directly into the artery during diastole and removing waste products or "sooty matter" during systole. He also believed that the arteries were covered in pores which were directly connected to the skin through which respiration took place, the pores being large enough for air to enter, but too small for blood to exit. Although this may not have been anatomically correct, it was an early indication of the role that the pulse may have in exchange mechanisms. The great English physician William Harvey (1578-1657) determined by experimentation that air was not present in the arteries. (Harvey, trans.1958) He also noted that blood vessels passively

dilated with ventricular systole. Having established the pulsatile nature of blood flow, the importance and role of the pulse has been the focus of much research effort. Gibbon's early pioneering work has produced the means by which many fundamental questions related to the circulation may be answered.

2.2 THE PHYSIOLOGICAL SIGNIFICANCE OF PULSATILE BLOOD FLOW.

The bulk of blood flow research, particularly prior to the advent of extracorporeal circulation (ECC), focused on studies of isolated organs (Selkurt, 1951). However, as ECC support became widely available, it became possible to study the effect of pulsatile blood flow on the body as a whole (Wesolowski et al, 1950, Shepard and Kirklin, 1969). The experiments performed to assess the importance of pulsatile blood flow can be characterised into two categories; metabolic and haemodynamic responses to pulsatile blood flow. In addition, many of the reported benefits of pulsatile blood flow have been associated with enhanced peripheral and micro-circulation.

2.2.1 The metabolic effects of pulsatile blood flow

The importance of the pulse to metabolic processes has been the focus of research for several decades and the literature on the subject is substantial. This research has determined, on the whole, that the pulsatile nature of blood flow is a significant factor in the maintenance of a physiological equilibrium in terms of control and function in relation to most of the major organs (Mavroudis, 1978).

2.2.1.1 Pulsatile blood flow and the kidney

As early as 1889, Hamel determined that the pulse had an important influence on kidney function. His conclusions were confirmed by Gesell (Gesell,1913). Gesell, in fact, postulated that the improved kidney function was the result of improved gas exchange at the capillary level together with freer flow of lymph. Kohlstaedt and Page (1940) confirmed the importance of the pulse pressure itself to kidney function and the secretion of renin by performing a series of experiments on the isolated kidney. During these experiments, blood flow to the kidney was depulsed. They found that the secretion of renin was much higher in the group which was exposed to non-pulsatile blood flow. In all of these experiments, they ensured that the mean pressure was the same in both the pulsatile and non-pulsatile groups. Mavroudis (1978), in his excellent review of the subject, points out that there were those who contested these findings. Selkurt (1951), Ritter (1952), Goodyer and Glenn (1951) and Oelert and Eufe (1974) all found that renal function was not affected by the presence or absence of a pulse in an isolated renal preparation, provided that the mean blood pressure was maintained. Mavroudis points out, however, that the blood flow architecture was quite different in the pulsatile flow groups involved in these experiments. In all of these experiments, the pulse pressure profiles were quite different to those employed by Hooker (1910) during experiments in which normal pressure architecture was maintained. Many et al (1968) confirmed the importance of the pulse to kidney function in a series of experiments in which the renal arteries in dogs underwent depulsation. They found that renin levels increased in those animals which underwent depulsation and that depulsation of the renal arteries was associated with a significant systemic electrolyte and fluid imbalance. Boucher et al (1974) found, using radioactively labeled microspheres, that renal blood flow was preserved under pulsatile flow conditions, resulting in preservation of renal function. Nakayama et al (1963) reported that renal venous return was preserved under pulsatile blood

flow conditions. Fintersbusch et al (1961) demonstrated a loss in normal renal artery configuration associated with non-pulsatile blood flow in a perfused dog model. Barger and Herd (1966), using the same model, associated this finding with a shift in intra-renal blood flow resulting in decreased sodium excretion. Mori et al (1988) discovered that, after a period of hypothermic circulatory arrest, renal blood flow was substantially higher and kidneys recovered function more fully and rapidly in dogs exposed to pulsatile blood flow during the reperfusion period. Studies of renal function in open heart surgical patients by German et al (1972) confirmed that non-pulsatile blood flow was associated with a more rapid onset of renal hypoxia and acidosis than pulsatile flow, despite adequate total blood flow rate and oxygen extraction. Paquet (1969) had already described a similar phenomenon in an isolated porcine kidney model. Mukherjee et al (1973) demonstrated decreased tissue PO_2 in the medulla with non-pulsatile blood flow, together with increased local lactate levels and decreased oxygen uptake. Taylor et al (1979(a)) described an increase in urine production and a decrease in plasma angiotensin II levels associated with the clinical use of pulsatile blood flow during open heart surgical procedures. Landymore et al (1979), working on essentially the same model found that urine output was enhanced with pulsatile flow and that plasma renin levels were higher with non-pulsatile flow. Williams et al (1979), in a study of infants undergoing open heart surgery with profound hypothermia found that urine output in the pulsatile flow group was twice that of the non-pulsatile flow group. Many investigators have had difficulty in discerning any advantage attributable to the pulsatile nature of blood flow in the clinical setting. This may be due to many factors. However, it is clear that the pressure/flow architecture is of importance (Mavroudis 1978). Louagie et al (1992) concluded that pulsatile blood flow was associated with reduced urine output and reduced creatinine clearance in patients undergoing open heart surgery. Although

these findings were at odds with the vast majority of the scientific literature, no explanation was offered nor was the flow regime employed described.

The effect of pulsatile flow on renal function may be most apparent and significant under extreme conditions. A number of clinical studies have focused on the importance of pulsatile flow to those patients undergoing open heart surgery with a pre-operative renal insufficiency. Matsuda et al (1986) on the basis of a substantial clinical trial recommended that pulsatile blood flow should be employed in just this group of patients, having established that renal function is preserved in this patient group under pulsatile flow conditions.

The preservation of renal preparations for transplantation is another area in which the effect of pulsatility has been studied. Belzer et al (1968) demonstrated that isolated non-pulsatile-perfused kidneys were associated with a gradual, but clearly defined, rise in perfusion pressure which was not present with pulsatile perfusion. They further demonstrated that the kidneys perfused in a pulsatile manner returned to normal function more quickly than those perfused with non-pulsatile flow once transplanted, confirming enhanced preservation associated, they surmised, with improved tissue perfusion.

2.2.1.2 Pulsatile blood flow and the brain

The brain, though protected by auto-regulation, is still susceptible to injury during open heart surgery. Taylor (1980), in his excellent review on the subject, showed that the autoregulatory mechanisms are capable of being modified by several factors, including temperature, pattern of blood flow, viscosity and oxygen and carbon dioxide tension together with the effects of various pharmacological agents. Simpson (1981) determined that certain brain tissues required substantially higher blood flow rates than others. He further suggested that these may be compromised by the breakdown of autoregulatory mechanisms and flow disruption associated with CPB.

Hill et al (1969) described significant neuropathological manifestations associated with cardiac surgery. These findings included histological evidence of focal brain lesions resulting from ECC during open heart surgery. Sanderson et al (1972), employing a canine model, demonstrated that this diffuse brain cell damage, which has been associated with non-pulsatile perfusion, could be prevented by employing pulsatile flow. Taylor et al (1980) using a canine perfusion model, demonstrated that the level of creatine kinase BB iso-enzyme in the cerebrospinal fluid was significantly higher in animals perfused with non-pulsatile blood flow than those in which pulsatile blood flow was employed. dePaepe et al (1979) described a significant reduction in cerebral capillary diameter when non-pulsatile flow was employed, when compared to pulsatile flow, indicating at least, a lowering of regional blood flow. Taylor et al (1978, 1982), in a series of studies, demonstrated that the activity of the hypothalmic-pituitary axis to surgical stress is markedly different in the presence of pulsatile and non-pulsatile blood flow. They found that the anterior pituitary fails to respond to thyrotrophin-releasing hormone (TRH) under non-pulsatile conditions which is in contrast to the normal profile exhibited during major non-bypass surgery. The secretion of cortisol were also found to be significantly reduced under non-pulsatile flow conditions. In all cases, they found that normal responses returned within one hour of cessation of non-pulsatile bypass. Taylor et al (1979(e)) further demonstrated that the pituitary-adrenal axis responded normally under pulsatile perfusion conditions. During these studies, the pulsatile and non-pulsatile groups were presented with the same mean blood pressure and blood flow rate. Philbin et al (1979) had demonstrated a similar response pattern with vasopressin secretion during non-pulsatile cardiopulmonary bypass. All of these findings reflect a major difference in the physiological response of the brain to the perfusion modality. In addition to maintaining the functional aspect of cerebral activity, pulsatile flow has the effect of preventing the cerebral acidosis normally encountered during the early phase of

cardiopulmonary bypass (Briceno and Runge, 1994). This may be due to the effect of pulsatile flow in maintaining regional cerebral blood flow. Kono et al (1990) demonstrated that there is a difference of up to 25% in the measured cerebral vascular resistance between pulsatile and non-pulsatile groups of patients. This highly significant difference in cerebral vascular resistance and the supposed improvement in regional blood flow and distribution may be responsible for the reduced cerebral excess lactate encountered by Mori et al (1983) who suggested that regional blood flow was maintained and anaerobic metabolism was suppressed with the application of pulsatile blood flow, particularly during the critical cooling and rewarming phases of the operative procedure. The maintenance of regional cerebral blood flow was confirmed by Tranmer et al (1986), using computerised mapping in a canine stroke model. In another canine cardiopulmonary bypass study, Onoe et al (1994) found that pulsatile blood flow preserved cerebral circulation, even during profound hypothermia. They suggested that this confirms a cerebral protective effect of pulsatile blood flow.

In common with the studies of the effects of pulsatile blood flow on the kidney, there have been a number of studies, focusing on the brain, which contest the evidence supporting pulsatile blood flow as the perfusion modality of choice. Invariably, these studies do not offer non-pulsatile blood flow as a superior mode of perfusion, but rather they indicate that there is little or no advantage in pulsatile blood flow over non-pulsatile flow. Hindman et al (1995), in a study focusing on cerebral blood flow and cerebral oxygen consumption in a rabbit model, found no difference, in terms of either parameter, between pulsatile and non pulsatile flow regimes. In this instance, the single aspect of pulsatile architecture which was controlled was the ejection time. The rabbits were randomised into one of three groups; those with an ejection period of 100ms, those with an ejection period of 140ms, and those perfused with non-pulsatile blood flow. All other aspects of pulse architecture, such as rise-

time and decay-time and frequency were uncontrolled. The results, therefore, do not give a true picture of the effects of pulsatile flow on cerebral perfusion and metabolism, but rather the effect of several non-physiological blood flow patterns. Despite this conflicting evidence, the vast majority of clinical and non-clinical studies supports pulsatile flow as a factor responsible for the maintenance of normal cerebral function during CPB.

2.2.1.3 Pulsatile blood flow and the liver and pancreas

Interest in the effects of cardiopulmonary bypass on pancreatic function was stimulated by sporadic and isolated findings which pointed to increased plasma amylase levels after non-pulsatile bypass and by the findings of Feiner (1976) who reported a 16% incidence of ischaemic pancreatitis in patients who had undergone open heart surgery. Baca et al (1979), using a canine model, found that pancreatic function was significantly better at the end of and 48 hours after bypass in dogs which were exposed to pulsatile blood flow during the perfusion period. Saggau et al (1980) monitoring insulin levels together with glucose, glucagon and growth hormone in both human and animal studies, concluded that pulsatile blood flow during the perfusion phase of the operation preserved pancreatic function. They commented on the apparent "normal function" of the pancreatic beta-cells in the pulsatile blood flow group. Using a clinical model, Murray et al (1982) were able to demonstrate improved pancreatic function associated with a reduction in the incidence of elevated amylase levels in patients undergoing CPB with pulsatile flow. Mori et al (1988) concluded that pancreatic function was preserved in those dogs perfused under both hypothermia and normothermia in the presence of pulsatile blood flow. In contrast, they found that pancreatic function was reduced in dogs which were exposed to a non-pulsatile regime. Employing serum glutamic-oxyloacetic transaminase (sGOT) as a marker of hepatic injury, Pappas et al (1975) concluded

that pulsatile blood flow was responsible for the preservation of hepatic tissues. Mathie et al (1984) showed that pulsatile CPB in dogs preserved both hepatic blood flow and function. This was echoed in the results of a series of clinical studies carried out by Chiu et al (1984) who found that hepatic function was preserved with pulsatile blood flow during CPB as reflected in postoperative sGOT levels. They demonstrated that hepatic blood flow showed a typical vasoconstrictive response to non-pulsatile CPB, coupled with a reduction in hepatic oxygen consumption. On balance, pulsatile flow appears to maintain physiological pancreatic and hepatic blood flow and function both during and after CPB (Taylor, 1986).

2.2.1.4 Pulsatile blood flow and the gut

Abdominal complications associated with CPB form a significant part of the reported operative mortality. In one study, Gauss et al (1994) reported that 1.8% of 500 patients undergoing open heart surgery had some form of abdominal complication associated with the operation. The mortality rate was high in this group at 44%. In a review of 5,924 patients, Baue (1993) noted that gastrointestinal problems were responsible for a significant amount of CPB-related mortality and morbidity. The suggested reason for these complications was mesenteric hypoperfusion. It has been reported that CPB is associated with endotoxaemia in some patients (Bowles et al, 1995). Endotoxaemia associated with cardiopulmonary bypass in children has been the focus of study for some time. Andersen and Baek (1992) postulated that the high levels of endotoxin found in children may be due to increased gut permeability associated with mesenteric ischaemia. The incidence of this undesirable occurrence is as yet undetermined. However, there have been reports of substantially elevated endotoxin levels reported in patients with no apparent pre-operative infection (Andersen et al, 1987). Rocke et al (1987) determined that peak levels of endotoxin could be measured 15 minutes after the release of the aortic cross-clamp. Jansen et al

(1992) suggested that the period just after the release of the aortic cross-clamp was the most critical with regard to gut perfusion as it corresponded to the period during which the previously underperfused and ischaemic gut underwent reperfusion with oxygenated blood. Ohri et al (1994), using a canine model of bypass confirmed the importance of the re-warming phase to the pathophysiology of endotoxaemia. They demonstrated that during this phase of the procedure, there was a disparity between the mesenteric oxygen consumption and oxygen delivery. Further studies using the same model confirmed an associated increase in gut permeability. Tao et al (1995), using a porcine model, demonstrated that gut mucosa does, indeed, become ischaemic during cardiopulmonary bypass and that this is due to two factors; blood flow redistribution and shifting tissue oxygen demand. This work was carried out under normothermic conditions, whereas clinical cardiopulmonary bypass is normally performed with some degree of hypothermia, which may reduce the tissue oxygen demand. This may correlate with finding of Rocke et al (1987) who demonstrated that rising endotoxin levels were to be found during the re-warming phase of CPB when the aortic cross-clamp is released. Riddington et al (1996) confirmed these findings in the clinical model. They found that patients undergoing CPB exhibited increased gut mucosal ischaemia and gut permeability and that endotoxin was detectable in the plasma of 42% of these patients. They further found that elevated pHi (intestinal pH) did not return to normal until the non-pulsatile flow regime was terminated and the heart took over the circulation. Quigley et al (1995) established that perfusion pressure was one important factor in preventing endotoxaemia. By showing that if the perfusion pressure was maintained in excess of 60mmHg throughout the perfusion period, with particular attention being paid to cardiac index during the normothermic phase, there was no measurable endotoxaemia. Transient episodes of mucosal ischaemia, leading to increased gut permeability, resulting in endotoxaemia, have been widely reported in the recent literature. A number of

preventative measures have been proposed to modify and reduce the impact of this potentially injurious course of events. Fiddian-Green et al (1990) suggested that pulsatile blood flow may result in improved blood flow to the gut, reducing mucosal ischaemia and increasing oxygen delivery. They further suggested the application of pre-operative gut lavage and parenteral antibiotics. Reilly et al (1993) proposed that the vasoactive response in the gut to circulatory shock was mediated by the activation of the renin-angiotensin system, resulting in increased gut permeability. Taylor et al (1979(a)) demonstrated that pulsatile blood flow employed during CPB does not activate the renin-angiotensin system, and does not, therefore, produce the significant vasoconstriction routinely encountered when non-pulsatile blood flow is employed. Pulsatile blood flow, therefore, may offer one simple, but significant method for avoiding the potentially catastrophic results of impaired gut perfusion.

2.2.2 The haemodynamic effects of pulsatile blood flow.

Since the advent of CPB, it has been demonstrated that non-pulsatile blood flow results in a steadily increasing peripheral vascular resistance which does not necessarily end at the cessation of CPB. Estefanous et al (1973) demonstrated that a period of hypertension/vasoconstriction may follow coronary bypass surgery, persisting into the post-operative phase. Stinson et al (1977) stated that during the post-operative period there was an increasing tendency towards administering vasodilatory agents such as sodium nitroprusside to counteract the vasoconstriction which was commonly encountered after bypass surgery. Taylor et al (1979(a)) determined that peripheral vascular resistance was greatly reduced when pulsatile blood flow was employed during the perfusion phase. They further demonstrated that this effect was carried over into the post-operative phase (Taylor et al 1979(b)) where, once again, those patients who were exposed to pulsatile blood flow during CPB exhibited a lower systemic vascular resistance. Philbin et al (1979) surmised that

this difference may be due to reduced plasma vasopressin levels in the pulsatile blood flow group. Taylor et al (1979(c)) suggested that the prolonged effect may be due to the effect of non-pulsatile flow on the renin-angiotensin system. In an early group of experiments They demonstrated, with a clinical model that plasma angiotensin II levels were significantly elevated with non-pulsatile blood flow. This rise in angiotensin II, a strong vasoconstricting agent, correlates with the well documented rise in peripheral vascular resistance seen when non-pulsatile blood flow is employed (Taylor et al, 1979(a)). The role of angiotensin II in the rise in peripheral vascular resistance was confirmed by the use of angiotensin II inhibitors during non-pulsatile CPB. This resulted in the preservation of a normal haemodynamic state during the perfusion period and in the immediate post-operative phase. Elevated angiotensin II levels present in the post perfusion period are thought to be responsible for the high peripheral vascular resistance encountered at this time. Taylor (1980) further suggested that this elevated peripheral vascular resistance may result in an excess work requirement for the heart at the point at which it takes over its circulatory role. At this point, when the heart is recovering from a period of myocardial arrest, it is not well suited to pumping against an increased resistance. This may result in further activation of the renin-angiotensin system, generating more plasma angiotensin II. It has been suggested that the use of non-pulsatile blood flow may be responsible for what has been described as a vicious circle syndrome which may lead to uncontrolled vasoconstriction, resulting in prolonged elevated peripheral vascular resistance after surgery (Taylor et al, 1986). There appear to be two strategies for dealing with this scenario; cure by inotropic action, or prevention by using pulsatile blood flow during the period of CPB.

The importance of the pulse per se in the maintenance of physiological haemodynamics was confirmed by studies of pulsatile versus non-pulsatile blood flow in which the same blood flow and mean pressures were employed. The only

difference between perfusion modalities being the presence or absence of the pulse. Taylor et al (1977) found that increasing the blood flow and pressure in the non-pulsatile blood flow group still resulted in increasing peripheral vascular resistance, indicating that it was the pulse itself which was responsible for the improved haemodynamic status. The maintenance of normal haemodynamics, particularly in relation to vascular resistance, may be due, in part, to the release of nitric oxide (NO) from the endothelium in the presence of pulsatile blood flow. Nitric oxide is an extremely potent endogenous vasodilator and in-vitro and ex-vivo studies have indicated that its release is strongly associated with both pulsatile amplitude and frequency (Hutcheson and Griffith, 1991). Hutcheson and Griffith found that increasing pulsatile blood flow pressure and amplitude resulted in increased NO activity in isolated arterial segments. In a recent study, Mathie et al (1996) concluded that there may be some clinical evidence to support the in-vitro findings in the clinical setting, and further, that temperature may modulate the effect of the flow modality on NO activity. The improvement in the post-perfusion/post-operative haemodynamic status of patients undergoing pulsatile perfusion is confirmed by outcome studies. Maddoux et al (1976) found that the use of pulsatile blood flow during CPB led to a reduction in the need for inotropes and in reduced intra-aortic balloon pump (IABP) usage. Bregman et at (1977) and Gourlay et al (1983) reported similar findings with reduced IABP usage and a reduction in peri-operative myocardial infarction in patients perfused with pulsatile blood flow. Taylor (1986) perhaps added the most convincing argument in favour of pulsatile blood flow by confirming that pulsatile perfusion was associated with lower overall operative mortality than non-pulsatile perfusion.

2.2.3 Microcirculatory effects of pulsatile blood flow.

Burton (1954) suggested that as arterial blood pressure begins to decay after systole, blood flow in the microcirculation continues until a specific critical closing pressure in the pre-capillary arterioles is reached, at which point blood flow within the capillaries will cease. They further demonstrated that pulsatility prolongs the period of capillary opening and blood flow. This concept is the basis of pulsatile blood flow as a preferred flow modality and may explain many of its perceived benefits. As early as 1938, McMaster and Parsons demonstrated that lymph flow is greatly reduced when blood flow is de-pulsed. Ogata et al (1960) showed that capillary blood flow and diameter are affected by the presence of a pulse, irrespective of total blood flow and mean pressure. Takeda (1960) demonstrated that there was a general collapse in capillary structure, coupled to a reduction in blood flow and an increase in capillary shunting with non-pulsatile blood flow. Once again, in these animal experiments, blood flow and mean pressure were precisely the same in both the pulsatile and non-pulsatile flow arms of the study, indicating that the pulse itself was responsible for the stated benefit. The reduction in capillary diameter and capillary shunting correlates extremely well with the clinical findings of increasing peripheral vascular resistance with non-pulsatile flow. It has been suggested, more recently, that it may not be the pulse pressure which is responsible for the maintenance of an open periphery under pulsatile blood flow conditions. Shepard et al (1966) postulated that the critical closing pressure argument is correct, but that it is energy which is responsible for the maintenance of an open periphery. They determined, using both mathematical and physical modeling, that pulsatile blood flow at the same mean pressure and flow contains up to 2.4 times the energy content of a non-pulsatile blood flow modality. Wilcox et al (1967) confirmed that pulsatile blood flow is responsible for the dissipation of much more energy through the tissues. Shepard et al (1966) suggested that the increased energy contained in pulsatile blood flow is responsible for

maintaining capillary patency, and that the pulse itself, which is discernible to the capillary level, is responsible for the exchange of fluids at the extracellular level maintaining cell metabolism. Using a rabbit model, Parsons and McMaster (1938) noted that edema developed in isolated ears when they were perfused with non-pulsatile blood flow and that those perfused in a pulsatile manner remained essentially normal. They also found that contrast dye cleared more rapidly from the ear perfused with pulsatile blood flow, suggesting that fluid exchange and clearance is enhanced by the presence of the pulse. Prior et al (1995) suggested that the pulse is responsible for the exchange of fluids at the capillary level and that the mean pressure is responsible for the maintenance of fluid balance. This complex principle, which Prior called "Pulsed Reverse Osmosis", suggests that the architecture of the pulse pressure profile at the capillary level together with the mean blood pressure and osmotic pressures in the blood and interstitium are the factors responsible for the maintenance of fluid balance and the exchange of nutrients at the cellular level. This is in keeping with the Starling Principle (Starling, 1896) with the exception that Starling did not recognize the presence or importance of the pulse at the capillary level. In Prior's model, the pulse is considered to be responsible for the exchange of metabolites and fluid and for the removal of waste products from the interstitium to the blood phase. Prior et al (1996) suggest that, during the systolic phase of the pulse cycle, fluid passes from the blood vessel into the tissues and that during the diastolic phase fluid passes from the tissues into the blood phase. The pulse, therefore, controls the exchange of fluids and the mean pressure and osmotic gradient together control fluid balance. This theory is gaining support, and is the focus of continued laboratory and clinical research.

2.2.3.2 Tissue oxygen consumption

Many investigators have used tissue oxygen consumption as an indicator of the quality of tissue perfusion during pulsatile and non-pulsatile CPB. Shepard and Kirklin (1969) described how oxygen consumption declined in calves perfused with non-pulsatile blood flow and that this contrasted with the preservation of tissue oxygen consumption levels in animals perfused with pulsatile blood flow. In the same study, they described the development of metabolic acidosis in animals perfused with non-pulsatile blood flow. The development of metabolic acidosis under non-pulsatile blood flow conditions has been confirmed by many investigators in both clinical and animal studies. Jacobs et al (1969) and Dunn et al (1974) both confirmed the development of tissue acidosis under non-pulsatile blood flow, a state which did not develop when pulsatile blood flow was employed. Ogata et al (1960) has confirmed the advantage of pulsatile flow over non-pulsatile flow in the development of tissue acidosis and oxygen consumption, but suggested that, at higher blood flow rates, this may be negated. Boucher et al (1974), in work on Rhesus monkeys, confirmed this, stating that, at flow rates in excess of 200 ml/kg/min, there was no advantage offered by pulsatile blood flow. Once again, however, there is no account taken of pulsatile blood flow/pressure architecture. In addition, 200ml/kg/min is well in excess of the normal clinical blood flow rate employed in clinical practice.

The mechanism by which pulsatile blood flow maintains normal tissue metabolism is still not completely understood. However, Shepard et al (1966) suggested that there may be three mechanisms which explain this advantage. They suggested that the pulse component may break down the boundary layer around tissue cells, enhancing diffusion. Recent work by Prior et al (1995) would appear to confirm this. They suggested that interstitial and lymph flow may be enhanced during pulsatile blood flow. This observation had been made by Parsons and McMaster (1938) Tissue oxygen consumption is a good marker of the adequacy of perfusion. Early

recognition of oxygen deficit and the development of tissue acidosis led clinicians to employ core cooling to reduce the metabolic demand of the patient undergoing CPB. This technique, though still employed today, simply delays the supply/demand imbalance from the beginning of the procedure to the re-warming phase. Even when cooling techniques are employed, pulsatile flow is associated with a higher oxygen demand (Sheperd and Kirklin, 1969), indicating that more tissue bulk is being perfused. Modern gas exchange devices can meet the increased oxygen demand associated with pulsatile flow with no difficulty (Gourlay et al, 1987, Fried et al, 1994, Shepard et al, 1996). By the time of maximum demand, however, patients who have been perfused with a non-pulsatile flow regime may have already suffered some degree of ischaemic injury and have created the conditions necessary for the development of reperfusion injury (Gourlay et al, 1995, Lucchesi, 1990). These issues form an important and substantial part of this thesis.

The evidence supporting the clinical use of pulsatile blood flow during CPB is, at first sight, overwhelming. All major organ systems appear to benefit from pulsatile CPB. Much of the recent evidence supporting pulsatile flow clinically is based upon use of the clinical model described by Taylor et al (1978). The control parameters employed in these early studies of roller pump-generated pulsatile flow were derived empirically and not by controlled experimentation. Using some of the markers employed by investigators cited in this chapter, the aim of this thesis is to investigate and ascertain which aspects of blood flow architecture are important from a physiological standpoint. To achieve these goals, it is important that attention is paid to the technology employed. This is important, particularly with regard to potential for controlling flow architecture and intrinsic safety.

CHAPTER 3

PULSATILE CARDIOPULMONARY BYPASS : EXTRACORPOREAL BLOOD PUMPS AND SAFETY CONSIDERATIONS

CHAPTER 3 PULSATILE CARDIOPULMONARY BYPASS EXTRACORPOREAL BLOOD PUMPS AND SAFETY CONSIDERATIONS.

3.1 INTRODUCTION

Blood pumping systems for both human and animal extracorporeal circulation applications pre-date the clinical use of CPB for the repair of cardiac lesions by several decades. Bayliss and Muller (1928), described a pumping system for circulatory support which offered, for the first time, a level of practicality. Development of pumping technology continued with both practical and impractical designs being produced. Daly (1933) described the use of a modified 7-horsepower motorcar engine as a blood pump for clinical and research applications. The surgical techniques required for performing open heart surgery existed prior to the development of the pumping technology. It was not until DeBakey (1934) developed the roller pump mechanism, previously described by van Allen (1932), for high flow blood pumping applications that open heart surgery looked like being a practical possibility. As interest and realization of the importance of the pumping technology developed in tandem with developing technology in other spheres, pumping systems evolved, some of which offered pulsatile blood flow as a clinical option. The principal pumping mechanisms can be described as follows;

1. Roller Pump
2. Compression Plate Pump
3. Ventricular Pump
4. Centrifugal Pump
5. Pulsatile Assist Device

3.2 BLOOD PUMPS FOR EXTRACORPOREAL APPLICATIONS

3.2.1 The roller blood pump

The roller pump mechanism is simple and reliable, factors which are extremely important for a clinical support mechanism. Such systems were employed for circulatory support without the use of oxygenators for some time before clinical extracorporeal circulation/oxygenation was employed. Wesolowski et al (1950) reported the early use of a roller pump mechanism in total circulatory support in animals. The roller pump mechanism, which works on the principal of two or more diametrically opposed rollers "milking" a constrained piece of tubing (fig.3.1), is both simple and predictable in terms of output.

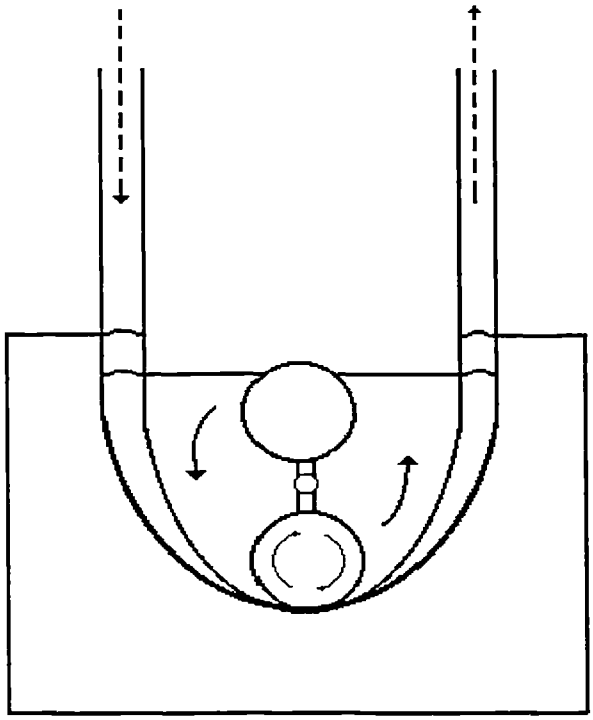


Figure 3.1 Typical roller pump head arrangement. The broken arrows show the direction of blood flow and the solid arrows show the direction of rotation of the head components. In this case, two rollers are shown on a common cross head. Each roller is capable of independent rotation in either clockwise or counter-clockwise direction. By rotating the roller mechanism over a constrained piece of tubing, positive displacement of the perfusate contained within the tube is achieved by a "milking" process.

The occlusive nature of the mechanism results in the generation of strong negative pressures at the inlet side, rendering this type of mechanism appropriate for both arterial blood pumping systems and for suction pumping (Gourlay et al, 1994). This inherent flexibility led to this mechanism being adopted as the pump of choice for heart lung machines from a very early point in the evolution of CPB.

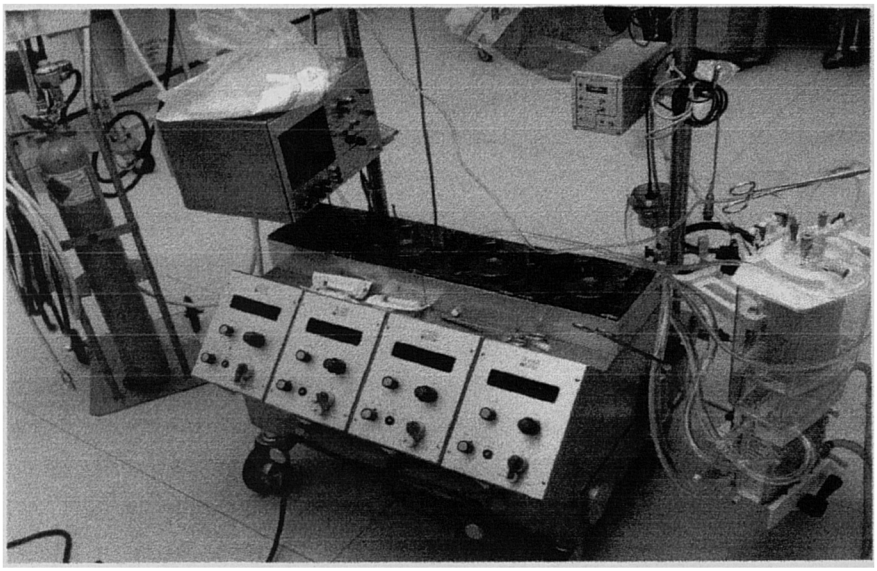


Figure 3.2. Stockert pulsatile roller pump. This was the first of the truly commercially available pulsatile roller pumps. The system shown in the operating theatre is a four pump console with PFCII pulsatile flow controller positioned above and to the left of the pumps. The membrane oxygenator is shown to the right of the console.

Initially, commercially available roller pumps did not offer a pulsatile flow option. However, interest in the investigation of pulsatile flow as a modality for clinical CPB led to the development of modified systems. Ogata et al (1959) reported the modification of a roller pump to generate pulsatile blood flow. This was followed by Nonoyama (1960) and Nakayama et al (1963), each employing essentially the same roller pump system with limited mechanical success, but with reported clinical benefit. The poor mechanical performance of these systems was probably due to the use of

high inertial pump heads and poor motor control which restricted overall control of the system. In the 1970's, a pulsatile roller pump for clinical use was made available for the first time by the Stockert Company (fig 3.2.).

This innovation was made possible by the development of a low inertial pump head made of aluminium and stainless steel and the incorporation of a "stepping" motor mechanism. The principal design requirement for this pumping system was that it should be capable of generating pulsatile blood flow during CPB. The combination of a light pump head and the stepping motor permitted the pump head to be precisely controlled during the rapid acceleration and deceleration phases of the pulse cycle. The manufacturers also recognised the need for control of flow architecture and offered, in a limited way, some degree of user determination of output profile. Using the pump control module, it is possible to adjust the output frequency, run-time and baseline flow rate, in addition to flow rate. A common fear amongst potential users was that the rapid acceleration and deceleration of the pump head during pulsatile flow could lead to the generation of increased levels of haemolysis. There is an increase in shear rate under pulsatile blood flow conditions (Wright 1986). However, in many in-vitro (Gourlay and Taylor, 1994) and ex-vivo studies (Taylor et al, 1978, Adams et al, 1986) this was shown not to be associated with a rise in generated haemolysis. Both clinical and laboratory experiments have been carried out using the Stockert pulsatile flow system with considerable success over almost two decades, and to this day this roller pump is in widespread use in the clinical field as a pulsatile pump. Wright et al (1989) indicated that the roller pump may not be the most efficient mechanism for generating pulsatile flow. They questioned whether the output generated by a roller pump in the pulsatile mode could truly be described as being pulsatile in the physiological sense. At best, they thought that the roller pump is capable of generating only a "ripple" flow pattern. Studies using a model of the systemic circulation and circuitry mimicking the typical perfusion, add weight to this

assertion (Gourlay and Taylor, 1994). It has been established that the roller pump is not capable of matching the hydraulic power output of the human heart (Gourlay and Taylor, 1994, Wright et al, 1988), but there is clear evidence that, even though the output of such systems is less than optimal, there are clinical benefits to be derived from its use.

3.2.2 Ventricular blood pumps

This mechanism is probably the most physiological method for generating pulsatile blood flow in that it operates in a similar manner to the ventricle of the heart. In simple terms, ventricular systems consist of compressible sac and two one-way valves, one permitting blood to flow into the ventricle and one to permit blood to flow out (figure 3.3). These systems can be driven by either hydraulic or pneumatic means. Hydraulic systems generally employ a non-compressible fluid such as distilled water as the drive medium. Total blood flow generated by ventricular systems is dependent on frequency and stroke volume and can be increased or decreased by increasing or decreasing these parameters. Any alterations to stroke volume or frequency, for example when the system is synchronized to a patient ECG, will affect the total output of the system. This problem may be solved by ensuring that total blood flow is maintained independently of all other control demands. For example an increase in pump frequency, which would ordinarily be associated with an increase in total blood flow, is compensated for by reducing the stroke volume to a level which maintains the pre-set desired flow rate at the new frequency. Conversely a reduction in the output frequency would effect an increase in stroke volume, thus maintaining total blood flow. This mechanism requires that a substantial reserve capacity is available within the ventricle itself to enable adjustments of output to be performed.

the venous reservoir to a feeder reservoir positioned with sufficient elevation to permit adequately rapid filling of the pump head (fig 3.4).

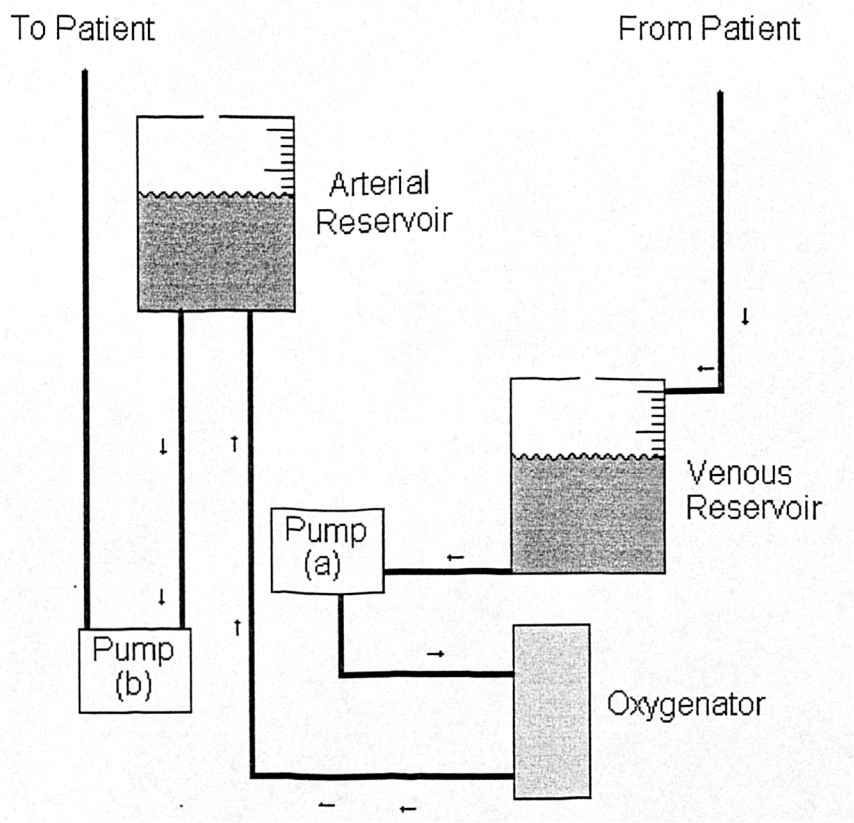


Figure 3.4 Circuit diagram of the feeder reservoir system for employing a passive filling ventricle pump system. Venous blood flows into the venous reservoir in the normal manner and is pumped from there by a roller pump (a) through the membrane oxygenator. Rather than passing into the patient, the blood is held in a second reservoir (arterial reservoir). The arterial reservoir is the most elevated part of the perfusion circuit and as such fills the pump head by gravity flow. Such a system permits the use of passive filling ventricles for routine CPB, but there are several problems associated with their use.

This technique has been employed clinically. However, the added circuit complexity and problems associated with balancing the two pumps, together with the potential for increased haemolysis, make this an unpopular option. The second alternative to passive filling systems is to adopt an active filling cycle. This is a relatively simple procedure and involves mechanically driving the drive piston during

the fill cycle. This bi-directional drive results in the generation of a negative pressure at the inlet side of the system, drawing blood into the ventricle. This type of system is well suited to routine CPB applications as it can be positioned anywhere within the circuit, even at the level of the arterial cannulae.

3.2.3 Compression Plate Pumps

The principle of the compression plate pumping system is simple and not dissimilar to the ventricular models and, like ventricular pumps, can only produce pulsatile flow. A length of tubing of known diameter is placed on a rigid back-plate and compressed by a moving compression plate which descends for a pre-selected stroke length thereby ejecting a volume of perfusate from the tube (fig 3.5). The direction of blood flow is ensured by valves positioned at the inlet and outlet of the ventricle or sac.

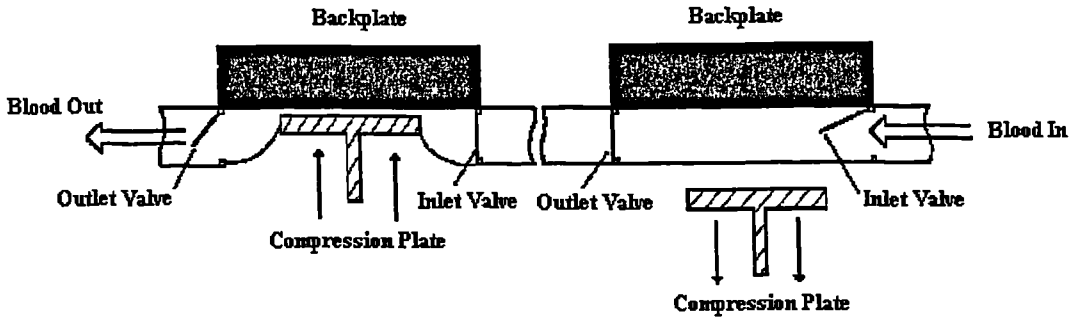


Figure 3.5 Typical compression plate mechanism. This diagram shows both the fill and ejection cycles. The valves which ensure flow direction can be either pressure or cam driven.

The rise-time can be controlled by the rate of compression of the tube, flow rate by either altering frequency or length of compression plate travel. These systems offer a significant level of control of output architecture. The filling aspect of the pumping cycle, like the ventricular mechanisms, can be either passive or active in nature. Passive filling systems depend upon a head of pressure at the inlet side of the device

to fill the ventricle after the ejection cycle has been completed. Such systems employ ventricles with little or no elastic memory, therefore, the filling is entirely passive. Active filling systems do not entirely depend upon a head of pressure at the inlet side to effect a filling cycle, rather a ventricle with an elastic memory effects the filing by generating a negative pressure within the ventricle which augments the positive pressure at the inlet side of the device. A similar outcome can be achieved by connecting the ventricle to both the constraining and compression plates, whereby the return of the compression plate to the neutral position will effect the filling of the ventricle by generating a negative pressure within the ventricle. Active filling systems are the only compression plate systems which can be considered for routine CPB applications. It is unlikely in the absence of a second or "priming" pump that sufficient inlet pressure can be generated with a passively filling system within a typical CPB circuit to effect filling in a sufficiently short time to generate a clinically acceptable output. The passive filling system has attractive attributes, notably that it does not generate negative pressures within the system, and can only pump the volume of blood supplied by the inlet conditions reservoir, matching output with inlet flow. Output demand and system architecture restraints render such systems unacceptable. The use of tubing with significant elastic memory has been the basis of several systems in the past (Sanderson, et al 1973) and has proven to be an adequate, though flow-limiting solution to the fill cycle problem. The valves employed in such pumping systems have produced significant problems. Internal valving has proven to be prohibitively expensive over the years and has led to many promising systems being shelved on economic grounds prior to clinical employment. One possible solution to this issue is to position the valves on the outside of the tubing or ventricle. This arrangement is employed in the University of Texas preload-responsive pump (Runge et al, 1989) and proved to be both economical and efficient. The use of mechanical externally positioned valves may require another compromise. The tubing employed in

the pump head must be soft enough to allow the passively operated valves to compress it to the point of closure. This removes to a great extent the strong elastic memory required to power an active fill cycle and the system reverts to being a passive filling system. The Texas Heart Institute pump is currently being employed as a circulatory assist pump where sufficient head of pressure is available for its operation with passive filling. The only pump of this type to be employed for routine clinical use is the Polystan compression plate pump. This pump employed both an active filling cycle driven by tubing with a high elastic memory and actively driven external valves. The compression plate and valves were driven by a single cam arrangement which permitted adjustable timing, offering delayed valve opening which produced increased rise-time and peak pressure. This system was rapidly withdrawn from clinical use due to excessive wear of the cam mechanism, leading to poor system co-ordination. This could be resolved by improving materials, but the pulsatile roller pump system was, by this time, well established and the Polystan project was terminated.

3.2.4 Centrifugal Blood Pumps

Centrifugal blood pumps are a relatively recent innovation in pumping technology for routine CPB applications. Leschinski et al (1991) described centrifugal pumps as pumps in which the working elements rotate a drive shaft and that they can be axial, nutational or rotary in nature. The drive for these pumps is invariably provided by an electric motor which is coupled to the drive shaft. The coupling of the motor to the drive shaft offers a complex design problem. The drive components must be sealed in order that sterility of the blood path can be guaranteed. The accepted solution to this problem is to couple magnetically the drive motor to the drive shaft (fig 3.6).

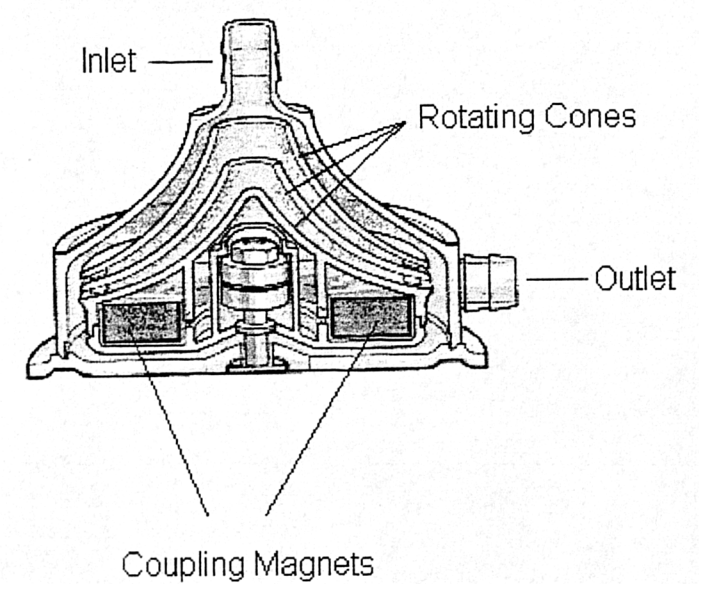
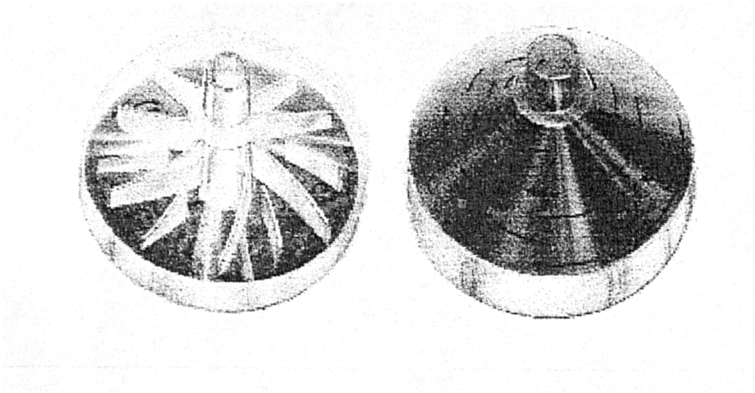


Figure 3.6 Schematic diagram of a Bio-pump head showing the rotating cone arrangement, inlet and outlet orientation and the drive magnets. The rotating components are held in place by a bearing arrangement.

Pennington et al (1982) determined that centrifugal pumps are afterload dependent since the output is related to pump speed and pressure gradient. It is, therefore, necessary to measure the pump output with a flow probe. There are many pump head designs. In general, these designs fall into two categories, vained pump mechanisms and concentric disc pump mechanisms (fig 3.7).



(a) (b)

Figure 3.7 Centrifugal pump heads of the vained impeller (a) and the rotating concentric disc types (b).

The main observed disadvantage with pumps of this type is that they are susceptible to the generation of stagnant zones and high vortex areas, which may result in haemolysis and thrombi formation on the working parts of the pump mechanism. The main application for centrifugal pumps has been in long-term circulatory assist (Nose', 1992). The primary safety feature of centrifugal pumps is related to air handling. When presented with a large quantity of air, the pump head will simply de-prime and rotate harmlessly rather than pump the air to the patient. This is of significant importance in long-term assist procedures where the device may be required to operate with minimal supervision for prolonged periods of time. Increasingly, however, centrifugal pumps are being employed for short-term, routine CPB procedures. Interest in employing centrifugal pumps for routine clinical practice has been fired by the stated safety attributes of these systems. Centrifugal pumps, particularly those of the disc type, have been associated with reduced haemolysis levels in clinical use. Berki et al (1992) noted that not only was operative haemolysis reduced with the disc centrifugal pump, but also there was improved post-operative haemostasis and preserved platelet count with the disc centrifugal pump when compared to the roller pump. They further noted that there was a reduced microembolic load with the centrifugal pump, which was attributed to the elimination of tubing spallation traditionally associated with the roller pump. These findings confirmed those of Mandl (1977) and Noon et al (1988) who noted that centrifugal pumps, particularly constrained vortex pumps, were associated with a lower particulate and gaseous embolic load than the roller pump. Improved blood handling with the centrifugal pump during routine clinical use was confirmed by Matsukura (1983) who noted platelet preservation with the centrifugal pump compared to the roller mechanism. Maas et al (1993) confirmed this clinically, observing reduced haemolysis and improved post-operative platelet counts with the centrifugal pump.

Since fluid displacement in such systems depends upon centrifugal impulsion, which requires a very high rotational speed to produce the requires blood velocity, a pulsatile output is difficult to achieve. To produce pulsatile flow, it would be necessary to accelerate the impeller aspect of the pump head to an extremely high rotational speed very rapidly. Attempts have been made to achieve this with varying degrees of success. The rapid acceleration of the impeller required for pulsatile flow can lead to a substantial heat build up at the magnetic coupling interface, which must be dissipated or damage can be caused to the drive bearings. This can be prevented by passing cooled haemocompatible fluids through the casing material. As pump systems, couplings and bearings evolved, cooling of the head assembly became redundant. More recently, the problem of bearing failure has been further addressed by the development of bearingless impeller mechanisms which employ magnetic suspension of the impeller component rather than a drive shaft. However, pulsatile blood flow with centrifugal systems has been extremely slow to develop. Recent studies by Nishida et al (1993) with the Terumo Capiox centrifugal pump in the pulsatile mode confirmed that physiological arterial wave profiles are difficult to achieve in the clinical setting. He reports that the radial artery pressure amplitude associated with a rapidly accelerating rotor head reached only 10mmHg. This is not significantly greater than the ripple pressure amplitude seen with a roller mechanism in the non-pulsatile mode of operation. Gobel et al (1997) described a new centrifugal pump which they determined in-vitro to be capable of generating pulsatile flow of physiological proportions. They further noted that from a comparative study, pumps without vanes were not capable of generating pulsatile flow at all due to the fact that energy is transferred to the perfusate by friction only in such systems. Vaned pumps were capable of pulsatile flow to a varying degree in their tests, but tended to de-couple under the strain. This was in keeping with the findings of Komoda et al (1992) who found that pulsatile blood flow generated by a centrifugal blood pump was not

associated with the normally observed reduced peripheral vascular resistance and that the pressure profiles observed were damped. They found, however, that the centrifugal system did offer other advantages normally associated with roller pump generated pulsatile blood flow, such as reduced angiotensin levels and a reduction in the need for post-operative inotropes. Ninomiya et al (1994) recognised the limitations of the centrifugal pump in terms of generating pulsatile blood flow and employed a centrifugal pump in conjunction with a pulsatile assist device (PAD) to generate pulsatile flow clinically. They concluded that under these complex conditions the centrifugal pump could produce sufficient pulsatile blood flow. Dreissen et al (1995) observed a reduction in complement activation when a pulsatile centrifugal pump was employed when compared with a non-pulsatile centrifugal pump. They further found that post-operative respiratory tract infection was greater in the non-pulsatile group and that, in general, the classical whole body inflammatory response appeared to be reduced when a pulse was added to centrifugal blood flow.

Centrifugal pump generated pulsatile flow has not been well accepted. This may be due to the fact that the generation of pulsatile blood flow of physiological dimensions is not currently possible with a centrifugal blood pump. This belief has been borne out in clinical practice. However, this is an area of research which continues to attract much attention.

3.2.5 Pulsatile Assist Device (PAD)

The pulsatile assist device (PAD) is an intermittent occlusive device which employs Intra-Aortic Balloon Pump (IABP) apparatus to produce pulsatile blood flow in the arterial line of a CPB circuit (figure 3.8). Bregman et al (1976) described this system and its use during CPB to produce pulsatile blood flow at the beginning and end of the surgical procedure to produce arterio-arterial counterpulsation. These devices function by inflating and deflating a balloon positioned in the arterial line of the

circuit. The balloon is inflated and deflated for a given time and at a given frequency, intermittently occluding the arterial line of the circuit through which blood is being continually pumped by a roller pump. During the period of inflation, a high pressure accumulates in the arterial line proximal to the PAD. When the balloon is deflated this pressure is released into the aorta as a pulse. The control module of the balloon pump permits control of the inflation and deflation times of the balloon together with the rate of inflation and the volume of gas infused into the balloon. The level of control offered by such a system is significant, and clinical studies involving this technology were promising. Maddoux et al (1976) and Philbin et al (1979) were both impressed by the versatility of the system. However, there were some concerns regarding the use of such systems, particularly regarding the possibility of balloon rupture. The PAD chamber is positioned in the arterial line of the circuit and, in the event of a balloon rupture, the contents of the balloon may be discharged into the arterial line, and from there into the aorta with potentially disastrous consequences. Possibly the most convincing argument against this technology was that it was significantly more complex than a traditional roller pump mechanism. Despite excellent clinical results with these devices, this increase in complexity led to the disuse of this technology in favour of the simple roller pump mechanism.

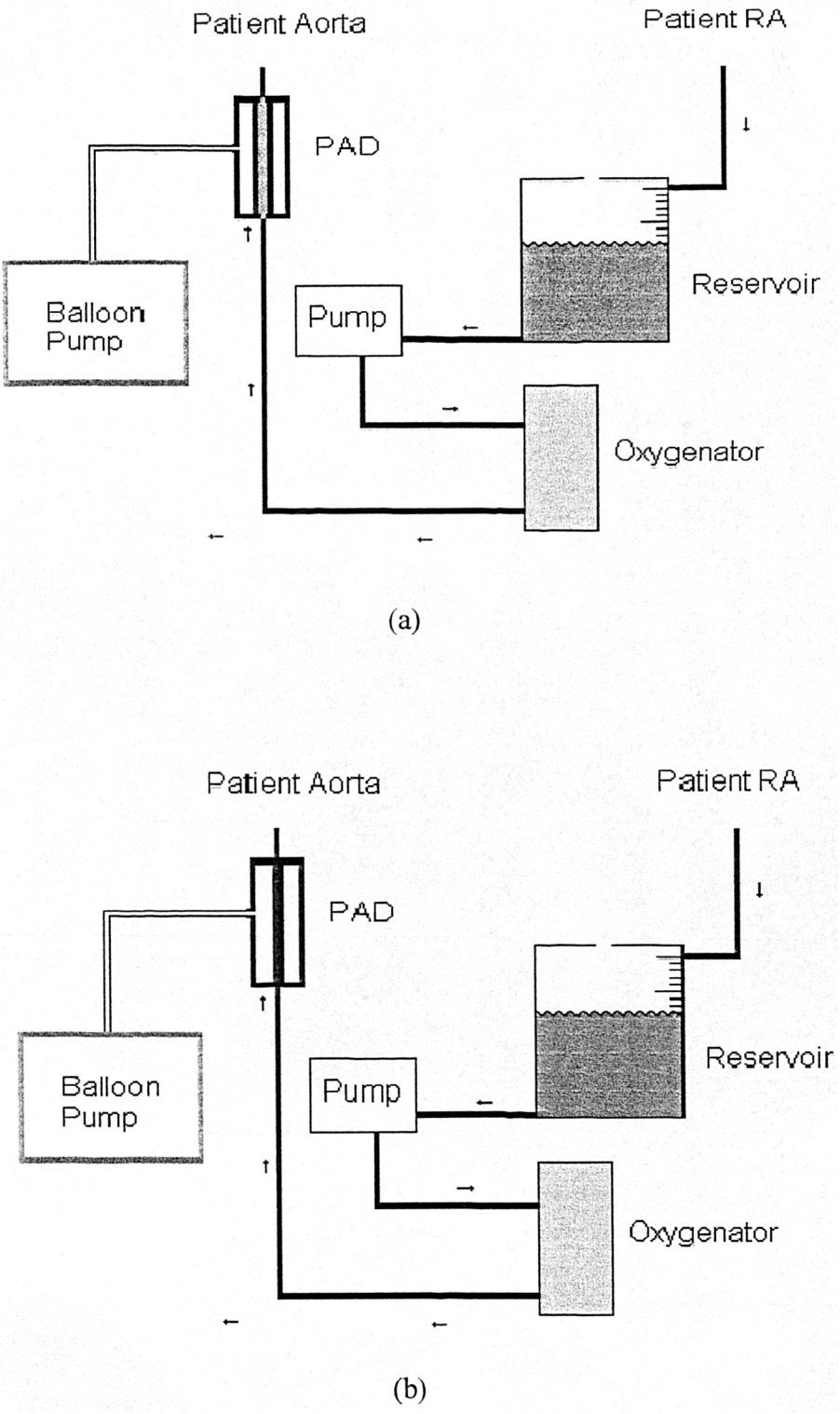


Figure 3.8 Diagram of mode of operation of pulsatile assist device. Blood from the roller pump passes through the device when the balloon is deflated (a). When the balloon is inflated the blood flow is prevented from passing through the device (b). This process is repeated at the desired pulse frequency. Timing of the mechanism is critical and extremely high circuit line pressures are normal.

3.3 PULSATILE BLOOD FLOW: SAFETY CONSIDERATIONS

Safety is a prime consideration when designing an extracorporeal circuit for clinical use. The use of a new blood flow regime requires that the combination of devices employed in the circuitry should be re-assessed to ascertain that the overall safety of the circuitry has not been compromised. It is important to identify the impact that a new device may have on the function of both the perfusion circuit as a whole, and the circuitry components individually, prior to clinical use.

3.3.1 The Compatibility of Pulsatile Blood Flow with Blood Oxygenators.

The blood oxygenator is generally positioned in the arterial line of the CPB circuit, between the pump and the patient. Generally the oxygenator is a membrane device of either hollow fibre or sheet membrane construction. These devices are inherently simple from a fluid dynamic standpoint, but their positioning in the arterial line of the circuit is critical if pulsatile blood flow is to be employed. Membrane oxygenators are generally microporous in nature and rely on a positive pressure gradient between the blood and gas phases to maintain integrity. It is possible for oxygenating gas to enter the blood phase in the form of microbubbles if the pressure gradient is positive in favour of the gas phase. Pearson et al (1986) described this phenomenon and described the presence of microbubbles in the arterial line of the perfusion circuit in association with large transient negative pressure "spikes" when pulsatile roller pumps were employed. Gourlay et al (1997) confirmed this with modern blood oxygenators, and described the relationship between the control profile of the pulsatile flow and the level of microbubbles in the arterial line of the circuit. The degree to which pulsatile blood flow affects the performance characteristics may be dependent upon the configuration of the device, whether the blood flows inside or outside of the fibres in the case of a hollow fibre device. Pulsatile blood flow may enhance gas exchange

within the membrane by breaking down the boundary layer at the fibre/blood interface. In devices in which blood flows on the outside of the fibres, the pulse may have the effect of achieving a more even distribution of blood by breaking down areas of stasis. The increase in oxygen demand associated with the clinical use of pulsatile blood flow is a significant factor when assessing the compatibility of an oxygenator with pulsatile blood flow. Careful attention must be paid to reserve capacity of oxygen and carbon dioxide exchange to ensure that all conditions of operation are considered. The majority of modern blood oxygenators are quite capable of meeting this requirement with ease (Stinkens et al, 1996, Freid et al, 1994, Gourlay et al, 1990)

The effect of pulsatile blood flow on the other main function of the modern blood oxygenator, heat exchange, has been the focus of recent study. Sheperd and Pierce (1995) determined that pulsatile blood flow enhanced the performance of the heat exchanger of one commercially available membrane oxygenator. They reasoned that the basis for this clinical finding is that under pulsatile blood flow conditions the boundary layer effect within the heat exchanger is broken down, thus leading to improved heat exchange performance. This factor in itself is important, for when pulsatile blood flow is employed clinically the improved tissue perfusion and reduced peripheral vascular resistance encountered may result in a greater demand on the heat exchanger, particularly during the re-warming phase of the procedure. Once again, it is important that the oxygenator employed during pulsatile flow has sufficient reserve capacity of heat exchange capability to meet this increased demand.

The energy absorption characteristics of the membrane oxygenator is another important consideration. Wright (1989) and Gourlay and Taylor (1994) described the energy absorption of membrane devices placed in the arterial line of the CPB circuit as being of varying significance, depending upon the device configuration. Since enhanced energy transfer is one of the perceived important attributes of pulsatile flow

in man (Shepard 1966), energy absorption and dissipation, therefore, are of importance when pulsatile blood flow is to be employed.

3.3.2 Aortic Cannulae for Pulsatile Flow

The cannula employed for connecting the extracorporeal circuit to the patient is of critical importance. Runge et al (1992) stated that it may be impossible for truly physiological pulsatile flow to be achieved with normal aortic cannulae. They further suggested that the excellent results achieved with pulsatile flow in animal studies cannot be repeated in the clinical environment without radically altering cannulation techniques. They asserted that the practical optimum aortic cannula is one which is 24F or 10.0mm in internal diameter, the same size as the typical arterial return line of the extracorporeal circuit. They further suggested that it would not be possible to find a cardiac surgeon who would be willing to insert such a large "pipe" into the aorta of a patient.

Special attention must be paid to shear stress associated with catheter size and tip geometry. Wright (1986) determined that the degree to which blood is haemolysed in an arterial cannula is dependent upon several factors. These include the shear rate, the velocity profile, and dimensions of the cannulae. Most importantly, however, this depended on whether the flow within the cannula becomes turbulent or not. Wright (1986) determined by experimentation that haemolysis can be expected to occur when a shear stress of $300Nm^{-2}$ is exceeded. Taylor (1986) described the level of shear stress measured under pulsatile blood flow conditions when two commonly used aortic cannulae were employed at varying flow rates. It was found that under normal conditions the commonly used "parrot beak" 90^{o} orientation cannulae were not associated with levels of shear stress which reach the critical haemolysis threshold. For this reason, the "parrot beak" type of arterial cannula has been the cannula of choice in the subsequent pulsatile blood flow studies by Taylor's group. Aortic

cannulae are essentially benign devices in relation to pulsatile blood flow generation if attention is paid to velocity profile, shear rate and pressure drop. Runge et al (1992) summed up the importance of aortic cannulae to pulsatile blood flow by saying simply that cannulae size should be maximised to optimize flow delivery.

There are many pumping systems which are described as being pulsatile in terms of their output architecture. This, in combination with the numerous membrane oxygenators, filters and cannulae, presents an almost infinite number of combinations. It is important from a clinical safety standpoint that the interaction between the devices in any selected combination be assessed prior to clinical use. This assessment of clinical safety must incorporate both functional and non-functional aspects. The systems selected for use in this thesis were evaluated from both points of view prior to the clinical aspect of this work.

CHAPTER 4

FUNCTIONAL DESCRIPTION OF TWO METHODS FOR PRODUCING PULSATILE CARDIOPULMONARY BYPASS.

CHAPTER 4 FUNCTIONAL DESCRIPTION OF TWO METHODS FOR PRODUCING PULSATILE CARDIOPULMONARY BYPASS.

4.1 INTRODUCTION

Of the many pump systems outlined in chapter 3, two were selected for study. The roller pump (Stockert/Shiley) was compared to a new ventricular system or True Pulsatile Pump (TPP) (Galram Corporation, Israel). Both systems have been approved for clinical use at the Hammersmith Hospital, London. The Stockert roller pump system is currently employed for clinical CPB at the Hammersmith Hospital and, as such, the clinical operators are familiar with its use. The TPP system is not familiar technology and, requires that the operators acquire some degree of pre-clinical experience. This experience would be gained during pre-clinical pump performance assessments which are the focus of Chapter 6.

Roller pump generated pulsatile blood flow for CPB has formed the basis for most of the research effort into pulsatile blood flow outlined in Chapter 2. The limitations of the roller pump system have been well documented and include poor control of the pump head and limited hydraulic power delivery (Wright 1989, Gourlay and Taylor 1994). However, there are advantages with this technology. These include familiarity, simplicity, safety and versatility. Ventricular pumps offer increased hydraulic power delivery (Chapter 2), but they are invariably more complex and lack versatility. The TPP pump is intended to offer an alternative to the roller pump as a method for generating pulsatile blood flow during CPB. The nature of this pump, being a ventricular mechanism, should make it possible to generate pulsatile blood flow/pressure output profiles of a physiological nature.

4.2 THE ROLLER PUMP

The roller mechanism has been employed as a clinical pump since before the advent of CPB (DeBakey, 1934). Use of this mechanism was motivated by the fact that such pumps are simple to operate, require no disposable parts and can be used for a number of ancillary applications. The Stockert/Shiley roller pump with output controlled by the Stockert/Shiley PFCII pulsatile blood flow controller will be employed throughout this work.

4.2.1 The Stockert/Shiley pulsatile roller pump system.

The Stockert/Shiley roller pump is shown in figure 4.1.

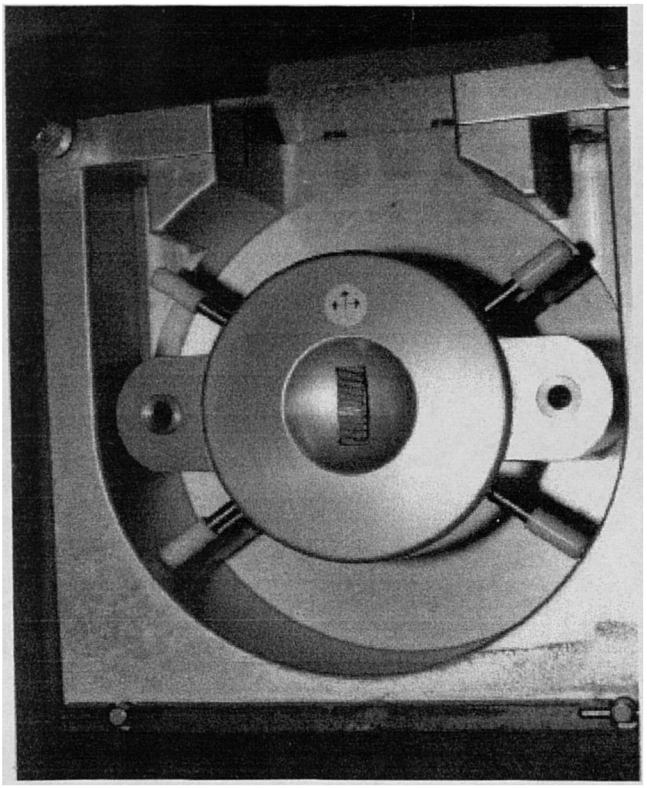


Figure 4.1 Pump head of the Stockert double roller pump. This shows the two opposed rollers and the occlusion setting adjuster in the centre of the pump head.

It is a conventional double roller pump with a stepping-motor drive mechanism. Blood output is a function of tubing diameter and the rotational speed of the pump head (Gourlay, 1994) and is calculated in the following manner:

$$Q = \pi r^2 l 2N$$

Where : Q = blood flow
r = tubing radius
l = roller stroke length
N = rotational speed of the pump head in revolutions per minute.

The output range of the system can, therefore, be increased by increasing the diameter of the tubing in the pump head. The pump is capable of employing tubing of various sizes, from 1/4" ID to 5/8" ID. Since the pump tubing size used at the Hammersmith Hospital is 1/2" internal diameter; this tubing size will be employed throughout the current work. Tubing of this size permits a maximum blood flow rate of 10.0 l/min to be delivered. This is well in excess of normal clinical requirements.

The mean flow rate is controlled from the pump module with the speed control. The flow potentiometer determines the output of the pump by controlling the rotational speed of the roller mechanism. In addition there is an control on the pump module for the baseline flow rate (automatic) when the pump is used in the pulsatile mode. This is normally set to 80% for routine clinical application, resulting a baseline flow of 20% of the mean flow rate, An LED display on the pump module can be programmed to display either flow rate or rotational speed in revolutions/minute (RPM).

4.2.2 Pulsatile Flow Controller II (PFC II)

The pulsatile flow controller (PFC II) (fig 4.2) is a device designed to offer some degree of control of the output profile of the roller pump.

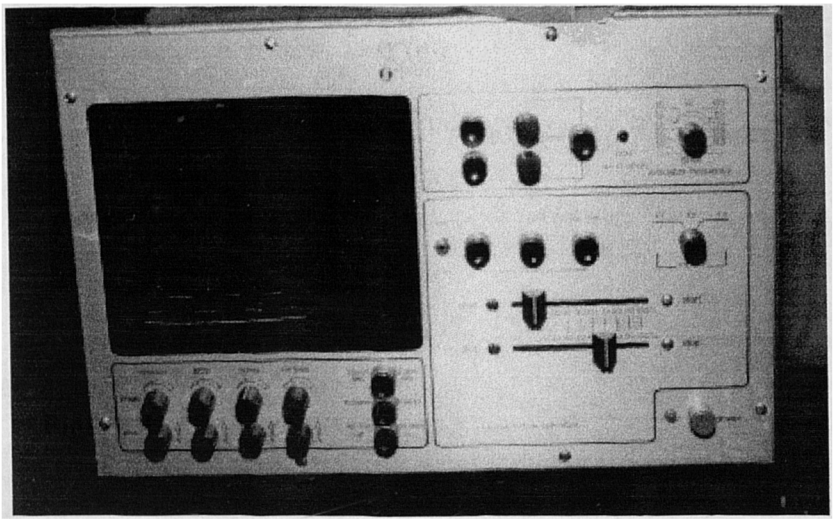


Figure 4.2 The Stockert PFCII pulsatile blood flow controller.

A number of control options are available on the flow controller, including output frequency, delay-time and run-time. A mode selection switch is available to select the required output mode from either internally-triggered pulsatile, externally-triggered pulsatile or non-pulsatile modes. The delay-time control is utilised during externally-triggered pulsatile mode to synchronize the pump pulse with either the ECG or arterial pressure in the same manner as a balloon assist pump. The run-time facility offers the user the capability to control the ejection time of the pump cycle. Rather than expressing the run-time and delay-time factors in absolute time, they are expressed as a percentage of the total cycle length. In the internally-triggered pulsatile mode of operation (the mode commonly employed during open heart surgery), shortening the run-time whilst maintaining the mean flow rate has the effect of increasing the pulse amplitude by decreasing the ejection time. Increasing the run-time has the opposite effect. Operating the system at a run-time of 100% would result in non-pulsatile flow. The frequency facility enables the user to control the output frequency of the pump during internally-triggered pulsatile flow.

During CPB at the Hammersmith Hospital, the output controls are pre-set and remain unchanged throughout the procedure. The run-time setting normally employed is 50% at a frequency of 70 beats per minute (BPM). These settings have been the basis of all of the research into the effects of pulsatile blood flow by this group.

4.3 THE VENTRICULAR TRUE PULSATILE PUMP (TPP)

The TPP was designed as a temporary heart assist system (THAS) (fig 4.3). The system was made available for routine clinical CPB use, as a replacement for the conventional roller arterial pump. It comprises two main components; the drive and control mechanism and the pump head. The pump head is a disposable single use device.

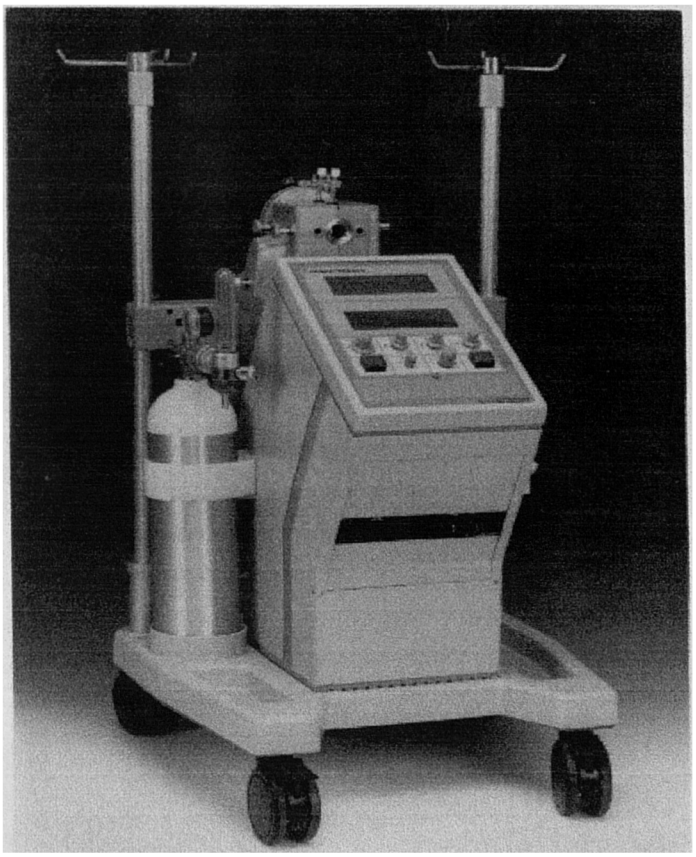


Figure 4.3 The TPP pump system. The device is a totally self contained circulatory assist system having its own ventilating gas supply and battery power.

4.3.1 The drive and control mechanism.

The pump is microprocessor driven in all respects. The system can operate in two modes, externally-triggered and internally-triggered pulsatile modes. Ventricular pumps offer no non-pulsatile mode. It offers control facilities for symmetry, phase, flow rate and frequency. Although the nomenclature is different, these factors are similar in function to those present on the Stockert system. The symmetry function allows control of ejection time, rather in the same manner as the run-time control on the roller pump. A low symmetry setting would correspond to a rapid ejection time and vice versa. A symmetry setting beyond 70% may result in the ejection phase being too prolonged and the filling phase too short for a predictable pump output to be achieved. The phase function controls the synchronization of the pulse with an external signal, in precisely the same way as the delay function on the roller mechanism. Lowering the phase will result in the pulse occurring earlier in the cycle. These functions, like those on the roller pump, allow the system to be employed for counterpulsation procedures to augment the heart during the recovery phase of CPB, rather like a balloon assist pump. The pump will maintain the pre-set blood flow rate independently of any alterations to the control functions other than the blood flow control.

The output profile from the control microprocessor is sent via a servomechanism to an electric motor in the pump housing. This motor drives a piston in the main housing. The piston is primed with sterile saline and connected to the disposable pump head. Saline is employed as a non-compressible hydraulic fluid in this system. The displacement of the saline by the piston results in the displacement of the diaphragm in the pump head which powers the positive displacement of blood from the pumping chamber. A pressure transducer is incorporated into the piston mechanism and the microprocessor control unit monitors the pressure within the

piston. Any substantial rise in pressure beyond the normal profile indicates a restriction either in the pump head or the tubing connecting the pump to the patient.

If a high output pressure state is detected by the control system, the pump will cease the output operation and sound an alarm. The pump will only continue to operate once the high output pressure state has been cleared. The control system also has a pressure sensor for the level of vacuum at the inlet side of the system to protect blood from damage caused by excessive vacuum. If a high vacuum is detected the pump will abort the ejection procedure.

4.3.2 The pump head

The pump head comprises six main components. The upper and lower pump housings, two valve conduits, the drive diaphragm and the housing retaining ring and screws (fig. 4.4).

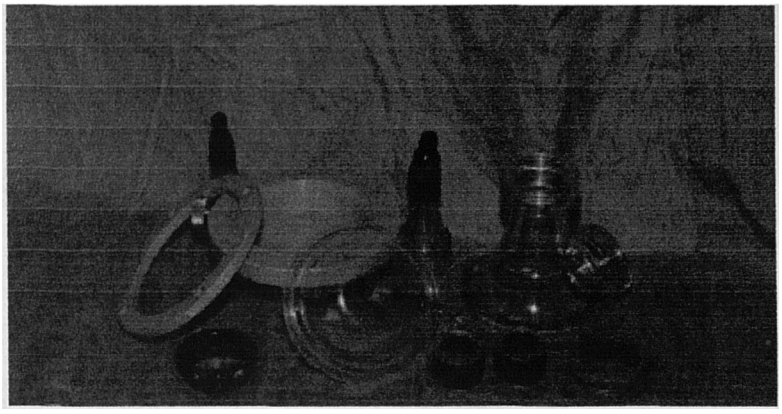


Figure 4.4 The components of the TPP ventricular pump head. The pump heads are assembled by the manufacturer in Israel prior to shipment for clinical use.

Once assembled (fig. 4.5) the pump head connects to the control/drive mechanism using a single compression coupling.

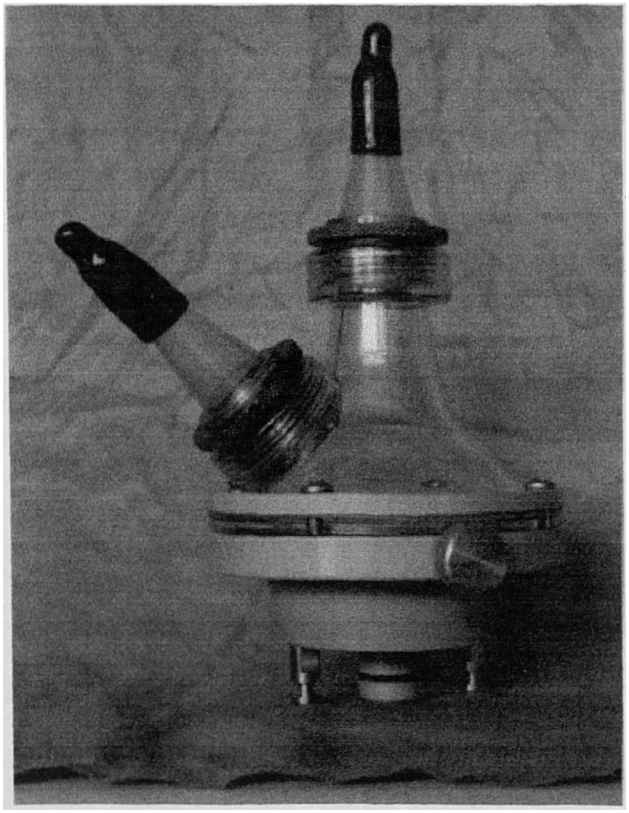


Figure 4.6 The assembled TPP ventricular pump head.

Prior to use, the drive side of the pump diaphragm is primed with sterile saline and care is taken to eliminate all possible air. The elimination of all air from the drive side of the system is necessary to avoid the risk of air crossing into the blood phase of the system in the unlikely event that the diaphragm should rupture during use. In addition, excess air in the drive side of the system may affect the transfer of power to the blood phase, resulting in a sub-optimal output profile.

The pump has two one-way valves to direct fluid flow. These are constructed of polyurethane and are housed in polyurethane conduits which are positioned within the inlet and outlet connectors. Positive displacement of perfusate is provided by the displacement of the pump head diaphragm by the piston-driven movement of the saline on the drive side of the system. Under normal conditions, the pump is capable

of pumping up to 8 l/min. However, flow rate is dependent on the output profile settings in both externally- and internally-triggered modes of operation. If the phase setting is too advanced, the pump may not have sufficient time at high output frequencies to effect a full filling cycle after ejection.

4.4 SUMMARY

Both pumps offer some degree of output control. The roller pump has been used for clinical CPB for a considerable time. The TPP on the other hand is relatively new to clinical CPB and the effect of the various output control parameters on the pulse architectures has not been investigated. This is a subject which was addressed prior to the clinical study, using a model of the human systemic circulation.

CHAPTER 5

DESIGN AND CONSTRUCTION OF A MODEL OF THE HUMAN SYSTEMIC CIRCULATION FOR THE STUDY OF PULSATILE PUMPING SYSTEMS.

CHAPTER 5 DESIGN AND CONSTRUCTION OF A MODEL OF THE HUMAN SYSTEMIC CIRCULATION FOR THE STUDY OF PULSATILE PUMPING SYSTEMS.

5.1 INTRODUCTION

Describing the output architecture of a pumping system is a complex issue. Clinical study alone can achieve little due to the constantly changing haemodynamic status of the patient undergoing CPB for open heart surgery. To study accurately the output architecture of a pulsatile pump, a set of standard, controlled, hydrodynamic conditions is required. The aim of modelling the systemic circulation, or any part of it, is to provide a set of circumstances by which a pulsatile inflow is reduced to a non-pulsatile outflow in the same manner as the physiological state. This can be achieved by constructing a model of the systemic circulatory system to mimic the hydrodynamic conditions encountered clinically. Models have been constructed in the past with this aim in mind. Westerhof et al (1969) suggested that there were two categories of models for this purpose, mathematical models and physical models. Both model types are capable of describing the propagation of a pressure/flow wave-form through a controlled and known vascular architecture. Mathematical models vary from simple pen and paper exercises to extremely complex models requiring considerable computer technology. However, all mathematical models have the common need for known input conditions. In studying the output architecture of pulsatile pumps, the output conditions cannot be described in any detail in terms of wave velocity or structure as they are unknown and dependent upon the input conditions of the model. It is the result of this interaction between the output wave

structure and the model vasculature which is the focus of these studies. Mathematical models, therefore, do not comply with the requirements for such studies. Physical modelling of this relationship is the only remaining option. There are two categories of physical models available for the study of blood flow; electrical and hydromechanical. Like mathematical models, electrical analogues can be simple or extremely complex in structure. Noordergraaf et al (1960) designed a system which employed features of telegraphy (wave transmission along a wire) together with simplified fluid dynamic principles of blood motion in short sections of simulated artery to describe wave motion and blood flow through the section. The found that it was possible to describe the effect of changing some aspects of the input conditions on the propagation of flow/pressure transmission. This was a simple segmental approach to electrical modelling and involved resistors, inductors and capacitors, representing the viscous and inertial properties of blood and the vessel wall. Westerhof et al (1969) further developed this model of the transverse and longitudinal impedance of arterial segments, expanding it to encompass multiple segments, mimicking, as far as possible, the whole systemic circulation. The model derived consisted of 121 segments (fig 5.1), each representing a particular section of artery. In this model, the total length of artery modeled was 720cm, considerably shorter than the human arterial system. Each segment ended with a terminal resistor which represented the terminal micro-vasculature (fig 5.2). Noordergraaf et al (1960) derived the values for the arterial segments from the work of Bergel et al (1960) and Patel et al (1963) who derived values by examination of human and animal cadavers. They employed in some instances the values of vessel elasticity and diameter previously published by Fry et al (1964), scaling up the values from the dog model by

its ratio in cross sectional area to the relevant human vessel. A tremendous amount of data was required to construct this model, but the outcome was a model in which the changing nature of pressure and flow through the model closely mimicked that of the systemic circulation.

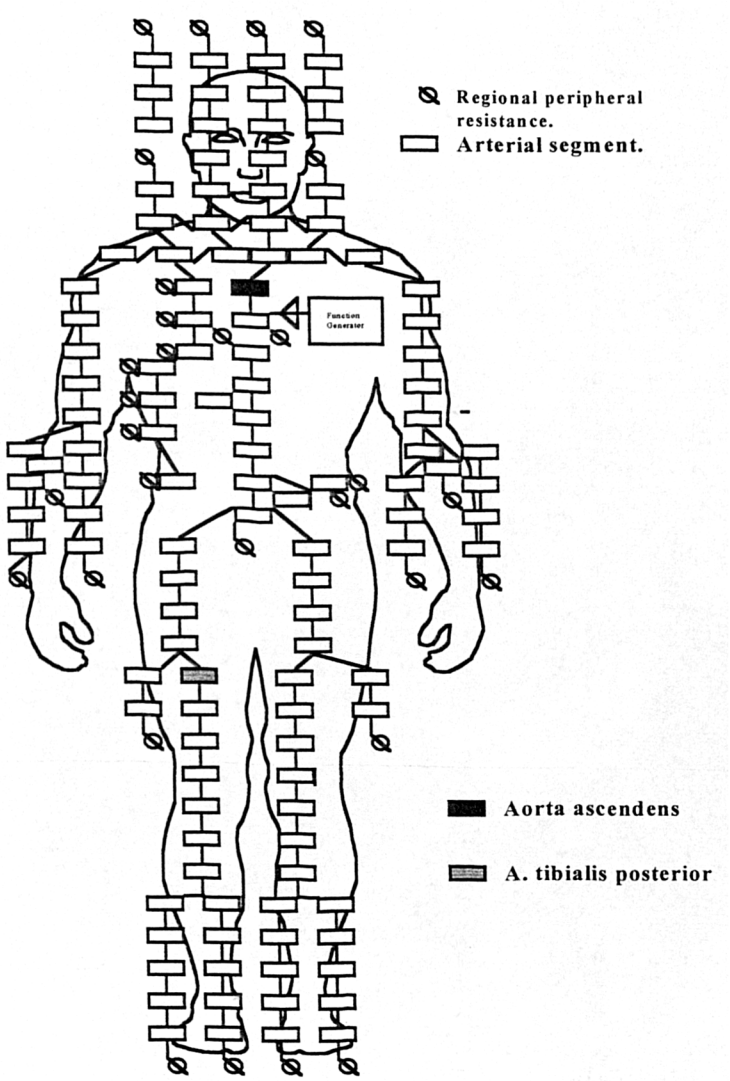


Figure 5.1 Electrical analogue of the human systemic circulatation (Westerhof et al 1969). The model consists of 121 segments, each of which represent defined arterial segments of the human vascular tree. Each segment has components representing the longitudinal and transverse impedance together with vessel wall thickness and elastic modulus.

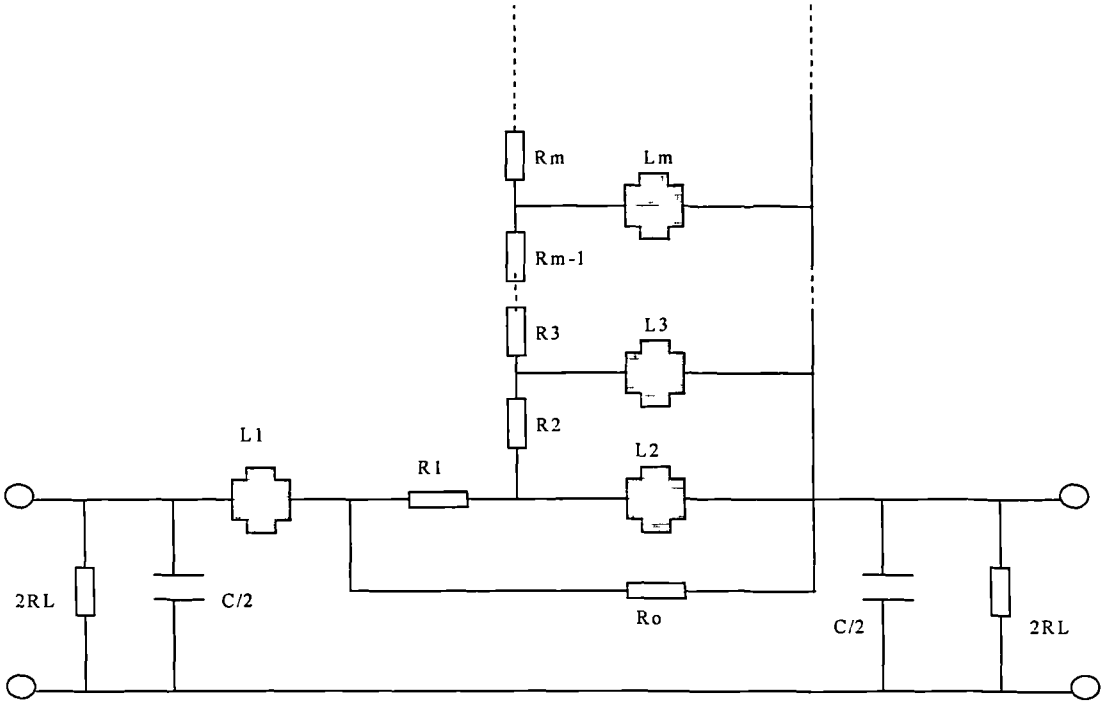


Figure 5.2 Electrical analogue of one section of artery as described by Westerhof et al (1969). The construction is complex and includes resistors and capacitors which take into account vessel compliance (C) and the viscous (R) and inertial (L) properties of blood. Resistors were also included to correct the model for leakage through small branches (RL) and boundary layer effects (Ro).

Data required to construct the two segments highlighted in fig 5.1, the ascending aorta and the posterior tibial artery are shown in table 5.1.

Name of Artery	Length of Artery (cm)	Wall thickness (cm)	Internal Radius (cm)	Young's modulus ($10^6 cm^{-1} sec^{-2}$)	Compliance C ($10^{-6} g^{-1} cm^4 s^2$)	L_1 (g cm^{-4})	R_1 (g $cm^{-4} s^{-1}$)
Ascending Aorta	2.0	0.164	1.47	4.0	53.4	0.309	0.0327
Posterior tibial artery	6.7	0.051	0.247	16.0	0.770	36.7	138

Table 5.1 Two arterial segments from the Westerhof model of the systemic circulation. The data shows the length of each segment together with the radius, compliance and elastic modulus. Some of this data was taken from direct examination of human cadaver material, others from extrapolation of data obtained from measurements made in large dogs.

In a later study, Westerhof et al (1971) described peripheral vascular resistance in more detail and detailed more accurately properties of the vascular beds which require to be considered when modelling the systemic circulation. They determined that these factors include vessel elasticity and correction for the influence of smooth muscle. These complex models are useful in assessing the influence of altering the resistive and compliant state of the vasculature on the propagation of a flow and pressure complex. However, such models offer little in helping to understand the output architecture associated with the extracorporeal pumping systems and the interaction between the pump and the systemic circulation. To achieve this, knowledge of the output architecture of the pump is required and, in common with the mathematical modelling techniques, this cannot be provided at the input side of an electrical analogue. To assess the pulsatile blood flow generation capabilities of a pumping

system and its interaction with the systemic circulation, rather than simply determining the propagation characteristics of a known pre-determined wave-form through the circulation, requires a different approach. The remaining alternative modelling technique is hydromechanical modelling. This involves the construction of resistors, compliance components and fluids, which directly mimic conditions in the systemic circulation. Such a model, which employs the pump itself rather that an electrical or graphical representation of its surmised output, offers the possibility to critically analyze and compare the pulsatile flow generating capabilities of pumping systems.

5.2 HYDROMECHANICAL MODELLING OF THE SYSTEMIC CIRCULATION

Hydromechanical modelling of the systemic circulation has been employed for the study of perfusion pumps and pumping hearts for a number of years. Westerhof et al (1971) described a lumped-parameter physical analogue for testing beating hearts or pumps. This model consisted of three main components; a characteristic resistance, a peripheral resistance and a compliance. The characteristic resistance represents the input impedence of the large vessels of the vasculature, the compliance represents the elasticity of the vasculature as a whole and the peripheral resistance represents the impedance of the peripheral circulation (fig 5.3).

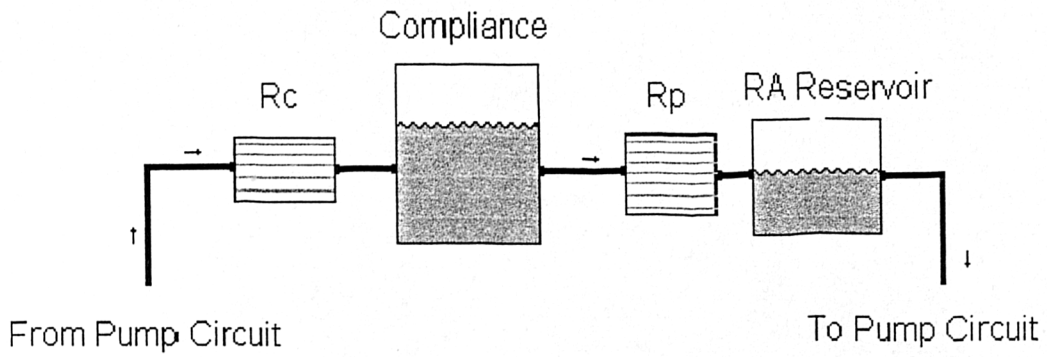


Figure 5.3 Lumped parameter model of the systemic circulation employed by Westerhof et al (1971) and Wright (1988) for the study of beating hearts and extracorporeal pumps. The characteristic and peripheral resistors were constructed of bundles of small bore tubes and the compliance was provided by a measured air space above the fluid level in the compliance reservoir.

The magnitude of each parameter was derived from experimental measurements and from scaling up measurements taken from canine studies (Wilcox et al, 1967). This model and derivatives of it have been employed as the basis of pump-related studies many times over the ensuing years. Sanderson et al (1973) employed this model to assess the hydraulic power output of an experimental pulsatile blood pump and found it to be suitable to this task in terms of the reproducibility of the data generated and in its similarity to the clinical model. Wright (1988) subsequently employed the model to study the hydraulic power output of three perfusion. They employed different values for resistance and compliance to those described by Westerhof et al. They based the values for these parameters on clinical observations (Wright et al, 1988) of patients undergoing open heart surgery. Comparative values for the resistors employed by Wright and Westerhof et al are shown in table 5.2.

	Westerhof et al (1971)	Measured Patient Values (Wright 1988)
Characteristic Resistance ($x10^6 kgm^{-4}s^{-1}$)	9.00	7.60
Peripheral Resistance ($x10^6 kgm^{-4}s^{-1}$)	120.00	140.3
Compliance ($x10^3 kg^{-1}m^4s^2$)	8.00	15.8

Table 5.2 Values of peripheral and characteristic resistance and compliance used by Westerhof in his model of the systemic circulation and those derived by Wright from clinical measurement.

The differences are significant, particularly with regard to compliance, which Wright et al (1988) found to be 100% higher than that employed by Westerhof et al (1971). Since those values employed by Wright (1988) were based upon clinical measurements taken during open heart surgery, they are more representative of the appropriate clinical scenario. In both models, the resistor elements were constructed of small bore tubes and the compliance was provided by an air reservoir of known volume. The pump with its associated CPB circuitry is connected to the model by an aortic cannula representative of those employed clinically. This is imperative if the model is to mimic the clinical setting as the choice of aortic cannula can substantially impact upon the fluid dynamics of the whole system Wright (1986). Wright (1988) also determined that the perfusate employed is a critical aspect of the model. They stated that the perfusate should, as far as possible, mimic the viscosity and density of

blood in the clinical setting. He achieved this by employing a mixture of gelatin and saline adjusted to the desired viscosity.

Overall, hydromechanical modelling offers the opportunity to physically study the dynamic interaction between the CPB system and the systemic circulation. The effect of the system on the propagation of a flow or pressure wave can be studied by taking measurements at a position in the model which is analogous to the region of interest in the clinical model. Aortic flow and pressure, essential for the computation of hydraulic power, together with an assessment of input wave architecture, can be taken from the input point of the system. Both Wright (1988) and Westerhof et al (1971) found that wave travel and propagation through the model were similar to clinical observations. Wright pointed out that the bulk nature of the resistors may lead to wave reflection, but this can be identified and eliminated at the analysis stage.

5.3 CONSTRUCTING A MODEL OF THE SYSTEMIC CIRCULATION

The typical hydromechanical model of the human systemic circulation consists of three main components. In order of assembly, these are the characteristic resistance, compliance and the peripheral resistance. In constructing these components for this study, the values determined by Wright et al (1988) for each component are the target values for which the components should be designed. The conditions under which these values were obtained, being the correct clinical model, justifies this choice. They stated that, as there was significant variation within the patient population with regard to these factors, a tolerance of 10% was quite acceptable. Bearing this in mind, a model was designed to offer the correct environment in which pulsatile perfusion

pumps could be tested. The design rationale for each component of the model is detailed in the following sections.

5.3.1 Resistor design.

The resistance components of hydromechanical circulatory models can be provided in a number of ways. In a simple Windkessel model, the resistance is provided by an adjustable clamp. This offers the relevant hydraulic resistance, but does not provide the correct fluid dynamic environment for the study of pulsatile blood flow. The mechanical resistance in such a model will lead to the transition from steady flow to turbulent flow. Two other methods are available; small bore tubes or narrow slits. Narrow slit models offer similar hydrodynamic conditions to small bore tubes, but are much more difficult to construct to an acceptable degree (Westerhof et al, 1971). Small bore tube resistors have been the most commonly used resistor type over the years and are the method selected to provide resistance for this thesis.

Two resistors are required for the model; the peripheral and the characteristic resistors. Both were constructed of small bore tubes with a 1.0mm internal diameter and 0.5mm wall thickness. Westerhof et al (1971) and Wright (1988) employed similar structures in their model systems. Most recently, Wright (1988) used tubes with an internal diameter of 0.8mm imbedded in a potting resin. Westerhof et al (1971) used a more complex construction involving imbedding nylon fishing line in dental cement. The fishing line was removed when the cement had hardened, leaving a series of long holes of known diameter in the cement. This process was carried out several times, each time building up a layer of holes until the resistor was completed

to the desired size. Calculating the physical proportions of the resistor element requires knowledge of the flow environment. The design of the resistor requires that a number of relationships are considered with regard to pressure, flow, viscosity and frequency. These were characterised by Westerhof et al (1971) as radius/frequency and radius/length relationships. Womersley et al (1957) determined that pressure drop over the length of a tube is in phase with flow if a resistive relationship exists. He determined that this relationship holds true only if the following is the case:

$$F = 6/\alpha^2 >> 1 \qquad (1)$$

F in this case is the "quality factor" of the resistor. If F is less than 1 an inductive relationship exists rather than a purely resistive one. The factor α in this case is derived from:

$$\alpha^2 = r^2\omega/\nu \qquad (2)$$

Where: $\omega = 2\pi j$ (j = frequency) (3)
$\nu = \mu/\rho$ (kinematic viscosity) (4)
r = radius
μ = dynamic viscosity
ρ = density

The factor α, therefore, involves terms relating to the cross-sectional area of the tube and the characteristics of the perfusate and the frequency. From equations 1 and 2 it can be seen that:

$$F = 6/(r^2(2\pi j)/(\mu/\rho)) \qquad (5)$$

From this equation it can be seen that as frequency increases the quality factor will decrease and that as frequency increases the radius of the tube will have to decrease to maintain a resistive relationship. It is imperative that not only are the flow rate, density and viscosity of the perfusate known, together with the desired resistance value, but that the resistive relationship is maintained throughout the range of frequencies of interest. The frequency of interest in this case is not the output frequency of the pump as such, but the frequency of the highest harmonic of pressure and flow. In this instance, the highest frequency of interest is around 20Hz (Gourlay et al, 1994, Wright 1988). Wright (1988) determined by experimentation that frequencies above this contribute little to pulsatile hydraulic power or flow. This has been borne out in our own experience (Gourlay et al, 1994). Having identified the frequency range of interest, the diameter of the tubes to be employed and the characteristics of the perfusate, it is possible to predict the quality factor of the intended resistor together with the other dimensional aspects. The radius-length relationship for a true resistor dictates that the pressure drop/flow relationship should be linear along the length of the tube. This means that the effects of turbulence and inlet length effects (tube length which permits the development of flow) must be eliminated. The flow should be non-turbulent. A reasonable way of predicting whether the flow will be turbulent or not is to calculate the Reynolds number of the flow. The Reynolds number is a dimensionless number which is used to describe the transition from laminar flow to turbulent flow through a straight tube. The Reynolds value which describes this transition point is the critical number, which occurs at 2300

(Schlichting 1968). Above this critical level the flow becomes turbulent. The Reynolds number is calculated in the following manner:

$$Re = \rho VD/\mu \qquad (6)$$

Where: ρ = density of fluid (g ml^{-1})
V = fluid velocity (cm s^{-1})
D = diameter of tube (cm)
μ = viscosity of fluid (poise)

The Reynolds number, therefore, considers the dimensional aspects of the relationship together with the inertial effects of the perfusate. The critical Reynolds number is defined by that calculated at maximum velocity. If the critical number is exceeded in a relationship, the imbalance can be rectified by either reducing the velocity of the fluid or reducing the tube diameter if no alterations can be made to the fluid itself. In common with many other such relationships outlined here, it is assumed that a Newtonian fluid is employed. Blood is not a Newtonian fluid in this regard. McDonald (1974) described a Newtonian fluid as one in which the coefficient of viscosity is constant at all levels of shear. This is the case for most homogeneous liquids. However, blood is not a homogeneous liquid; it is a particle suspension and as such exhibits markedly different properties. Blood has an apparent high viscosity at low shear rates. In small tubes, the apparent viscosity at high rates of shear is smaller than that at high shear rates in larger tubes. These factors are of considerable importance in the clinical model. However, for the benefit of in-vitro modelling, the

non-Newtonian blood will be replaced with a homogeneous liquid of similar density, and with a viscosity similar to that of blood in the microcirculation.

The remaining major component required to estimate the dimensions of the resistor component is the length of the tubes. This is determined by calculating the inlet length, or the length required to ensure that the flow profile within the tube is parabolic rather than flat. The profile is assumed to be flat at the entrance to the tube. The length of the resistor tube, therefore, should exceed the calculated inlet length in order that the flow profile is laminar at maximum flow rates. The inlet length is calculated in the following manner (McDonald, 1974):

$$L = 4.2Vr^2 \qquad (7)$$

Where: L = inlet length
V = average velocity (cm s^{-1})
r = radius of tube (cm)

$$V = (Q/N)/\pi r^2 \qquad (8)$$

Where: Q = Flow rate ($cm^3 s^{-1}$)
N = The number of tubes

Having pre-determined the value of the resistors, it is possible to calculate the number of tubes in parallel which will be required to construct the resistors to the desired value. This can be done in the following manner:

$$R = 8\mu L/(\pi r^4 N) \qquad (9)$$

Where: R is the resistance and, N is the number of tubes.

L refers to the overall length of the tube which must substantially exceed the inlet length of the resistor if flow is to be laminar for most of its effective length.

The diameter of the tubes was pre-determined, by availability of materials, to be 1.0mm. As already indicated, this was not substantially different to the diameter employed by Wright (1988), and double that employed by Westerhof et al.(1971) The perfusate employed was a glycerol/saline mix which had a viscosity of 2.2cP at 37°C measured on a Waters viscometer. The target resistance values for the characteristic and peripheral resistors were 7.6 $x10^6$kg $m^{-4}s^{-1}$ and 140.3 $x10^6$kg $m^{-4}s^{-1}$ respectively.

To estimate the number of tubes to be used in the construction of the resistors, it is reasonable to employ a combination of equations 7 and 8, together with an estimated length for the resistor tube, to derive an N value for the argument in which the assumed L is the minimum acceptable resistor length. A convenient length for the resistor bundles is 10cm as this would enable easy construction of the resistor elements. By introducing this value into equation 10, a derived N value for which 10cm is the inlet length can be obtained.

$$L = 4.2\ ((Q/N)/\pi r^2)r^2 \qquad (10)$$

Employing the dimensions outlined for the resistor elements, an inlet length of 10cm is achieved by 10 tubes in parallel. Since the inlet length reduces with increasing number of tubes and subsequent reducing velocity, it should be possible to construct a purely

resistive element from tubes of this diameter and length and with an acceptably short inlet length (table 5.3).

Inlet Length (L) (cm)	Number of Tubes (N)
0.1	1003.570
1	100.360
5	20.072
10	10.036

Table 5.3 The relationship between inlet length and the number of tubes when tube of diameter 1mm is employed at a blood flow rate of 4.5l/min.

The number of tubes to be employed to give the desired resistance for both characteristic and peripheral resistors can be calculated by applying equation 10. A length of 10cm will be employed as this is a manageable length from a manufacturing standpoint and is the inlet length for a resistor of only 10 tubes at 4.5 l/min, significantly less than can be manufactured in a resistor bundle. The number of tubes required to manufacture the resistor elements to the required value, using tubes of 1mm diameter and 10cm length at 4.5 l/min, are shown in table 5.4.

Required Resistance ($10^6 kgm^{-4}s^{-1}$)	Number of Tubes
Characteristic 7.6	1181.52
Peripheral 140.3	62.23

Figure 5.4 The number of tubes required to construct the resistors using 1mm tubing of 10cm length. at 4.5 l/min fluid flow.

Applying equations 1, 6, 7 and 9, it is possible to characterize the resistors and ascertain that they are truly resistive. The characteristics of both resistors are shown in table 5.5.

	Characteristic Resistance	Peripheral Resistance
Tube Diameter (cm)	0.1	0.1
Tube Length (cm)	10	10
Number of Tubes	1200	63
Velocity ($cm\ s^{-1}$)	7.96	151.65
Quality Factor	187	187
Inlet Length (cm)	0.0835	1.592
Reynolds Number	36.18	68.63
Resistance ($10^6 kgm^{-4}s^{-1}$)	7.65	143.56

Table 5.5 Characteristics of the resistors designed for the assessment of extracorporeal blood pumps. The factors derived assume that the blood flow rate will be 4.5 l/min. This is the standard test flow rate for these experiments.

The design criteria for both resistive elements have now been established. The magnitude of the resistors is well within the intended tolerance of 10% of the values described by Wright (1988). The quality factor confirms that the resistors will be purely resistive over the frequency range of interest and the Reynolds number is suitably small, confirming that the resistors will not be associated with turbulent flow. In both cases the inlet length is small relative to the overall length, 16% in the case of the peripheral resistor and 0.8 % for the characteristic resistor. The 16% value was

not thought to be excessive for this application and did not merit changing the resistor design. This arrangement should, therefore, be appropriate for the intended application.

5.3.2 Resistor construction.

The resistors were constructed of bundles of 1mm internal diameter, 0.5mm external diameter rigid plastic tubes. The ends of the tubes having been sealed with rubber plugs, the bundles were placed into a holder and encased in wax and wrapped in rubber tape (fig 5.3).

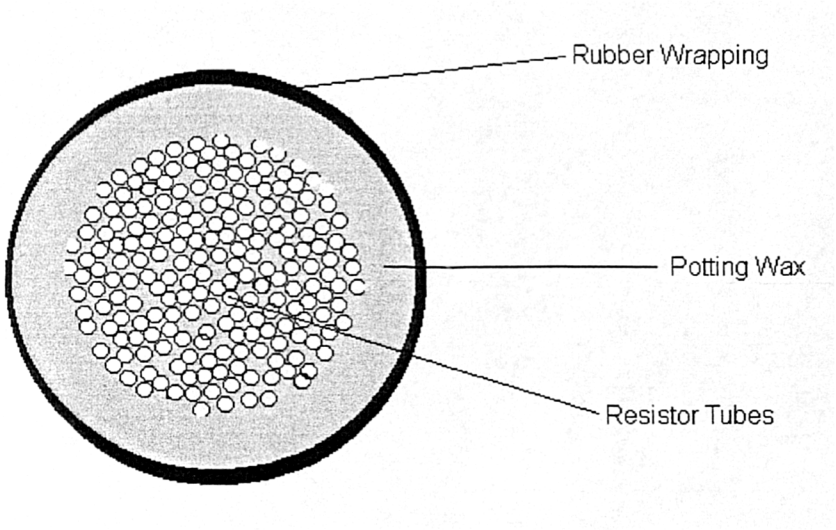


Figure 5.3 End View of the resistor element. The wax/fibre bundle is wrapped in rubber webbing to hold the unit together and to provide a seal once the assembly is press fitted into the resistor housing.

The whole apparatus was then placed into a 5°C water bath at which was allowed to cool . Once cool, the resistor element was pressed into a prepared perspex housing and the ends sealed with tapered threaded end caps (fig 5.4).

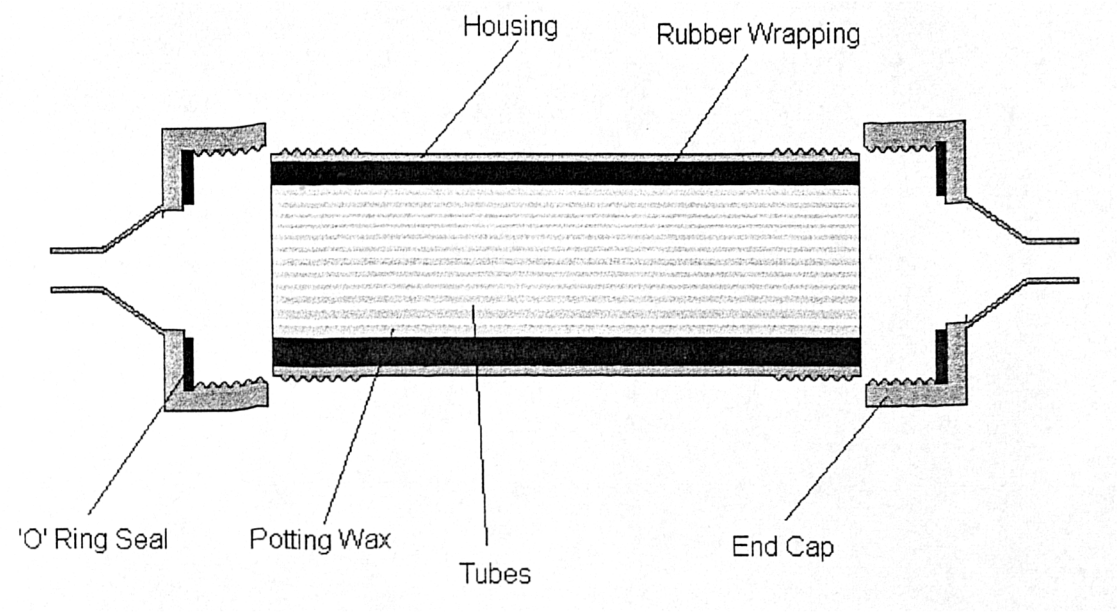


Figure 5.4 Longitudinal cross section of a flow resistor showing the seal arrangement. The rubber wrapping leads to the resistor having to be forced into the housing, causing a fluid seal. The tapered end caps encompass the connectors to the circuit together with an 'O' ring seal which seals the end cap against the resistor surface.

The end caps enabled the connection to be made between the resistor and the other components of the circuit. The value of the resistor could be increased by altering the number of open tubes as determined by equation 9. This can be achieved by plugging the number of tubes required, working from the outer circumference of the element inwards, with rubber plugs to produce the desired resistance. Both resistors were constructed in the same way, the only difference being the number of tubes in the resistor element and the diameter of the housing.

5.3.3 Compliance design and construction.

The compliance or hydrodynamic capacitance represents the compliance of the arterial tree. A convenient way to construct a hydrodynamic capacitance is to employ an air reservoir (Westerhof et al, 1971). Westerhof determined that in such a model a capacitance of 8 x $10^3 kg^{-1}m^4s^2$, which is close to normal human values, can be provided by an air space of 900 cm^3 in a reservoir. Wright et al (1987) showed by clinical study that this capacitance was insufficient to truly represent the patient undergoing open heart surgery and employed a capacitance of 15.8 x $10^3 kg^{-1}m^4s^2$ in his model. These direct measurements of capacitance in the clinical setting are more representative of the environment being modelled in this work and, therefore, the capacitance values employed by Wright (1988) are employed in this model. Since the relationship between capacitance and air volume is linear, the capacitance can be provided by an entrapped air space of 1800 cm^3 in the reservoir.

A reservoir was constructed with a sliding piston mechanism to permit the air volume above the fluid to be adjusted whilst the fluid level was kept constant (fig 5.5).

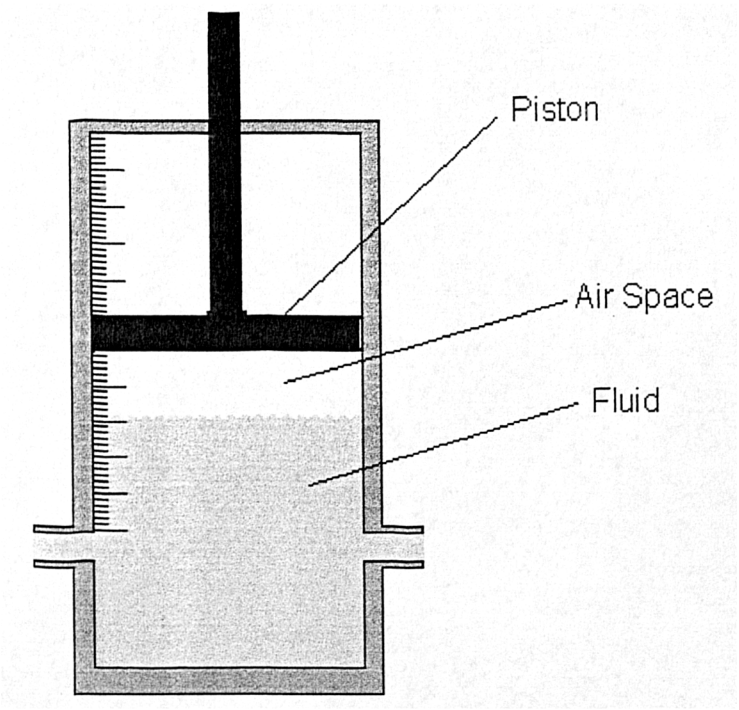


Figure 5.5 Diagram of the compliance reservoir employed in the model of the human systemic circulation. The piston made it possible to adjust the compliance. Increasing the air volume increased the compliance, decreasing the air volume had the opposite effect.

Such an arrangement permits the effect of varying the compliance on the pump output architecture to be assessed.

5.4 CONSTRUCTION OF THE MODEL

The three main component parts of the circulation model were interfaced with each other by short lengths of rigid perspex large bore tubing. The connections between the component parts were made using Allen bolts and recessed rubber 'O' ring seals. These tubes were kept as short as possible to avoid any undesired affect on the model. The whole apparatus was connected to the CPB circuit (fig 5.6), the connection being

made at the inflow end of the circulatory model by a 24F aortic cannula. At the venous (outflow) end of the model, the fluid flowed into the right atrial reservoir (RA). The RA reservoir, like the oxygenator reservoir, is open to atmosphere and does not act as a second circuit compliance. The fluid level in this reservoir was maintained at the same level as that in the compliance chamber (equivalent to a venous pressure of 5mmHg) by adjusting the gate clamp on the venous return line.

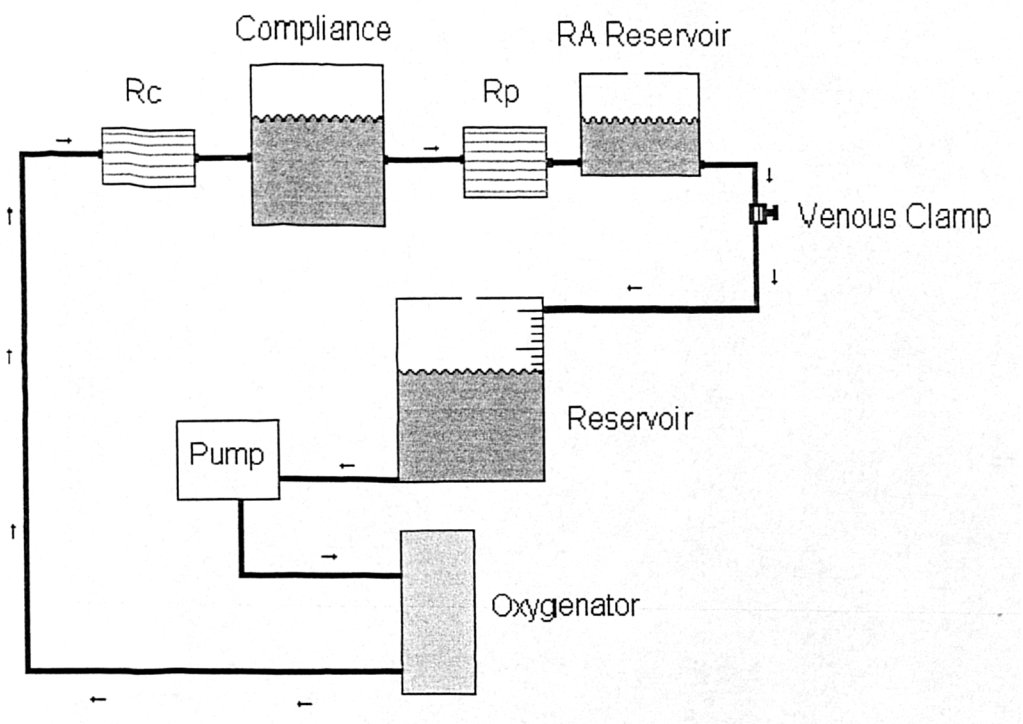


Figure 5.6. Diagram of the circulatory model showing the connection to the CPB circuit and the positioning of the venous clamp to control the return flow rate.

Venous return was effected by gravity in the conventional manner.

5.4.1 Flow and pressure measurement.

Fluid pressure and flow are measured immediately after the characteristic resistor (Fig 5.7).

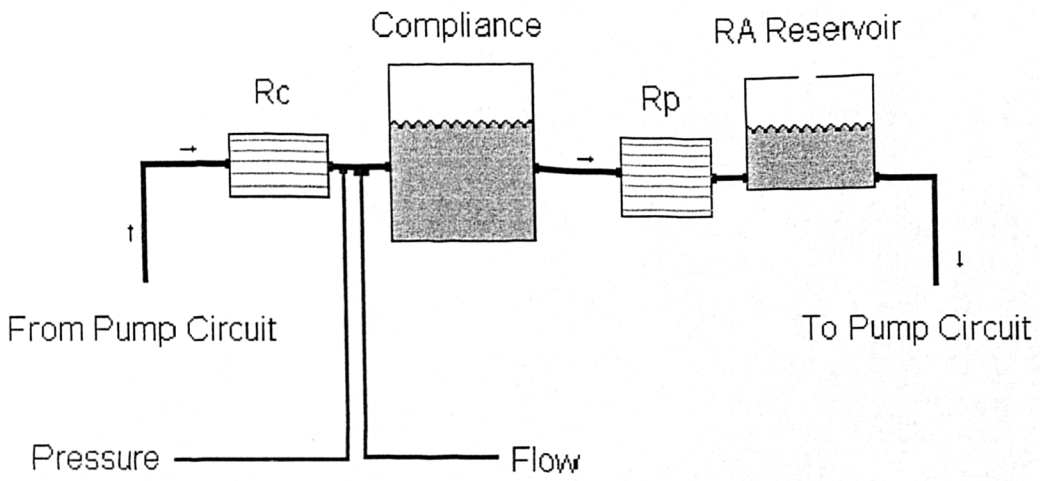


Figure 5.7 Model of the circulatory system showing the position of the pressure and flow probes.

This point corresponds to the aorta in the clinical setting. Blood flow was measured by means of a 15.0mm ID electromagnetic flow probe positioned in-line. This flow probe (Hellige, Germany) was designed for extracorporeal use and was recessed into the perspex conduit in such a manner that its presence did not create turbulence. Pressure was measured by means of a Hellige strain gauge transducer connected directly to the conduit. Both pressure and flow signals were fed from the pressure and flow monitors to a Naga 486SX PC computer via a DAS8 PGA programmable gain A/D converter board. The digitized signals were then processed using ASYST signal processing software. Both the pressure and flow systems were calibrated statically and dynamically using the perfusate designed for the circulatory system model. The

apparatus used and the results of the static calibration of the flow probe is shown in figures 5.8 and 5.9.

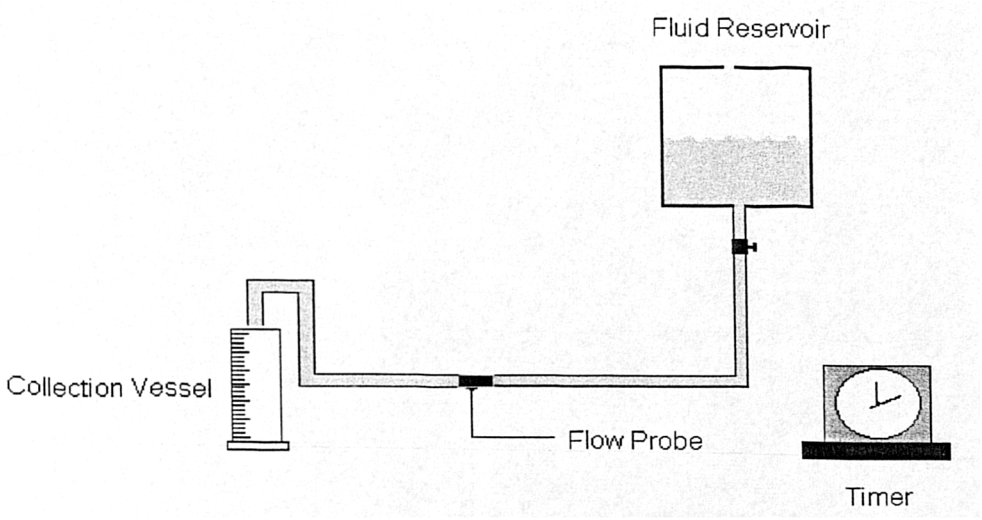


Figure 5.8 Apparatus for static calibration of the flow probe. This simple apparatus permits the flow rate of fluid to be accurately measured. The delivery rate of the fluid can be controlled by adjusting the valve at the outlet to the reservoir. At various known delivery flow rates the corresponding electromagnetic flow is noted and a calibration curve can be plotted. Changes in fluid flow associated with changing reservoir volume are minimizes by employing a larger supply reservoir and short measurement times.

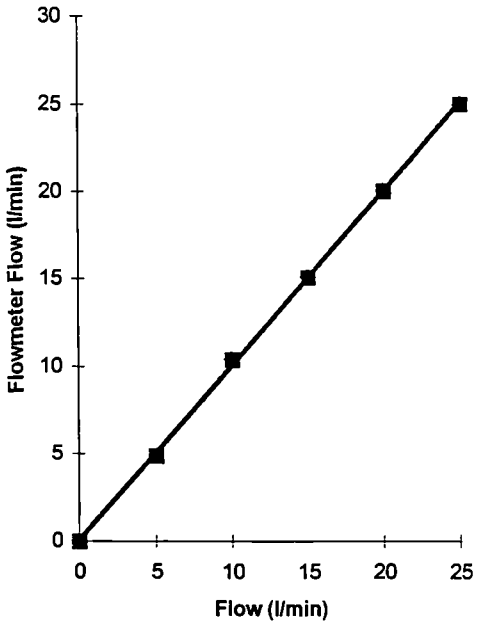


Figure 5.9 Calibration curve for the static calibration of the electromagnetic flow probe. The relationship was found to be linear with no deviation at either end of the range.

Under static calibration conditions, the electromagnetic flow probe was found to exhibit a linear response to known flow rate. This was also true of negative flow which was simulated by reversing the position of the reservoir and collection vessel, causing the fluid to flow in the opposite direction through the magnetic field. The pressure transducer exhibited a linear response under static pressure calibration conditions using a sphygmomanometer.

Dynamic calibration differs from static calibration in that the aim is to assess the response of the instruments to changing rather than continuous pressure and flow conditions . McDonald (1974) highlighted a number of ways in which this could be

carried out. Both electrical and physical calibration techniques were described. Physical calibration using sinusoidal pumping mechanisms is extremely difficult to perform due to the difficulty in producing a pump mechanism capable of generating adequate flows at extremely high frequencies. The alternative physical method is to oscillate the flow probe in a saline bath. This will simulate a bi-directional flow over a frequency band as wide as the oscillatory frequency. Mills and Shillingford (1967) used this technique and found it to be a satisfactory method of achieving calibration. Bergel and Gessner (1966) found that the flow probe, itself, was not responsible for limiting the frequency characteristics of a flowmeter system. On the contrary they determined that the dynamic characteristics are associated with the electronics. Electronic rather than physical dynamic calibration is therefore the method of choice for determining the frequency response of flow systems. The method employed for this calibration technique has been well described by McDonald (1974) and involves feeding a signal from a sine-wave generator to the input of the flowmeter and from there feeding the flow output to the *Y* input on the oscilloscope. The *X* input is provided by the sine-wave generator. The two signals can be compared by employing a Lissajou loop. The phase lag associated with changing frequency can then be computed for the flow-metering system. The frequency response of the Hellige system was assessed in the laboratory using this technique. The critical 3dB down frequency (the frequency at which the amplitude response was 30% down) was found to be at 50Hz. The phase lag was found to be in the order of $3.6^{\circ}Hz^{-1}$. This information allows the flow data to be corrected after collection for frequency associated errors.

The instruments were found to be adequate for the intended study of pumping systems. The model itself was simple to construct and should prove to be an

acceptable model of the systemic circulation. The limitations of this type of model have been described previously and include the Newtonian nature of the perfusate and the block nature of the resistors which may produce wave reflections uncharacteristic of the human circulatory system. These problems are not major and will be considered and corrected where possible after data collection.

CHAPTER 6

IN-VITRO STUDY OF THE PULSATILE OUTPUT ARCHITECTURE AND HYDRAULIC POWER DELIVERY OF TWO PULSATILE PUMP SYSTEMS DESIGNED FOR CARDIOPULMONARY BYPASS APPLICATIONS.

CHAPTER 6 IN-VITRO STUDY OF THE PULSATILE OUTPUT ARCHITECTURE AND HYDRAULIC POWER DELIVERY OF TWO PULSATILE PUMP SYSTEMS DESIGNED FOR CARDIOPULMONARY BYPASS APPLICATIONS.

6.1 INTRODUCTION

Since the overall aim of this thesis is to study the clinical benefits of controlled pulsatile blood flow architecture, it is essential that the degree of output architectural control offered by the pump systems is established. Determination of the pulsatile flow generating capabilities of pulsatile blood pumps is a complex issue. A number of factors require to be studied in this regard. Wright (1988) stated that the performance of a pulsatile pumping system can be characterized by its power output. This may be true, but there are other aspects of output architecture which may be of equal importance. Whatever the necessary requirements of physiological pulsatile blood flow, the requirements of the pump are clear: to generate a pulsatile flow profile which in terms of power delivery and architecture, are as similar to the natural, physiological state as possible. In addition, the pump should meet this requirement without compromising the safety of the patient. As shown in Chapter 3, there are many methods of generating pulsatile blood flow. Two such methods have been selected for study in this thesis. One a roller pump mechanism, the other a ventricular mechanism; these have been described in detail in Chapter 4. Claims have been made in favour of roller pump generated pulsatile blood flow in terms of patient morbidity and mortality (see Chapter 2). However, Wright (1988) demonstrated that the roller

pump mechanism is limited in terms of pulsatile hydraulic power delivery, particularly in comparison with the beating heart. Despite this apparent limitation, the roller pump has been associated with considerable clinical benefits. Runge et al (1989), however, stated that ventricular pumps are capable of delivering a more physiological flow pattern than roller pump mechanisms when tested in a bovine model. However, clinical use of ventricular systems has been hampered by difficulty in matching the ventricular mechanisms with the CPB circuitry employed for routine extracorporeal circulation (ECC). The additional cost element involved is another factor limiting the use of ventricular systems. Whatever the cause, ventricular pumping systems are not generally employed in CPB for open heart surgery. Roller pumps and centrifugal pumps remain the major systems of choice for routine clinical applications. No centrifugal pump is currently capable of generating pulsatile flow.

The aim of this aspect of this thesis is to determine whether the true pulsatile pump (TPP) ventricular pump mechanism is associated with improved pulsatile flow generation when compared to roller pump generated pulsatility. One important aspect of this study will be to assess whether the TPP allows better control of output architecture. This will be studied with respect to hydraulic power, dp/dt and pressure amplitude. The studies will be carried out in-vitro, employing the model of the human systemic circulation detailed in Chapter 5. The effect of arterial-line devices on output architecture will also be studied. The presence of a membrane oxygenator, for example, may have a damping effect on the output architecture which may be related to the membrane configuration (Gourlay et al, 1987, Gourlay and Taylor, 1994, Wright, 1989). This effect will be studied and the optimum membrane/pump configuration for application on the clinical aspect of this work will be established.

6.2 MATERIALS AND METHODS

The aim of this study is to assess the pulsatile flow generating capabilities of the Stockert roller pump and the TPP ventricular pump. The model of the human systemic circulation, described in Chapter 5, will be employed for this purpose. The test circuitry, including the pump, will be connected to the model in the manner described in Chapter 5, using a 24F aortic cannula to make the arterial connection and 12mm internal diameter PVC tubing for the venous connection. Pressure and flow in the model will be measured by pressure and flow transducers positioned after the characteristic resistance component of the model. From the pressure and flow measurements, hydraulic power in both the mean and pulsatile modes will be computed together with dp/dt, the rate of rise in pressure over time, at the ejection phase of the pressure signal. These measurements will be made under a number of conditions designed to assess both the range of output control offered by each system, and to assess the effect of the inclusion of arterial-line membrane devices on the output characteristics. The conditions under which these studies were employed are detailed in table 6.1.

Group No	Pump Type	Auto	Run-Time	Membrane
1	s	100	30	no
2	s	100	50	no
3	s	100	70	no
4	s	100	100	no
5	s	80	30	no
6	s	80	50	no
7	s	80	70	no
8	s	50	30	no
9	s	50	50	no
10	s	50	70	no
11	s	100	30	Affinity
12	s	100	30	Terumo
13	T	n/a	30	no
14	T	n/a	50	no
15	T	n/a	70	no
16	T	n/a	30	Affinity
17	T	n/a	30	Terumo

Table 6.1 Conditions under which the output architecture of the pump systems was tested. s designates the Stockert pump, T the TPP pump. The Automatic setting is appropriate for the Stockert pump only. An automatic setting of 100% corresponds to no baseline flow.

Ten experimental procedures, in which ten pressure and flow cycles were collected during each repetition, were performed in each group. These studies cover the usable range of each relevant control parameter. The perfusate employed was a mixture of glycerol and 0.9% saline which was similar to blood in the microcirculation in terms of density and viscosity (see chapter 5). All studies were carried out at 4.5 l/min flow rate. This flow rate represents the average clinical flow rate employed at Hammersmith Hospital and is the flow rate for which the model of the systemic circulation was designed.

6.2.1 The Test Circuit.

Throughout this test procedure, the model of the human systemic circulation described in Chapter 5 was employed as the basis of the test circuit. The pumps undergoing study were connected to the model using a 24F aortic cannula which was connected to the output side of the pump by a 2m length of 12mm internal diameter PVC tubing (fig 6.1).

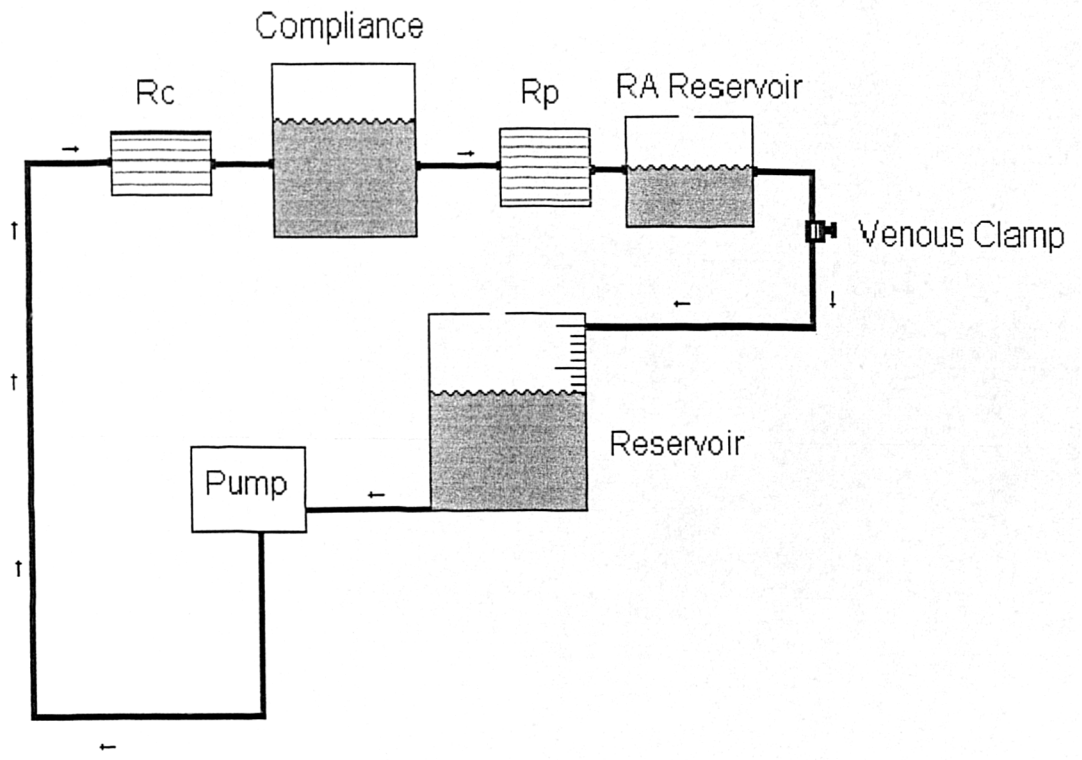


Figure 6.1 Diagram of the circuit employed for assessing the output architecture associated with each of the pump systems. The venous clamp was employed to regulate the venous return flow at the input level.

The 2m length of tubing is similar in size and hardness to that employed in the construction of the clinical circuit employed at Hammersmith Hospital (Gourlay et al 1987, Adams et al 1986). The venous return from the model is affected by the height difference between the RA reservoir and the pump holding reservoir, flow, therefore, is by gravity. The flow from the model to the holding reservoir is matched to the input flow using the venous flow regulator clamp positioned on the venous return line. The perfusate is pumped by the perfusion pump from the open holding reservoir to the input side of the model.

Two membrane oxygenator types were employed in this aspect of the study. One (Terumo Capiox E) was designed for positioning on the venous side of the circuit (fig 6.2) and the other (Avecor Affinity) was designed to be positioned on the arterial side of the circuit (fig 6.3.).

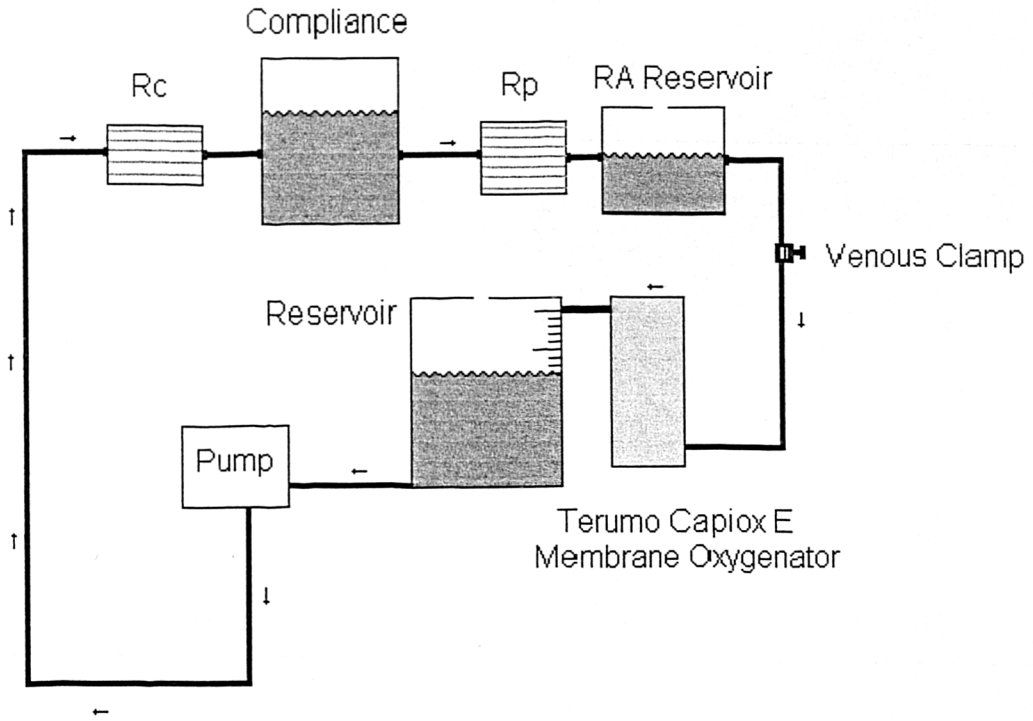


Figure 6.2 Circuit diagram showing the position of the Terumo Capiox E membrane oxygenator in the venous return line of the circuit.

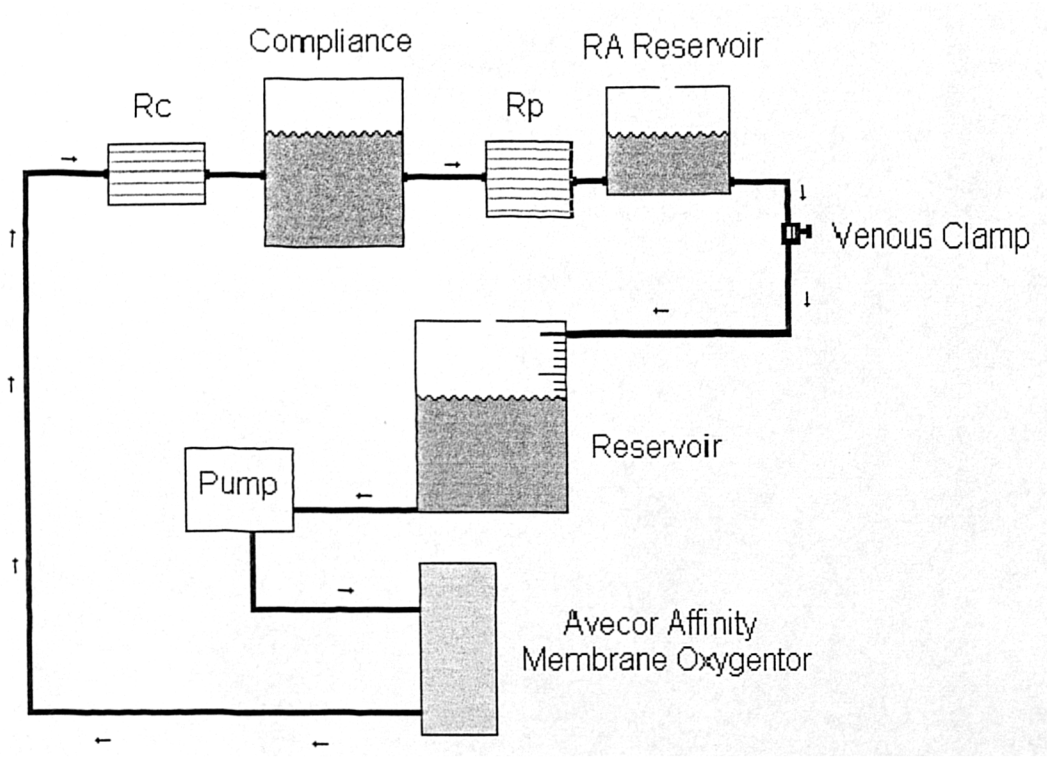


Figure 6.3 Circuit diagram showing the position of the Avecor Affinity membrane oxygenator for hydraulic power and architecture tests. The oxygentor is positioned between the pump and the model in the conventional manner.

These membrane types were selected for use in this study for two reasons. The Terumo oxygenator is recommended for use by the manufacturers of the TPP (see instructions for use) due to the non-modulating effect expected by its unique positioning within the perfusion circuit. In addition to the non-modulation of pump output architecture expected with the use of this device, it is envisaged that such a device will not be associated with the generation of microbubbles related to pulsatile

flow in the arterial line of the circuit (Pearson, 1978, Wright, 1988, Gourlay et al, 1994). The generation of microbubbles will be the focus of study in Chapter 7.

6.2.2 Pressure and Flow Measurement

Circuit pressure and flow were measured in the conduit connecting the characteristic resistor to the compliance chamber. Wright (1988) determined that this point was equivalent to the aorta in the human model. This is a convenient sample point since any computation of hydraulic power output in the clinical setting will be performed employing probes positioned on the aorta of the perfused patient. The positioning of the flow and pressure probes in this conduit, therefore, represents an excellent clinical analogue.

Pressure was measured by a Hellige pressure monitoring system using a catheter-tip strain gauge transducer. Perfusate flow rate was measured using a Hellige electromagnetic flowmeter system employing a 15mm extracorporeal flow probe. The flow probe was positioned inside the conduit. The probe was recessed into the internal wall of the conduit in order that it did not interfere with the flow of perfusate through the tubing. Both the pressure and flow metering systems were statically and dynamically calibrated in the manner described in Chapter 5. Calibration of both systems were carried out before and after each test run to assess the calibration drift. It was found that there was no measurable baseline or range drift at any time during the in-vitro study.

Analogue signals from the flow and pressure meters were fed to an Analogue to Digital converter (DAS8 PGA) with a programmable gain amplifier and from there to a NAGA 486SX PC computer. Signal processing software was running on this system

(ASYST, Easyest) which processed the incoming signals. This software package permitted software control of the sampling rate and had a range of filters available for controlling the input signals in terms of frequency band. In addition to high, low and band pass filtering of the signals, the software package could carry out Fourier analysis of the data in both flow and pressure domains. The raw signals and analysed profiles could be stored on disc and /or exported to other software packages in a number of formats. For the purposes of this study, the data were exported to Microsoft Excel spreadsheets.

6.2.3 Computation of Hydraulic Power

Hydraulic power is energy per unit time and can be determined in the following manner:

$$W = E/t$$

W = Hydraulic Power ($J.s^{-1}$)
E = Mechanical Energy (J)
t = time (s)

In the context of blood flow in hydromechanical models, or in the physiological state this can be computed in the following manner since the power in the system is equivalent to the product of pressure and flow.

$$W = Q \times P$$

W = Hydraulic Power ($J.s^{-1}$)
Q = Perfusate Flow Rate ($m^3.s^{-1}$)
P = Perfusate Pressure ($N.m^{-2}$)

To assess total hydraulic power in a pulsatile system, mean and pulsatile terms must be considered. Total hydraulic power is the sum of the mean power and pulsatile

power. Mean power is the product of mean flow and pressure and pulsatile hydraulic power is the sum of a number of harmonics of pressure and flow. This relationship can be described in the following way:

$$W_t = W_m + \Sigma^n W_p$$

W_t = Total Hydraulic Power
W_m = Mean Hydraulic Power
W_p = Pulsatile Hydraulic Power
n = The number of samples per pulse cycle.

Pulsatile hydraulic power components are derived from Fourier analysis of the pressure and flow waveforms. The Fourier analysis in this instance is carried out by the ASYST system as the pressure and flow complexes are collected. Previous experience (Gourlay and Taylor, 1994) has shown than components beyond the 10^{th} harmonic do not contribute significantly to pulsatile hydraulic power. Discrimination at this level is well within the capability of the measurement apparatus. The highest harmonic component which can be assessed is given by the equation;

$$F_{(max.)} = N/2$$

$F_{(max.)}$ = Highest Harmonic Available
N = Number of samples per pulse cycle

Since the sample rate of the system employed for these studies is 250 samples per second, and the repetition rate of the pump systems is 75 BPM, the number of samples per complex is 200. In this example, the number of harmonics available for study is 100. This analysis is carried out on 10 complexes of pressure and flow taken from each of the ten runs which comprise each test group. The mean values for each

test group are, therefore, computed from 100 measurements. All data are expressed as power in the mean and pulsatile domains. As the pump systems are operating against similar afterloads, with a similar perfusate and flow rate, any quantifiable differences between the systems should be apparent in terms of these factors.

6.2.4 Analysis of pressure waveforms.

In addition to the contribution made to computation of hydraulic power, the pressure waveforms are analysed for dp/dt and pressure amplitude in each study group (fig 6.4)

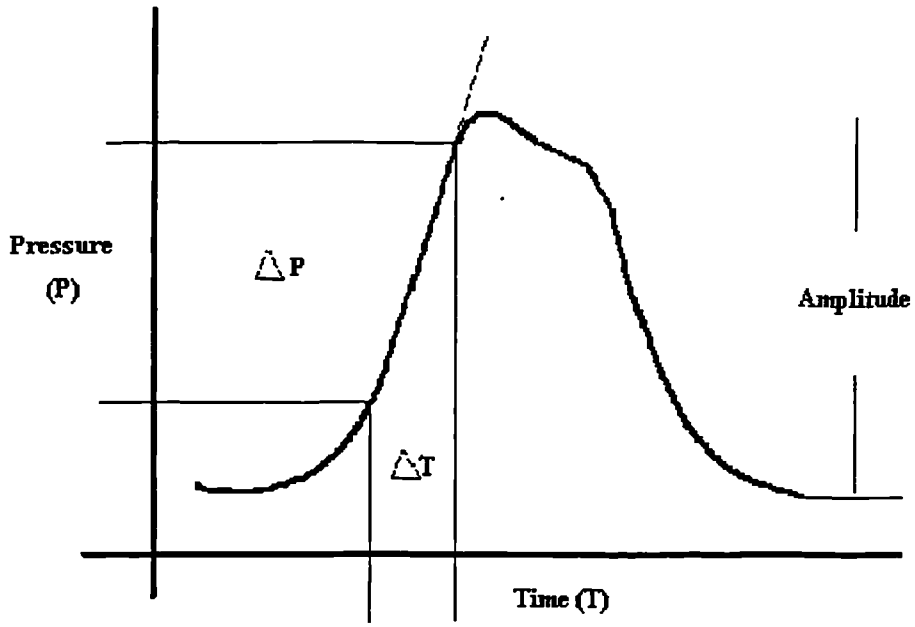


Figure 6.4 Method for determining $dp/dt_{(max.)}$ and pressure amplitude from a pressure complex. The max. designates that this should represent the tangent of maximum change with respect to time.

This measurement of simple waveform attributes is carried out by the ASYST software as the pressure and flow complexes are collected. As this is performed on each complex gathered; 100 complexes in all are analysed in each group.

6.3 STATISTICAL ANALYSIS

Statistical analysis of all data is carried out by STATA statistical analysis software (Stata Corporation, USA) reading from and writing to Microsoft Excel spreadsheets. The STATA package performed forward elimination multiple regression analysis with a level of significance set at <0.05. This analysis method was applied due to its multi-factorial approach and the elimination of the need for multiple t tests.

6.4 RESULTS

6.4.1 Hydraulic power delivery.

The effects of altering the ejection time on the pulsatile hydraulic power output of both pumps can be seen in figures 6.4, 6.5 and 6.6 and in table 6.2. Where the Stockert pump is employed (groups 1 - 12), the data are presented with respect to the automatic setting on the Stockert pump. Being a purely pulsatile pump system with no baseline flow capability, this is not the case with the TPP pump.

Group Number	Total Hydraulic Power (Js^{-1})	Pulsatile Hydraulic Power (Js^{-1})
1	0.661 ± 0.0015	0.013 ± 0.0010
2	0.658 ± 0.0014	0.010 ± 0.0015
3	0.656 ± 0.0013	0.008 ± 0.0011
4	0.648 ± 0.0009	0.000 ± 0.0000
5	0.654 ± 0.0011	0.007 ± 0.0021
6	0.653 ± 0.0008	0.005 ± 0.0005
7	0.651 ± 0.0009	0.003 ± 0.0005
8	0.650 ± 0.0007	0.002 ± 0.0004
9	0.649 ± 0.0007	0.001 ± 0.0002
10	0.648 ± 0.0009	0.0003 ± 0.0000
11	0.655 ± 0.0011	0.006 ± 0.0004
12	0.661 ± 0.0009	0.012 ± 0.0007
13	0.963 ± 0.0011	0.315 ± 0.0012
14	0.944 ± 0.0014	0.296 ± 0.0009
15	0.869 ± 0.0013	0.220 ± 0.0007
16	0.959 ± 0.0015	0.311 ± 0.0007
17	0.964 ± 0.0014	0.314 ± 0.0010

Table 6.2 Total and pulsatile hydraulic power associated with each of the groups detailed in table 6.1. The data shown are mean and standard deviation.

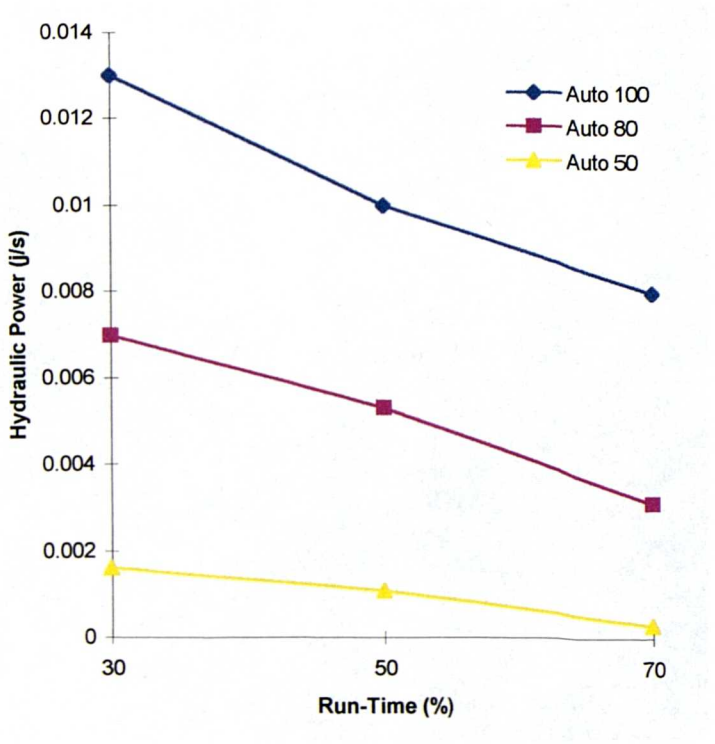


Figure 6.4 Pulsatile hydraulic power associated with the Stockert roller pump operated in the pulsatile mode at automatic settings of 50, 80 and 100. Mean values only are shown, the standard deviations are presented in table 6.3.

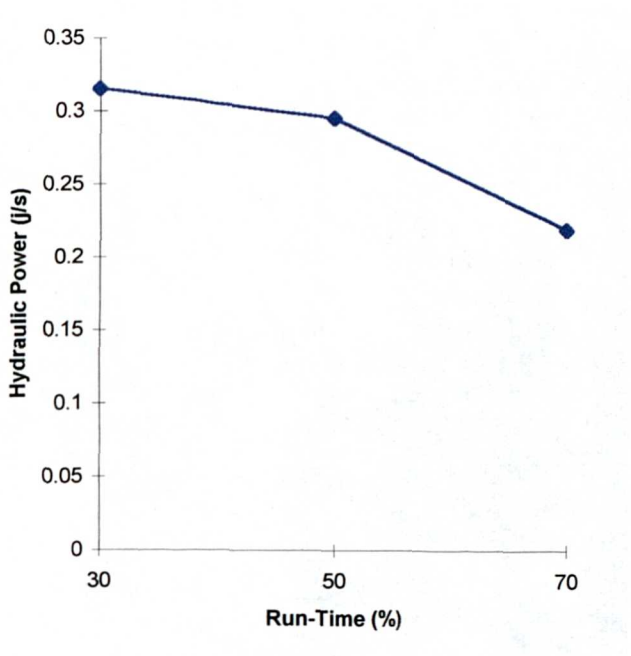


Figure 6.5 Pulsatile hydraulic power output associated with the TPP pump at incrementally increasing run-times. Only mean values are shown, the standard deviations are in table 6.2.

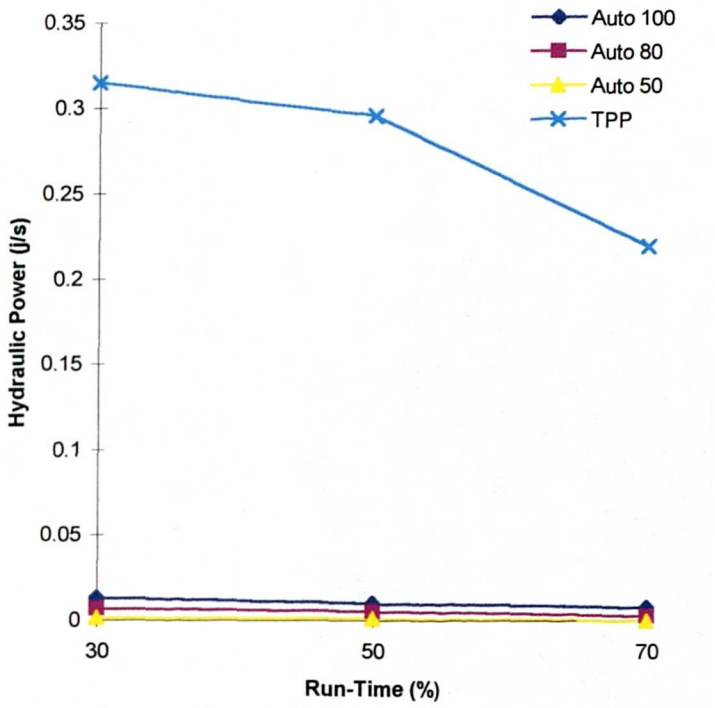


Figure 6.6 Pulsatile hydraulic power relationship with run-time for both pump systems. Only mean values are shown.

There is a clear relationship between run-time and hydraulic power for both pump systems. The run-time pulsatile hydraulic power relationship is associated with an R^2 value of 0.8929 for the TPP pump and a minimum of 0.9868 for the Stockert roller pump at the 50% automatic level. The differences between the pulsatile hydraulic power output of the Stockert pump and the TPP was highly statistically significant ($p<0.0001$) as were the differences between the Stockert groups defined by automatic setting, ($p<0.001$ for all comparisons at all levels). Apart from the highly statistically significant differences, there was a clear difference in terms of the overall magnitude of the pulsatile hydraulic power output of the two systems. The TPP was associated with a pulsatile hydraulic power output which was 30 times greater than that of the roller pump when both were at the optimum output settings (fig 6.6 and table 6.2).

The total Hydraulic power (mean plus pulsatile power) puts the pulsatile element into context in terms of the contribution made to the total power output. Figs 6.7, 6.8 and 6.9 show that the pulsatile component of total hydraulic power for the roller mechanism is relatively insignificant (< 3%(max.) of total power output), whereas pulsatile hydraulic power contributes significantly to total hydraulic power with TPP generated pulsatile flow (>28%(max.)).

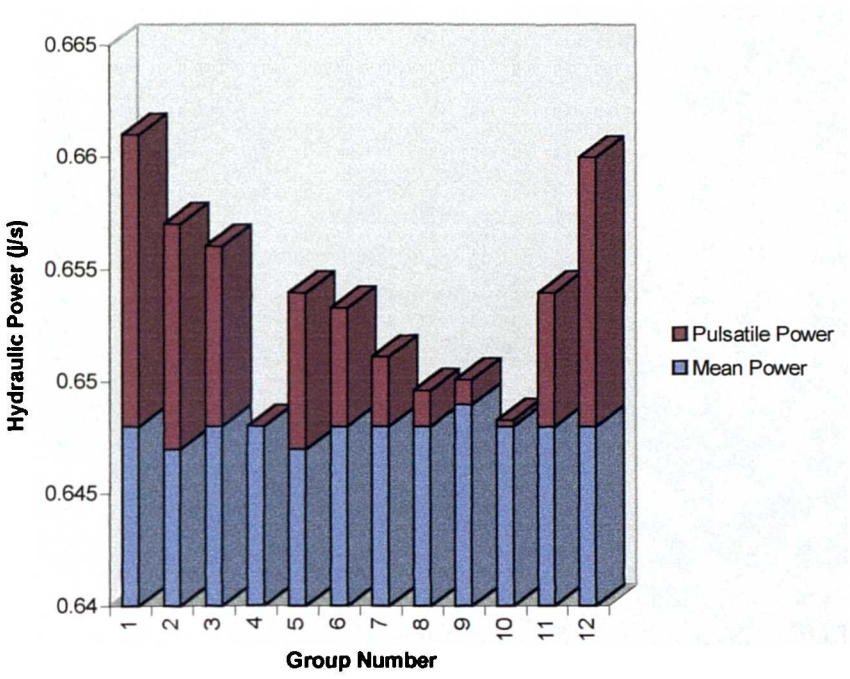


Figure 6.7 Stacking column graph showing the combination of pulsatile and mean hydraulic power for the Stockert roller pump.

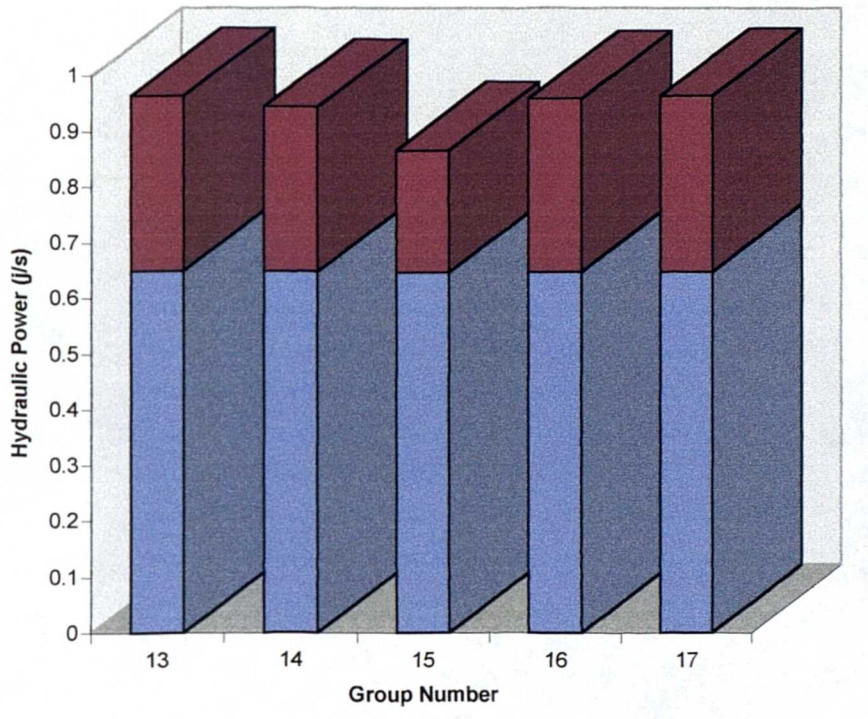


Figure 6.8. Stacking column graph showing the combination of pulsatile and mean hydraulic power for the TPP pump system.

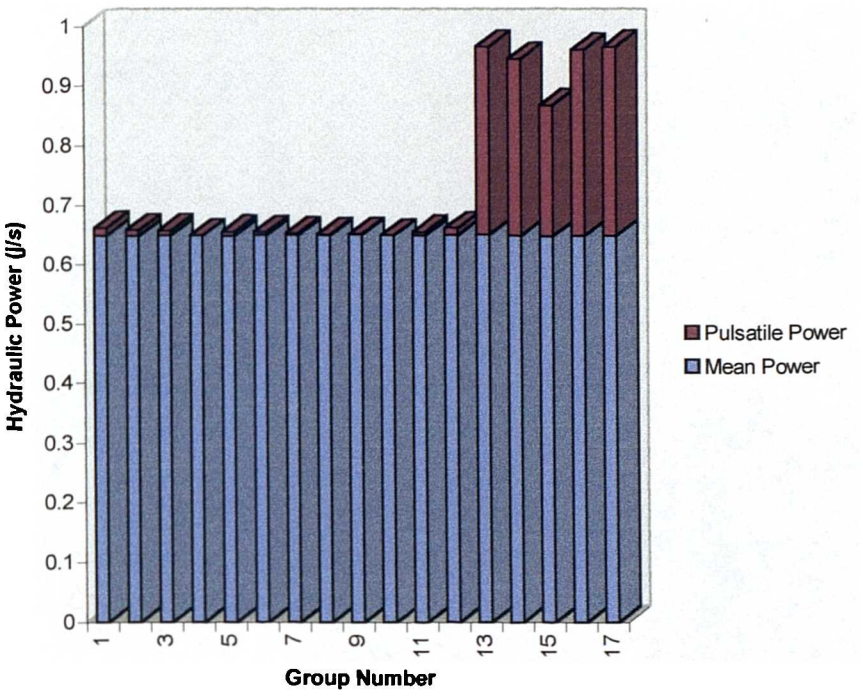


Figure 6.9. Stacking column graph showing pulsatile and mean hydraulic power associated with both pump systems.

The inclusion of the Terumo membrane oxygenator had no effect on either total or pulsatile hydraulic power output with either system when the pumps were being operated at maximum pulsatility. The Affinity membrane, which is positioned in the arterial line of the perfusion circuit, did modulate the power output (Table 6.3 and figs 6.10 and 6.11).

Group Number	Total Power (Js^{-1})	Pulsatile Power (Js^{-1})
1	0.661 ±0.0015	0.013 ± 0.0010
12	0.661 ± 0.0009	0.012 ± 0.0007
11	0.655 ± 0.0011	0.006 ± 0.0004
13	0.963 ± 0.0011	0.315 ± 0.0012
17	0.964 ± 0.0014	0.314 ± 0.0010
16	0.959 ± 0.0015	0.311 ± 0.0007

Table 6.3 The effect of introducing the Terumo and Affinity membrane oxygenators on total and pulsatile hydraulic power delivery.

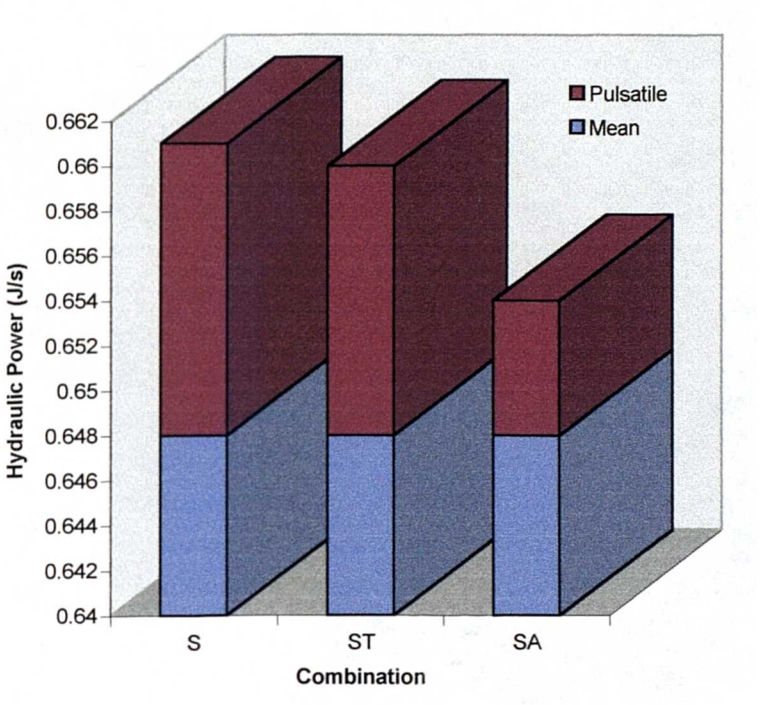


Figure 6.10 The effect of introducing the Terumo (ST) and the Affinity (SA) membranes on mean and pulsatile hydraulic power using the Stockert roller pump.

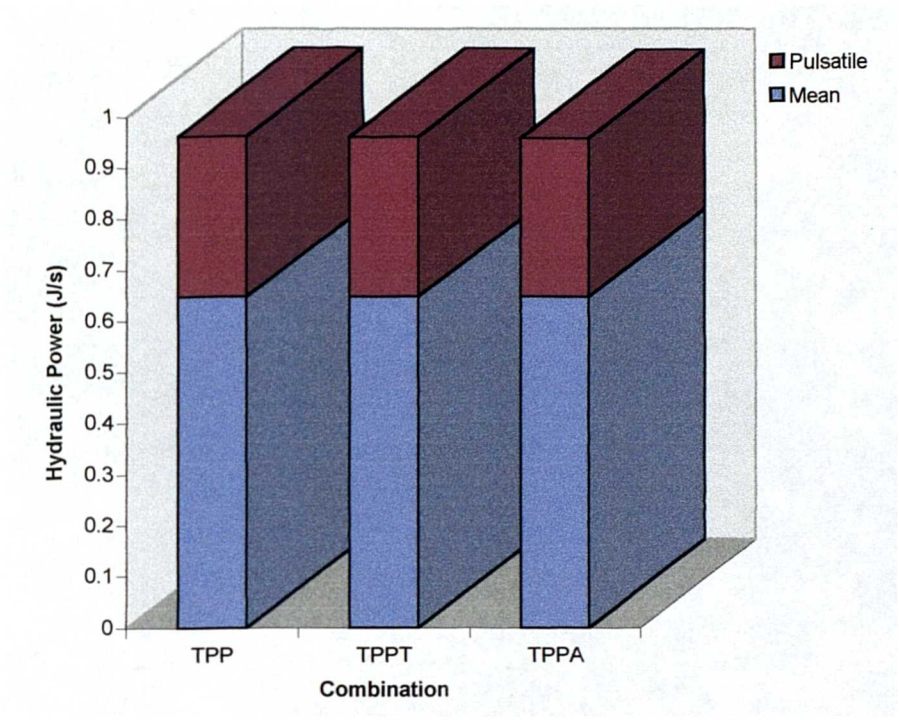


Figure 6.11 The effect of introducing the Terumo (TPPT) and Affinity (TPPA) membrane oxygenator on mean and pulsatile hydraulic power delivery with the TPP pump.

Not surprisingly, the Terumo oxygenator, which is positioned at the venous inlet to the circuit, does not have any effect on either mean or pulsatile hydraulic power delivery by either pump system. The Affinity membrane, on the other hand, did affect power delivery in both systems. Its presence had a profound effect on the hydraulic power deliver of the roller mechanism, reducing the power in the pulsatile domain by 50%. This difference was statistically significant ($p<0.001$) on comparison with the un-modulated pulsatile power, but not statistically significantly different in terms of total hydraulic power delivery. This effect can be accounted for by the fact that pulsatile hydraulic power is an extremely small (<3%) proportion of total power delivery. The presence of the Terumo membrane had no effect on hydraulic power delivery in either the pulsatile or mean domains with the TPP pump. The Affinity membrane affected the power delivery in the pulsatile domain only, reducing pulsatile power delivery by <1%. This reduction is not statistically significant and has no significant effect on total hydraulic power delivery as mean power is unaffected by the presence of the Affinity membrane.

6.4.2 Analysis of pressure waveforms

The pressure waveforms were analysed for $dp/dt_{(max.)}$ and pressure amplitude. The measurements were taken from the point in the model described in section 6.2.2, which corresponds to the aorta in the clinical setting. Assessments of $dp/dt_{(max.)}$ and pressure amplitude were carried out by the ASYST software package as the signals were collected. The results were subsequently verified by manual assessment. These measurements were carried out in all of the groups shown in table 6.1. Ten cycles were recorded for measurement and 10 repetitions were performed in each test group.

Examples of the pressure waveforms generated within the model by the pump systems operating at maximum pulsatility and additionally in the case of the Stockert pump, operating in the non-pulsatile mode, are shown in figure 6.12

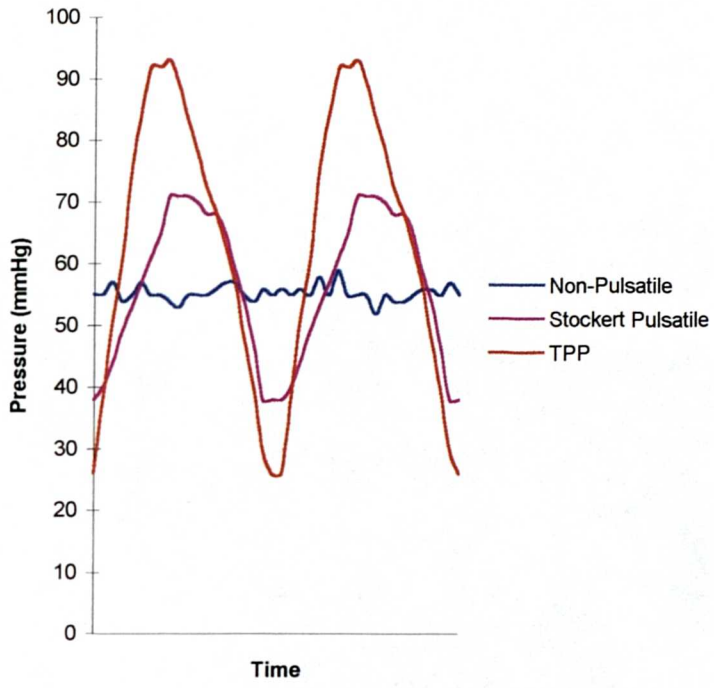


Figure 6.12 Graph showing representative waveforms taken from the model of the systemic circulation using the TPP pump and the Stockert pump, each running with optimum pulsatility (30% run-time (Stockert) and 30% symmetry (TPP)). In addition this figure shows the waveform generated within the model by the Stockert pump running in the non-pulsatile mode.

Group Number	$dp/dt_{(max.)}$ ($mmHg.s^{-1}$)	Amplitude (mmHg)
1	602.4 ± 31.2	47.3 ± 4.4
2	481.6 ± 44.4	34.6 ± 4.1
3	197.3 ± 17.7	27.3 ± 4.4
4	31.4 ± 6.9	9.3 ± 1.1
5	523.7 ± 44.5	41.2 ± 3.4
6	401.3 ± 51.1	31.6 ± 4.3
7	144.6 ± 22.2	22.3 ± 3.7
8	457.2 ± 31.5	36.7 ± 3.3
9	347.6 ± 27.5	28.1 ± 1.8
10	126.8 ± 33.2	21.1 ± 3.2
11	511.9 ± 47.7	41.6 ± 4.1
12	614.8 ± 38.2	48.6 ± 4.1
13	781.8 ± 48.7	58.1 ± 12.1
14	611.3 ± 38.8	47.6 ± 10.5
15	407.6 ± 47.3	41.2 ± 12.5
16	605.5 ± 58.3	51.1 ± 13.3
17	776.5 ± 44.2	56.3 ± 11.8

Table 6.4 $dp/dt_{(max)}$ and pressure amplitude for all groups described in table 6.1.

The effect of increasing run-time on $dp/dt_{(max.)}$ and pressure amplitude at different automatic settings for the Stockert pump is shown in figures 6.13 and 6.14. The effect of increasing run-time on $dp/dt_{(max.)}$ and pressure amplitude with the TPP pump is shown in figure 6.15. and 6.16.

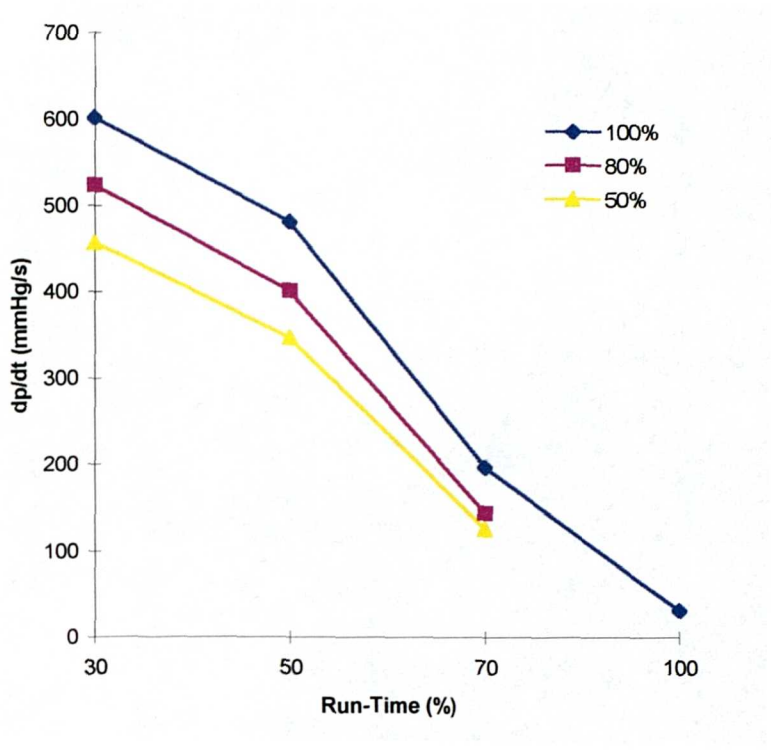


Figure 6.13 The effect of changing run-time on $dp/dt_{(max.)}$ at automatic settings of 100, 70 and 50 %. Non-pulsatile flow was generated by increasing the run-time to 100% in the 100% automatic group.

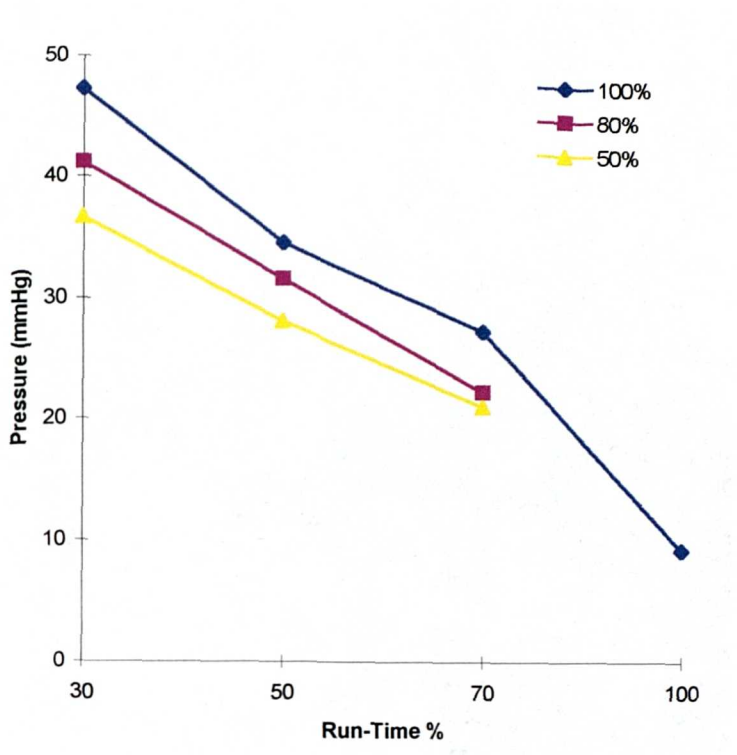


Figure 6.14 The effect of increasing run-time on pressure amplitude at automatic settings of 100%, 80% and 70% with the Stockert pump. Non-pulsatile flow was provided by running at a run-time of 100% in the 100% automatic group.

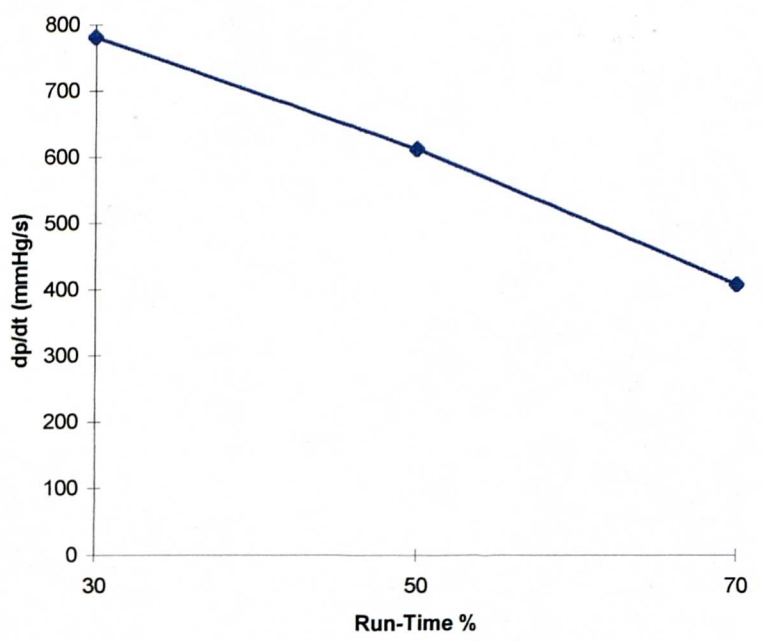


Figure 6.15 The effect of run-time on $dp/dt_{(max.)}$ with the TPP pump.

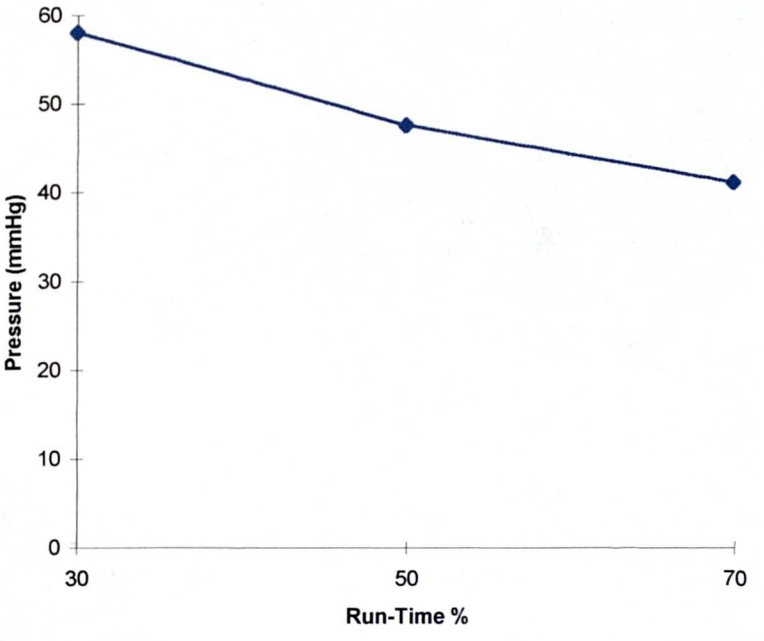


Figure 6.16 The effect of increasing run-time on pressure amplitude with the TPP pump.

Altering the run-time of the pump cycle had an effect on both pressure amplitude and $dp/dt_{(max.)}$ in the model, with both pump systems. The relationship between run-time and both amplitude and $dp/dt_{(max.)}$ was strong with the Stockert pump (minimum $R^2 = 0.978$ for $dp/dt_{(max.)}$ and 0.9736 for amplitude). For the TPP pump, these relationships were also strong ($R^2 = 0.9973$ for $dp/dt_{(max.)}$ and 0.9808 for amplitude). This would indicate that there is a high level of control of both pressure rise-time and amplitude by both systems. The automatic control on the Stockert system had the effect of reducing both the $dp/dt_{(max)}$ and pressure amplitude. This reduction was more significant at the shorter run-time levels ($p<0.001$) compared to the higher levels ($p<0.01$). The very small variation in the data collected, linked to the high number of samples (n=100) for each group, results in all comparisons returning statistically significant differences. The TPP was associated with a higher $dp/dt_{(max.)}$ generating capability than the Stockert pump across the range of run-time settings (fig 6.17). The differences were statistically significant at all levels ($p<0.01$ minimum).

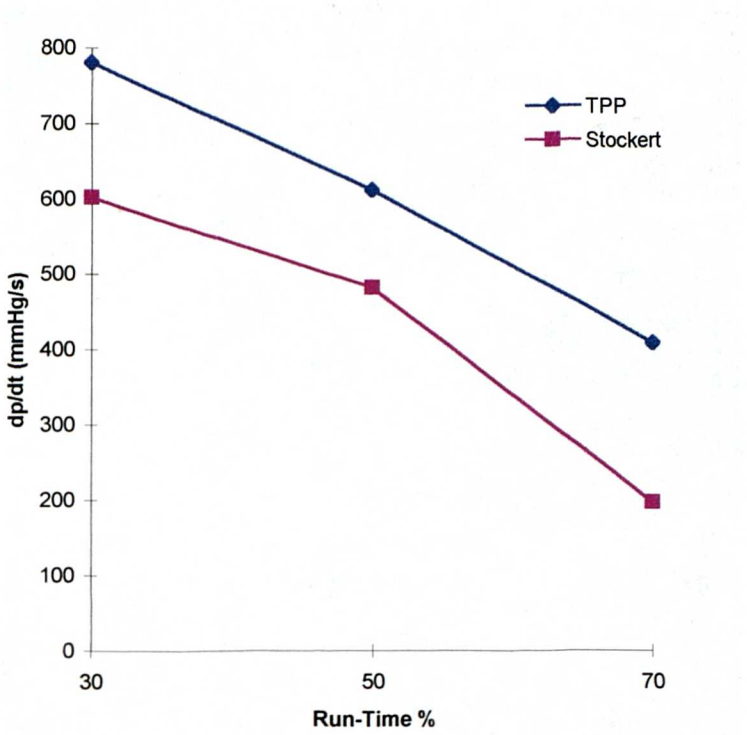


Figure 6.17 The effect of run-time on pressure $dp/dt_{(max.)}$ for both pump systems. The data for the Stockert pump were collected using an automatic setting of 100%, generating no baseline flow.

When pressure amplitude in the model circulation was considered in relation to run-time, it was found that the TPP pump, once again, was associated with higher levels (fig 6.2.4.6). The pressure amplitude ranged from 41 to 58 mmHg with decreasing run-time for the TPP pump, and from 27 to 47 for the Stockert roller pump.

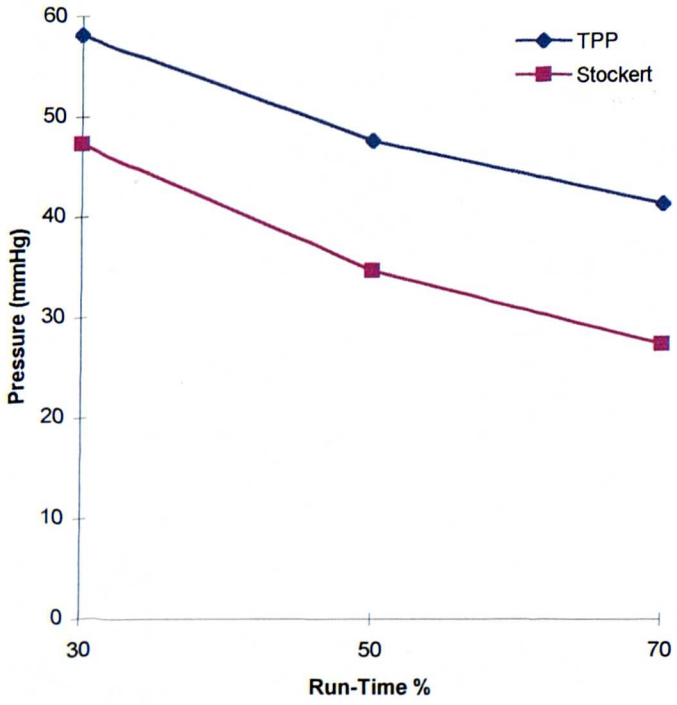


Figure 6.18 The effect of run-time on pressure amplitude in the model circulation with both pumps. The Stockert was operating in the maximum pulsatility mode (Automatic 100%).

These difference were statistically significant at all levels ($p<0.01$ minimum) The inclusion of the Terumo membrane oxygenator had no effect on either $dp/dt_{(max.)}$ or pressure amplitude. This is due to its positioning before the pump. The Affinity membrane did have and effect on both pressure characteristics with both pump systems (figs 6.19, 6.20).

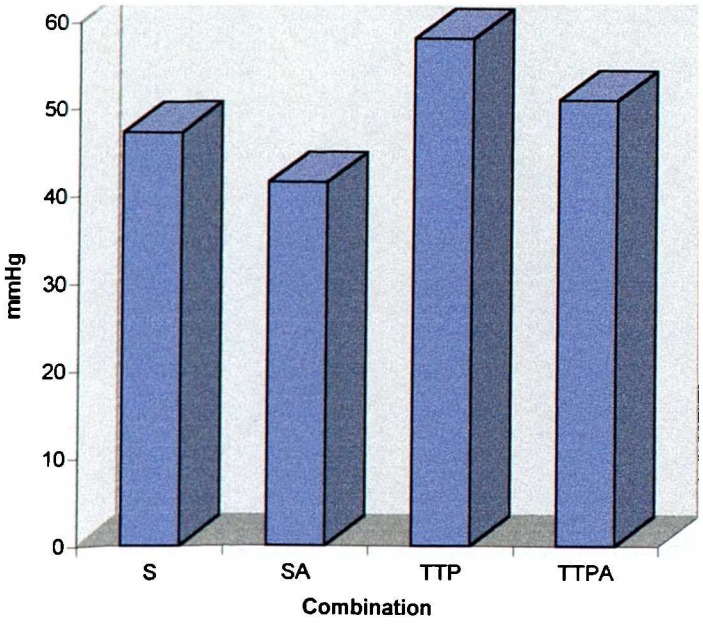


Figure 6.19 The effect of introducing the Affinity membrane oxygenator into the arterial line of the CPB circuit on pressure amplitude with the Stockert (S, SA) and TPP (TPP, TPPA) pumps.

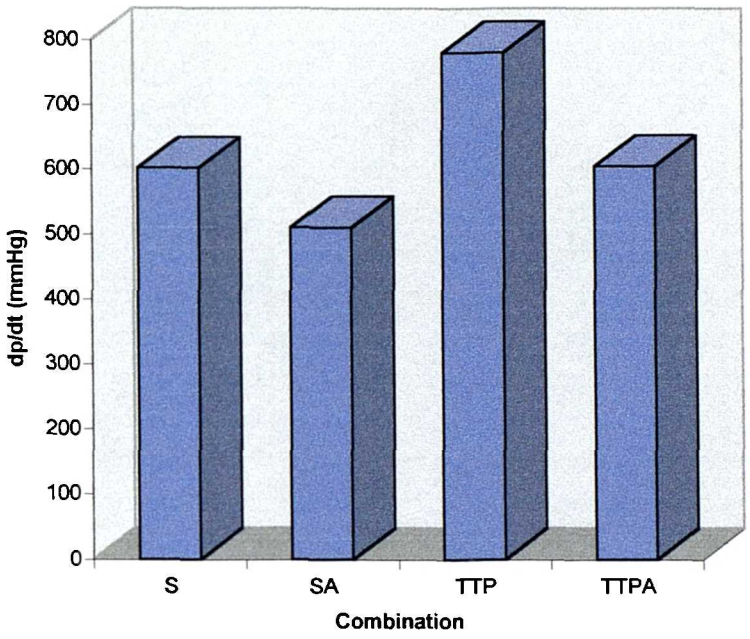


Figure 6.20 The effect of introducing the Affinity membrane oxygenator into the arterial line of the CPB circuit on $dp/dt_{(max.)}$ with both pump systems (Stockert = S,SA, TPP= TPP, TPPA)

The inclusion of the membrane oxygenator reduced both $dp/dt_{(max.)}$ and amplitude in both pump groups. The reduction in both was substantial and statistically significant

($p<0.01$ in both groups). The reduction in $dp/dt_{(max.)}$ and amplitude in the TPP group brought the levels of both down to the un-modulated level exhibited by the Stockert group.

6.5 DISCUSSION

The aim of this study was to characterize the output architecture of two pulsatile perfusion pumps. The basis of this process was to assess the hydraulic power output of the pumps when operating against a known set of hydrodynamic conditions. This load was provided by a model of the human systemic circulation based upon the work of Sheperd et al (1966). Perfusate pressure and flow measurement were made from a point within the model which was equivalent to the aorta in clinical procedures. This position was selected due to the fact that it is possible in a clinical study to access the same position without requiring any additional surgical intervention. In this way, it is anticipated that results generated in the clinical environment will have a direct correlation with those obtained from the model circulation. Hydraulic power was computed from the pressure and flow signals and separated by Fourier analysis (McDonald, 1974) into its pulsatile and mean components. In this way, it was possible to describe the pulsatile nature of the flow pattern in dynamic terms (Wright, 1989). Hydraulic power delivery has been associated with the maintenance of capillary architecture during pulsatile blood flow perfusion (Taylor, 1986) and may be one of the factors associated with the maintenance of fluid balance and exchange during clinical perfusion (Prior et al, 1995). In addition to the assessment of hydraulic power delivery, the assessment of pulsatile blood flow architecture associated with the pump systems include an assessment of $dp/dt_{(max.)}$ and pulse amplitude. The $dp/dt_{(max.)}$ is

often cited as an important factor in terms of determining what constitutes physiological pulsatile blood flow. There is sparse evidence to support this initial rise in pressure in this regard. Runge et al (1992), however, points out that there may be some baroreceptors which are particularly responsive to this factor, and its potential role in instantaneous shear stress may indicate a role in NO associated vaso-activity (Hutcheson and Griffith, 1991). Pressure amplitude measurement is another factor which tells very little about the quality of the pulse delivery. It may, however, have a role to play in the maintenance of fluid balance and exchange at a capillary level (Prior et al, 1995, Prior et al, 1996). In addition, pressure amplitude has been employed as a method for assessing the pressure "damping" effect of arterial-line devices during CPB.

The results were interesting and appeared to confirm the superiority of the TPP system in terms of all factors studied. The TPP was associated with the generation of hydraulic power levels in the pulsatile domain well in excess of the roller pump. This difference reached a level in excess of 30 times greater under maximum levels of pulsatility. The output of both pumps was affected by the presence of the Affinity membrane oxygenator in the arterial line of the CPB circuit. This finding confirms that of an earlier study (Gourlay et al 1994) and a study by Wright et al (1988) in which this damping effect was noticed. The reduction in hydraulic power delivery is presumed to be due to the compliance of the membrane oxygenator together with the resistance of the fibre bundle. In both cases, the reduction in hydraulic power was substantial, but a discernible level of pulsatile hydraulic power was still present in the aorta of the circulatory model after exposure to the membrane oxygenator.

The assessment of pulse pressure showed a similar picture. The TPP pump was associated with greater pressure amplitude and $dp/dt_{(max.)}$ than the Stockert roller pump mechanism. The differences were statistically significant across the range studied. Both $dp/dt_{(max.)}$ and pressure amplitude showed a drop in magnitude with increasing run-time in both pump groups.

Both pumps were associated with highly predictable output architecture when presented with the controlled conditions of the systemic circulatory model. The TPP system exhibited greater pulsatile power than the roller system. The roller pump was capable of greater power output than that generated under the conditions normally employed in the clinical setting (Automatic = 80%, Run-Time = 50%) which offers some hope for improved clinical benefit from optimising the output profile of this system. The TPP, however, offers a higher pulsatile blood flow delivery capability in all aspects of this assessment. This is coupled with a high degree of output architecture control in terms of all factors studied. This increased power and high degree of control may offer significant advantages when the technology is applied clinically. During the pressure architecture tests, there was evidence of large transient negative pressure spikes when both systems were employed under optimum pulsatility conditions. The importance of these large negative pressure complexes (-300mmHg max. for the TPP and -80 for the Stockert) is not yet clear. The origin is unknown, but may be due to reflections from within the circuitry or from the recoil of the roller pump tubing in the case of the Stockert pump. The magnitude of the spikes associated with the TPP, in particular, is of considerable concern. One possible source for these large complexes is incompetent valves causing the large negative pressure generated during the fill cycle to be transmitted downstream of the pump head. This

phenomenon has been described before (Gourlay et al 1997) with the valveless Stockert system in combination with an arterial-line membrane oxygenator. It was believed to be associated with the negative phase transfer of gas across the membrane into the blood path causing streams of microbubbles in the arterial line. This factor will need to be investigated, together with an assessment of the impact of the increased hydraulic power of the TPP, with a view to determining a safe output profile range, prior to clinical study.

CHAPTER 7

IN-VITRO PRE-CLINICAL ASSESSMENT OF PULSATILE BLOOD FLOW SYSTEMS: HAEMATOLOGICAL AND SAFETY CONSIDERATIONS.

CHAPTER 7 IN-VITRO PRE-CLINICAL ASSESSMENT OF PULSATILE FLOW SYSTEMS: HAEMATOLOGICAL AND SAFETY CONSIDERATIONS.

7. 1 INTRODUCTION

The circuitry employed for extracorporeal circulatory support of the patient undergoing open heart surgery consists of three main components; the membrane lung, the blood reservoir and the pumping system. In addition to these main components, there are a number of ancillary devices that may be employed. These perform additional tasks, such as suction, filtration, and haemofiltration or dialysis. The addition of ancillary components or changes made to the fundamental components impacts upon the general safety of the system as a whole. Any such addition or alteration requires that the safety of the system as a whole be reassessed. Clearly, it would be unacceptable for a new technology to offer an advantage in terms of one aspect of performance if its use compromises the existing circuitry. Therefore, the issue of compatibility must be addressed prior to any clinical application.

Pulsatile flow systems have been associated with increased haemolysis and platelet depletion (Komoda et al, 1992). The factors influencing the overall level of haemolysis generated from a perfusion circuit are complex (Wright, 1986). Pulsatile blood flow is associated with momentarily very high blood flow rates, in some instances as high as 20 l/min. It is possible that such high blood flow rates may be associated with increased levels of haemolysis. Wright (1986) described the effect of shear stress on both haemolysis and platelet depletion, and suggested that pulsatile blood flow may influence their levels. The inclusion of a membrane oxygenator in the arterial line of a CPB circuit further complicates the fluid dynamic properties of the overall circuit. The complex fluid dynamic environment presented by the presence of the membrane may not be compatible with pulsatile blood flow, since the threshold of

haemolysis and platelet aggregation, in terms of shear stress, may be exceeded by the altered fluid patterns. In addition, it has been suggested that the presence of transient negative pressure "spikes", associated with pulsatile flow, may give rise to negative-phase gas transfer, where ventilating gas is drawn from the gas phase into the blood phase in the presence of negative pressure in the blood compartment, when used in combination with membrane oxygenators (Gourlay et al, 1994, Pearson 1986). This may lead to an increase in arterial-line microbubble load. Both haematological and microbubble factors potentially affect the quality of the perfusion delivered to the patient.

A series of in-vitro tests have been designed to assess the compatibility of both pumping systems with the other main circuitry components. The focus of these in-vitro, pre-clinical tests is blood compatibility, microbubble generation and energy transfer. Having established in Chapter 5 that the TPP offers better control of output architecture than the roller pump during in-vitro tests, the compatibility tests will enable a decision to be reached regarding whether the TPP is safe to employ in-vivo.

7.2 MATERIALS AND METHODS

7. 2.1 Generated Haemolysis and Platelet Depletion

In assessing the effects of the new pump on haemolysis and platelet depletion, comparisons were made with a conventional roller-pump operating in both the pulsatile and non-pulsatile modes. The circuitry employed for these tests (fig. 7.1) consisted of the test device, an open reservoir and PVC tubing.

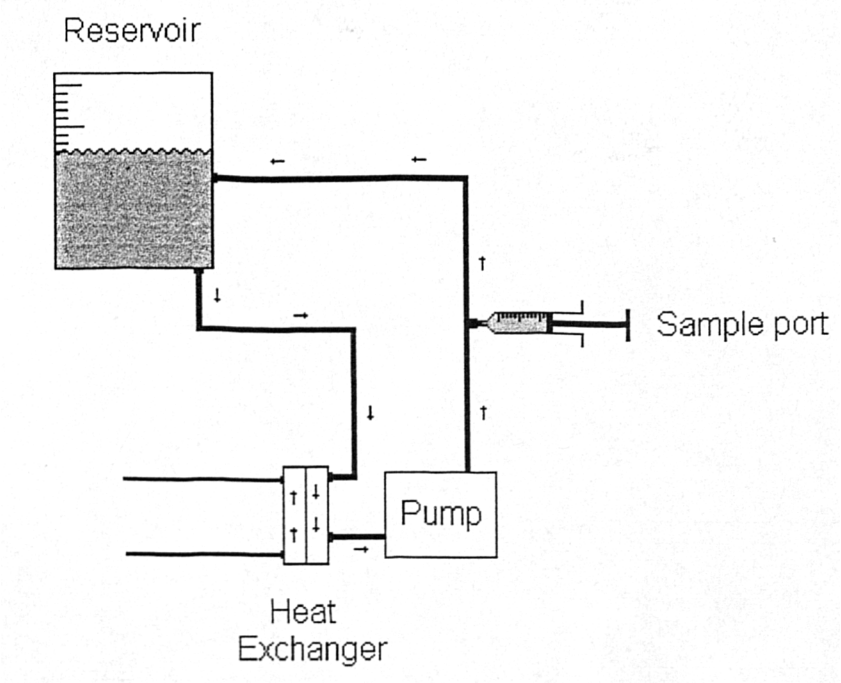


Figure 7.1 Test circuit for the assessment of generated plasma free haemoglobin and platelet depletion studies. The heat exchanger is in the circuit to maintain the circuit temperature at 37°C.

A pump output of 4.5 l/min was selected for the test procedure, since this reflects the average clinical flow rate at this centre. Fresh heparinised bovine blood was employed as the perfusate. The blood was used within 90 minutes of collection. Prior to use, the blood was diluted with Ringer's lactate to a haematocrit of 27% and filtered prior to use. Throughout the test procedure, the activated clotting time (ACT) was maintained in excess of 480 seconds by the addition of heparin and monitored with an ITC Hemochron ACT analyser. The test procedure was carried out at 37 degrees Celsius. The temperature was maintained by the inclusion of an in-line heat exchanger connected to a Sarns 3M High Flow heater/cooler unit. The circuit was primed with bovine blood and re-circulation commenced at 4.5 l/min for a period of 90 minutes. Blood samples (5ml) were taken at 0 and 90 minutes via a three-way stopcock positioned at the outlet of the reservoir. The reservoir was of a bottom-entry design which insured thorough mixing of the blood throughout the procedure.

1ml of each blood sample was placed into an EDTA tube for platelet count, the remainder was centrifuged at 2500 RPM (1500g) for 15 minutes using a Heraeus Christ centrifuge, and the plasma removed for plasma free haemoglobin levels. Platelet counts were performed manually (in duplicate) using Neubauer haemocytometer cells. Plasma free haemoglobin was measured using the spectrophotometric method described by Dacie (1975). The control for the test procedure consisted of a static sample of blood held in a water bath and gently agitated at 37 degrees Celsius for the duration of the test procedure. Correction for changes in control values were performed using simple subtraction in the following manner:

$$\Delta PlHb = PlHb_{(test)} - PlHb_{(control)}$$

$\Delta PlHb$ = Difference in plasma free haemoglobin.

This correction for control values was performed at each test point and the change in each generated value over the time period from the start (zero) time point was calculated. Generated plasma free haemoglobin was computed in the following manner:

$$GPlHb = \Delta PlHb - PlHb_{control(zero)}$$

Platelet depletion was expressed with reference to the static control in the same manner described for haemolysis. The depletion value was, however, expressed as a percentage of the baseline value.

The assessment of generated haemolysis and platelet depletion rate was repeated ten times for each of the following test groups:

Group 1. Pulsatile flow (TPP) at 30% symmetry.

Group 2.	Pulsatile flow (TPP) at 50% symmetry.
Group 3.	Pulsatile flow (TPP) at 70% symmetry.
Group 4.	Pulsatile flow (Roller) at 30% Run-time
Group 5.	Pulsatile flow (Roller) at 50% Run-time.
Group 6.	Pulsatile flow (Roller) at 70% Run-time.
Group 7.	Roller pump non-pulsatile (100% Run-time).

7. 2. 2 Microbubble generation.

The use of pulsatile blood flow for CPB has been associated with the generation of microbubbles (Pearson, 1986). There are several potential sources for these bubbles, including cavitation, displacement of trapped air from within the circuit and negative-phase gas transfer (Karichev et al, 1997; Gourlay et al, 1997). Negative-phase gas transfer may occur when blood is pulsed through a semi-porous membrane oxygenator at high flow rates and with rapidly varying pressure . Under these conditions, large transient negative pressure spikes may occur which may be substantial enough for ventilating gas to be drawn from the gas phase of the membrane oxygenator to the blood phase, and possibly to the patient. Although arterial-line filters have been designed to remove such a possibility, it is important to characterise this interaction and the magnitude of the problem prior to any clinical use. A performance profile for the pump in combination with a membrane oxygenator would be required prior to clinical evaluation. The performance profile should be compared with a standard pulsatile roller pump operating in both the pulsatile and non-pulsatile modes. Two oxygenators were employed for this assessment. Both were hollow-fibre and of polypropylene construction. One was designed for placement before (Avecor Affinity Membrane, Avecor Cardiovascular, Strathclyde, Scotland) and one for placement after (Terumo Capiox E Membrane, Terumo Corporation, Japan) the arterial pump. In the case of the Terumo oxygenator, blood flow through the oxygenator compartment is driven by gravity from the venous cannulation site. No pumps are involved in the propulsion of blood through the oxygenating compartment. Arterial blood is pumped from a reservoir positioned after the oxygenating

compartment to the patient by the pump. This type of configuration is thought not to be affected by a negative-phase gas transfer, since the generation of large negative pressure spikes in the oxygenation compartment is negated by the positioning of the device. However, the Avecor Affinity oxygenator is designed for conventional placement after the arterial pump and this offers the correct environment for the generation of a negative-phase gas transfer. The aim of this study was to assess the degree of microbubble generation associated with the two oxygenators with both pumping systems under controlled output conditions.

Fresh heparinised bovine blood was employed for all test procedures. A blood flow rate of 4.5 l/min was selected as being representative clinical flow rate. The three-component model of the systemic circulation (outlined in Chapter 5) was used to provide resistance and compliance conditions representative of the clinical setting. A bubble detector was connected to the circuit to monitor the degree of gaseous microembolic activity (GMA) in the arterial line. The system employed for this purpose was the Hatteland BD100. The analogue output on the bubble detector was connected via a DAS8 PGA A/D converter to a PC486 personal computer. The resultant signals were integrated and expressed as GMA activity by the software. The GMA activity is an index of the microbubble population passing the transducer. Its calculation involves frequency and bubble size data, using dynamic and BUD (bubble size distribution) outputs from the BD100 (Gourlay et al 1994). The output was updated every minute. For all microbubble tests, a bypass line was positioned around the membrane oxygenator (fig 7.2.(a) and (b)). This allowed the level of microbubble activity both with and without the oxygenator present in the circuit, to be assessed. This allows confirmation of the relationship between the pulse and the membrane in the generation of microbubbles.

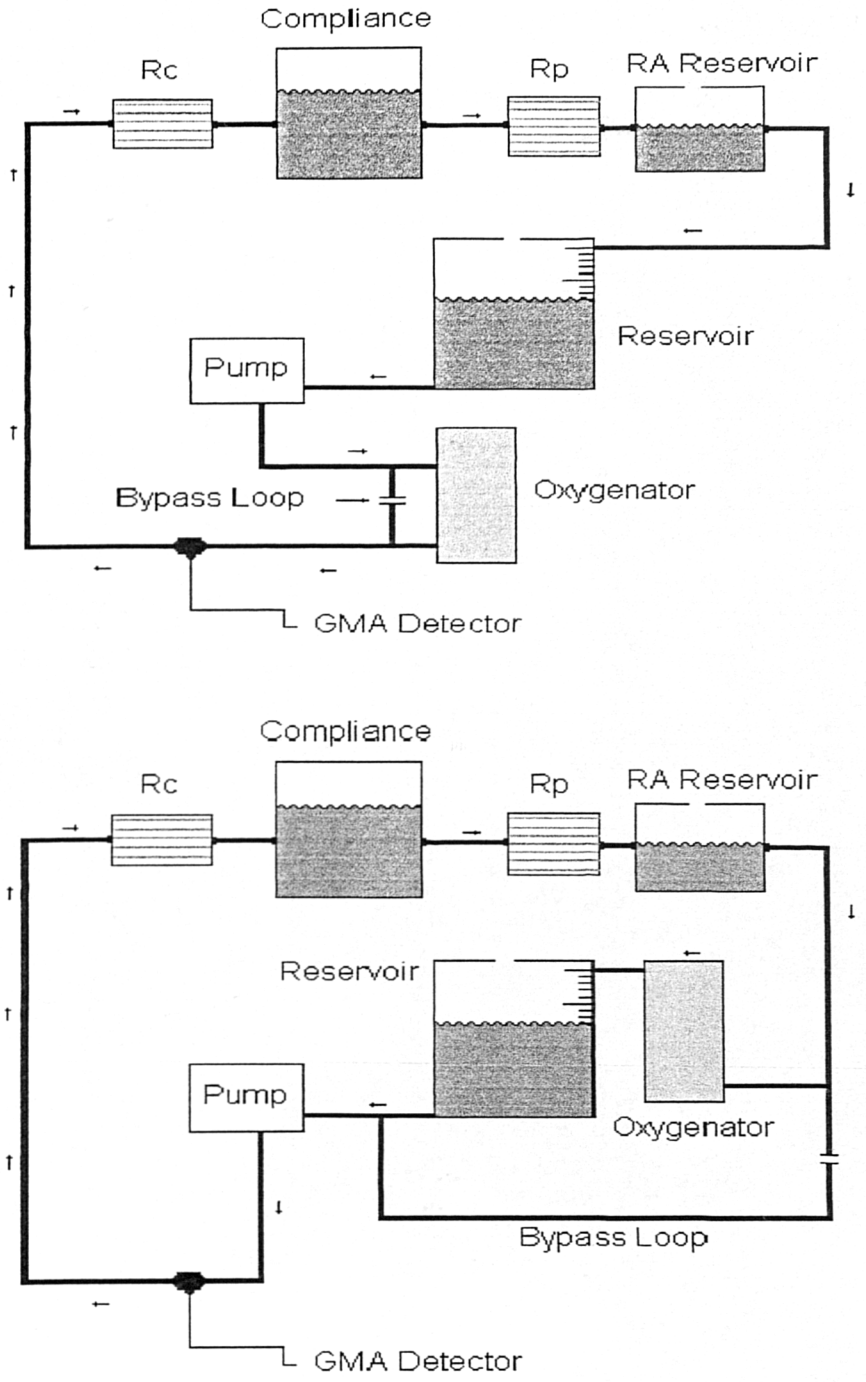


Figure 7.2 Circuit for assessing microbubble generation employing the Avecor oxygenator (a) and the Terumo oxygenator (b). The pump is positioned between the venous reservoir and the oxygenator when the Avecor oxygenator is used (a) and after the oxygenator when the Terumo oxygenator is used (b). A bypass loop around the oxygenator permits microbubble generation to be measured in the absence of the oxygenator. The GMA detector is positioned downstream of the oxygenator in both cases.

With the oxygenator in the circuit, the blood was pumped around the primed CPB circuit at the pre-selected output configuration for a period of 10 minutes. Thereafter, the membrane was excluded by opening the bypass line for a further period of 10 minutes. No ventilating gas was employed during these tests. GMA activity was measured throughout the test period. This process was repeated ten times on each of the following groups.

Group 1. TPP symmetry 70% with Affinity membrane.
TPP symmetry 50% with Affinity membrane.
TPP symmetry 30% with Affinity membrane

Group 2. TPP symmetry 70% with Terumo membrane.
TPP symmetry 50% with Terumo membrane.
TPP symmetry 30% with Terumo membrane.

Group 3. TPP symmetry 70% no membrane.
TPP symmetry 50% no membrane.
TPP symmetry 30% no membrane.

Group 4. Stockert pump 100% run-time with Affinity membrane.
Stockert pump 70% run-time with Affinity membrane.
Stockert pump 50% run-time with Affinity membrane.
Stockert pump 30% run-time with Affinity membrane.

Group 5. Stockert pump 100% run-time with Terumo membrane.
Stockert pump 70% run-time with Terumo membrane.
Stockert pump 50% run-time with Terumo membrane.
Stockert pump 30% run-time with Terumo membrane.
Stockert pump 100% run-time with Terumo membrane.

Group 6. Stockert pump 100% run-time with no membrane.
Stockert pump 70% run-time with no membrane.
Stockert pump 50% run-time with no membrane.
Stockert pump 30% run-time with no membrane.

A run-time of 100% with the Stockert pump represents non-pulsatile blood flow.

7. 2. 3 The effectiveness of arterial line filtration in removing gaseous microemboli produced from within the perfusion circuit.

It is common practice during open heart surgery to place a filtration device in the arterial line of the perfusion circuit. This filter is designed to perform two primary functions. Firstly, to remove and retain any particulate debris which may be present within the perfusate (such as platelet aggregates or surgical debris), and secondly, to remove gaseous microemboli. The filter is positioned between the membrane oxygenator and the patient to maximise protection. The effectiveness of these devices in removing gaseous microemboli has been well documented (Pearson et al, 1978, Gourlay et al, 1987, 1994) and have been shown to reduce post-operative mortality and morbidity (Braithwaite 1975, Taylor 1983).

Filtration efficiency was studied, employing similar circuitry to that detailed in section 7.2.1, and under similar conditions (fig 7.3)

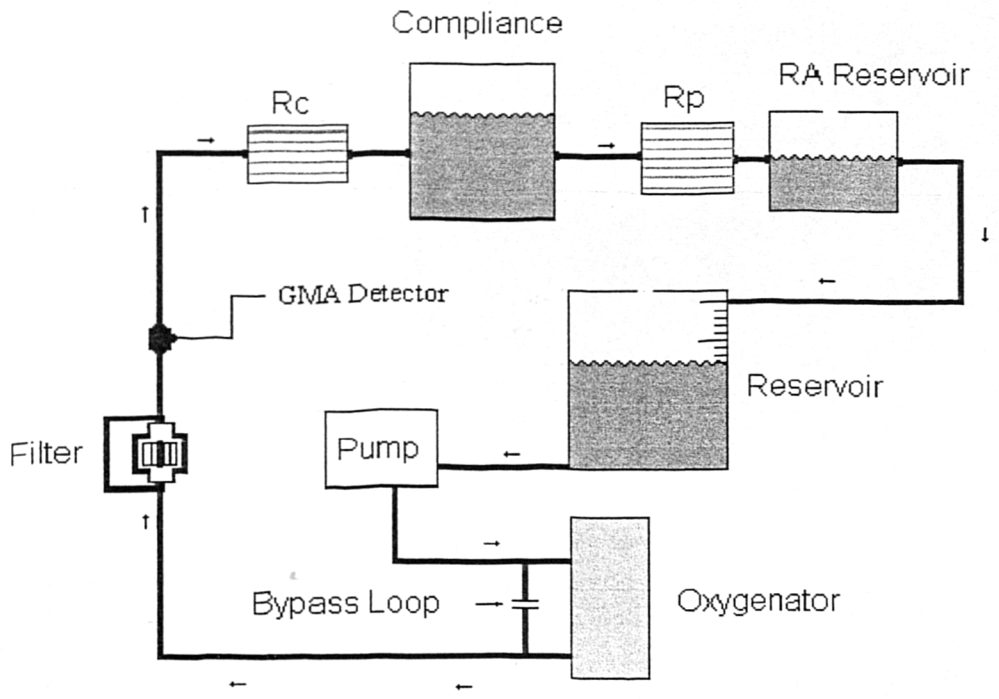


Figure 7.3 Circuit for assessing the microbubble removal characteristics of the EC+ arterial-line filter. The filter and its bypass loop can be seen in circuit with the GMA detector positioned downstream.

The addition of the arterial-line filter (Pall EC3840 with bypass line attached) being the only change. The filtered GMA activity was measured for 10 minutes with the oxygenator in-line, and for 10 minutes with the oxygenator excluded. Using the techniques outlined in Chapter 5, the effect of including the arterial-line filter on hydraulic power was also studied.

7.2.4 Statistical analysis

Statistical analysis of all data was carried out using STATA statistical analysis software (Stata Corporation, USA) reading from and writing to Microsoft Excel spreadsheets. The STATA package performed forward elimination multiple regression analysis with a level of significance of <0.05. This analysis method was applied due to its multi-factorial approach and the elimination of the need for multiple t-tests.

7. 3 RESULTS.

7. 3.1 Generated haemolysis and platelet depletion.

Generated plasma free haemoglobin levels associated with both pumping systems and at the various levels of symmetry (TPP) and run-time (Stockert) are shown in figure 7.4 and Table 7.1.

RUN-TIME/SYMMETRY	STOCKERT PUMP	TPP	P
30	41 ± 9.7 mg%	58.3 ± 6.2 mg%	< 0.01
50	38.2 ± 7.1 mg%	44 ± 8.3 mg%	NS
70	33.4 ± 8.3 mg%	40.7 ± 7.6 mg%	NS
100	24.16 ± 7.7 mg%		

Table 7.1 Generated haemolysis data for both pump systems at various output profiles.

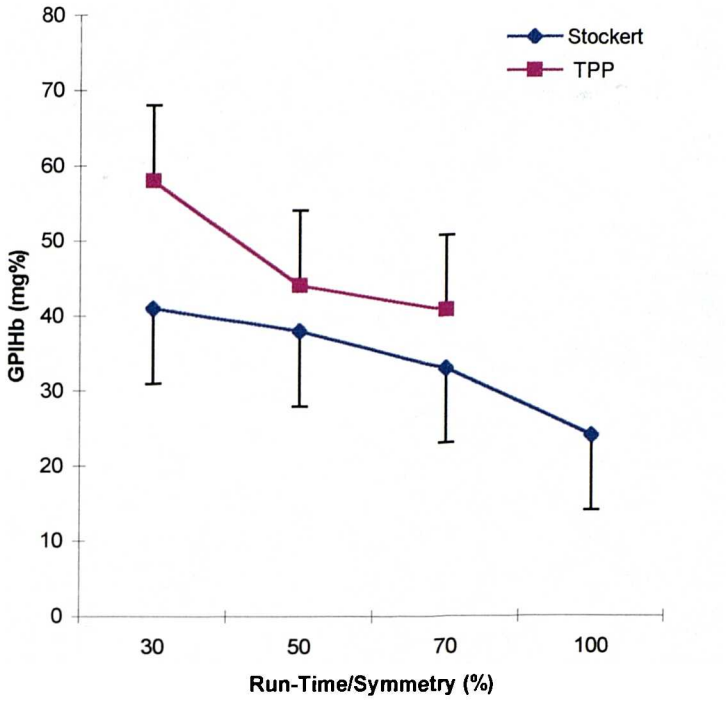


Figure 7.4 Generated haemolysis data for both pump systems at various output profiles. Results from in-vitro bovine blood studies at 4.5 l/min.

The differences in generated plasma free haemoglobin levels between the two pumping systems were found to be statistically significant ($p<0.01$) only at the shortest ejection times. The generated haemolysis decreased with increasing ejection time with both pumping systems and haemolysis and Run-time/Symmetry are strongly associated (R^2 (TPP) = 0.907, R^2 (Stockert) = 0.98).

There were no statistically significant differences encountered between the pumping systems with regard to generated platelet depletion (fig 7.5 and table 7.2).

RUN-TIME/SYMMETRY	STOCKERT PUMP	TPP	P
30	84.7 ± 16 %	83 ± 19.2 %	NS
50	85.3 ± 11 %	88.4 ± 13 %	NS
70	81 ± 9 %	86.1 ± 14 %	NS
100	87.1 ± 10.3 %		

Table 7.2 Platelet survival data from both pump systems at various output profiles.

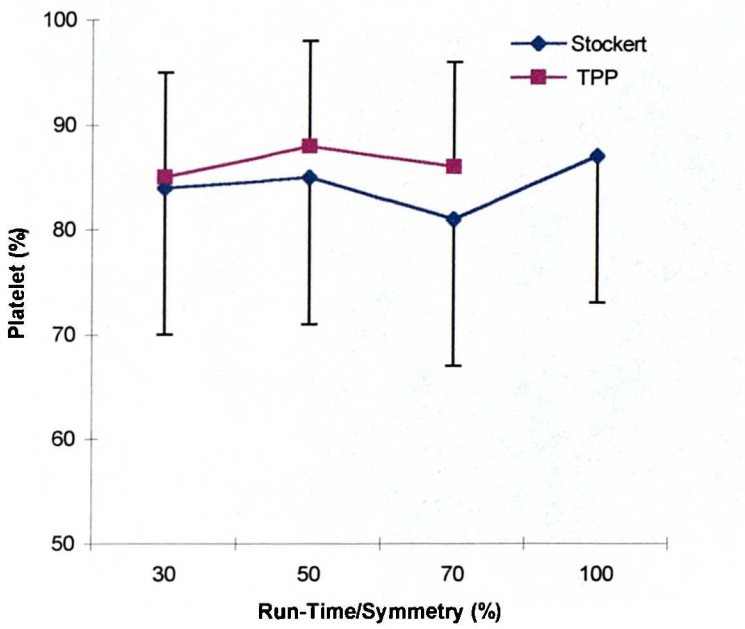


Figure 7.5 Platelet survival data from both pump systems at various output profiles. Results from in-vitro bovine blood studies at 4.5 l/min.

Platelet survival was relatively unaffected by changes in symmetry or run-time. No statistically significant differences were found between the pumping systems at any of the output profiles evaluated.

7.3.2 Microbubble generation

The microbubble emissions exhibited with both pumps reached a plateau within the first minute of introducing or removing the oxygenator, or when altering the output profile.(fig 7.6).

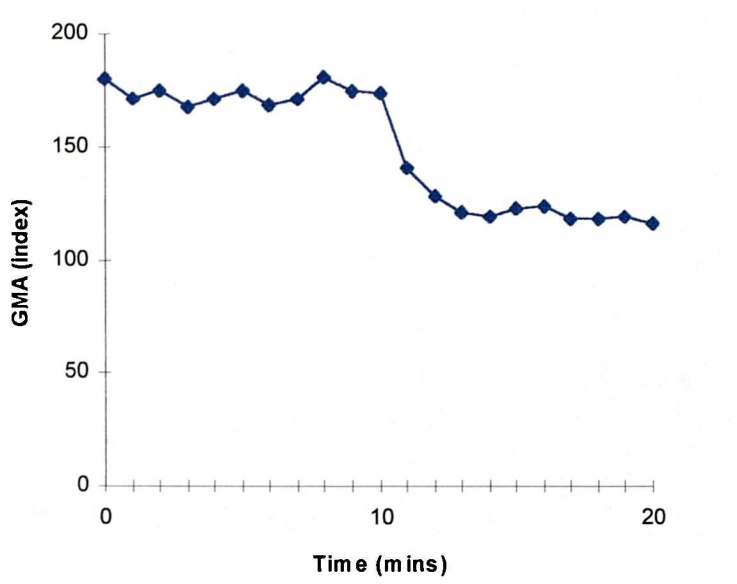


Figure 7.6 Gaseous Microembolic Activity (GMA) profile during a test involving a Stockert roller pump in the pulsatile mode. A blood flow rate of 4.5 l/min was employed with the Affinity membrane incorporated in the circuit for the first ten minutes and removed for the last ten minutes. The time of one minute to reach a plateau after the circuit change is typical.

The GMA activity profiles for the six study groups are shown in figures 7.7 - 7.9 and in table 7.3.

GROUP	30% RUN-TIME	50% RUN-TIME	70% RUN-TIME	100% RUN-TIME
1. TPP with Affinity.	273 ± 43 units/min	207 ± 32 units/min	173 ± 24 units/min	N/A
2. TPP with Terumo.	221 ± 31 units/min	197 ± 27 units/min	153 ± 26 units/min	N/A
3. TPP with no membrane.	209 ± 33 units/min	185 ± 31 units/min	133 ± 22 units/min	N/A
4. Stockert with Affinity.	174 ± 38 units/min	151 ± 24 units/min	130 ± 25 units/min	109 ± 19 units/min
5. Stockert with Terumo.	110 ± 14 units/min	107 ± 17 units/min	100 ± 17 units/min	107 ± 15 units/min
6. Stockert no membrane.	116 ± 19 units/min	101 ± 18 units/min	97 ± 19 units/min	102 ± 15 units/min

Table 7.3 GMA activity for both pumping systems at all output profiles. The activity is expressed as average index units per minute recorded over ten minutes during ten successive runs at each output setting

.

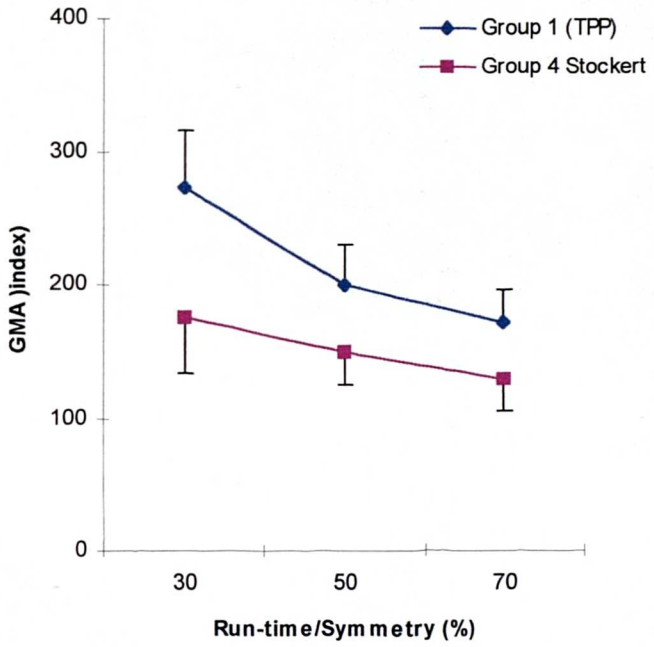


Figure 7.7 Gaseous microembolic activity (GMA) in group 1 (TPP pump) and group 4 (Stockert pump), both with the Affinity oxygenator in the circuit. Run-time/Symmetry levels were varied between 30 and 70% at a blood flow rate of 4.5 l/min. In addition, the Stockert pump was operated at a run-time of 100%, delivering non-pulsatile flow.

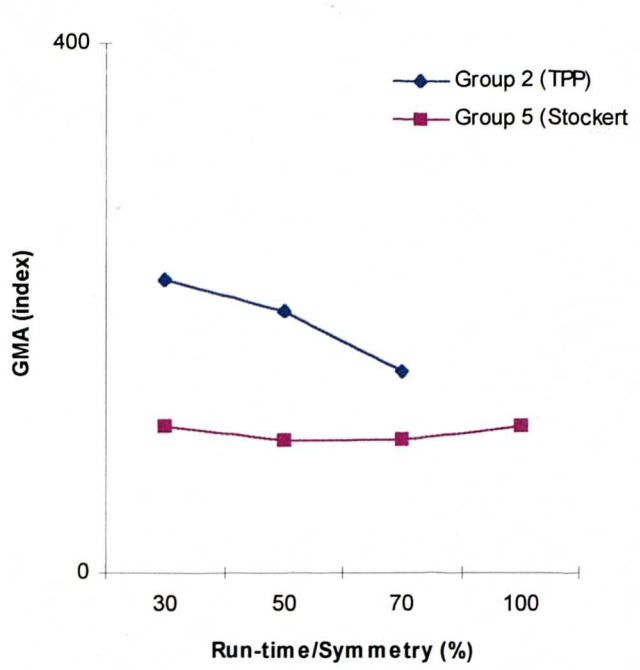


Figure 7.8 Gaseous microembolic activity (GMA) in group 2 (TPP pump) and group 5 (Stockert pump), both with the Terumo oxygenator in the circuit. Run-time/Symmetry levels were varied between 30 and 70% at a blood flow rate of 4.5 l/min. In addition, the Stockert pump was operated at a run-time of 100%, delivering non-pulsatile flow.

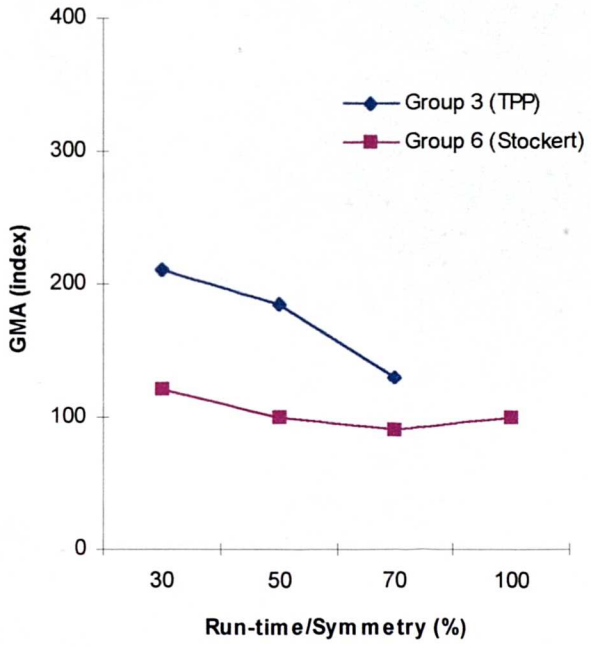


Figure 7.9 Gaseous microembolic activity (GMA) in group 3 (TPP pump) and group 6 (Stockert pump), both with no membrane in the circuit. Run-time/Symmetry levels were varied between 30 and 70% at a blood flow rate of 4.5 l/min. In addition, the Stockert pump was operated at a run-time of 100%, delivering non-pulsatile flow.

There was a clear relationship between ejection time and microbubble generation with both pumps in the presence of the Affinity membrane oxygenator. Microbubble generation was highest with the lowest or shortest ejection time. The differences were statistically significant within each group on comparison of the highest and lowest ejection times ($p<0.05$ for both pumps with the Affinity membrane). In the absence of the Affinity membrane oxygenator with the roller pump, there was no difference in microbubble generation with increasing ejection time (fig. 7.10).

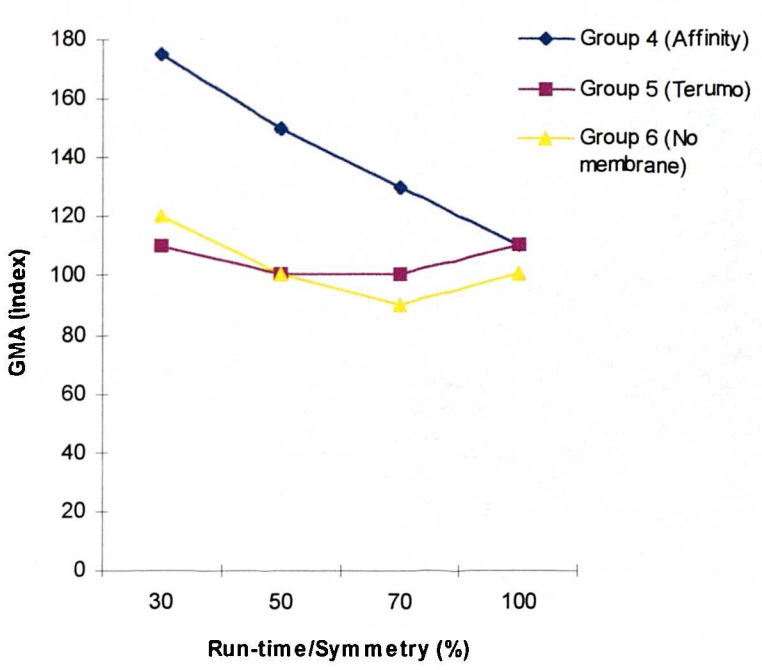


Figure 7.10 Gaseous microembolic activity profile associated with the Stockert roller pump in combination with the Affinity membrane (Group 4), the Terumo membrane (Group 5) and no membrane (Group 6). These tests were carried out with a blood flow rate of 4.5 l/min and variable run-time of between 30 and 100%

However, in the case of the TPP, the difference between the 30% and 70% ejection time groups in the absence of the membrane was statistically significant ($p<0.01$) This indicates that something other than the oxygenator was contributing to microbubble load (figure 7.11).

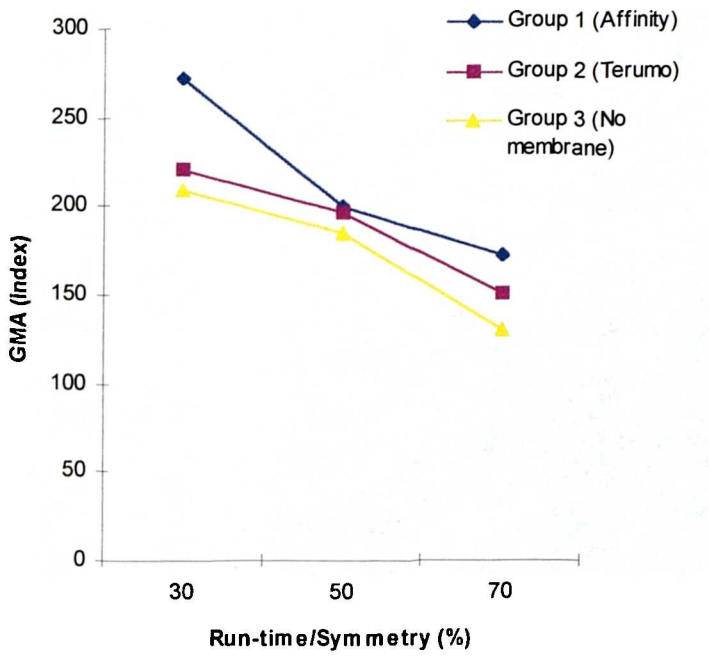


Figure 7.11 Gaseous microembolic activity profile associated with the TPP pump in combination with the Affinity membrane (Group 1), the Terumo membrane (Group 2) and no membrane (Group 3). These tests were carried out with a blood flow rate of 4.5 l/min and variable symmetry of between 30 and 100%

The Terumo oxygenator did not influence the GMA activity with either pump. The GMA activity level remained largely at the "no oxygenator" level. The TPP system exhibited a higher level of GMA with reducing ejection time, even in the absence of an arterial-line membrane oxygenator. It was associated with significantly higher levels of GMA at every output profile level and membrane combination compared to the Stockert Roller pump (maximum $p<0.01$).

Regression analysis of the GMA/Run-time data confirmed a relationship exists between GMA and run-time/symmetry. There was a strong relationship in all cases where an arterial-line membrane oxygenator (Affinity) was present (R^2 = 0.934 for TPP and 0.996 for Stockert pump). There was an extremely weak correlation between run-time and GMA in the roller pump group in the absence of the Affinity membrane or in the presence of the Terumo membrane (R^2 = 0.02 and 0.31 respectively). There was a strong correlation between GMA and run-time with the TPP even in the absence of a membrane (R^2 = 0.955). This would suggest that reducing the ejection time of the TPP system would result in an increase in the arterial-line GMA activity per se. However, this response was not dependent upon the presence of an oxygenator in the arterial line. In addition to assessing the GMA with each study group outlined, the GMA activity associated with each pump was also assessed with and without the Affinity membrane. This was performed by incrementally increasing blood flow rate at 30% run-time/symmetry (fig 7.12, 7.13).

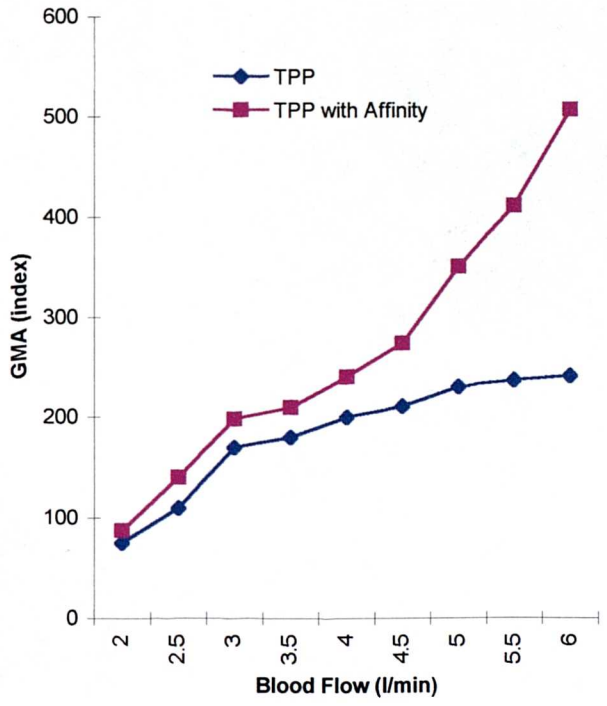


Figure 7.12 GMA profile for the TPP with and without the Affinity membrane at blood flow rates of between 2 and 6 l/min. This flow rate range was selected to reflect the clinical range.

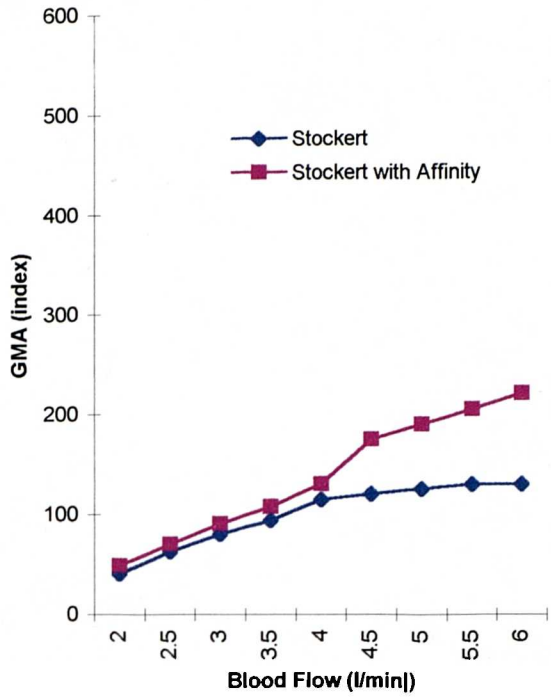


Figure 7.13 GMA profile for the Stockert roller pump with and without the Affinity membrane at blood flow rates of between 2 and 6 l/min. This flow rate range was selected to reflect the clinical range.

Increasing blood flow rate at the highest level of pulsatility had the effect of increasing the arterial-line microembolic load with both pumps. Blood flow and GMA were strongly correlated (R^2 = 0.96 for the TPP pump with the membrane in-line and R^2 = 0.98 for the Stockert pump under similar conditions).

Overall, the TPP system was associated with significantly higher GMA activity than the Stockert roller pump system. This was the case whether an oxygenator was present or not. It would appear that the TPP itself was generating microbubbles in the arterial line with reducing ejection time. However, the mechanism involved in this phenomenon remains undefined and must be considered if the device is to be used clinically.

7. 3.3 Arterial-line filtration of gaseous microbubbles during pulsatile flow.

The presence of the arterial-line filter had the effect of decreasing the microbubble count in the arterial line of the perfusion circuit under each of the test conditions described in section 6.2.2. The arterial-line filter maintained GMA at baseline levels irrespective of the presence of a membrane oxygenator or changing flow architecture (figs. 7.14, 7.15). Therefore, the filter was capable of reducing the circulating GMA associated with each of the pumping systems under all output conditions to a baseline level.

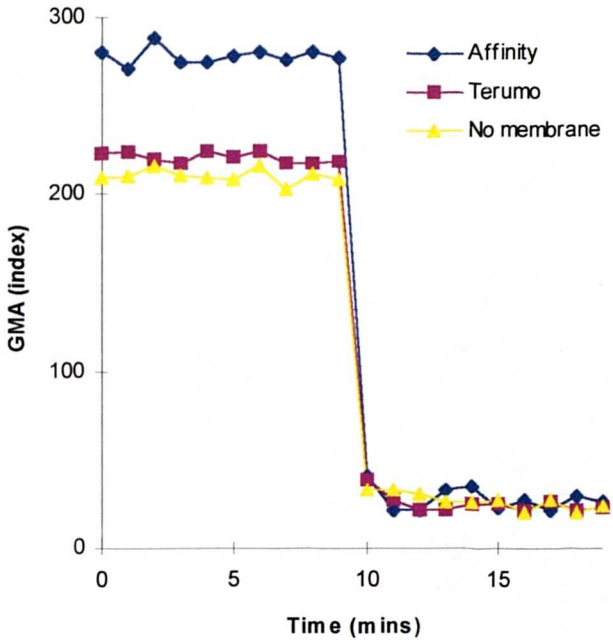


Figure 7.14 Effect on GMA in the arterial line of the perfusion circuit on the introduction of an arterial-line filter. Three combinations of devices are shown; the TPP with the Affinity, the Terumo and with no membrane oxygenator. There was no filter in the circuit for the first ten minutes and then the filter was introduced.

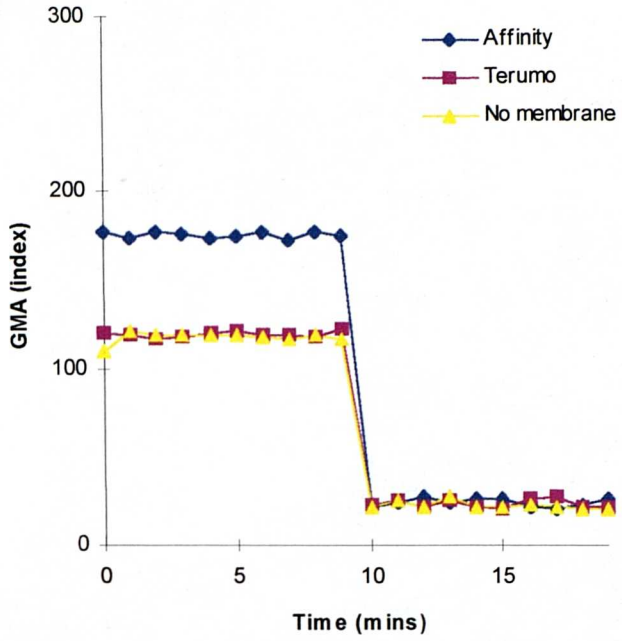


Figure 7.15 Effect on GMA in the arterial line of the perfusion circuit on the introduction of an arterial-line filter. Three combinations of devices are shown; the Stockert roller pump with the Affinity, with the Terumo and with no membrane oxygenator. There was no filter in the circuit for the first ten minutes and then the filter was introduced.

Using the TPP at low ejection times (50% and 30%), air was observed fluxing into and out of the EC+ filter. This did not occur with the roller pump in the presence of standard baseline flow rate of 20%. Removing the baseline flow during roller pump generated pulsatile flow did result in some degree of fluxing. This would indicate that this phenomenon may be associated with some form of inertial effect which is eliminated by incorporating a baseline flow. Fluxing with the TPP system was substantial at the 30% ejection time setting, although there was no evidence from the bubble detection system of increasing microbubble load. However, this process does present the possibility of air reaching the filtration cassette. An additional concern was prolonged use of the filter (in excess of 90 minutes) with the TPP system. It was found that the hydrophilic membrane (responsible for the air separation function of the filter) moved under extreme pulsatile flow conditions. This results in the membrane

adopting a pink coloration indicating that it may have been compromised. Further duration tests with pulsatile blood flow at high flow rates (5.5 l/min) resulted in blood foam emanating from the filter vent port. This mechanical breakdown of the important air separation section of the filter may present serious clinical implications.

7.3.4 The effect of an arterial line filter on hydraulic power delivery.

The presence of an arterial-line filter had no measurable effect on hydraulic power delivery under the most extreme flow conditions with either pumping system (figs. 7.16).

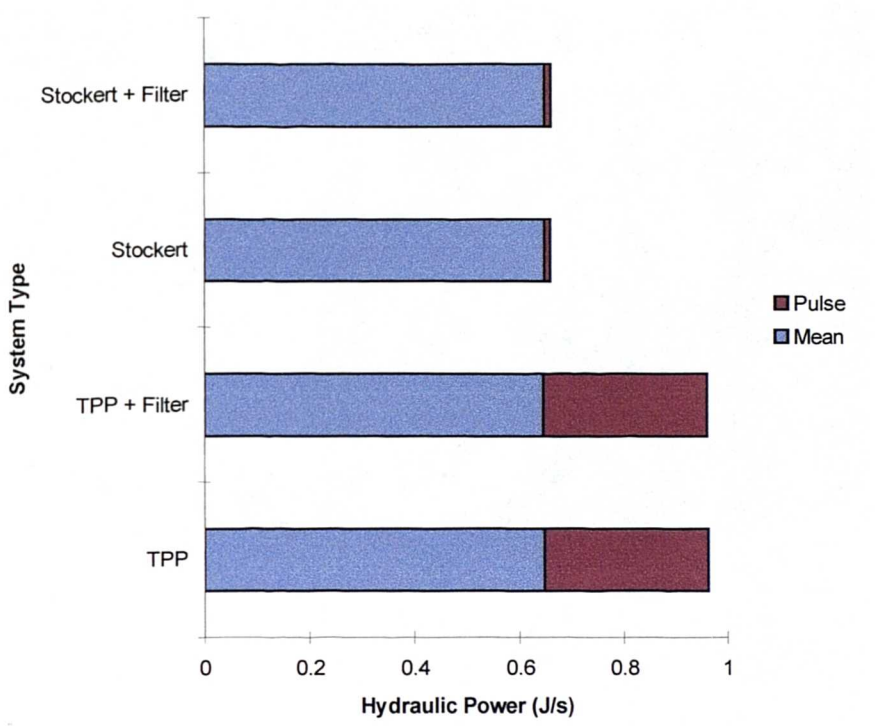


Figure 7.16 The effect of an arterial line-filter on the hydraulic power output of both pump types running at 30% run-time/symmetry and 4.5 l/min. The values shown are mean values, the standard deviations for all data sets were insignificantly small. There was no statistically significant difference between the level of hydraulic power generated with or without the filter in-line.

7.4 DISCUSSION

The aim of this study was to establish a safety profile for the TPP pumping system and to compare this to the conventional roller pump. In addition, the safety of the pump in combination with arterial-line filters and membrane oxygenators was investigated. In surveys of North American and British open heart centres, Kurusz et al (1986), Kurusz and Wheeldon (1990) and Kurusz, (1997) highlighted the relatively high incidence of accidents occurring during open heart surgery. Although most of these are not life threatening, a high proportion are directly attributable to the type of technology employed in extracorporeal perfusion circuits. Therefore, it is imperative that when a new technology is to be employed clinically, it is characterised properly and interactions between the new technology and existing circuitry components are fully determined.

The focus of this study is the flow architecture delivered by a new ventricular pulsatile pump (TPP). The areas where the new pump may have an impact on clinical safety were considered to be haemolysis generation, platelet depletion and microbubble generation. A series of in-vitro studies were designed to determine the impact of the TPP on these factors in the context of a complete CPB circuit.

. This study demonstrated that there was a relationship between the use of pulsatile blood flow and the generation of haemolysis. The level of haemolysis increased with increasing degree of pulsatility (decreasing ejection time) and may be a result of shear stress. Wright (1986) described the relationship between shear rate and the generation of haemolysis and concluded that under normal non-pulsatile flow conditions, haemolysis levels are of little consequence, provided cardiotomy suction is controlled.

However, it is possible under extreme pulsatile blood flow conditions (extremely short ejection time), using standard perfusion circuitry, that the threshold of shear relating to haemolysis generation will be exceeded. There was a statistically significant difference between the two pumping systems in terms of haemolysis only at the shortest ejection time, but this did not appear to be clinically significant. Despite the reported relationship between shear rate and platelet aggregation, there was no significant difference between the two systems in terms of this parameter.

Microbubble generation was found to be higher with the TPP system compared to the roller mechanism. This difference was found to be reduced in the presence of an arterial-line filter. which reduced the microembolic load to a level approaching the normal background count. This finding is in agreement with the work of Pearson et al. (1986) and Gourlay et al. (1997), who have both emphasised the importance of arterial-line filtration in general perfusion safety, specifically under microbubble challenge. The presence of the arterial-line filter did not reduce hydraulic power delivery under any of the pulsatile flow conditions. This is in agreement with Wright (1988) who obtained similar findings under similar conditions.

Overall, this series of in-vitro studies gave rise to considerable concern regarding the clinical application of the TPP. The pump was associated with greater microbubble generation than the roller pump. at all levels of pulsatility. Although microbubbles can be removed by the inclusion of an arterial-line filter, the filter showed some significant signs of mechanical strain under low ejection time conditions. However, this was not evident when the roller pump was employed. At

the lowest ejection times, the TPP was associated with a higher haemolysis generation ($p<0.01$). Although this is thought to be of little clinical significance, it must be closely monitored when clinical studies are undertaken. The concerns expressed regarding haemolysis and microbubble generation may render the pump unacceptable in the clinical context, without significant alterations to the clinical circuitry. The concerns regarding haemolysis and microbubble generation can be resolved to acceptable levels by limiting the output of the pump to high ejection times. However this may defeat the purpose of applying such advanced technology clinically. Limiting the range of output control available renders the TPP unacceptable as a device for clinical study. The concerns over the generation of haemolysis and gaseous microemboli remain to the extent that the performance of clinical studies with this pump system must be in doubt.

CHAPTER 8

CLINICAL STUDY OF CONTROLLED PULSATILE BLOOD FLOW ARCHITECTURE - PATIENTS AND METHODS

CHAPTER 8 : CLINICAL STUDY OF CONTROLLED PULSATILE BLOOD FLOW ARCHITECTURE PATIENTS AND METHODS.

8.1 INTRODUCTION

The previous chapters have outlined the technology available for generating pulsatile blood flow during clinical CPB. In Chapter 4, the two methods selected for this study were described in more detail. The Stockert pulsatile roller pump was selected because it was the basis of the early pulsatile blood flow studies by Taylor's group and because the roller mechanism remains the most widely used clinical pump system for either pulsatile or non-pulsatile perfusion. The second pump system selected was the TPP system which it was hoped, by virtue of its ventricular pumping action and high degree of output control, would offer a higher degree of pulsatile blood flow control during clinical use. Studies of the output profiles generated by both systems in an in-vitro model of the human systemic circulation (Chapter 6) confirmed the superiority of the TPP system over the Stockert pump in terms of pulsatile power output, and control and magnitude of the pressure in the model aorta. Based upon this finding, ethical committee approval was obtained from the Hammersmith Hospital Trust Ethics Committee for clinical studies to be carried out with the pump during routine open heart procedures. Prior to the onset of the clinical studies, however, assessment of the safety profile for the new pump in terms of microbubble generation and haemolysis was carried out in the laboratory (Chapter 7). The results of these studies caused some concern regarding the potential of the new device for microbubble generation when used both in combination with arterial line membrane oxygenators and in isolation. The magnitude of this microbubble response and the

non-compatibility of the pump with conventional arterial line filters which could reasonably be expected to reduce the microbubble threat to acceptable levels (Gourlay and Taylor, 1994(a), Pearson et al, 1981) led to the termination of the TPP study. This decision was taken with the safety of the patients in mind and with the hope that some form of solution to the microbubble generation problem with the TPP could be reached in the future. It was felt that the problem lay with the valving system which was found to be incompetent. Valve re-designing is underway and it is anticipated that a solution will be found. Further studies may be carried out once the function of the new valves has been validated.

The study of controlled pulsatile blood flow architecture was carried out using the Stockert roller pump alone. This limits the range of the clinical study, but it does not affect the aims or objectives in any way. From Chapter 6 of this thesis, it can be seen that the Stockert roller pump is capable of a considerable degree of output control. This manifested itself in an ability to control the architecture of blood flow and pressure in the aorta of the model of the human systemic circulation to a high degree. The two systems studied in these earlier chapters did not differ in terms of the degree of predictability of aortic flow and pressure architecture; the differences were in terms of the magnitude of the flow, pressure and power outputs. The aim of this clinical aspect of the thesis was limited to identifying any significant clinical benefits which may be associated with controlling the output architecture of the roller pump mechanism. Two aspects of output control of the pump were studied; ejection time and frequency.

The patients were allocated randomly (computer random number generator at the start of the study) to one of the four groups shown in table 8.1.

Group	Run-Time (%)	Automatic (%)	Frequency (bpm)
1	30	80	75
2	50	80	75
3	100	100	n/a
4	30	80	120

Table 8.1 Details of the four groups of patients studied and the various control values for the three parameters determining the output architecture of the Stockert roller pump.

The aim with these groups was to study what was established in Chapter 6 to be three clinically acceptable grades of pulsatility. The first group, having the lowest ejection time (30%), is the most pulsatile in that results in Chapter 6 indicate that this configuration maximises the dp/dt and amplitude of the pulse. The second group represents the standard clinical pulsatile output profile employed at the Hammersmith Hospital and the profile employed for all of the clinical studies of pulsatile blood flow carried out by Taylor's group. The third group is a non-pulsatile control group. Group four employs the maximum pulsatility profile with a higher output frequency. The frequency of 120 bpm is the highest frequency which can be employed with an ejection time of 30% whilst maintaining a blood flow rate of up to 5.0 l/min. A frequency higher than 120 bpm would limit the blood flow rate to unacceptably low levels. A baseline flow of 20% of mean (Automatic of 80%) was maintained in the pulsatile groups to limit the generation of negative flow at the aortic cannula. Laboratory studies have shown (Chapter 7 and Gourlay et al, 1994) that these output profiles are within the safety envelope of the Stockert system in terms of haemocompatibility and microbubble generation. This range of output settings covers the operational range of the pump system in terms of its major control parameters and

permits conclusions to be drawn as to the effect on the clinical model of controlling the output architecture of this particular pump system.

8.1.1 Patient groups

Forty eight patients undergoing elective coronary artery bypass surgery were randomly allocated to one of the four study groups shown in table 8.1. The pre-operative demographic data of the patient groups are shown in table 8.2.

Group	1	2	3	4
Number (n =)	12	12	12	12
Age	61.2 ± 9.9	56.6 ± 12.4	66 ± 6.32	60 ± 6.5
Height (m)	168 ± 9.02	174.4 ± 8.9	169.6 ± 13.4	166.8 ± 12.3
Weight (kg)	72.48 ± 6.9	80.2 ± 13.6	81 ± 6.1	77.6 ± 12.3
BSA (m^2)	1.77 ± 0.15	1.85 ± 0.09	1.86 ± 0.13	1.86 ± 0.09
Sex	100% male	100% male	100% male	100% male

Table 8.2 Pre-operative demographic data relating to the four patient groups undergoing study. All data are expressed as mean and standard deviation.

All patients were scheduled for routine coronary artery bypass grafting, patients requiring additional cardiac repair procedures were excluded from the study. In addition diabetic patients and those presenting with pre-operative coagulopathy were excluded from the study. In keeping with normal practice patients who are diabetic were excluded as were patients who had identified occult coronary artery disease, chronic arterial hypertension, existing vital organ insufficiency and patients with significant arterial disease.

There were no statistically significant differences between the patient groups in terms of the demographic parameters (using forward elimination multiple regression analysis).

8.1.2 Anaesthetic protocol

All patients had the same anaesthetic regime consisting of pre-medication with lorazepam (2mg oral) one hour prior to operation, induction of anaesthesia with fentanyl (10mg/kg), midazolam (1-4mg) and pancuronium (0.1mg/kg), and maintenance with propofol infusion (5-15ml/hour) and fentanyl (5mg/kg) as required. Radial artery and jugular vein catheters were inserted to facilitate pressure measurement and the administration of pharmacological agents. Nasopharyngeal temperature was measured throughout the procedure. Heparin (3mg/kg) was administered intravenously as the anticoagulant ten minutes prior to the onset of cardiopulmonary bypass. The activated clotting time (ACT) was monitored using a Hemocron ACT machine and additional doses of heparin were administered as required to maintain the ACT in excess of 480 seconds during the perfusion period. Ten minutes after the termination of bypass and after decannulation, protamine (6mg/kg) was administered to reverse the heparin induced anticoagulation. No nitrate therapy was administered before or during the CPB period. Blood pressure was controlled by adjusting the pump output alone.

8.1.3 Perfusion protocol

In all cases, the patients were cannulated using a single "super-pipe" (Sarns Corp. USA) right atrial cannulae and a 90 degree 8.0mm arterial cannulae (Sarns Corp. USA) positioned in the ascending aorta. The pump employed for the clinical study was the same as that employed in the earlier chapters, a Sorin Stockert roller pump (Sorin Biomedica, Midhurst, UK) with a Sorin Stockert PFC2 flow control unit. Half-inch internal diameter PVC arterial line pump tubing (Bard, West Sussex, UK) was connected to the patient by 2m of 3/8"ID PVC tubing (fig 8.1).

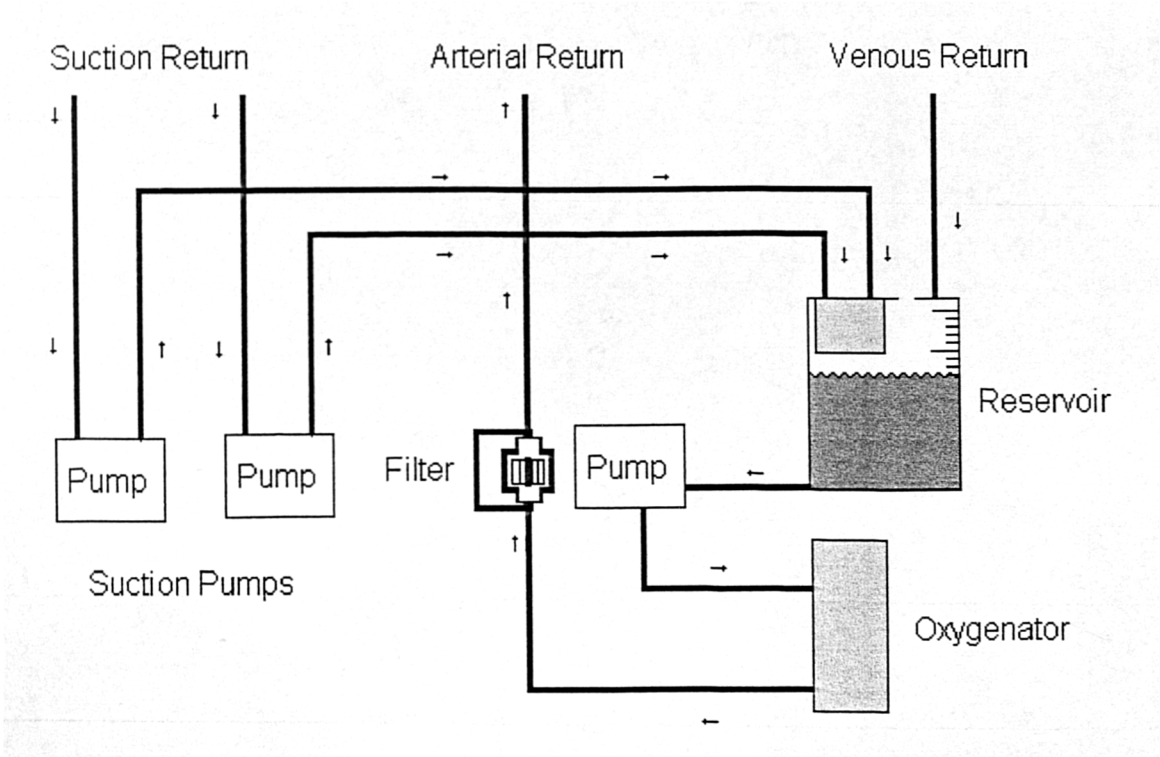


Figure 8.1 Circuit diagram of the CPB circuit employed in the clinical study of pulsatile blood flow architecture.

A Pall AV6 40 micron (Pall Biomedical, Portsmouth, UK) auto-venting arterial line filter was positioned between the Affinity membrane oxygenator and the patient. The perfusion circuit was primed with 1500ml Ringer's solution, into which was added 500ml Haemacel (Behring, Germany) and 25ml of 8.4% $NaHCO_3$. Once cardiopulmonary bypass was established, blood flow was initiated at a cardiac index of 2.4 l/min/m^2 and adjusted to maintain a mean arterial pressure of around 60 mmHg (measured in the radial artery). Temperature was allowed to drift during the CPB period to a minimum of 32°C and re-warming was initiated 5-10 minutes prior to the release of the aortic cross clamp. Myocardial protection was provided by crystalloid cardioplaegia using a modified St. Thomas's cardioplaegic solution delivered under pressure at 4°C into the aortic root.

8.1.4 Sampling protocol

The sampling protocol has been designed to comprehensively cover the major events which take place before, during and immediately after the CPB phase of cardiac surgery. In addition the recovery phase after the operation and into the intensive care period was monitored, with particular emphasis on outcome measures. The sampling protocol is shown in table 8.3.

In addition to the sample protocol shown in table 8.3, data were taken from the patient records from the ITU and ward, relating to a number of outcome measures.

Sample Number	Event
1	5' Post Induction.
2	5' Post Heparin administration.
3	5' On bypass.
4	15' On bypass.
5	5' Pre cross clamp removal.
6	10' Post cross clamp removal.
7	30' Post cross clamp removal.*
8	End of bypass. *
9	60 ' Post bypass.

Table 8.3 Sampling protocol used for all aspects of the clinical study. Sample points 7 and 8 may coincide depending on the number vein grafts carried out.

8.2 PARAMETERS STUDIED

A number of parameters were studied in these groups of patients. These encompassed haemodynamic, metabolic and output parameters. The emphasis of the study protocol related primarily to the CPB phase of the operative procedure, but the study continued, less intensively, through the immediate post-CPB period and into the intensive care period and beyond. It was anticipated that any advantage offered by controlling output architecture during the period of CPB would be identified by the parameters selected for study. These parameters are detailed in the following sections of this chapter. This study was carried out in addition to the normal routine clinical monitoring process which takes place during and after CPB. The only difference to the normal clinical course undergone by this group of patients was the change of flow regime. In all other respects the clinical course followed by these patients remained unaltered.

8.2.1 Haemodynamic factors

In addition to the normal clinical monitoring which accompanies CPB, a number of haemodynamic measurements were made on the patients involved in this clinical study. These included;

1. Measurement of Aortic Blood Flow.
2. Measurement of Aortic Pressure.
3. Calculation of Aortic $dp/dt_{(max.)}$.
4. Calculation of Aortic Pressure Amplitude.
5. Measurement of Hydraulic Power in the Aorta.
6. Calculation of Systemic Vascular Resistance.

The aim in employing these measurements was to characterise the pulsatile blood flow associated with the different study groups, and to assess whether it was possible to predict the output architecture associated with the pump under controlled clinical conditions. To perform these measurement tasks, a combination of existing and new technologies had to be employed.

8.2.1.1 Measurement of aortic blood flow

In most respects, the measurement of aortic blood flow is similar to that of measurement of fluid flow in the model of the systemic circulation detailed in Chapter 6. There are, however, some clear differences. The environment in which the measurement is performed presents several challenges not faced when carrying out flow measurements in-vitro. There are two main constraints involved in this process. Firstly, the measurement system must not interfere to any great extent with the

operative field, and secondly, the measurement process must not interfere with the normal performance of the operation. Ideally, the measurements should not involve the surgical team with the exception, perhaps, of positioning the transducer at the beginning of the operation. A number of methods are available for measuring blood flow, including ultrasonic and electromagnetic methods. Both of these are appropriate for measuring and assessing aortic blood flow dynamics. There are two primary methods of measuring blood flow using ultrasonics, transit time ultrasonic flowmetry and Doppler-shift ultrasonic flowmetry. The transit time method employs two diametrically opposed crystals which emit bursts of ultrasound in timed sequence. The blood flow is proportional to the time lapse between the transmission and reception of the burst of sound. Baker (1966) determined that the response of such a system is linear up to 180ml/s, but Gessner (1969) showed that the instrument was associated with large errors (up to 33%), related to the fact that such devices assess the average velocity across the vessel. The Doppler-shift method was first described in this regard by Franklin et al (1961) and employed the red blood cells as moving reflectors of ultrasound. Using the Doppler-shift principle such devices measure the shift in frequency between the transmitted and received signals to compute the velocity of the red blood cell. A simple calculation incorporating the vessel diameter and the velocity results in a good estimate of blood flow in the vessel. The electromagnetic system for measuring blood flow is described in Chapter 6. Having employed this technology for the measurement of blood flow in the model of the systemic circulation, it was considered to be reasonable to employ the same technology in the clinical setting. This should have eliminated any errors introduced by the application of new technology at this stage. Employing the electromagnetic flow measurement system in the aorta of

patients undergoing CPB is not without problems. The space available for applying the probe or transducer is limited by the presence of cannulae and other devices connected to the heart (fig 8.1). In addition, it is essential that the positioning of the probe does not interfere with the normal exposure required to perform the operation. A range of flow probes were available for this study covering a range of sizes from 19mm to 30mm in internal diameter. These probes were of a standard pattern used for animal research purposes (fig 8.2).

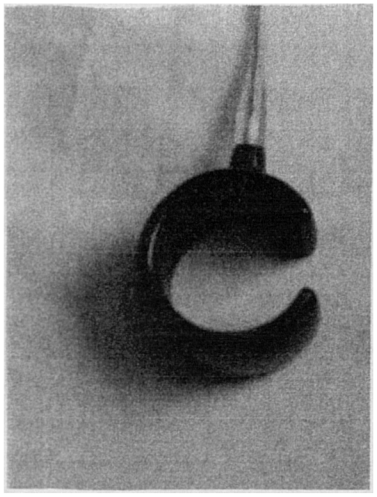


Figure 8.2 Blood flow probe of the type employed for animal and laboratory studies. This is a 28mm internal diameter probe intended for aortic blood flow measurement.

However, it was clear from a very early stage that the probes were not suitable for clinical application due to their overall dimensions and limited gate size. The large probe width made it impossible to apply the probe when the cannulae connecting the CPB system to the patient were in place. The anatomy of the aorta did not permit safe location of the probe safely anywhere along its length. In addition, the extremely

narrow gate of the flow probes made applying the probes a difficult and, some thought, risky task. Applying probes of this pattern requires that the aorta be compressed to around 4 mm in thickness in order that the aorta can pass through the gate in the probe structure. Some clinical staff felt that this could result in the release of atheromatus plaque from the interior of the aorta with potentially catastrophic results. This is an unacceptable additional risk to the patient. Since probes with a more acceptable pattern, and were compatible with the metering system, were not available commercially, the pattern of the existing probes had to be modified if aortic blood flow was to be measured. Two aspects of the existing probe design required alteration if they were to be acceptable, clinically. The gate or opening in the circumference of the probe would have to be widened, and the width of the probes would have to be made narrower. X-ray examination of the probes showed the internal structure quite clearly and indicated the extent to which the profile of the probes could be altered (fig. 8.3).

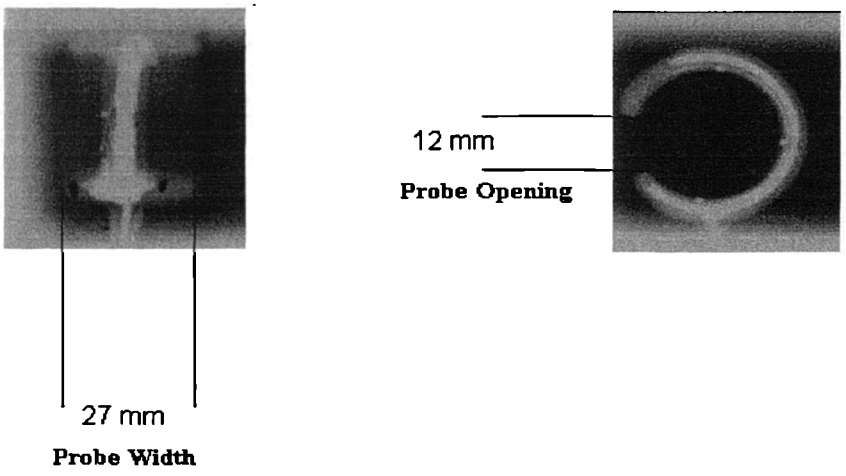


Figure 8.3 X-ray image if the probe structure. The internal structure can be clearly seen and the extent of the excess housing material can be identified.

The existing structure permitted major changes to be made to the probe profile. The gate was capable of being increased by 66% from 12mm to 20mm and the width reduced by 60% from 27mm to 11 mm (fig. 8.4).

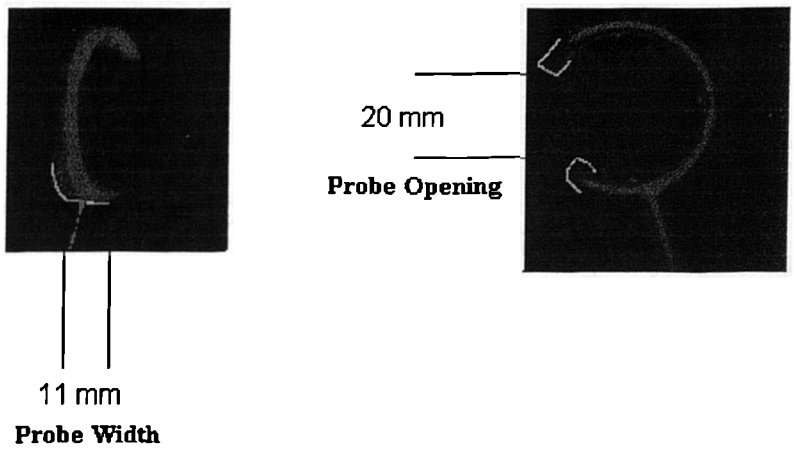


Figure 8.4 X-ray image of the probe shown in fig.8.2.1.1.2 after machining of both the width of the probe and the gate opening.

This result was achieved by machining the resin structure of the probe housing using the x-ray analysis as a guide. The width of the probe was reduced as much as possible, up to the limit of the internal mechanism. Similarly, gate width of the probe was machined up to the limit of the internal mechanism. The new probe pattern more closely met the requirements of the clinical team in terms of application (fig. 8.5), and was found under static and dynamic calibration (see Chapter 6.) not to differ from the original probe design in terms of performance.

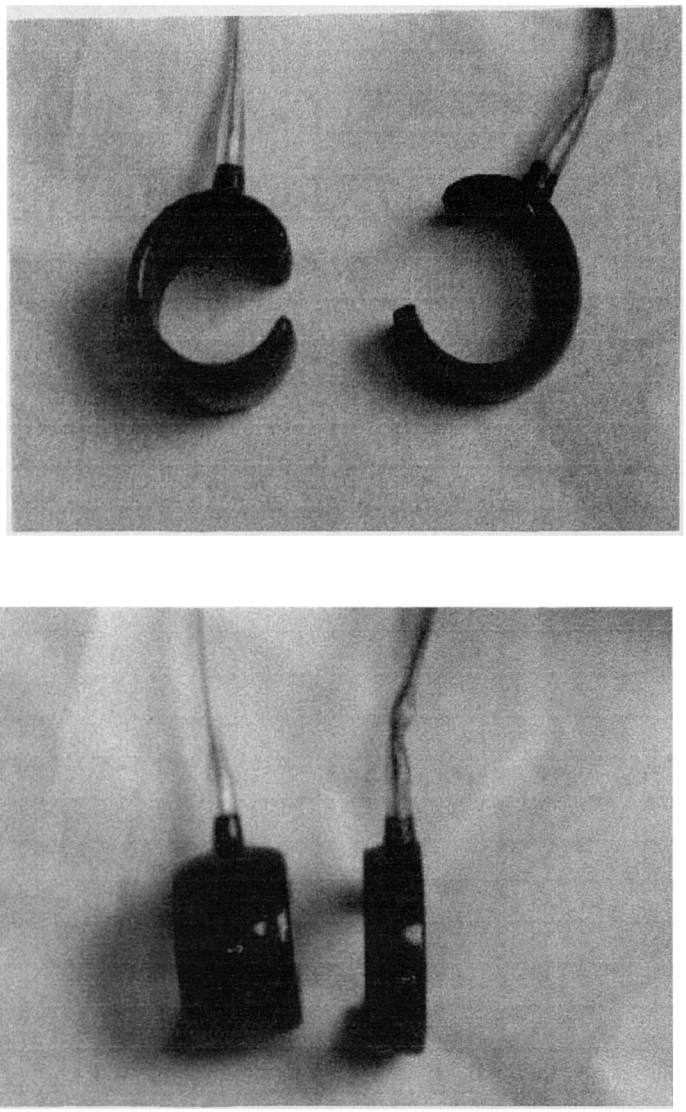


Figure 8.5 The new flow probe design showing the larger gate and the narrower probe profile when compared to the original design.

Since the re-designing did not appear to alter the performance of the flow probe, machining to the limits of the internal structure was performed on the range of probes intended for clinical application. This new probe structure facilitated easier application in the clinical setting and, therefore, permitted aortic blood flow to be measured throughout the CPB period. In clinical use, the probe was applied as far downstream

of the aortic cannulae as possible. There were two reasons for this, firstly to permit the maximum length of aorta between the cannulae and the flow probe to minimise inlet length effects, and secondly, to prevent the probe from having to be moved during application of the proximal ends of the vein grafts. Any substantial movement of the flow probe, which must have a restrictive fit when in place, results in the generation of artefact in the flow. Remote placement of the probe is, therefore, necessary if blood flow is to be measured accurately and without artefact.

When blood flow measurements were taken, the analogue output signal from the flowmeter was sent to a DAS8 PGA programmable gain-amplified analogue to digital converter housed in a portable 486 PC. The signals were processed by the laptop PC, running ASYST signal processing software. This system was similar to that employed for the in-vitro studies (Chapters 6 and 7) with the exception that the 486 PC computer was replaced with a laptop system which was easier to use in the confined space of the clinical setting. The sample rate of 250 Hz employed for the in-vitro was employed in the clinical setting.

The flow meter system was zero calibrated at the beginning and end of each clinical procedure. In addition, static calibration of the probe was carried out after each clinical procedure.

8.2.1.2 Aortic blood pressure measurement

Aortic blood pressure was measured using the Hellige system described in Chapter 6. The pressure was taken from a needle inserted into the aorta as close to the flow probe as possible. The pressure and flow take-off points should be as close as possible to reduce disparity when combining the signals when hydraulic power is being

computed. Any disparity associated with placement of the transducers can be rectified during the signal processing stage. In common with the flow signals, the analogue output from the Hellige pressure metering system was passed via the DAS8 A/D conversion board to the laptop PC where the resultant digital signals were processed by the ASYST software package. The pressure measuring system was calibrated every 15 minutes during the clinical procedure and any drift corrected.

8.2.1.3 Calculation of aortic $dp/dt_{(max.)}$

The maximum up-slope of the aortic pressure profile, $dp/dt_{(max.)}$ was calculated for each pressure complex recorded by the ASYST software package during the clinical CPB procedure. The value, which is returned as $mmHg.s^{-1}$, was then written to a Microsoft Excel spreadsheet, specific to the patient undergoing CPB, for future analysis.

8.2.1.4 Calculation of aortic pressure amplitude

The amplitude of the aortic pressure profile was calculated automatically by the ASYST software package as each complex was recorded. The resultant value was returned to a Microsoft Excel spreadsheet, specific to the patient undergoing CPB, for future analysis.

8.2.1.5 Calculation of hydraulic power

Wright and Furness (1985) suggested that enhanced hydraulic power delivery of pulsatile pump systems is the basis for the many clinical advantages associated with its use. Chapter 6 has confirmed that the roller pump mechanism which was employed in the clinical aspect of this thesis is capable of delivering various levels of hydraulic power depending upon the output control configuration employed. The clinical groups had been designed to reflect this effect. The methodology employed in calculating hydraulic power has been discussed in detail in Chapter 6. Hydraulic power calculation requires both flow and pressure signals taken from the aorta. The converted signals undergo a Fourier transformation and from this transformation the hydraulic power was computed in both the mean and pulsatile domains (see Chapter 6.). Prior to calculation of hydraulic power any shift in the time domain associated with the placement of the transducers was corrected by superimposition of the diastolic aspect of both complexes (Wright et al, 1988). The computed values were then exported to Microsoft Excel spreadsheets specific to the patient undergoing CPB, for future analysis.

8.2.1.6 Calculation of peripheral vascular resistance index (PVRI)

Many previous investigations have described a peripheral vascular response to the presence or absence of a pulse during CPB. Takeda (1960) described a rise in peripheral vascular resistance associated with non-pulsatile CPB. Taylor et al (1979) confirmed this and further investigation by his group showed that this response could be eliminated by employing pulsatile flow during the CPB period. They further

demonstrated that the rise in peripheral vascular resistance was not affected by mean pressure. They showed that the peripheral vascular resistance increased in two groups of patients perfused with non-pulsatile flow, one with a mean pressure of 50 mmHg and the other with a mean pressure of 70 mmHg. In the same study, they demonstrated that the rise in peripheral vascular resistance did not occur in a similar group of patients perfused with pulsatile flow at the lower mean pressure. Peripheral vascular resistance is expressed in index units and was calculated in the following manner;

$$PVRI = (MAP - MVP) / (Q/BSA)$$

PVRI = Peripheral Vascular Resistance Index
MAP = Mean Arterial Pressure (mmHg)
MVP = Mean Venous Pressure (mmHg)
Q = Blood flow (l/min)
BSA = Body Surface Area (m^2)

MAP and MVP measurements are taken from the radial artery and central venous pressure manometer sites, blood flow is the mean blood flow of the arterial pump and the BSA is taken from a nomogram derived from measured patient height and weight. PVRI is calculated from manually recorded data.

8.2.1.7 The effect of local vascular vasoactive substances.

The area of local vascular vasoactive substances and their role in the haemodynamic response to pulsatile and non-pulsatile CPB is currently the focus of much interest. This interest has focused on the many species of local vascular vasoactive substances. The role of the these vasoactive substances is not entirely clear, but their vasoactive effects have been well established. Some of these substances, prostacyclin and

angiotensin, have been discussed elsewhere in this thesis and have been the focus of many previous studies (Watkins et al, 1982, Taylor et al, 1979, Bretschneider et al, 1975). Many of these substances have been shown to have opposing vasoactive effects and play a part in a complex homeostatic control mechanism. One of the more recently established local vasoactive substances, Nitric Oxide (NO), has been the focus of study during clinical and experimental CPB. The haemodynamic disturbances exhibited by patients undergoing CPB have been well described. Pulsatile blood flow has been shown to reduce these unwanted effects. Previous studies have shown that angiotensin II and vasopressin are lower in patient's undergoing pulsatile CPB when compared to those undergoing non-pulsatile flow (Taylor et al, 1980, Levine et al, 1981). It has been shown that the endogenous vasodilator NO is sensitive to the presence of pulsatile blood flow (Pohl and Lamontagne, 1991, Hutcheson and Griffith, 1991). Mathie et al (1996) suggested, after clinical study, that there may be a mechanism whereby NO release contributes to the improved peripheral haemodynamics associated with pulsatile CPB. Hutcheson et al (1991) suggested that the effects of NO may be modulated by frequency and amplitude of the pulse, but these studies were carried out in a small animal model and have not been replicated clinically. Mathie et al (1996) were unable to confirm these findings in his clinical model, where only one model of pulsatility was used. It was anticipated that the patient groups available in this clinical study would help in the determination of the role of NO in the maintenance of improved peripheral haemodynamics.

NO was measured in plasma collected from the patients in accordance with the protocol detailed in fig. 8.2. The plasma was separated from the whole blood sample at the point of collection by refrigerated centrifugation, transferred to cryo-tubes and

placed into liquid nitrogen for transfer to a -80°C freezer for storage prior to assay. In the absence of an electrochemical probe specific for nitric oxide (NO) for clinical use, we utilised measurement of plasma nitrite (NO_2^-) and nitrate (NO_3^-) as an index of total NO activity in vivo. A Seivers (Seivers Inc. USA) nitric oxide analyser with ozone chemiluminescence detector was employed to determine the combined plasma concentration of NO_2^- and NO_3^- following thawing, deproteinisation with ethanol and reduction with vanadium III chloride in 1M hydrochloric acid (HCl) at 95°C. The machine was calibrated against known standard solutions before, during and after each experiment. The measurements were performed in duplicate on each plasma sample.

8.3 METABOLIC MEASUREMENTS

The metabolic response to CPB has been the focus of many studies over the last few decades. Tissue oxygen consumption and the development of acidosis have been used as indicators of the adequacy of tissue perfusion and the state of capillary blood flow (Jacobs et al, 1969, Shepard and Kirklin 1969, Dunn et al, 1974). Dunn et al showed that the development of tissue acidosis together with reduced oxygen consumption were both associated with non-pulsatile blood flow. Jacobs et al had earlier shown a similar response using a modified roller pump to deliver pulsatile blood flow. Taylor et al (1995) postulated that this acidotic response may well indicate poor tissue perfusion leading to poor metabolic function. Harken (1975) showed that increasing the blood flow rate to 110 ml/kg/min eliminated these unwanted effects. Blood flow rates of this magnitude are in excess of normal clinical blood flow rates (60 - 100ml/kg/min), and may not be possible to achieve without considerable blood cell

trauma with current technology. Since the metabolic disturbance has been shown to be reduced or even eliminated when pulsatile blood flow is used, this would seem to be a reasonable approach. Although pulsatile blood flow has, in most instances, been shown to maintain normal tissue metabolism during CPB, there have been some investigations which question this finding. Frater et al (1980) found that the presence of pulsatile blood flow during CPB had little or no influence on the metabolic response. No standard output architectural conditions were employed in these studies, and no detailed description of those employed were given. In this study we used tissue oxygen consumption as a marker of cell metabolism in the four flow groups. It was anticipated that the structure of these groups would enable the factors associated with improved tissue metabolism to be determined. Tissue oxygen consumption was assessed using blood samples taken from the venous and arterial circulation together with the blood flow rate taken from the arterial pump. Tissue oxygen consumption was calculated in the manner shown below ;

$$O_2C = (Q) \,.\, (VO_{2(arterial)} - VO_{2(venous)}) \times 0.01 \times \frac{0.1M}{}$$

Where ;

O_2C = Oxygen Consumption ($ml(STPD)min^{-1}$) per 100g body mass
Q = Blood flow ($ml.min^{-1}$)
$VO_{2(arterial)}$ = Arterial blood oxygen content per 100ml.
$VO_{2(venous)}$ = Venous blood oxygen content per 100 ml.
M = body mass (kg)

Where ;

$VO_{2(arterial)}$ = (Arterial O_2 saturation . 1.35 . Hb) + (0.00314 . PO_2)
$VO_{2(venous)}$ = (Venous O_2 saturation . 1.35 . Hb(gm%)) + (0.00314 . PO_2)

Where ;

O_2 saturation = Haemoglobin saturation fraction.
1.35 = ml O_2 at STPD which combine with 1g of haemoglobin.
Hb (gm%) = Grams of haemoglobin in 100ml of blood.
0.00314 = oxygen solubility in blood. (ml O^2 (STPD)/100ml.mmHg)
PO_2 = Blood oxygen partial pressure (mmHg)

The assessment of oxygen consumption was performed throughout the perfusion period and where possible, before and after the perfusion period when the blood flow rate was provided by the aortic flow sensor. The calculation of O_2 consumption was based upon measurements taken from venous and arterial blood samples drawn from the extracorporeal circuit. PO_2 and O_2 saturation were measured using an ABL III (Radiometer Ltd, Rickmansworth, UK) blood gas analyser and haemoglobin was measured by a Sysmex K100 automated haematology analyser (Sysmex UK Ltd., Milton Keynes, UK). Both systems were calibrated regularly with known standards.

8.4 ORGAN DAMAGE

Most major organs have been the focus of pulsatile blood flow studies. It has been shown, almost without exception, that these vital organs are affected by the presence or absence of a pulse during CPB. It was not within the scope of this study to investigate the effect of pulsatile flow on every major organ system. Therefore the focus of this aspect of the study was on one organ, the brain. There are many investigative techniques which have been employed in investigating cerebral events and dysfunction during and following CPB. Westaby et al (1996) pointed out that almost 70% of the brain is intellectually silent, making it difficult to detect defects of a sub-clinical nature with cognitive response studies (Breuer et al, 1983, Shaw et al,

1985). Despite this, Smith et al (1986) reported a high number of cerebral incidents associated with CPB. Sanderson et al (1972), using a dog model, demonstrated histological evidence of brain cell death associated with non-pulsatile CPB. In view of the difficulty in interpreting cognitive response data, a number of studies have been carried out focusing on biochemical markers of both brain function and injury associated with pulsatile and non-pulsatile CPB. These tests of function included response to thyrotrophin-releasing hormone (TRH), corticotrophin (ACTH) secretion and secretion of cortisol. Taylor et al (1981) showed that CKBB (creatine kinase B (B iso-enzyme)) was elevated in dogs perfused with non-pulsatile CPB, indicating some degree of cerebral injury. Clinically, cerebral function tests are difficult to perform. Therefore, a number of other methods for assessing the degree of cerebral injury, the end result of poor perfusion, have been developed. Westaby et al (1996) determined that the measurement of serum S-100 levels were an extremely promising marker for cerebral injury during CPB. The measurement of S-100 offers the advantage that it is present in serum and as such can be measured without sampling cerebro-spinal fluid (CSF), normally required for markers of cerebral injury (adenylate kinase, creatinine kinase BB,) (Aberg et al, 1982, Lundar and Storke 1983). S-100 is an acidic calcium binding protein found predominantly in the nervous system. The physiological role of S-100 is not fully understood, but raised S-100 levels have been shown to be associated with cerebrovascular disorders and to be present after cerebral infarction. Westaby et al (1996) showed that the magnitude of post-operative S-100 levels was associated with the length of CPB, and in one case, highly elevated levels were seen in a patient who had a profound intra-operative cerebrovascular incident. He concluded that S-100 leaks into the blood during CPB and reflects both the degree of cerebral

injury and the increased permeability of the blood brain barrier. The increased permeability of the blood brain barrier has been associated with the increase in cerebral oedema often seen in even apparently normal patients undergoing CPB (Gillinov et al, 1991, Harris et al, 1993). There remains no conclusive link between S-100 activity and clinical outcome, but this is currently being investigated.

S-100 protein is measured using an enzyme immunoassay technique. The kit (InRo/Medisera) is a double monoclonal-antibody enzyme immunoassay (sandwich - EIA). The methodology is relatively simple. Antibody directed against S-100, bound to the wells, react with S-100 in the samples. After washing, the antibody-S-100 complex remains on the plate. A second antibody, directed against the S-100, and conjugated with the enzyme beta-galactosidase reacts with the bound S-100. After washing the antibody-S-100-antibody-galatosidase complex remains on the plate. The enzyme is then released with glutathione (reduction) and reacts with the substrate o-nitrophenol-beta-galactoside to form a yellow coloured product, o-nitrophenol and clear galactose. The adsorbance is measured in a spectrophotometer at 410nm is proportional to the amount of S-100 in the sample. Comparison with standard solutions allows calculation of absolute values.

Measurement of S-100 was performed in serum taken from venous blood samples. The serum was stored in liquid nitrogen immediately after separation and transferred to a -80°C freezer for storage prior to assay. The blood samples were taken from all patients in accordance with the sample protocol shown in table 8.2.

8.5 HAEMATOLOGICAL MEASUREMENTS

Cardiopulmonary bypass has been associated with significant haematological disruption. The reasons for this are manifold and include the haemodilution which results from the use of crystalloid priming solutions and the disruption to cell and vital organ metabolism and function eluded to in earlier chapters. The haematological effects manifest themselves in several ways and involve all of the major blood cell groups.

8.5.1 Platelets, white blood cells and the inflammatory response

The activation of white blood cells during CPB has been well described and the various sources of this response identified. Despite this identification of several sources of cellular activation, this is one area of pathophysiology which remains generally poorly understood. This is particularly true of platelet and white cell responses to CPB. Activation of platelets and white cells is mediated by contact with the foreign surfaces of the CPB circuitry. This results in the formation of platelet and white cell aggregates which exert their pathological effects in two ways. Firstly, by blocking small vessels in the circulation (Blauth et al, 1986), causing local ischaemia and secondly by releasing the contents of their secretory granules into capillaries or interstitial space. The first of these pathologies was confirmed by Blauth et al (1986) using retinal angiography, which confirmed that there were small vessel occlusions present in all CPB patients studied. This confirms the magnitude of the problem. Other factors which have been shown to influence the activation and formation of microaggregates by these cell species is shear stress (Wright et al, 1986). They

determined that there is a threshold level of shear stress above which white cell and platelet activation takes place. The pathophysiological effects of activated white cells and platelets is important in the development of a number of post-operative disorders such as reperfusion injury in which the blockage of capillaries by microaggregates, coupled with the local ischaemia caused by the use of non-pulsatile blood flow during the CPB, promotes the correct environment for this undesirable development. The effect of pulsatile and non-pulsatile blood flow on platelets and white blood cells was assessed primarily by monitoring the cell population. In addition the active state of the white cells, specifically the neutrophils, was measured by assaying for Lactoferrin (LTF). LTF is a glycoprotein found in most body fluids and secretions. LTF in blood is secreted from neutrophils and its plasma concentration is positively related to the total pool of neutrophils and to the rate of neutrophil turnover. Under conditions of inflammation, LTF is released from secondary granules of neutrophilic leukocytes into the extracellular medium. The extracellular concentration of LTF, under these conditions, can be used as a marker of neutrophil activation (Lash, 1983). The assay method employed for LTF measurement is an enzyme-linked immunoassay (ELISA). A commercial assay kit supplied by Bioxytech was employed. Plasma was separated from blood samples collected in accordance with the sample protocol shown in table 8.3, i.e. under refrigerated centrifugation. Once separated, the plasma was transferred into cryo-tubes and placed in liquid nitrogen for transfer to a -80°C freezer for storage prior to assay. In addition to measuring LTF, tumour necrosis factor α (TNF-α) was employed as an indicator of the inflammatory response. TNF-α is a pro-inflammatory cytokine which has been, and continues to be, employed as an indicator of the inflammatory response. This major inflammatory mediator, which plays a critical role

in normal host resistance to infections serves as an immunostimulant and has been associated with white cell activation, with the reperfusion injury syndrome and has been shown to be moderated by a number of different perfusion techniques. Ito et al (1997) showed that TNF-α activity was positively associated with the development of respiratory distress syndrome after CPB and that TNF-α activity rose after the release of the aortic cross clamp, peaking well after CPB in these patients. TNF-α was measured using a commercially available quantitative sandwich enzyme immunoassay (R&D Systems, Abingdon, UK). The peripheral circulatory effects of maximising the pulse during CPB, may, have a beneficial effect upon those aspects of the inflammatory process related to peripheral ischaemia and reperfusion injury. The study of LTF and TNF-α was undertaken to indicate whether such a relationship exists.

In addition to blood samples taken for the LTF and TNF-α assays blood samples were taken at each sample point and stored in EDTA primed tubes for assessment of full blood count using a Sysmex K100 automatic haematology analyser.

8.5.2 Red blood cells

Red blood cells are susceptible to mechanical damage during CPB. Wright (1986) described the degree to which red blood cells are damaged by shear stresses during mechanical circulation. Pulsatile cardiopulmonary bypass, with increased peak blood flows and jetting of the blood stream in the aorta, may give rise to increased haemolysis. The level of haemolysis can be measured during the CPB by spectrophotometric assessment of plasma free haemoglobin (Dacie 1975). Using this technique, together with cell counts performed using an automated haematology analyser, enables the effect of various pulsatile blood flow profiles on blood cell

trauma to be monitored. More importantly, these haemolysis studies were used as a marker for mechanical trauma, enabling the study to be terminated if a particular profile is associated with an unacceptably high degree of haemolysis without waiting for evidence from further biochemical assays. Blood samples were taken in accordance with the sample protocol detailed in table 8.3 for the assessment of both haemolysis and red blood cell count. One aliquot of the blood was centrifuged and the plasma removed and stored in cryo-tubes in liquid nitrogen. The specimens were then transferred to a -80°C freezer for future analysis. Since excessive haemolysis is apparent on manual inspection of plasma specimens, extreme levels resulted in the immediate termination of the experimental procedure and the reversion to a less traumatic flow pattern (continuous flow or Hammersmith pattern pulsatile blood flow).

Red blood cell counts were assessed as part of the full blood count detailed in 8.5.1.

8.6 OUTCOME MEASUREMENTS

Outcome studies, though difficult to perform with any great accuracy, are perhaps the most profound measures of the effects of any new technology, or flow regime. Outcome studies relating to pulsatile and non-pulsatile CPB have been performed in the past (Gourlay et al, 1983, Taylor 1983) and have expressed significant differences between flow modalities in terms of a number of parameters. Gourlay et al (1983) showed a reduction in intra aortic balloon pump (IABP) usage associated with the use of pulsatile blood flow. In a larger study, Taylor et al (1983) demonstrated a reduction in IABP usage together with a reduction in the use of inotropes in the

postoperative period. Overall, these studies showed a reduction in both post-operative morbidity and mortality associated with the use of pulsatile blood flow. Outcome measures continue to be employed in CPB studies. Ortolano (1995) showed that the use of leukocyte depletion during the perfusion phase of cardiac surgery had a marked effect on postoperative lung function, and ITU and hospital stay. These factors may be affected by the flow architecture and this was monitored in this study. A number of factors were studied in this regard, including;

1. Intubation time.
2. ITU stay.
3. Hospital stay.
4. Blood use.
5. Urine output.
6. Inotrope usage.
7. Temperature.
8. IABP usage.
9. Fluid balance.

Using these factors, the clinical course of the patient groups and any effects relating to the flow modality employed was assessed throughout their stay in the hospital.

8.7 SUMMARY

A study protocol was designed to evaluate the effects of four blood flow modalities employed during CPB. The flow modalities were designed to permit the study of the effects of controlling the four primary factors relating to pulsatile flow architecture generated by the roller pump mechanism. The degree to which the roller mechanism facilitates control of these factors, amplitude, rise-time, ejection time and hydraulic

power, has been established in a previous chapter (Chapter 6.). Four groups of patients were studied in this regard, all of which were similar in terms all general pre-operative demographic factors (table 8.1). The parameters selected for study covered all of the major areas where advantages are perceived to exist in relation to pulsatile blood flow compared to non-pulsatile flow. These include, metabolic, haemodynamic, inflammatory and outcome factors.

CHAPTER 9

CLINICAL STUDY OF CONTROLLED PULSATILE BLOOD FLOW ARCHITECTURE - RESULTS AND DISCUSSION

CHAPTER 9. CLINICAL STUDY OF CONTROLLED PULSATILE BLOOD FLOW ARCHITECTURE -RESULTS AND DISCUSSION

9.1 THE PATIENT GROUPS

The study progressed without incident and all forty-eight patients were included in the study. The similarity between the study populations in terms of pre-operative demographic factors was shown in table 8.1 of the previous chapter. No female patients were studied, reflecting the difficulty in recruiting females in sufficient numbers during the period of this study. The percentage of males undergoing elective coronary artery bypass grafting in this unit during the year 1996-1997, the study period, was 77.2%, compared to 22.8% for females undergoing the same procedure. Due to the potential difficulty in producing a balanced study population within the time-scale of this study, it was decided that females would not be studied. Details of the number of grafts performed on these patients and other intra-operative factors are shown in table 9.1.

There were no statistically significant differences between the groups in terms of any of these operative parameters. The number of grafts in each of the groups are shown as median values and all patients recruited to the study received one internal mammary graft. The fact that all groups are similar in terms of the operative procedures performed is reflected in the similarity in bypass and cross clamp times. All patients were allowed to temperature drift towards a core temperature of between 32 and 34°C. The uniformity of this cooling process is represented by the similarity in mean minimum core temperature values in each of the study populations. All forty eight patients experienced a normal clinical course with no serious adverse events.

Group	1	2	3	4
Bypass Time (min)	72.8 ± 6.9	67.4 ± 6.7	68.6 ± 7.43	69.8 ± 4.14
Cross Clamp (min)	44.2 ± 11.3	39.6 ± 4.7	38.8 ± 10.8	37.8 ± 5.9
Flow Rate (l/min)	4.39 ± 0.42	4.4 ±0.65	4.16 ± 0.13	4.44 ± 0.43
Number of Grafts	2 + IMA	2 + IMA	2 + IMA	2 + IMA
Temperature Achieved on bypass (°C)	33.8 ± 0.27	33.75 ± 0.22	33.55 ± 0.40	33.35 ± 0.31

Table 9.1 Operative data for all four patient groups. The data shown represents the mean and standard deviation for each factor. IMA refers to internal mammary artery graft.

9.2 PULSE ARCHITECTURE

The result of the assessment of the pressure component of pulsatile architecture in the aorta of the patients is shown in table 9.2. These data are presented in the form of pressure amplitude, mean and $dp/dt_{(max.)}$ measured at three sample points. These sample points (3,5and 7), taken from the sampling protocol described in Chapter 8, represent the beginning, middle, and end of the perfusion period of the operation and were the maximum number of samples which could be taken without causing some degree of interruption to the operative procedure. It was not possible to gather pressure and flow data to coincide with other sample points as this would have necessitated requesting a "hands off" period too frequently during the operation. The number of samples taken therefore, was limited to those which could be gathered without undue interruption. This is reflected in the number of samples taken per

sample point (n value) in each group. The n value varies, reflecting the fact that it was not always possible to acquire a sample of pressure or flow.

	Group 1	Group 2	Group 3	Group 4
$dp/dt_{(max.)}$ ($mmHg.s^{-1}$) (3)	36.52 ± 10.33	55.26 ± 12.86	2.97 ± 0.92	93.53 ± 22.19
Amplitude (mmHg) (3)	14.61 ± 3.16	15.03 ± 3.11	3.06 ± 2.04	16.07 ± 2.94
Mean (mmHg) (3)	61.38 ± 4.42	58.77 ± 3.97	60.19 ± 4.02	58.33 ± 3.67
$dp/dt_{(max.)}$ ($mmHg.s^{-1}$) (5)	32.11 ± 8.26	60.42 ± 13.41	3.16 ± 0.66	78.67 ± 19.34
Amplitude (mmHg) (5)	12.84 ± 3.41	16.35 ± 2.24	2.31 ± 1.87	13.84 ± 2 01
Mean (mmHg) (5)	62.07 ± 4.97	60.11 ± 4.26	59.91 ± 4.39	62.87 ± 5.04
$dp/dt_{(max.)}$ ($mmHg.s^{-1}$) (7)	41.05 ± 9.17	68.87 ± 13.31	2.01 ± 1.13	81.44 ± 17.34
Amplitude (mmHg) (7)	16.72 ± 5.03	18.61 ± 4.07	2.77 ± 1.93	14.36 ± 2.87
Mean (mmHg) (7)	58.13 ± 4.48	60.16 ± 5.10	58.58 ± 5.01	59.11 ± 3.69

Table 9.2 Pressure architecture associated with each patient group. The values shown are mean and standard deviation for all measurements taken from the aorta of the subjects at the sample points 3,5 and 7. The number in brackets in the left hand column refers to the sample point. 12 determinations were made at each sample point.

There were quite considerable differences between the patient groups in terms of all of the factors selected to characterise pressure architecture, with the exception of the mean pressure. There were no statistically significant differences between any of the groups at any sample point in terms of mean pressure. Both $dp/dt_{(max.)}$ and amplitude increased with decreasing run-time, but only in $dp/dt_{(max.)}$ were the differences between these groups (1 and 2) statistically significant ($p<0.01$ max. at

sample point 5). Although the amplitude differences between groups 1 and 2 were consistent, with group 2 showing greater amplitude, they did not reach statistical significance. With the exception of sample 3, the high frequency group (group 4) showed the lowest amplitude, though once again there were no statistically significant differences between this and the other two pulsatile groups in this regard. The $dp/dt_{(max.)}$ was highest in this group, the differences being statistically significant at all sample points ($p<0.01$ max. at sample point 3). In all parameters except mean pressure, the non-pulsatile group differed from the pulsatile groups. It was associated with lower $dp/dt_{(max.)}$ and amplitude. All of these differences reached statistical significance (p value for all comparisons was <0.0001)

In addition to the pressure measurements taken from the aorta of the study subjects, the radial artery pressure was recorded during the procedures. The radial artery pressure was recorded and subjected to the same analysis as the aortic pressure. This was carried out in order that the effects of pulsatile flow, generated and assessed in the aorta, could be studied from a site further downstream and closer to the peripheral circulation where many of the effects of pulsatile blood flow are reported to be exhibited. These results are shown in table 9.3.

Analysis of the radial artery pressure architecture shows that, in all respects, it reflects the aortic profile. The amplitude at each of the sample points is slightly elevated in comparison with the aortic profile, and the mean pressure is slightly depressed. These changes are consistent, but not significant and are consistent with previously reported data (McDonald,1974).

	Group 1	Group 2	Group 3	Group 4
$dp/dt_{(max.)}$ ($mmHg.s^{-1}$) (3)	57.06 ± 18.22	71.85 ± 17.01	4.07 ± 3.38	119.17± 31.11
Amplitude (mmHg) (3)	20.48 ± 7.41	20.57 ± 4.81	5.01 ± 3.17	21.5 ± 6.45
Mean (mmHg) (3)	58.91 ± 3.81	54.42 ± 3.94	57.11 ± 2.83	53.78 ± 4.42
$dp/dt_{(max.)}$ ($mmHg.s^{-1}$) (5)	44.11 ± 8.89	82.32 ± 26.14	4.81 ± 1.77	109.82 ± 17.93
Amplitude (mmHg) (5)	17.66 ± 2.51	22.25 ± 4.52	3.76 ± 2.5	19.25 ± 3.27
Mean (mmHg) (5)	59.13 ± 5.59	57.79 ± 3.84	57.07 ± 5.54	60.17 ± 4.98
$dp/dt_{(max.)}$ ($mmHg.s^{-1}$) (7)	61.64 ± 7.53	98.07 ± 21.36	4.13 ± 2.21	122.2 ± 19.92
Amplitude (mmHg) (7)	24.64 ± 14.1	28.25 ± 2.87	3.51 ± 1.91	20.86 ± 4.08
Mean (mmHg) (7)	55.53 ± 3.34	56.05 ± 6.61	53.25 ± 4.88	55.07 ± 3.31

Table 9.3 Analysis of the output architecture of the radial artery pressure during the perfusion phase of the operation. The numbers in brackets in the left hand column refer to the sample points 3,5 and 7. 12 determinations were made at each sample point.

The results of the calculation of pulsatile and mean hydraulic power in the aorta of the subjects, using the method described in detail in Chapter 6, are shown in tables 9.4 and 9.5. Once again, these measurements were taken at sample points 3,5,and 7 of the sample protocol described in Chapter 8.

The number of patients in which flow measurements could be carried out was variable (see n values). This was due to a number of factors including inadequate probe fit or difficulty in positioning the probe sufficiently far from the aortic cannula to avoid the jetting effect at the exit from the cannula. Inadequate fit rendered the flow measurements useless due to the intermittent nature of the signal from the probe

under these conditions. Positioning the probe too near the cannula site resulted in the probe being swamped with signal noise. Under these conditions, if a sufficiently small probe was not available, or if the flow probe could not be re-positioned further downstream of the aortic cannula, the flow measurements were terminated. The pressure measurements could, however, be taken in these patients and are included in the pressure analysis data (table 9.2).

Sample Point	Group 1 Pulsatile Hydraulic Power (Js^{-1})	Group 2 Pulsatile Hydraulic Power (Js^{-1})	Group 3 Pulsatile Hydraulic Power (Js^{-1})	Group 4 Pulsatile Hydraulic Power (Js^{-1})
3	0.0041 ± 0.0007 n = 7	0.0054 ± 0.0003 n = 6	0.0000 n = 8	0.0049 ± 0.0007 n = 8
5	0.0050 ± 0.0009 n = 7	0.0061 ± 0.0006 n = 7	0.0000 n = 9	0.0063 ± 0.0009 n = 8
7	0.0054 ± 0.0006 n = 6	0.0063 ± 0.0005 n = 9	0.0000 n = 9	0.0071 ± 0.0008 n = 9

Table 9.4 Analysis of pulsatile hydraulic power in each patient group at the sample points 3,5,7. Pulsatile Hydraulic Power is calculated using the method described in Chapter 6.

Sample Point	Group 1 Mean Hydraulic Power (Js^{-1})	Group 2 Mean Hydraulic Power (Js^{-1})	Group 3 Mean Hydraulic Power (Js^{-1})	Group 4 Mean Hydraulic Power (Js^{-1})
3	0.5976 ± 0.066 n = 7	0.5879 ± 0.061 n = 6	0.6002 ± 0.072 n = 8	0.5916 ± 0.054 n = 8
5	0.5979 ± 0.053 n = 7	0.6005 ± 0.067 n = 7	0.5393 ± 0.049 n = 9	0.6119 ± 0.039 n = 8
7	0.5790 ± 0.049 n = 6	0.6023 ± 0.053 n = 5	0.5284 ± 0.037 n = 9	0.5934 ± 0.051 n = 9

Table 9.5 Mean hydraulic power measured at sample points 3,5 and 7.

Overall the mean hydraulic power levels were lower than one would have expected from normal, non-CPB patients. Wright et al (1986) reported significantly higher hydraulic power measurements in non-CPB patients. The reason for this lower than normal hydraulic power lies in the level of peripheral resistance exhibited by patients during CPB. Many previous studies in which the cardiac output was measured prior to the onset of CPB show a decrease in peripheral vascular resistance index (PVRI) once CPB has been initiated. The haemodilution caused by the priming solution certainly accounts for this to some extent. The haemodilution effect (fig 9.1) is quite substantial and this, together with lower than normal peripheral vascular resistance, may explain the lower than normal mean hydraulic power.

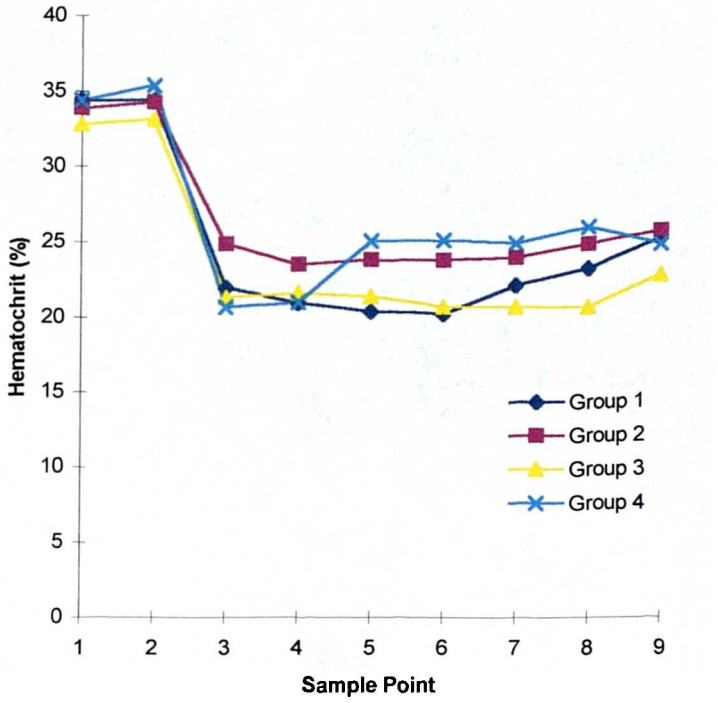


Figure 9.1 Haematocrit in all four groups. The effect of the CPB prime can be seen at sample point 3. Only the mean values are shown, the standard deviation for each sample point will be shown later in this chapter.

There were no significant differences between any of the pulsatile flow groups in terms of mean hydraulic power measurements at any of the sample points. The non-pulsatile group (Group 3) had a different profile. The hydraulic power level was lower in this group than in the other groups at sample points 5 and 7. This is almost certainly due to the reduction in blood flow at these points required to maintain the radial artery pressure at or around 60 mmHg (see Chapter 8) in this group of patients. This alteration in blood flow as a response to arterial pressure changes may be due to increased peripheral vascular resistance in this group of patients.

There were differences between the groups in terms of pulsatile hydraulic power. The non-pulsatile group exhibited a pulsatile hydraulic power level which was too low to measure accurately and a zero value was returned for the first 5 decimal places in this group at all sample points. The difference in pulsatile hydraulic power between the non-pulsatile flow group and all others was highly statistically significant ($p<0.00001$) and the non-pulsatile flow group was truly non-pulsatile in this regard. There were also differences between the pulsatile flow groups in terms of hydraulic power in the pulsatile domain. At sample point 3 there were no statistically significant differences between the pulsatile flow groups. However by sample point 5 significant differences develop. Both 30% run-time groups (groups 2 and 4) exhibit significantly higher pulsatile hydraulic power levels than group 1 subjects at sample point 5 ($p<0.05$). The significant difference persists at sample point 7 ($p<0.05$). There were no statistically significant differences between the 30% run-time groups at any sample point.

9.3 THE HAEMODYNAMIC RESPONSE

Although the systemic vascular response to pulsatile blood flow can be expressed in the measured architecture, there are a number of other factors which reflect this response. Two of these factors were measured in this study; peripheral vascular resistance index (PVRI) and nitric oxide secretion both of which are said to be responsive to or affected by the presence of pulsatile blood flow and the flow/pressure architecture (Hutcheson and Griffith 1991).

9.3.1 Peripheral vascular resistance index (PVRI).

The effect of the four flow modalities on PVRI can be seen from table 9.6 and figure 9.2.

Sample Point	Group 1 Peripheral Vascular Resistance Index	Group 2 Peripheral Vascular Resistance Index	Group 3 Peripheral Vascular Resistance Index	Group 4 Peripheral Vascular Resistance Index
3	12.05 ± 3.70	11.75 ± 2.98	13.01 ± 2.44	10.25 ± 3.30
4	12.95 ± 1.24	12.07 ± 2.44	15.25 ± 3.09	11.75 ± 2.21
5	13.04 ± 3.62	11.50 ± 3.10	16.25 ± 5.18	12.1 ±4.78
6	13.54 ± 1.59	11.75 ± 2.21	16.05 ± 4.99	13.01 ± 4.60
7	13.90 ± 1.74	11.75 ± 0.95	18.07 ± 3.65	12.04 ± 3.36
8	14.07 ± 2.16	13.75 ± 0.53	15.16 ± 1.91	12.75 ± 4.19

Table 9.6 Peripheral vascular resistance index (PVRI) for all four flow regimes during the CPB period. In all cases n = 12.

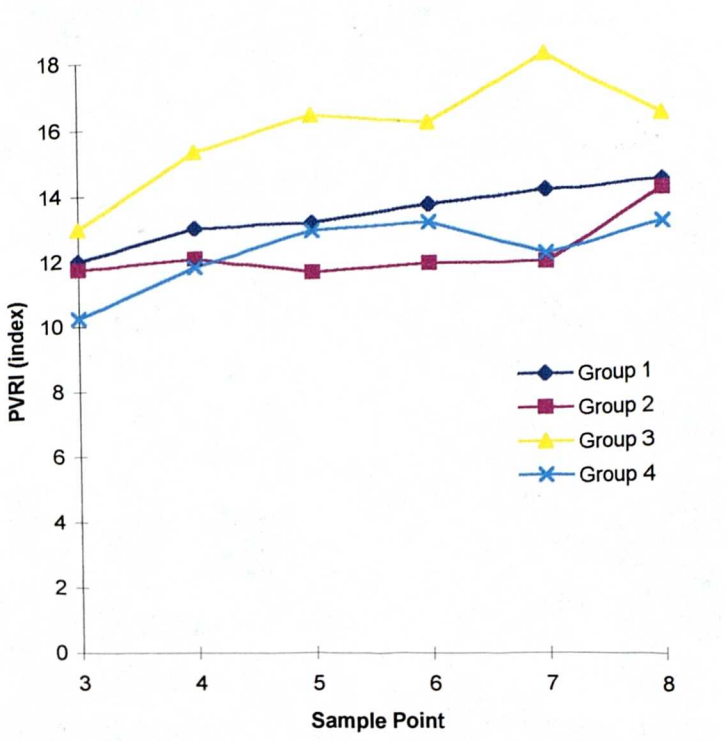


Figure 9.2 Peripheral vascular resistance index during CPB.

There were differences between the flow regimes in terms of PVRI. The three pulsatile flow groups showed little change in PVRI during the perfusion period. This contrasts with the non-pulsatile flow group which exhibited a rising profile throughout the perfusion period. There were no statistically significant differences between the pulsatile flow groups with regards to PVRI at any of the sample points. The comparison of pulsatile groups with the non-pulsatile group gave rise to statistically significant differences. At sample point 4, the difference between group 3 and the other groups was significant at the $p < 0.01$ level of significance. This rose to $p < 0.001$ at sample point 7 when comparing group 3 with group 2. At the end of the perfusion period the difference between the non-pulsatile group and all pulsatile groups remained significant ($p < 0.05$).

9.3.2 Nitric oxide (NO) Response.

The nitric oxide response to the four flow modalities as reflected by the measurement of plasma nitrate plus nitrite levels in blood, is shown in table 9.7 and in figure 9.3.

Sample Point	Group 1 Plasma Nitrate plus Nitrite ($\mu mol\ l^{-1}$)	Group 2 Plasma Nitrate plus Nitrite ($\mu mol\ l^{-1}$)	Group 3 Plasma Nitrate plus Nitrite ($\mu mol\ l^{-1}$)	Group 4 Plasma Nitrate plus Nitrite ($\mu mol\ l^{-1}$)
1	22.23 ± 4.06	22.6 ± 5.27	24.33 ± 4.07	18.32 ± 5.81
3	24.13 ± 4.95	17.25 ± 4.58	41.51 ± 7.41	8.25 ± 3.77
5	25.86 ± 3.36	24.21 ± 4.50	40.95 ± 5.12	6.75 ± 3.58
7	22.8 2 ± 3.40	23.36 ± 4.51	45.25 ± 6.33	12.5 1± 6.11
9	20.33 ± 3.21	19.5 ± 4.70	48.75 ± 4.95	7.95 ± 3.28

Table 9.7 Plasma nitrate plus nitrite for all four flow modalities, corrected for haemodilution. The results are expressed as mean and standard deviation and n = 12 in all groups.

There were differences between the groups with regard to nitric oxide production. There were three clear profiles. Groups 1 and 2 showed very little change in NO production throughout the operative period. Group 4 (the high frequency, 30% run-time group) showed a fall in NO levels over the early part of the procedure, followed by a rise back to baseline levels towards the end of the operation and into the post-bypass period. The differences between group 4 and the other pulsatile flow groups (1,2) were significant ($p < 0.01$) at all sample points with the exception of sample point 1 (post-induction) where there was no statistically significant difference. The

differences between group 3 (non-pulsatile) and all other groups were statistically significant at all sample points except sample point 1 at which there were no significant differences. The level of significance varied from $p < 0.01$ at sample point 2 comparing group 3 with group 1 and $p < 0.0001$ at sample point 9, comparing group 3 with group 4. Groups 1 and 2 did not differ significantly at any sample point.

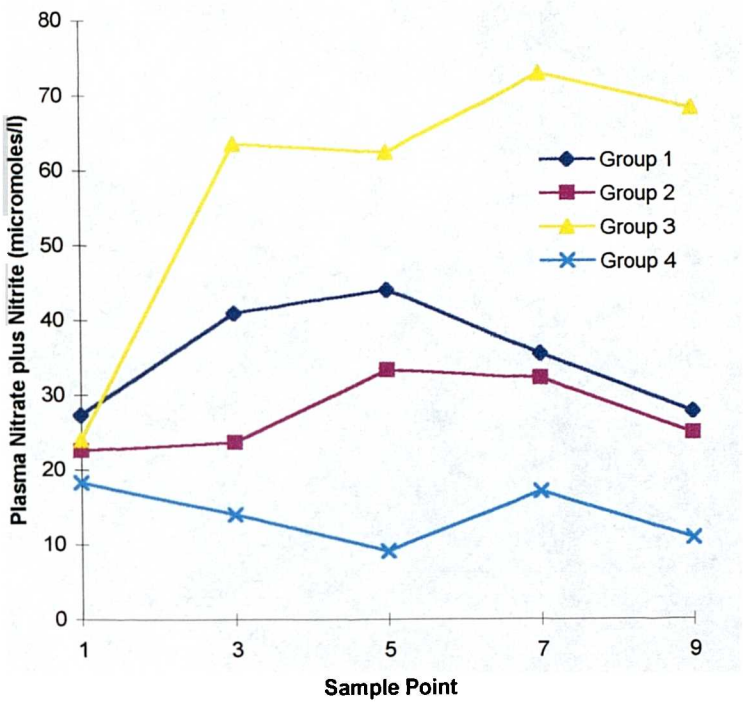


Figure 9.3 Plasma nitrate plus nitrite for all four groups. These results are corrected for haemodilution and show only mean results (SD in table 9.7), but there are clearly different profiles exhibited.

The three profiles exhibited were clearly quite specific to the groups and at first glance appeared to be associated with frequency. The high frequency group (4) had the lowest NO levels during the procedure, the lowest frequency group (3) had the highest NO levels and the intermediate frequency groups (1,2) exhibited very little change in NO production throughout the operative period. This finding is in contrast

to that of Hucheson and Griffith (1991) who found that NO production increased with increasing frequency and amplitude.

9.4 OXYGEN CONSUMPTION

Oxygen consumption has often been employed as a marker for the adequacy of perfusion during CPB, and increased oxygen consumption, indicating improved tissue perfusion, has been cited as one benefit of pulsatile CPB. Oxygen consumption was measured in the four patient groups throughout the perfusion period of the operation and the results are shown in table 9.8 and figure 9.4.

Sample Point	Group 1 Oxygen Consumption (ml/min/100g body mass)	Group 2 Oxygen Consumption (ml/min/100g body mass)	Group 3 Oxygen Consumption (ml/min/100g body mass)	Group 4 Oxygen Consumption (ml/min/100g body mass)
3	0.423 ± 0.071	0.386 ± 0.051	0.390 ± 0.088	0.421 ± 0.091
4	0.478 ± 0.091	0.377 ± 0.069	0.359 ± 0.091	0.493 ± 0.091
5	0.440 ± 0.037	0.388 ± 0.080	0.336 ±0.083	0.502 ± 0.088
6	0.441 ± 0.077	0.387 ± 0.057	0.352 ± 0.081	0.502 ± 0.070
7	0.488 ± 0.023	0.415 ± 0.061	0.341 ± 0.069	0.530 ± 0.075
8	0.522 ± 0.037	0.446 ± 0.065	0.349 ± 0.066	0.589 ± 0.073

Table 9.8 Total oxygen consumption for all four patient groups. The results are expressed as mean and standard deviation and n = 12 for each sample point.

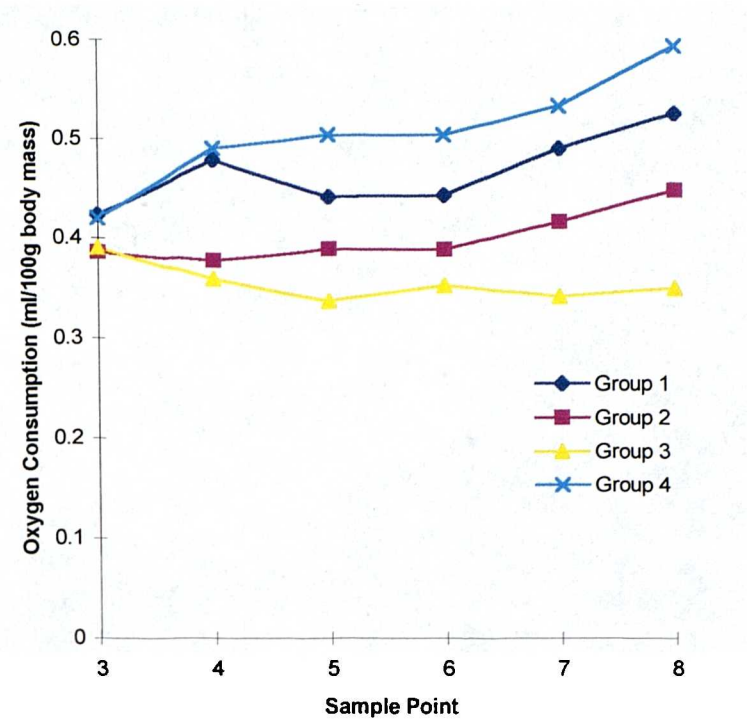


Figure 9.4 Tissue oxygen consumption for all groups. The results presented are mean values only, the standard deviations for each sample point are shown in table 9.8.

There were statistically significant differences between the study groups in terms of oxygen consumption. There were also differences in the general profile exhibited. The non-pulsatile group (group 3) showed the lowest oxygen consumption levels and a decline in oxygen consumption during the early part of the perfusion period (sample points 3,4,5). After this initial decline, the oxygen consumption levelled off until the end of the CPB period. The initial fall in oxygen consumption in this group coincided with the lowering of body temperature (see table 9.1) and the increase in PVRI exhibited solely by group 3 subjects (see fig. 9.2). The pulsatile flow groups exhibited a different profile. Subjects in the high frequency group exhibited the highest levels of oxygen consumption and had a rising trend from sample point 3 to the end of the procedure. The initial rise from sample point 3 to 5 was followed by a further increase

from sample point 5 to sample point 7. This bi-phasic response is echoed in the other pulsatile flow groups although, in groups 1 and 2, the magnitude of the oxygen consumption level was lower overall than that of group 4. The second aspect of the bi-phasic response corresponded, in all cases, to the rewarming phase of the operation and the release of the aortic cross-clamp. The difference between group 4 and group 3 subjects was statistically significant at the $p < 0.001$ level at all sample points. Group 1 subjects were also statistically significantly different to those of group 3 at all sample points ($p < 0.005$). The difference between group 2 subjects and the non-pulsatile group did not reach statistical significance until sample point 5 at which point the oxygen consumption in group 2 was significantly higher and the difference became statistically significant ($p < 0.01$). This relationship persisted to the end of the perfusion period. The group 1 and 4 subjects were associated with a higher oxygen consumption level than group 2 subjects at all sample points ($p < 0.01$ minimum) with the exception sample point 3.

9.5 S100 PROTEIN MEASUREMENT

Plasma S100 protein was measured as a marker for cerebral injury before, during and immediately after the perfusion period. The assessment was carried using a commercial assay kit with standard controls supplied. All assays were performed in duplicate on the same plasma fraction. The results of the assay procedure are shown in table 9.9 and figure 9.5.

Sample Point	Group 1 S100 $\mu g\ l^{-1}$	Group 2 S100 $\mu g\ l^{-1}$	Group 3 S100 $\mu g\ l^{-1}$	Group 4 S100 $\mu g\ l^{-1}$
1	0.097±0.041	0.088±0.021	0.121±0.069	0.073±0.013
2	0.126±0.092	0.122±0.044	0.152±0.081	0.107±0.029
3	0.155±0.112	0.107±0.027	0.158±0.053	0.161±0.061
4	0.113±0.019	0.121±.058	0.131±0.072	0.138±0.061
5	0.110±0.073	0.151±0.101	0.133±0.107	0.131±0.072
6	0.177±0.088	0.162±0.092	0.174±0.102	0.299±1.18
7	0.216±0.116	0.302±0.114	0.338±0.231	3.27±2.00
8	0.293±0.134	0.407±0.211	0.391±0.114	0.411±1.37
9	0.389±0.201	0.381±0.212	0.422±0.221	0.453±1.72

Table 9.9 Plasma S100 protein results for all groups. The results are shown as mean and standard deviation. n = 12 for all sample points

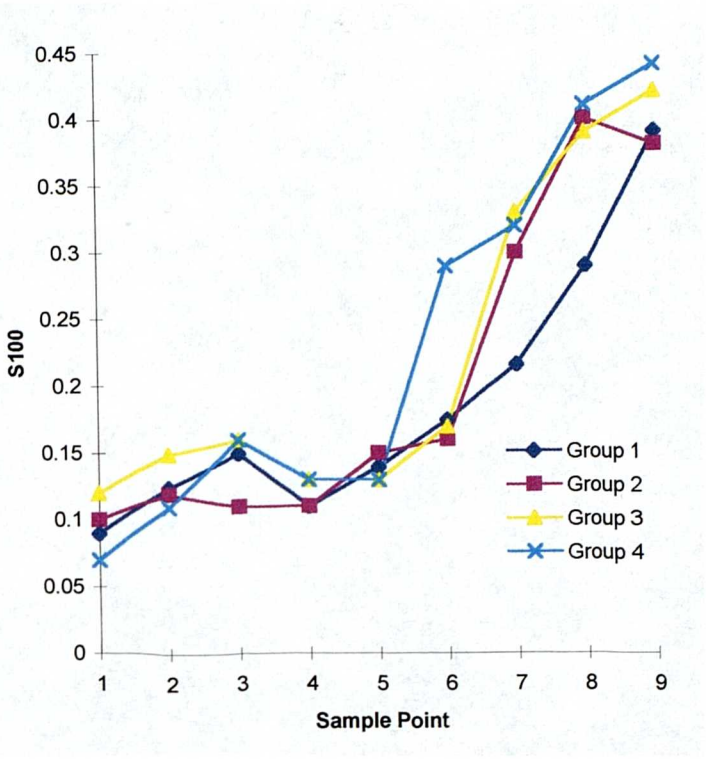


Figure 9.5 Plasma S100 protein levels for all groups. These results are shown as mean values only.

The plasma S100 protein levels appeared to rise throughout the perfusion period. There were no differences between the groups with regard to S100.

9.6 BLOOD AND INFLAMMATORY RESPONSES

The haematological response to the four flow modalities is reflected in the cell counts taken throughout the surgical procedure. These counts were corrected for the haemodilution effect of the CPB priming fluid to the original post-induction PCV. The haemodilution effect is significant and consistent from group to group showing little variation (table 9.10 and figure 9.2)

Sample Point	Group 1 Haematocrit (%)	Group 2 Haematocrit (%)	Group 3 Haematocrit (%)	Group 4 Haematocrit (%)
1	34.44 ± 2.57	33.85 ± 2.74	32.77 ± 2.93	34.37 ± 7.41
2	34.38 ± 2.10	34.27 ± 3.27	33.15 ± 3.41	35.41 ± 4.32
3	21.98 ± 4.37	24.39 ± 4.86	21.37 ± 3.61	21.71 ± 5.18
4	22.32 ± 8.2	23.55 ± 3.87	21.67 ± 3.51	21.07 ± 4.13
5	21.46 ± 3.67	23.85 ± 3.81	21.45 ± 3.51	25.17 ± 5.66
6	21.28 ± 4.81	23.82 ± 3.21	20.77 ± 3.51	25.15 ± 5.22
7	22.16 ± 2.63	24.05 ± 3.62	21.75 ± 3.41	25.00 ± 5.62
8	23.26 ± 1.66	24.9 ± 3.93	20.71 ± 3.48	26.02 ± 5.71
9	25.22 ± 1.64	25.65 ±3.21	22.75 ± 2.81	24.83 ± 2.34

Table 9.10 Haematocrit for all study groups and all sample points. There were no statistically significant differences between the various groups. All groups exhibited the same profile (see fig. 9.1) with the greatest change being associated with haemodilution by the CPB priming fluid (see sample point 3). n = 12 for all sample points

9.6.1 Cell counts

A number of cell species populations were analysed, including; red cells, white cells and platelets. The white cell population was further assessed to determine the neutrophil count. The red cell count is shown in table 9.11 for all four study groups at all sample points during the operative period.

Sample Point	Group 1 Red Cell Count ($\times 10^{12}$ l^{-1})	Group 2 Red Cell Count ($\times 10^{12}$ l^{-1})	Group 3 Red Cell Count ($\times 10^{12}$ l^{-1})	Group 4 Red Cell Count ($\times 10^{12}$ l^{-1})
1	3.93 ± 0.13	4.01 ± 0.21	3.88 ± 0.30	3.89 ± 0.41
2	3.91 ± 0.16	4.04 ± 0.18	3.73 ± 0.09	3.95 ± 0.29
3	3.91 ± 0.09	3.79 ± 0.44	3.37 ± 0.18	3.89 ± 0.32
4	3.60 ± 0.85	3.76 ± 0.32	3.39 ± 0.31	3.95 ± 0.22
5	3.92 ± 0.15	3.85 ± 0.37	3.34 ± 0.33	3.88 ± 0.24
6	3.95 ± 0.13	3.85 ± 0.26	3.57 ± 0.22	3.91 ± 0.31
7	3.91 ± 0.09	3.82 ± 0.21	3.49 ± 0.25	3.89 ±0.19
8	3.93 ± 0.12	3.75 ± 0.09	3.52 ± 0.19	3.89 ± 0.41
9	3.91 ± 0.14	3.86 ± 0.29	3.58 ± 0.24	3.92 ± 0.28

Table 9.11 Red cell count for all operative sample points. The counts are shown as mean and standard deviation for each sample point. n = 12 for all sample points.

Sample Point	Group 1 Plasma Free Haemoglobin (mg%)	Group 2 Plasma Free Haemoglobin (mg%)	Group 3 Plasma Free Haemoglobin (mg%)	Group 4 Plasma Free Haemoglobin (mg%)
1	1.02 ± 0.77	0.87 ± 0.66	0.91 ± 0.77	0.31 ± 0.29
2	1.88 ± 1.32	1.07 ± 0.84	1.18 ± 1.02	1.39 ± 0.98
3	1.63 ± 1.43	1.17 ± 1.01	1.58 ± 0.79	1.21 ± 0.62
4	1.69 ± 1.55	1.44 ± 0.81	1.87 ± 1.14	1.38 ± 0.91
5	8.87 ± 5.51	9.93 ± 5.29	7.79 ± 5.18	11.38 ± 6.90
6	11.12 ± 8.91	14.11 ± 8.19	9.86 ± 6.69	14.19 ± 11.06
7	10.09 ± 4.41	13.01 ± 6.61	9.72 ± 10.2	15.01 ± 8.77
8	13.92 ± 8.91	16.03 ± 7.09	11.92 ± 9.11	15.32 ± 9.18
9	13.37 ± 6.72	15.44 ± 8.17	10.83 ± 5.49	17.96 ± 11.4

Table 9.12 Haemolysis levels in each group as reflected in plasma free haemoglobin measured by spectrophotometry. These data are corrected for haemodilution in the same manner as the cell counts. n = 12 for all sample points.

The corrected red cell counts show that there is very little change to the size of this population in any of the groups, but these were of no statistically significance. The haemolysis levels also showed differences between the flow groups, and these once again failed to reach statistical significance (table 9.12). All groups exhibited rising plasma free haemoglobin levels as the operation proceeded. The value for the non-pulsatile flow group was lowest at the one hour post-operation sample point (sample point 9), but, this was not statistically significant, and the haemolysis was not sufficient to alter the red cell count in any of the study groups.

The white cell count produced a different profile to that of the red cell count. There were differences between the groups in terms of the white cell count (table 9.13 and fig.9.6).

Sample Point	Group 1 White Cell Count ($\times 10^9$ l^{-1})	Group 2 White Cell Count ($\times 10^9$ l^{-1})	Group 3 White Cell Count ($\times 10^9$ l^{-1})	Group 4 White Cell Count ($\times 10^9$ l^{-1})
1	6.04 ± 1.27	5.42 ± 0.77	5.66 ± 2.01	7.42 ± 1.06
2	7.25 ± 2.03	6.21 ± 0.71	6.09 ± 2.29	7.51 ± 1.67
3	8.38 ± 3.04	6.52 ± 1.52	6.35 ± 2.03	7.81 ± 2.07
4	7.05 ± 3.32	8.71 ± 2.08	6.43 ± 1.62	9.67 ± 3.14
5	17.28 ± 5.31	14.46 ± 3.32	7.25 ± 2.18	12.66 ± 3.26
6	15.56 ± 4.17	14.77 ± 5.18	8.9 ± 3.01	15.36 ± 3.81
7	14.49 ± 4.53	16.51 ± 1.53	9.26 ± 1.62	16.93 ± 3.44
8	15.16 ± 2.64	16.77 ± 2.12	10.76 ± 1.72	18.91 ± 5.16
9	15.96 ± 2.52	15.33 ± 3.47	12.50 ± 1.88	17.05 ± 4.21

Table 9.13 Total white cell count. Results are expressed as mean and standard deviation and have been corrected for haemodilution. n = 12 for all sample points.

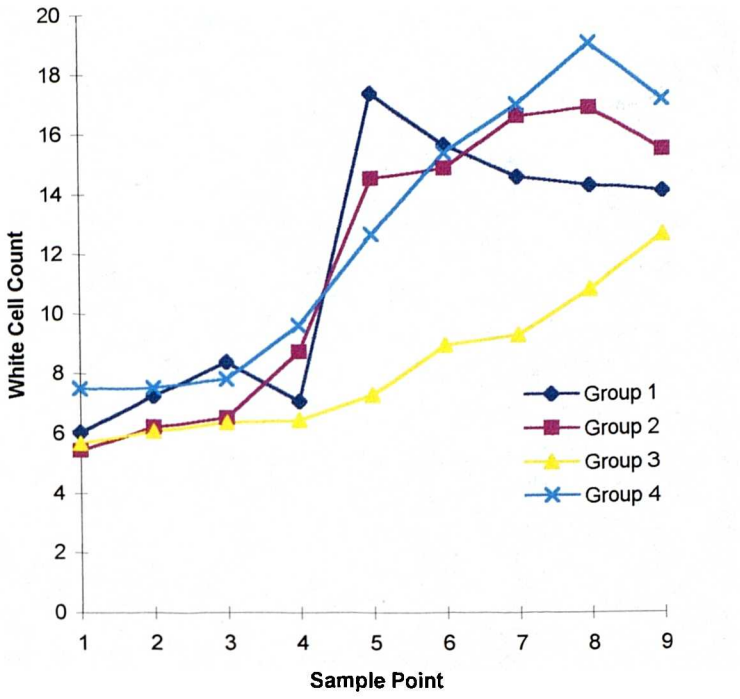


Figure 9.6 Total white cell count ($\times 10^9$ l^{-1}) for all four groups. The results are shown as mean values only.

There were no differences between the pulsatile blood flow groups with regard to total white cell count. There were differences between all three pulsatile groups and the non-pulsatile group. All three pulsatile groups showed a sharp rise at sample point 5, just before the release of the aortic cross clamp and at the point where re-warming begins. This rise resulted in a doubling of the total white cell count in all pulsatile groups. After this extremely sharp rise, the white cell count reached a plateau which was maintained for the remainder of the procedure. The non-pulsatile group exhibited an entirely different profile. The total white cell count rose in this group at the same sample point, but the rise was substantially smaller and continued gradually for the remainder of the procedure.

The total white cell count in the non-pulsatile group was lower than all of the pulsatile flow groups from sample point 5 through to the end of the procedure. At all sample points from 5 onwards the difference between the non-pulsatile flow group and its pulsatile flow counterparts was statistically significant ($p < 0.01$ minimum).

The neutrophil count for all four groups are shown in table 9.14 and figure 9.7.

Sample Point	Group 1 Neutrophil Count ($\times 10^9$ l^{-1})	Group 2 Neutrophil Count ($\times 10^9$ l^{-1})	Group 3 Neutrophil Count ($\times 10^9$ l^{-1})	Group 4 Neutrophil Count ($\times 10^9$ l^{-1})
1	3.28 ± 0.75	3.25 ± 0.97	3.41 ± 0.94	4.18 ± 0.96
2	4.15 ± 1.22	3.68 ± 1.01	3.76 ± 2.19	5.06 ± 1.06
3	4.43 ± 1.72	4.02 ± 2.03	3.97 ± 1.61	4.74 ± 0.92
4	3.01 ± 0.97	6.16 ± 2.21	3.75 ± 1.90	5.36 ± 2.05
5	8.45 ± 2.61	11.05 ± 4.6	4.41 ± 2.02	7.57 ± 2.05
6	13.82 ± 5.61	12.37 ± 2.23	5.80 ± 1.65	11.62 ± 4.1
7	11.82 ± 5.54	14.58 ± 2.19	6.28 ± 2.21	12.93 ± 5.01
8	13.24 ± 4.13	14.11 ± 2.77	8.18 ± 1.69	14.46 ± 5.13
9	14.24 ± 3.01	12.70 ± 1.55	9.79 ± 1.34	16.07 ± 4.11

Table 9.14 Neutrophil count data for all flow groups. The results are presented as mean and standard deviation corrected for haemodilution for all sample points. n = 12 for all sample points.

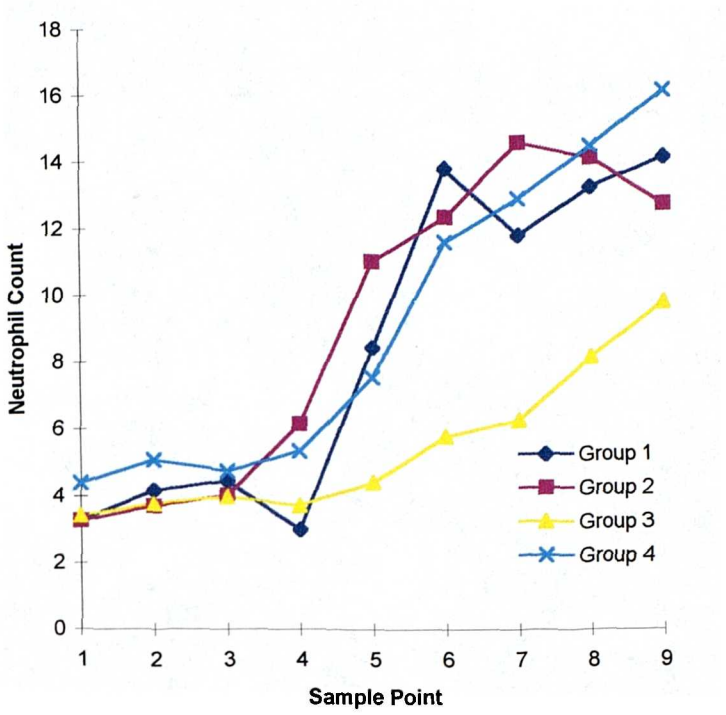


Figure 9.7 Neutrophil count ($\times 10^9$ l^{-1}) for all flow groups. The results are presented as mean values only, the standard deviations for all sample points can be seen in table 9.14.

The analysis of the white cell profiles fits the neutrophil profiles exactly. There were no differences between the pulsatile blood flow groups at any of the sample points. The non-pulsatile blood flow group exhibited an entirely different profile. In line with the total white cell count, the neutrophil profile in the non-pulsatile flow group exhibited a gradual rising profile after sample point 5 (the cross clamp release and re-warming) to the end of the procedure. The magnitude of the neutrophil count after sample point 5 was significantly less than that of the pulsatile flow groups and these differences were statistically significant throughout ($p < 0.01$ minimum).

The platelet count showed very little change in total count when corrected for haemodilution in any of the four groups (table 9.15 and fig. 9.8).

Sample Point	Group 1 Platelet Count ($\times 10^9$ l^{-1})	Group 2 Platelet Count ($\times 10^9$ l^{-1})	Group 3 Platelet Count ($\times 10^9$ l^{-1})	Group 4 Platelet Count ($\times 10^9$ l^{-1})
1	217.4 ± 70.1	186.2 ± 42.5	193.3 ± 32.6	209.4 ± 35.5
2	204.6 ± 44.2	188.3 ± 54.5	246.5 ± 43.3	215.5 ± 28.6
3	190.5 ± 61.0	196.3 ± 53.2	209.4 ± 66.1	199.9 ± 59.4
4	214.1 ± 54.5	204.0 ± 32.0	212.2 ± 50.9	217.1 ± 23.9
5	231.3 ± 44.0	228.6 ± 67.5	201.9 ± 44.1	200.2 ± 68.1
6	278.9 ± 66.8	234.7 ± 54.7	248.1 ± 29.5	242.2 ± 26.8
7	230.2 ± 51.3	231.5 ± 55.2	233.4 ± 42.6	223.6 ± 33.8
8	202.1 ± 34.4	225.8 ± 54.1	223.2 ± 63.5	197.8 ± 26.6
9	187.2 ± 33.7	173.8 ± 27.6	179.9 ± 33.0	164.3 ± 37.1

Table 9.15 Platelet count for all four groups. The results shown are mean and standard deviation and n = 12 for all sample points.

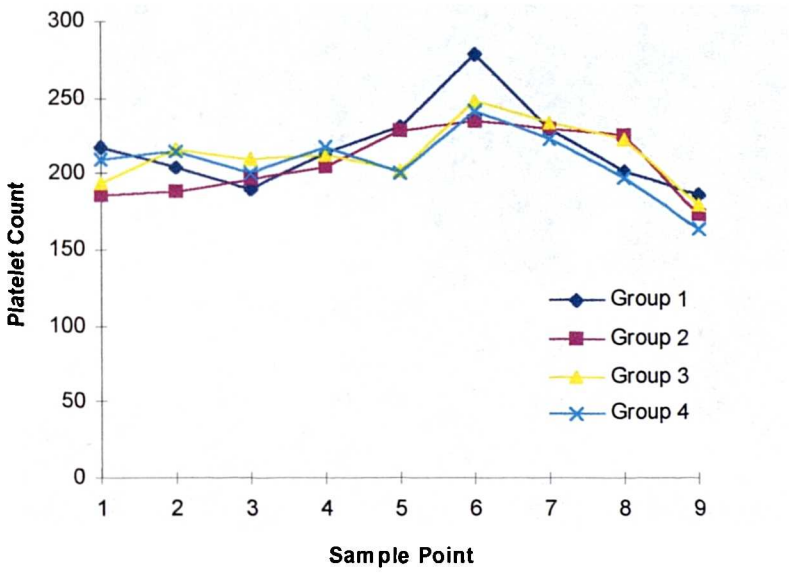


Figure 9.8 Platelet count ($\times 10^9$. l^{-1}) for all groups.

All groups showed a moderate rise in platelet count on re-warming and removal of the aortic cross clamp, but this rise was not statistically significant on comparison with the start values in any group. There were no statistically significant differences between groups at any sample point.

9.6.2 Lactoferrin and TNFα measurements.

Lactoferrin, a marker for neutrophil activation, was measured using a commercial ELISA kit. The results are shown in table 9.16 and figure 9.9.

In all four groups, the lactoferrin (LTF) response profile was similar. There was a rise at sample point 2 after the administration of heparin, followed by a further sharp rise at sample point 5, the re-warming phase and the release of the aortic cross clamp. LTF remained at these elevated levels in all four groups until the end of the perfusion period and had returned to near post-induction levels by sample point 9 (one hour post-bypass). There were differences between the groups which reached statistical significance, but only between groups 2 and 3 at sample points 6,7 and 8 ($p < 0.05$ maximum). Group 2 exhibited the highest LTF levels and group 3 the lowest . Other than the differences stated there were no significant differences found between the study groups with regard to LTF levels.

Sample Point	Group 1 Lactoferrin (LTF) Levels ($ng.ml^{-1}$)	Group 2 Lactoferrin (LTF) Levels ($ng.ml^{-1}$)	Group 3 Lactoferrin (LTF) Levels ($ng.ml^{-1}$)	Group 4 Lactoferrin (LTF) Levels ($ng.ml^{-1}$)
1	339.8 ± 127.3	464.5 ± 163.4	345.5 ± 165.9	629.4 ± 185.4
2	1232.7 ± 131.9	1460.5 ± 130.4	1127.4 ± 267.3	1015.3 ± 274.3
3	1157.6 ± 192.9	1327.7 ± 104.5	997.6 ± 235.8	771.7 ± 167.5
4	1116.7 ± 430.2	1401.6 ± 201.5	1266.3 ± 330.5	1090.4 ± 367.4
5	1865.6 ± 196.4	1860.5 ± 294.3	1528.3 ± 354.6	1904.2 ± 417.6
6	1556.2 ± 188.2	2350.5 ± 217.3	1375.6 ± 255.4	1866.6 ± 278.8
7	1504.5 ± 208.2	2107.5 ± 357.2	1417.3 ± 401.3	1701.3 ± 381.4
8	1522.5 ± 203.2	2123.4 ± 397.3	1533.4 ± 432.6	1661.6 ± 297.4
9	897.7 ± 129.8	445.3 ± 111.8	640.1 ± 188.5	791.4 ± 218.5

Figure 9.16 Lactoferrin results for all four groups. n = 12 at all sample points. All results are corrected for haemodilution.

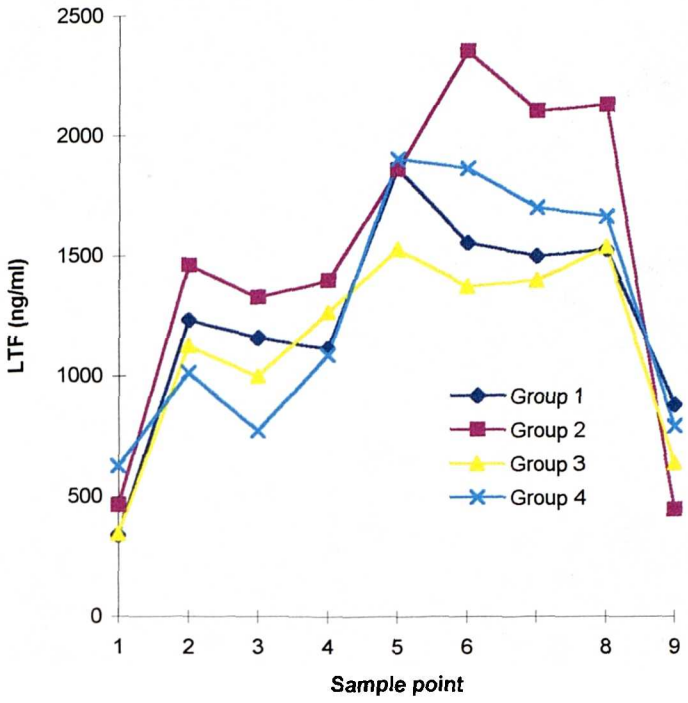


Figure 9.9 Lactoferrin results. The figure shows mean corrected values only.

Of the hundreds of samples processed, it was only possible to detect TNFα in three samples. These samples belonged to two groups, 1 and 3. The source of this response remains unresolved as TNFα was only detectable in one of the two duplicate samples in two specimens and in both duplicates in the other.

9.7 OUTCOME MEASURES

The outcome measures referred to in this section are simple measures of hospital outcome, but these do reflect to overall performance of the patient during the clinical course. Any major difference between the patients groups associated with the clinical course, should be apparent from these studies.

Group	1	2	3	4
ITU Temp (°C)	35.13 ± 1.41	36.05 ± 0.45	34.75 ± 1.9	36.3 ± 1.15
Time to re-warm (hr)	2.5 ± 1.0	1.75 ± 0.5	3.25 ± 2.69	2.65 ± 1.2
Intubation Time (hr)	10.5 ± 4.12	9.1 ± 1.73	12.3 ± 2.8	9.75 ± 3.2
ITU Time (hr)	15.25 ± 1.89	17.6 ± 5.5	16.75 ± 0.97	18.5 ± 4.2
Total Urine (ml)	2066 ± 1068	2671 ± 998	1980 ± 535	1822 ± 458
12 hr. Blood loss (ml)	356 ± 112	385 ± 162	437 ± 196	525 ± 188
16 hr. Fluid Balance (ml)	993 ± 295	1233 ± 156	1162 ± 258	1412 ± 379
Hospital Stay (days)	7.25 ± 0.95	7.25 ± 3.2	7.5 ± 1	7.33 ± 1.5

Table 9.17 Summary of patient outcome measures selected for study.

These outcome measures indicated a number of areas where there were apparent differences between the patient groups. Group 3 patients arrived in the ITU with a lower core temperature than those in the pulsatile groups and took longer to re-warm to 37.0°C. The difference in core temperature between groups 3 and 4 and 3 and 2, on arrival, was statistically significant ($p < 0.05$), but the difference in re-warming time was not. Patients in groups 2 and 4 were associated with the shortest intubation time. Group 2 patients were intubated for significantly less time that those in group 3 ($p < 0.05$). This was the only comparison regarding this factor which reached statistical significance. There were no statistically significant differences between the groups with regard to total ITU stay. All groups exhibited a mean ITU stay of around 15 to 20 hours. There were no statistically significant differences between the groups

associated with any of the other outcome measures employed and generally with regard to these coarse measures of the success of the clinical procedure the patients appeared to be very similar. In addition, there was no need for post-operative circulatory support by way of balloon pumping in any of the patient populations and only sparse use of inotrope therapy, which occurred in all groups.

9.8 DISCUSSION

This clinical study was designed to assess whether there were any clinical benefits associated with controlling the output architecture of the perfusion pump during CPB. The level of control offered by the Stockert system had been established in the laboratory environment under controlled standard load conditions. Measurements in the clinical setting, though limited in number, confirmed that the laboratory findings with regard to flow/pressure architecture were relevant to this setting. These measurements indicated that the patients undergoing CPB during this study were markedly vasodilated. This was reflected in both hydraulic power and pressure assessments. All measurements exhibited a decreased value in the clinical setting in comparison with the laboratory. However, the overall trend of increasing amplitude and $dp/dt_{(max.)}$, together with increasing pulsatile hydraulic power, with decreasing ejection time seen in the laboratory, was confirmed under clinical conditions. There were a number of significant responses to this controlled architecture. The haemodynamic response was considerable, with the non-pulsatile flow group exhibiting a marked increase in PVRI during the early phase of the perfusion period. This was in stark contrast to the constant and unchanging PVRI levels associated

with the pulsatile groups. These differences were significant between the pulsatile and non-pulsatile groups, but not between the pulsatile groups. This confirmed the early work by Taylor et al (1979) who described a rise in PVRI associated with non-pulsatile blood flow during clinical CPB which was eliminated by the incorporation of a pulse. Analysis of the data showed that frequency was not associated with this change in PVRI as the correlation between the two was very weak (R^2 = 0.041). Nitric oxide activity also exhibited a varying response to the different flow regimes. Previous work using an animal model by Hutcheson and Griffith (1991) had indicated that both pulse amplitude and frequency would elicit an effect on NO activity, with the higher amplitude and frequency profiles being associated with greater NO activity. This was not found to be the case in this study where the higher NO levels were found in those patients undergoing a non-pulsatile regime and the lowest by those undergoing a high frequency low ejection time regime. There were differences between the animal model and the clinical situation, most notably the presence of extreme haemodilution in the clinical setting. It had been anticipated that the local vasoactive action of NO may be an explanation for the previously reported maintenance of low PVRI in patients undergoing pulsatile CPB. This is certainly not the case in this series of studies where the highest NO levels (group 3) were associated with the highest PVRI. There was an extremely weak correlation between PVRI and NO with an R^2 value of 0.165. This R^2 increases to 0.1815 when the non-pulsatile patients are eliminated from the data set. This, however, remains a weak correlation and inconclusive. Similarly, the non-pulsatile group alone shows an equally weak correlation between NO activity and PVRI (R^2 = 0.1703).

The relationship between NO activity and the frequency and amplitude of aortic pressure was also investigated, since these are factors said to exert an influence on NO production (Hutcheson and Griffith, 1991). This aspect of the investigation was limited by the fact that only three frequencies were employed in this study (0, 75 and 120bpm). There was no correlation between pressure amplitude and NO activity (R^2 = 0.0071).When the non-pulsatile groups are eliminated from this correlation, the R^2 value improves to 0.295 showing that the relationship between pressure amplitude and NO activity does exist in the pulsatile flow groups, although the correlation is very weak. Analysis of the relationship between NO activity and frequency produced a similarly poor correlation (R^2 =0 .0068). Frequency, therefore, appears to have no role to play in the level of NO activity seen in the four groups. Amplitude and PVRI correlate weakly with NO production. The results of the forward elimination regression analysis are summarised in table 9.18

Aspect of Pulse Architecture	R^2
Amplitude	0.0071
Frequency	0.0068
$dp/dt_{(max.)}$	0.535
Pulsatile Hydraulic Power	0.5094

Table 9.18 The correlation between NO activity and the major components of blood flow architecture.

From table 9.18 it is clear that the two factors of architecture which show the strongest correlation with NO activity are $dp/dt_{(max.)}$ and pulsatile hydraulic power. However, the relationship in both cases is not strong and these factors can only partially contribute to the NO activity profile.

Since NO is a free radical, another potential source of nitric oxide is the reperfusion phenomenon which occurs, to a varying degree, during CPB. It has been suggested (Royston et al, 1986) that free radicals mediate in this complex and undesirable event, and that this event is associated with the activation of neutrophils which may be marginated in the peripheral circulation during the cooling phase of the CPB. When the patient is re-warmed, the peripheral circulation is re-established and the marginated cells are eventually returned to the systemic circulation. At this time, the peripheral circulation and, in particular, areas which have been ischaemic during the cooling phase of the operation are exposed to blood with a high oxygen content. This set of circumstances are required for the development of reperfusion injury. Under such circumstances, high PVRI and low oxygen consumption levels would be apparent prior to the re-warming phase of the operation, indicating some degree of peripheral shutdown and ischaemia. High levels of neutrophil activation products and markers of tissue injury would be apparent together with rising neutrophil and white cell counts after the re-establishment of peripheral circulation. The pulsatile blood flow groups exhibited none of these characteristics prior to the re-warming phase of the CPB. Although oxygen consumption in these groups varied, it was consistently higher than the non-pulsatile group. The non-pulsatile flow group exhibited a depressed oxygen consumption profile. The oxygen consumption levels in this group of patients initially fell from a common baseline early in the perfusion period, and

remained depressed to the end of the CPB period. Similarly, the non-pulsatile group was the only one which exhibited a rising PVRI profile prior to the release of the aortic cross clamp and the start of the re-warming period. These factors tend to indicate a peripheral shutdown with a subsequent decrease in tissue oxygen consumption, presenting the possibility for regional ischaemia to develop. The presence of the pulse tended to eliminate this set of circumstances. LTF, the marker for neutrophil activation, initially appeared to indicate that the non-pulsatile flow group was associated with lower levels of neutrophil activation. This would cast doubt on the development of reperfusion injury associated with non-pulsatile blood flow, certainly with regard to the role of the neutrophil. Further examination of the data, however, indicated that although the LTF levels in the non-pulsatile group were considerably lower than the pulsatile flow groups, the neutrophil were also significantly lower. Correction of the LTF data for the neutrophil count demonstrated that the neutrophils released under non-pulsatile flow were significantly more activated than those in the pulsatile groups (fig 9.12)

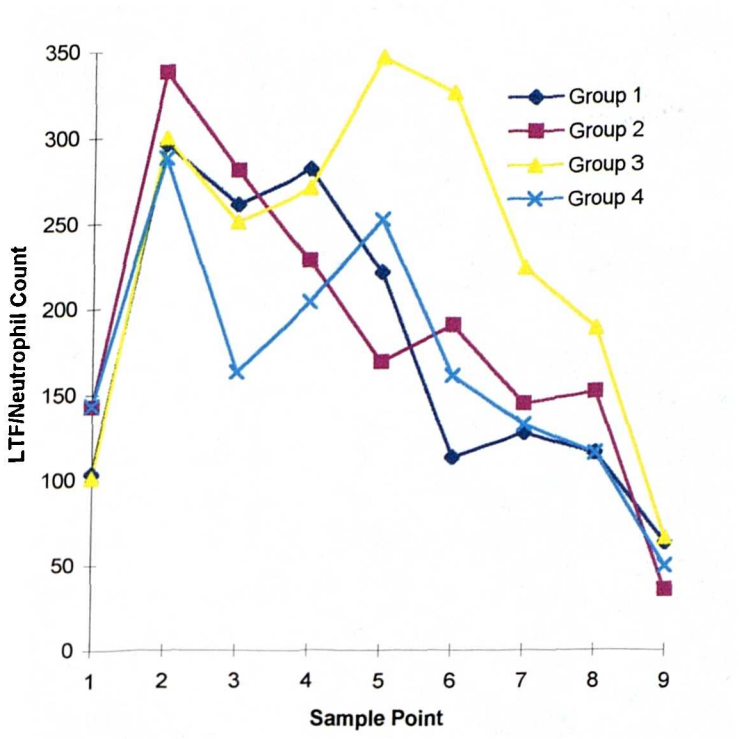


Figure 9.12 LTF results corrected for neutrophil count. These data are presented as mean values only.

The LTF activity in all groups rose sharply with the administration of heparin. There was a further small increase in activity in the pulsatile flow groups with the release of the cross-clamp. This was followed by a decay in activity through to the post-bypass period. The non-pulsatile flow group was associated with a much sharper rise in LTF levels upon the release of the cross-clamp, which endured until sample point 6 and then decayed in line with the other flow modalities. The difference in neutrophil count-corrected LTF levels upon the release of the cross-clamp between the pulsatile groups and the non-pulsatile group was statistically significant. There were also differences apparent between the pulse groups with regard to LTF levels and it appeared that there may have been a relationship between LTF levels and the

architecture in the pulsatile groups during the period of CPB. This was investigated and the results are shown in table 9.19.

Aspect of Pulse Architecture	R^2
Amplitude	0.072
Frequency	0.044
$dp/dt_{(max.)}$	0.035
Pulsatile Hydraulic Power	0.284

Table 9.19 The correlation between LTF levels and the major components of blood flow architecture.

There were no strong links between pulsatile architecture and LTF levels. There was a weak association highlighted between the LTF levels and hydraulic power delivery, but larger numbers would be required to confirm this finding.

Some degree of confirmation of the reperfusion injury theory could have been made by the TNFα study. This, however, was inconclusive as TNFα was found in trace quantities in only three samples. It is conceivable that sampling later in the procedure could have elicited more information in this regard.

Organ damage during clinical CPB focused on the brain. S100 protein was employed as a marker of cerebral damage during the operative period. There was S100 present in all groups and this followed a constant and consistent profile, but there were no differences specific to the various groups in this regard.

The focus of this study was to assess whether the output architecture of the pumping system, confirmed in the laboratory, was present in the clinical setting. An

additional aim was to assess, using coarse tools, the effects of controlled pulsatile blood flow architecture during and immediately after CPB and to assess the manner in which these effects manifest themselves later in the patient's clinical course. Only coarse outcome measured were employed in the post-operative aspect of the study, and these did indicate to some differences between clinical groups.

CHAPTER 10

DISCUSSION AND FUTURE WORK

CHAPTER 10 DISCUSSION AND FUTURE WORK

10.1 CONTROLLED PULSATILE BLOOD FLOW ARCHITECTURE

Many studies have been carried out with the intention of assessing the importance of the pulse to the maintenance of physiological equilibrium (Mavroudis, 1978). These studies have very rarely defined precisely what flow/pressure architecture was employed (Wright, 1994). The description of pulsatile flow tends to be limited to one or two factors. In this study, we set out to describe the pulsatile flow employed in every arm of the study in terms of every aspect of its architecture. The parameters selected included $dp/dt_{(max.)}$ (the initial rise of pressure on the upstroke of the pressure complex), pressure amplitude (the overall magnitude of the pressure complex), frequency (the repetition rate of the pressure complex) and mean pressure. In addition, the flow was characterised in terms of hydraulic power delivery in both the pulsatile and mean domains. The importance of these various aspects of pulsatile blood flow architecture has been the focus of studies in the past (Gourlay and Taylor, 1994), although this study of all of these aspects, performed in the clinical environment, is fairly unique.

Controlled pulsatile architecture refers to pre-determining the output architecture of the pump delivering the blood flow. Establishing this architecture required that the output profiles were established in the laboratory prior to the clinical study. To achieve this, a model of the human circulation was constructed.

10.2 CONSTRUCTING THE MODEL CIRCULATION

It was established that there were many methods for modelling the circulation. Principally, these belonged to two categories, electrical and hydromechanical. Electrical analogues have been employed for a number of years for modelling the circulation and some of these models have been extremely complex such as the one described by Noordergraaf et al (1969) which consisted of 122 components each representing one arterial segment. These models rely on knowledge of the input architecture for assessing the effects of mechanical or pharmacological interference with blood or fluid flow. When studying pump generated pressure/flow architecture, the input architecture is precisely the factor which is under investigation and the lack of knowledge of its structure renders electrical analogue of the circulation useless. The remaining option was to employ a hydromechanical modelling technique. These systems have been employed for testing pulse structure and output power in beating hearts and in perfusion pumps. Westerhof et al (1971) described such a system for assessing beating hearts and this model was further developed by Wright (1988) for the assessment of perfusion pumps. For our purposes we designed and constructed a 3 component model of the systemic circulation based, to a great extent, on the early work of Westerhof et al (1971), and on the clinical work carried out by Wright (1988) in measuring the compliance and impedance in patients undergoing heart surgery. The three components of the model consisted of; a characteristic resistance representing the input impedance of the circulatory system, a peripheral resistance and a compliance. The components were constructed after considerable computation of the fluid mechanics required to produce to desired values for each aspect of the model.

The model was designed to offer normal resistance and compliance under normal blood flow conditions encountered in the clinical situation and with a perfusate which was designed to mimic blood in the microcirculation. The use of normal values for these components would prove to be significant when comparing the laboratory derived results with those of the clinical model. Using this model, the various aspects of pump output architecture were assessed. In addition, the model was employed to offer hydrodynamic conditions similar, to those encountered in the clinical environment, when testing other aspects of pump and CPB circuit performance.

10.3 PRE-CLINICAL ASSESSMENT OF OUTPUT ARCHITECTURE AND DEVICE SAFETY.

Two pumping systems were selected for use in this study. One was a conventional roller pump mechanism, the type of system which has been in use for many years at the Hammersmith Hospital. This pump was a Stockert double roller pump with the output controlled by a PFCII pump control module. This combination of devices permits some degree of control of pulse shape from the pump. Laboratory trials using this system have confirmed its safety and ease of use, but have highlighted its limitations in terms of generating pulsatile blood flow. Wright et al (1989) demonstrated that such a system was not capable of matching the pulse generating capabilities of a ventricular pumping system, particularly in terms of pulsatile hydraulic power generation. Despite these recognised limitations, the roller pump mechanism has been attributed with the maintenance of normal function in a number of organ systems when employed in the pulsatile mode (Taylor et al, 1988). The initial intention of this thesis was to assess the benefits of the enhanced control and

magnitude of the pulse offered by ventricular pumping systems. Ventricular pump systems are not generally available for routine CPB applications. There are some systems which are available for heart support use, but, such systems are beyond the scope of this investigation. A ventricular pump, however, was made available for use in this study. The TPP pump is a modified heart assist pump which was modified to offer true pulsatile perfusion (TPP) during routine heart surgery. The modifications carried out to the ventricle included the incorporation of one piece polyurethane valves which reduced the cost of the disposable pump head from several thousand pounds to a few tens of pounds. This pump had been employed elsewhere in the world, and it was our intention to apply for ethics committee approval for its clinical use after first assessing its performance profile.

The two pumps were assessed for the effects of the various control parameters on the pulsatile architecture in the model circulation which offered standard loading conditions. It was clear, immediately, that the ventricular pump was associated with superior performance in every aspect of pulse architecture. The level of reproducibility exhibited by both systems in terms of each control parameter and the effect on pulse architecture in the model was extremely high (Chapter 6). This was encouraging in so far as the potential clinical study was concerned as this high level of pulse architecture control was essential if the clinical effects were to be studied. The TPP system was associated with greater pulsatile power output than the roller mechanism for all architecture configurations. The TPP system was associated with up to twenty times the hydraulic power in the pulsatile domain than that of the roller pump. This finding was exciting and promising in terms of the proposed clinical study. On the basis of this data ethics committee approval was sought and received for a

clinical trial involving the new pump system. Prior to the start of the clinical study, a further series of tests were carried out focusing on the safety and compatibility of the new system with the CPB circuitry employed in the clinical setting. These studies concentrated on the haemocompatibility of the new pump systems under controlled conditions together with the assessment of microbubble generation when the pump was employed with two membrane oxygenator configurations, one for arterial line placement and one for the venous line. Previous studies have implicated pulsatile pumps in the generation of the microembolic load present in the arterial line of the CPB circuit (Pearson et al, 1986, Gourlay and Taylor, 1987). While the source of this micro-bubble load still remains undetermined, it presents a serious safety issue to patients undergoing CPB.

The haemocompatibility trials confirmed that the ventricular pump was associated with greater haemolysis than the roller mechanism. This may be due to greater shear stresses in this group, particularly at low ejection times (Wright, 1986, Taylor, 1986). The effect of changing the pump control configuration on the generation of haemolysis indicated that there was a relationship in this regard and confirmed that care would need to be taken during the clinical trial to minimize this effect. The differences between the pump types in terms of haemolysis generation were statistically significant, in favour of the roller mechanism, but were not thought to be of a magnitude which would be of any clinical significance.

Of greater concern was the level of microbubble generation associated with the TPP pump. This was significantly higher than that associated with the roller pump. A clear relationship between ejection time and microbubble generation was established for the TPP pump. A similar relationship was established for the roller pump, but the

microbubble load generated by the TPP system was significantly higher for all configurations. This problem would have to be addressed if the TPP pump was to play a full part in the clinical study. Several approaches were available to address this problem, two of which were tried. A venous line membrane oxygenator could be incorporated into the circuit to eliminate pulsatile blood flow through the membrane compartment itself. Previous studies of the compatibility of arterial-line membrane oxygenators with pulsatile blood flow using a roller pump (Gourlay and Taylor, 1994) had indicated that the presence of large transient negative pressure spikes in the membrane compartment may be responsible for the generation of microbubbles. Pearson et al (1986) also implicated cavitation when pulsatile flow was employed. Certainly, there are a number of sources for negative pressure generation when pulsatile flow is employed in CPB circuits. Negative phase gas transfer across the membrane oxygenator placed in the arterial-line together with cavitation associated with inertial effects may be significant causes. Replacing the arterial line oxygenator with a venous line device was partially successful. However, the microembolic load in the arterial line remained significantly higher in the TPP group when compared to the roller pump group, even when the arterial line oxygentor remained in the circuit with the roller pump. The presence of an arterial line filter further reduced the microembolic load to acceptable levels. However, the highly dynamic flow characteristics associated with the TPP system caused mechanical damage to the filter, rendering it unusable and unsafe. This was particularly the case at high flow rates and low ejection times and resulted in the hydrophobic membrane, employed for air separation in the filter element, becoming detached from its retaining structure and ultimately rupturing. This clearly illustrates the power of the TPP system and the

highly dynamic nature of the flow architecture associated with it. This final problem resulted in the TPP system being withdrawn from the study. It was clear that the system posed a risk, however small, to the patients and it was decided to withdraw the pump until the problems could be resolved.

Further investigation of the TPP indicated that the problem may have been associated with the valving structures. These were found to be incompetent and relatively inflexible. This resulted in the valves not closing properly after each cycle. This was a problem particular to the arterial valve as this incompetence resulted in the failure of the valve to effect a mechanical seal between the ventricle and the arterial line, this resulted in a regurgitation of perfusate through the valve at every pulse cycle. It was found that this problem was associated primarily with the hard polyurethane material employed in constructing the valves (figure 10.1).

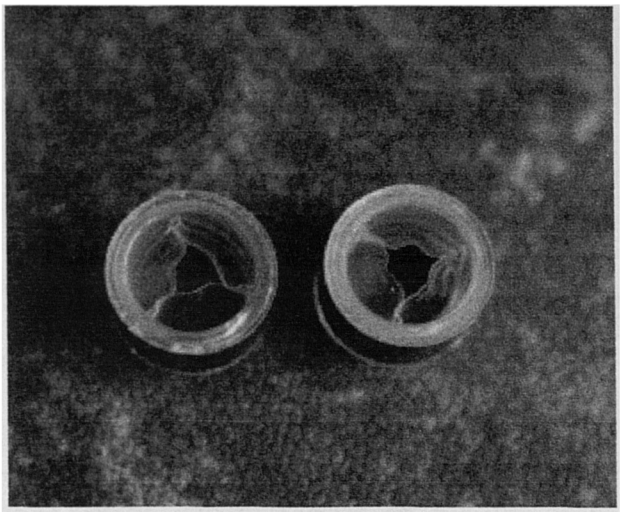


Figure 10.1 The inlet and outlet valves from the TPP pump system. These were found to be incompetent under clinical flow conditions and appeared to be largely responsible for the generation of microbubbles in the arterial line of the CPB circuit.

Once replaced by a softer material, the valves seated more precisely and the problem of microbubble load was significantly diminished. The manufacturer was not able to replace the valves in time for the clinical study and at this time the problem is still being handled by them. The remaining embolic load is thought to be associated with the inertial effects of flow and the recoil of the arterial line tubing. However, this is the case with both TPP and roller pump generated pulsatile flow and there is hope that once the valving material problems have been resolved, a TPP pump head suitable for clinical use will be available.

The clinical study proceeded with the roller pump alone. The roller pump was associated with a high level of pulse architectural control. In general the aspects of pulse architecture of interest in this study were of a lesser magnitude than those of the TPP system, but as the roller pump is in general use clinically, the results of controlling the output from the system are of direct clinical relevance.

10.4 CLINICAL ASSESSMENT OF CONTROLLED PULSE ARCHITECTURE AND THE ASSOCIATED CLINICAL EFFECTS.

Four groups of patients were studied, differing only in terms of the output profile of the arterial pump. There were two aims in the clinical study; firstly, to determine whether the pulse architecture, established to be associated with the control profiles, in the laboratory, was found to be present in the clinical setting. Secondly, the aim was to establish whether there was any clinical advantage to be gained from any particular pulse architecture.

The relationship between the control configurations employed and the associated effects exerted on the various aspects of pulse architecture observed in the laboratory

was confirmed in the clinical trial. All aspects of pulse architecture exhibited a similar profile in both environments. There was a difference, however, in the magnitude of each parameter. All parameters were shown to be lower in the clinical setting than in the laboratory. This may be due to a number of factors, the most likely cause being a lower level of vascular resistance in the clinical situation than that exerted by the model circulation. This may be caused by the pharmacological interventions which take place during and immediately before CPB or by the fact that the blood is haemodiluted during CPB. Haemodilution has a reducing effect on blood viscosity (Wright 1986), one of the determinants of resistance in the vasculature. The model was designed to employ a fluid which presents the same viscosity as whole blood in the microcirculation. The profiles exhibited were, however, quite similar, in terms of trend, to those of the laboratory studies, and were extremely reproducible. There were significant differences between the groups in terms of most aspects of pulse architecture, including pulsatile hydraulic power.

Despite the low magnitude of the various aspects of pulse architecture, there were statistically significant differences between the groups with regard to many of the factors studied in establishing the clinical effects of the various flow regimes. There were differences in oxygen consumption, reflecting different metabolic profiles. The non-pulsatile group exhibited the lowest level of oxygen consumption. This finding confirms some of the very earliest observations relating to the difference between pulsatile and non-pulsatile blood flow, with regard to tissue metabolism (Shepard and Kirklin 1969, Jacobs et al. 1969). There were differences between the pulsatile groups in this regard, which tended to favour the low ejection time models. However, these differences, unlike the comparison between the pulsatile and non-pulsatile

groups, were not statistically significant. This metabolic difference between pulsatile and non-pulsatile blood flow is one of the foundations upon which the arguments in favour of the use of pulsatile flow during CPB are based (Taylor et al, 1979). The failure to produce statistically significant metabolic differences between the pulse groups may be due to the small differences between the groups in terms of pulse architecture. Alternatively it is possible that a larger study would add sufficiently to the statistics to determine a difference. Whatever the cause, the difference in pulse architecture between the pulsatile flow groups did not elicit a significant metabolic response in terms of oxygen consumption.

The reduced oxygen consumption in the non-pulsatile group was associated with a higher peripheral vascular resistance than the pulsatile groups. This factor, once again, would indicate sub-optimal tissue perfusion. The pulse groups, on the whole, were associated with lower peripheral vascular resistance and there were no statistically significant differences between the pulse groups in this regard. This echoes a common finding when pulsatile blood flow is employed clinically (Estefanous ae al, 1973). Nitric oxide was measured in the four groups as it was believed that the local vasodilatory effects reported to be associated with nitric oxide activity under pulsatile blood flow conditions may be responsible for the reported maintenance of relatively normal haemodynamics in patients undergoing pulsatile CPB. Mathie et al (1996) and Hutcheson and Griffith (1991) had both reported evidence supporting the role of nitric oxide in this regard. Hutcheson and Griffith (1991) suggested that both pulse frequency and amplitude have an effect on nitric oxide activity and that these high frequencies and amplitudes up-regulate nitric oxide activity. However, this model was non-clinical and comparisons with clinical data are, to say the least, tenuous.

Mathie et al (1996) used a clinical CPB model, but they offered no description of the architecture of the pulse profile employed. They could not correlate nitric oxide activity with peripheral vascular resistance, and in fact, found no difference between the pulsatile and non-pulsatile groups with regard to peripheral vascular resistance. Their conclusion was that nitric oxide activity may be higher in the pulsatile group, but that it appeared to be more affected by temperature in another arm of the study. Overall they found no statistically significant differences between the study groups. In the present study, the temperature was well controlled and the pulsatile architectures were both controlled and described. We found that nitric oxide activity was highest in the non-pulsatile group and that it was lowest in the pulsatile group with the lowest ejection time. There was no correlation between nitric oxide and peripheral vascular resistance and, therefore, no evidence to support the theory that nitric oxide activity was responsible for the lower peripheral vascular resistance encountered in the pulsatile groups. Clearly this merits further investigation. The fact that nitric oxide is a free radical presents the possibility that there may be another mechanism behind nitric oxide activity during pulsatile and nom-pulsatile CPB. Free-radical mediated injury has for some time been associated with CPB and the mechanisms involved and complex (Lucchesi 1990). It is generally attributed to the so called "reperfusion injury" scenario in which an area of tissue experiences a period of low perfusion and subsequent low oxygenation, leading to ischaemic changes. The injury results from the reperfusion of the ischaemic region with oxygenated blood (Gourlay, 1994). The activation of neutrophils during this period, promoted by free-radical activity in the reperfused region, has been implicated in the resultant damage. The non-pulsatile group exhibited the correct combination of circumstances for the development of this

unwanted sequelae. It was associated with a high peripheral vascular resistance and low oxygen transfer during the early period of the CPB. This would indicate inadequate tissue perfusion together with poor regional blood distribution. This low flow, low oxygen transfer period was followed, in this study, by a period of high neutrophil activation and nitric oxide activity, which was not present in the pulsatile groups, as a whole. Plasma lactoferrin levels, used as a marker of neutrophil activation, rose sharply in the non-pulsatile group during the rewarming/reperfusion phase of the procedure. This was not the case with the pulsatile groups and is consistent with the role of the neutrophil in response to inflammation. The period of ischaemia is necessary to activate the neutrophils which in turn release free radical species and further damage an already injured area of tissue. All the evidence is consistent with the non-pulsatile flow being associated with this sequence of events and exhibiting some degree of reperfusion or hypoperfusion associated response during the rewarming period of the CPB. there was no administration of nitrates during the perfusion period, therefore the rising NO profile must be associated with indigenous NO. Royston et al (1986) found that these circumstances were associated with high pulmonary permeability and impaired pulmonary performance. Although there were no statistically significant differences in terms of intubation time, the only measure of pulmonary performance available in this series, the non-pulsatile group was associated with a longer period of intubation than the other groups.

TNFα was measured as a marker of the inflammatory response. TNFα was found in a total of only three samples taken from all of the four groups. The fact that the sampling regime terminated within one hour of the end of bypass may account for this. TNFα may be only detectable at a later stage in the procedure (Ito et al, 1997).

Future studies will bear this in mind, however, the focus of this study was the effects of the difference pulse architecture profiles during the perfusion period and to establish whether this made any substantial difference.

Vital organ damage associated with CPB has been well documented and it is generally agreed that the CPB period is not conducive to normal organ function. The brain has been one of the organs studied most frequently and this was the organ selected for study in this series. Rather than apply complex psychometric evaluations or cannulation of the carotid artery and vein, a more simple approach was adopted. S100 protein, present in the plasma, is one of the assay methods currently accepted as a marker of cerebral injury during CPB (Westaby et al, 1996, Gao et al, 1997). The S100 protein assay is available as a commercial kit and can be applied to human plasma. In this series of studies, S100 protein was found in all patients. There were no significant differences between the patient groups with regard to S100 levels and all aptients showed a rising S100 profile from the start of bypass through to the post-bypass period. In another study, Harris et al (1993) described using NMR techniques to detect the presence of cerebral oedema in patients undergoing CPB. They found that cerebreal oedema was present in all patients after operation. This may be the cause of the S100 in all patients in our series. The S100 levels correlated with no other factor and there were no cerebral incidents at any time associated with any of the patient groups.

The patient clinical course was followed into the ITU and there were no serious complications with any of the patients studied. The non-pulsatile group was associated with a lower core temperature on reaching the ITU, despite the use of warming blankets after bypass and rewarming to a core temperature of 38°C. This

may be associated with the high peripheral vascular resistance in this group and the slow return to normal after the perfusion period. This group of patients took significantly longer to reach normothermia in the ITU than any other group. Apart from these factors and the difference in intubation time, there were no significant differences between the groups in terms of the outcome measures and all patients returned home at the end of the hospital stay.

In summary, there were many differences between the flow groups. The pulse architecture established in the laboratory was consistent with that measured clinically. The high degree of output control offered by the pump was significant. By far the greatest difference in any factor was encountered on comparison between the pulsatile groups as a whole and the non-pulsatile group. Differences between each of the pulsatile groups were present in terms of pulse architecture, but generally, not in terms of other factors studied. There is some evidence to support the use of low ejection time pulsatile flow, particularly if nitric oxide is accepted as being associated with free radical injury during CPB, rather than simply as a vasoactive substance. This study would have benefited greatly from the inclusion of the TPP system as this would have offered a massive leap in terms of the magnitude of pulse architecture. This, unfortunately, was not possible for safety reasons. The roller pump was certainly associated with controllable pulse architecture, but the differences between the various pulse groups in terms of the magnitude of the various factors contributing to the architecture was possibly not significant enough to establish clinically or statistically significant differences. The roller pump remains the best option for delivering pulsatile flow during clinical CPB. However, this may not be the case once ventricular mechanisms become available for clinical use. At this stage, it can be said

that within the constraints of a sub-optimal pumping system, there is evidence supporting the importance of all aspects of pulse architecture during CPB, and clearly pulsatile flow remains superior to non-pulsatile flow for this application.

10.5 FUTURE WORK.

It is anticipated that, in the near future, the TPP system will become available for clinical use. The valving problem is currently being resolved and an early resolution is expected. At this point, the new material will be tested in the laboratory for durability and microbubble generation prior to a further clinical trial. The next clinical trial will focus on many of the same parameters, but the study will be carried into the post operative period much more intensively.

It is conceivable that the clinical model is not the best one for assessing the effects of controlled pulse architecture. The constraints placed upon the investigator with regard to not interfering with the patient's clinical course may place too many constraints on the study. A small animal model would be the most appropriate for this research, but, to date, a controllable small animal pulsatile pump has not been available. We have designed and constructed such a pump for plasma-pheresis studies at the Hammersmith Hospital (figure 10.2) and are currently modifying the system for use as a small animal CPB pump (figure 10.3).

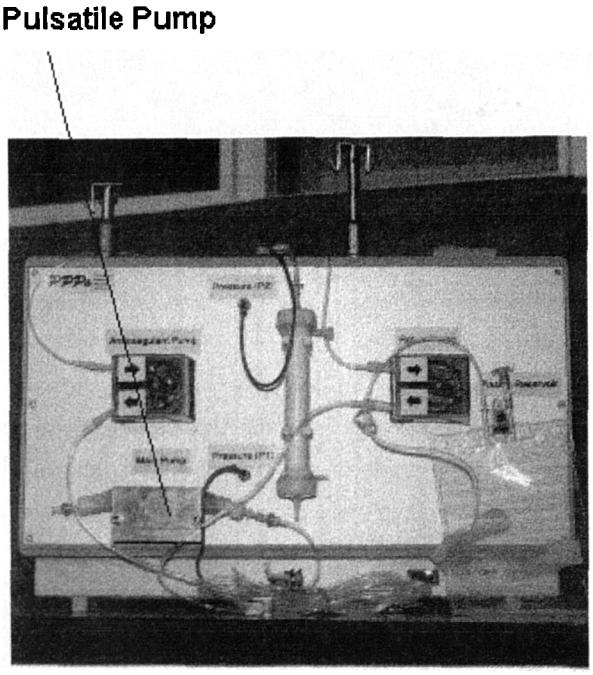


Figure 10.2 A prototype of the Hammersmith pulsatile flow plasma pheresis system

This pump enables every aspect of output architecture to be controlled and assessed independently, which should ultimately provide the information which will help in establishing which aspects of pulse architecture are responsible for the advantages pulsatile blood flow offers over non-pulsatile flow during clinical CPB..

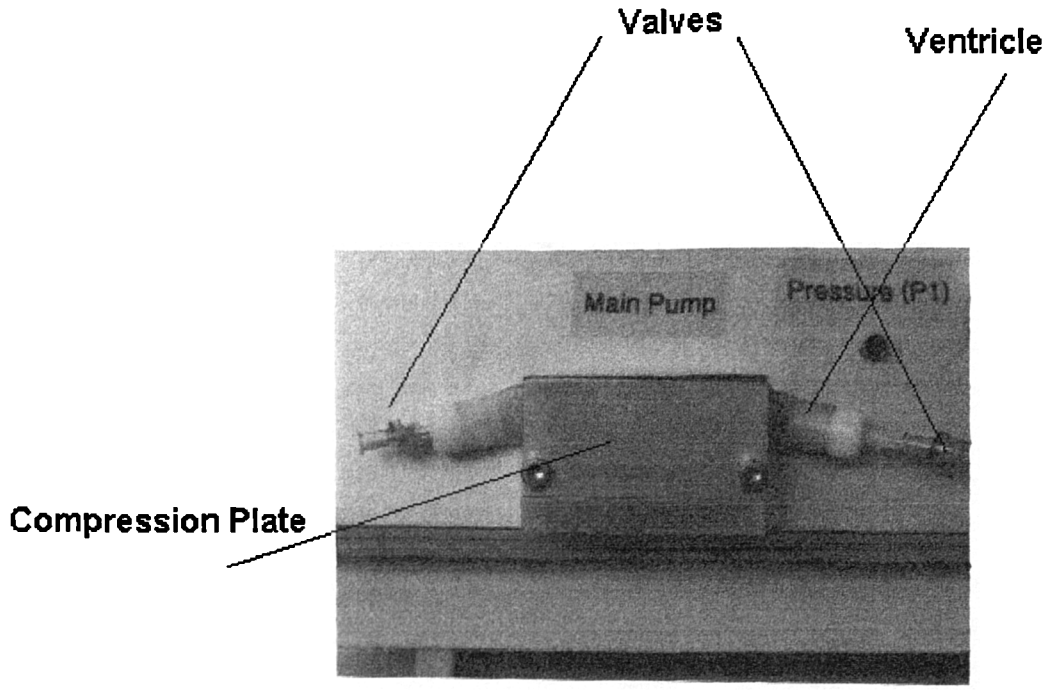


Figure 10.3 Pulsatile pump component of the pulsatile plasma pheresis system. The pump has two externally housed valves and a compression plate mechanism. It is capable of pumping up to 200ml/min at frequencies of up to 220 bpm.

REFERENCES

Aberg T, Ronquist G, Tyden H. Release of adenylate kinase into cerebrospinal fluid during open heart surgery and its relation to postoperative intellectual function. Lancet 1982;ii:1139-1142

Adams S, Fleming J, Gourlay T, Taylor KM. Clinical experience with the Sarns pulsatile pump during open heart surgery. Perfusion 1986;1:53-56

Andersen LW, Baek L. Transient endotoxaemia during cardiac surgery. Perfusion 1992;7:53-58

Andersen LW, Baek L, Degen H, Lehd J, Krasnik M, Rasmussen JP. Presence of circulating endotoxins during cardiac operations. J. Thorac. Cardiovasc. Surg 1987;93:115-119

Baca I, Beiger W, Mittmann U, Saggau W, Schmidt-Gayk H, Storch HH. Comparitive studies of pulsatile and continuous flow during extracorporeal circulation. Effects on liver function and endocrine pancreas secretion. Chir. Forum Exp. Klin. Forsch. 1979;49-53

Baker DW. Pulsed ultrasound flowmeter. Meth. Med. Res. 1966;11:107-117

Barger AC, Herd JA. Study of renal circulation in the un-anaesthetized dog with inert gases (proceedings of the Third International Congress of Nephrology). Nephrology 1966;1:174

Baue AE. The role of the gut in the development of multiple organ dysfunction in cardiothoracic patients. Ann. Thorac. Surg 1993;55:822-829

Bayliss WM, Muller EA. Red blood cell survival after perfusion with a membrane oxygentor. Am. J. Surgery 1974;127:535-540

Bayliss WM, Muller EA. A simple high speed rotary pump. Journal of Scientific Instrumentation 1928;5:278-279

Bellhouse BJ. Design of the Oxford membrane oxygenator and its performance during prolonged support of newborn lambs. Membrane Lungs for Acute Respiratory Failure (Zapol WM ed.), Academic Press, New York ,1976

Belzer FO, Ashby BS, Huang JS. Etiology of rising perfusion pressure in isolated organ perfusion. Ann Surg. 1968;168:382

Bergel DH. Vasoelastic properties of the arterial wall. 1960. Thesis, Univ. London

Bergel DH, Gessner U. The electromagnetic flowmeter. Meth. Med. Res;1966;11:70-82

Berki T, Gurbuz A, Isik O, Akkaya H, Bayezid O, Yakut C. Cardiopulmonary bypass using a centrifugal pump. Vasc. Surg 1992;26:123-134

Bethune D. Bubble Oxygenators. In (Taylor KM ed.) Cardiopulmonary Bypass Principles and Management. Chapman and Hall, London 1986.

Blauth C, Kohner EM, Arnold J, Taylor KM. Retinal microembolism during cardiopulmonary bypass demonstrated by fluorescein angiography. Lancet 1986;ii:837-839

Boucher JK, Rudy LW, Edmunds LH. Organ blood flow during pulsatile cardiopulmonary bypass. J Appl Physiol 1974; 36: 86-90.

Bowles CT, Ohri SK, Nongchana K, Keogh BE, Yacoub MH, Taylor KM. Endotoxaemia detected during cardiopulmonary bypass with a modified Limulus amoebocyte lysate asay. Perfusion 1995;10:219-228

Braithwaite MA. Prevention of neurological damage during open-heart surgery. Thorax 1975;30:258-261

Bretschneider HJ, Hubner G, Knoll D, Lohr B, Norbeck H, Speikermann PG. Myocardial resistance and tolerance to ischaemia: physiological and biochemical basis. J. Cardiovasc Surg 1975;16:241-260

Briceno JC, Runge TM. Monitoring of blood gasses during prolonged cardiopulmonary bypass and their relationship to brain pH, PO2 and PCO2. ASAIO 1994;40:M344-350

Bregman D, Bowman FO Jr, Parodi EN, Haubert SM, Edie RN, Spotnitz HM, Reemtsma K, Malm JR. An improved method of myocardial protection with pulsation during cardiopulmonary bypass. Circulation 1977; 56: Suppl II: 157-160.

Bregman D, Parodi EN, Hanbert SM, Szarnick R, Spotnitz HM, Bowman FO Jr, Reemtsma K, Malm JR. Counterpulsation with a new pulsatile assist device (PAD) in open-heart surgery. Med Instrument 1976; 10: 232-238.

Breuer AC, Furlan AJ, Hanson MR. Central nervous system complications of coronary bypass graft surgery: a prospective analysis of 421 patients. Stroke 1983;14:682-687

Burton AC. Relationship of structure to function of the tissues of the wall of blood vessels. Physiol. Rev. 1954;34:618

Chiu IS, Chu SH, Hung CR. Pulsatile flow during routine cardiopulmonary bypass. J Cardiovasc Surg Torino 1984; 25 (6): 530-536.

Converse Peirce C. Membrane oxygenation. In (Taylor KM ed.) Cradiopulmonary Bypass Principles and Management. Chapman and Hall, London 1986.

Dacie JV ed. Practical Haematology, fifth edition. Edinburgh and London: JA Churchill & Livingstone, 1975

Daly, I de B. A seven horse-power Austin engine adapted as a blood pump. Journal of Physiology (London) 1933;77: 36-37

DeBakey, ME. A simple continuous flow blood instrument. New Orleans Medical and Sugical Journal 1934;87:387-389

DePaepe J, Pomerantzeff PMA, Nakiri K, Armelin E, Verginalli G, Zerbini EJ. Observations of the microcirculation of the cerebral cortex of dogs subjected to pulsatile and non-pulsatile flow during extracorporeal circulation. In: A Propos Du Debit Pulse. Belgium: Cobe Laboratories Inc. 1979

Driessen JL, Dhaese H, Fransen G, Verrelst P, Rondelez L, Gevert L, van-Becelaere M. Pulsatile conpared with non-pulsatile perfusion using a centrifugal pump for cardiopulmonary bypass during coronary artery bypass grafting. Effects on systemic haemodynamics, oxygenation and inflammatory response parameters. Perfusion 1995;10:3-12

Dunn J, Kirsh MM, Hrness J, Carroll M, Straker J, Sloan H. Hemodynamic, metabolic and hematologic effects of pulsatile cardiopulmonary bypass J Thorac Cardiovasc Surg 1974; 68 (1): 138-147.

Estefanous FG, Tarazi RC, Viljoen JF, El Tawil MY. Systemic hypertension following myocardial revascularization. Am Heart J 1973; 85: 732-738.

Feiner H. Pancreatitis after cardiac surgery. Am. J. Surg. 1976;131:684

Fiddian-Green RG. Gut mucosal ischaemia during cardiac surgery. Semin. Thorac. Cardiovasc. Surg 1990;4:389-399

Fintersbusch W, Long DM, Sellers RD. Renal arteriography during extracorporeal circulation in dogs with preliminary report upon effects of low molecular weight dextran. J. Thorac. Cardiovasc. Surg 1961;41:252-260

Franklin DL, Schlegel W, Rushmer RF. Blood flow measured by Doppler frequency shift back-scattered sound. Science 1961;134:564-565

Frater RW, Wakayama S, Oka Y, Becker RM, Desai P, Oyama T, Blaufox MD. Pulsatile cardiopulmonary bypass: failure to influence hemodynamics or hormones. Circulation 1980; 62 (2): I19-25.

Fried DW, DeBenedetto BN, Leo JJ, Mattioni GJ, Mohamed H, Zombolas TL. Clinical oxygen transfer performance of the Sorin Monolyth membrane oxygentor. Perfusion 1994;9:119-126

Fry DL, Griggs DM, Greenfield JC. In vivo studies of pulsatile blood floe. the relationship of pressure gradient to the blood velocity. In Pulsatile Blood Flow. 1964.(Attinger EO ed.), pp 101-114

Gao F, Harris DNF, Sapsed-Byrne S, Sharp S. Neurone specific enolase and Sangtec 100 assays during cardiac surgery part I - the effects of heparin , protamine and propofol. Perfusion 1997;12:163-166

Gauss A, Druck A, Hemmer W, Georieff M. Abdominal complications following heart surgery. Anaesthesiol. Intensivmed. Notfallmed Schmerzther 1994;29:23-29

German JC, Chalmers GS, Hirai J, Mukherjee ND, Wakabayashi A, Connolly JE. Comparison of nonpulsatile and pulsatile extracorporeal circulation on renal tissue perfusion. Chest 1972; 61 (1): 65-69.

Gesell RA. On relation of pulse pressure to renal function. Am. J. Physiol. 1913;32:70

Gessner U. The performance of the ultrasonic flowmeter in complex velocity profiles. IEEE Trans. Biomed. Engng 1969;16:139-142

Gibbon JH Jr. Artificial maintenance of circulation during experimental occlusion of pulmonary artery. Arch. Surg.1937;34:1105-1031

Gibbon JH Jr. Application of a mechanical heart and lung apparatus to cardiac surgery. Minnesota Med. 1954;37:171-185

Gillinov AM, Davis EA, Curtis WE. Cardiopulmonary bypass and the blood brain barrier. An experimental study. J. Thorac. Cardiovasc. Surg 1991;104:1110-1115

Gobel C, Eilers R, Reul H, Schwindke P, Jorger M, Rau G. A new blood pump for cardiopulmonary bypass: the HiFlow centrifugal pump. Artif. Organs 1997;21:841-845

Goodyer AVN, Glenn WL. Relation of arterial pulse pressure to renal function. Am. J. Physiol 1951;167:689-97

Gourlay T, Taylor KM, Russell M, Wheatley D. Comparative retrospective study of pulsatile and non-pulsatile flow in 380 consecutive cardiac patients. Proc. First World Congress on Extracorporeal Circulation. Brighton England 1983.

Gourlay T, Gibbons M, Taylor KM. Evaluation of a range of arterial line filters : Part II. Perfusion 1987(a);3:29-35

Gourlay T, Gibbons M, Taylor, KM. Pulsatile flow compatibility of a group of membrane oxygenators. Perfusion 1987(b);2:115-126

Gourlay T. The role of arterial line filters in perfusion safety. Perfusion 1988;3:195-204

Gourlay T, Fleming J, Taylor KM, and Aslam M. Evaluation of a range of membrane oxygenators. Perfusion 1990;5:117-133

Gourlay T, Taylor KM. Pulsatile flow and membrane oxygentors. Perfusion 1994(a);9:189-196

Gourlay T, Taylor KM. Perfusion Pumps. In Cardiopulmonary Bypass in Neonates and Young Childern (Jonas RA and Elliott MJ eds.)Butterworth Heinemann, London 1994 (b).

Gourlay T, Taylor KM. The role of Leukocyte Depletion in the Prevention of Reperfusion Injury. In: Clinical Benefits of Leukodepleted Blood Products. Sweeney J. ed. R.G. Landes Company. Austin USA. 1995;137-51

Gourlay T, Taylor KM, Courtney JM. The effects of pulsatile blood flow during extracorporeal circulation on the generation of microemboli and filtration efficiency. Abstract in Artif. Organs 1997;21:521

Hamel G. Dei Bedeutung des pulses fur den blutstrom. Ztschr Biol NSF 1889;474-497

Harken AH. The influence of pulsatile perfusion on oxygen uptake by the isolated canine hind limb. J. Thorac. Cardiovasc. Surg;70:237-241

Harris DNF, Baily SM, Smith PLC. Brain swelling in first hour after coronary artery bypass surgery. Lancet 1993;342:586-587

Harvey W: Circulation of the blood. Edited and translated from Latin by Kenneth J, Franklin. Oxford, England. Blackwell Scientific Publications, 1958

Hill JD, Aguilar KJ, Baranco A, de Lanerolle P, Gerbode F. Neuropathological manifestations of cardiac surgery. Ann Thorac Surg 1969;7:409

Hindman BJ, Dexter F, Smith T, Cutkomp J. Pulsatile versus nonpulsatile flow. No difference in cerebral blood flow or metabolism during normothermic cardiopulmonary bypass in rabbits. Anaesthesiology 1995; 82 (1): 241-250.

Hooker DR. A study of the isolated kidney: The influence of pulse pressure upon renal function. Am J Physiol 1910; 27: 24-44.

Hutcheson IR. Griffith TM. Release of endothelium-derived relaxing factor is modulated both by frequency and amplitude of pulsatile flow. Am. J. Physiol 1991;261:H257-262

Ito H, Hamano K, Gohra H, Katoh T, Fujumara Y, Tsubi H, Esato K. Relationship between respiratory distress and cytokine response after CPB. Surg. Today 1997;27:220-225

Jacobs LA, Klopp EH, Seamone W, Topaz SR, Gott VL. Improved organ function during cardiac bypass with a roller pump modified to deliver pulsatile flow. J Thorac Cardiovasc Surg 1969; 58 (5): 703-712.

Jansen NJ, van Oeveren W, Gu YJ, van Vliet MH, Eijsman L, Wildevuur CR. Endotoxin release and tumor necrosis factor formation during cardiopulmonary bypass. Ann. Thorac. Surg 1992;54:744-747

Karichev Z, Muler A, Vishnevsky M. Unusual oxygen transfer in microporous blood oxygenator. Abstract in Artif. Organs 1997;21:522

Kohlstaedt LA, Page IH. The liberation of renin by perfusion of kidneys following reduction of pulse pressure. J. Exp. Med.1940;72:201-211

Komada T, Maeta H, Imawaki S, Shiraishi Y, Tanaka S. Haematologic and endocrinologic effects pulsatile cardiopulmonary bypass using a centrifugal pump. Nipon.Kyobu.Geka.Zashii 1992;40:901-911

Kono M, Orita H, Shimanuki T, Fukasawa M, Inui K, Wasio M. A clinical study of cerebral perfusion during pulsatile and non-pulsatile cardiopulmonary bypass. Nippon Geka Gakki Zasshi 1990;91:1016-1022

Kurusz M, Conti VR, Arens JF, Brown JP, Faulkener SC, Manning JV. Perfusion accident survey. Proc. Am. Acad. Cardiovasc. Perfusion 1986;7:57:57-65

Kurusz M, Wheeldon DR. Risk containment during cardiopulmonary bypass. Sem. Thorac. Cardiovasc. Surg. 1990;2:400-409

Kurusz M. Lessons from perfusion surveys. Perfusion 1997;7:221-227

Landymore RW, Murphy DA, Kinley CE, Parrott JC, Moffitt EA, Longley WJ, Qirbi AA. Does pulsatile flow influence the incidence of postoperative hypertension? Ann Thorac Surg 1979; 28 (3): 261-268.

Lash JA, Coates J, Lafuze TL, Baehner L Boxer L. Plasma lactoferrin refects granulocyte activation in-vivo. Blood 1983;61:885-888

Leschinski, BM, Itkin, GP, Zimin, NK. Centrifugal blood pumps - a brief analysis: development of new changes. Perfusion 1991;6:115-123

Levine FH, Philbin DM, Kono K, Coggins CH, Emerson CW, Austin WG, Buckley MJ. Plasma vasopressin levels and urinary sodium excretion during cardiopulmonary bypass with ans without pulsatile flow. Ann. Thorac. Surg 1981;32(1):63-67

Long JA. Pulsating perfusion apparatus. Science 1946; 103: 170.

Louagie YA, Gonzalez M, Collard E, Mayne A, Gruslin A, Jamart J, Buche M, Schoevaerdts JC. Does flow character of cardiopulmonary bypass make a difference? J Thorac Cardiovasc Surg 1992; 104 (6): 1628-1638.

Lucchesi BR. Myocardial ischaemia, reperfusion and free radical injury. Am. J. Cardiol 1990;65:15 - 23

Lundar T, Stokke O. Total creatinine activity in cerebrospinal fluid as an indicator of brain damage during open heart surgery. Scand. J. Thorac. cardiovasc. Surg. 1983;17:157-161

McDonald D.A. Blood Flow in Arteries. 2nd Edition 1974. Edward Arnold, London

McMaster PD, Parsons RJ. The effect of the pulse on the spread of substances through tissues. J Exp Med 1938; 68: 377-400.

Maas C, Kok R, Segers P. Comparison between a centrifugal and a roller pump. Abstract of presentation at Pthophysiology & Techniques of cardiopulmonary bypass, SanDiego CA, February 1993

Maddoux G, Pappas G, Jenkins M, Battock D, Trow R, Smith SC Jr, Steele P. Effect of pulsatile and nonpulsatile flow during cardiopulmonary bypass on left ventricular ejection fraction early after aortocoronary bypass surgery. Am J Cardiol 1976; 37 (7): 1000-1006.

Mandl JP. Comparison of emboli production between a constrained vortex pump and a roller pump; Proc. AnSECT 1977

Many M, Soroff HS, Birtwell WC, Giron F, Wise H, Deterling RA Jr. The physiologic role of pulsatile and nonpulsatile blood flow. II. Effects on renal function. Arch Surg 1968; 95 (5): 762-767.

Mathie R, Desai J, Taylor KM. Hepatic blood flow and metabolism during pulsatile and non-pulsatile cardiopulmonary bypass. Lifr Support Systems 1984;2:303-305

Mathie RT, Ohri SK, Keogh BE, Williams J, Siney L, Griffith TM. Nitric oxide activity in patients undergoing cardiopulmonary bypass. J. Thorac. Cardiovasc. Surg. 1996;112:1394-1395

Matsuda H, Hirose H, Nakano S, Shirakura R, Ohtani M, Kaneko M, Koh Y, Nomura F, Kawashima Y. Results of open heart surgery in patients with impaired renal function as creatinine clearance below 30ml/min. The effects of pulsatile perfusion. J Cardiovasc Surg (Torino) 1986; 27 (5): 595-599.

Matsukura H. An experimental study of the preservation of platelet during extracorporeal circulation. Japan. J. Thorac. Surg. 1983;36:11

Mavroudis C. To pulse or not to pulse. Ann Thorac Surg 1978: 25: 259-271.

Melrose DG. A heart-lung machine for use in man. Br. J. Physiol 1955;127:52-53

Mills CJ, Shillingford JP. A catheter-tip electromagnetic flow probe and its evaluation. Cardiovasc. Res. 1967;1:263-273

Mori A, Tabata R, Matsuda M, Nakamura Y, Takeuchi T, Okada Y. Carbohydrate metabolism during pulsatile cardiopulmonary bypass under profound hypothermia. Jpn Circ J 1983; 47 (5): 528-535.

Mori A, Watanabe K, Onoe M, Watarida S, Nakamura Y, Magara T, Tabata R, Okada Y. Regional blood flow in the liver, pancreas and kidney during pulsatile and nonpulsatile perfusion under profound hypothermia. Jpn Circ J 1988: 52 (3): 219-227.

Mukherjee ND, Beran AV, Hirai J. In vivo determination of renal tissue oxygenation during pulsatile and non-pulsatile left heart bypass. Ann. Thorac. Surg. 1973;15:334

Murray WR, Mittra S, Mittra D, Roberts LB, Taylor KM. The amylase creatinine clearance ratio following cardiopulmonary bypass. J. Thorac. Cardiovasc. Surg. 1982;82:248-253

Nakayama K, Tamiya T, Yamamoto K, Izumi T, Akimoto S, Hishizume S, Iimori T, Odaka M, Yazawa C. High amplitude pulsatile pump in extracorporeal circulation with particular reference to hemodynamics. Surgery 1963; 54: 798.

Ninomiya J, Shoji T, Tanaka lS, Ikeshita M, Ochi M, Yamauchi S, Yajima T, Ymauchi H, Sugimoto lT, Aizawa T. Clinical evaluation of a new type of centrifugal pump. Artif Organs 1994; 18 (9): 702-705.

Nishida H, Yamaki F, Nakatani H, Endo M, Koyanagi H, Oshiyama H, Horiuchi K, Kijima T, Nojiri C, Fukasawa H, Akutsu T. Development of the Terumo Capiox centrifugal pump and its clinical application to open heart surgery; a comparative study with the roller pump. Artif. Organs 1993;17:323-327

Nonoyama, A. Haemodynamic studies on extracorporeal circulation with pulsatile and non-pulsatile blood flows. Archives of Japan Chirurgie 1960;29:381-406

Noon GP, Sekela ME, Glueck, Coleman CL, Feldman L. Comparison of in vitro blood trauma and spallation produced by the Bio-medicus and roller pump during hypothermia. Int'l Workshop on rotary blood pumps 1988; Baylor College

Noordergraaf A, Boom HBK, Verdouw PD. A human sytemic analog computer. In Proc. 1st Congr. Soc. for Ballistocariographic Res. (Noordergraaf ed.) 1960

Nose' Y. Nonpulsatile mode of blood flow required for cardiopulmonary bypass and total body perfusion. Artif. Organs 1993;17:92-102

Oelert H, Eufe R. Dog kidney function during total left heart bypass with pulsatile and non-pulsatile flow. J. Cardiovasc.Surg.(Turino) 1974;15:674

Ogata T, Ida Y, Takeda J. Experimental studies on the extracorporeal circulation by use of our pulsatile arterial pump. Lung 1959;6:381

Ogata T, Ida Y, Takeda J, Saski H. A comparative study of the effectiveness of pulsatile and nonpulsatile blood flow in extracorporeal circulation. Arch Jpan Chir 1960; 29: 59-65.

Ohri SK, Bowles CT, Siddiqui A, Khaghani A, Keogh BE, Wright G, Yacoub MH, Taylor KM. The effect of cardiopulmonary bypass on gastric and colonic mucosal perfusion. a tonometric assessment. Perfusion 1994;9:101-108

Onoe M, Mori A, Watarid S, Sugita T, Shiraishi S, Nojima T, Nakajima Y, Tabata R, Matsuno S. The effect of pulsatile perfusion on cerebral blood flow during profound hypothermia with total circulatory arrest. J Thorac Cardiovasc Surg 1994; 108 (1): 119-125.

Ortolano GA. Potential for reduction in morbidity and cost with total leukocyte control for cardiac suegery. Perfusion 10;5:281

Pappas G, Winter SD, Kopriva CJ, Steele PP. Improvement of myocardial and other vital organ functions and metabolism with a simple method of pulsatile flow (IAPB) during clinical cardiopulmonary bypass. Surgery 1975; 77: 34-44.

Paquet KJ. Hemodynamic studies on normothermic perfusion of the isolated pig kidney with pulsatile and non pulsatile flows. J Cardiovasc Surg (Torino) 1969; 10 (1): 45-53.

Parsons RJ, McMaster PD. The effect of the pulse upon the formation and flow of lymph. J Exp Biol 1938; 68: 353-376.

Patel DJ, De Freitas FM, Fry DL, Hydraulic input impedance to aorta and pulmonary artery in dogs. J Appl Physiol. 1963; 18: 134-140.

Patterson RH, Kessler J. Microemboli during cardiopulmonary bypass detected by ultrasound. Surg. Gyn. Obstet. 1969;129:505-510

Pearson DT, Watson BG, Waterhouse PS. An ultrasonic analysis of the comparitive efficiency of various cardiotomy reservoirs and blood filters. Thorax 1978;33:352-358

Pearson DT. Microemboli. In (Taylor. KM ed) Cradiopulmonary Bypass Principles and management. Chapman and Hall London 1986

Pennington DG, Merjavy JP, Swarz MT, Williams VL. Clinical experience with centrifugal pump ventricular assist devices. Trans. Am. Soc. Artif. Internal Organs 1982;28:93-99

Philbin DM, Coggins CH, Emerson CW et al. Plasma vasopressin levels and urinary sodium excretion during cardiopulmonary bypass: a comparison of halothane and morphine anesthesia. J Thorac Cardiovasc Surg 1979; 77: 582.

Philbin DM, Levine FH, Emerson CW, Coggins CH, Buckley MJ, Austen WG. Plasma vasopressin levels and urinary flow during cardiopulmonary bypass in patients with valvular heart disease: effects of pulsatile flow. J Thorac Cardiovasc Surg 1979; 78 (5): 779-783.

Philbin DM, Hickey PR, Buckley MJ. Should we pulse? J Thorac Cardiovasc Surg 1982; 84 (6): 805-806.

Pohl U, Lamontagne D. Impaired tissue perfusion after inhibition of endothelium-derived nitric oxide. Basic Res.Cardiol. 1991;86 Suppl 2:97-105

Prior FGR, Moorcroft V, Gourlay T, Taylor KM. Further testing of pulse reverse osmosis. A new theory of the maintenance and control of blood pressure. Int. J. Artif. Organs. 1995;18(8): 469-

Prior FGR, Moorecroft V,_Gourlay T, Taylor KM. The Therapeutic Significance of Pulse Reverse Osmosis. Int. Jour. Artif. Organs, 1996; 19(8):487-92

Quigley RL, Caplain MS, Perkins JA, Arentzol CE, Alexander JC, Kuehn BE, Hoff WJ, Wallock ME. Cardiopulmonary bypass with adequate flow and perfusion pressure prevents endotoxaemia and pathologic cytokine production. Perfusion 1995; 10:27-33

Reilly PM, Bulkey GB. Vasoactive mediators and splanchnic perfusion. Crit. Care Med.1993;21:S55-68

Riddington DW, Venkatesh B, Boivin CM, Elliott TS, Marshall T, Mountfield PJ, Bion JF. Intestinal permeability, gastric intramucosal pH, ans systemic endotoxemia in patients undergoing cardiopulmonary bypass. JAMA 1996;275:1007-1012

Ritter ER. Pressure-flow relations in kidney: alleged effects of pulse pressure. Am J Physiol 1952; 168: 480-489.

Rocke DA, Gaffin SL, Wells MT, Keon Y, Brock Utine JG. Endotoxaemia associated with cardiopulmonary bypass. J. Thorac. Cardiovasc. Surg 1987;93:832-837

Royston DJ, Fleming J, Desai JB, Taylor KM. Neutrophil activation and pulmonary injury during open-heart surgery. J. Thorac. Cardiovasc. Surg 1986;91:758-766

Runge TM, Grover FL, Cohen DJ, Bohls FO, Ottmers SE. Preload-responsive, pulsatile flow, externally valved pump: cardiovascular bypass. J Invest Surg 1989; 2 (3): 269-279.

Runge TM, Cohen DJ, Hantler CB, Bohls FO, Ottmers Se, Briceno JC. Achievement of physiologic pulsatile flow on cardiopulmonary bypass with a 24 French cannula. ASAIO 1992;38:M726-729

Saggau W, Baca I, Ros E, Storch HH, Schmitz W. Clinical and experimental studies on pulsatile and continuous flow during extracorporeal circulation. Herz.1980;5:42-50

Sanderson JM, Morton PG, Tolloczko TS, Vennart T, Wright G. The Morton-Keele pump - a hydraulically activated pulsatile pump for use in extracorporeal circulation. Med.. Biol. Eng 1973;182-190

Sanderson JM, Wright G, Sims FW. Brain damage in dogs immediately following pulsatile and non-pulsatile blood flows in extracorporeal circulation. Thorax 1972; 27 (3): 275-286.

Schlichting H. Boundary layer theory , 6th edn. McGraw-Hill, New York, 1968, 536-537

Selkurt EE. Effects of pulse pressure and mean arterial pressure modification on renal haemodynamics and electrolyte and water excretion. Circulation 1951;4:541

Shaw PJ, Bates D, Cartlige NEF, Heaviside D, Julian DG, Shaw DA. Early neurological complications of coronary artery bypass surgery. Br. Med. J. 1985;291:1384-1386

Shepard RB, Kirklin JW. Relation of pulsatile flow to oxygen consumption and other variables during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1969; 58 (5): 694-702.

Shepard RB, Simpson DS, Sharp JF. Energy equivalent pressure. Arch Surg 1966; 93: 730-740.

Shepherd S, Pierce JMT. Pulsatile flow during cardiopulmonary bypass speeds thermal energy transfer: a possible explanation for the reduced afterdrop. Perfusion 1995; 10: 111-114.

Simpson JC. Cerebral perfusion during cardiac surgery using cardiac bypass. In Towards Safer Cardiac Surgery (Longmore D. ed) MTP, Lancaster, 1981

Smith PLC, Treasure T, Newman SP. Cerebral consequences of cardiopulmonary bypass. Lancet 1986;i:823-825

Starling EH. On absorbtion of fluids from the connective tissue spaces. J. Physiol. (London) 1896;19:312-326

Stinkens D, Himpe D, Thyssen P, De Bakker A, Smets W, Borms S, Suy M, Muylaert P, van Hove M, Theunissen W, van Cauwelert P. Clinical evaluation of the oxygenation capacity and controllability of 15 commercially available membrane oxygenators during alpha-stat regulated hypothermic cardiopulmonary bypass. Perfusion 1996;11:471-780

Stinson EB, Holloway EL, Derby GC, Copeland JG, Oyer PE, Beuler DL, Greipp RB. Control of myocardial performance early after open heart operations by vasodilator treatment. J. Thorac. Cardiovasc. Surg. 1977;73:523

Takeda J. Experimental study on peripheral circulation during peripheral circulation, with a special reference to a comparison of pulstile flow with non-pulsatile flow. Arch Japan Chir 1960; 29: 1407-1430.

Tao W, Zwischenberger JB, Nguyen TT, Vertrees RA, Nutt LK, Herndon DN, Kramer GC. Gut mucosal ischaemia during normothermic cardiopulmonary bypass results from blood flow redistribution and increased oxygen demand.J. Thorac. Cardiovasc. Surg 1995;110:819-828

Taylor KM, Devlin BJ, Mittra S, Gillan JG, Brannan JJ, McKenna JM. Assessment of cerebral damage during open heart surgery. A new experimental model. Scand. J. Thorac. Cardiovasc. Surg. 1980;14:197-203

Taylor KM. Effect of pulsatile flow and arterial line filtration on cerebral cellular damage during open-heart surgery. Proceedings of Second International Symposium on Psychopathological and Neurological Dysfunctions following Open-Heart Surgery. 1980.

Taylor KM, Bain WH, Davidson KG, Turner MA. Comparative clinical study of pulsatile and non-pulsatile perfusion in 350 consecutive patients. Thorax 1982; 37 (5): 324-330.

Taylor KM, Bain WH, Maxted KJ, Hutton MM, McNab WY, Caves PK. Comparative studies of pulsatile and nonpulsatile flow during cardiopulmonary

bypass. I. Pulsatile system employed and its hematologic effects. J Thorac Cardiovasc Surg 1978; 75 (4): 569-573.

Taylor KM, Bain WH, Russell M, Brannan JJ, Morton IJ. Peripheral vascular resistance and angiotensin II levels during pulsatile and no-pulsatile cardiopulmonary bypass. Thorax 1979; 34 (5): 594-598.

Taylor KM, Bain WH, Morton JJ. The role of angiotensin II in the development of peripheral vasoconstriction during open heart surgery. Am. Heart J. 1980;100:935-937

Taylor KM, Casals J, Morton JJ, Mittra S, Brannan JJ, Bain WH. The haemodynamic effects of angiotensin blockade after cardiopulmonary bypass. Br. Heart J. 1979;41:380

Taylor KM, Brannan JJ, Bain WH, Caves PK, Morton IJ. Role of angiotensin II in the development of peripheral vasoconstruction during cardiopulmonary bypass. Cardiovasc Res 1979; 13 (5): 269-273.

Taylor KM, Wright GS, Bain WH, Caves PK, Beastal GH. Comparitive studies of pulsatile and non-pulsatile flow during cardiopulmonary bypass. III Anterior pituitary response to thyrotrophin-releasing hormone. J. Thorac. Cardiovasc. Surg. 1979;75:579

Taylor KM, Wright GS Reid JS, Bain WH, Caves PK, Walker MS, Grant JK. Comparitive studies of pulsatile and non-pulsatile flow during cardiopulmonary bypass. II The effects on adrenal secretion of cortisol . J. Thorac. Cardiovasc. Surg 1979; 75:574

Taylor KM,. Assessment of cerebral damage during cardiopulmonary bypass with particular reference to perfusion and microembolic damage. Am. Acad. Cardiovasc. Perf. 1983;4:110-113

Taylor KM. The present status of pulsatile perfusion. Curr. Med. Lit. Cardiovasc. Med. 1984;3:66-69

Taylor KM. Pulsatile Perfusion. In Cardiopulmonary Bypass-Principles and management (KM Taylor ed). Chapman and Hall, London 1986.

Tranmer BI, Gross CE, Kindt GW, Adey GR. Pulsatile versus nonpulsatile blood flow in the treatment of acute cerebral ischemia. Neurosurgery 1986; 19 (5): 724-731.

vanAllen CM. A pump for clinical and laboratory purposes which employs the milking principle. Annals of Thoracic Surgery 1932;98:1806-1806

Watkins WD, Peterson MB, Kong K, Buckley MJ, Levine FH, Philbin DM. Thromboxane and prostacyclin changes during cardiopulmonary bypass with and without pulsatile flow. J Thorac Cardiovasc Surg 1982; 34 (4): 439-445.

Wesolowski SA, Miller HH, Halkett AE. Experimental replacement of the heart by a mechanical extracorporeal pump. Bulletin of the New England Medical Centre 1950;12:41-50

Westaby S, Johnsson P, Parry AJ, Blomqvist S, Solem J, Alling C, Pillai R, Taggert D, Grebenik C, Stahl E. Serum S100 protein: A potential marker for cerbral events during cardiopulmonary bypass. Ann Thorac. Surg 1996;61:88-92

Westerhof N, Bosman F, De Vries CJ, Noordergraaf A. Analog studies of the human systemic arterial tree. J Biomech 1969; 2: 121-143.

Westerhof N, Elzinga G, Sipkema P. An artificial arterial system for pumping hearts. J Appl Physiol 1971; 31 (5): 776-781.

Wilcox BR, Coulter NA, Peters RM, SDtacey RW. Power dissipation in the systemic and pulmonary vascualture of dogs. Surgery 1967;62:25

Williams GD, Seifen AB, Lawson NW, Norton JB, Readinger RI, Dungan TW, Calliway JK, Campbell GS. Pulsatile perfusion versus conventional high flow non-pulsatile perfusion for rapid core cooling and rewarming of infants for circulatory arrest in cardiac operation. J,Thorac.Carciovasc.Surg 1979;78:667-77

Womersley JR. An elastic tube theory of pulse transmission and oscillatory flow in mammalian arteries. Wright Air Development Centre. Tech Report. TR56-614, 1957

Wright G and Sanderson JM. Cellular aggregation and destruction during blood circulation and oxygenation. Thorax 1976;31:405

Wright G, Furness A. What is pulsatile flow ? Ann. Thorac. Surg. 1985;39:401-402

Wright G. Factors affecting the pulsatile hydraulic power output of the Stockert roller pump. Perfusion 1989; 4: 187-195.

Wright G. Hemodynamic analysis could resolve the pulsatile blood flow controversy. Annals of Thoracic Surgery 1994; 58 (4): 1199-1204.

Wright G. The hydraulic power outputs of pulsatile and nonpulsatile cardiopulmonary bypass pumps. Perfusion 1988; 3: 251-262.

Wright G. Blood cell trauma. In Cardiopulmonary Bypass (KM Taylor ed.), Chapman and Hall, London 1986:249-276

Wright G, Ping J, Campbell C, Tobias M. Computation of haemodynamic power and input impedance in the ascending aorta of patients undergoing open heart surgery. Cardiovasc. Res 1988;22:179-184