ANAESTHESIA AND HYPOTHERMIC

CARDIOPULMONARY BYPASS:

HAEMODYNAMIC AND METABOLIC VARIABLES

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DECLARATION and ACKNOWLEDGEMENTS

The author declares that all work in this thesis, with the exception of that noted below, was undertaken by himself and further, that this thesis was written solely by himself.

SUMMARY

Despite extensive investigation, the effects of some aspects of cardiopulmonary bypass upon haemodynamic and metabolic variables remain unresolved. Also, there have been great changes in the practice of cardiopulmonary bypass over the years and the findings of early research may no longer be applicable to present day techniques. Three aspects of cardiopulmonary bypass were identified as requiring investigation regarding their haemodynamic and metabolic effects: low flow rates; flow character *ie* nonpulsatile or pulsatile perfusion; and acid–base management *ie* pH or alpha–stat control.

Anaesthesia during cardiopulmonary bypass has been found in the past to have important metabolic effects which could be used to improve patient wellbeing and hence, outcome. However, these agents have been largely superseded by modern drugs that are metabolically untested. Although the effects on haemodynamic variables of most modern anaesthetics have been extensively studied before and after cardiopulmonary bypass, their actions during the abnormal conditions of cardiopulmonary bypass have not been rigorously examined.

It was hypothesised that cardiopulmonary bypass and anaesthetic techniques have important haemodynamic and metabolic effects. This thesis was undertaken to test this hypothesis.

In all the studies, arterial and mixed venous blood samples were analysed for oxygen content, saturation and tension, pH, carbon dioxide tension, base excess and lactate concentration. Systemic oxygen uptake and delivery were calculated.

Initially, a computerised system was developed to act as a data logger for haemodynamic, arterial pH and temperature measurements as well as to

enhance thermostatic and acid–base control. This system was tested and found to function well both as a recording device and as a means of obtaining good thermostatic control. However, the system performed poorly with regard to arterial pH control.

The haemodynamic and metabolic effects of flow rate, flow character and acid–base management during hypothermic cardiopulmonary bypass were studied in a factorial experiment. Of the three factors, only alternation of flow rate between 1.5 and 2.0 $L.min^{-1}.m^{-2}$ was found to have a significant effect on systemic oxygen uptake. Flow rate was also found to have a significant effect on mean arterial pressure and peripheral vascular resistance. Arterial pH and stage during cardiopulmonary bypass were found to significantly interact to influence mean arterial pressure but not peripheral vascular resistance. Alternation of flow character between pulsatile and nonpulsatile perfusion had no significant effect on haemodynamic variables. Over and above these effects, a progressive vasoconstriction throughout cardiopulmonary bypass was noted.

Isoflurane's effects on haemodynamic and metabolic variables were examined during hypothermic cardiopulmonary bypass. Isoflurane was found to be a vasodilator during these abnormal haemodynamic conditions although no systemic metabolic effects were identified.

Next, the haemodynamic and metabolic effects of atracurium during hypothermic cardiopulmonary bypass were studied. Neither haemodynamic nor metabolic effects were found from the use of atracurium.

Finally, the haemodynamic and metabolic effects of alfentanil and it's antagonism with naloxone during hypothermic cardiopulmonary bypass were investigated. Neither alfentanil nor its antagonism with naloxone had any significant metabolic effect. However, administration of alfentanil prevented the expected increases in mean arterial pressure and peripheral vascular resistance that occur during the course of cardiopulmonary bypass. In contrast, antagonism of alfentanil with naloxone produced greater increases in mean arterial pressure

and peripheral vascular resistance than would be predicted to occur simply as a result of stage.

Flow rate proved to be an important determinant of haemodynamics and metabolism during hypothermic cardiopulmonary bypass. This finding makes questionable the practice of reducing the pump flow rate to low levels after induction of hypothermia. The lack of difference in haemodynamic and metabolic effects between nonpulsatile and pulsatile perfusion would add weight to the body of opinion which holds that flow character has no important actions during clinical cardiopulmonary bypass. Arterial pH interacted with stage during cardiopulmonary bypass to influence mean arterial pressure. However, the clinical importance of this finding is uncertain as the size of effect was small. This haemodynamic finding and the lack of any difference in metabolic effect add no weight to the use of either alpha or pH-stat acid-base management.

The progressive vasoconstriction, found throughout these studies, is an important and well recognised phenomenon of cardiopulmonary bypass. The lack of any impairment in systemic oxygen uptake associated with this rise in peripheral vascular resistance contrasts strongly with the marked reduction in systemic oxygen uptake associated with the increase in peripheral vascular resistance that resulted from decreasing the flow rate. The metabolic effects associated with the increases in peripheral vascular resistance, either as a result of decreasing the flow rate or due to vasoconstriction during the course of cardiopulmonary bypass, suggest passive and active mechanisms, respectively.

Isoflurane's lack of metabolic effect contrasts with previous work in the intact cardiovascular system at normothermia. Possible explanations for this difference in findings are the use of hypothermia and a constant flow rate. However, isoflurane proved to be a vasodilator which could be used to control hypertension during cardiopulmonary bypass whilst ensuring anaesthesia without the risk of awareness.

The absence of any metabolic action with the use of atracurium is in contrast to tubocurarine which has previously been been found to reduce systemic oxygen uptake. The use of hypothermia in the present study and the fact that atracurium, unlike tubocurarine, has minimal haemodynamic effects may account for the differing findings.

Alfentanil's lack of metabolic effect may have been predictable as opioids only have metabolic actions in a few specialised circumstances. However, the haemodynamic effects of alfentanil were unexpected considering its minimal actions in the intact cardiovascular system at normothermia. The present findings indicate that opioids, such as alfentanil, play an important role in ameliorating the vasoconstriction that is ongoing throughout cardiopulmonary bypass.

In conclusion, the hypothesis that cardiopulmonary bypass technique has important haemodynamic and metabolic effects was proved true only with respect to flow rate. With regard to anaesthesia, the hypothesis held true for haemodynamic effects but could not be supported for metabolic actions.

CHAPTER 1

INTRODUCTION

Cardiopulmonary bypass is the keystone that presently enables cardiac surgery to be undertaken on hundreds of thousands of patients every year. In a remarkably short time, cardiopulmonary bypass has become a routine clinical technique as it was only in 1937 that Gibbon first proposed the use of cardiopulmonary bypass to enable surgeons to operate on intracardiac abnormalities under direct vision [1]. What was pioneering work just over four decades ago is now an everyday occurrence in most major hospitals around the world.

The purpose of cardiopulmonary bypass is to allow the normal function of the heart and lungs to be suspended whilst surgery on these vital structures is performed. This function is achieved mechanically by supplying oxygenated blood to the tissue in sufficient quantity to allow continued aerobic metabolism. Basically, cardiopulmonary bypass involves syphoning blood from the patient's venous system into a reservoir, where carbon dioxide is removed and oxygen added to the blood before it is pumped back into the patient's arterial system. However, this activity requires major physiological trespass with considerable risk to the patient. At the outset, a high mortality and morbidity were implicit in cardiopulmonary bypass [2]. When balanced against the potential to remedy life threatening and previously untreatable cardiac disease, the risks of cardiopulmonary bypass were considered acceptable. Today, the mortality for all types of surgery involving cardiopulmonary bypass in the United Kingdom is 8.5% and for coronary artery surgery alone, it is only 3.2% [3]. Because of the present relatively low risk from cardiopulmonary bypass, the focus of cardiac surgery has moved from the correction of life threatening cardiac conditions, such as congenital and valvular heart diseases, to the mostly symptomatic treatment of coronary artery disease.

Undoubtedly, the present low risk of surgery involving cardiopulmonary bypass stems from much fundamental research during the pioneering years to establish a modus operandi as well as from technical advances in equipment [2]. Although patient outcome will always be the final criteria, systemic haemodynamic and metabolic variables have been employed from the beginning as sensitive measures of the adequacy of cardiopulmonary bypass and to date, they remain important indices.

Early subjects for investigation of cardiopulmonary bypass were the haemodynamic and metabolic effects of flow rate, hypothermia and pulsatile perfusion [4-8]. Despite continued study, the haemodynamic and metabolic effects of some basic cardiopulmonary bypass techniques, for example low flow rates [9,10], pulsatile perfusion [11,12] and acid–base management [13-15], have remained largely unresolved. Moreover, there have been great changes in the practice of cardiopulmonary bypass over the last forty years, for example hypothermia and haemodilution are both now standard in most centres. Extrapolation from early findings to modern practice may therefore be no longer appropriate.

The actions of anaesthetic drugs before and after cardiopulmonary bypass have been extensively studied [16,17]. In contrast, their actions during cardiopulmonary bypass have been largely ignored. Anaesthesia for cardiac surgery has changed out of all recognition over the last four decades and this is, at least in part, because of the introduction of modern anaesthetic drugs. The metabolic and haemodynamic effects of only a few anaesthetic agents have ever been studied during cardiopulmonary bypass and virtually none of the modern anaesthetic drugs have been investigated. Yet anaesthetic agents are known to have important haemodynamic and metabolic effects which could be used to advantage during cardiopulmonary bypass to improve still further the outcome from cardiac surgery [18].

Modern cardiac anaesthesia in the United Kingdom, with the notable exception of high dose opioid techniques, is based on Lundy's concept of

balanced anaesthesia [19]. By using a combination of specific agents in small amounts to produce the triad of anaesthesia that is analgesia, hypnosis and muscle relaxation, the adverse effects of anaesthesia are minimised compared to employing a high dose of a single agent to produce all three components. A vast array of drugs are used to produce this triad for cardiac anaesthesia though they can be classified into four groups which are; opioids, neuromuscular blockers, intravenous and inhalational anaesthetic agents [20]. Opioids and neuromuscular blocking drugs are almost universally employed to produce analgesia and muscle relaxation respectively whereas either inhalational or intravenous anaesthetic agents are used for hypnosis. Because of the large number of drugs that are presently used for cardiac anaesthesia, Lundy's triad makes a suitable basis upon which to study the effects of anaesthesia on haemodynamic and metabolic variables during cardiopulmonary bypass.

In conclusion, the purpose of this thesis is to re-evaluate the effects of certain unresolved aspects of cardiopulmonary bypass technique on haemodynamic and metabolic variables in the light of present day anaesthetic and cardiopulmonary bypass practice. It will then examine the effects of balanced anaesthesia during cardiopulmonary bypass upon these variables. Ultimately, it is hoped to determine the most efficacious combination of cardiopulmonary bypass and anaesthetic techniques in terms of the haemodynamic and metabolic wellbeing of the patient during cardiopulmonary bypass.

CHAPTER 2

HISTORICAL REVIEW

In order to establish the background to this thesis, this chapter will review the methods that have been used to measure systemic haemodynamics and metabolism during cardiopulmonary bypass and how different techniques of cardiopulmonary bypass affect these variables. Anaesthesia's effect upon these variables during cardiopulmonary bypass will then be considered.

Cardiopulmonary bypass has important actions on many systems other than haemodynamics and metabolism. For example, it can cause severe coagulopathy and cerebral dysfunction. Also, there have been major advances in equipment design over the years, such as the development of roller pumps, which have contributed greatly to the present improved safety of cardiopulmonary bypass. As they have been extensively examined previously [21-24], these aspects of cardiopulmonary bypass will not be considered further in this review which will concentrate first, on systemic metabolism and then, systemic haemodynamics during cardiopulmonary bypass.

METABOLISM

The German physiologist, Pflüger, was the first to realise that the primary functions of the cardiopulmonary system were to guarantee cellular oxygen supply and to remove waste products of metabolism. Pflüger stated that all else was secondary:

> "Arterial oxygen content, arterial pressures, blood flow
> velocity, mode of cardiac work and mode of respiration, all
> are incidental and subordinate; they all combine their
> actions only in service to the cells." [25]

This concept remains totally applicable to the function of cardiopulmonary bypass today. The bulk of oxygen consumed by the cells is used in the release of energy from foodstuffs by oxidative phosphorylation in the mitochondria although a considerable fraction of it is required for other enzymatic functions. Cone and Dennison have both recently reviewed in detail the cellular usage of oxygen and so, it will not be considered further here [26,27]. This review will instead consider the measures of systemic metabolism that have been used to assess the adequacy of cardiopulmonary bypass.

MEASURES OF METABOLISM

Systemic oxygen uptake

As the essential function of cardiopulmonary bypass is to supply oxygenated blood to the tissues in quantities sufficient to allow continued aerobic metabolism, systemic oxygen uptake is the prime metabolic measure of the adequacy of cardiopulmonary bypass. Systemic oxygen uptake is determined by the balance between oxygen delivery and tissue oxygen demands. If the delivery of oxygen is adequate then systemic oxygen uptake is dependent on metabolic rate. Should oxygen delivery become inadequate, systemic oxygen uptake is limited as there are little or no tissue stores of oxygen. Continued metabolism beyond this point becomes anaerobic; lactic acid is produced and metabolic acidosis results. For these reasons, systemic oxygen uptake has long been established as an important measure of the performance of cardiopulmonary bypass [4-7].

In the intact cardiovascular system, systemic oxygen uptake can be measured by direct or indirect methods [28]. The direct method involves analysing the composition of gases inspired and expired from the lungs over a known period of time. As the lungs are excluded from the circulation and gases are

exchanged by the oxygenator, this method is not applicable during cardiopulmonary bypass. Theoretically, systemic oxygen uptake could be ascertained directly by measurement of the composition and volume of gases supplied to and exhausted from the oxygenator over a known time, but this method has not been validated. The simpler and established method of determining systemic oxygen uptake during cardiopulmonary bypass is indirectly, using Fick's principle [29]. Although Fick originally proposed his method as a means of determining cardiac output in the intact cardiovascular system, simple substitution of the formula allows determination of systemic oxygen uptake during cardiopulmonary bypass using the product of the arterio-venous oxygen content difference and pump flow rate.

Carbon dioxide production

Carbon dioxide is the major end product of metabolism. Therefore, for similar reasons to systemic oxygen uptake, carbon dioxide output could also be used to measure systemic metabolism and so, the adequacy of cardiopulmonary bypass. However, carbon dioxide is often added to the oxygenator in variable amounts to control the acid-base balance and this unquantifiable factor would confound the reliability of any measurements of carbon dioxide production.

Systemic oxygen delivery

As low levels of oxygen supply can limit systemic oxygen uptake and result in anaerobic metabolism, systemic oxygen delivery is an important metabolic indice during cardiopulmonary bypass. Oxygen delivery to the tissues is dependent on the product of flow rate and arterial oxygen content. Pump flow rate is generally set at pre-determined levels during cardiopulmonary bypass. If hypothermia is used in conjunction with cardiopulmonary bypass, flow rate is often reduced to low levels so restricting systemic oxygen delivery and this important aspect will discussed in detail later. If flow rate is fixed, then arterial blood oxygen content becomes the critical measure that determines systemic oxygen delivery.

Arterial oxygen variables

Arterial hypoxaemia can limit systemic oxygen uptake [30] and therefore, it's prevention is important during cardiopulmonary bypass. The oxygen content of arterial blood is related to the haemoglobin concentration and the saturation of haemoglobin with oxygen plus the amount of oxygen dissolved in plasma which is dependent on the oxygen tension [28]. Although it can be determined indirectly using these variables, blood oxygen content is more accurately measured directly [31].

Venous oxygen variables

Mixed venous blood oxygen content, saturation and tension have all been widely advocated as indices of systemic metabolism during cardiopulmonary bypass [32-39], the assumption being that they reflect the average state of tissue oxygenation. Mixed venous oxygen tension has been advanced by Stanley and Isern-Amaral as being more sensitive than saturation in predicting perfusion requirements and so, allowing earlier detection of imbalance between oxygen supply and demand [38]. However, interpretation of these variables can be very difficult as they may be confounded by a variety of unquantifiable factors and capillary shunting is an excellent example of this problem. As a result, it is unclear whether low or high values of mixed venous blood content, saturation or tension indicate adequate perfusion [22,40].

Lactic acid

When systemic oxygen delivery decreases, oxygen extraction by the tissues increases to maintain a normal systemic oxygen uptake. Should systemic oxygen delivery fall below a critical level that is associated with near maximal oxygen extraction, then cells must resort to anaerobic biochemical pathways for vital energy production [41,42]. At this point oxygen uptake becomes supply dependent. Lactic acid, being the end product of anaerobic metabolism, accumulates intracellularly and is then released into the blood. For this reason lactate concentration has been widely used as an index of the adequacy of

cardiopulmonary bypass [5,43-48]. Early studies found that lactic acid concentration progressively increased over the course of cardiopulmonary bypass [5,48]. In severe cases, there was lactic acidosis and this was associated with a high mortality [5]. However, the value of monitoring lactate concentration during low flow cardiopulmonary bypass has been questioned by Harris, Seelye and Barratt-Boyes as they found that important changes in systemic oxygen uptake occured without concommitant alteration in lactate concentration [48].

Base excess

If anaerobic metabolism occurs, the increase in fixed acids will result in metabolic acidosis with a decrease in plasma bicarbonate. In the past, arterial pH has been used as a measure of the adequacy of perfusion during cardiopulmonary bypass and a progressive acidosis was a frequent finding [4,5,34]. Marked acidosis was associated with a high mortality [5]. However, as pH is mainly controlled and readily adjusted during cardiopulmonary bypass by the respiratory component of acid-base balance (the amount of dissolved carbon dioxide), base deficit rather than pH is now used as an index of acid-base balance and so, of anaerobic metabolism [6,36,43].

Invasive measurements

All the above variables are indices of the adequacy of systemic perfusion. However, they may not represent the adequacy of perfusion in all tissues. For this reason, Pranger and colleagues have used tissue PO_2 histograms and they have detected changes in shape of the histograms to occur before changes in any systemic variables [49]. However, as it is uncertain which tissues should be monitored and because of it's invasive nature, tissue PO_2 histograms will not be used here.

EFFECTS OF CARDIOPULMONARY BYPASS ON METABOLISM

Cardiopulmonary bypass includes many factors that may influence metabolism. This section will review the metabolic effects of these factors and identify those which remain unresolved. The effect of anaesthesia during cardiopulmonary bypass on metabolic variables will then be considered.

Hypothermia

Although a few centres still use normothermia, the majority employ some degree of hypothermia in conjunction with cardiopulmonary bypass. By reducing the rate of biochemical reactions, hypothermia causes a marked decrease in systemic oxygen uptake. The quantitative inter-relationships between these factors have been described mathematically in various ways [22]. Some, such as Ross [50], have used a linear model. Others, including Harris Seelye and Squire [51], have used a model based on Arrhenius's theory, which states that the logarithm of a chemical reaction is inversely proportional to the reciprocal of the absolute temperature. A sigmoid curve represents this relationship such that at very high temperatures the reaction rate ceases to increase with temperature. However, at physiological temperatures, biochemical systems operate only on the upswing of the curve. This relationship, especially if the temperature range is small, is expressed by van't Hoff's law which relates the logarithm of the chemical reaction directly to temperature. According to this equation, the reaction rate increases by two to three times for each 10°C rise in temperature and this ratio is called the Q_{10}. Studies of tissue slices confirm this relationship [22] although, in humans, the Q_{10} is variable and dependent on the timing of hypothermia [22,51]. However, this discrepancy in humans may be explained by uneven cooling of the body [52].

The reduction in metabolism induced by hypothermia is used to advantage during cardiopulmonary bypass as tissue ischaemia or hypoperfusion can be tolerated for a longer time, before irreversible functional or structural damage

occurs, than would be the case at normothermia. Originally, hypothermia was clumsily achieved by immersion in iced water or external application of ice packs [22]. Today, hypothermia and rewarming are easily obtained by using heat exchangers incorporated into the oxygenator [22]. Thus, hypothermia is a valuable and easily spread safety net in the event of perfusion mishap or inadequate perfusion.

As well as systemic benefits, hypothermia also has advantages for myocardial protection. Even during aortic cross clamping, systemic blood may enter the heart via non-coronary collateral vessels and rewarm the heart. Therefore, using low body temperatures helps to slow rewarming and provide myocardial protection. Kirklin and Barratt-Boyes [54] have reviewed this aspect of systemic hypothermia and so, it will not be considered further here.

Hypothermia may also have an adverse metabolic effect as it causes a leftward shift of the oxygen haemoglobin dissociation curve. This leftward shift results from an increased affinity of oxygen to haemoglobin and may limit the availability of oxygen to the tissues [36,54]. However, a local decrease in pH, an increase in local carbon dioxide tension and an increase in 2,3-diphosphoglycerate will shift the curve to the right and counteract this undesirable effect of hypothermia [55].

Although hypothermia is generally agreed to be valuable, there is widespread disagreement as to the optimum degree of hypothermia. Mild hypothermia (29-35°C) is used by some centres whilst others employ profound hypothermia (<25°C). Although there are metabolic advantages with more profound degrees of hypothermia there are also practical disadvantages. When profound degrees of hypothermia are used, longer is required to cool and, subsequently, to rewarm the patient back to normothermia. During cooling, and more especially rewarming, the patient is vulnerable to hypoperfusion and therefore, it is best to spend the minimum possible amount of time in these phases. Moreover, cardiovascular instability and shivering, which is associated

with an increased systemic oxygen uptake, can result during the crucial postoperative period due to an afterdrop in body temperature. The more profound the degree of hypothermia used then the greater the likelihood that there will be a serious afterdrop in body temperature. For these reasons, many centres compromise by using moderate hypothermia (25–28°C) [22] as will the presented series of studies.

Haemodilution

Originally cardiopulmonary bypass circuits were primed only with blood. In the desire to conserve blood, haemodilution with crystalloid or colloid solutions was introduced and is now widely employed [56,57]. However, haemodilution decreases the oxygen carrying capacity of the blood which can limit systemic oxygen delivery. Nonetheless, systemic oxygen uptake is maintained during haemodilution in animal experiments until the haematocrit falls below 20%, at which point it becomes directly proportional to the haematocrit [58]. Furthermore, Roe and colleagues found that metabolic acidosis was remarkably absent when a clear priming solution was employed [59].

Flow rate

Pump flow rate is an important determinant of systemic oxygen uptake during low flow cardiopulmonary bypass [22]. At low levels of flow, systemic oxygen uptake is directly related to pump flow rate. As flow rate increases, a point is reached where systemic oxygen uptake becomes independent of flow and plateaus out (Figure 1). Maintenance of flow rate at or above this point would be the optimum as lower rates will result in metabolic acidosis [5].

Although the general relationship between flow rate and systemic oxygen uptake is agreed, the actual flow rate at which systemic oxygen uptake plateaus remains disputed. Rates varying from 1.2 to 2.0 $L.min^{-1}.m^{-2}$ and even higher have been proposed [4-7,40,60-62]. Because such wide differences exist in the control of body temperature in previous studies, ranging from normothermia to
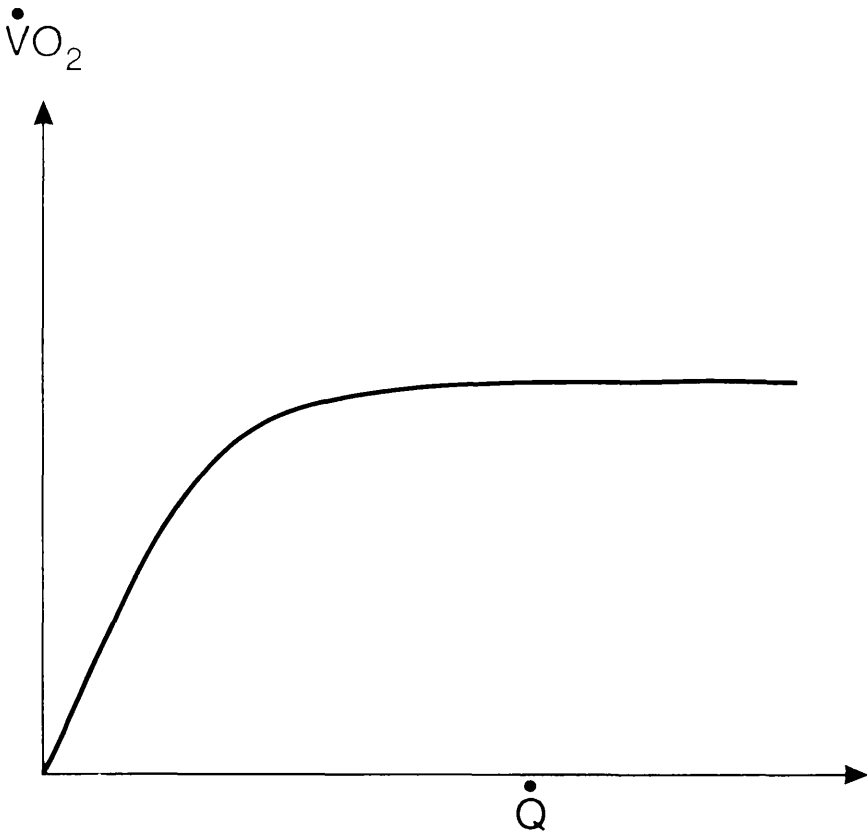
Figure 1. Relationship between flow rate ($\dot{Q}$) and systemic oxygen uptake ($\dot{V}O_2$) during cardiopulmonary bypass

profound hypothermia, it is difficult to make a valid overall comparison of them. Even studies which have used similar degrees of hypothermia have produced conflicting results [40,61]. Some of the previous work can also be criticised for their choice of experimental design and statistical analysis. Hickey and Hoar, who concluded that systemic oxygen uptake plateaued at 1.2 $L.min^{-1}.m^{-2}$ during moderate hypothermia [63], used a fixed order of investigation and did not control for stage during cardiopulmonary bypass. Fox and co-workers, using profound hypothermia, did control for stage of investigation and also concluded that systemic oxygen uptake plateaued at 1.2 $L.min^{-1}.m^{-2}$ [61]. This conclusion was made despite their results apparently showing increases in systemic oxygen uptake at higher flow rates. A decision to analyse data as individual points, rather than examine within patient changes, may account for their finding as this will have resulted in a marked loss of sensitivity.

The importance of the relationship between systemic oxygen uptake and flow rate lies in the frequent use of low levels of flow during hypothermic cardiopulmonary bypass. During cooling and rewarming, relatively high flows of about 2.4 $L.min^{-1}.m^{-2}$ are commonly used [22,63]. However, flow rates are often cut back to between 1 and 2 $L.min^{-1}.m^{-2}$ after induction of hypothermia and some centres even use flow rates as low as 0.25 $L.min^{-1}.m^{-2}$ for short periods [60]. The main reason for using low flow rates is to reduce non-coronary collateral blood flow and thereby, improve myocardial preservation [53,64]. Increased risk of gaseous microemboli, decreased bleeding into the surgical field and reduced haemolysis are other important reasons for using low rates of flow [22]. Underpinning this manipulation of flow rate is the physiological rationale that sufficient oxygen will still be delivered to the tissues to maintain systemic oxygen uptake, despite the low flow rate, because of the reduced metabolic rate induced by hypothermia [22,60,61]. However, if this premise does not hold true then large numbers of patients are experiencing sub-optimal levels of oxygen uptake.

Although a few centres may use flow rates around 1.2 $L.min^{-1}.m^{-2}$ during moderate hypothermia, the greater majority normally employ rates between 1.5 and 2.0 $L.min^{-1}min^{-2}$. For this reason, it is important to determine whether or not systemic oxygen uptake is flow dependent at the low levels of flow rate commonly used during hypothermic cardiopulmonary bypass.

Flow character

Many of the early cardiopulmonary bypass pumps were designed to reproduce the natural pulsating character of blood flow generated by the heart. However, the complexity of these systems proved to be an insurmountable barrier to their continued use [65]. Roller pumps, which produced continuous or nonpulsatile perfusion, proved to be reliable and safe. This, along with the lack of conclusive evidence that pulsatile perfusion had any benefits, over nonpulsatile perfusion, resulted in roller pumps becoming the standard by the end of the 1960s [23,65]. However, evidence began to accumulate that nonpulsatile flow was detrimental to cellular metabolism and organ function [65]. As a result, modified roller pumps that can produce a pulsatile flow character were developed and have been commercially available for some years now. These have been demonstrated to be safe, reliable and simple to operate in routine clinical use [65]. No technical barrier now exists to the use of pulsatile perfusion but whether there are metabolic advantages to the use of pulsatile over nonpulsatile flow character remains unsettled [12,65,66].

Pulsatile perfusion is advocated by Taylor, amongst other reasons, as being metabolically superior to nonpulsatile perfusion [65]. This recommendation is based on a number of studies that have found pulsatile perfusion to increase systemic oxygen uptake and improve other indices of metabolism compared to nonpulsatile perfusion [43-45,67-70]. Close examination of several of these studies reveals them to be statistically unsound as flow rates were higher in pulsatile than nonpulsatile groups [45,67,68]. As discussed previously, systemic oxygen uptake is inversely related to flow rate at low levels of flow. Therefore, any increases in the pulsatile, compared to the nonpulsatile groups, may be related

to the differences in flow rate rather than any differences in flow character. Also, most studies of flow character have employed an unpaired, parallel group design which raises serious problems of matching when comparing a size dependent variable such as systemic oxygen uptake [47]. Furthermore, several animal and human studies have been unable to demonstrate any metabolic superiority of pulsatile over nonpulsatile perfusion [47,71,72]. These differences in findings have been reconciled by Hickey, Buckley and Philbin [12] on the basis that those studies, which failed to find that pulsatile perfusion had any advantages over nonpulsatile, employed high flow rates (>100 ml.min^{-1}.kg) and that the difference between flow characters only become apparent when low flow rates (60–100 ml.min^{-1}.kg) are used.

Another serious criticism raised by Hickey, Buckley and Philbin [12] of many previous studies is the failure to quantify the pulsatile nature of the flow produced. This fact, along with the great variety of devices used to create pulsatile perfusion, makes comparison of previous findings extremely difficult. Thus, if any differences in metabolic effects exist between nonpulsatile and pulsatile perfusion, particularly during low flow cardiopulmonary bypass, they remain unclear.

Acid–base management

Conventionally, the aim of acid–base management was to maintain homeostasis by guarding the arterial pH around 7.4 and this concept was perpetuated into routine cardiopulmonary bypass practice [73]. Under this pH–stat theory of acid–base management, arterial pH is maintained at 7.4 when the blood sample is measured by bench blood gas at 37ºC and the results interpreted following correction for body temperature [73]. From the introduction of hypothermia until the present day, this concept has been disputed [13,14,73–76]. Some authors have advocated that acidosis should be induced with the addition of carbon dioxide or even hydrochloric acid [75]. Others have favoured alkalosis [48,76] and in recent years, support for this view has been given by the work of

Rahn and Reeves and Howell and colleagues on the grounds of stability of the hydroxyl/hydrogen ion ratio and maintenance of a constant net charge of imidazole [77-79]. This alpha-stat theory of acid-base management allows the arterial pH to rise with decreasing temperature as would occur in a closed system [80]. Alpha-stat control is achieved by maintaining the arterial pH at 7.4 when the results, measured by bench blood gas analysis at 37°C, are interpreted without correction for body temperature [73].

It has been estimated that over 50% of centres for cardiac surgery now employ alpha-stat acid-base management [74]. Blayo and colleagues have applied alpha-stat acid-base management in humans and found normal levels of systemic oxygen uptake [81]. However, Harken demonstrated a significant correlation between arterial pH and oxygen uptake using a canine hind limb model [82]. Human research, performed at or near normothermia, has produced conflicting results as Springer and co-workers found systemic oxygen uptake to diminish with increases in arterial carbon dioxide [83] whereas Patterson found the opposite [84].

At present, there is insufficient data available on the effects of acid-base management on systemic metabolism during hypothermic cardiopulmonary bypass in humans.

Having considered how metabolic variables are affected by the different factors of cardiopulmonary bypass, this review will now concentrate on how they are influenced by anaesthesia during cardiopulmonary bypass.

EFFECTS OF ANAESTHESIA DURING CARDIOPULMONARY BYPASS ON METABOLISM

Remarkably few studies of anaesthesia's effects upon metabolic variables during cardiopulmonary bypass have been undertaken despite the early work of Underwood, Roth and Starr [85] which demonstrated that the choice of anaesthesia affected systemic oxygen uptake. However, most anaesthetic agents used at the time of their work have fallen into disuse as they have been superseded by modern drugs. The effects on metabolic variables during cardiopulmonary bypass of these modern anaesthetic drugs have not been tested. If the findings of Underwood, Roth and Starr [85] hold true with present day anaesthetic agents, then the choice of anaesthesia during cardiopulmonary bypass may have important actions on systemic metabolism and may, in turn, influence outcome from cardiac surgery.

Anaesthesia has two potential means of benefitting patients metabolically during cardiopulmonary bypass. Direct metabolic depression by anaesthetic agents may, like hypothermia, have a systemic protective action thus allowing ischaemia or hypoperfusion to be tolerated longer before structural damage occurs. Alternatively, some anaesthetics are potent vasodilators. This vasodilation could be used to advantage by increasing perfusion within areas of excessive vasoconstriction and thereby improving metabolism.

Presently, a tremendous variety of techniques are used by anaesthetists in the United Kingdom and Ireland to produce anaesthesia during cardiopulmonary bypass [20]. Although diverse in their constituents, these techniques are, with the notable exception of opioid anaesthesia, based on Lundy's principle of balanced anaesthesia [19]. Balanced anaesthesia uses a combination of agents to produce the classic triad of analgesia, anaesthesia and muscle relaxation [19]. Although a great variety of drugs are used to produce this triad, they can be classified into four groups which are opioids, neuromuscular blocking agents, inhalational and

intravenous anaesthetics. Opioids are used for analgesia; neuromuscular blocking agents for muscle relaxation; and either inhalational or intravenous anaesthetics can be used for hypnosis. The effects of anaesthesia during cardiopulmonary bypass will be considered on the basis of this grouping.

Cardiopulmonary bypass has important effects on the pharmacokinetics of anaesthetic drugs which are beyond the scope of this thesis. These actions have been reviewed previously [18] and will therefore not be considered further in this review which will now concentrate on the metabolic effects of each separate anaesthetic group.

Inhalational anaesthetics

Since the early days of cardiopulmonary bypass inhalational anaesthetic agents have been used during cardiopulmonary bypass and they are still frequently employed [20,85,86]. Inhalational anaesthetic agents, by definition, are usually administered via the lungs. However, exclusion of the lungs from the circulation during the larger part cardiopulmonary bypass makes inhalation an impracticable method of delivery. In this situation, they can be administered simply by vaporising the agents into the gas supply to the oxygenator and halothane has long been employed in such a manner [86].

Halothane is known to reduce systemic oxygen uptake in the intact cardiovascular system at normothermia [87]. Its effect on systemic oxygen uptake during hypothermic cardiopulmonary bypass has not been studied, although Nordén found that the use of halothane prevented the base excess from decreasing [88]. Because of its potential to cause hepatitis in a small number of patients on repeated exposure [89], halothane is falling into disuse and is now infrequently used during cardiopulmonary bypass [20]. Isoflurane also decreases systemic oxygen uptake in the intact cardiovascular system at normothermia [90-92] and therefore, it may have a systemic protective effect during cardiopulmonary bypass. As discussed later, isoflurane has a vasodilatory action which may reduce the relatively elevated peripheral vascular resistance that

exists during low flow, hypothermic cardiopulmonary bypass. If this is so, improved perfusion in areas of ischaemia or hypoperfusion will result in an increase in systemic oxygen uptake. However, the metabolic effects of isoflurane during cardiopulmonary bypass have not been previously studied.

Neuromuscular blocking agents

Neuromuscular blocking agents are almost invariably employed to produce muscle relaxation during cardiac anaesthesia [20]. Systemic oxygen uptake has been found by Underwood, Roth and Starr to be lower in patients during normothermic cardiopulmonary bypass if an anaesthetic technique involving a neuromuscular blocking agent (decamethonium or tubocurarine) is used compared to one employing cyclopropane alone [85]. A decrease, from preoperative values, in systemic oxygen uptake has also been found during normothermic cardiopulmonary bypass by Harris, Seelye and Squire [51] who attributed the decrease to the administration of the tubocurarine. The findings of these two studies would indicate that neuromuscular blocking agents have a systemic protective effect during cardiopulmonary bypass similar to that of hypothermia.

Decamethonium is no longer used clinically as a neuromuscular blocking agent. Tubocurarine, as discussed later, can result in de-stabilisation of the cardiovascular system and therefore, is infrequently used now for cardiac anaesthesia [20]. Atracurium and vecuronium are two modern neuromuscular blocking agents which have similar actions to each other. For haemodynamic reasons which are discussed later, they are now commonly used during cardiac anaesthesia [93,94]. However, the effects on metabolic variables of these neuromuscular blocking agents during cardiopulmonary bypass have not been investigated.

Opioids

Opioids are nearly always used to produce the analgesic component of balanced anaesthesia during cardiopulmonary bypass [20,95]. Morphine was

formerly the standard opioid for cardiac anaesthesia but it has been superseded, for reasons discussed later, by synthetic opioids such as fentanyl and alfentanil [95].

No direct evidence exists to suggest that opioids have any metabolic effect during cardiopulmonary bypass. However, antagonism of opioids in animals and humans can result in marked increases in systemic oxygen uptake which might imply that opioids could have important metabolic effects during cardiopulmonary bypass [96,97]. Yet none of the modern opioids that are used for cardiac anaesthesia have been tested for their metabolic effects during cardiopulmonary bypass.

Some workers even employ opioids in high doses as the sole agent to produce anaesthesia [95]. This technique has been advocated because it produces good cardiovascular stability [95]. However, the reliability of opioids on their own to produce anaesthesia is open to question [95,98]. For this reason, opioids are usually supplemented with a volatile or intravenous anaesthetic agent to obtain hypnosis [20].

Intravenous anaesthetics

Intravenous anaesthetics are a large and disparate group of drugs that are often used, as an alternative to inhalational anaesthetics, to produce the hypnosis component of balanced anaesthesia during cardiopulmonary bypass [20]. Of these agents, chlorpromazine is the only one that has been investigated for its effects on systemic oxygen uptake during cardiopulmonary bypass. Arikawa and colleagues found that chlorpromazine increased systemic oxygen uptake when patients were cooled below 32°C [99]. However, their use of simple regression analysis makes their conclusions questionable. Also, chlorpromazine is now rarely used during cardiac anaesthesia [20]. This declined usage is probably because of chlorpromazine's cardiovascular side effects which are discussed later. A large variety of other types of intravenous anaesthetic agents such as barbiturates, benzodiazepines and other unrelated drugs are used [20] but their

systemic metabolic effects during cardiopulmonary bypass have not been investigated.

As there is no single intravenous anaesthetic that is representative of the group and because of the great number of different types of drugs that can be classified as intravenous anaesthetics, this thesis will not attempt the exhaustive process that would be required to determine the metabolic effects of this group of drugs. However, this omission should not belittle the importance of this group of drugs as anaesthetic agents during cardiopulmonary bypass.

Having considered the effects of the different aspects of cardiopulmonary bypass and the effects of anaesthesia during cardiopulmonary bypass on metabolic varaibles, this review will move on to deliberate on the haemodynamic aspects of cardiopulmonary bypass.

HAEMODYNAMICS

Cardiopulmonary bypass is unique in clinical practice because it allows study of the vascular system in isolation from the heart. However, cardiopulmonary bypass causes major haemodynamic derangement and moreover, this derangement is a dynamic one. Following an initial marked decrease in peripheral vascular resistance with hypotension, there is a progressive vasoconstriction which continues into the postoperative period and can result in hypertension.

The initial drop in peripheral vascular resistance was originally attributed to inadequate perfusion [100]. However, this decrease occurs even if the pump flow rate is set at or even higher than the patients own cardiac output [100]. Other theories that have been proposed and discredited are that it is due to a shock like state, dilution of vasoactive substances, inundation of the vascular system with cold priming solution or as a reaction to blood prime [100-102]. However, it is

now accepted that haemodilution is responsible as it has been demonstrated to cause a sudden profound drop in peripheral vascular resistance by reducing the blood viscosity [100,103].

Following the initial hypotensive phase, there is a progressive rise in peripheral vascular resistance and arterial pressure [100]. A variety of mechanisms, both humoral and neural, have been proposed for this vasoconstriction. Catecholamines, vasopressin and thromboxanes have all been implicated as mediators of this vasoconstriction as have increases in sympathetic tone and the use of nonpulsatile perfusion [12,65,104-110]. The ongoing vasoconstriction continues into the post-cardiopulmonary bypass period and has important implications for mycocardial oxygen balance [111]. However, this thesis will confine itself only to its importance during cardiopulmonary bypass.

Despite these complex alterations in vascular dynamics, cardiopulmonary bypass has been advocated by Levy and Hug [112] as a suitable model for studying the circulation. This review will now concentrate on the various haemodynamic variables that have been used to monitor and measure the circulation during cardiopulmonary bypass.

MEASURES OF HAEMODYNAMICS

A variety of haemodynamic variables have been used to measure the systemic circulation during cardiopulmonary bypass. All but one of these variables are common to those employed in the intact cardiovascular system. Unlike the intact cardiovascular system, an estimate of the venous compliance can be obtained from the pump reservoir volume. In even greater contrast to the intact cardiovascular system, systemic blood flow rate is determined and delivered mechanically rather than being a function of cardiac performance that has to be measured.

Systemic arterial pressure

Extremes of systolic arterial pressure in either direction can have adverse effects on patient wellbeing. Of the two extremes, hypotension is the more common though hypertension is potentially far more catastrophic.

No consensus of opinion exists as to what level of systemic arterial pressure constitutes hypotension during cardiopulmonary bypass. Usually, it is stated in terms of mean arterial pressure. Some workers define hypotension as a mean arterial pressure less than 50 mmHg [9] whilst others use a level as low as 30 mmHg [10,63]. Although there is no agreement as to what constitutes hypotension, its adverse effects on tissue perfusion are generally accepted and in particular, that cereberal and myocardial damage may occur [9,10,63,113].

Even less agreement exists as to the level of systemic arterial pressure which constitutes hypertension during cardiopulmonary bypass. There is not even accord as to which variable to monitor, as systolic and mean arterial pressures are used in different centres. In general, vasodilators will be administered to patients when their mean arterial pressure exceeds 80–100 mmHg. The major danger of hypertension during cardiopulmonary bypass is disruption of the aorta at the cannulation site. This complication is fortunately extremely rare as the consequences are dire. Vasodilating agents which have no anaesthetic action, such as phenoxybenzamine, phentolamine and sodium nitroprusside, are commonly used to control this hypertension.

During cardiac surgery, systemic arterial pressure is usually recorded directly via a cannula inserted into the radial artery. However, radial artery pressure may not always accurately reflect the aortic pressure, especially the systolic pressure during rewarming [114]. Aortic pressure must therefore be the most accurate site for measuring systemic arterial pressure but this is complicated to undertake during surgery. Also, movement of the manometer line may create artefacts and lead to inaccurate measurements. In any case, the mean arterial pressure at the radial artery is usually closely related to that within the aorta [114].

Central venous pressure

Measurement of central venous pressure during cardiopulmonary bypass is of limited value as it merely indicates the state of venous return which is better measured directly by changes in reservoir volume. However, central venous pressure measurement comes into its own following weaning from cardiopulmonary bypass when the reservoir volume is no longer available for determination of venous return. One exception to the case during cardiopulmonary bypass is the finding of unduly high central venous pressures which, in combination with poor venous return to the reservoir, indicates obstruction of the venae cava. If uncorrected, this is a serious complication as cerebral perfusion will be impaired. Venous hypertension should therefore be corrected as soon as possible. Most commonly, simple manipulation of the venous cannulae by the surgeon will rectify this problem.

Central venous pressure is measured directly during cardiac anaesthesia using a cannula inserted into the jugular or subclavian veins. Because venous blood is syphoned by gravity to the cardiopulmonary bypass pump, central venous pressure often drops to zero or below. Care has to be taken to avoid inaccuracies in measurements due to obstruction or kinking of the cannula which may occur during cross clamping.

One important advantage to measuring central venous pressure during cardiopulmonary bypass is that it enables the calculation of peripheral vascular resistance.

Peripheral vascular resistance

Although it is probably the most valuable indice of systemic perfusion, peripheral vascular resistance is not monitored routinely in every centre. As described in Chapter 4, peripheral vascular resistance is simply calculated using the mean arterial pressure, central venous pressure and pump flow rate. But there is, as with mean arterial pressure, little agreement as to what value represents normal peripheral vascular resistance during cardiopulmonary bypass.

Generally, it is believed that tissue perfusion is better at lower rather than higher levels of peripheral vascular resistance and that the progressive vasoconstriction has adverse effects on tissue perfusion [65,88,115]. That vasoconstriction has adverse effects on tissue perfusion during cardiopulmonary bypass may only be a perceived truth as there is little evidence to directly link increased peripheral vascular resistance with impaired tissue perfusion. Indeed, the use of vasodilators, such as trimetaphan and sodium nitroprusside, during cardiopulmonary bypass do not result in any change in systemic oxygen uptake [46,115].

Reservoir level

Venous compliance has been measured using forearm plesthmography during cardiopulmonary bypass by Gall and colleagues [116] who found it to be little affected. Assuming stable conditions, reservoir volume is also a measure of venous capacitance and therefore, venous tone. For this reason, cardiopulmonary bypass has been used as a model to study the effects of drugs on the venous system independent of any cardiac action [100,117-120]. However, during cardiopulmonary bypass ongoing haemorrhage leads to progressive blood loss. Also, partial obstruction of the venous lines can markedly reduce the venous return and so cause the reservoir level to fall. Vice versa, relief of venous obstruction can cause sudden increases in the reservoir level. Furthermore, very low reservoir levels require rapid fluid replacement or a reduction of pump flow rate to prevent massive embolism. Therefore, caution has to be taken in the interpretation of reservoir levels as a measure of venous compliance.

EFFECTS OF CARDIOPULMONARY BYPASS ON HAEMODYNAMIC VARIABLES

This section will review the effects of different aspects of cardiopulmonary bypass on the aforementioned haemodynamic variables. The effects of factors which remain uncertain will be highlighted.

Hypothermia

Hypothermia, by increasing the viscosity of blood, produces a rise in peripheral vascular resistance during cardiopulmonary bypass that may impair tissue perfusion [121]. This haemodynamic disadvantage of hypothermia is, however, greatly outweighed by its metabolic benefits which have been discussed previously. Moreover, this adverse effect of hypothermia is counteracted by haemodilution.

Haemodilution

The use of a crystalloid or colloid priming solution produces haemodilution which is measured by reduction in haematocrit. As well as the advantages of avoiding a blood prime, for example transfusion reactions and infection, this reduction in haematocrit decreases the blood viscosity and counteracts the adverse effects of hypothermia which are discussed above [122].

Flow rate

It has long been recognised that peripheral vascular resistance is inversely related to flow rate during cardiopulmonary bypass [34,123]. However, there have been major changes in cardiopulmonary bypass technique over the decades. Not only are haemodilution, hypothermia and pulsatile perfusion now commonly employed but, as discussed ealier, flow rate is frequently reduced to low levels during hypothermic cardiopulmonary bypass. Considering its importance, the effect of flow rate on peripheral vascular resistance has been insufficiently studied under present conditions of practice.

Flow character

Along with its metabolic effects, a pulsatile flow character has been stated by Taylor [65] and Hickey, Buckley and Philbin [12] to be haemodynamically superior to a nonpulsatile one. The basis for this statement lies in the findings of many studies which have concluded that pulsatile perfusion results in a lower peripheral vascular resistance than nonpulsatile flow [43-45,67,68,70,106]. As with the metabolic effects discussed earlier, some of these studies can be criticised because of the use of a higher flow rate in the pulsatile than the nonpulsatile group, which must invalidate their findings [45,68,106]. If peripheral vascular resistance is inversely related to flow rate, then the lower peripheral vascular resistance may be due to the use of a higher flow rate and not to pulsatile perfusion. Although fewer in number, some studies have been unable to demonstrate any haemodynamic differences between nonpulsatile and pulsatile perfusion [8,47,71,72,124] and one study even found peripheral vascular resistance to be raised when pulsatile perfusion was used [69]. As discussed before, these differences in findings have been reconciled by Hickey, Buckley and Philbin [12] on the basis that differences in flow character only become apparent during low flow rates. However, the effects of flow character on haemodynamic variables during hypothermic cardiopulmonary bypass remain unclear and they are especially uncertain at the low rates of flow that are often used.

Acid-base management

Under normal conditions, acid-base balance is known to have important actions on the cardiovascular system yet few studies have considered its effects on systemic haemodynamics during cardiopulmonary bypass. Bove and co-workers, using a canine model, were unable to demonstrate any significant difference in haemodynamic variables during hypothermic cardiopulmonary bypass between pH and alpha-stat acid-base managements [125]. Human studies using cardiopulmonary bypass at or near normothermia have had conflicting findings. Paterson found that hypocapnoea produced an increase in arterial

pressure [84] whereas Springer and colleagues could demonstrate no significant difference in peripheral vascular resistance when arterial carbon dioxide tension was altered by 5 mmHg [83].

The differences in the effects on systemic haemodynamic variables during cardiopulmonary bypass between alpha and pH–stat acid–base management have not been previously investigated. Acid–base management during hypothermic cardiopulmonary bypass is known to have important effects on cerebral blood flow and as these have been reviewed previously, they will not be considered here [126]. Instead, this review will now attend to the effects that anaesthesia during cardiopulmonary bypass has on haemodynamic variables.

EFFECTS OF ANAESTHESIA DURING CARDIOPULMONARY BYPASS ON HAEMODYNAMICS

Cardiac anaesthesia's effects on the intact cardiovascular system at normothermia have been extensively investigated. However, most attention has been paid to the effects of anaesthetic agents on the cardiovascular system before and after cardiopulmonary bypass and, in particular, their effects on the coronary circulation. Relatively little systematic enquiry has been made into the effects of anaesthesia on the vasculature during the abnormal conditions of hypothermic cardiopulmonary bypass when the heart is isolated from the circulation. This section will review the known effects of anaesthesia during cardiopulmonary bypass on systemic haemodynamic variables.

Some agents used for cardiac anaesthesia have marked haemodynamic effects in the intact cardiovascular system whilst others have but minimal actions [16,17]. Increasingly, it is being recognised that anaesthesia also has important haemodynamic effects during cardiopulmonary bypass [18]. Moreover, these effects may not be limited to the period of cardiopulmonary bypass and may influence overall outcome following cardiac surgery [18]. Therefore, the choice of anaesthetic agents may have important actions on the vascular system that could be used to advantage during cardiopulmonary bypass.

Inhalational anaesthetics

Of the inhalational anaesthetic agents, halothane has been found by Nordén not to reduce arterial pressure although it slowed the rate of increase in peripheral vascular resistance over the course of hypothermic cardiopulmonary bypass [88]. Isoflurane has marked vasodilatory effects compared to halothane [91,92,127]. Therefore, there may be benefits in using isoflurane during hypothermic cardiopulmonary bypass as its vasodilatory action could be used to prevent or control hypertension. However, isoflurane's effects on haemodynamic variables during cardiopulmonary bypass have not been previously studied in a systematic manner.

Neuromuscular blocking agents

Tubocurarine was one of the original neuromuscular blocking agents used during cardiac anaesthesia [85]. Like other anaesthetic agents of its time, tubocurarine has largely fallen into disuse [20]. One reason for this is that tubocurarine produces histamine release and ganglion blockade [128] and thereby causes hypotension and vasodilation [129]. Tubocurarine has been largely superseded by modern neuromuscular blocking agents which were designed to have minimal cardiovascular side effects. Vecuronium and atracurium are two recently introduced neuromuscular blocking agents which are both noted for their minimal effects on the cardiovascular system [93,94]. Although the haemodynamic effects of these agents have been extensively investigated, their effects during hypothermic cardiopulmonary bypass have been little studied, even though their pharmacodynamics are known to be altered in other ways at this time [130-133].

Opioids

Opioids are sometimes used in high doses as the sole agent for cardiac anaesthesia although this practice is uncommon in the United Kingdom and Ireland [20]. More often they are used during cardiopulmonary bypass as one component of balanced anaesthesia [20]

In the past, morphine was the standard opioid for cardiac anaesthesia [95]. During cardiopulmonary bypass, Hsu, Hickey and Forbes [118] have found morphine to decrease peripheral vascular resistance and increase venous capacitance. These haemodynamic effects of morphine were not altered by prior administration of naloxone but were partially attenuated by promethazine and, therefore, they concluded that morphine's haemodynamic effects were mediated by histamine. Morphine is now less often used because, in the high doses that are usually employed for cardiac anaesthesia, it causes histamine release and so cardiovascular instability [95].

Fentanyl and more recently alfentanil, which cause little histamine release [95,133], have largely replaced morphine. These opioids have been found to have minimal effects on the cardiovascular system and to be suitable agents for cardiac anaesthesia [95,134]. However, there has been little systematic study of their effects on haemodynamic variables during cardiopulmonary bypass. This thesis will examine the haemodynamic actions of alfentanil.

Intravenous anaesthetics

Chlorpromazine is a neurolept agent with an alpha-adrenergic blocking action that was commonly used in the past during cardiopulmonary bypass. It has been found to be a vasodilator and to reduce peripheral vascular resistance during hypothermic cardiopulmonary bypass [121]. Chlorpromazine is now infrequently used [20], perhaps because of its prolonged duration of action and the difficulty in reversing its effects. These effects may lead to cardiovascular system instability during the crucial period of weaning from cardiopulmonary bypass. Droperidol is another neuroleptic agent which is used during cardiopulmonary bypass. Droperidol, in doses of 0.15 or 0.3 mg kg [1], produces arterial vasodilation and decreases peripheral vascular resistance during hypothermic cardiopulmonary bypass, as well as increasing venous capacitance [117]. Because it is a vasodilator, droperidol is used to treat hypertension during cardiopulmonary bypass though, like chlorpromazine, it has the disadvantage of

having a prolonged duration of action.

The haemodynamic effects of a variety of other intravenous anaesthetics, including etomidate, propofol and thiopentone, during cardiopulmonary bypass have recently been investigated by Boer, Ros and Bovill [135, 136] and they have all been found to decrease peripheral vascular resistance. Pauca and Roy have also studied thiopentone during hypothermic cardiopulmonary bypass and found that the hypotension was preceeded by an initial hypertensive response [137]. They attributed the initial vasoconstriction to a peripheral effect and the secondary vasodilation to a central effect.

As most of the commonly used intravenous anaesthetics have been studied during cardiopulmonary bypass and found to cause vasodilation, this thesis will not examine this groups of anaesthetics.

STUDY DESIGN

Most commonly, parallel group comparisons have been used to study haemodynamic and metabolic variables during cardiopulmonary bypass. This form of study design, although sometimes necessary, has been criticised by Singh, Barratt–Boyes and Harris [47] as being inappropriate for comparison of size dependent variables such as systemic oxygen uptake. Relative to within group comparisons, between group studies result in considerable loss of sensitivity. Previous studies in humans have examined the effects of individual factors on haemodynamic and metabolic variables, none have considered whether these factors interact, either beneficially or detrimentally. Yet this is potentially extremely important as clinical cardiopulmonary bypass is constructed from a combination of techniques rather than one in isolation. Factorial experiments allow not only study of the main effects of individual factors but also the interaction between factors. For these reasons, a factorial study design should

be valuable in cardiopulmonary bypass research [138,139]. Factorial study designs have been applied successfully by Utley and colleagues [122] in an animal cardiopulmonary bypass experiment but they have not previously been used in human work. In this thesis, a factorial experiment was used in Chapter 5 to examine the effects of different cardiopulmonary bypass techniques, but was not used to study the effects of different combinations of anaesthesia because the increased complexity of multiple anaesthetic techniques could have adversely affected patient safety.

Another questionable aspect of most previous studies which have investigated the effects on haemodynamic and metabolic variables of the various components of cardiopulmonary bypass is that they have not controlled the anaesthesia employed. This failure may have confounded their findings as different techniques of anaesthesia may have existed between groups or even different depths of anaesthesia according to the quantities of drugs used.

AIMS

From the foregoing review, it is apparent that the haemodynamic and metabolic effects of certain basic aspects of cardiopulmonary bypass remain unresolved or require re-evaluation in the light of present day practice. Furthermore, the haemodynamic and metabolic effects of modern cardiac anaesthetic agents during cardiopulmonary bypass remain largely unknown. Determination of the most effective combination of cardiopulmonary bypass and anaesthetic technique, in terms of haemodynamics and metabolism, should improve patient wellbeing during cardiopulmonary bypass and thereby, the ultimate outcome of cardiac surgery.

For the above reasons, it is hypothesised that cardiopulmonary bypass and anaesthetic technique have important influences on haemodynamic and metabolic variables during hypothermic cardiopulmonary bypass. This thesis was therefore undertaken to study the effects of the following factors on haemodynamic and metabolic variables : –

1. Cardiopulmonary bypass

a) flow rate

b) flow character

c) acid–base management

2. Anaesthesia

a) isoflurane

b) atracurium

c) alfentanil

CHAPTER 3

METHODS AND MEASUREMENTS

This chapter describes the methods and measurements that are common to all of the following studies. Those methods specific to individual studies are presented in their respective chapters. All studies were undertaken in Theatres F and G of Glasgow Royal Infirmary.

Ethical considerations

Approval for all studies was obtained from the Glasgow Royal Infirmary Ethics Committee. All studies were conducted according to the Declaration of Helsinki and in every case, informed consent was obtained from each patient before admission to every study.

Patient selection

Only patients scheduled for elective coronary artery bypass surgery by one specific surgical team were selected, with the exception of the study in Chapter 6 when patients planned for heart valve surgery by the same team were also admitted. Patients with carotid artery and cerebro-vascular disease, poor left ventricular function, severe hepatic disease, renal failure or diabetes melitus were excluded.

Cardiopulmonary bypass

Following injection of heparin 3 mg.kg^{-1} into the right atrium, both venae cavae were cannulated with two straight polyvinyl bevelled and bell tipped 8mm diameter cannulae (American Bentley, Irvine, California, USA.). A right angled tapered cannula with a terminal diameter of 6 mm (Gambrio Dialysatoren KG, Henchigen, FRG.) was inserted into the aorta so that the tip pointed towards the arch.

The cardiopulmonary bypass circuit consisted of a bubble oxygenator (BOS 10 or BOS 10 Plus, American Bentley.) and a roller pump (10-00-00, Stöckert Instrumentes, Munchen, FRG.) which could be controlled to produce nonpulsatile or pulsatile perfusion using a pulsatile control unit (EC 26, Stöckert Instrumentes.). When used in the pulsatile mode, the unit was set to deliver a pulse rate of $70.min^{-1}$ with the pulse run time set to 50% of the total cycle length. With the exception of studies in Chapters 4 and 5, when flow character was being examined, nonpulsatile perfusion was used in all studies.

The cardiopulmonary bypass circuit was primed with a mixture of lactated Ringers solution 2L, mannitol 20% 100 ml, potassium chloride 15 mmol and heparin 8000 units. An arterial filter (C1040, American Bentley.) and a GasSTAT cell (Cardiovascular Devices, Irvine, California, USA.) were inserted into the arterial line.

Arterial blood pH and carbon dioxide and oxygen tensions were measured during cardiopulmonary bypass using an inline monitor (GasSTAT, Cardiovascular Devices.). Arterial pH was controlled by manipulation of the gas concentrations (O_2 100% and/or O_2 95% and CO_2 5%) and the flow rate supplied to the oxygenator. Perfusionists were instructed, according to study protocols, to maintain arterial pH as close as possible to 7.4. The inline monitor was set either in the mode that measurements are displayed at the actual patient blood temperature for pH-stat acid-base management or in that which internally corrects the results to 37°C for alpha-stat acid-base management [140]. Acid-base management was according to alpha-stat principles in all studies with the exception of those in Chapters 4 and 5 when it was alternated between pH and alpha-stat control as dictated by the study protocol.

Throughout the series of studies, the pump was regularly calibrated volumetrically with water at room temperature. The pump flow rate during induction of hypothermia and rewarming was 2.4 $L.min^{-1}.m^{-2}$. During stable hypothermia the flow rate was reduced to and maintained at 1.6 $L.min^{-1}.m^{-2}$ in

all studies with the exception of the studies in Chapters 4 and 5 when the flow rate was alternated between 1.5 and 2.0 L.min^{-1}.m^{-2}.

Haemodynamic control

In all studies, isoflurane was administered up to a vaporiser setting of 3% before and after cardiopulmonary bypass when sodium nitroprusside or glyceral trinitrate IV were given to control systemic arterial pressure. All vasoactive drugs were discontinued at the start of cardiopulmonary bypass. Hypotension during cardiopulmonary bypass was defined as a mean systemic arterial pressure less than 35 mmHg measured at the radial artery and it was treated with boluses of methoxamine 2 mg IV as required to maintain the pressure equal to this level. A mean arterial pressure greater than 95 mmHg was identified as hypertension and it was corrected to this level using an infusion of sodium nitroprusside IV. Hypovolaemia was defined as a reservoir level less than 400 ml. If the haematocrit was 20% or greater, hypovolaemia was treated with lactated Ringers solution whereas, concentrated red cells were given if the haematocrit was less than 20%.

Blood sampling

Blood samples were aspirated by the author at the end of each 10 minute study period from the arterial and venous lines of the cardiopulmonary bypass circuit into glass syringes. Arterial blood was withdrawn from the arterial filter after discarding dead space blood. Venous blood was taken from a sampling port situated in the venous line immediately before its entry into the oxygenator. Air was excluded from the syringes and they were then capped and placed in iced water until analyses which were undertaken within one hour of sampling. All analyses were performed in duplicate by technicians who were blind to the study. The two measurements were averaged and this mean used in all statistical analyses.

Blood oxygen content

The oxygen content of blood was measured using an elecrolytic method with a Lex-O_2-Con TL (Lexington Instruments, Waltham, Massachusetts, USA.). The accuracy of the instrument was verified against the Van Slyke method using a Natelson Microgasometer (650, Scientific Industries, Springfield, Massachusetts, USA.). Before use in each patient the analyser was calibrated with air.

Systemic oxygen uptake

Systemic oxygen uptake was calculated according to Fick's principle [29] using the difference in arterial and venous oxygen contents and the pump flow rate standardised for body surface area. The following formula was employed:

$$\dot{V}O_2 = (CaO_2 - C\bar{v}O_2) \times \dot{Q}$$

Where:

$\dot{V}O_2$ =   systemic oxygen uptake ($ml.min^{-1}.m^{-2}$)

CaO_2 =   arterial oxygen content ($ml.L^{-1}$)

$C\bar{v}O_2$ =   mixed venous oxygen content ($ml.L^{-1}$)

$\dot{Q}$ =   pump flow rate ($L.min^{-1}.m^{-2}$)

Systemic oxygen delivery

Systemic oxygen delivery was calculated as the product of arterial oxygen content and pump flow rate standardised for body surface area. The following formula was employed :

$$\dot{D}O_2 = CaO_2 \times \dot{Q}$$

Where:

$\dot{D}O_2$ =   systemic oxygen delivery ($ml.min^{-1}.m^{-2}$)

CaO_2 =   arterial oxygen content ($ml.L^{-1}$)

$\dot{Q}$ =   pump flow rate ($L.min^{-1}.m^{-2}$)

Systemic oxygen delivery was calculated only in the study in Chapter 5 as the flow was kept constant in all other studies and therefore, it would only be affected by a change in arterial blood oxygen content.

Haemoglobin concentration and oxygen saturation

Haemoglobin concentration and saturation of haemoglobin with oxygen were measured with an IL 282 CO-oximeter (Instrumentation Laboratories, Lexington, Massachusetts, USA.). Routine quality control checks were performed (Levels 1, 2 and 3, Certain Advance, Ciba Corning Diagnostics Corp., Medfield, Massachusetts. USA.). The coefficients of variation for measurements of haemoglobin and haemoglobin oxygen saturation were respectively; 1.10%, 0.58% and 0.61% and 0.98%, 0.01% and 0%.

Blood gases and acid–base

Bench measurement of oxygen and carbon dioxide partial pressures, pH and base excess were done on a Corning 178 (Ciba Corning Diagnostics Corp.)

blood gas analyser. The blood gas analyser self calibrates automatically to one point half hourly and to two points every hour. Regular quality control checks were undertaken with tonometered samples (Levels 1,2 and 3, Certain Advance, Ciba Corning Diagnostics Corp.) and throughout the course of the studies, there was good electrode stability [141]. All acid–base and blood gas results presented are those of the bench blood gas analysis measured at 37°C and uncorrected for patient temperature unless otherwise indicated.

Lactate concentration

Venous blood samples were analysed for lactate concentration. A portion of the venous sample was placed in sodium fluoride tubes, the plasma was then separated and stored at –20°C until later analysis for lactate concentration. Lactate concentration was measured using a method modified from Noll [142]. Estimation was performed with an enzyme kit (149993, Boering Mannheim GmbH, Lewes, United Kingdom.) which was adapted for use on a centrifugal analyser (C400, Centrifichem, Baker Instruments, Windsor, United Kingdom.). The coefficients of variation for the analyses at 0.5, 1.0 and 2.0 $mmol.L^{-1}$ were respectively; 0.1%, 0.5% and 2.68%.

Haematocrit

Packed cell volume was measured using a microcapillary method. Samples were centrifuged for 10 minutes before being read using a graduated scale (Micro–haematocritometer, Hawksley and Sons Ltd, England).

Reservoir volume

At the end of each study period the volume of blood in the oxygenator plus that, if any, in the cardiotomy suction reservoir was noted as the reservoir volume.

Isoflurane during cardiopulmonary bypass

In all studies in which isoflurane was administered during cardiopulmonary bypass (Chapters 6-8), it was given via the same vaporiser (Isotec Mk3) inserted into the gas supply line to the oxygenator. The output of the vaporiser

was measured with a calibrated portable interference refractometer (Riken Keiki Instrument Co, Ltd, Tokyo, Japan). At a setting of 5%, the isoflurane output was 4.20%, at a setting of 2% it was 1.54% and at 1%, it was 0.77%.

Isoflurane concentration

Arterial blood samples were analysed for isoflurane concentration in all studies, except Chapters 4 and 5, using the following method. One millilitre of blood was added to carbon tetrachloride (analar grade), to which chloroform (analar grade) had previously been added, in a 4ml glass bottle. The chloroform acted as internal standard in the calibration. The bottle was roller mixed for 20 minutes and it was then centrifuged. One microlitre was then removed from the bottle for analysis. The chromatograph was a Pye Unicam 104 series flame ionisation detector fitted with a 3 m by 4 mm glass column packed with 5% OV-101 (Phase Separation Ltd.). The operating conditions were: column temperature, 353 K; detector temperature, 423 K; nitrogen flow, 50ml.min [1], hydrogen flow, 50 ml.min^{-1} and air flow, 500ml.min [1]. Calibration was performed using standard solutions made from a gravimetrically prepared stock solution of isoflurane in carbon tetrachloride. Peak height ratios of isoflurane to chloroform in the standard solutions were determined and plotted against the corresponding isoflurane concentration. This graph was then used to convert the extracted samples peak height ratios to isoflurane concentration. The extraction efficiency was 100%. The accuracy of the method was checked using spiked blood samples. The coefficient of variation for the analyses were 5.4% at a concentration of 40 ug.ml^{-1} and 4.3% at a concentration of 100 ug.ml [1].

CHAPTER 4

A COMPUTERISED SYSTEM FOR THE STUDY OF OXYGEN UPTAKE AND HAEMODYNAMICS DURING CARDIOPULMONARY BYPASS

INTRODUCTION

Before undertaking accurate haemodynamic and metabolic investigation during cardiopulmonary bypass, it is first necessary to ensure stable conditions. As discussed in Chapter 2, there are four fundamental aspects of cardiopulmonary bypass technique which may influence haemodynamics and metabolism; these are pump flow rate, flow character, temperature and acid–base management. Employment of a pump which will produce flow rates with reasonable accuracy and reliability is essential and modern roller pumps, if regularly calibrated, will fulfil this requirement [143]. The flow character used, that is either nonpulsatile or pulsatile perfusion, is important but quantification of the pulse pressure generated is also necessary [12]. Unlike flow rate and character, which are determined by the relevant pump controls, temperature and acid–base control require the perfusionist to measure, decide on the alteration necessary and then to effect the change needed to produce the desired values. During cardiopulmonary bypass, the perfusionist performs multiple tasks and can be distracted by events of more immediate importance than temperature and acid–base management [144]. Thus the accuracy of temperature and acid–base control, although generally acceptable for clinical purposes, may be less than satisfactory for research purposes.

With regard to haemodynamic measurement during cardiopulmonary bypass, single readings may be prone to inaccuracy both because of artefacts,

which are common, and also because there are spontaneous oscillations in systemic arterial pressure [145]. Using the mean of a series of sequential recordings performed over a specific period of time should overcome this problem and thus improve the reliability of measurements. Although this would be a difficult task to perform manually, computers are well suited to the rapid acquisition of data [144].

For these reasons, a computerised system was developed which would not only make repeated recordings of haemodynamic, temperature and arterial pH data, but also facilitate enhanced thermostatic and acid–base control. The aim of this study was to evaluate the performance of the computerised system.

SYSTEM DESIGN

The system (Figures 2 and 3) consisted of a GasSTAT inline blood gas monitor (Cardiovascular Devices) and a Kone Patient Data Monitor (565, Kone Corporation, Ospoo, Finland.) linked to an Apple 11e personal computer (Apple Computer Inc., Cupertino, CA, USA.). The inline blood gas monitor was mounted on the cardiopulmonary bypass machine and was connected to, but electrically isolated from, the computer.

The inline monitor has recently become commercially available (Figure 4). It's function is based on the novel principle of chemofluorescence. Sensors, which consist of spots of chemical dyes, are placed inline in the cardiopulmonary circuit. When stimulated with pulses of light, the dyes fluoresce in proportion to the concentration of carbon dioxide, oxygen and hydrogen ions present in the blood. The fluorescence is transmitted to the monitor by fibreoptic cable where it is quantified by a photodetector. A microprocessor then converts the information, as appropriate, into pH units or mmHg which is then displayed and transmitted to a serial interface port. Incorporated within the monitor's connector is a thermistor which allows measurement of blood temperature and
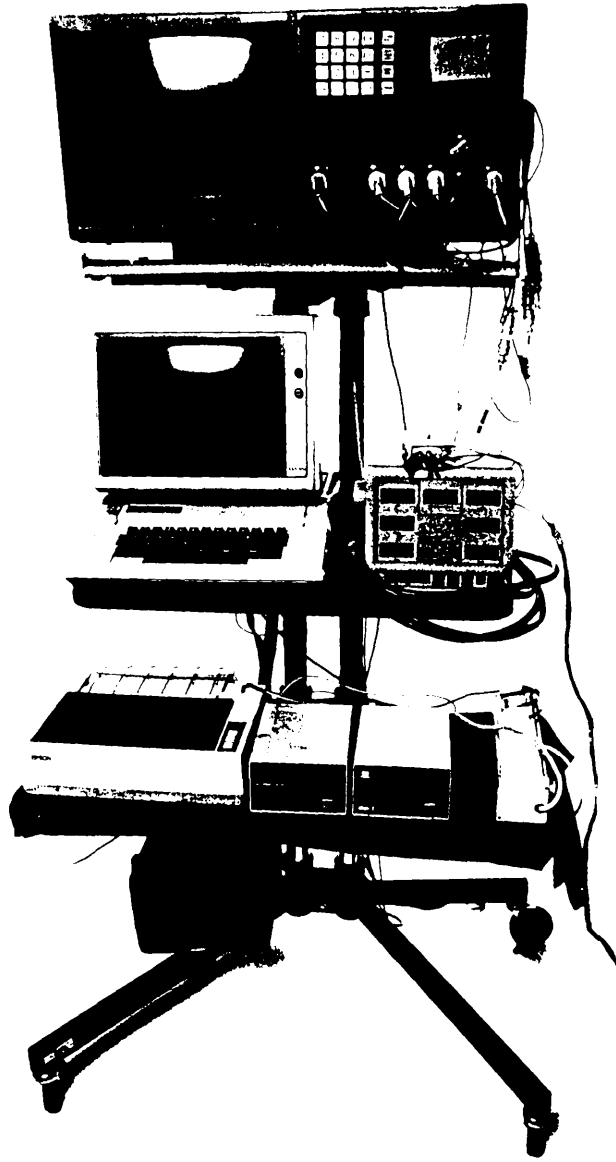
Figure 2. Computerised system mounted on trolley.
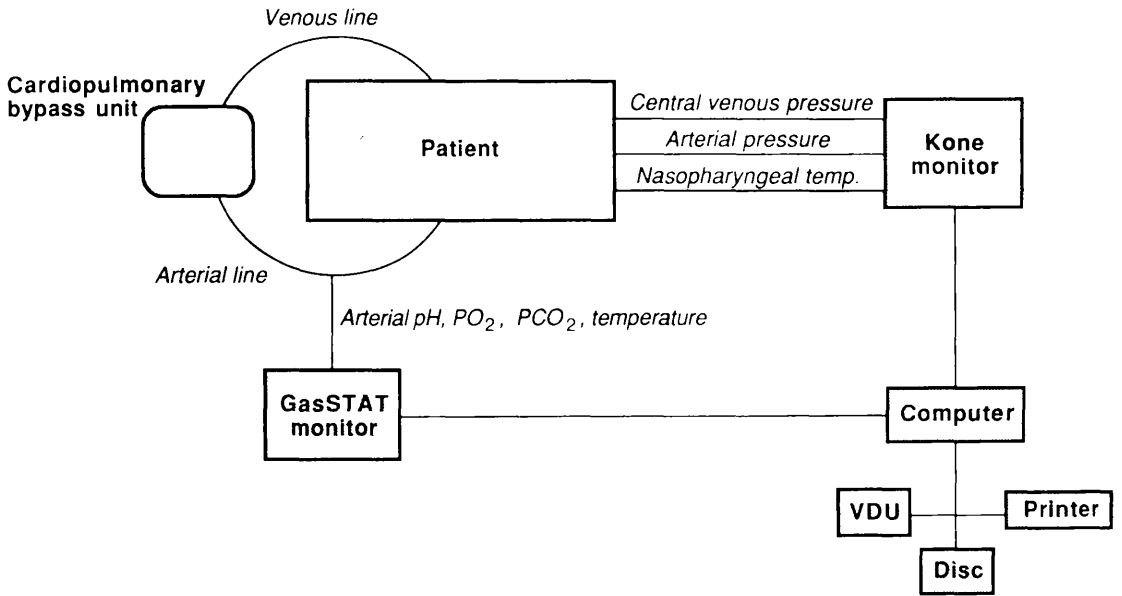
Figure 3. Diagramatic illustration of computerised system
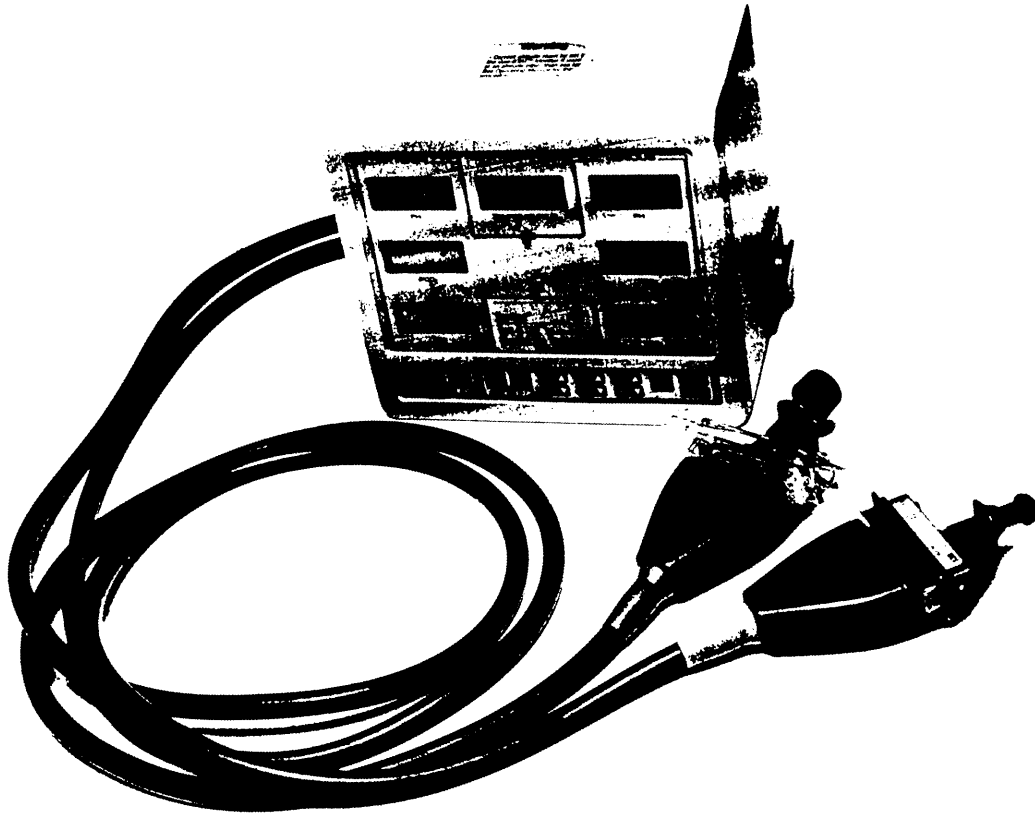
Figure 4. GasSTAT inline blood gas monitor

this information is also displayed and transmitted to the serial interface port. On checking against an accurate mercury in glass thermometer, the monitor was found to consistently over-estimate the temperature by about 0.6°C. The monitor can be switched to display the results at the actual blood temperature at which it measures the blood gases or corrected to 37°C. This allows the use of pH or alpha-stat acid-base management respectively [140].

The monitor was set to transmit data every 6 seconds at a Baud rate of 9600. The signal is transmitted as TTL levels (0-5 Volts) and therefore, a TTL to RS-232 converter was built to convert it into RS-232 standard levels to allow interface with the computer.

Systemic arterial and central venous pressures were measured via cannulae inserted percutaneously into the radial artery (20g Teflon cannula, Quick Cath, Travenol Laboratories Ltd, Thetford, UK.) and internal jugular vein (7g cannula, Arrow International Inc., Reading, Pa, USA.). The same transducers (Trantec 800, Bentley, Irvine, California, USA.) and Patient Data Monitor were used in all patients. Before use, transducers were zeroed and manometrically calibrated using a column of saline that was of a known height. Transducers were then maintained manometrically zeroed to the mid-axillary line throughout the operation. Nasopharyngeal temperature was measured using the temperature module of the Patient Data Monitor and a thermistor temperature probe (YST 700, Yellow Springs Instrument CO., Yellow Springs, Ohio, USA.) which was confirmed as accurate against a mercury in glass thermometer.

Information from the Patient Data Monitor is transmitted as an RS-232 signal at 9600 baud. Transmission is triggered by QRS complexes on the electro-cardiograph. During a large part of cardiopulmonary bypass the heart is maintained in asystole therefore, an electro-cardiograph simulator was built to produce a signal at the rate of one hertz. A program was developed for the computer which allowed real time haemodynamic, temperature and blood gas data to be shown on the visual display unit. The program also stored data from the previous 10 minutes and calculated a running mean with one standard

deviation for the arterial temperature and pH.   This information was shown on the visual display unit.   When the investigator was satisfied that stable conditions had been maintained, he signalled the computer. Data from that period were stored on magnetic disc and the real time data were printed as hard copy. A 10 minute duration was chosen because of the limited amount of time available during stable hypothermia. A longer duration might have improved data reliability but would have reduced the number of patients in which two or more periods could be achieved for within patient comparison. The program also allowed stored data to be edited and a hard copy to be printed at a later time. It enabled calculation from stored data of the mean and one standard deviation for systolic, diastolic and mean arterial pressures, arterial pulse and central venous pressures and, following entry of pump flow rate, the peripheral vascular resistance for each period. Peripheral vascular resistance was calculated using the following formula:

$$PVR = \frac{(MAP - CVP) \times 80}{\dot{Q}}$$

Where; PVR = peripheral vascular resistance (dynes.s.cm^{-5})

MAP = mean arterial pressure (mmHg)

CVP = central venous pressure (mmHg)

$\dot{Q}$ = pump flow rate (L.min^{-1})

METHODS

Clinical evaluation of the system was undertaken during the course of the studies which are outlined in detail in Chapter 5. It was planned to produce, with the exception of the variable under investigation, three 10 minute periods of stable hypothermic cardiopulmonary bypass for study in each of 24 consecutive patients. Stable cardiopulmonary bypass was defined as both arterial and nasopharyngeal temperatures between 27–29°C, arterial pH between 7.38–7.42 and constant flow rate and character.

At the end of each 10 minute period, blood samples were withdrawn from the arterial line of the cardiopulmonary bypass circuit and measured for pH using a bench blood gas analyser as described in Chapter 3. A comparison of pH, as measured by the inline blood gas monitor at the end of each period, was made with the results obtained from the bench blood gas analyser using linear regression.

Variables recorded by the computer were analysed using estimation of confidence limits. Results are presented as means with 95% confidence limits in parenthesis. The calculated means of each parameter from every period were used in analysis of within patient changes.

RESULTS

Data acquisition

Because of limited time at stable hypothermia, only 12 of a possible 24 third periods were obtained giving a total of 60 periods for inclusion in the analysis. The average number of readings in each period was 73.5 (95% CL 70.1, 77.0). After exclusion of data outwith three standard deviations of the mean or zero recordings in any parameter except central venous pressure, the

average number of acceptable readings was 71.2 (95% CL 67.3, 75.1). For one patient, in all three periods, only intermittent readings were recorded because of a loose electrical connection. Occasionally, isolated single zero recordings occurred in a few periods and an occasional reading was found which was either markedly lower, or more usually, markedly higher than that which either immediately preceded or followed it.

Thermostatic control

In all but five periods, the 95% confidence limits for the means of arterial temperature fell within the preset target range (27–29°C). The 95% confidence limits of the means in those periods lay between 26 and 27°C and occurred during the first period of study in five separate patients. Overall, there was a small but significant mean within patient increase in arterial temperature from Period 1 to 2 of 0.21 (95% CL 0.07, 0.35)°C and a small decrease from Periods 2 to 3 of –0.13 (95% CL –0.05, –0.21)°C. Between Periods 1 and 3, there was no significant change [–0.003 (95% CL –0.205, 0.198)°C]. Without exception, all the 95% confidence limits for the means of nasopharyngeal temperature fell within the preset target range (27–29°C). There was a small but nonsignificant mean within patient decrease in nasopharyngeal temperature from Periods 1 to 2 of –0.13 (95% CL –0.27, 0.00)°C, from Periods 2 to 3 of –0.12 (95% CL –0.33, 0.08)°C and Periods 1 to 3 of –0.19 (95% CL –0.43, 0.05)°C. Nasopharyngeal temperature was on average 0.60 (95% CL 0.48, 0.72)°C higher than arterial temperature.

Acid–base management

During the studies described in Chapters 5 and 6, comparison of arterial pH measurements made by the inline blood gas monitor with bench blood gas analyses of blood samples found a significant, though less than complete, correlation (Figure 5).

In only 43 of the total 60 periods did the 95% confidence limits of the means for arterial pH fall within the prescribed target range (7.38 – 7.42). There
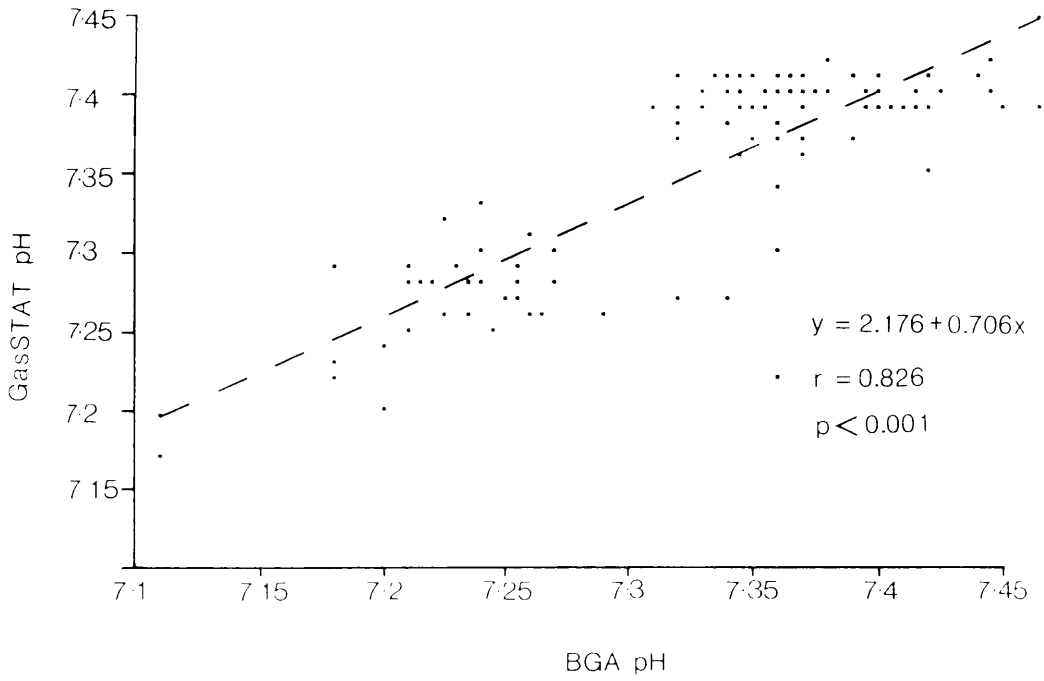
Figure 5. Relationship between arterial pH measured by the bench blood gas analyser (BGA) and by the inline blood gas monitor (GasSTAT)

were small, but nonsignificant, within patient increases in arterial pH of 0.007 (95% CL −0.009, 0.024) from Periods 1 to 2, of 0.005 (95% CL −010, 0.021) from Periods 2 to 3 and of 0.006 (95% CL −0.016, 0.028) from Periods 1 to 3. Alteration in pump flow rate and flow character had no significant effect on the arterial pH measurements made by the inline monitor, unlike alteration in acid–base management between pH and alpha–stat which produced a mean difference in pH of 0.026 (95% CL 0.006, 0.046) (Figure 6). In these same periods, the mean arterial pH, as measured by the inline blood gas monitor, during pH–stat acid–base management was 7.404 (95% CL 7.384, 7.424) whereas it was 7.381 (95% CL 7.357, 7.405) during alpha–stat control.

DISCUSSION

The main findings of this study are that the computerised system functioned well in recording data and facilitated good control of temperature but not of arterial pH.

Data acquisition

Data collection and recording were good with the one exception when a fault developed in a connector. Occasional isolated readings were recorded which were obviously spurious. During pressure measurements, these most likely originated from inadvertent flushing of the manometer lines or resonance in the lines produced by accidental movement. With nasopharyngeal temperature measurements, the use of diathermy possibly accounts for the few erroneous recordings. Zero recordings are more difficult to explain but may be due to differences in the timing of data collection from online monitors. Both these forms of error were simply identified and removed without affecting the overall validity of the data which were otherwise very consistent. This acquisition of frequent recordings from multiple measured parameters demonstrates that
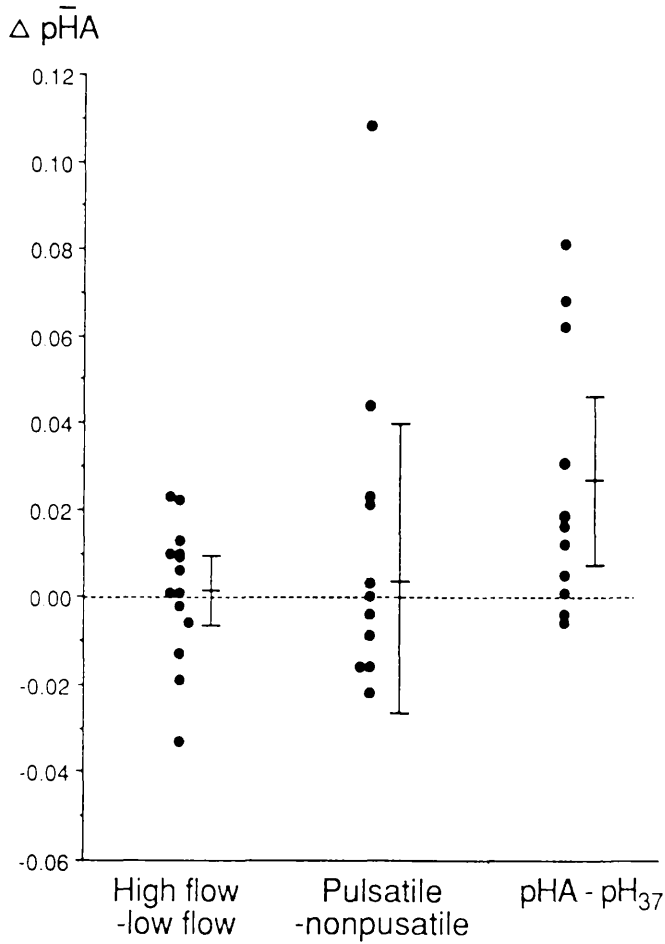
Figure 6. The effect of alternating flow rate between high and low (1.5 and 2.0 $L.min^{-1}.m^{-2}$), flow character betweeen nonpulsatile and pulsatile perfusion and acid–base management between pH and apha-stat on arterial pH as measured by the inline blood gas monitor. Vertical bars represent 95% confidence limits of the means of the changes.

computers, as has been previously suggested [144], are an effective tool for this purpose.

Thermostatic control

Excellent nasopharyngeal temperature control was obtained using this system, although arterial temperature control was not quite as good. The periods of low arterial temperature can be explained by the necessity of cooling the arterial blood to lower than the desired body temperature in order to induce hypothermia rapidly. Lack of observation on the part of the investigator and pump technician account for their occurrence and emphasise the potential for error in studies where investigator observation alone is used. Because nasopharyngeal temperature was always brought into range before arterial, the choice of displaying arterial temperature to the investigator as a running mean with one standard deviation appears justified as arterial temperature stability indicated nasopharyngeal temperature stability but not vice versa. The failure to achieve good arterial control during some first periods of study, combined with fluctuations of temperature within the preset range, highlights the need for a well considered study design. As has been previously stated by Davies, Paramelzhagen and Harris [146], the study design must control any influence that fluctuations in temperature or other such variables might have on haemodynamics and metabolism during the course of cardiopulmonary bypass.

The use of only two sites for temperature measurement to determine stable hypothermia is perhaps open to criticism as there are known to be many temperature gradients within the body during hypothermic cardiopulmonary bypass. Temperature monitoring at multiple sites, for example muscle, rectal and tympanic membrane, would possibly have improved reliability in determining and maintaining stable hypothermia. However, it is only with an animal model that true thermostatic stability can be achieved [52] and furthermore, nasopharyngeal temperature has been found to accurately reflect venous, oesophageal and hepatic temperatures during steady state hypothermic

cardiopulmonary bypass in man [146]. Moreover, maintaining both arterial and nasopharyngeal temperatures within the same small preset range for 10 minutes must indicate good thermal stability and, with a few exceptions, it proved a reliable and repeatable method.

Given the above qualifications, good thermostatic control was achieved using this system in the greater majority of periods. This is partially a reflection on the accuracy of temperature monitoring but more importantly, due to the capacity of the oxygenator's heat exchanger to effect control. This is in contrast to acid–base control which was generally poor because of less than accurate monitoring and only a limited capacity to effect control.

Acid–base management

One advantage of using the GasSTAT monitor for comparative investigation of pH and alpha-stat methods of acid–base management, is that with both methods the perfusionist aims for the same target range. Thus, no bias is introduced as might be the case if different values were used. However, if good acid–base control had been achieved there should have been no significant within patient changes in arterial pH. This was indeed the case where acid–base control was kept constant and either pump flow rate or flow character were alternated. Nevertheless, there was a small but significant difference, measured by the inline blood gas monitor, between pH and alpha–stat acid–base management. The 95% confidence limits of the means during pH–stat control approximated to the target range, whereas during alpha–stat control they overlapped at the lower end of the range. This implies that the latter was more difficult to attain. Also, the low success rate in achieving satisfactory control of pH was a surprising finding as it would be expected that inline pH monitoring would enable continuous accurate measurement of pH and so facilitate more effective control [141,147]. The explanation for this poor control is two fold. Firstly, correlation between pH as measured by the inline blood gas monitor and bench blood gas analysis was less than complete which may be attributed to differences in sites of measurement, problems with temperature correction and

systematic errors by the inline blood gas monitor [141,147]. Secondly, and more importantly, the type of bubble oxygenator employed has gas exchange characteristics during hypothermia which lead to poor arterial pH control, especially if an alpha–stat approach is taken to acid–base management [140,148]. A membrane oxygenator would have enabled better acid–base control but would have required the use of an extra roller pump to produce pulsatile perfusion. Since this study was undertaken bubble oxygenators which are designed to enable improved control of arterial pH during alpha–stat acid–base management have become commercially available [140].

In conclusion, the computerised system functioned well as a recording device. However, in terms of improved thermostatic and arterial pH control, the system only performed well if the method of monitoring was accurate and the means of effecting control was good.

CHAPTER 5

CHANGES IN HAEMODYNAMIC AND METABOLIC VARIABLES DURING HYPOTHERMIC CARDIOPULMONARY BYPASS:

EFFECTS OF FLOW RATE, FLOW CHARACTER AND ACID-BASE MANAGEMENT

METHODS

Study Design

A factorial study design was employed [138,139]. Patients were randomly allocated to one of three groups of eight. One group studied alternation in flow rate between 1.5 and 2.0 $L.min^{-1}.m^{-2}$, another group examined flow character, which was either nonpulsatile or pulsatile, and a third group investigated acid-base management, which was either according to pH or alpha-stat principles. Each group was constructed of two subsets that were identical in structure except that the order of investigation was reversed. A subset contained the four possible combinations of other variables under examination and these were kept constant throughout the study periods. Patient data was only accepted for analyses if a minimum of two periods had been completed before rewarming was started. Should this requirement not be achieved, then the next patient sequentially was studied.

Anaesthesia

Patients received their usual medication on the day of surgery. Premedication was with lorazepam 2-4 mg orally on the night prior to surgery and temazepam 20-50 mg orally approximately one hour before surgery.

Anaesthesia was induced with fentanyl 5 ug.kg^{-1} and a sleep dose of midazolam IV. Neuromuscular blockade was obtained with vecuronium 0.15 mg.kg^{-1} IV. The trachea was intubated and the lungs were ventilated with oxygen (50%) and nitrous oxide (50%) to obtain eucapnoea. Anaesthesia was maintained with fentanyl 0.1 ug.kg^{-1}.min^{-1} and neuromuscular blockade was continued with vecuronium 2.5 ug.kg^{-1}.min^{-1} IV throughout the operation.

Statistical analysis

Data was analysed using statistical modelling and factorial analysis of variance on a main frame computer with a GLIM program [149]. Because the groups construction were heterogeneous whereas the induced changes were homogeneous, results are presented as mean differences. Ninety five percent confidence limits of the means (95% CL), probability value (p) or F-statistic (F) are given in parenthesis where appropriate.

RESULTS

Patient details

Twenty seven patients were investigated although only 24 were admitted to the study because the minimum of two periods were not completed in three of them. Demographic details and relevant durations are given in Table I. All patients were receiving one or more of the following anti-anginal therapies; atenolol, propanolol, isosorbide nitrate, nifedipine and glyceryl trinitrate (sub-lingual and transcutaneous). Because of the short time clinically available at stable hypothermia only 10 of a possible 24 third study periods were obtained. These were all included in the analyses.

Thermostatic control

As described in Chapter 4, good overall temperature control was achieved.

Table I. Demographic details and durations.

	Mean	Standard deviation
Sex (F/M)	3/21	–
Age (yr)	54	9.2
Weight (kg)	76.1	9.4
Height (m)	1.71	0.06
Surface area (m²)	1.87	0.14
Cardiopulmonary bypass (min)	98	23
Cross clamp (min)	56	14

Acid–base management

Analyses of the arterial pH results (Table II), as measured by bench blood gas analyser at 37°C and uncorrected for patient temperature, in periods of pH and alpha–stat acid–base management revealed the 95% confidence limits of the means to be respectively; 7.216, 7.250 and 7.325, 7.363. As these limits did not include the expected target values for pH–stat (7.27) and alpha–stat (7.40) acid–base management, arterial pH results were treated as a continuous regression variable in all further analyses.

Metabolic variables

Systemic oxygen uptake. Multiple statistical modelling of the systemic oxygen uptake results (Table III) from all patients found that the simplest and most significant model, which described the data, included only the individual patient and flow rate. Neither flow character, arterial pH nor stage during the course of cardiopulmonary bypass (*i.e.* Period 1, 2 or 3) were included in the model. Alternation in flow rate between low and high (1.5 and 2.0 $L.min^{-1}.m^{-2}$) resulted in a mean change in systemic oxygen uptake of 18 (95% CL 7, 30) $ml.min^{-1}.m^{-2}$ (Figure 7). Systemic oxygen uptake was not significantly affected by alternation of flow character between nonpulsatile and pulsatile perfusion (–4 [95% CL –16, 7] $ml.min^{-1}.m^{-2}$) nor with variation in arterial pH (–2 [95% CL –12, 8] $ml.min^{-1}.m^{-2}$ per 0.1 pH unit) (Figures 7 and 8).

Systemic oxygen delivery. Analyses of the systemic oxygen delivery results (Table III) revealed that the simplest significant model to describe the data included only the individual patient and flow rate. The mean within patient increase in systemic oxygen delivery from low to high flow rate being 82 (95% CL 66, 98) $ml.min^{-1}.m^{-2}$. No significant effects on systemic oxygen delivery resulted when flow character or arterial pH were alternated (16 [95% CL –27, 6] $ml.min^{-1}.m^{-2}$ and –3 [95% CL –16, 10] $ml.min^{-1}.m^{-2}$ per 0.1 pH unit respectively).

Table II

Flow / Rate (Pulsatile & Nonpulsatile)

Group	Period	Variable	Pulsatile/pH Stat Patient	pH	PCO2	BE	Lactate	Pulsatile/Alpha Stat Patient	pH	PCO2	BE	Lactate	Nonpulsatile/pH Stat Patient	pH	PCO2	BE	Lactate	Nonpulsatile/Alpha Stat Patient	pH	PCO2	BE	Lactate
	1	High flow		7.11	77	-7	2.32		7.34	40	-4	1.72		7.24	62	-4	2.11		7.36	39	-3	-
	2	Low flow	JF	7.18	62	-6	1.29	JC	7.32	41	-4	1.37	ON	7.24	56	-4	2.1	RM	7.34	38	-3	-
Flow	3	High flow		-	-	-	-		7.34	38	-4	2.57		-	-	-	-		7.35	37	-	-
	1	Low flow		7.26	56	-3	2.63		7.26	60	0	2.79		7.27	55	-2	1.2		7.39	34	-2	2.84
Rate	2	High flow	JM	7.32	45	-3	2.34	JH	7.27	60	-2	2.43	MS	7.28	50	-3	1.41	FM	7.4	36	-1.5	2.36
	3	Low flow		7.22	60	-3	2.14		7.26	58	-2	2.04		-	-	-	-		7.39	37	-2.5	2.12

Flow / Character (High & Low Flow)

Period	Variable	High Flow/pH Stat Patient	pH	PCO2	BE	Lactate	High Flow/Alpha Stat Patient	pH	PCO2	BE	Lactate	Low Flow/pH Stat Patient	pH	PCO2	BE	Lactate	Low Flow/Alpha Stat Patient	pH	PCO2	BE	Lactate
1	Pulsatile		7.22	62	-4.5	-		7.36	42	0	2.1		7.26	54	-3.5	3.29		7.26	57	-2	2.23
2	Nonpulse	EH	7.26	54	-4	-	RS	7.35	42	-1	2.39	AH	7.25	55	-4	2.48	GS	7.2	66	-3	2.25
3	Pulsatile		-	-	-	-		7.34	44	-2	1.92		-	-	-	-		-	-	-	-
1	Nonpulse		7.21	67	-3.5	1.78		7.34	42	-3.5	3.15		7.18	72	-3	1.9		7.38	41	-1	1.62
2	Pulsatile	JT	7.21	61	-3.5	2.47	JG	7.32	41	-4	3.45	JD	7.22	60	-3	1.9	WS	7.38	42	0	1.12
3	Nonpulse		7.24	60	-3.5	1.87		7.32	38	-5	2.88		-	-	-	-		-	-	-	-

Arterial pH (Low & High Flow, Pulsatile & Nonpulsatile)

Group	Period	Variable	Low Flow/Pulsatile Patient	pH	PCO2	BE	Lactate	Low Flow/Nonpulsatile Patient	pH	PCO2	BE	Lactate	High Flow/Pulsatile Patient	pH	PCO2	BE	Lactate	High Flow/Nonpulsatile Patient	pH	PCO2	BE	Lactate
	1	pH Stat		7.24	72	3	1.51		7.24	62	-3	1.94		7.24	53	-6	1.6		7.2	64	-4	3.39
	2	Alpha Stat	JS	7.31	62	-2	1.29	DG	7.34	44	-2	2.25	MH	7.39	34	-4	1.09	GM	7.36	41	-2	3.45
Arterial	3	pH Stat		7.22	65	-3	1.15		-	-	-	-		-	-	-	-		-	-	-	-
pH	1	Alpha Stat		7.34	72	0	1.78		7.39	34	-4	2.57		7.46	28	-2	1.85		7.32	47	-1	2.06
	2	pH Stat	JF	7.22	66	-2	1.32	IM	7.29	46	-6	2.65	CB	7.34	40	-4	1.63	DT	7.23	60	-3	1.91
	3	Alpha Stat		-	-	-	-		-	-	-	-		-	-	-	-		7.34	43	-2	1.67

Table III

Pulsatile/pH Stat, Pulsatile/Alpha Stat, Nonpulsatile/pH Stat, Nonpulsatile/Alpha Stat

Group	Period	Variable	Patient	Q	CaO2	CvO2	DO2	VO2	Patient	Q	CaO2	CvO2	DO2	VO2	Patient	Q	CaO2	CvO2	DO2	VO2	Patient	Q	CaO2	CvO2	DO2	VO2
	1	High flow		4	13	10.4	259	51		3.8	14.6	10.7	292	75		3.87	13.1	9.3	256	75		3.42	16.8	11.4	339	109
	2	Low flow	JF	3	13.6	10.6	205	46	JC	2.8	13.8	10.2	207	54	ON	2.95	12.3	9.3	186	45	RM	2.5	16	11.5	235	66
Flow	3	High flow		-	-	-	-	-		3.8	16.2	11.2	324	100		-	-	-	-	-		3.4	18.9	14.2	378	103
Rate	1	Low flow		2.9	13.8	9.1	207	70		2.96	19.1	14.4	288	70		3.01	11.8	9.4	174	36		2.52	11.1	7.6	166	52
	2	High flow	JM	3.86	14	9.5	281	91	JH	3.92	19.4	16.2	387	63	MS	4	12.8	10	250	54	FM	3.37	12.1	9.6	243	49
	3	Low flow		2.9	14.9	10.2	224	71		2.9	18.9	14.2	280	69		-	-	-	-	-		2.53	12	9.7	181	35

High Flow/pH Stat, High Flow/Alpha Stat, Low Flow/pH Stat, Low Flow/Alpha Stat

Group	Period	Variable	Patient	Q	CaO2	CvO2	DO2	VO2	Patient	Q	CaO2	CvO2	DO2	VO2	Patient	Q	CaO2	CvO2	DO2	VO2	Patient	Q	CaO2	CvO2	DO2	VO2
	1	Pulsatile		4.28	15.3	13	306	47		3.5	14.1	11	279	62		2.84	14.2	8.9	219	81		2.74	14.2	10.3	211	58
	2	Nonpulse	EH	4.27	15.7	14.2	313	31	RS	3.52	14.2	12.8	282	28	AH	2.82	14.2	12.8	212	74	GS	2.77	14	10.4	210	55
Flow	3	Pulsatile		-	-	-	-	-		3.5	13	11.5	257	30		-	-	-	-	-		-	-	-	-	-
Character	1	Nonpulse		4.03	13.6	10.5	272	63		3.69	12.4	10.5	248	39		2.67	14.2	8.9	214	80		2.74	13	10.9	198	33
	2	Pulsatile	JT	4.03	13.4	11.6	264	36	JG	3.7	11.6	10.4	232	23	JD	2.67	14.2	9.2	212	74	WS	2.74	13.4	11.8	204	25
	3	Nonpulse		3.99	15.8	11.7	313	82		-	-	-	-	-		-	-	-	-	-		-	-	-	-	-

Low Flow/Pulsatile, Low Flow/Nonpulsatile, High Flow/Pulsatile, High Flow/Nonpulsatile

Group	Period	Variable	Patient	Q	CaO2	CvO2	DO2	VO2	Patient	Q	CaO2	CvO2	DO2	VO2	Patient	Q	CaO2	CvO2	DO2	VO2	Patient	Q	CaO2	CvO2	DO2	VO2
	1	pH Stat		2.92	13	9.2	192	58		2.88	17.2	12.3	257	73		3.32	10.1	8	200	39		4	14.9	10.6	291	86
	2	Alpha Stat	JS	3	13	9.5	198	54	DG	2.86	18.6	14.1	278	68	MH	3.32	11.2	8.5	223	54	GM	4	13.8	10	269	74
Arterial	3	pH Stat		3	12.8	9.8	193	49		-	-	-	-	-		-	-	-	-	-		-	-	-	-	-
pH	1	Alpha Stat		2.82	12.8	8.8	192	60		2.4	10.4	9	156	21		3.7	14	11.4	276	51		3.52	11.7	10.2	234	30
	2	pH Stat	JF	2.82	16	10.4	240	84	IM	2.39	10.2	7.9	152	32	CB	3.7	14.8	11.6	292	61	DT	3.52	14.2	12.4	285	35
	3	Alpha Stat		-	-	-	-	-		-	-	-	-	-		-	-	-	-	-		3.54	13.4	12	271	30
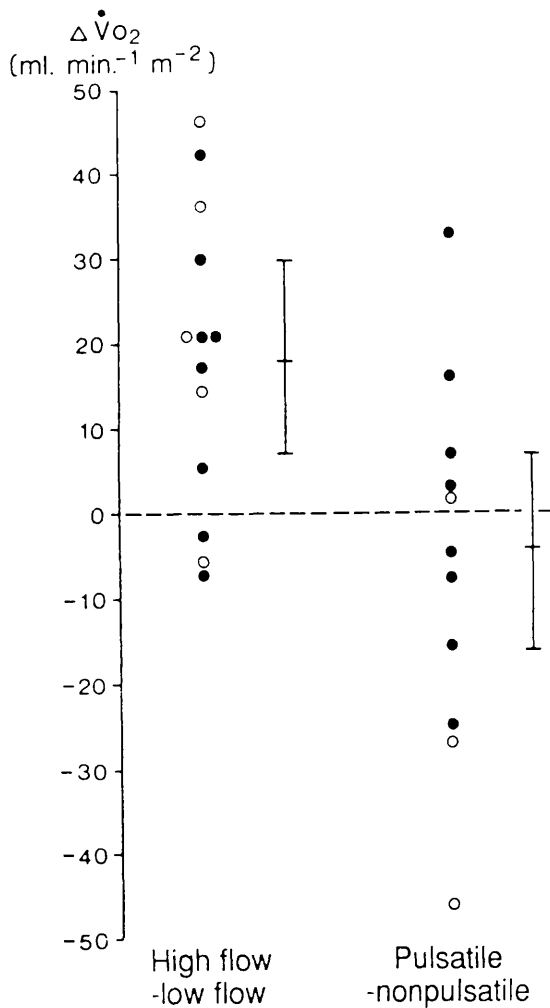
Figure 7. The effect of alternating flow rate between high and low (1.5 and 2.0 L.min⁻¹.m²) and flow character between pulsatile and nonpulsatile perfusion on systemic oxygen uptake ($\dot{V}O_2$) during hypothermic cardiopulmonary bypass. Closed circles represent changes between Periods 1 and 2 and open circles changes between Periods 2 and 3. Vertical bars represent 95% confidence limits of the means of the changes.
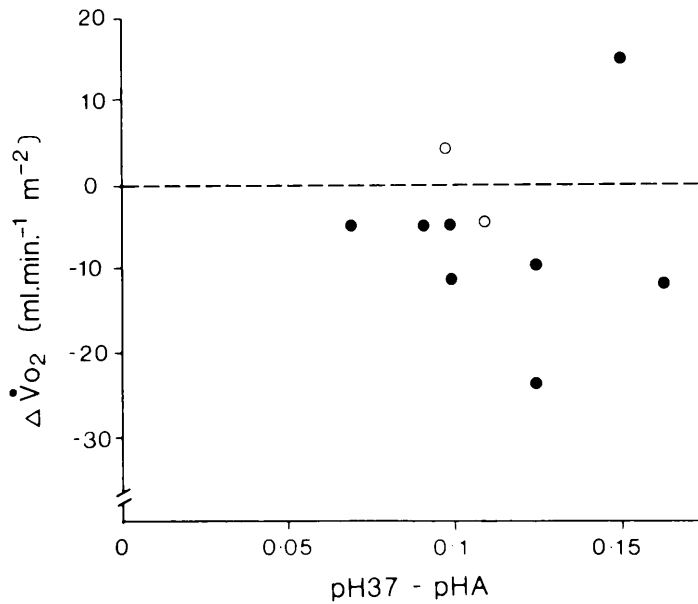
Figure 8. The relationship between change in systemic oxygen uptake ($\dot{V}O_2$) and change in arterial pH as a result of altering acid–base management between attempted pH and alpha–stat control (pHA and pH37) during hypothermic cardiopulmonary bypass. Closed circles represent changes between Periods 1 and 2 and open circles represent changes between Periods 2 and 3.

Blood oxygen variables. Modelling of the data for the measured blood oxygen variables (Table IV) found that some were significantly affected by alternation in flow rate whilst others were not. Mixed venous blood oxygen content, saturation and tension were all significantly higher at 2.0 compared to 1.5 L.min^{-1}.m^{-2} (F = 5.51, 18.37, and 20.88; critical value = 4.17) whereas arterial blood oxygen content, saturation and tension and oxygen extraction were not significantly affected (F = 4.08, 3.99, 1.37, 0.01 ; critical value oxygen saturation = 4.21, others = 4.17). However, the increases in both arterial blood oxygen content and oxygen extraction approached significance.

No significant changes in either the measured arterial and mixed venous blood oxygen variables nor oxygen extraction were found to occur with alternation of flow character, arterial pH or with stage during cardiopulmonary bypass.

Haemoglobin concentration. Statistical modelling of the haemoglobin concentration data (Table IV) found no significant relationships with flow rate, flow character and arterial pH nor with stage during cardiopulmonary bypass.

Base excess. Modelling of base excess data (Table II) demonstrated a strongly significant relationship between base excess and arterial pH (F = 83.68, critical value = 4.28) although the magnitude of the effect was very small. No significant relationships were found between base excess and alternation of flow rate or flow character nor with stage during cardiopulmonary bypass.

Lactate concentration. Modelling of plasma lactate concentrations (Table II) found no significant relationship with flow rate, flow character or arterial pH. In all patients there was a small but significant decrease in the average lactate concentration during the course of cardiopulmonary bypass. There was a mean decrease in lactate concentration of 0.17 (95% CL –0.01, 0.34) mmol.L^{-1} from Periods 1 to 2, 0.25 (95% CL –0.05, 0.55) mmol.L^{-1} from Periods 2 to 3 and 0.42 (95% CL 0.17, 0.65) mmol.L^{-1} from Periods 1 to 3.

Table IV

Band 1 — Group: Flow Rate

Pulsatile/pH Stat

Period	Variable	Patient	Arterial SO2	PO2	Hb	Venous SO2	PO2	Hb
1	High flow		99	184	96	84	82	94
2	Low flow	JF	99	312	98	86	70	96
3	High flow		98	-	-	-	-	105
1	Low flow		98	122	100	76	45	105
2	High flow	JM	98	240	100	89	56	100
3	Low flow		100	316	100	84	53	100

Pulsatile/Alpha Stat

Period	Variable	Patient	Arterial SO2	PO2	Hb	Venous SO2	PO2	Hb
1	High flow		98	562	88	89	54	90
2	Low flow	JC	99	552	91	84	47	92
3	High flow		98	434	90	89	52	86
1	Low flow		99	186	114	85	53	115
2	High flow	JH	99	210	85	89	56	116
3	Low flow		99	311	89	87	58	120

Nonpulsatile/pH Stat

Period	Variable	Patient	Arterial SO2	PO2	Hb	Venous SO2	PO2	Hb
1	High flow		98	228	93	85	60	88
2	Low flow	QN	98	274	88	82	58	91
3	High flow		-	-	-	-	-	-
1	Low flow		94	74	99	76	46	100
2	High flow	MS	100	272	96	86	58	95
3	Low flow		-	-	-	-	-	-

Nonpulsatile/Alpha Stat

Period	Variable	Patient	Arterial SO2	PO2	Hb	Venous SO2	PO2	Hb
1	High flow		99	338	92	89	55	92
2	Low flow	RM	99	490	94	82	48	94
3	High flow		98	470	86	90	58	94
1	Low flow		100	493	68	82	45	72
2	High flow	FM	100	467	76	92	78	75
3	Low flow		100	607	80	88	53	80

Band 2 — Group: Flow Character

High Flow/pH Stat

Period	Variable	Patient	Arterial SO2	PO2	Hb	Venous SO2	PO2	Hb
1	Pulsatile		98	477	110	91	68	110
2	Nonpulse	EH	98	488	114	90	66	115
3	Pulsatile		-	-	-	-	-	-
1	Nonpulse		98	256	90	89	65	92
2	Pulsatile	JT	98	316	88	90	68	88
3	Nonpulse		98	432	88	91	68	90

High Flow/Alpha Stat

Period	Variable	Patient	Arterial SO2	PO2	Hb	Venous SO2	PO2	Hb
1	Pulsatile		98	210	87	87	54	98
2	Nonpulse	RS	99	307	90	90	59	96
3	Pulsatile		99	350	91	91	62	96
1	Nonpulse		99	407	93	93	63	86
2	Pulsatile	JG	100	553	93	93	63	84
3	Nonpulse		100	542	96	96	72	78

Low Flow/pH Stat

Period	Variable	Patient	Arterial SO2	PO2	Hb	Venous SO2	PO2	Hb
1	Pulsatile		99	375	68	92	54	62
2	Nonpulse	AH	99	318	70	88	-	56
3	Pulsatile		-	-	-	-	-	-
1	Nonpulse		99	242	96	74	-	44
2	Pulsatile	JD	99	271	90	83	-	52
3	Nonpulse		-	-	-	-	-	-

Low Flow/Alpha Stat

Period	Variable	Patient	Arterial SO2	PO2	Hb	Venous SO2	PO2	Hb
1	Pulsatile		99	182	104	78	45	102
2	Nonpulse	GS	99	218	102	78	48	101
3	Pulsatile		-	-	-	-	-	-
1	Nonpulse		98	409	88	87	55	92
2	Pulsatile	WS	98	406	92	83	49	93
3	Nonpulse		-	-	-	-	-	-

Band 3 — Group: Arterial pH

Low Flow/Pulsatile

Period	Variable	Patient	Arterial SO2	PO2	Hb	Venous SO2	PO2	Hb
1	pH Stat		100	412	90	78	47	90
2	Alpha Stat	JS	100	432	92	68	52	91
3	pH Stat		100	348	92	84	56	92
1	Alpha Stat		99	264	90	70	38	93
2	pH Stat	JF	98	210	90	84	55	96
3	Alpha Stat		-	-	-	-	-	-

Low Flow/Nonpulsatile

Period	Variable	Patient	Arterial SO2	PO2	Hb	Venous SO2	PO2	Hb
1	pH Stat		98	250	117	77	46	116
2	Alpha Stat	DG	98	232	120	86	49	126
3	pH Stat		-	-	-	-	-	-
1	Alpha Stat		99	617	71	89	52	72
2	pH Stat	IM	99	403	72	91	51	71
3	Alpha Stat		-	-	-	-	-	-

High Flow/Pulsatile

Period	Variable	Patient	Arterial SO2	PO2	Hb	Venous SO2	PO2	Hb
1	pH Stat		99	380	76	89	-	63
2	Alpha Stat	MH	99	632	64	94	-	68
3	pH Stat		-	-	-	-	-	-
1	Alpha Stat		99	644	90	94	-	60
2	pH Stat	CB	99	554	96	92	-	60
3	Alpha Stat		-	-	-	-	-	-

High Flow/Nonpulsatile

Period	Variable	Patient	Arterial SO2	PO2	Hb	Venous SO2	PO2	Hb
1	pH Stat		99	284	84	88	64	84
2	Alpha Stat	GM	99	604	90	95	78	92
3	pH Stat		-	-	-	-	-	-
1	Alpha Stat		99	306	86	88	56	84
2	pH Stat	DT	99	440	86	92	68	84
3	Alpha Stat		99	491	87	94	68	88

Haemodynamic variables

Pulse pressure. Examination of systolic and diastolic arterial pressures (Table V) revealed that the mean pulse pressure during pulsatile perfusion was 23.7 (95% CL 19.3, 28.0) mmHg. However, there was a mean pulse pressure of 14.1 (95% CL 12.1, 16.0) mmHg during nonpulsatile perfusion. The mean within patient change in pulse pressure produced by alternating flow character between nonpulsatile and pulsatile was 11.5 (95% CL 5.9, 17.1) mmHg. Because of the sizeable pulse pressure during periods of nonpulsatile perfusion and a large variability in pulse pressure during periods of pulsatile perfusion, pulse pressure was treated as a continuous regression variable in the analyses of haemodynamic variables.

Mean arterial pressure. Within patient changes in mean arterial pressure produced by alternations in pump flow rate, flow character and arterial pH are plotted in Figure 9. Analyses of mean arterial pressure data (Table V) found, when all other variables were excluded, that both patient and stage were individually significant (F = 8.323). When all variables under study were included in the model, only flow rate was found to have a significant effect on mean arterial pressure (F = 4.765, critical value = 4.184). If only patient stage and flow rate were fitted to the model, the combined effects of flow character and arterial pH upon mean arterial pressure were not significant (F = 0.65, critical value = 3.334). On average, mean arterial pressure was 7.2 (95% CL 1.6, 12.9) mmHg higher at 2.0 compared to 1.5 L .min^{-1}.m^{-2}.

Mean arterial pressure increased on average from Period 1 to 2 by 9.4 (95% CL 5.8, 13.0) mmHg, from Period 1 to 3 by 15.7 (95% CL 10.6, 20.9) mmHg and from Period 2 to 3 by 6.3 (95% CL 1.2, 11.4) mmHg. Tabulation of the average values of mean arterial pressure for all six combinations of flow rate and stage during pH and alpha–stat control (Table VI) demonstrates not only the main effects of stage and flow rate but also, interaction between arterial pH and

Table V

Flow Rate

Group	Period	Variable	Pulsatile/pH Stat						Pulsatile/Alpha Stat						Nonpulsatile/pH Stat						Nonpulsatile/Alpha Stat					
			Patient	SAP	DAP	MAP	CVP	PVR	Patient	SAP	DAP	MAP	CVP	PVR	Patient	SAP	DAP	MAP	CVP	PVR	Patient	SAP	DAP	MAP	CVP	PVR
Flow Rate	1	High Flow	JF	97	48	65	3	1244	JC	85	63	73	2	1482	ON	66	57	61	-14	1544	RM	76	61	68	11	1334
	2	Low flow		74	44	54	10	1185		86	67	75	0	2132		66	57	61	-14	2034		82	71	77	4	2333
	3	High flow		-	-	-	-	-		83	63	36	5	1392		60	80	84	-10	1937		87	80	87	8	1866
	1	Low flow	JM	71	40	51	-3	1493	MS	39	34	36	1	942	FM	51	44	47	0	1495		43	34	38	-21	1852
	2	High flow		93	49	64	-1	1350		61	48	53	2	1042		70	54	60	-2	1462		83	65	74	-8	1946
	3	Low flow		93	53	66	-3	1888		66	52	58	8	1375		-	-	-	-	-		62	70		-7	2358

Flow Character

Group	Period	Variable	High Flow/pH Stat						High Flow/Alpha Stat						Low Flow/pH Stat						Low Flow/Alpha Stat					
			Patient	SAP	DAP	MAP	CVP	PVR	Patient	SAP	DAP	MAP	CVP	PVR	Patient	SAP	DAP	MAP	CVP	PVR	Patient	SAP	DAP	MAP	CVP	PVR
Flow Character	1	Pulsatile	EH	82	48	59	2	1058	RS	54	42	47	1	1051	AH	58	45	50	0	1426	GS	67	41	51	9	1224
	2	Nonpulse		74	57	65	2	1180		73	60	69	2	1529		53	47	50	1	1383		71	53	62	8	1157
	3	Pulsatile		-	-	-	-	-		88	63	74	2	1646		-	-	-	-	-		-	-	-	-	-
	1	Nonpulse	JT	80	64	71	8	1242	JG	73	57	79	-3	1473	JD	63	47	53	-18	2112	WS	58	44	50	-11	1793
	2	Pulsatile		88	58	70	8	1237		90	51	66	1	1398		73	43	53	-20	2196		62	53	57	-11	1768
	3	Nonpulse		91	69	80	0	849		86	62	74	-3	1534		-	-	-	-	-		-	-	-	-	-

Arterial pH

Group	Period	Variable	Low Flow/Pulsatile						Low Flow/Nonpulsatile						High Flow/Pulsatile						High Flow/Nonpulsatile					
			Patient	SAP	DAP	MAP	CVP	PVR	Patient	SAP	DAP	MAP	CVP	PVR	Patient	SAP	DAP	MAP	CVP	PVR	Patient	SAP	DAP	MAP	CVP	PVR
Arterial pH	1	pH stat	JS	52	33	41	4	988	DG	58	42	49	8	1112	MH	66	37	48	1	1118	GM	95	73	84	0	1674
	2	Alpha stat		70	44	55	3	1538		90	69	77	11	1831		79	52	63	2	1474		109	87	98	-7	2105
	3	pH stat		72	44	55	-2	1480		92	72	73	4	2089		-	61	-	-	-		-	-	-	-	-
	1	Alpha stat	JF	61	43	50	-4	1530	IM	72	61	67	-13	2654	CB	84	70	70	2	1489	DT	46	37	41	1	911
	2	pH stat		70	52	60	-3	1786		85	70	78	-4	2772		90	-	73	2	1533		52	42	47	1	1044
	3	Alpha stat		-	-	-	-	-		-	-	-	-	-		-	-	-	-	-		70	55	62	-2	1472

Figure 9. The effect of alternating flow rate between low and high (1.5 and 2.0 L.min⁻¹.m⁻²), flow character between pulsatile and nonpulsatile perfusion and acid–base management between pH and alpha–stat control (pHA and pH37) on mean arterial pressure (MAP). Closed circles represent changes between Periods 1 and 2 and open cirles changes between Periods 2 and 3. Vertical bars represent 95% confidence limits for the mean change.

Table VI. Averaged mean arterial pressures (mmHg) for all combinations of flow rates and study periods during **a)** pH–stat and **b)** Alpha–stat acid–base management.

a) pH–stat	2.0 $L.min^{-1}.m^{-2}$	1.5 $L.min^{-1}.m^{-2}$
Period 1	58	53
Period 2	63	58
Period 3	72	67
b) Alpha–stat		
Period 1	58	53
Period 2	72	66
Period 3	76	71

stage during cardiopulmonary bypass. Little or no difference in mean arterial pressure exists between attempted pH and alpha–stat acid–base management during Period 1, but by Period 2, mean arterial pressure is higher with alpha than pH–stat control and this interaction is continued in Period 3.

Central venous pressure. Analyses of the central venous pressure data (Table V) demonstrated no significant relationships with any of the variables investigated nor with stage during cardiopulmonary bypass.

Peripheral vascular resistance. Within patient changes in peripheral vascular resistance resulting from alternation in flow rate, flow character and arterial pH are plotted in Figure 10. Modelling of the peripheral vascular resistance data (Table V) found that if all other variables were excluded, patient and stage during cardiopulmonary bypass were individually significant (F = 10.706). When the variables under study were fitted to the model, only flow rate was found to have a significant effect on peripheral vascular resistance (F = 15.892, critical value = 4.184). When only patient, stage and flow rate were included in the model, the combined effects of flow character and arterial pH were nonsignificant (F = 1.745, critical value = 3.334). Tabulation of the average peripheral vascular resistance for all six combinations of flow rate and stage (Table VII) shows that there were mean increases from Period 1 to 2 of 239 (95% CL 135, 343) dynes.s.cm^{-5}, from Period 1 to 3 of 324 (95% CL 175, 473) dynes.s.cm^{-5} and from Period 2 to 3 of 85 (95% CL –64, 234) dynes.s.cm^{-5}. Also, there was a mean increase in peripheral vascular resistance of 316 (95% CL 152, 480) dynes.s.cm^{-5} at the low compared to the high flow rate. However, no significant interaction between these variables was found.

A significant correlation between within patient changes in peripheral vascular resistance and contemporaneous systemic oxygen uptake measurements which were produced by alternation in pump flow rate between high and low was found (Figure 11).
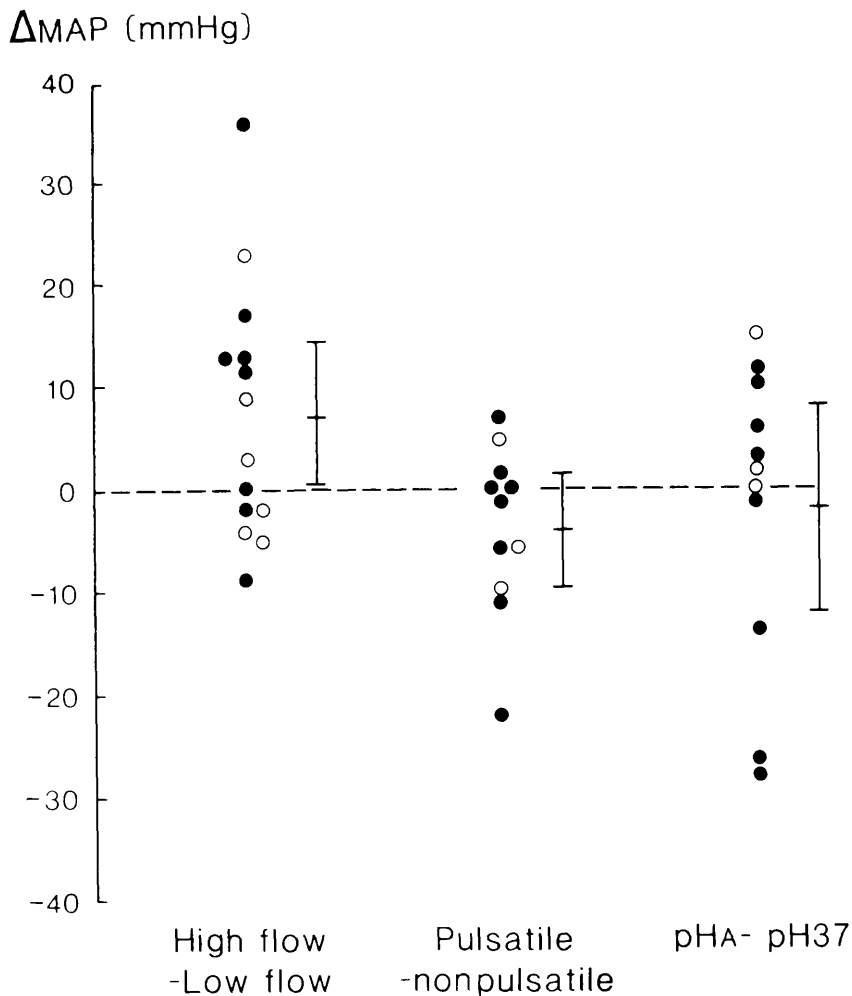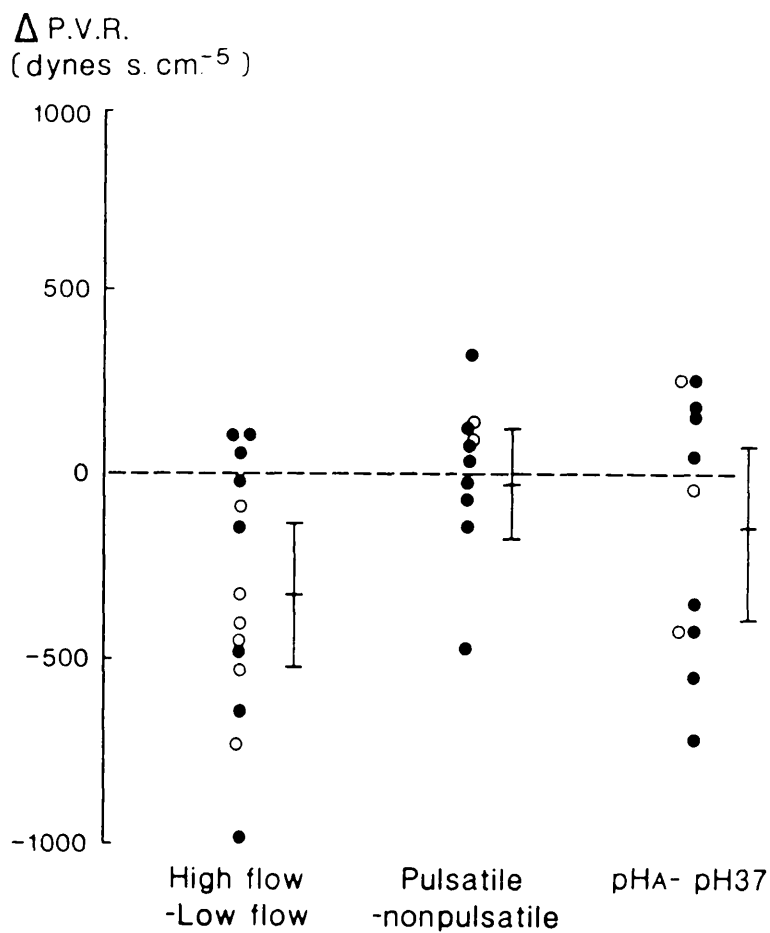
Figure 10. The effect of alternating flow rate between low and high (1.5 and 2.0 L.min $^{-1}$.m $^{-2}$), flow character between pulsatile and nonpulsatile perfusion and acid-base management between pH and alpha-stat control (pHA and pH37) on peripheral vascular resistance (PVR). Closed circles represent changes between Periods 1 and 2 and open cirles changes between Periods 2 and 3. Vertical bars represent 95% confidence limits for the mean change.

Table VII. Averaged peripheral vascular resistances (dynes. s. cm^{-5}) for all combinations of flow rates and study periods.

	2.0 L.min^{-1}.m^{-2}	1.5 L.min^{-1}.m^{-2}
Period 1	1269	1585
Period 2	1508	1823
Period 3	1593	1908
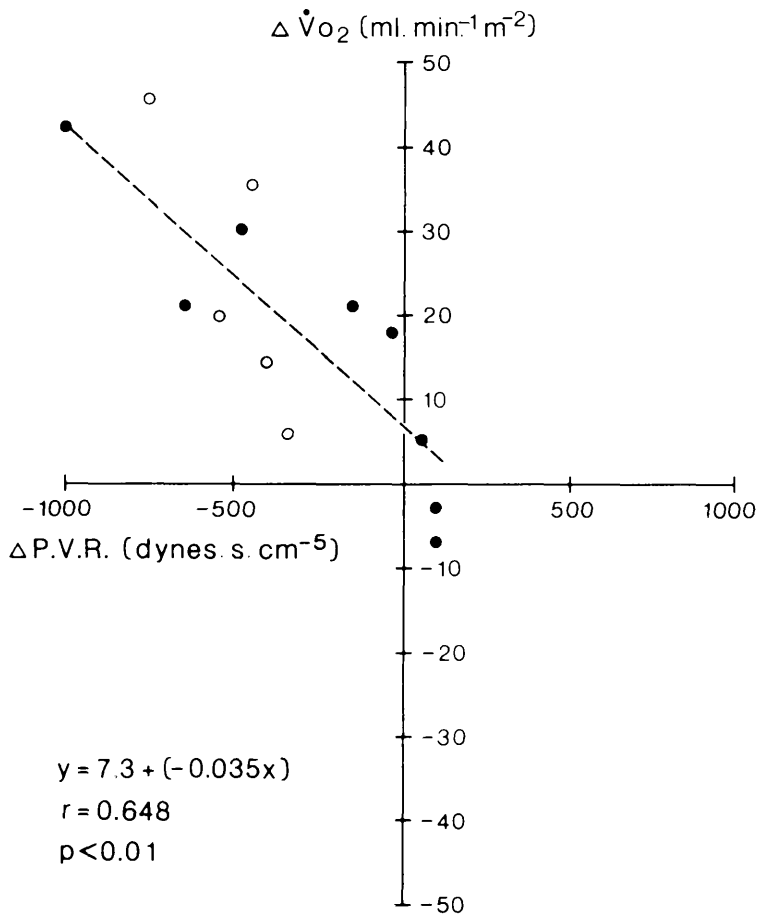
Figure 11. The relationship between changes in systemic oxygen uptake ($\dot{V}O_2$) and peripheral vascular resistance (PVR) produced by alternating the flow rate between 1.5 and 2.0 L.min⁻¹.m⁻². Closed circles represent changes between Periods 1 and 2 and open cirles changes between Periods 2 and 3.

Haematocrit. Over all periods, the mean haematocrit was 27.6 (95% CL 26.4, 28.8)%. Analyses of the haematocrit results found that the simplest significant model which described the data included patient, stage, pump flow rate and a factor for interaction between stage and pump flow rate. Tabulation of the average haematocrit values for all six combinations of stage and pump flow rate (Table VIII) shows that there were minimal differences in haematocrit during Periods 1 and 2 but by Period 3 haematocrit at the high flow rate was approximately 3% less than the low flow rate.

Reservoir volume. A significant interaction between stage of study period during cardiopulmonary bypass and flow rate was found (Table IX). Average reservoir volumes were less at the high compared to the low flow rate during Periods 1 and 2 but the situation was reversed during Period 3.

Vasoactive drugs. There were no significant relationships between sodium nitroprusside or methoxamine administration and any of the variables investigated. However, there was an overall tendency for greater methoxamine usage in Period 1 (Table X) and greater sodium nitroprusside usage in Periods 2 and 3.

DISCUSSION

The outstanding findings of this study are that systemic oxygen uptake and peripheral vascular resistance were significantly affected by alternation in flow rate between 1.5 and 2.0 $L.min^{-1}.m^{-2}$ but not by alternation of flow character or arterial pH.

Table VIII. Averaged haematocrits (%) for all combinations of flow rate and study periods.

	2.0 $L.min^{-1}.m^{-2}$	1.5 $L.min^{-1}.m^{-2}$
Period 1	27.2	27.2
Period 2	27.5	27.6
Period 3	26.5	29.5

Table IX. Averaged reservoir volumes (ml) for all combinations of flow rates and study periods.

	2.0 L.min^{-1}.m^{-2}	1.5 L.min^{-1}.m^{-2}
Period 1	790	1309
Period 2	755	1185
Period 3	946	736

Table X. Methoxamine (M) and sodium nitroprusside (SNP) administration.

Patient	Period 1	Period 2	Period 3
	2.0 L.min^{-1}.m^{-2}	1.5 L.min^{-1}.m^{-2}	2.0 L.min^{-1}.m^{-2}
1	0	0	–
2	SNP	SNP	SNP
3	0	0	–
4	0	0	SNP
	1.5 L.min^{-1}.m^{-2}	2.0 L.min^{-1}.m^{-2}	1.5 L.min^{-1}.m^{-2}
5	0	SNP	SNP
6	M	0	0
7	0	0	–
8	M	0	0
	Pulsatile	Nonpulsatile	Pulsatile
9	0	0	–
10	0	0	0
11	0	0	–
12	0	0	–
	Nonpulsatile	Pulsatile	Nonpulsatile
13	0	SNP	SNP
14	0	SNP	SNP
15	0	0	–
16	0	SNP	–
	pH–stat	Alpha–stat	pH–stat
17	M	0	0
18	0	SNP	–
19	0	0	–
20	0	SNP	–
	Alpha–stat	pH–stat	Alpha–stat
21	0	0	–
22	SNP	SNP	–
23	SNP	SNP	–
24	0	0	0

Study design

Clearly statistically significant effects were found in this study using a relatively small population. A larger population might have resulted in other significant findings and it would certainly have enabled narrower confidence limits to have been calculated. However, if significant effects can be found with a small population then it is ethically unsound to study a larger number of patients. To obtain the same degree of precision using a non–factorial design would have required much larger numbers and detection of interaction would not have been possible [138,139].

Metabolism

Flow rate. The change in systemic oxygen uptake induced by alternating flow rate must have been mediated by either changes in tissue oxygen extraction, distribution of blood flow through the microcirculation or a combination of both factors. Lack of variation in oxygen extraction implies that the change in systemic oxygen uptake was purely related to the distribution of blood flow through the tissues. Therefore, it would appear that systemic oxygen uptake was decreased at 1.5 $L.min^{-1}.m^{-2}$ due to impaired tissue perfusion. This conclusion is supported by the associated changes in haemodynamic variables as well as by the similar findings of Harris, Seelye and Squire [51]. In contrast to the present study, Fox and colleagues [60] found an increase in oxygen extraction to be associated with reduction in flow rate during cardiopulmonary bypass using profound hypothermia. However, their use of extremely low flow rates (down to 0.25 $L.min^{-1}.m^{-2}$) may account for this difference in findings. Flow rates used in the present study were chosen to lie within the higher range of commonly employed low rates of flow. As the present study examined only two flow rates, it cannot determine the rate of flow at which systemic oxygen uptake might plateau though the findings clearly show that systemic oxygen uptake is less than maximal at 1.5 $L.min^{-1}.m^{-2}$. In contrast, both Hickey and Hoar [63] and Fox

and co-workers [60] found that during moderate and profound hypothermia respectively, systemic oxygen uptake reached a plateau at 1.2 $L.min^{-1}. m^{-2}$. As discussed in Chapter 2, these findings may have been influenced by choice of study design and statistical analysis. The findings from the present study indicate that systemic oxygen uptake was not maintained and therefore, the physiological rationale for using low flow rates is flawed.

With the decrease in systemic oxygen uptake found at the lower flow rate, a resultant increase in anaerobic metabolism would be expected. However, no significant increases in base excess or lactate concentration were found at the lower compared to the higher flow rate. These apparently conflicting results have been found in the past by Harris, Seelye and Barratt-Boyes [40]. They postulated that anaerobic metabolism occurs at low flow rates but does not register on a systemic scale because there is little or no perfusion in the areas where it is occurring. Thus, although there was no measured increase in anaerobic metabolism at the lower flow rate in the present study, its occurrence may have been concealed.

In contrast to earlier studies [5,48], the present study found an overall reduction in lactate concentration with stage and this is perhaps accounted for by metabolism or redistribution of lactate present in the crystalloid prime during the course of cardiopulmonary bypass.

Flow character. Unlike many previous studies [43-45,69,70,72], this study failed to detect any metabolic superiority of pulsatile over nonpulsatile perfusion. The most fundamental explanation may lie in the device used to generate pulsation as the Stöckert pump used in the present study has been found by Wright to produce less pulsatile power than others [5,51]. Thus, flow character's failure to influence metabolism in the present study could simply be the result of failing to generate sufficient pulsatile power. Another factor that may account for the different findings is the use of hypothermia in the present study as this was not employed in most early studies. In addition this study, unlike the majority of previous studies, not only continuously quantified the pulse pressure but also

demonstrated it to be significantly different between nonpulsatile and pulsatile perfusion [12]. However, pulse pressure alone may not be a good index of pulsatility [152]. Moreover, during nonpulsatile perfusion in the present study, there was a sizeable mean pulse pressure which is an artefact of roller pumps. Therefore, this study may be criticised for comparing two forms of pulsatile flow character rather than true nonpulsatile and pulsatile perfusion [12]. For these reasons, this study cannot exclude the possibility that there are metabolic differences between truly nonpulsatile and pulsatile flow characters. Nonetheless, nonpulsatile and pulsatile perfusion are commonly produced in the manner used in this study during clinical practice and therefore, the present comparison has validity.

Although the majority of previous studies have found pulsatile to have metabolic superiority to nonpulsatile perfusion [12], this study is not isolated in its failure to demonstrate that flow character has any influence on metabolic variables [47,71,72]. As discussed in Chapter 2, other negative findings have been dismissed on the grounds that high flow rates were employed [12]. However, both flow rates examined in the present study are within the low range and no significant differences between nonpulsatile and nonpulsatile perfusion were found. This would imply that differences in flow character are not more apparent at low flow rates.

Acid-base management. As discussed in Chapter 4, neither true alpha nor pH-stat conditions were obtained despite using inline blood gas monitoring. Thus, this study cannot exclude the premise that differences in systemic oxygen uptake may exist between pH and alpha-stat acid-base management. However, a reasonably large and significant change in arterial pH was induced and this should give an indication of the possible differences between the two forms of acid-base management. Nonetheless, under the conditions of this study, the lack of a significant relationship between arterial pH and systemic oxygen uptake indicates that the choice of acid-base management has little influence on systemic metabolism.

The strongly significant relationship between arterial pH and base excess, although very small in magnitude, could imply that lower pH produces more metabolic acidosis. It is more likely that these changes result from inducing acute changes in arterial carbon dioxide tension as this is known to cause a fall in base excess in dogs and can be mistakenly interpreted as metabolic acidosis [153].

Haemodynamics

Flow rate. The increase in peripheral vascular resistance with reduction in flow rate in this study confirms the recognised inverse relationship between these two variables [34,123]. This relationship may possibly be explained by a passive capillary mechanism [34,123] because capillaries behave as Starling resistors (Figure 12). For flow to occur in a capillary, the pressure at the arterial end must exceed that at the venous end which in turn must exceed the closing pressure exerted by the surrounding tissue. Thus, unlike a rigid tube in which flow increases linearly with pressure (Figure 13a), flow commences in a capillary at the critical closing pressure then increases exponentially with increasing pressure (Figure 13b) [154]. Therefore, the increase in peripheral vascular resistance at the lower compared to the higher flow rate in the present study could represent a proliferation of capillaries in which the critical closing pressure was no longer exceeded. Thus, the increase in peripheral vascular resistance with decreasing flow rate would indicate impaired tissue perfusion. Indeed, this conclusion is supported by the significant correlation between within patient changes in peripheral vascular resistance and systemic oxygen uptakes that resulted from alternation of flow rate.

Flow character. As with metabolism and unlike many previous studies [43–45,67–70,106], no haemodynamic superiority was found to be associated with a pulsatile compared to a nonpulsatile flow character. Possible explanations for these results are similar to those stated previously concerning the metabolic findings. Furthermore, recent work by Sohma and colleagues using a canine

Arterial
pressure

Tissue pressure

Venous
pressure

Figure 12. Starling resistor.

a) flow
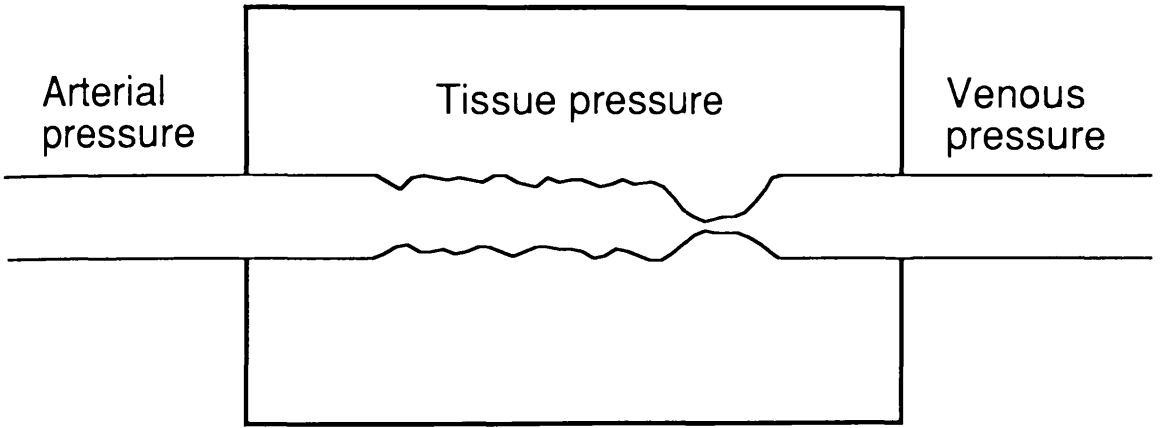
Rigid tube

pressure

b) flow

Capillary

critical
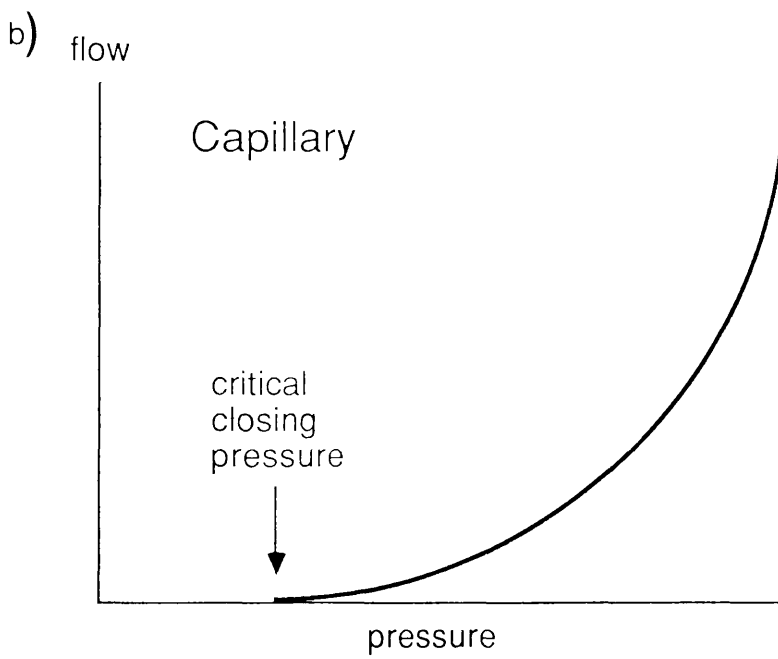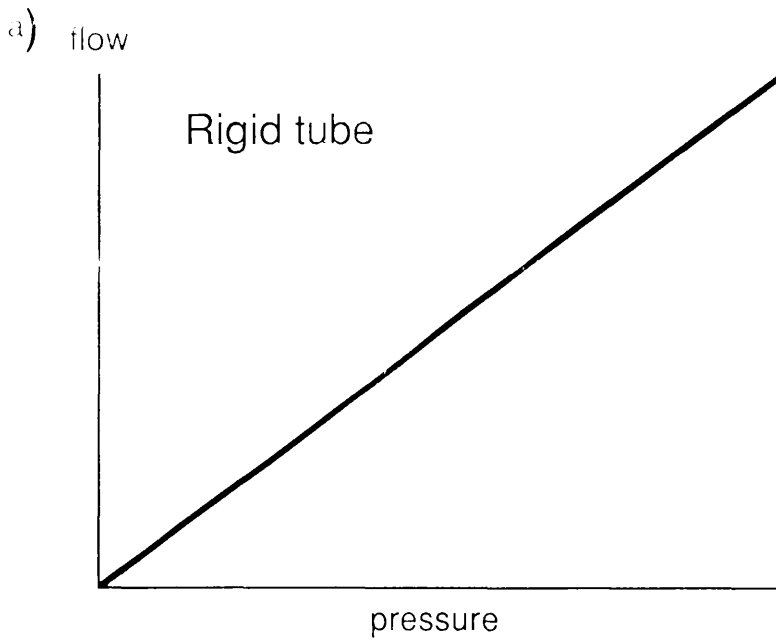closing
pressure

pressure

Figure 13. Relationship between pressure and flow in **a)** a rigid tube and **b)** a capillary.

hind limb model concluded that peripheral vascular resistance is a function of both flow rate and character [155]. The present work, as with that of Sohma and colleagues, confirms the supposition made in Chapter 2 that the findings from studies comparing pulsatile and nonpulsatile perfusion are invalid unless the flow rate was controlled in both groups. As with the metabolic findings, the present study is not isolated in its failure to demonstrate any haemodynamic superiority of pulsatile over nonpulsatile perfusion [8,47,71,72,124].

As no significant differences were found between nonpulsatile and pulsatile perfusion, and also because of the great variability in pulse pressure found during pulsatile perfusion, a nonpulsatile flow character was used in all further studies.

Acid-base management. Arterial pH had little or no effect on mean arterial pressure during Period 1 but, by Period 2 mean arterial pressure was higher with alpha than pH-stat control and this difference was maintained in Period 3. Increased mean arterial pressure at lower carbon dioxide tension and higher pH and vice versa would fit with the known vasoactive effects of carbon dioxide and hydrogen ions in the intact cardiovascular system at normothermia [156]. However, commensurate significant changes in peripheral vascular resistance would have been expected and these did not occur. It is possible that this study simply failed to detect this change, due to the increased variability introduced by the inclusion of central venous pressure data in the calculated peripheral vascular resistance. The lack of difference in mean arterial pressure during Period 1 is more difficult to explain, although it may be due to initial vasomotor paralysis after which tone and reactivity to carbon dioxide tension and hydrogen ion concentration is progressively regained.

Although the findings of the present study are inconclusive as to the advantages of one form of acid-base management over the other, as the present weight of evidence is in favour of alpha-stat acid-base management [126,157], this form of pH control was used in all further studies.

Progressive vasoconstriction. During the course of cardiopulmonary bypass there were progressive increases in mean arterial pressure and peripheral vascular resistance which, as discussed in Chapter 2, are well recognised phenomena. The inexorable increase in peripheral vascular resistance, as with the rise which occurred with reduction in flow rate, might indicate impairment of tissue perfusion. However, systemic oxygen uptake did not significantly change during the course of the study and in fact, there was a small but significant decrease in lactate concentration. It is most likely that the disparity in metabolic effects reflect differing mechanisms causing the increase in peripheral vascular resistance. Unlike the passive mechanism, argued previously for the effects of flow rate on peripheral vascular resistance, the progressive increase in peripheral vascular resistance during cardiopulmonary bypass may result from active vasoconstriction of metarterioles and pre–capillary sphincters [123]. If the rise in peripheral vascular resistance is due to an increase in vasomotor tone, rather than capillary closure, tissue metabolism will be unimpaired. This difference in the mechanism affecting peripheral vascular resistance would explain why Evans and colleagues, using sodium nitroprusside, were unable, despite producing a marked decrease in peripheral vascular resistance, to detect any change in systemic oxygen uptake [46] as sodium nitroprusside acts by reducing vasomotor tone.

One of the suggested haemodynamic advantages of pulsatile over nonpulsatile perfusion is the prevention of progressive vasoconstriction [12]. In the present study, interaction between flow character and stage during cardiopulmonary bypass was specifically examined for, yet none was found. Pulsatile perfusion was not found to ameliorate the increase in peripheral vascular resistance. Other workers have also been unable to find any difference in the rate of vasoconstriction between pulsatile and nonpulsatile perfusion [47,72,124]. It is difficult to resolve these contrary haemodynamic findings unless there are important differences in anaesthetic or cardiopulmonary bypass techniques between those studies that have found pulsatile perfusion to ameliorate the ongoing vasoconstriction and those which have not.

Haematocrit and reservoir volume. A possible explanation for the interaction between flow rate and stage during cardiopulmonary bypass on haematocrit might be ongoing haemorrhage. By Period 3, blood loss may have reached a sufficient amount in some patients, such that hypovolaemia would be apparent if a high flow rate was used, but would be disguised if a low flow rate was employed. Thus, low reservoir volumes would occur more often with a high flow rate and would likely be treated with lactated Ringer's solution to produce haemodilution, a series of events which would be less likely to occur with a low flow rate. Indeed, the lower mean reservoir volume at the high flow rate during Periods 1 and 2 followed by a higher volume in Period 3 would support this supposition. Nonetheless, it is unlikely that this effect of interaction between flow rate and stage on haematocrit would have any important effect on haemodynamic variables as it was of such small magnitude.

In conclusion, this study has found that flow rate had important effects on both systemic oxygen uptake and peripheral vascular resistance. In contrast, the choice of flow character and acid–base management had no significant effect on either systemic oxygen uptake or peripheral vascular resistance.

CHAPTER 6

HAEMODYNAMIC AND METABOLIC EFFECTS OF ISOFLURANE DURING HYPOTHERMIC CARDIOPULMONARY BYPASS

METHODS

Study design

Twenty patients scheduled for elective heart valve or coronary artery surgery were allocated randomly into two equal groups in an open, crossover study. During cardiopulmonary bypass, patients in Group I were given isoflurane from the beginning until the end of Period 1 when it was discontinued. In Group II, patients were given no isoflurane during cardiopulmonary bypass until the end of Period 1 and this was then continued until the end of cardiopulmonary bypass. In both groups, the vaporiser was set at 5% for 5 minutes then reduced to 2% until discontinued.

Anaesthesia

Patients were premedicated with lorazepam 2-4 mg orally on the night prior to surgery and temazepam 20-50 mg orally approximately one hour before surgery. Anaesthesia was induced with fentanyl 5 ug.kg^{-1} and a sleep dose of midazolam IV. Neuromuscular blockade was obtained with vecuronium 0.15 mg.kg^{-1} IV and then maintained with an infusion at 2.5 ug.kg^{-1}.min^{-1}. The trachea was intubated and the lungs ventilated with nitrous oxide and oxygen (50/50%) to achieve eucapnoea. Anaesthesia was maintained throughout the procedure with an infusion of fentanyl 0.1 ug.kg^{-1}.min^{-1} IV and was supplemented, before and after cardiopulmonary bypass, with isoflurane.

Statistical analysis

All data were analysed by regression of within patient changes in measured variables between Periods 1 and 2 upon the corresponding changes in blood isoflurane concentration. Data identified as being of most importance (systemic oxygen uptake, lactate concentration, base excess, mean arterial and central venous pressures and peripheral vascular resistance) were subjected to more rigorous examination with multiple regression analysis and factorial analysis of variance. The level of statistical significance was taken as 5% and Bonferonni's correction for multiple comparisons applied. Probability values are presented uncorrected.

RESULTS

Patient details

Patients demographic details and relevant durations are presented in Tables XI. Six of the patients underwent heart valve replacements and 14 of them had coronary artery bypass surgery.

Thermostatic control

Good temperature control was achieved as there was only one patient period in which the 95% confidence interval for the repeated measurements of nasopharyngeal temperature fell outwith the prescribed range (27–29°C) and the mean in that instance was 26.8°C.

Acid–base management

Over all, similar values of arterial pH were found during periods when isoflurane was and was not administered (Table XII). No significant correlation was found between changes in arterial pH or carbon dioxide tension and changes in blood isoflurane concentration (Table XIII).

Table XI. Demographic details and durations.

	Mean	Standard deviation
Sex (F/M)	6/14	–
Age (yr)	57	9.8
Weight (kg)	75	11.5
Height (m)	1.68	0.11
Surface area (m^2)	1.84	0.21
Cardiopulmonary bypass (min)	86	16
Cross clamp (min)	59	12

Table XII. Mean variables (standard deviation) during Periods when isoflurane was (Isoflurane) and was not (No isoflurane) administered (n = 20).

Variable	No isoflurane	Isoflurane
Isoflurane ($ug.ml^{-1}$)	7.1 (7.1)	54.3 (20.7)
Arterial pH	7.38 (0.03)	7.38 (0.03)
$PaCO_2$ (mmHg)	41 (5.2)	41 (4.4)
CaO_2 ($ml.L^{-1}$)	126 (22)	130 (22)
$C\bar{v}O_2$ ($ml.L^{-1}$)	95 (16)	97 (17)
$Ca-\bar{v}O_2$ ($ml.L^{-1}$)	31 (10)	33 (10)
$\dot{V}O_2$ ($ml.min^{-1}.m^{-2}$)	49 (18)	52 (15)
SaO_2 (%)	98 (1.0)	98 (1.1)
$S\bar{v}O_2$ (%)	82 (5.4)	83 (4.5)
PaO_2 (mmHg)	428 (176)	421 (167)
$P\bar{v}O_2$ (mmHg)	48 (5.3)	50 (5.5)
Hba ($g.L^{-1}$)	84 (13.7)	84 (12.7)
Hbv ($g.L^{-1}$)	84 (13)	84 (14)
Lactate ($mml.L^{-1}$)	2.3 (0..77)	2.4 (0.8)
Base Excess	0.8 (1.8)	0.2 (1.7)
Haematocrit (%)	25 (4.1)	26 (3.8)
MAP (mmHg)	57 (13.1)	43 (8.2)
PVR ($dynes.s.cm^{-5}$)	1564 (396)	1159 (329)
CVP (mmHg)	0.1 (5.9)	0.5 (5.5)
Reservoir level (ml)	1402 (846)	1245 (543)

Table XIII . Changes in metabolic variables between Periods 1 and 2 regressed upon corresponding changes in blood isoflurane concentration ($ug.ml^{-1}$). $y = a + bx$.

Variable	a	b	95% CL of b	r	p
Arterial pH	−0.005	0	$-2.44 . 10^{-4}$, $2.44 . 10^{-4}$	0.157	0.500
$PaCO_2$ (mmHg)	0.752	−0.004	$-3.94 . 10^{-2}$, $3.86 . 10^{-2}$	0.055	0.825
CaO_2 ($ml.L^{-1}$)	−3.34	0.07	$-3.55 . 10^{-2}$, $1.75 . 10^{-1}$	0.312	0.164
$C\bar{v}O_2$ ($ml.L^{-1}$)	−2.45	0.02	$-8.013 . 10^{-2}$, $1.201 . 10^{-1}$	0.111	0.636
$Ca-\bar{v}O_2$ ($ml.L^{-1}$)	−0.041	−1.45	$3.807 . 10^{-3}$, $9.807 . 10^{-3}$	0.189	0.414
$\dot{V}O_2$ ($ml.min^{-1}.m^{-2}$)	−6.89	0.793	-0.248, 1.834	0.124	0.596
SaO_2 (%)	−1.493	0.007	$8.74 . 10^{-5}$, $1.39 . 10^{-2}$	0.424	0.048
$S\bar{v}O_2$ (%)	28.5	0.042	$4.00 . 10^{-3}$, $8.00 . 10^{-2}$	0.476	0.022
PaO_2 (mmHg)	−2.46	2.496	$2.37 . 10^{-1}$, 4.755	0.480	0.021
$P\bar{v}O_2$ (mmHg)	0.007	0.035	$-1.2 . 10^{-2}$, $8.2 . 10^{-2}$	0.352	0.111
Hba ($g.L^{-1}$)	−0.147	0.001	$-3.85 . 10^{-3}$, $5.85 . 10^{-3}$	0.067	0.776
Hbv ($g.L^{-1}$)	−6.527	0.408	$-8.2 . 10^{-3}$, $-3.8 . 10^{-3}$	0.049	0.834
Lactate ($mmol.L^{-1}$)	−0.219	−0.006	-0.021. $6.72 . 10^{-4}$	0.507	0.013
Base Excess	−0.83	−0.010	-0.021, $6.77.10^{-4}$	−0.414	0.054

Isoflurane concentrations

A large interpatient variability in blood isoflurane concentration was found though a steady state was achieved during the study periods (Figure 14 and Table XII).

Metabolic variables

Average values of metabolic variables during periods when isoflurane was and was not administered are presented in Table XII. No significant correlation between changes in blood isoflurane concentration and changes in systemic oxygen uptake from Periods 1 to 2 was found (Figure 15 and Table XIII). Statistical modelling of the systemic oxygen uptake data found no sensitivity to isoflurane nor any effect due to period of study during cardiopulmonary bypass.

No significant correlations were found between change in blood isoflurane concentration and changes in arterial and venous oxygen content, venous oxygen tension or base excess (Table XIII). On individual analyses of each variable, significant correlations were found between changes in blood isoflurane concentration and changes in arterial and venous haemoglobin oxygen saturation, venous oxygen tension and lactate concentration (Table XIII). However, after application of Bonferonni's correction for repeated comparisons, all these findings were nonsignificant.

Modelling of the base excess and lactate concentration data found no sensitivity to isoflurane concentration but stage had a significant effect. Base excess decreased on average by 0.47 (95%CL 0.09, 0.86) from Period 1 to 2 and lactate concentration decreased by 0.30 (95%CL 0.10, 0.51) mmol.L^{-1} over the same time.

Haemodynamic variables

Average mean arterial pressures, peripheral vascular resistances, central venous pressures and reservoir levels during periods of no isoflurane and isoflurane administration are presented in Table XIV. Changes in mean arterial
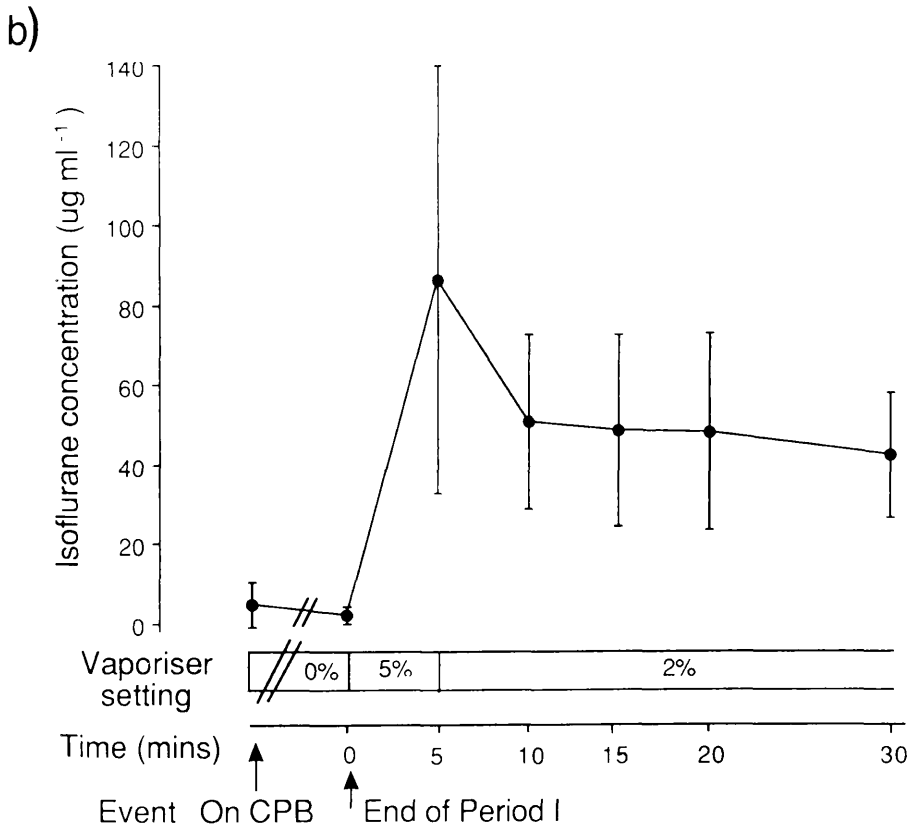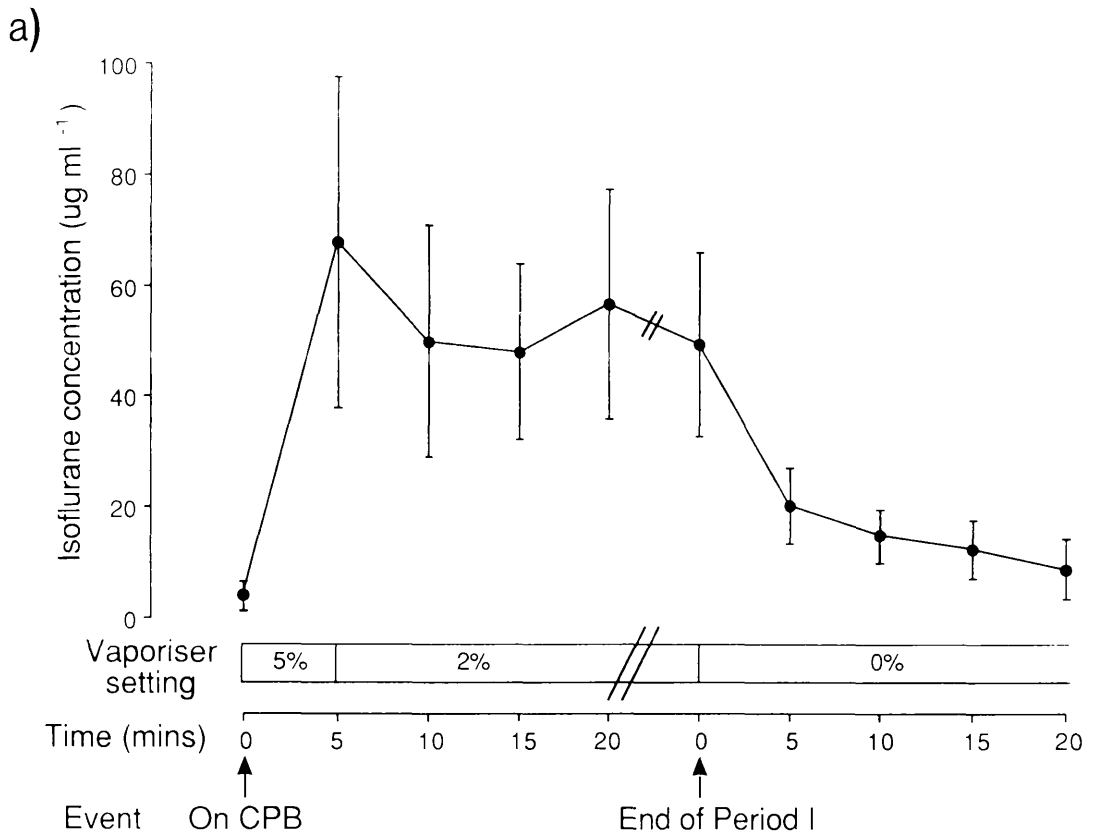
Figure 14. Blood isoflurane concentration in **a)** Group I and **b)** Group II. Closed circles represent mean concentration and vertical bars one standard deviation.

Figure 15. Relationship between changes in blood isoflurane concentration between Periods 1 and 2 and corresponding changes in systemic oxygen uptake ($\dot{V}O_2$). Continuous lines represent changes in Group 1 and dashed lines changes in Group 11.

Table XIV. Changes in haemodynamic variables between Periods 1 and 2 regressed upon corresponding changes in blood isoflurane concentration.

Variable	a	b	95% CL of b	r	p
Haematocrit (%)	−5.75	2.5	−7.98, 13.01	0.123	0.598
MAP (mmHg)	−8.02	−0.254	−0.302, −0.206	−0.777	0.001
CVP (mmHg)	−0.83	−0.003	$-8.379 \cdot 10^{-3}$, $1.24 \cdot 10^{-2}$	0.043	0.855
PVR (dynes.s.cm^{-5})	−212	−7.266	−10.16, −4.38	−0.793	0.001
Reservoir level (ml)	265	−3.794	−8.66, 1.07	−0.375	0.867

pressure and peripheral vascular resistance between Periods 1 and 2 were found, after application of Bonferonni's correction, to correlate significantly with the change in blood isoflurane concentration (Figures 16 and 17). Modelling of the mean arterial and peripheral vascular resistance data found there to be significant main effects due to isoflurane concentration and period of study during cardiopulmonary bypass. In addition, there was a significant interaction between isoflurane concentration and period. There was a difference in the haemodynamic response to isoflurane according to the period of study. Mean arterial pressure decreased on average during Period 1 by 0.59 (95% CL 0.36, 0.82) mmHg per 1 $ug.ml^{-1}$ increase in isoflurane whereas during Period 2, it decreased on average only by 0.03 (95%CL –0.17, 0.24) mmHg per 1 $ug.ml^{-1}$ increase in isoflurane. Similarly, peripheral vascular resistance decreased during Period 1 by 15.8 (95% CL 9.3, 22.4) $dynes.s.cm^{-5}$ per 1 $ug.ml^{-1}$ increase in isoflurane whereas during Period 2, it decreased on average by 0.3 (95% CL –5.6, 6.3) $dynes.s.cm^{-5}$ per 1 $ug.ml^{-1}$.

No significant correlation was found between changes in central venous pressure, reservoir level or haematocrit and changes in isoflurane concentration (Table XIV). Modelling of the central venous pressure data found no sensitivity to isoflurane concentration or to period of study.

Vasoactive drugs

In Period 1, more patients who received isoflurane compared to those who did not, were given methoxamine (Table XV). No methoxamine was given in Period 2 in either group. One patient in Group 2 required sodium nitroprusside to control hypertension in both the first and second periods.

Mean arterial pressure (mmHg)

Blood Isoflurane concentration $(\mu g.ml^{-1})$

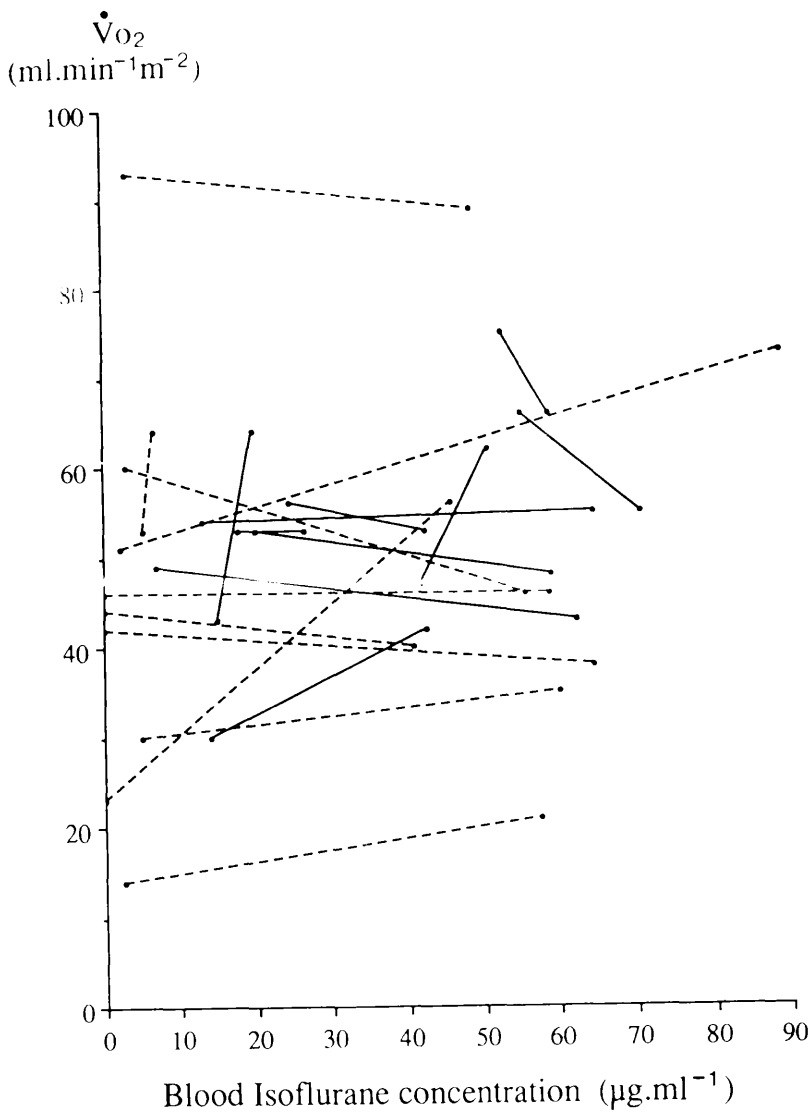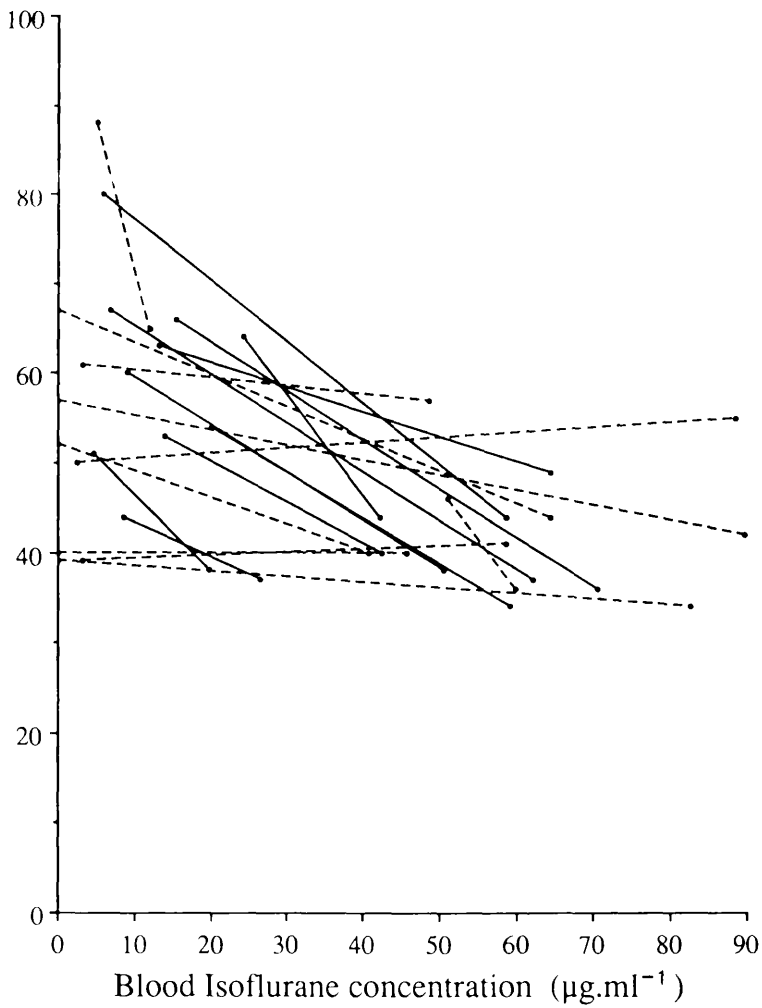**Figure 16.** Relationship between changes in blood isoflurane concentration between Periods 1 and 2 and corresponding changes in mean arterial pressure. Continuous lines represent changes in Group 1 and dashed lines changes in Group 11.

Peripheral vascular
resistance (Dynes.s.cm^{-5})

Blood Isoflurane concentration (μg.ml^{-1})
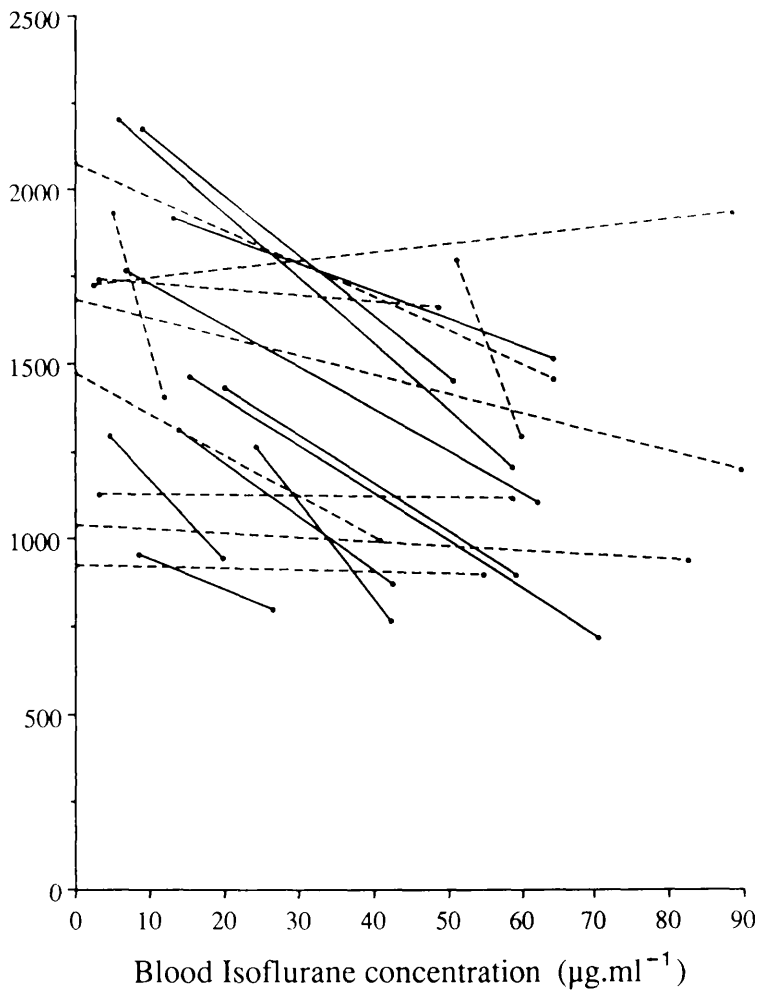
Figure 17. Relationship between changes in blood isoflurane concentration between Periods 1 and 2 and corresponding changes in peripheral vascular resistance. Continuous lines represent changes in Group 1 and dashed lines changes in Group 11.

Table XV. Incidence of methoxamine administration (n = 10).

	Group I (isoflurane/ no isoflurane)	Group II (no isoflurane/ isoflurane)
Period 1	7	2
Period 2	0	0

DISCUSSION

The principal findings of this study are that change in blood isoflurane concentration had significant effects on mean arterial pressure and peripheral vascular resistance whereas it had no significant action on systemic oxygen uptake.

Isoflurane concentration

A large interpatient variability in blood concentration of isoflurane was found despite using a standardised regime for isoflurane administration. The pharmacokinetics of isoflurane, when delivered into the the oxygenator during hypothermic cardiopulmonary bypass, are poorly understood as they have not been rigorously studied. Haemodilution reduces the solubility of isoflurane [158] whereas hypothermia increases it [159] but how these and other effects interact during hypothermic cardiopulmonary bypass is poorly understood. Loomis and colleagues examined the arterial concentrations of isoflurane that were required to produce electro-encephalographic burst suppression during cardiopulmonary bypass at 25°C and found similar levels and variablity to the present study at a mean vaporiser setting of 2.2% [160]. As the pump flow rate was constant during the present study, the variability is most likely accounted for by differences in gas flow rates to the oxygenator. The gas flow rate to the oxygenator was altered, as required to control the arterial pH and blood gases, from less than 1 L.min^{-1} to over 5 L.min^{-1}. This manipulation will have caused considerable changes in the rate of isoflurane delivery. However, isoflurane has been found to decrease cerebral metabolic rate during cardiopulmonary bypass with moderate hypothermia at lower vaporiser settings than the present study [161]. Therefore, if there are sytemic metabolic effects from isoflurane during hypothermic cardiopulmonary bypass then they should be detectable at the concentrations obtained in this study.

Because of the poorly understood pharmacokinetics, it is difficult to relate directly any changes in variables induced by isoflurane during cardiopulmonary

bypass to those that occur in the intact cardiovascular system at normothermia. The actions of volatile anaesthetic agents are usually related to the minimal alveolar concentration which, under standard conditions, can be readily calculated from blood concentration. As the relevant solubility coefficients for isoflurane under the conditions of hypothermia and haemodilution are not available, it is not possible to determine the minimal alveolar concentration related to the blood isoflurane concentrations found in the present study.

Metabolism

No relationship was found in the present study between isoflurane concentration and systemic oxygen uptake. In the intact cardiovascular system at normothermia, isoflurane decreases systemic oxygen uptake [90-92] and similar effects might be expected during cardiopulmonary bypass. A possible explanation for the failure of the present study to detect any change in systemic oxygen uptake is that isoflurane did produce metabolic depression but this effect was counteracted by vasodilation which improved tissue oxygen uptake in areas otherwise hypoperfused. However, it is more likely that isoflurane did not have any direct systemic metabolic effect in the blood concentrations obtained in this study as vasodilation in itself has not been found to improve sytemic oxygen uptake [46]. Two important differences exist between this and previous studies which have found isoflurane to reduce systemic oxygen uptake. Hypothermia, which was used in this study, markedly decreases metabolism and this effect may be far greater than that of isoflurane. Thus, any metabolic effect may be too small to detect with the present methods. Also, isoflurane may decrease systemic oxygen uptake in the intact cardiovascular system largely by decreasing cardiac output and not by direct metabolic depression [91]. If this is the case then isoflurane will not affect systemic oxygen uptake as the heart is isolated from the circulation and the pump flow rate was kept constant during cardiopulmonary bypass. If this is not the case, it is difficult to resolve the lack of systemic metabolic effects found in the present study with the detectable

cerebral metabolic effects that have been found previously [161].

On the basis of the present study, there would appear to be no systemic metabolic advantage in the use of isoflurane during hypothermic cardiopulmonary bypass as it either has no metabolic effect under these conditions or the effects are too small to be clinically useful. However, isoflurane may have a cerebral protective effect during cardiopulmonary bypass and this would be an important indication for its use [161].

Haemodynamics

Undoubtedly, the high incidence of methoxamine administration during Period 1 in those patients who were given isoflurane only in Period 1 will have reduced the measured changes in their mean arterial pressures and peripheral vascular resistances. This high incidence of methoxamine administration reflects the strong interaction between isoflurane and stage of the study period during cardiopulmonary bypass. This interaction may be explained by isoflurane's blunting effect on the progressive rise in noradrenaline that occurs during the course of cardiopulmonary bypass [162]. Progressive vasoconstriction during cardiopulmonary bypass also accounts for the more marked changes in haemodynamic variables in those patients who received isoflurane only in the first period and the less marked changes in those patients who were given isoflurane only in the second. In some patients who received isoflurane only in the second period, isoflurane did not produce vasodilation though it did ameriolate the ongoing vasoconstriction. For the same reason, some of the increases in mean arterial pressure and peripheral vascular resistance in those patients who were given isoflurane only in Period 1 are accounted for by progressive vasoconstriction during the course of cardiopulmonary bypass.

The high incidence of hypotension, as indicated by the need for methoxamine, is clinically important. Marked hypotension is dangerous as it may produce cerebral hypoperfusion and ischaemia [9]. However, this hypotension is readily corrected by using vasoconstrictors or increasing the flow rate until the

condition resolves spontaneously as a result of ongoing vasoconstriction. Furthermore, isoflurane's potential for hypotension must be balanced against the risk of hypertension if isoflurane is not used and that can result in catastrophic aortic disruption at the cannulation site

The vasodilatory effects of isoflurane found in this study during the abnormal conditions of low flow, hypothermic cardiopulmonary bypass are consistent with the known actions of isoflurane in the intact cardiovascular system at normothermia [90]. The findings of this study imply that isoflurane could be used as a vasodilator to control systemic arterial pressure in a dose related manner during hypothermic cardiopulmonary bypass. Controlling systemic arterial pressure with isoflurane would be a more appropriate choice than other non-anaesthetic vasodilators as isoflurane would at least lessen the risk of awareness and at best obviate it.

In conclusion, isoflurane is a vasodilator and produces dose related change in mean arterial pressure during hypothermic cardiopulmonary bypass but has no significant metabolic effects.

CHAPTER 7

HAEMODYNAMIC AND METABOLIC EFFECTS OF ATRACURIUM DURING HYPOTHERMIC CARDIOPULMONARY BYPASS

METHODS

Study design

Twenty patients scheduled for elective coronary artery surgery were allocated randomly into two equal groups. A parallel group study design was employed. Patients in the Control Group were given no atracurium during the study. In contrast, patients in the Atracurium Group received no atracurium until the end of Period 1 when they were given a bolus of atracurium 0.6 mg.kg^{-1} IV followed by an IV infusion at 0.7 ug.kg^{-1}.min^{-1}. On completion of the study, patients in the Control Group were also given atracurium.

Anaesthesia

Patients were premedicated with lorazepam 2–5 mg orally on the night prior to surgery and temazepam 20–50 mg orally approximately one hour before induction of anaesthesia. Anaesthesia was induced with fentanyl 5 ug.kg^{-1} IV followed by a sleep dose of midazolam IV. Ventilation was controlled and isoflurane was administered in 100% oxygen until the systolic arterial pressure was reduced to 80% of the pre-induction value. After topical application of lignocaine 4% to the pharynx and glottis, the trachea was intubated. In the event of difficulty with tracheal intubation or opioid rigidity, suxamethonium was administered. Before and after cardiopulmonary bypass, the lungs were ventilated with nitrous oxide and oxygen (50/50%) to maintain eucapnoea. Anaesthesia was maintained throughout surgery with an infusion of fentanyl

0.1 ug.kg^{-1}.min^{-1} IV. This was supplemented with isoflurane before and after cardiopulmonary bypass. Throughout cardiopulmonary bypass, 1% isoflurane was administered to maintain anaesthesia.

Statistical analysis

Data were analysed by comparison of within patient changes between Periods 1 and 2 in both the Control and Atracurium Groups using a paired Student's t test. Comparison of between groups differences during Periods 1 and 2 were made using an unpaired Student's t test. Bonferonni's correction for multiple comparisons was then applied. Results are presented in the tables in their uncorrected form.

RESULTS

Patient details

Demographic details and relevant durations are presented in Table XVI. There were similar distributions of anti-anginal drugs in both groups (Table XVII).

Thermostatic control

Temperature control was excellent as all the 95% confidence limits of the means for the repeated arterial and nasopharyngeal temperature readings were within the prescribed limits (27-29°C; Table XVIII).

Acid-base managment

Arterial pH measurements by bench blood gas analysis found that alpha-stat acid-base management was not always accurately achieved although there were no significant differences in arterial pH either within or between groups (Table XVIII). Similarly, there were no significant changes in arterial carbon dioxide tension between or within groups (Table XVIII).

Table XVI. Demographic details and durations [mean (standard deviation)].

	Control Group	Atracurium Group
Sex (F/M)	0/ 10	2/ 8
Age (yr)	52.3 (10.3)	60.8 (7.8)
Weight (kg)	78.3 (8.9)	74.7 (8.3)
Height (m)	1.72 (0.067)	1.68 (0.063)
Surface area (m²)	1.91 (0.137)	1.85 (0.135)
Cardiopulmonary bypass (min)	85 (15)	88 (18)
Cross clamp (min)	55 (10)	56 (15)

Table XVII. Anti-anginal drugs.

	Control Group	Atracurium Group
Beta-adrenergic blockers	8	7
Nitrites	8	9
Calcium channel bockers	8	7

Table XVIII. Changes in arterial and nasopharyngeal temperatures (T_a, T_{np}) arterial pH and $PaCO_2$ in the Control and Atracurium Groups between Periods 1 and 2 [mean (standard deviation)].

Variable	Control Group			Atracurium Group		
	Period 1	Period 2	d	Period 1	Period 2	d
T_a (°C)	27.6 (0.2)	27.8 (0.3)	−0.23	27.6 (0.3)	27.9 (0.3)	−0.31
95% CL			−0.35,−0.11			−0.38,−0.24
T_{np} (°C)	28.4 (0.4)	28.3 (0.3)	0.14	28.3 (0.3)	28.2 (03)	0.2
95% CL			0.04, 0.24			−0.05, 0.45
Arterial pH	7.36 (0.04)	7.36 (0.05)	0.0	7.38 (0.03)	7.39 (0.05)	−0.01
95% CL			−0.01, 0.01			−0.03,0.00
$PaCO_2$ (mmHg)	43 (4.1)	43 (5.1)	0.0	42 (4.8)	42 (6.1)	0.35
95% CL			−1.01, 1.01			−1.7, 2.4

Metabolic variables

There were no significant differences in systemic oxygen uptake within either group between Periods 1 and 2 nor any between the groups (Figure 18). In both groups, there were small but nonsignificant increases in mean arterial blood oxygen content from Period 1 to 2. There were no significant differences in arterial blood oxygen content between groups (Table XIX) and no significant differences in mixed venous oxygen content or oxygen extraction were found (Table XX).

No significant within or between group changes in arterial haemoglobin oxygen saturation were found (Table XX). In both groups, there were no significant changes in arterial oxygen tension between Periods 1 and 2 (Table XX) nor were there any significant differences between the groups during Period 1. However, arterial oxygen tension was significantly higher in the Atracurium Group during Period 2. Between Periods 1 and 2, there were small nonsignificant increases in the average mixed venous blood oxygen tensions in both groups (Table XX). Mixed venous haemoglobin oxygen saturation did not change significantly between Periods 1 and 2 in either group (Table XX). Small increases in mean arterial haemoglobin concentration, that were nonsignificant, occurred between Periods 1 and 2 in both groups (Table XX). There were no significant changes in mixed venous haemoglobin concentration in either group (Table XX).

There were small decreases in mean base excess in both groups which were nonsignificant (Table XIX) and no significant between group differences in base excess were found. From Period 1 to 2, there were small, nonsignificant decreases in mean lactate concentration in both groups (Table XIX) and there were no significant between group differences in lactate concentration.

Haemodynamic variables

In both the Control and Atracurium Groups, there were increases in the average mean arterial pressure from Periods 1 to 2 which were non-significant
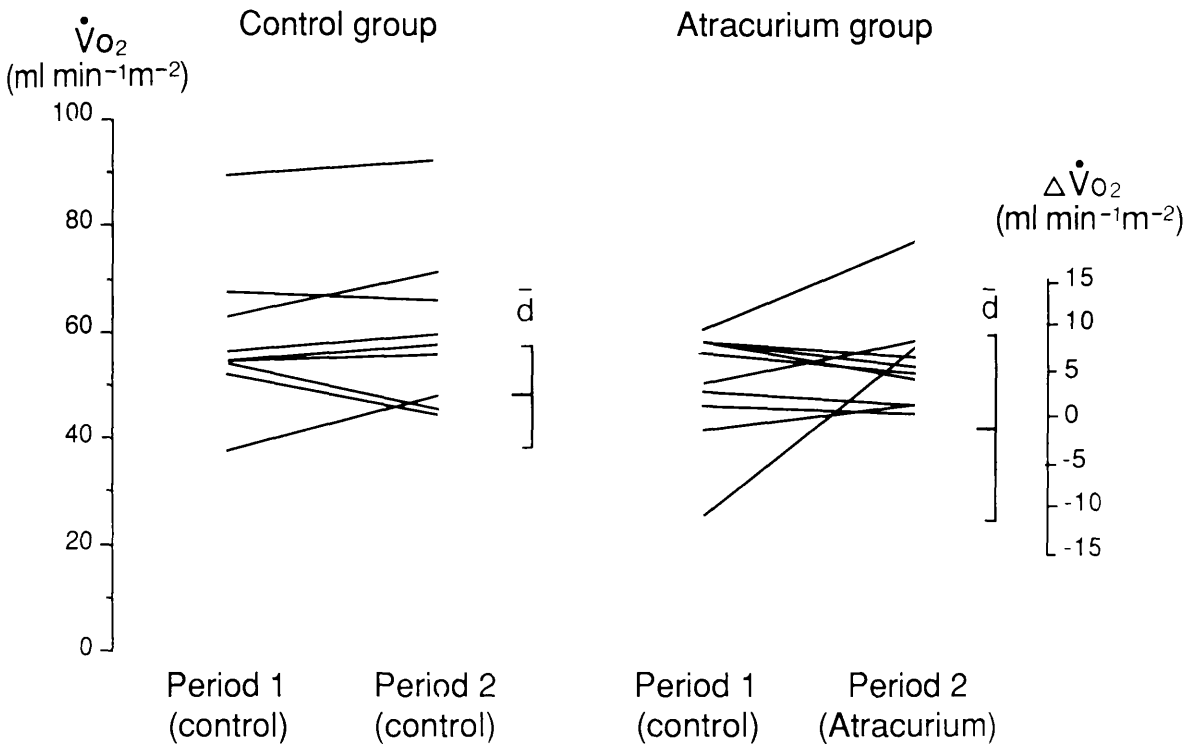
Figure 18. Changes in systemic oxygen uptake ($\dot{V}O_2$) between Periods 1 and 2 in the Control and Atracurium Groups.

Table XIX. Changes in arterial and mixed venous blood oxygen contents, oxygen extraction, systemic oxygen uptake, base excess and lactate concentration in the Control and Atracurium Groups between Periods 1 and 2 [mean (standard deviation)]

Variable	Control Group			Atracurium Group		
	Period 1	Period 2	d	Period 1	Period 2	d
CaO_2 (ml.L^{-1})	127 (15)	130 (16)	−1.6	118 (17)	126 (18)	−8.4
95% CL			−5.2, 1.9			−16.2, −0.5
$C\bar{v}O_2$ (ml.L−1)	93 (15)	94 (13)	−1.4	86 (18)	91 (17)	−5.0
95% CL			−6.5, 3.7			−11.3, 1.2
$Ca-\bar{v}O_2$ (ml.L^{-1})	37 (9)	37 (10)	−0.5	31 (7)	34 (6)	0.5
95%CL			−3.6, 2.6			−6.2, 5.2
$\dot{V}O_2$ (ml.min^{-1}.m^{-2})	59 (14)	60 (15)	−1.0	50 (11)	54 (9)	−4.2
95%CL			−5.8, 3.9			−12.8, 4.4
Base Excess	−1.3 (1.2)	−1.2 (1.5)	−0.05	−0.3 (1.5)	0.6 (1.6)	−0.9
95% CL			−0.91, 0.82			−1.6, −0.2
Lactate (mmol.L^{-1})	2.6 (0.6)	2.4 (0.5)	0.23	2.4 (0.6)	2.2 (0.6)	0.2
95% CL			0.02, 0.35			−0.0, 0.4

Table XX. Changes in arterial and venous oxygen saturations and tensions and haemoglobin concentration in the Control and Atracurium Groups between Periods 1 and 2 [mean (standard deviation)].

Variable	Control Group			Atracurium Group		
	Period 1	Period 2	d	Period 1	Period 2	d
SaO_2 (%)	98.0 (0.5)	97.5 (0.8)	0.4	98.2 (0.5)	98.2 (0.5)	−3.6
95% CL			0, 0.9			−6.2, 0.9
$S\bar{v}O_2$ (%)	76.3 (7.9)	78.0 (3.7)	−1.6	78.8 (4.8)	82.3 (4.4)	−3.4
95% CL			−6.1, 2.8			−5.6, −1.1
PaO_2 (mmHg)	345 (94)	360 (148)	−15	352 (121)	520 (248)	−167
95% CL			−77, 47			−350, 15
			−190, −130			
$P\bar{v}O_2$ (mmHg)	44 (5.7)	45 (4.3)	−1.5	44 (4.0)	48 (4.3)	−3.4
95% CL			−5.2, 2.2			−5.0, −1.8
Hba (g.L^{-1})		85.8 (11.2)	−1.1	75.0 (6.7)	78.4 (8.1)	0
95% CL	84.6 (10.7)		−2.4, 0.2			−0.3, 0.3
Hb$\bar{v}$ (g.L^{-1})		84.5 (10.7)	0.3	75.4 (10.8)	78.0 (8.1)	−2.6
95% CL	84.8 (11.6)		−2.9, 3.6			−7.7, 2.5

(Figure 19). There were no significant between group differences in mean arterial pressure. No significant differences in central venous pressure were found (Table XXI). Small, but nonsignificant, increases in mean peripheral vascular resistance occurred in both groups between Periods 1 and 2 (Figure 20). There were no significant between group differences in peripheral vascular resistance.

There were no significant differences in central venous pressure, reservoir volumes or haematocrit (Table XXI).

Isoflurane concentration

Between Periods 1 and 2, there was a small decrease in mean blood isoflurane concentration in the Control Group whereas there was a small increase in the Atracurium Group (Table XXI). These changes were not significant nor were there any significant differences in isoflurane concentration between groups.

Vasoactive drugs

Methoxamine was administered to treat hypotension in one patient during Period 1 in the Control Group and in three patients during Period 1 and in one of the same patients during Period 2 in the Atracurium Group. No patient was given sodium nitroprusside.

DISCUSSION

The notable features of this study are the absence of any significant effects of atracurium on either haemodynamic variables or systemic oxygen uptake. A variety of factors must be considered as providing possible explanations for these findings. These factors will now be considered individually to assess the likelihood that they have influenced the results.
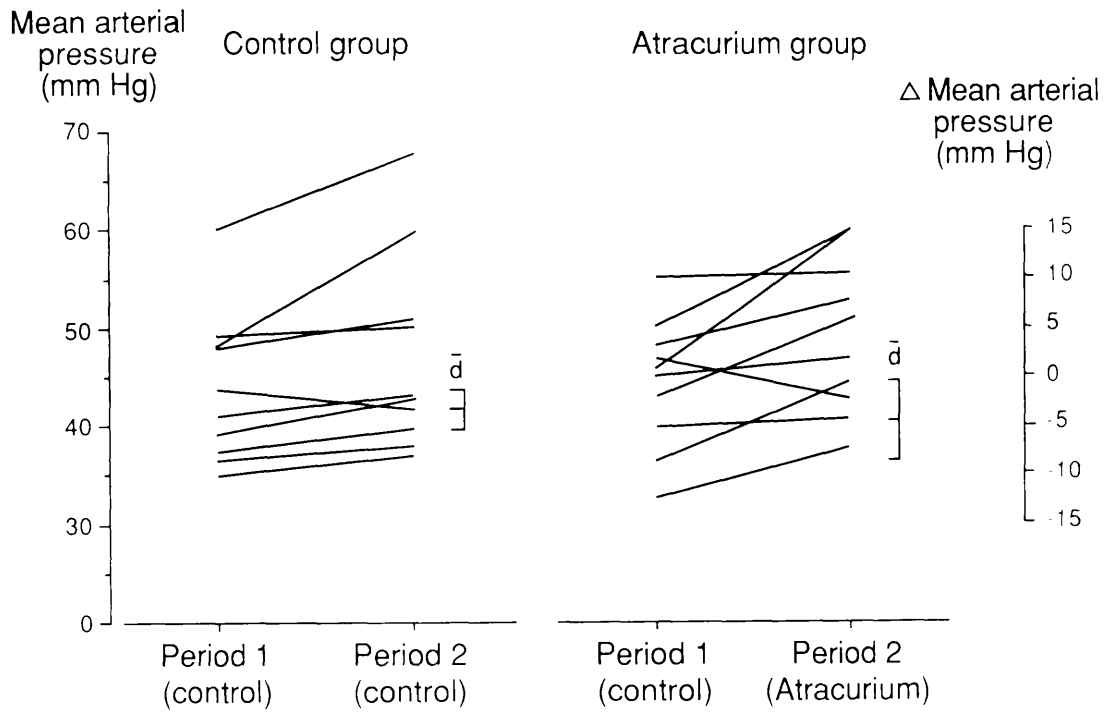
Figure 19. Changes in mean arterial pressure between Periods 1 and 2 in the Control and Atracurium Groups.

Table XXI. Changes in blood isoflurane concentration, haematocrit, mean arterial and central venous pressures, peripheral vascular resistance and reservoir level in the Control and Atracurium Groups between Periods 1 and 2.

| Variable	Control Group			Atracurium Group		
	Period 1	Period 2	d	Period 1	Period 2	d
Isoflurane (ug.ml^{-1})	35 (10.2)	32 (14.1)	2.8	26 (11.5)	31 (10.1)	−4.8
95% CL			−3.5, 9.1			−9.0,−0.5
Hct (%)	26 (3.4)	25 (3.9)	0.8	23 (3.7)	23 (3.0)	−0.2
95% CL			−1, 2.6			−2.6, 2.3
MAP (mmHg)	41 (9.2)	47 (9.5)	−5.6	44 (6.1)	50 (7.4)	−5.3
95% CL			−11.2, −0.1			−9.0, −1.5
CVP (mmHg)	0.8 (5.1)	2.2 (5.4)	−1.5	1.7 (4.4)	3.1 (5.5)	−1.4
95% CL			−4.2, 1.3			−3.4, 0.6
PVR (dynes.s.cm^{-5})	1137 (305)	1180 (335)	−43	1166 (194)	1280 (331)	−114
95% CL			−133, 47			−231, 4
Reservoir level (ml)	890 (277)	865 (286)	25	788 (203)	800 (234)	−12
95% CL			−124, 174			−135, 110
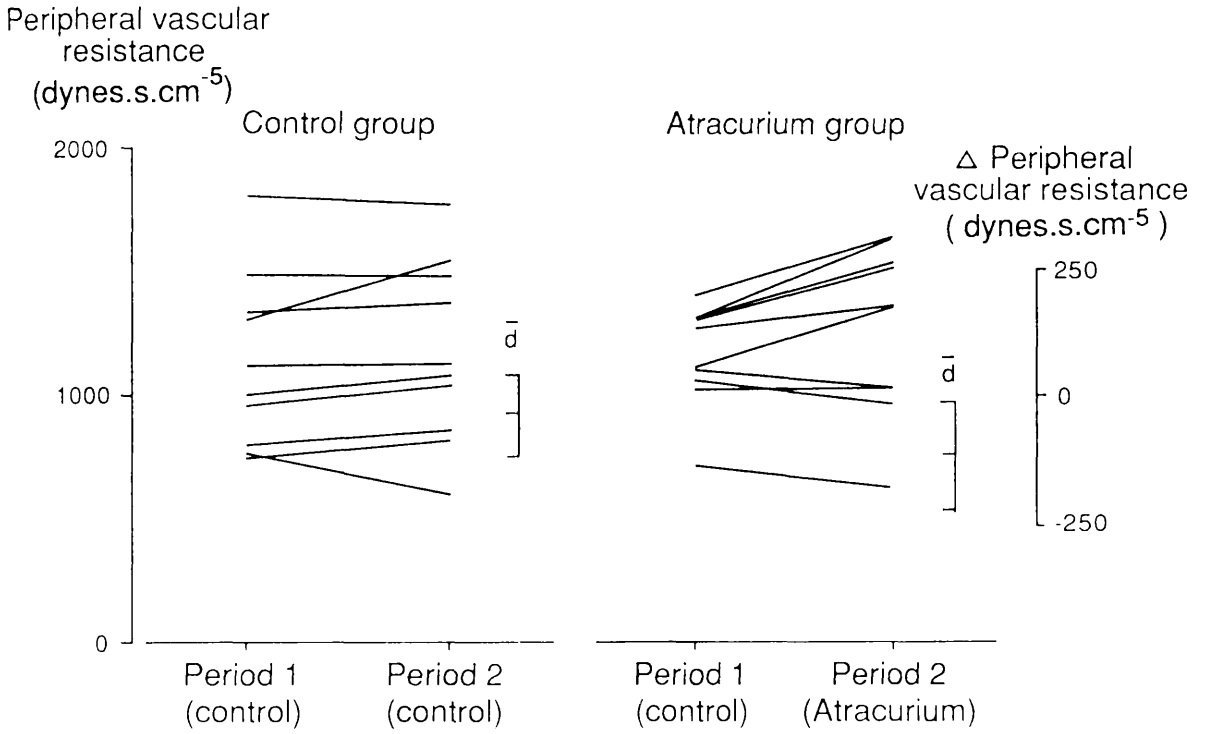
Figure 20. Changes in peripheral vascular resistance between Periods 1 and 2 in the Control and Atracurium Groups.

Neuromuscular blockade

It could be argued that a complete neuromuscular block may not have been produced during Period 2 in the Atracurium Group and therefore, the effects of atracurium would not be demonstrated. As no neuromuscular monitoring was undertaken, it is not possible to establish if this was the case. However, previous studies would suggest that the dose of atracurium employed was more than sufficient to produce maximal neuromuscular blockade at normothermia [131,132]. Furthermore, hypothermia is known to cause neuromuscular blockade in itself and thereby, it reduces the required dosage requirements of neuromuscular blocking agents [130]. For these reasons, inadequate neuromuscular blockade may be discounted as an explanation for the study's findings.

Statistical analysis

Bonferonni's correction for multiple comparisons, whilst reducing the risk of significant findings being due to chance, can overcompensate when analysing large numbers of variables with the result that real changes come to be discounted as nonsignificant. For this reason, the true probability of the statistical tests will lie between the uncorrected and corrected values. This point should be born in mind when considering the following discussion.

Metabolism

The present study was unable to confirm the previous work of Underwood, Roth and Starr [85] and Harris, Seelye and Squire [51] which found that neuromuscular blocking agents reduced systemic oxygen uptake during cardiopulmonary bypass. These contrasting findings require consideration.

In the Atracurium Group, there was a small rise in arterial oxygen content between Periods 1 and 2 which, although nonsignificant after correction for multiple comparisons, may have resulted in an increased systemic oxygen delivery. This increase in oxygen delivery could have disguised a decrease in systemic oxygen uptake induced by atracurium. However, this is an unlikely

explanation for not finding a significant decrease in systemic oxygen uptake associated with the administration of atracurium as there was no concomitant increase in oxygen extraction by the tissues.

Another possible explanation for the difference in findings between the present and previous work may be the use of hypothermia. It is likely that neuromuscular blocking agents reduce systemic oxygen uptake at normothermia by decreasing skeletal muscle tone and thereby, metabolism. If so, this effect may be diminished or abolished at moderate hypothermia as metabolism is already markedly reduced and muscle tone decreased. In contrast to Underwood, Roth and Starr's study [85], no gross skeletal nor even any diaphragmatic movements were observed in the present study and this fact alone could account for the differences in findings.

Yet another explanation for not finding significant metabolic effects could lie in atracurium's absence of effect on haemodynamic variables, as discussed below. Unlike atracurium, tubocurarine causes vasodilation during cardiopulmonary bypass in humans [129]. Therefore, the decrease in systemic oxygen uptake found by Underwood, Roth and Starr [85] could have resulted from tubocurarine causing a maldistribution of blood flow through tissues, due to shunting, rather than direct metabolic depression.

Anaerobic metabolism

Small decreases in mean lactate concentration which occurred in both groups between Periods 1 and 2 were nonsignificant after Bonferonni's correction. A decrease in lactate concentration during the course of cardiopulmonary bypass would fit with the similar findings in other studies of this series.

Haemodynamics

Two factors that should be borne in mind when interpreting the changes in haemodynamic variables are the administration of methoxamine and the

increase in isoflurane concentration in the Atracurium Group between Periods 1 and 2. Methoxamine administration, by causing vasoconstriction in Period 1, will have reduced the apparent magnitude of the increases in mean arterial pressure and peripheral vascular resistance that occurred. The increase in isoflurane concentration between Periods 1 and 2 in the Atracurium Group, which was not as marked in the Control Group, can only be ascribed to chance as there was no difference in the method of isoflurane administration between the two groups. This increase in isoflurane concentration in the Atracurium Group between Periods 1 and 2, although small, may have reduced the magnitude of the rise in mean arterial pressure and peripheral vascular resistance. Thus, the measured increases of these variables may have been underestimated.

In both groups, there were increases of similar magnitude in mean arterial pressure between Periods 1 and 2 although these increases were nonsignificant following correction for multiple comparisons. A progressive rise in mean arterial pressure is a well recognised phenomenon of cardiopulmonary bypass and has been found previously in this project. It is therefore likely that the increase was true and the nonsignificant result is due to overcompensation by Bonferonni's correction.

Although there were small mean increases in peripheral vascular resistance in both groups, they were not significant even before application of Bonferroni's correction. The most likely explanation for these contradictory findings, relative to mean arterial pressure, is that the study failed to detect a true increase in peripheral vascular resistance. Increased variability introduced into the calculated peripheral vascular resistance by the central venous pressure data, which were highly variable, could indeed account for these findings.

From the findings of the present study, atracurium would appear to have little or no effect on haemodynamic variables during hypothermic cardiopulmonary bypass. In contrast, tubocurarine causes a drop in mean arterial pressure during cardiopulmonary bypass due to vasodilation [129]. This difference

in effect is unsurprising as atracurium, unlike tubocurarine, is already noted for its minimal haemodynamic effects in the intact cardiovascular system at normothermia [93]. The present findings indicate that atracurium, as opposed to tubocurarine, has the same minimal haemodynamic actions during hypothermic cardiopulmonary bypass as it does in the intact cardiovascular system at normothermia. The likely explanation for these differences in actions is that atracurium, compared to tubocurarine [128], produces much smaller amounts of histamine release and also, does not cause autonomic ganglion blockade [93].

In conclusion, the administration of atracurium during hypothermic cardiopulmonary bypass had no significant effects on haemodynamic and metabolic variables.

CHAPTER 8

HAEMODYNAMIC AND METABOLIC EFFECTS OF ALFENTANIL DURING CARDIOPULMONARY BYPASS

METHODS

Study design

Twenty patients scheduled for elective coronary artery surgery were studied. The study was planned to have an open crossover design. Patients were randomly allocated into two equal groups of ten. After achieving stable hypothermic cardiopulmonary bypass, patients in Group I underwent a control period (Period 1). They were then given alfentanil as a 50 ug.kg^{-1} bolus IV followed by an infusion at 1 ug.kg^{-1}.min^{-1} and a second 10 minute study period performed (Period 2). At the beginning of Period 1, Group II patients were given alfentanil 50 ug.kg^{-1} as an IV bolus followed by an infusion at 1 ug.kg^{-1}.min^{-1}. The infusion was discontinued at the end of Period 1 and a bolus of naloxone 0.4 mg IV was given just before the start of Period 2. Haemodynamic measurements were recorded during and blood sampling performed at the ends of Periods 1 and 2 in both groups according to the methods outlined in Chapters 3 and 4. At the end of Period 2, the study was terminated in both groups and the alfentanil infusion was continued in Group I and recommenced in Group II.

Anaesthesia

Patients were premedicated with lorazepam 2-5 mg orally on the night prior to surgery and omnopon 10-20 mg and hyoscine 0.2-0.4 mg IM approximately one hour pre-operatively. Anaesthesia was induced with a sleep dose of midazolam IV and neuromuscular blockade was then obtained with atracurium 0.6 mg.kg^{-1} IV. Ventilation was controlled and isoflurane administered

until the systolic arterial pressure was reduced by 10–20% of preoperative value before tracheal intubation. Neuromuscular blockade was maintained throughout the procedure with an IV infusion of atracurium 0.7 ug.kg^{-1}.min^{-1}. Prior to cardiopulmonary bypass, the lungs were ventilated with nitrous oxide and oxygen (50/50%) to achieve eucapnoea and anaesthesia was supplemented with isoflurane. During cardiopulmonary bypass, anaesthesia was continued with isoflurane 1% vaporised into the gas supply to the oxygenator.

Statistical analysis

The study was planned as an open crossover design. However, examination of the data found that there was a strong interaction between stage of the study period during cardiopulmonary bypass and alfentanil administration on the haemodynamic data. Because of this interaction, the study was treated as a parallel group comparison. Data were analysed using Student's t test (paired and unpaired as appropriate) and Bonferonni's correction for multiple comparisons was then applied.

RESULTS

Patient details

Demographic details and relevant durations are presented in Table XXII. All patients were receiving one or more anti–anginal therapies (Table XXIII).

Thermostatic control

Good temperature control was achieved (Table XXIV).

Acid–base management

There were no significant differences in arterial pH or carbon dioxide tension either between Groups or within Groups from Period 1 to 2 (Table XXIV).

Table XXII. Demographic details and durations [mean (standard deviation)].

	Group I	Group II
Sex (F/M)	1/9	2/8
Age (yr)	55 (4.6)	54 (9.8)
Weight (kg)	80 (10.2)	77 (8.4)
Height (m)	1.72 (0.08)	1.72 (0.09)
Surface area (m^2)	1.91 (017)	1.88 (0.16)
Cardiopulmonary bypass (min)	90 (17)	79 (15)
Cross clamp (min)	52 (10)	47 (11)

Table XXIII. Anti-anginal drugs.

	Group I	Group II
Beta-adrenergic blockers	7	8
Nitrites	7	6
Calcium channel bockers	6	8

Table XXIV. Changes in arterial and nasopharyngeal temperatures (T_a, T_{np}), arterial pH and $PaCO_2$ in Groups I and II between Periods 1 and 2 [mean (standard deviation)].

Variable	Group I			Group II		
	Period 1	Period 2	d	Period 1	Period 2	d
T_a (°C)	27.4 (0.3)	27.7 (0.2)	−0.28	27. 6 (0.5)	27.8 (0.2)	−0.15
95% CL			−0.52, −0.05			−0.43, 0.14
T_{np} (°C)	28.7 (0.3)	28.3 (0.4)	0.42	28.4 (0.3)	28.4 (0.3)	0.04
95% CL			0.13, 0.72			−00.6, 0.15
Arterial pH	7.41 (0.06)	7.44 (0.06)	−0.03	7.38 (0.05)	7.37 (0.05)	0.01
95% CL			−0.08, 0.01			0.00, 0.03
$PaCO_2$ (mmHg)	39 (5.7)	38 (6.0)	0.9	44 (5.7)	44 (6.3)	−0.6
95% CL			−0.6, 2.5			−2.1, 0.9

Metabolic variables

There were no significant differences in systemic oxygen uptake between the groups nor within the groups between Periods 1 and 2 (Figure 21). With the exception of arterial oxygen tension, there were no significant differences in oxygen variables between or within groups (Table XXV and XXVI). Within patient arterial oxygen tension did not change significantly between Periods 1 and 2 in either group. However, arterial oxygen tension was significantly higher in Group I during Period 2.

Before application of Bonferonni's correction, there was a small but significant decrease in lactate concentration between Periods 1 and 2 in Group I which did not occur in Group II (Table XXV). However after correction, this change was nonsignificant. There were very small mean decreases in base excess in both groups (Table XXV) but again these were nonsignificant after application of Bonferonni's correction.

Haemodynamic variables

Haemodynamic data for one patient in Group I were lost due to an operator error when saving the data to disc. In Group I, mean arterial pressure and peripheral vascular resistance did not change significantly from Period 1 to 2 whereas they increased significantly in Group II between the two periods (Figures 22 and 23). Central venous pressure, reservoir volumes and haematocrit were not significantly different between the groups nor within the groups between Periods 1 and 2 (Table XXVII).

Isoflurane concentration.

No significant within patient changes in isoflurane concentration were found between Periods 1 and 2 in either Group (Table XVII). The mean isoflurane concentration was higher in Group I than Group II in both Periods but the differences were marginally nonsignificant after application of Bonferonni's correction.
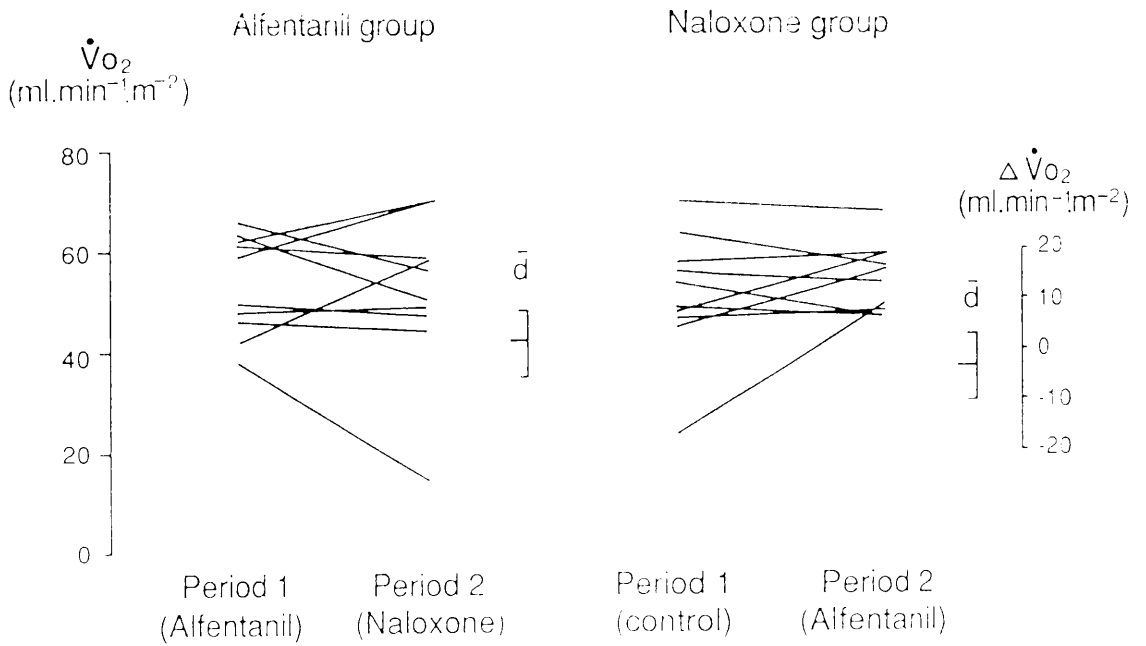
Figure 21. Changes in systemic oxygen uptake ($\dot{V}O_2$) between Periods 1 and 2 in Group I (Alfentanil) and Group II (Naloxone).

Table XXV. Changes in arterial and mixed venous blood oxygen contents, oxygen extraction, systemic oxygen uptake, base excess and lactate concentration in Groups I and II between Periods 1 and 2 [mean (standard deviation)].

Variable	Group I			Group II		
	Period 1	Period 2	d	Period 1	Period 2	d
CaO_2 (ml.L^{-1})	137 (14)	136 (14)	1.1	132 (13)	137 (14)	−4.8
95% CL			−1.7, 3.9			−10.8, 1.1
$C\bar{v}O_2$ (ml.L−1)	103 (13)	103 (14)	0.4	100 (8)	103 (12)	−2.6
95% CL			−4.3, 5.2			−6.8, 1.6
$Ca-\bar{v}O_2$ (ml.L^{-1})	34 (6)	33 (9)	1.4	32 (8)	34 (4)	2.2
95%CL			−3.0, 5.8			−6.4, 2.1
$\dot{V}O_2$ (ml.min^{-1}.m^{-2})	54 (10)	52 (15)	2.5	51 (12)	55 (6)	−3.33
95%CL			−4.8, 9.7			−10.2, .3.6
Base Excess	0.4 (2.4)	0.1 (2.7)	0.3	0.8 (1.6)	0.6 (1.4)	0.4
95% CL			−0.4, 1			0, 0.7
Lactate (mmol.L^{-1})	2.5 (0.4)	2.4 (0.4)	0.17	2.3 (1.0)	2.2 (1.0)	0.05
95% CL			0.06, 0.28			−0.06, 0.16

Table XXVI. Changes in arterial and mixed venous oxygen saturations and tensions and haemoglobin concentration in Groups I and II between Periods 1 and 2 [mean (standard deviation)].

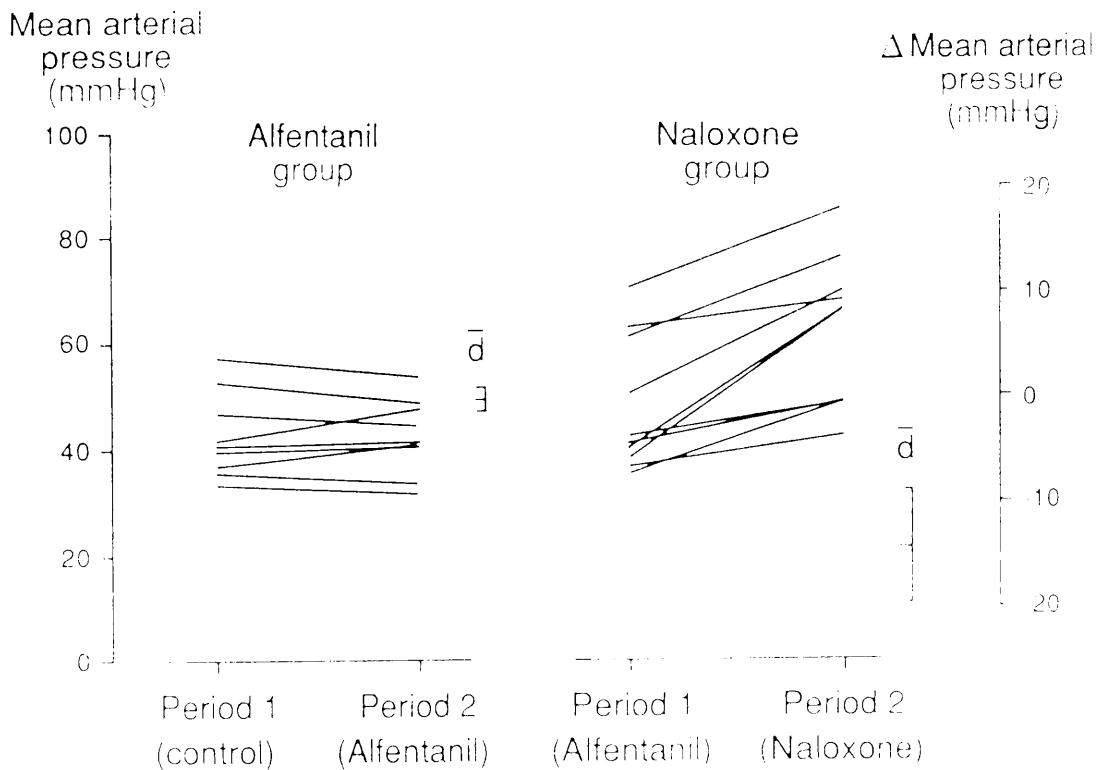| Variable	Group I			Group II		
	Period 1	Period 2	d	Period 1	Period 2	d
SaO_2 (%)	98 (.2)	98 (1.6)	0.5	98 (0.7)	98 (1.0)	0.2
95% CL		-0.6, 1.5				-0.1, 0.5
$S\bar{v}O_2$ (%)	82 (4.4)	84 (3)	-1.8	81 (4.7)	82 (4.8)	-0.6
95% CL		-4.1, 0.4				-2.7, 1.5
PaO_2 (mmHg)	351 (139)	341 (140)	10	262 (153)	258 (139)	15
95% CL		-63. 83 / 66, 101				-25, 35
$P\bar{v}O_2$ (mmHg)	46 (3.8)	46 (3.8)	-0.5	47 (5.8)	47 (5.9)	-0.5
95% CL		-2.8, 1.9				-1.9, 1.0
Hba (g.L^{-1})	89 (11.2)	89 (11)	-0.1	87 (9)	89 (7)	-2.2
95% CL		-1.4, 1.2				-4.5, 0
Hb$\bar{v}$ (g.L^{-1})	89 (11.2)	89 (11)	-0.4	87 (8)	89 (7)	-2.1
95% CL		-1.8, 1.0				-4.2, 0

Figure 22. Changes in mean arterial pressure between Periods 1 and 2 in Group I (Alfentanil) and Group II (Naloxone)
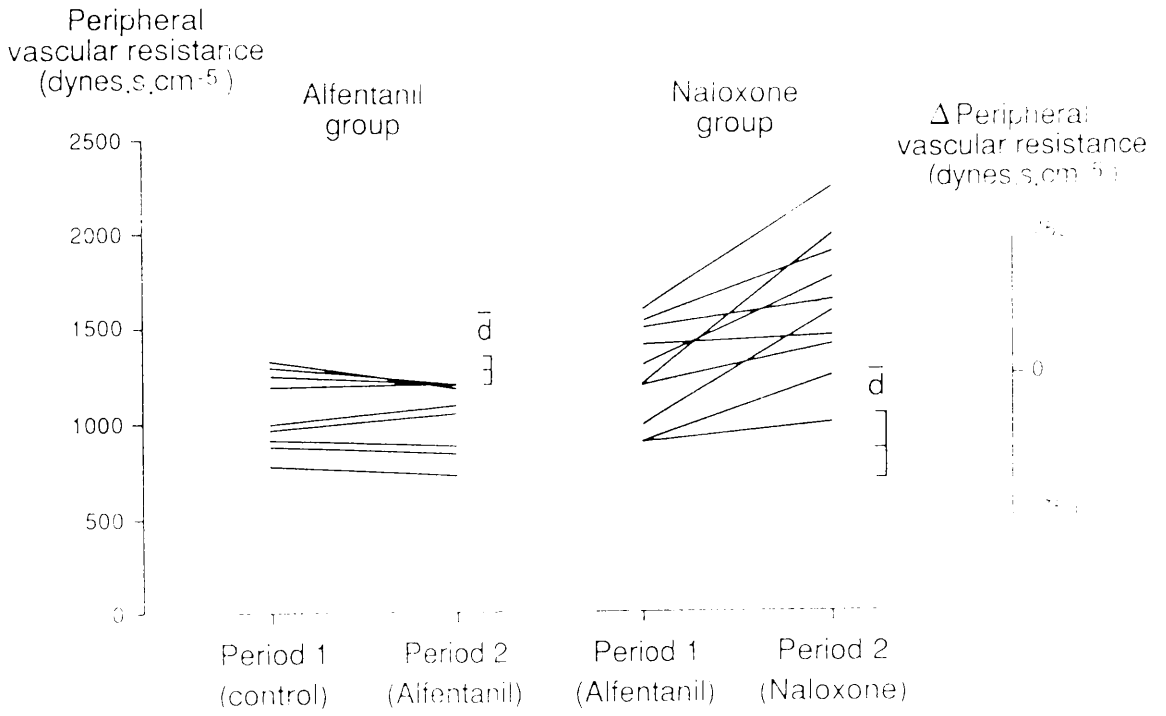
Figure 23. Changes in peripheral vascular resistance between Periods 1 and 2 in Group I (Alfentanil) and Group II (Naloxone).

Table XXVII. Changes in blood isoflurane concentration, haematocrit, mean arterial and central venous pressures, peripheral vascular resistance and reservoir level in Groups I and II between Periods 1 and 2 [mean (standard deviation)].

Variable	Group I			Group II		
	Period 1	Period 2	d	Period 1	Period 2	d
Isoflurane (ug.ml^{-1})	33 (10)	33 (11)	0.1	21 (7)	24 (9)	−2.8
			3, 21			
95% CL			−4.2, 4.4			−7.7., 2.2
			4, 14			
Hct (%)	27 (2.4)	27 (2.5)	−0.2	27 (3.6)	27 (3.6)	−0.8
95% CL			−1.2, 1.0			−1.9, 0.4
MAP (mmHg)	43 (7.6)	43 (6.6)	0.1	48 (11.8)	63 (13)	−14.2
95% CL			−2.6, 2.9			−19.6, −8.7
			−27, −12			
CVP (mmHg)	1.9 (2.6)	2.7 (3.2)	−0.8	0.6 (3.2)	1.4 (3.9)	−0.8
95% CL			−1.4, −0.1			−2.7, 1.1
PVR (dynes.s.cm^{-5})	1070 (193)	1047 (172)	23	1254 (251)	1632 (350)	−377
95% CL			−51, 97			−551, 204
			−621, −547			
Rervoir level (ml)	1660 (506)	1500 (612)	160	1380 (624)	1350 (535)	241
95% CL			−132, 452			−142, 202

Vasoactive drugs

During Period 1, two patients in each group were given methoxamine. A further patient in Group I received methoxamine during Period 2. Two patients in Group II were given sodium nitroprusside during Period 2.

DISCUSSION

The outstanding findings of this study are that mean arterial pressure and peripheral vascular resistance did not increase as expected during cardiopulmonary bypass when alfentanil was given, although they increased markedly when alfentanil was antagonised with naloxone. In contrast, there were no significant changes in metabolism.

Metabolism

Comparison of systemic oxygen uptake during Period 1 demonstrated that there was no significant difference between the two groups. Furthermore, neither administration of alfentanil nor antagonism of alfentanil had any significant effect on systemic oxygen uptake. There is no previous work with which to directly compare these results. Tigerstedt and Tammisto found that antagonism of opioids with naloxone after balanced anaesthesia at normothermia causes marked increases in systemic oxygen uptake [97]. However, their findings could be explained by increased muscular work as a result of restlessness and shivering whereas in the present study the patients were given sufficient atracurium to produce complete neuromuscular blockade. Malin and colleagues found that chronic, but not acute, exposure of conscious rats to naloxone resulted in an abstinence–like state and a marked increase in systemic oxygen uptake [98]. In the present study, only a single bolus dose of naloxone was given whereas, in Malin and colleagues study, it took a continuous infusion of naloxone over 24 hours to produce an increase in systemic oxygen uptake.

Also, Malin and colleagues could not reproduce the response with bolus doses of naloxone. In contrast, Dick, Lotz and Traub [163] found that naloxone 0.4 mg IV given to opioid naive volunteers caused a small but significant decrease in systemic oxygen uptake. The present study's findings would suggest that alfentanil and its antagonism with naloxone have no important effect on systemic oxygen uptake in humans during hypothermic cardiopulmonary bypass.

Comparison of lactate concentrations in Period 1 between Groups I and II found no significant difference which would suggest that alfentanil does not influence anaerobic metabolism. Although nonsignificant, small decreases in lactate concentration occurred between Periods 1 and 2 in both groups. This is in agreement with previous findings as lactate concentration would be expected to decrease slightly over the course of cardiopulmonary bypass.

Haemodynamics

Comparison of haemodynamic variables in Period 1 showed no significant difference between the groups. This finding would imply that alfentanil has little or no effect on haemodynamic variables during this stage of cardiopulmonary bypass. However, within patient comparison of mean arterial pressure from Periods 1 to 2 found a difference in effect between the Groups. In Group I, there was little if any change in mean arterial pressure or peripheral vascular resistance from the control measurements in Period 1 to those after alfentanil was administered in Period 2. Yet during the course of cardiopulmonary bypass, a progressive increase in both of these variables would be expected. This consistency in mean arterial pressure and peripheral vascular resistance throughout the test periods might suggest that alfentanil ameliorated the ongoing vasoconstriction. Indeed, the findings from Group II would add weight to this supposition as reversing alfentanil with naloxone produced a 30% average increase in mean arterial pressure and peripheral vascular resistance from Periods 1 to 2. This is a greater increase than would be expected, given the findings in Chapter 5, as solely attributable to ongoing vasoconstriction.

Antagonism of opioids with naloxone results in abrupt increases in systemic arterial pressure and peripheral vascular resistance in the intact cardiovascular system at normothermia [164]. These increases are most likely mediated by catecholamines and are ascribed to sudden awakening and reversal of analgesia. Naloxone has been reported to reverse hypotension in some specific situations such as endotoxic shock and high cervical spine injury [165,166]. For this reason, the rise in mean arterial and peripheral vascular resistance in the present study could be, in theory, due to the direct action of naloxone. However, naloxone has not been shown to have any cardiovascular effects in humans during halothane anaesthesia [167]. Thus, it is likely that the vascular effects in the present study are due to antagonism of alfentanil rather than as a direct action of naloxone.

In an anaesthetised canine model with an intact cardiovascular system, Flacke and co-workers found that antagonism of fentanyl with naloxone produced marked increases in catecholamines, mean arterial pressure and peripheral vascular resistance [164]. They postulated that the haemodynamic effects were as a result of an increase in sympathetic tone mediated by the central nervous system. It is likely that the increases in mean arterial pressure and peripheral vascular resistance produced by antagonism of alfentanil in this study is a result of the same mechanism. These findings would suggest that opioids have an important role in the prevention of the progressive vasoconstriction that occurs during cardiopulmonary bypass.

Isoflurane concentration

Marked interpatient variation in blood isoflurane concentrations were again found in this study. Mean isoflurane concentration was about 50% higher in Group I than Group II during both Periods though this difference was not statistically significant. The likely explanation for this chance difference is a higher gas to blood ratio in the oxygenator in Group I allowing greater delivery of isoflurane. The higher arterial oxygen tension in Group I would support this

conclusion. Isoflurane concentration could then account for the slightly lower mean arterial pressure and peripheral vascular resistance in Group I during Period 1 and in part for the between group differences in Period 2. However, there were only small nonsignificant changes in isoflurane concentration between Periods 1 and 2 in both groups therefore any within group changes in mean arterial pressure and peripheral vascular resistance over this time is unlikely to be caused by isoflurane.

In conclusion, neither the administration of alfentanil nor antagonism of alfentanil with naloxone had any significant effect on systemic oxygen uptake. In contrast, expected increases in mean arterial pressure and peripheral vascular resistance did not occur after alfentanil was given, but marked increases occurred when alfentanil was antagonised with naloxone. These haemodynamic findings would suggest that alfentanil is an important moderator of the progressive vasoconstriction associated with cardiopulmonary bypass.

CHAPTER 9

CONCLUDING DISCUSSION

This chapter will draw overall conclusions, based on the presented studies and with reference to previous literature, as to the effects of cardiopulmonary bypass and anaesthesia on haemodynamic and metabolic variables. Areas requiring further research will be identified. Finally, the place of cardiopulmonary bypass as a haemodynamic model and the function of anaesthesia during cardiopulmonary bypass will be considered.

From the foregoing studies, it is clear that the most important factor in terms of systemic metabolism is flow rate. Anaesthesia, acid-base management and flow character during hypothermic cardiopulmonary bypass had little if any metabolic actions. With reference to haemodynamic variables, these were markedly affected by some of the anaesthetic agents which were tested as well as by flow rate and acid-base management but they were not influenced by flow character.

METHODOLOGY

The greatest difficulty in comparing previous work is the tremendous variety and combination of anaesthetic and cardiopulmonary bypass techniques which have been used. An excellent example of this problem is the controversy, despite extensive investigation, that still surrounds pulsatile perfusion [12]. Care was taken in this series of studies to standardise, with the exception of the variable under study, both anaesthetic and cardiopulmonary bypass techniques. As previously discussed, using a factorial experimental design for the studies in Chapter 5 largely overcomes most of the difficulties in standardisation. With

regard to anaesthesia, although two opioids and neuromuscular blocking agents were used in this series of studies, the known effects of these agents are readily comparable [93,94,95]. Thus, it is possible to make a valid over all comparison from these studies.

Ideally, no vasoactive drugs would have been used during these studies other than those which were under investigation. However, for the reasons discussed in Chapter 2, it would be ethically unsound to allow patients to suffer unacceptably low or high levels of systemic arterial pressure. Because of this, the changes which were found with regard to haemodynamic variables may be less than precise. An animal model might have allowed greater trespass but whether animal findings can be extrapolated to humans must always be questionable. Although the present series of studies in humans may have underestimated the magnitude of any effects, they would have accurately reflected their directions. It might also be argued that the vasoactive drugs used to control hypertension and hypotension may have influenced metabolism. However, sodium nitroprusside has been shown to have no effect on systemic oxygen uptake during cardiopulmonary bypass [46] and methoxamine, being a pure alpha-adrenergic agonist, has no metabolic actions.

Patient medication with beta-adrenergic and calcium channel blocking agents are known to modify the haemodynamic responses to vasoactive agents during cardiopulmonary bypass [120]. Any effects these agents might have had will have been controlled in the crossover studies of Chapters 5 and 6. In the parallel group studies of Chapters 7 and 8 there was a similar distribution of these agents in both the control and active groups. It is therefore unlikely that pre-operative medication with beta adrenergic or calcium channel blockers will have in any way invalidated the findings of this thesis.

EFFECTS OF CARDIOPULMONARY BYPASS ON METABOLISM

Of the three aspects of cardiopulmonary bypass studied, that is flow rate, flow character and acid-base management, only flow rate had a significant effect on metabolism. Pump flow rate is frequently decreased to low levels during hypothermia on the basis that this manipulation improves myocardial preservation, reduces haemolysis and gaseous microembolisation and provides a clearer surgical field [22,54,62]. The findings of this project would suggest that the physiological rationale for this manipulation is flawed and that systemic oxygen uptake was markedly reduced when flow rate was decreased from 2.0 to 1.5 $L.min^{-1}.m^{-2}$. Interpretation of this finding in terms of clinical outcome is difficult as low flow cardiopulmonary bypass is well tolerated [10,168]. Undoubtedly many tissues can withstand hypoperfusion in the presence of hypothermia for long periods of time without structural damage and cerebral perfusion may be preferentially preserved [169]. Physiologically, and as others have proposed [170,171], it should be better to ensure that the systemic oxygen uptake is on the plateau rather than the upslope of the curve. However, the question remains whether, with modern cardioplegic techniques, the use of low flow cardiopulmonary bypass to enhance myocardial preservation can still be justified. Determination of the flow rate at which systemic oxygen uptake becomes unrelated requires further investigation under the current conditions of cardiopulmonary bypass.

Flow character

Unfortunately, the findings of the experiments in Chapter 5 do not conclusively resolve the long established controversy that continues to surround the use of nonpulsatile versus pulsatile perfusion [12,23,65,66]. Pulsatile flow has been advocated on the basis that it improves metabolism [65], yet no significant differences between pulsatile and nonpulsatile flow characters were found in these studies. These findings cannot completely exclude the theory that pulsatile flow is metabolically superior to nonpulsatile perfusion, but they would

add weight to the body of opinion which maintains that there are no important metabolic differences between the two types of flow character during routine cardiopulmonary bypass [22,66].

In this area of research, there remains a great deal of confusion as to what constitutes truly pulsatile perfusion [12]. Recent studies by several groups [150-152,155], which have identified the complex nature of pulsatile perfusion, may help resolve this important question. The modified roller pump system used in the present study may account for pulsatile perfusion's lack of effect on haemodynamic and metabolic variables as it produces only limited pulsatile power [150,151]. However, the same pulsatile system was used previously in a series of studies by Taylor which found significant haemodynamic and hormonal differences between nonpulsatile and pulsatile perfusion [172]. These findings are difficult to resolve although Taylor employed normothermia as opposed to the hypothermia used in the present studies. Also, plebotomy prior to cardiopulmonary bypass for later autologous transfusion was routinely practised at that time in the centre in which Taylor undertook his studies. This plebotomy may have caused an abnormally high state of vasoconstriction which, in turn, may have resulted in an altered response to flow character.

Further study is required to determine if there are truly advantages during clinical cardiopulmonary bypass to the use of pulsatile over nonpulsatile perfusion. A clearly agreed definition of what constitutes pulsatile and nonpulsatile perfusion is required, as well as the use of an accurate measurement of pulsatility, before this controversy can be resolved.

Acid-base management

Acid-base management during hypothermic cardiopulmonary bypass has attracted a lot of attention since Rahn and Reeves and Howell and colleagues put forward their arguments, based on comparative physiology, for using an alpha-stat rather than a pH-stat acid-base management during hypothermia [77-79]. The findings of the experiment in Chapter 5 add no weight to the use of either type of acid-base management in terms of systemic metabolism.

However, employment of alpha-stat control would appear to have favourable regional effects on cerebral and myocardial metabolism [173,174].

Anaerobic metabolism

Lactate concentration and base excess proved to be poor indices of metabolism during hypothermic cardiopulmonary bypass in this series of studies. Even when marked changes in systemic oxygen uptake occurred, such as produced by alternation in flow rate, there were no significant changes in either lactate concentration or base excess. The only consistent pattern throughout the studies, although not always statistically significant, was a small mean reduction in lactate concentration during the course of cardiopulmonary bypass. This is in contrast to earlier studies which observed progressive increases in lactate concentration [5,48]. Metabolism or the redistribution of lactate present in the pump priming solution may account for the present results. The implication of this finding is that cardiopulmonary bypass today causes less physiological trespass than it has done in the past.

EFFECTS OF ANAESTHESIA DURING CARDIOPULMONARY BYPASS ON METABOLISM

None of the anaesthetic agents examined in the preceding studies were found to have any significant effect on metabolism during hypothermic cardiopulmonary bypass. This was an unexpected finding given previous research which has found anaesthetic agents to reduce systemic oxygen uptake both in the intact cardiovascular system and during cardiopulmonary bypass [85,87,90-92]. Several possible explanations for the differences between present and previous findings can be mooted. As discussed in Chapter 7, atracurium's minimal haemodynamic effects, unlike tubocurarine's potent vasodilatory actions, may account for the lack of any metabolic effect in the present studies. Vasodilation alone seems an unlikely explanation as this was produced by isoflurane in the study documented in Chapter 6 and also, by Evans and co-workers [46] using sodium nitroprusside without concomitant metabolic changes.

Theye and Michenfelder have argued that in the intact cardiovascular system, the decrease in systemic oxygen uptake induced by anaesthetic agents may be mediated through a decrease in cardiac output rather than systemic metabolic depression [91]. As pump flow rate was kept constant during the present studies of anaesthetic agents, this effect would not occur. However, this is unlikely to be the whole explanation as anaesthesia has regional metabolic effects during cardiopulmonary bypass which cannot be ascribed to flow rate [161].

Another important difference from early studies is the current use of hypothermia in conjunction with cardiopulmonary bypass. Moderate hypothermia causes approximately a 50% reduction in metabolic rate [22] and therefore, it may be that the size of any systemic metabolic effect induced by anaesthetic agents is very small at hypothermia in comparison to normothermia. Thus, the measurement techniques used in the present studies may not have been

sensitive enough to detect any changes. If the metabolic effects of anaesthesia are indeed so small during hypothermia, it is unlikely that they are of any clinical relevance. However, the present studies cannot exclude the possibility that anaesthesia has important systemic metabolic effects during cooling and, in particular, the rewarming stages of hypothermic cardiopulmonary bypass. Moreover, future anaesthetic drugs may prove to have systemic metabolic actions.

One important group of drugs which were not examined in this thesis, because of their large number and disparate nature, are the intravenous anaesthetics. Chlorpromazine has been found by Arikawa and colleagues to increase systemic oxygen uptake below 32°C [99]. However, its use is not presently favoured for cardiopulmonary bypass [20]. Many of the other intravenous agents used could potentially be systemic metabolic depressants as most are known to decrease regional metabolism. Propofol is a new agent which is worthy of further study because of its increasing use during cardiopulmonary bypass [20].

The regional metabolic effects of anaesthesia during cardiopulmonary bypass, and in particular the effects on cerebral metabolism, require investigation. There is an important neuropsychological morbidity following cardiopulmonary bypass [175,176] and thiopentone is the only agent that has been demonstrated to reduce this morbidity [177]. Most likely this effect is mediated by thiopentone's cerebral depressant action [161]. However, in the doses of thiopentone that are required for cerebral protection, there is an increased need for ionotropes and prolonged ventilatory support [177]. Other anaesthetic agents such as isoflurane or propofol, which also depress cerebral metabolic rate [161], may prove to be cerebrally protective if administered during cardiopulmonary bypass without the adverse cardiovascular and ventilatory effects of thiopentone. This aspect of anaesthesia during cardiopulmonary bypass requires thorough investigation.

EFFECTS OF CARDIOPULMONARY BYPASS ON HAEMODYNAMICS

Of the three technical aspects of cardiopulmonary bypass examined in the present series of studies, only flow rate had a significant and sizeable effect on haemodynamic variables. Although arterial pH was found to interact significantly with stage on mean arterial pressure, the magnitude of this effect was small. No differences in haemodynamic variables were found between nonpulsatile and pulsatile perfusion. Regardless of flow rate, flow character and acid–base management, there was a progressive increase in both mean arterial pressure and peripheral vascular resistance throughout the course of cardiopulmonary bypass.

Flow rate

The increase in peripheral vascular resistance associated with decreasing flow rate, which was found in the present study, confirms that the inverse relationship between these two variables still exists despite the major changes in cardiopulmonary bypass that have occurred over the years[34,123]. Of interest, and not previously described, is the significant correlation between the changes in peripheral vascular resistance and systemic oxygen uptake which resulted from alternation of the flow rate. This proportional relationship implies that the more peripheral vascular resistance is reduced by increasing flow rate, then the greater is the improvement in tissue perfusion.

In contrast, the progressive increase in peripheral vascular resistance over the course of cardiopulmonary bypass was not associated with any decrease in systemic oxygen uptake. As discussed in Chapter 5, these conflicting results may indicate that both passive and active capillary mechanisms are operating to cause the increases in peripheral vascular resistance.

Flow character

Pulsatile perfusion is stated to be haemodynamically superior to continuous perfusion as it reduces peripheral vascular resistance as well as preventing ineluctable vasoconstriction. The results of this project do not support this view as there were no significant differences in haemodynamic variables between nonpulsatile and pulsatile perfusion nor any significant difference in the rate at which these variables increased during cardiopulmonary bypass. As discussed previously, there may be technical explanations as to why the modified roller pump system used in this thesis did not produce truly pulsatile perfusion. Nonetheless, the findings of the present studies would support the view that there are no important haemodynamic differences between nonpulsatile and pulsatile perfusion even during low flow cardiopulmonary bypass [22,66].

Acid-base management

Some differences in haemodynamic effects between alpha and pH–stat acid–base management were found in the present studies but the clinical consequences of these differences is uncertain. There is a growing body of research which would indicate that alpha–stat acid–base management may be advantageous as it maintains cerebral blood flow autoregulation and gives improved myocardial preservation [173,174]. Until otherwise determined, an alpha–stat approach would, therefore, appear the more appropriate choice of acid–base management during hypothermic cardiopulmonary bypass. However, this series of studies demonstrates that achieving alpha–stat acid–base management is not staightforward when using bubble oxygenators.

EFFECTS OF ANAESTHESIA DURING CARDIOPULMONARY BYPASS ON HAEMODYNAMICS

The second hypothesis of this project was that anaesthesia had important effects on haemodynamic variables. Of the three main components of balanced anaesthesia which were studied, this hypothesis was supported with regard to the inhalational and opioid anaesthetic agents but this was not the case with the neuromuscular blocking agent.

Inhalational anaesthetics

Isoflurane was found to be a vasodilator during the abnormal conditions of hypothermic cardiopulmonary bypass as is the case in the intact cardiovascular system at normothermia. Given that awareness is a recognised complication during cardiopulmonary bypass [179,180], the use of isoflurane to control hypertension during cardiopulmonary bypass, as opposed to non-anaesthetic vasodilators, would have important advantages as it would at least lessen, and at best obviate, the risk of awareness. It would seem most appropriate to use isoflurane during rewarming when the flow rate is increased and the ongoing vasoconstriction reveals itself as hypertension.

Nevertheless, there may be drawbacks to the use of isoflurane in high concentrations throughout cardiopulmonary bypass. Once hypothermia has been achieved, the flow rate is often reduced to low levels. This reduction in flow rate, combined with a low peripheral vascular resistance, can result in hypotension at this stage. Using high concentration of isoflurane at an early stage during cardiopulmonary bypass may exacerbate this problem and result in unacceptably low systemic arterial pressures. However, awareness is unlikely to occur at this stage of cardiopulmonary bypass because of the hypothermia and, therefore, isoflurane could be used in low concentrations at this time. Alternatively, short acting vasoconstrictors could be administered to maintain

the arterial pressure at acceptable levels. Another drawback to using high concentrations of isoflurane throughout cardiopulmonary bypass may be it's effects when weaning back to the patient's own cardiovascular system. At this crucial time, high concentrations of isoflurane may impair myocardial performance and this may already be depressed as a result of cross clamping ischaemia. For that reason, low concentrations of isoflurane may be advisable at this point. However, this is readily achieved as it takes only 10 minutes for the blood isoflurane concentration to drop to low levels after discontinuing administration during cardiopulmonary bypass [180].

As discussed earlier, cerebral protection may be another reason for using isoflurane during cardiopulmonary bypass. Suppression of the stress response to cardiopulmonary bypass may yet prove to be a further indication for the use of isoflurane [18,181].

Although there may be drawbacks to the use of isoflurane during cardiopulmonary bypass, these can be readily overcome and this study would suggest that any disadvantages are greatly out-weighed by the advantages.

Neuromuscular blocking agents.

In recent years, there has been a move towards the use of neuromuscular blocking agents, such as atracurium and vecuronium, which, unlike the established agents, have minimal effects on the cardiovascular system. This is particularly true in anaesthesia for coronary artery surgery when stable haemodynamics and avoidance of tachycardia are important in order to prevent myocardial ischaemia. The present study found atracurium to have no significant effect on haemodynamic variables during cardiopulmonary bypass, which fits with previous studies in the intact cardiovascular system at normothermia [131,132]. Atracurium, because of its minimal cardiovascular effects, before, during and after cardiopulmonary bypass, would appear to be a suitable agent for neuromuscular blockade during cardiac surgery.

Whether any neuromuscular blocking agent is in fact required, given the risk of patient awareness during cardiopulmonary bypass [178,179], is more questionable. Depth of anaesthesia is almost impossible to determine during cardiopulmonary bypass as all the major clinical signs are ablated. One of the perceived truths regarding depth of anaesthesia is that movement in response to a painful stimulus indicates a level of consciousness which is close to awareness and signifies that anaesthesia should be deepened. This vital sign is lost when movement is inhibited by neuromuscular blocking agents. During cardiac surgery, muscle relaxation is not required, even during sternotomy, for surgical access. If neuromuscular blockers were not used then unduly light anaesthesia would become readily apparent and could be quickly remedied [96]. In contrast, preventing movement with neuromuscular blocking agents may disguise awareness [179] and result in serious psychological trauma to the patient, which may lead to litigation.

Opioids

Alfentanil's actions on the vascular system in the present studies were unexpected as it has minimal effects on haemodynamic variables in the intact cardiovascular system at normothermia [95,134]. Indeed comparison of haemodynamic variables between groups in Period 1 without consideration of the results from Period 2 would support these findings. However, when the findings during Period 2 are included, they would suggest that alfentanil may reduce the rate of progressive vasoconstriction that occurs during the course of cardiopulmonary bypass. It is unlikely that opioids prevent the progressive vasoconstriction altogether, as in Chapter 5 a significant rise in peripheral vascular resistance was found during the course of cardiopulmonary bypass. In that experiment, patients were anaesthetised during hypothermic cardiopulmonary bypass with an infusion of fentanyl which is a similar opioid to alfentanil [95]. Therefore, it is more likely that opioids reduce the rate at which peripheral vascular resistance rises. The use of opioids like alfentanil during

cardiopulmonary bypass would seem to be beneficial in minimising the adverse increase in peripheral vasoconstriction that originates during cardiopulmonary bypass and continues into the postoperative period.

Another advantage to the use of opioids during cardiopulmonary bypass is that, if used in high doses, they block the stress response [95]. However, without supplementation by an inhalational or intravenous anaesthetic, there is a risk of awareness with opioid techniques [95.96].

Intravenous anaesthetics

Only three drugs, chosen as representative of the three main components of balanced anaesthesia, were investigated in the foregoing studies. One group of drugs not investigated in this project, because of its large size and disparate nature, were the intravenous anaesthetic agents. These agents include barbiturates, benzodiazepines, neurolepts and other non-related drugs like propofol and are sometimes used alone or, more commonly, in conjunction with opioids during cardiopulmonary bypass [20]. Most of these agents have been found to cause decreases in peripheral vascular resistance during cardiopulmonary bypass [117,121,135–137].

Barbiturates, like thiopentone and methohexitone, are now less frequently used than in the past. This decreased use is perhaps because of their long elimination half life and the profound cardiovascular depression which they produce, as this is disadvantageous during the post-bypass period. However, the use of thiopentone in high doses has recently been advocated, despite its adverse side effects, on the basis that it provides cerebral protection during cardiopulmonary bypass [178]. Benzodiazepines, like midazolam and diazepam, are frequently used during cardiopulmonary bypass. These agents also have a long half life though, unlike the barbiturates, they are noted for their minimal haemodynamic effects in the intact cardiovascular system. Neurolept anaesthetic agents such as chlorpromazine and droperidol, are known to be vasodilators during cardiopulmonary bypass and are used for this effect [99.117].

Recently, their use during cardiac anaesthesia has declined [20]. Why this should be is uncertain though perhaps the decline in the popularity of neurolepts can be ascribed to their prolonged action.

Propofol is a new, short acting intravenous anaesthetic agent which has become commercially available since these studies were undertaken. During hypothermic cardiopulmonary bypass, propofol is a vasodilator [135,136]. Therefore, propofol could be a suitable alternative to isoflurane as an anaesthetic agent to control systemic arterial pressure and ensure anaesthesia without the risk of awareness.

HAEMODYNAMIC MODEL

Cardiopulmonary bypass has been advocated by Levy and Hug as a suitable experimental model for study of the circulation [100] and others have used it as such [117-120,129]. The findings of the foregoing studies indicate the difficulties involved in interpreting complex haemodynamic changes that occur during hypothermic cardiopulmonary bypass. Not only are there multiple factors, which influence haemodynamic variables during cardiopulmonary bypass, but these influences are dynamic so a steady state is never achieved. Throughout cardiopulmonary bypass, there is a progressive arterial vasoconstriction. Moreover, there is an altered response of the vasculature depending on the stage of cardiopulmonary bypass. This is demonstrated by the interaction between arterial pH and stage in Chapter 5 and also by the altered responses to isoflurane and alfentanil in Chapters 6 and 8 according to the stage of cardiopulmonary bypass in which they were administered. Although study of these influences are important for their own sake, it is doubtful whether findings made during the abnormal conditions of hypothermic cardiopulmonary bypass can be extrapolated directly to the intact cardiovascular at normothermia.

ANAESTHESIA DURING CARDIOPULMONARY BYPASS

After ensuring the patients safety, the prime duty anaesthetists owe their patients is to render them insensible to surgery. This duty can be difficult to fulfil during cardiac anaesthesia when occasionally a life threatening cardiovascular collapse may necessitate the lightening of anaesthesia to eliminate any adverse cardiovascular effects of anaesthesia. Also, during cardiopulmonary bypass the clinical signs indicating depth of anaesthesia, such as heart rate and arterial blood pressure, are rendered useless by the induced haemodynamic derangement. There may be mitigating circumstances for patient awareness before and after cardiopulmonary bypass but not during, when the circulation is mechanically supported. A very small minority of anaesthetists do not administer any form of anaesthesia during cardiopulmonary bypass [20] with the result that some patients can clearly recall intra-operative events [179]. Although the type of anaesthetic technique that should be used can be argued, there can be no acceptable reason for not administering some form of anaesthesia during cardiopulmonary bypass.

In conclusion, this thesis has proven the hypothesis that cardiopulmonary bypass technique has an important influence, in terms of flow rate, on haemodynamic and metabolic variables to be valid. With regards to the hypothesis that anaesthesia has important metabolic and haemodynamic effects during hypothermic cardiopulmonary bypass, it can be accepted for haemodynamic effects but must be rejected in the case of metabolic effects.

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GLOSSARY OF ABREVIATIONS

BE	base excess
CaO_2	arterial blood oxygen content
$C\bar{v}O_2$	venous blood oxygen content
$Ca-\bar{v}O_2$	oxygen extraction
CVP	central venous pressure
d	mean difference
$\bar{d}$	95% confidence limits of mean difference
DAP	diastolic arterial pressure
$\dot{D}O_2$	systemic oxygen delivery
F	F-statistic or female
GLIM	generalised linear interactive modelling
Hba	arterial haemoglobin concentration
Hbv	venous haemoglobin concentration
kg	kilogram
L	litre
m	metre
m^2	square metre
min	minute
M	male
MAP	mean arterial pressure
p	probability
PaO_2	arterial blood oxygen tension
$PaCO_2$	arterial blood carbon dioxide tension
$P\bar{v}O_2$	mixed venous blood oxygen tension
$P\bar{v}CO_2$	mixed venous blood carbon dioxide tension
pHa	arterial pH
pHA	pH-stat acid-base management
pH_{37}	alpha-stat acid-base management
PVR	peripheral vascular resistance

r	regression coeficient
SaO_2	arterial haemoglobin oxygen saturation
$S\bar{v}O_2$	mixed venous haemoglobin oxygen saturation
SAP	systolic arterial pressure
SD	standard deviation
$\dot{V}O_2$	systemic oxygen uptake
yr	year
95% CL	95% confidence limit
$\triangle$	change