VENOARTERIAL MODIFIED ULTRAFILTRATION VERSUS CONVENTIONAL ARTERIOVENOUS MODIFIED ULTRAFILTRATION DURING CARDIOPULMONARY BYPASS SURGERY

By

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This study represents original work by the author and has not been submitted in any form to another University. Where use was made of the work of others, it has been duly acknowledged in the text.

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DEDICATION

I dedicate this work to:

Cardiovascular perfusion in the interest of patients undergoing cardiac surgery;

My parents, Mr & Mrs Mohanlall and my in-laws Mr & Mrs Rampersadh;

My wife, Nishara Mohanlall and my family for her continuous support and encouragement and

"GOD" for being my guide.

ABSTRACT

VENOARTERIAL MODIFIED ULTRAFILTRATION VERSUS CONVENTIONAL ATERIOVENOUS MODIFIED ULTRAFILTRATION DURING CARDIOPULMONARY BYPASS SURGERY

INTRODUCTION: The role of modified ultrafiltration (MUF) in removing inflammatory mediators, reducing the need for homologous donor blood and decreasing pulmonary vascular resistance after cardiopulmonary bypass (CPB) has already been established. Different types of MUF systems evaluated illustrated that none of the MUF techniques adhered to the normal venous to arterial blood flow dynamics.

OBJECTIVES: This experimental study compared a conventional arteriovenous modified ultrafiltration (AVMUF) system to a custom designed venoarterial modified ultrafiltration (VAMUF) system. This technique of VAMUF was designed to mimic the pro-grade flow pattern of the body and cardiopulmonary bypass circuit as compared to the conventional retrograde AVMUF systems.

METHODS: Sixty patients that underwent MUF were divided into two groups, the AVMUF (n = 30) and the VAMUF (n=30) groups. Modified ultrafiltration was performed for a mean time of 12 minutes in both groups. In AVMUF blood was removed from the aorta, haemoconcentrated and infused into the right atrium (RA). In VAMUF blood flow was from the RA through a haemoconcentrator and re-infused into the aorta.

RESULTS: There was no significant difference in any of the demographic variables, CPB or cross-clamping time. Results showed significant difference in the ventilation times, with the VAMUF requiring a shorter ventilation time than the AVMUF group. Intensive care unit (ICU) stay, Hospital stay and discharge days were all significantly lower in the VAMUF group as well. The VAMUF also showed a lower percentage fluid balance than the AVMUF. The systolic and mean blood pressure was significantly higher after VAMUF with a decrease in heart rate, and central venous pressure (CVP). The VAMUF group showed a significantly greater decrease of Creatinine, serum lactacte and uric acid over time with no significant differences in oximetry.

CONCLUSION: Results prove that VAMUF is more effective compared to the conventional AVMUF regarding the haemodynamics and clinical parameters of the patient and is more physiological with regards to blood flow dynamics. The VAMUF is, therefore, a more physiological technique than AVMUF.

ABSTRACT PUBLICATION ARISING FROM THIS DISSERTATION

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A new technique of performing AVMUF

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LIST OF ABBREVIATIONS

ABC	-	avidin - biotin complex
ACT	-	activated clotting times
ADH	-	anti-diuretic hormone
ADP	-	adenosine diphosphate
AIDS	-	acquired immune deficiency syndrome
ANH	-	acute normovolemic hemodilution
ARDS	-	acute respiratory distress syndrome
ASD	-	atrial septal defect
ATP	-	adenosine triphosphate
AVMUF	-	arteriovenous modified ultrafiltration
BCD	-	blood cardioplegic delivery
BPM	-	beats per minute
BP	-	blood pressure
BSA	-	body surface area
BUN	-	blood urea nitrogen
BV	-	blood volume
Ca^{2+}	-	serum calcium
CABG	-	coronary artery bypass grafting
CCU	-	cardiac care unit
CDS	-	cardioplegic delivery set
CI	-	cardiac index
CK	-	creatinine kinase
CK-MB	-	creatinine kinase myocardial band
cmH_2O	-	centimetres of water
CO	-	cardiac output
COP	-	colloid osmotic pressure
CPB	-	cardiopulmonary bypass
CPD	-	citrate-phosphate-dextrose
CPK	-	creatinine phosphokinase
CPU	-	central processing unit
CSU	-	cardiac surgical unit

CUF	-	conventional ultrafiltration
CVP	-	central venous pressure
DIC	-	disseminated intravascular coagulation
DUF	-	dilutional ultrafiltration
ECCO	-	mini extracorporeal circulation optimized
ECMO	-	extracorporeal membrane oxygenation
Gel	-	Gelufusine
GOSH	-	Great Orlmond Street Hospital
Hb	-	haemoglobin
Hct	-	haematocrit
HIV	-	human immunodeficiency virus
HR	-	heart rate
IABP	-	Intra Aortic Balloon Pump
ICD	-	Intraoperative Cell Salvage Devices
ICS	-	intraoperative cell salvage
ICU	-	intensive care unit
IJV	-	internal jugular vein
IL	-	interleukin
K^+	-	serum potassium
LA	-	left atrium
Lab	-	laboratory
LV	-	left ventrical
LVAD	-	left ventricular device
MAP	-	mean arterial blood pressure
MECC	-	minimal extracorporeal circulation
Mg^{2+}	-	serum magnesium
MI	-	myocardial infarction
mmHg	-	millilitres mecury
MUF	-	modified ultrafiltration
Na^+	-	serum sodium
$NaHCO_3$	-	sodium bicarbonate
NWAFH	-	Northwest Armed Forces Hospital
O_2	-	oxygen
OPCABG	-	off pump coronary artery bypass grafting

Pa	-	arterial or inlet blood pressure
PA	-	pulmonary artery
PAD	-	preoperative autologous donation
PAP	-	pre-operative autologous prime
pCO_2	-	partial pressure of carbon dioxide
PCR	-	polymerized chain reaction
PCV	-	packed cell volume
PLT	-	platelets
pO_2	-	partial pressure of oxygen
pO_4^-	-	serum phosphate
PRP	-	platelet rich plasmapheresis
Ps	-	amount of negative pressure applied to the effluent side of the membrane
Pv	-	venous or outlet blood pressure
PV	-	pulmonary vein
PVR	-	pulmonary vascular resistance
R	-	review
RA	-	right atrium
RAP	-	retrograde autologous priming
RBC	-	red blood cells
RV	-	right ventricle
RVAD	-	right ventricular assist device
S-Alb	-	serum albumin
SaO_2	-	oxygen saturation
SASECT	-	Saudi Arabian Society for Extracorporeal Technology
SMB	-	shed mediastinal blood
SVR	-	systemic vascular resistance
TBW	-	total body water
TMP	-	trans-membrane pressure
TNF	-	tumour necrosis factor
TP	-	transmembrane pressure
TPA	-	tissue plasminogen activator
TSH	-	thyroid stimulating hormone
VAMUF	-	venoarterial modified ultrafiltration

VAVD	-	vacuum assisted venous drainage
Vent. Time	-	ventilation time
VSD	-	ventricular septal defect
VVMUF	-	venovenous modified ultrafiltration
WT	-	weight
ZBUF	-	zero-balance ultrafiltration

CHAPTER ONE : INTRODUCTION

In all forms of surgery today, medical professionals are always trying to explore new ideas and techniques that would be beneficial to the patient population. Cardiac surgery is no exception. Dr. Gibbon's made history when he first used the heart lung machine on human patient. In 1953, Cecelia Bavolek became the first to successfully undergo open heart bypass surgery, with the aid of a machine that totally supported her heart and lung functions (Gibbon, 1954).

Although significant improvements in this complex field were accomplished with the institution of coronary artery bypass grafting, valve surgery and repairs to complex cardiac congenital abnormalities, there is always room for further advancement (Lawrence and Cohn, 2003). These advances can only be accomplished by the invention of new ideas and techniques and the re-exploration of old ones. Modified Ultrafiltration (MUF) is one of those techniques.

Cardiopulmonary bypass (CPB) is a technique by which the pumping action of the heart and the gas exchange functions of the lung are replaced temporarily by a mechanical device, the pump oxygenator, which is attached to a patient's vascular system. During CPB a number of physiologic variables are directly under external control, and another group of variables is determined in part by the externally controlled factors and in part by the patient (Dennis, Spreng, Nelson, Karlson, Nelson, Thomas, Eder and Varco, 1951).

A number of undesirable side effects occur to a greater or lesser degree with CPB. Some temporary dysfunction of organs and systems are the sequelae of present techniques. In its most severe form, this adverse response to CPB has been called the "post-perfusion syndrome" and may, to an extent, include clinical signs of pulmonary dysfunction (Meliones, Gaynor, Wilson, Kern, Schulman and Shearer, 1995), renal dysfunction (Philbin, Goggins, Emerson, Levine and Buckley, 1979), abnormal bleeding diathesis (Kirklin, Westaby and Blackstone, Kirklin, Chenoweth and Pacifico, 1983), increased susceptibility to infection, (Murphy, Connery, Hicks

and Blumberg, 1992) increased interstitial fluid, leukocytosis, fever, dysorientation, vasoconstriction and haemolysis.

Numerous advances in CPB circuits and perfusion techniques have been accomplished over the last 50 years following open heart surgery (Lawrence and Cohn, 2003). Elevated capillary permeability, increased water weight gain and inflammatory mediators still complicate post-operative recovery and organ function. Several approaches have been adopted to reduce the accumulation of excess extravascular fluids and compliment activation. These include the use of smaller and more biocompatible oxygenators, shorter lines in CPB circuits, use of corticosteroid anti-inflammatory agents and ultrafiltration (Darling, Halloway, Kern, Ungerleider, Jaggers, Lawson, and Shearer, 2000) .

The technique of conventional AVMUF was developed in the early 1990's at the Great Ormond Street Hospital (GOSH) for Sick Children in London, U.K. by Naik, Knight and Elliot (1991). It is performed after separation of bypass. It entails haemoconcentrating the total circulating blood volume in patient and residual blood volume in the cardiopulmonary bypass circuit. The concentrated blood is thereafter returned to the patient. Blood is removed from the aorta and passes through a haemoconcentrator (artificial kidney) and is pumped back into the heart via a cannula in the right atruim (RA). The blood flow is retrograde in relation to CPB and the patients physiological blood flow dynamics.

The implementation of MUF to CPB has shown to decrease post-operative oedema due to haemofiltration. Thus reducing the need for blood transfusion and thereby preventing the complications associated with homologous blood transfusion (Draasima, Hazekamp, Frank, Anes, Schoof, and Huysmans, 1997). Literature suggests that MUF is an effective tool in reducing inflammatory mediators that causes organ dysfunction and undesirable haemodynamic changes (Larustovskii; Ll'in, Abramian, Grigor'iants, Vedernikova, Mikhailova, Samsonova and Shelepova, 1998).

Numerous types of MUF circuits were investigated in a preliminary study during the trial phase and later animal studies were conducted. This included the AVMUF used by Naik, Knight and Elliott (1991). A few methods of performing MUF were selected after feedback was obtained from other hospitals. From these investigations a circuit was selected for the preliminary background study. The results of these investigations and studies led to the design of a unique VAMUF circuit which was used in this study.

Exploration of numerous studies over the past few years from previous publications suggest that the effectiveness of MUF has been established . Therefore too much emphasis was not placed in proving the results of previous trials once again. Instead efforts were concentrated on attempting to find the most efficient and physiological method of performing MUF. ”Dry CPB circuit” trials where performed with each of the different techniques before any elimination could occur and a conclusion was reached.

The preliminary experimental study which explored the different ways of performing MUF led to the design of a technique that mimics the normal physiological pathway of a traditional conventional CPB circuit. In this method of performing MUF blood removed from the right atrium (RA) is haemoconcentrated and re-infused into the aorta through the arterial cannula. This method of performing ultrafiltration after CPB was referred to as Veno-Arterial Modified Ultrafiltration (VAMUF) in relation to the blood flow through the CPB circuit and patient .

A total of sixty patients were included in this study. They were randomised into two groups of thirty each. Each group underwent one of the two selected methods of performing MUF.i.e., the conventional AVMUF technique and the VAMUF technique. The aim of this study was to explore the effectiveness of the VAMUF compared to the AVUMF technique which had a different design. It was hypothesized that VAMUF was a more, physiological and effective technique of performing MUF. It was also a safe technique to be performed on patients undergoing cardiac surgery under CPB.

CHAPTER TWO: LITERATURE REVIEW

2.1 CARDIOPULMONARY BYPASS

2.1.1 Historical aspect of cardiopulmonary bypass

After being inspired by the tragic death of a pregnant woman from a pulmonary embolus, Dr. John Gibbon originated the idea of coupling extracorporeal circulation and oxygenation and surgical repair of the heart. In 1953, he successfully used extracorporeal circulation in a young woman, Celia Bavole, to facilitate open cardiac repair of an atrial septal defect. In 1954 a technique of controlled cross-circulation was used on compatible adults as the pump oxygenator to repair congenital heart defects. Over a period of 16 months, 47 patients were operated on and 28 survived (Lillehei,Varco, Cohen, Warden, Patton, and Moller, 1986).

Lillihei et al. (1986) pioneered the repair of intra-cardiac defects with the luxury of time as the patient's body was provided with nutrient perfusion by an exogenous pump/oxygenator. This led to the development of safer extracorporeal circuits. The inclusion of heat exchangers facilitated core cooling and re-warming of internal organs in a way that surface cooling could not allow pump flow rates to be decreased thereby, prolonging the period of a safe operation. The concept of using hypothermia during cardiac surgery was first demonstrated by Bigelow in 1950 by showing that dogs that cooled to 20^0C could survive for a period of 15-minute on total circulatory arrest (Bigelow, Callaghan and Hopps, 1950). Lewis and Taufic (1953) were the first to apply hypothermia and inflow occlusion for repair of an atrial septal defect in humans (Ungerleider, 1995).

The mechanism of oxygenation has undergone significant evolution since Gibbon's first oxygenator, the rotating film oxygenator. Kirklin, DuShane, Patrick, Donald, Hetzel, Harshbarger and Wood (1955) adopted the stationary film oxygenator that was developed with technical support from IBM. Bubble oxygenators were developed in the

late 1950's and was mass produced by the 1960's. This revolutionized the field of cardiac surgery. Membrane oxygenators which utilized thin sheets of permeable Teflon were developed and this had some advantages over bubble oxygenators. However, the rapid expansion of cardiac surgery in the 1960's required a preassembled, sterile, and disposable oxygenator and the membrane oxygenator was far from ready. The advent of coronary and valve surgery in the 1960's corresponded to the use of mass-produced bubble oxygenators. By the 1970's many centres switched to membrane oxygenators because of its increased safety and fewer complications with longer exposure time. With the advancement of the gas-permeable extra-luminal flow oxygenator fibres, the production of bubble oxygenators had disappeared.

Miniaturization of some of the elements of the CPB circuit has made heart surgery safer and more efficient. The next great advances should be in the modulation of the systemic inflammatory response resulting from CPB. This chapter reviews the basic physiology of CPB, the systemic inflammatory effects of CPB and the strategies employed in the application of CPB (including the use of MUF post CPB).

2.1.2 The effects of CPB

CPB remains a marvel of cardiac surgery, but all marvels are attained at a price. The risk of some sort of injury or another occurs in all patients who undergo CPB. Unfortunately, unlike other marvels, the longer the bypass run, the more serious the degree of injuries are likely to be. Advances in biomedical engineering such as, membrane oxygenators, arterial filters, bubble detectors, level sensors and other innovative products have all contributed to the decrease in incidence of serious injury during CPB.

2.1.2.1 Physiology of CPB

Improvements in technology have reduced the morbidity associated with CPB. Conducting CPB safely in patients requires a comprehensive understanding of the

physiological alterations associated with CPB. These important parameters include: circuit design; haemodilution; choice of prime; choice of cannulae; degree of hypothermia; pharmacological strategies and selected flow rates.

2.1.2.2 Effects of hypothermia during CPB

The aim behind using hypothermia during CPB is to reduce the metabolic rate of tissue and organs. As the temperature is lowered, both basal and functional cellular metabolism is reduced. The rate of adenosine triphosphate (ATP) consumption is therefore decreased. The entire body oxygen demand decreases directly with decreased body temperature. As the temperature of the patient decreases, oxygen consumption becomes independent of the blood flow rate. This is the basis for which minimal pump flow rates necessary to meet metabolic demands can be predicted (Kern, Ungerleider, Reves, Quill, Smith, Baldwin, Croughwell, and Greeley, 1993).

Advantages and disadvantages of hypothermia during CPB

Table 1 represents the advantages of hypothermia during CPB. It shows the effects that hypothermia has on total body oxygen consumption, on the rate of cellular ATP consumption, on the operative field vision, on myocardial warming during aortic cross-clamping, on cerebral protection and on protection of the major organs during low flow states.

Table 2 represents the disadvantages of hypothermia during CPB. It shows the effects of hypothermia on the production of serum catecholamines, regulation of catecholamines receptors, level of circulating insulin, peripheral response to insulin, length of the procedure and on the use of additional devices.

Table 1: Advantages of hypothermia during CPB

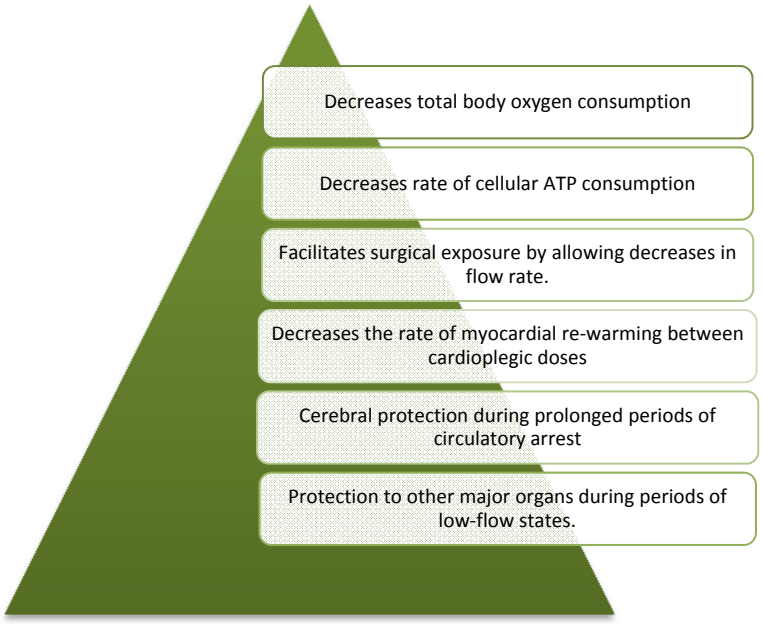
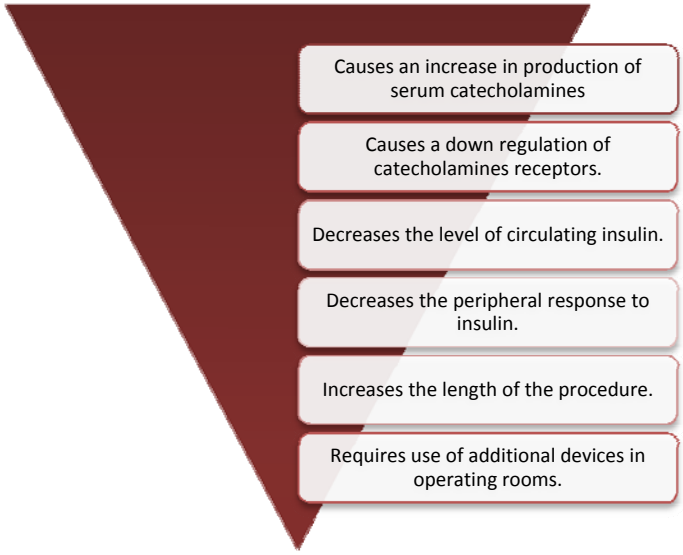


Table 2: Disadvantages of hypothermia during CPB



2.1.2.3 The effects of CPB on infants

Procedures performed on infants and children may require extremes of temperature, haemodilution, and perfusion flow rates. The priming volume of the CPB circuit and its capacity cannot, be proportionately reduced to the size of the patient. This results in sig-

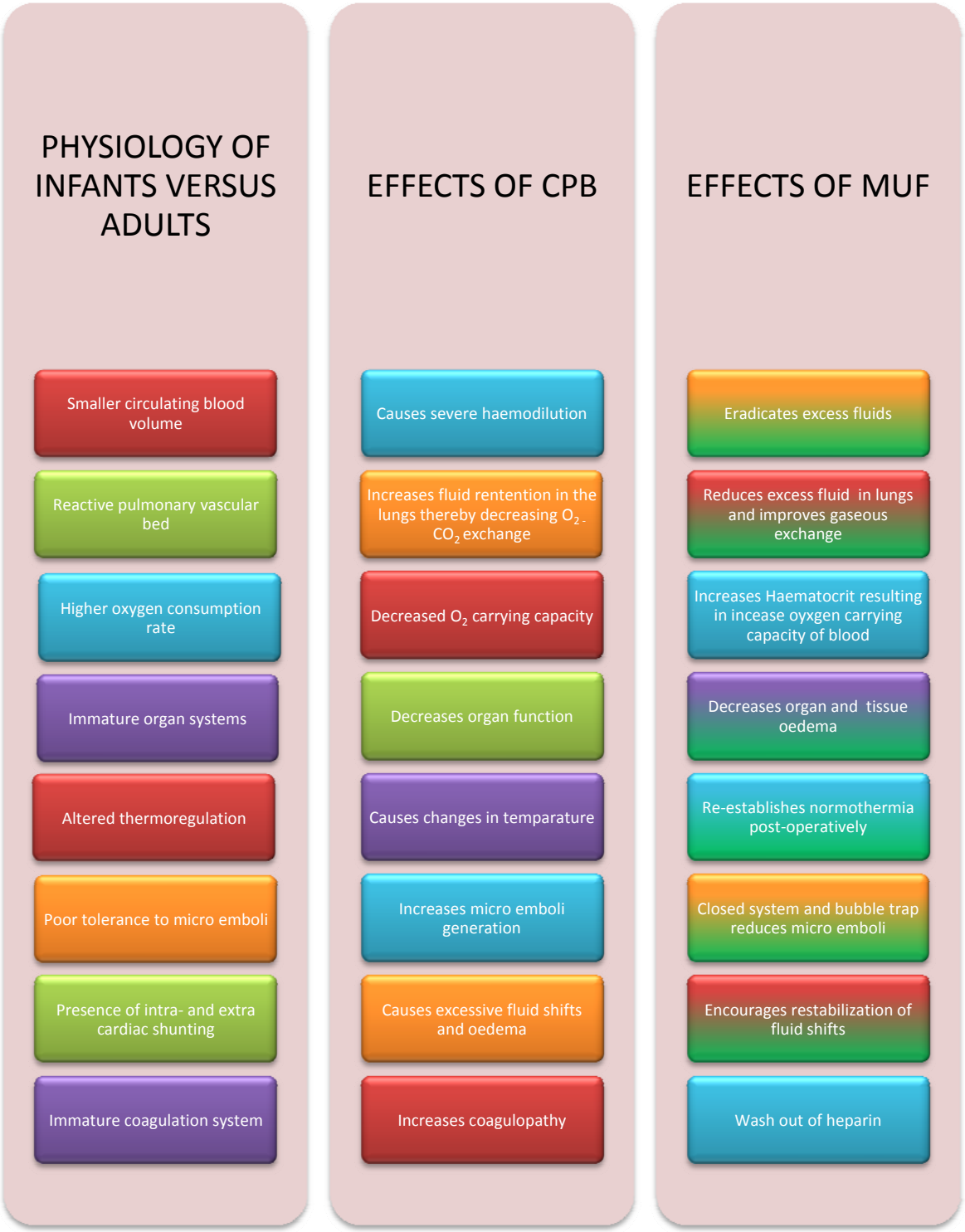
nificant haemodilution in infant and neonate patients. This haemodilution results in a significant decrease in haematocrit, clotting factors and plasma proteins thus, leading to a dilutional coagulopathy. To compound the problem production of vitamin K-dependent clotting factors by the liver is diminished due to the fact that organ systems in neonates and infants are not mature. Neonates and infants require much higher flow rates per body surface area (BSA) to meet metabolic demands. Small children also have impaired thermoregulation that requires significant attention to temperature monitoring.

The lungs are immature at birth and lung development proceeds up to about 8 years of age (Thuribeck and Angus, 1975). The number of alveoli present at birth is approximately one tenth of an adult. The lungs of a neonate are quite fragile and have increased potential for pulmonary oedema and hypertension (McGiffin and Kirklin, 1994). The kidneys of neonates and infants have high vascular resistance with preferential blood flow away from the outer cortex. Sodium re-absorption and excretion, concentrating and diluting mechanisms, and acid-base balance capacity are limited. These characteristics must be taken into account in the management of CPB in infants. Finally, the immune system of the neonate is immature. Complement generation is impaired and neonatal mononuclear cells are dysfunctional (Kirklin and Barratt -Boyes, 1993). These characteristics make bypass surgery in the infant and neonate a more complicating task than in adult surgery and demands greater attention in realizing these obstacles and working to overcome these limitations.

2.1.2.4 The effects of CPB and MUF on infants as compared to adults

Table 3 represents the effects that CPB and MUF have on infant patients as compared to adults. The effects are more serious in infants because of their immature organ systems and infants are relatively smaller in size than adults. This results in smaller circulating blood volumes, more reactive pulmonary vascular bed, higher oxygen consumption rate, altered thermoregulation, poor tolerance to micro emboli and the presence of intra- and extra cardiac shunting.

Table 3: Physiological effects of CPB and MUF on infants versus adults



2.1.2.5 Effects of CPB on myocardial function

Cardiopulmonary bypass was instated with the aim of attempting to repair the heart during cardiac surgery. Unfortunately the heart is also one of the major organs that sustain numerous injuries due to various deleterious effects of CPB. With time, as the complexity of the CPB procedure increases, the need for effective and optimal myocardial protection should increase as well. It is unclear what the ischaemic tolerance of the myocardium is when there is inadequate pulmonary blood flow which results in an increase bronchial collateral flow. This increased blood returned to the left heart can result in insufficient myocardial protection caused by warming the heart and washing out cardioplegia (Hetzer, Warnecke, Wittock, Engel and Borst, 1980).

Pro-grade cardioplegia is delivered through a catheter placed in the aortic root on CPB after the cross-clamp has been applied. Retrograde cardioplegia delivery is mainly used in the adult population (especially in valve cases) and coronary artery bypass grafting where patients have very significant proximal stenosis main stem disease. Blood cardioplegia has proven to be superior to crystalloid cardioplegia, especially for cases where the myocardial ischaemic time is longer than one hour (Corno, Bethencourt, Laks, Haas, Bhuta, Davtyan, Flynn, Drinkwater, Laidig and Chang, 1987).

The use of hypothermia is an important factor for successful myocardial protection in infants (Corno et al., 1987). Electromechanical arrest, ventricular decompression, and hypothermia all work together to decrease myocardial oxygen consumption. Ice slush is applied topically to reduce the metabolism of myocardial tissue. However, it often interferes with the operative procedure and may result in phrenic nerve palsy. It is therefore advised that topical cooling should be used intermittently (Yung, Leung, Chan, Mok, Lee, Chiu, Cheung and Sudhaman, 1993).

Ideally, cardioplegic solutions should have a calcium concentration that is below the serum concentration (Baker, Olinger and Baker, 1991). Despite the potential for excessive calcium influx secondary to hyperkalaemia-induced membrane

depolarization, potassium remains the most widely used cardiac arresting agent in all of cardiac surgery. Magnesium helps to maintain negative resting membrane potential and also inhibits sarcolemmal calcium influx (Kraft, Katholi, Woods and James, 1980). The addition of magnesium to blood cardioplegia results in significantly improved functional recovery (Rebeyka, Diaz, Waddell, Coles and Williams, 1992). Magnesium enrichment of hypocalcaemia cardioplegic solutions can result in near complete functional recovery, but even high dose magnesium supplementation cannot reverse dysfunction in severely stressed hearts that receive normocalcaemic cardioplegia (Kronon, Allen, Hernan, Halldorsson, Rahman, Buckberg, Wang and Ilbawi, 1999).

Intra-myocardial air has also been suggested as a contributing factor for myocardial dysfunction after paediatric cardiac surgery despite aggressive "de-airing" maneuvers before removing the aortic cross-clamp (Bell, Rimar and Barash, 1989). Significant improvements were demonstrated in patients with intramyocardial air after the administration of phenylephrine or reperfusing the heart with high pump flow rates and high perfusion pressures on CPB (Greeley, Kern, Ungerleider and Kisslo, 1990).

2.1.2.6 Effects of CPB on the endocrine system

The endocrine system is defined as the ductless glands that secrete hormones directly into the bloodstream. They cause target organs to react in a manner that affects many of the body's functions. The endocrine glands also affect secretion of each other. The endocrine system includes the adrenal glands, thyroid, parathyroid, the pituitary, the pancreas, the gonads and the pineal gland. The supra-optic and para-ventricular nuclei of the hypothalamus in conjunction with the pituitary gland secretes vasopressin (also known as antidiuretic hormone) that decreases urine output.

The adrenal glands are bilateral and each one is found on top of each kidney. The gland consists of the medulla and the cortex. The adrenal medulla secretes epinephrine and norepinephrine (catecholamines). There are tremendous increases in native catecholamines during CPB, particularly epinephrine and norepinephrine. These

catecholamines increase blood pressure by vasoconstriction and are increased during bypass after an initial dilutional effect This release is due to surgical stress, peripheral vasoconstriction, changes in blood flow dynamics and changes in pH (Lodge, Undar, Daggett, Runge, Calhoon and Ungerleider, 1997; Malm, Manger, Sullivan, Papper and Nahas, 1966). These elevations of catecholamines extend into the postoperative period (Engelman, Haag, Lemeshow, Angelo and Rousou, 1983). The initial increases in catecholamine levels fall considerably upon reperfusion of the lungs resulting from the uptake and metabolism of the catecholamines in the lungs. There is significant accumulation of norepinephrine caused by hypothermia occurring during the x-clamping phase of CPB. Hypothermia increases serum catecholamine levels not only by increasing production, but also by the down-regulation of catecholamine receptors and decreasing the metabolism. Catecholamine levels fall rapidly at normothermia once bypass is terminated. Anaesthesia has a significant influence on the surge of catecholamines associated with bypass and cardiac surgery. High dose narcotic induction and maintenance can result in reduction of catecholamine and reduce postoperative complications (Anand and Hickey, 1992). However, there is a rise in serum cortisol after induction of anaesthesia and surgery. Following the onset of CPB, the cortisol levels fall secondary to haemodilution. After CPB, the level again begins to rise and this continues for 24 hours, after which it gradually falls to normal. The effect of ultrafiltration on the levels of glucocorticoids is not known.

The thyroid gland releases the thyroid hormones. Thyroid stimulating hormone (TSH) governs the release of triiodothyronine (T3) and tetraiodothyronine (T4). These hormones are associated with an increased heart rate, contractility and cardiac output. Thyroid hormone also regulates agonist sensitivity of beta-adrenergic receptors. Other functions such as body temperature and metabolic functions are also affected by these hormones. Haemodilution causes thyroid hormones to decrease during the CPB period and into the first several days after surgery (Mitchell, Pollock, Jamieson, Donaghey, Paton and Logan, 1992; Chu, Huang, Hsu, Wang and Wang, 1991). Lower levels are associated with poor patient outcome. Triiodothyronine is reduced in response to CPB. Triiodothyronine is used by some open heart teams for patients who cannot be weaned

from bypass after the usual measures. It is administered after going back on bypass and continued in the recovery phase if successful.

Insulin is a hormone released by the pancreas in response to increased blood glucose levels. Insulin regulates the metabolism of glucose and other processes necessary for metabolism of fats, carbohydrates and proteins. Insulin promotes the transport of glucose into the cells. Cardiopulmonary bypass and hypothermia causes a decrease in the level of insulin. Hypothermic bypass also causes a decrease in insulin response which results in a rise in serum glucose levels. Hyperglycaemia usually continues for an hour or two after bypass is terminated. The level of insulin and insulin response increases during the re-warming phase after reperfusion has initiated (Ratcliffe, Wyse, Hunter, Alberti and Elliott, 1988). Glucagon is also released as a general stress response during CPB and peaks at about 6 hours post operatively (Kirklin and Barratt - Boyes, 1993).

2.1.2.7 The effects of CPB on renal function

Renal dysfunction after CPB is a relatively common occurrence and is a major cause of morbidity and mortality after CPB. Ordinarily large volumes of blood are filtered by the kidneys although adequate perfusion of the kidneys on bypass is subject to many factors. Therefore, the volume of the blood filtered may be decreased as a result of low arterial systemic blood pressure or reduced pump flows. Ordinarily, approximately twenty five percent of one's cardiac output is directed to the kidneys. Numerous factors affect blood flow through the kidneys, namely, composition of the pump prime, the sympathetic nervous system and hormones (angiotensin, bradykinin, epinephrine and prostaglandins).

Surgical stress results in decreased renal blood flow and glomerular filtration rate secondary to the central nervous system influences. There is also an increase in vasopressin release that results in fluid accumulation. Cortical blood flow within the kidney is decreased in favour of medulla blood flow. This regulation of the removal of

water and solutes from the body assists in the control of blood pressure. This elevation in vasopressin may last for 48 to 72 hours after surgery (Philbin, Levine, Emerson, Coggins, Buckley and Austen, 1979).

Hypothermia has been shown to decrease renal perfusion (Lodge, et al., 1997; Utley, Wachtel, Cain, Spaw, Collins and Stephens, 1981). The duration of CPB is a risk factor for injury as is preoperative renal dysfunction and heart failure. Other factors that contribute to renal failure are the profuse use of homologous blood, multiple exposures to angiographic dyes and the prolonged use of the intra-aortic balloon pump. The effects of changes to the endocrine system as a result of haemodilution of the bypass circuit may also result in decreased renal function.

Testing the level of serum creatinine is an excellent indicator of renal function. Normal serum creatinine is 0.8 - 1.4 mg/dl in adult males (values are slightly higher in males due to larger muscle mass) and 0.6 - 1.1 mg/d in adult females. Higher levels indicate possible renal failure and the possibility of renal failure post-op. Haemodilution from the pump prime reduces the viscosity of the blood and this causes increased renal blood flow and greater urine output with its beneficial effects. Renal function generally returns to normal as cardiac function and systemic perfusion improve in the first 24 to 48 hours of post bypass.

2.1.2.8 The effects of CPB on pulmonary function

During CPB the lung receives a portion of the blood from the right atrium (RA) and right ventricle (RV) that was not completely drained out by the venous cannula. This blood enters the lungs via the pulmonary arteries and from the bronchial arteries that supply blood to nourish the lung tissues.

Most of the blood from the lungs returns to the heart through the pulmonary veins. This makes left heart venting necessary during CPB. Bypassing the lungs during cross-clamping initiates the creation of abnormal physiological changes. Damage to the lungs

is the most common serious injury of CPB considering that the thickness of the respiratory membrane is only approximately six microns. The duration of the pump run is directly proportional to the extent of pulmonary dysfunction.

Cardiopulmonary bypass affects both the parenchymal (functional part an organ) and the vascular component-stroma (structural tissue of an organ) of the lungs. Parenchymal effects of CPB are reflected by alterations in pulmonary compliance most commonly related to an increase in lung water. The impact of this on the patient is a requirement for increased ventilator support and a diminished ability of the lungs to perform their function in gas exchange. Vascular effects are manifested by changes in pulmonary vascular resistance (PVR), which in turn affects the function of the right ventricle (Jaggers, Neal, Smith, Ungerleider and Lawson, 1999).

The lung is an important source and target of the inflammatory response to CPB. This is manifested as decreased functional residual capacity, compliance and gas exchange as well as increased PVR and pulmonary artery pressure (Meliones et al., 1995). During CPB after cross-clamping, the lungs undergo a significant decrease in antegrade blood flow via the pulmonary artery. During this period the lungs receive minimal blood flow from their bronchial supply. This incidence of ischaemia, in addition to the inflammatory effect of CPB may result in significant clinical pulmonary dysfunction (Chai, Williamson, Lodge, Daggett, Scarborough, Meliones, Cheifetz, Jaggers and Ungerleider, 1999). Lungs are subjected to injury from the blood mediated inflammatory response as a result of contact activation caused by the bypass circuit. Complement activation of C3a and C5a leads to activation of leukocytes. This may cause leukoembolization to occur in the lungs along with the release of oxygen free radicals and proteolytic enzymes by the neutrophils. Both the inflammatory and ischaemic factors contribute to the damage of pulmonary endothelium which leads to increases in PVR and pulmonary artery (PA) pressures after CPB (Chai et al., 1999; Kirshbom, Tsui, DiBernardo, Meliones, Schwinn, Ungerleider and Gaynor, 1995; Kirshbom, Page, Jacobs, Tsui, Bello, Ungerleider, Schwinn and Gaynor, 1997).

Pump lung (congested lungs with intra-alveolar oedema, interstitial oedema and atelectasis) is a form of acute respiratory failure. This is caused by an increase in vascular permeability caused by capillary leak in the lungs as a result of complement activation, neutrophil arachidonic acid metabolites and haemodilution. The reduction in colloid osmotic pressure (COP), due to haemodilution and an increase in hydrostatic pressure, contributes to interstitial pulmonary oedema (fluid accumulation in the lungs). Steroids administered peri-operatively may reduce the inflammatory response to CPB. Steroids given before exposure to CPB reduce lung water accumulation, improve pulmonary compliance after CPB and limit pulmonary hypertension after CPB (Lodge, Chai, Daggett, Ungerleider and Jaggers, 1999). Modified ultrafiltration after CPB seems to improve pulmonary function immediately, compared to patients who do not undergo ultrafiltration (Meliones et al., 1995; Koutlas, Gaynor, Nicolson, Steven, Wernovsky and Spray, 1997; Ungerleider, 1998).

2.1.2.9 The effects of CPB on cerebral function

The incidence of injury to the brain due to the effects of CPB is very real and has been illustrated in many studies (Kirklin and Barratt -Boyes, 1993; Ferry, 1987; Fessatidis, Thomas, Shore, Sedgwick, Hunt and Weller, 1993). This risk of neurological impairment seems to consist of three components: (1) Pre-existing risk in patients with congenital defects and smokers (Limperopoulos, Majnemer, Shevell, Rohlicek, Tchervenkov and Gottesman, 1999); (2) Injury sustained due to exposure to prime and foreign surfaces and (3) Injury induced by CPB and the various CPB strategies. It is often difficult to ascertain which of these components play the most prominent role in neurologic injury that is manifested in patients who undergo CPB, or whether it is a combination of all three.

During CPB, microembolic events may occur and this can contribute to end-organ injury (Clark, Dietz and Miller, 1976; Turley, Roizen, Vlahakes, Graham and Ebert, 1980). These injuries are often minimal and usually cause no lasting problems. However, in a small percentage of the cases, serious permanent damage and cerebrovascular

accident (stroke) does occur as a result of an embolic event. The embolus resulting from air, blood clot, fat, atheroma, calcific debris or circuit debris results in the lack of oxygen delivery to a localized area of the brain. The use of membrane oxygenators, arterial filters, and adequate heparinization (ACT >480 sec) for CPB decreases the number of microemboli produced and may reduce the incidence of embolic events during CPB (Young, Kisker and Doty, 1978; Blauth, Smith, Newman, Arnold, Siddons, Harrison, Treasure, Klinger and Taylor, 1989).

Air embolism during CPB is caused by nitrogen which does not dissolve into the prime. This is the primary reason for flushing the bypass circuit with highly dissolvable CO_2 gas pre-operatively in order to displace and flush out the nitrogen from the circuit. Indicators of air embolisms include seizures, cardiac arrhythmias and ventricular dysfunction. Embolization due to cannulation and cross-clamping of the aorta is thought to be the most common cause of embolic neurological damage.

The effects of a stroke may cause paralysis, loss of vocal ability, the inability to understand language and sometimes death. If the injury is not serious, cerebral function may return to normal after a few days probably due to reduction in brain oedema or disintegration of the embolus. Although cerebral function may return to normal after a few days if the injury is not serious, air embolism remains to be an important factor contributing to postoperative neurologic dysfunction. Table 4 outlines the steps taken to ensure successful reduction in embolism formation or migration of an embolism from the CPB circuit to the patient.

Table 4: Precautions to eliminate possible sources of embolism during CPB

CO_2 Flushing	•Displaces nitrogen adhering to the CPB circuit
Pre-bypass filters	•Filters the circuit prime to reduce pump debris
Arterial filters	•Traps micro and macro emboli from entering the patient
In-line gas filter	•Prevents any foreign materials entering the oxygenator
10-12^{0}C Temperature gradient	•Prevents air from coming out of the solution
Level sensors	•Prevents air from the reservoir from entering the circuit
Bubble detectors	•Stops the pump before air reaches the patient
LV venting during the removal of cross-clamp	•Prevents air from the LA and LV from entering the aorta
Proper venous cannulation	•Reduces air entering the venous line
Alert perfusionist	• Should be continuously on guard

2.1.2.10 Systemic inflammatory response to CPB

The complement system involves complex proteins in the blood that bind with antibodies against infection and foreign bodies. Systemic inflammatory responses that occur due to CPB involve a complex interaction of systems and cellular elements in the body. The biochemical events and pathways are a complex interaction with regulatory

and counter-regulatory effects. The complement proteins react sequentially and mediate a number of the immune responses. Inappropriate activation of the complement system can result in injury to the patient.

Inflammatory response

Numerous components of the body become stimulated due to contact activation during CPB. Blood components include platelet activation, neutrophil activation and mast cell activation. Systems include the complement system, kinin system, fibrinolytic system and the coagulation cascade (extrinsic and intrinsic).

Factors that contribute to the inflammation during CPB

The inflammatory response that occurs during CPB is commonly due to exposure of the blood to foreign surfaces of the CPB circuit. Another contributing factor is the hypovolaemic shock that occurs during the initiation of CPB as blood is drained quickly from the patient into the bypass circuit. Severe hypotension and tissue ischaemia that occurs during bypass at certain periods are another factor. Reperfusion injury may occur to varying degrees during removal of the aortic cross clamp during which stage blood enters the coronaries after a period of anoxia. Blood flow changes from pulsatile to non-pulsatile blood flow and this enhances stimulation of an inflammatory response. Anaemia due to haemodilution which leads to homologous blood transfusion and administration of homologous blood products is another major cause of complement activation. Heparin and protamine administration also stimulates an inflammatory response.

One of the initial responses to CPB is complement activation which composes of more than 30 different proteins (Sonntag, Dahnert, Stiller, Hetzer and Lange, 1998). The alternate pathway of activation results in the formation of important anaphylotoxins C3a and C5a (Kirklin and Baratt-Boyes, 1993). These chemotactic agents which are important for neutrophils and inflammatory mediators result in the production of other

cytokines and activation of cellular elements such as macrophages and platelets (Moat, Shore and Evans 1993). Neutrophil activation and the neutrophil endothelial cell interaction result in direct tissue injury and elaboration of other cytokines and probably play a role in the ischaemia-reperfusion injury which is associated with pulmonary and neurologic injury (Seghaye, Duchateau, Grabitz, Nitsch, Marcus, Messmer and von Bernuth, 1994).

Complement activation and cytokines

Complement activation results in the following types of cytokines: monocytes, macrophages and endothelial cells. These cytokines mediate many of the inflammatory reactions, some regulatory (TNF, IL-1, IL-6, IL-8 and LPS) and some counter-regulatory (IL- 4 and IL-10) (Finn, Naik, Klein, Levinsky, Strobel and Elliott, 1993). These cytokines have been associated with CPB and increases with bypass duration (Steinberg, Kapelanski, Olson and Weiler, 1993).

Responses to the inflammatory insult

The responses to the inflammatory insult are characterized post bypass by pulmonary hypertension, acute respiratory distress syndrome (ARDS), total body oedema, coagulation abnormalities, haemodynamic instability and myocardial dysfunction. These adverse anomalies results in prolonged inotropic support after bypass, prolonged post operative ventilation time, renal dysfunction, bleeding and later thrombosis, inability to close the chest in the operating room and the potential need for mechanical support, e.g., extracorporeal membrane oxygenation (ECMO).

Therapeutic interventions

Therapeutic approaches to reduce inflammatory responses during CPB include:

1) Reducing the size of the CPB circuit allows reduction in priming volumes.

2) Some adopt the use of heparin-bonded or physio-coated circuits to reduce contact activation (Lorusso, Cicco, Totaro, and Gelsomino, 2009)
3) Pre-bypass filters aid in eradicating micro-emboli and debris from the CPB circuit (Kaza et al, 2003)
4) Adopting the use of anticytokines or anti-adhesion molecule therapy (Grunenfelder, 2000).
5) The use of anti-inflammatory agents added to the bypass circuit and patient.
6) Leukocyte depleting filters trap activated leukocytes during bypass.
7) Pulsatile flows mimic the patient's normal blood flow dynamics, reducing complement activation (John and Lee, 2008).
8) The use of CUF during re-warming eliminates some of the circulation inflammatory mediators (Berdat et al, 2004).
9) MUF reduces circulating cytokines post CPB and reduces the need for homologous blood transfusion (Li et al, 2004).
10) Mini bypass eliminates blood air interface thereby reducing the inflammation that occurs using a conventional bypass circuit.

Corticosteroids affect the inflammatory process by reducing complement activation decreasing complement-mediated neutrophil adhesion and de-granulation and acting as inhibitors of some cytokine release and promoters of others. They decrease the production of acute phase reactants and decrease production of antibody. Steroids that are given several hours before exposure to CPB, produce a more significant reduction in the inflammatory response than when steroids are given in the pump prime or not at all (Lodge et al., 1999).

2.1.2.11 The effects of CPB on the hepatic system

The liver which is the largest and complex organ of the body contains about 13% of the total blood volume. The hepatic artery supplies oxygenated blood from the heart while the hepatic portal vein supplies nutrient filled blood from the stomach and the intestines. Among other functions the liver processes glucose, proteins and fats.

Studies at the Milton Hershey Medical Centre have shown that during bypass, hepatic oxygen consumption is maintained if pump flows are at least 2.2 l/kg/min (Flaim, Minteer, Clark and Zelis, 1979). Liver enzymes are often elevated post bypass, indicating possible hepatic injury. As with other organs longer bypass times are associated with increased injuries. Some patients become jaundiced after surgery. This may be the result of hepatic injury, excessive bilirubin due to blood transfusions or blood trauma (Mastoraki, Karatzis, Mastoraki, Kriaras, Sfirakis and Geroulanos, 2007). Jaundice is usually self-limiting and usually clears in a week.

2.1.2.12 Haematological effects of CPB

When blood is exposed to the CPB circuit and systemic heparinization is used, changes are caused in the blood and its coagulation ability (Kirklin and Barratt-Boyes, 1993). The presence of plasma free hemoglobin in the patient post-operatively indicates that the red blood cells were damaged by bypass (Cheung, Cruz-Shiavone, Meng, Pochettino, Augoustides, Bavaria and Ochroch, 2007). Dilution with the priming solution is another major factor affecting the blood viscosity and oxygen carrying capacity and coagulation.

Post-operative haemorrhage is a common complication of cardiac surgery causing patients to return to the operating room for post-operative bleeding that needs re-exploration. Patients with pre-existing diseases that compromise coagulation or those on certain medicines such as aspirin and plavix are especially at risk during cardiac surgery (Van der Linden, Lindvall and Sartipy, 2005). Liver disease, uraemia and other illnesses can leave the patient vulnerable to coagulopathy (Shen and Frenkel, 2004). Accurate reversal of the heparin given for CPB is important to prevent bleeding. Extra protamine is often given if there is any doubt of the adequacy of heparin reversal.

Haemodilution on bypass or the interaction of the blood with air and foreign materials of the CPB circuit may be the result of platelet dysfunction. Frequent and incorrect use of cell saver blood and the use of intraoperative drugs may also be precipitating factors (Harker, Malpass, Branson, Hessel and Slichter, 1980). Critical thrombocytopenia is

defined as a platelet count below 50,000 per microlitre and is treated with administration of platelets. Platelet counts greater than 100,000 per microlitre post CPB do not require treatment.

Disseminated intravascular coagulation (DIC) rarely occurs post bypass. In this serious problem the coagulation factors of the patient become inappropriately activated and bleeding occurs systemically. Fibrinolysis occurs as a result of contact with the pump circuit (Kucuk, Kwaan, Frederickson, Wade and Green, 1986). Heparin inhibits fibrinolysis and maintenance of appropriate activated clotting times is necessary to prevent significant complications.

2.1.3 Normal ranges of parameters measured during this study

Cardiopulmonary bypass has an adverse effect on electrolytes, metabolites, haemodynamics, blood pressure, blood proteins and release of cardiac markers. The following parameters were considered as important indicators for the efficiency of MUF and were therefore measured.

a) Sodium

The normal range for serum sodium (Na^+) in adults is 135 - 148 mmol/l with an optimal reading of 140.5 mmol/l. Sodium is the most abundant cation in blood and its chief base, chloride. It functions in the body to maintain osmotic pressure, acid-base balance and to transmit nerve impulses. A very low Na^+ value in patients can lead to seizure and neurological problems.

b) Potassium

The normal range for serum potassium (K^+) is 3.5 - 5.5 mmol/l with an optimal adult reading of 4.5 mmol/l. Potassium is the major intracellular cation and is essential for many body functions including muscle and nerve activity. Hypokalaemia (very low

values) of K^+ leads to cardiac arrhythmias. Hyperkalaemia (very high levels) can be fatal and is used in cardioplegia to cause cardiac arrest it is also responsible for palpitations and muscle weakness.

c) Calcium

The normal adult range for serum calcium (Ca^+) is 1.13 - 1.32 mmol/l or 8.5 and 10.5 mg/dL (milligrams of calcium per decilitre of blood) (normally slightly higher in children). Calcium is involved in bone metabolism, protein absorption, fat transfer, muscular contraction, transmission of nerve impulses, blood clotting and cardiac function. Calcium ions strengthen cardiac contractions while a deficiency of Ca^+ results in a cardiac flaccidity similar to the effects of Hyperkalaemia.

d) Serum Phosphate

About 85% of the body's phosphate is located in the skeletal system where it combines with calcium to give bones their hardness. The remaining amount (15%) exists in the cells where it plays an important role in the formation of key nucleic acids, such as DNA, as well as in the process by which the body turns food into energy (metabolism). The normal serum phosphate range in adults is 0.81 - 1.45 mmol/l with an optimal reading of 1.13. mmol/l. The normal range in children is 0.97 – 1.94 mmol/l with an optimal range of 1.45 mmol/l. Hypophosphatemia symptoms include muscle weakness, tingling sensations, tremors and bone weakness. Hypophosphatemia may also result in confusion and memory loss, seizures and coma. Hyperphosphatemia is generally asymptomatic. However, it can occur in conjunction with hypocalcemia. The symptoms of hyperphosphatemia are numbness and tingling in the extemities, muscle cramps, spasms, depression, memory loss and convulsions.

e) Serum Magnesium

The normal range for serum magnesium (Mg) is 0.75 - 1.0 mmol/l. Magnesium is an

important electrolyte needed for proper muscle, nerve and enzyme functions. It is also an important co-enzyme in the metabolism of both carbohydrates and proteins and the energy is used to move other electrolytes (potassium and sodium) into and out of cells.

f) Heart rate

The average normal range of heart rate in adults is 72 beats per minute and 50 - 180 beats per minute in infants and paediatric patients.

g) Systolic pressure

The normal systolic blood pressure in adults ranges from 100 - 120 millimetres mercury (mmHg). Infants and paediatric patients have lower systolic pressures.

h) Diastolic pressure

The normal diastolic blood pressure in an adult ranges from 60 - 80 mmHg, with neonates, infants and paediatrics having lower diastolic blood pressures.

i) Mean blood pressure

The normal range mean for arterial BP is 60 - 80 mmHg in adults with infants and paediatrics having lower mean pressures. Mean arterial BP is an indication of the pressure exerted by the blood against the walls of the blood vessels, especially the arteries. It varies with the strength of ventricular contraction, the elasticity of the arterial walls, the volume and viscosity of the blood and a person's health, age and physical condition.

j) Mean central venous pressure (CVP)

The normal CVP range is 8 - 12 centimetres of water (cm H_20). Central venous pressure

refers to the pressure of the blood within the superior and inferior vena cava. This is depressed in circulatory shock and deficiencies of circulating blood volume and increased with cardiac failure and congestion of circulation. Conversely, a decrease in CVP without drug intervention could possibly suggest an improvement in ventricular emptying and this could be related to cardiac function.

k) Oxygen saturation (SaO_2)

In medicine, SaO_2 measures the percentage of haemoglobin binding sites in the bloodstream occupied by oxygen. Oxygen saturation of blood is expressed as a percentage. The normal value for SaO_2 in an arterial blood sample is 97% and 75% for a venous sample is. The normal value for venous blood gas is 40 mmHg. An arterial oxygen saturation value below 90% causes hypoxemia due to low SaO_2.

l) Haematocrit (HCT)

Haematocrit is expressed as a percentage of blood and the normal range for an adult female is 37 - 47% with an optimal of 42%. The normal range for an adult male is 40 - 54% with an optimal reading of 47%. The normal range for a newborn is 42 - 62% with an optimal reading of 56%.

m) Haemoglobin (Hb)

Haemoglobin in a normal adult female ranges from 12 - 16 g/dl with an optimal reading of 14 g/dl. The normal adult male ranges from 14 - 18 g/dl with an optimal reading of 16 g/dl. The normal newborn ranges from 14 - 20 g/dl with an optimal reading of 17 g/dl.

n) Red blood cell count (RBC)

The normal RBC count in adult females range from 3.9 - 5.2 M/µl with an optimal reading of 4.55 M/µl. The normal adult male ranges from 4.2 - 5.6 M/µl with an optimal

reading of 4.9 M/µl. Lower ranges are found in children, newborns and infants.

o) White blood cell count (WBC)

The normal range for WBC in adults is 3.8 - 10.8 K/µl with an optimal reading of 7.3 K/µl.

p) Serum albumin concentration (S-Alb)

The normal range for S-Alb circulating in blood is between 32 - 50 g/l with an optimal reading of 41 g/l. Albumin is a major constituent of serum protein (usually over 50%). High levels are seen in liver disease, shock, dehydration or multiple myeloma. Lower levels are seen in poor diets, diarrhoea, fever, infection, liver disease, inadequate iron intake, third-degree burns and oedemas or hypocalcaemia.

q) Serum blood urea nitrogen (BUN)

The BUN test measures the level of urea nitrogen in a sample of the patient's blood. Urea is a substance that is formed in the liver when the body breaks down protein. Urea then circulates in the blood in the form of urea nitrogen. The normal range for BUN in adults is 2.5 - 8.9 mmol/l with an optimal range of 5.7mmol/l. Abnormally low BUN may indicate over-hydration, malnutrition, celiac disease, liver damage or disease or use of corticosteroids. Abnormally high BUN may indicate kidney disease or failure, blockage of the urinary tract by a kidney stone or tumour, a heart attack or congestive heart failure, dehydration, fever, shock, or bleeding in the digestive tract. A BUN level higher than 100 mg/dl points could be associated with severe kidney damage.

r) Serum creatinine

Creatinine is a break-down product of creatinine phosphate in muscle and it is usually produced at a fairly constant rate by the body (depending on muscle mass). Chemically,

creatinine is a spontaneously formed cyclic derivative of creatine. The normal range for serum creatinine in an adult is 62 - 124 µmol/l with an optimal reading of 88.4 µmol/l. Low levels are sometimes seen in kidney damage, protein starvation, liver disease or pregnancy. Elevated levels are sometimes seen in kidney disease due to the kidney's function of excreting creatinine. It may be due to muscle degeneration and some drugs involved in impairment of kidney function.

s) Serum uric acid

Serum uric acid is the final oxidation (breakdown) product of purine metabolism and is excreted in urine. The normal range of serum uric acid in an adult female is 147 - 442 µmmol/l with an optimal reading of 295 µmmol/l and the normal range in an adult male is 206 - 442 µmmol/l with an optimal reading of 325 µmmol/l. High levels of serum uric acid are noted in gout, infections, kidney disease, alcoholism, high protein diets and with toxemia in pregnancy. Low levels may be indicative of kidney disease, malabsorption, poor diet, liver damage or an overly acid kidney.

t) Creatinine Kinase (CK)

Creatine kinase is also known as creatine phosphokinase (CPK). The normal range for CPK is 25 - 200 µ/l in adults and 32 - 150 µ/l in paediatrics. The levels rise 4 to 8 hours after an acute MI, peaking at 16 to 30 hours and returning to baseline within 4 days. Creatine kinase catalyzes the conversion of creatine and consumes ATP to create phosphocreatine and adenosine diphospate (ADP) (McLeish and Kenyon, 2005). In tissues that consume ATP rapidly, especially skeletal muscle, but also brain and smooth muscle, phosphocreatine serves as an energy reservoir for the rapid regeneration of ATP. Thus, creatine kinase is an important enzyme in such tissues. Clinically, CK is assayed in blood tests as a marker of myocardial infarction (MI) (heart attack), rhabdomyolysis (severe muscle breakdown), muscular dystrophy and in acute renal failure.

u) Percentage Creatinine kinase myocardial band (CK-MB)

Cardiac markers are tests used to evaluate heart function. They are often discussed in the context of myocardial infarction, but other conditions can lead to an elevation in cardiac marker level. Most of the early markers identified were enzymes and as a result, the term "cardiac enzymes" is sometimes used. Creatinine kinase myocardial band tests are relatively specific when skeletal muscle damage is not present. The approximate peak period is 10-24 hours after infarct. Creatinine kinase myocardial band resides in the cytosol and facilitates high energy phosphates into and out of mitochondria. It is distributed in a large number of tissues as well as in the skeletal muscle. Since it has a short duration, it cannot be used for late diagnosis of acute MI but can be used to suggest infarct extension if levels rise again. This usually goes back to normal in 2-3 days. The normal value for CK-MB is < 12 iu/l if total CK is < 400 iu/l and < 3.5% of total CK if total CK is > 400 iu/l.

v) Serum Lactate

Lactate is found predominately in blood serum. The level of serum lactate gives an indication of tissue perfusion. The results are interpreted conversely i.e., a higher serum lactate reading is interpreted as decreased tissue perfusion and a low serum lactate level suggests increased or adequate tissue perfusion. The normal range for serum lactate is 1.40 – 2.8 mmol/l.

2.2 BLOOD CONSERVATION DURING CPB

2.2.1 Introduction

In general, surgical procedures are inevitably associated with bleeding and blood loss. The degree of blood loss can vary widely between different surgical procedures and is dependent on surgical as well as non-surgical factors (Porte and Leebeek, 2002). Risk

factors associated with increased peri-operative bleeding in patients undergoing cardiac operations are well known. Although the majority of operations can be performed with no or minimal use of blood products, procedures such as heart-lung or double-lung transplantation, aortic dissection repair, insertion of left ventricular assist devices (LVADs) and, of course, reoperations have all been associated with haemostatic problems. Prolonged bypass times and hypothermic circulatory arrest in certain of these patient populations compound the problem (Smith, 1998).

Peri-operative bleeding and the need for blood transfusions is generally associated with increased morbidity, mortality and costs. This is further compounded by the continued concern for the risk of transmitting transfusion-mediated infections. These are the major reasons for stimulating interest in strategies that can be adopted in order to reduce peri-operative blood loss (Vanvakas, 2002). Ideally the priority of any blood-conservation program should be to firstly minimize bleeding and secondly to minimize transfusion requirements (Smith, 1998).

2.2.2 History of blood transfusions

The re-infusion of shed blood during surgical procedures was first reported 160 years ago (Blundell, 1818). Public awareness regarding the need for blood transfusions and the banking of blood developed around the time of World War II. Right until the year 1940, large quantities of blood were not readily available for reinfusion into patients that were bleeding excessively. Between the wars there were over 1500 reports of autologous blood transfusions being used in ectopic pregnancy alone (Wilson and Taswell, 1968). Under the impetus of World War II a large network of blood banks became established and homologous transfusion became the method of choice.

The quantity of donor blood and blood products needed for individual open-heart procedures has declined over the years with the introduction of oxygenators requiring reduced priming volumes and the adoption of haemodilution techniques. In the mid 1960's the average donor blood usage for each operation in most units was in the

region of 15 units whereas in 1985 it was reported as 4 units (Wheeldon and Bethune 1990). Similar requirements were reported in a previous publication (MacDonald, Hutchinson, Herring, McAfee and Briseno, 1982). However, with time due to more advanced diagnostic procedures and early diagnosis of diseases there has been a steady increase in the number of open-heart operations with even more rapid expansion over the past few years.

The result is that the overall demand for blood for open-heart surgery has increased dramatically. This has prompted those involved in cardiac surgery to take a fresh look at existing blood conservation techniques in order to reduce the need for homologous blood and the deleterious effects associated with it, as homologous transfusion is associated with a number of potential hazards.

2.2.3 Risks associated with homologous blood transfusion

Numerous complications are associated with allogenic blood transfusion. Some of these complications are defined and can be quantified, such as the problem of rising cost or the risk of viral infection. But some of the problems are not well defined and it is only outcome data that point to allogenic blood transfusion contributing to patient mortality and morbidity (Cross, 2001).

Risks of infection following a blood transfusion have fallen with the advent of improved screening techniques and with the recent introduction of polymerized chain reaction (PCR) techniques which identify the nucleic acids of viruses. The chances of contracting human immunodeificiency virus (HIV) or hepatitis C is now approximately 1:1000 000 units transfused. Bacterial contamination is slightly more common, possibly 2:1000 000 units transfused. Transfusion mediated immunomodulation can be demonstrated in all patients receiving a blood transfusion and therefore, the rate of post-operative infection increases with exposure to allogenic blood. It has long been suspected that there is an association between cancer recurrence and allogenic blood transfusion (Goodnough, Brecher, Kanter and Aubuchon, 1999).

Data suggesting that allogenic blood transfusion may contribute to altered peri-operative morbidity has started to become available only over the last few years. Two important studies published during the last few years have suggested that a restrictive strategy of red cell transfusion is at least as effective as, and possibly superior, to a liberal transfusion policy (Hebert, Wells, Blajchman, Marshall, Martin, Pagliarello, Tweeddale, Schweitzer and Yetisir, 1999). In the intensive care setting, a large multicentre study showed that the 30 day mortality of younger patients (< 55 years) and less acutely ill patients (APACHE II score < 20) could be reduced from 13.0% to 5.7% and from 16.1% to 8.7% respectively with the use of a restrictive transfusion policy (Agarwal, 2007).

In the cardiac surgical setting, the cardiac surgery database has been analyzed, dividing patients into three groups depending upon the haematocrit (Hct) on admission to the intensive care unit following coronary artery bypass grafting (CABG) surgery (Hct $\leq$ 24%, 25 – 33% or > 33%). The three groups were assumed to have undergone a restrictive, a moderate and a liberal intra-operative transfusion strategy. Peri-operative myocardial infarction rate decreased significantly with a restrictive intra-operative transfusion strategy (8.3%, 5.5%, and 3.6%, respectively). Although this study was unable to prove whether it was the high Hct with its associated increased viscosity or the use of allergenic blood that gave rise to this increased complication. Clearly all is not well with allogenic blood transfusion (Spiess, Ley, Body, Lawrence, Siegel, Stover, Maddi, D'Ambra, Jain, Liu, Herskowitz, Mangano and Levin, 1998).

The financial implications associated with many of the techniques of auto transfusion are not as insignificant as compared with the use of allogenic blood transfusion. The cost of allogenic blood and blood products has risen sharply over the last few years due to the introduction of universal leuko-depletion. The hidden costs of infection, immune-modulation or increased morbidity are far more difficult to calculate, but should not be forgotten when the costs of auto transfusion techniques are considered (Cross, 2001). Some reactions to homologous blood may have serious consequences. However, the severity of the reaction depends on the social, economic and medical background of the community and the country. It was ensured that homologous blood used at the NWAFH

was less than 10 days old from the day of collection and not the date of cross-matching at the hospital's laboratory. This protocol was due to the rate of the decline in the quality of homologous blood stored for long periods of time before use.

Table 5 represents complications associated with homologous blood transfusions with regards to haemolytic complication, bacterial implications, febrile reactions and transmission of diseases.

Table 5: Complications associated with homologous blood transfusions

Haemolytic	• Immediate - intravascular • Slow - extravascular • Delayed - sensitization • High antibody titre
Bacterial	• Heat stable pyrogens • Pseudomonas
Febrile Reactions	• Atopic individuals • Reaginic IgE • Leukocyte platelet HLA antibodies • Anti IgA,anti Gm antibodies
Disease Transmission	• Syphilis • Cytomegalovirus • Malaria, toxoplasmosis • Brucellosis • Trypanosomiasis • Viral hepatitis • Herpes • Epstein Barr and mononucleosus

Table 6 outlines the decline in quality of stored homologous blood in relation to time. Citrate-phosphate-dextrose (CPD) refers to the medium in which homologous blood is suspended and stored in the blood bank in order to be used for surgery if required. Each unit of stored blood contains 450 ml of blood and 63 ml of CPD (Tobias, 1986).

Table 6: The decline in quality of stored homologous blood (Tobias, 1986)

Electrolytes	Serum sodium increases by 20 mmol per litre Serum potassium increases to 20 mmol per litre by 21 days High lactate and ammonia
Erythrocytes	Viability falls to 80% by 21 days 2,3-DPG and ATP levels decline rapidly
Leucocytes	Neutrophils lose all phagocytic activity after 48 hours Some lymphocytes survive 21 days
Platelets	No viable platelets after 24 hours
Coagulation proteins	Factors V and VIII only about 10% after 24 hours Factor XI only about 20% after 24 hours Factors IX and X rapidly decline after 7 days

2.2.4 Methods of blood conservation

Today modern cardiac surgery adopts several approaches in order to reduce postoperative anaemia and the need for homologous blood and blood product transfusion (Edmunds, 1999). They can be categorized as three major approaches that can be adopted in order to conserve blood. These include technical methods, surgical techniques and pharmacological approaches.

Review of published reports by The Society of Thoracic Surgeons Blood Conservation Guideline Task Force and The Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion**,** identified a high-risk profile associated with increased postoperative blood transfusion. Six variables stood out as important indicators of risk: (1) advanced age, (2) low preoperative red blood cell volume (preoperative anemia or small body size), (3) preoperative antiplatelet or antithrombotic drugs, (4) reoperative or complex procedures, (5) emergency operations, and (6) noncardiac patient comorbidities. Preoperative interventions that are likely to reduce blood transfusion include identification of high-risk patients who should receive all available preoperative and perioperative blood conservation interventions and limitation of antithrombotic drugs. Perioperative blood conservation interventions include use of antifibrinolytic drugs, selective use of off-pump coronary artery bypass graft surgery, routine use of a cell-saving device, and implementation of appropriate transfusion indications. An important intervention is application of a multimodality blood conservation program that is institution based, accepted by all health care providers, and that involves well thought out transfusion algorithms to guide transfusion decisions (Ferraris, V.A., Ferraris, S.P., Saha, S.P., Hessel, E.A., Haan, C.K., Royston, B.D., Bridges, R., Higgins, R., Despotis, G. and Brown, R., 2007).

2.2.4.1 Technical blood conservation measures

Technical measures include attempting to achieve minimal autologous blood loss by means of pre-operative autologous blood donation where patients are requested to pre-donate blood in the days, weeks and even months preceding elective surgery. Another measure entails pre-operative autologous blood salvaging which refers to the removal of one or two units of whole blood from the patient just before initiating CPB and the volume is replaced with crystalloid solution. The next technical method includes pre-operative autologous “cell saving” which involves the salvaging and re-infusion of shed blood and residual pump circuit volume using an auto-tranfusion device. Haemostatic surgical techniques together with proper control of blood pressure and temperature of the patient contribute to the reduction of bleeding during cardiac surgery.

Minimal haemodilution is a key to reducing the need for homologous blood requirements. Various bypass techniques can be used to achieve this aim, one of which includes using volume controlled anaesthesia which limits crystalloid infusion administration. Another technique that can be adopted is retrograde autologous priming (RAP). This entails priming of the bypass circuit using the patient's own blood thereby reducing haemodilution. Mini bypass is relatively new and involves reduction in the circuit in order to achieve the same results as RAP. Conventional ultrafiltration (CUF) is performed on bypass to concentrate circulating volume in the bypass circuit whereas MUF reduces fluid in the patient and bypass circuit post-operatively thereby, increasing the haematocrit and reducing the need for homologous blood transfusion.

2.2.4.2 Heparin-coated circuits

Although heparin is a valuable tool in cardiac surgery, it's imperfection as an anticoagulant allows for the formation of micro-thrombi in the pump-oxygenator. Biomedical engineering is continuously making every effort to ensure that the artificial surfaces are more biocompatible. Heparin's strong acidity makes it possible to bind it ionically or covalently to plastic surfaces. This has been shown to decrease thrombus formation and platelet adhesion upon artificial surfaces (Bannan and Martin, 1998).

Heparin-coated circuits have been subjected to vigorous testing both experimentally and clinically for the past two decades. Heparin is known for its ability to inhibit coagulation activation. Heparin coating was, indeed, initially designed to minimize blood clotting associated with the use of certain medical devices (Gott and Daggett, 1999). Although the thrombo-resistance properties of heparin-coated devices continue to play an important role in CPB, heparin also possesses several other physical and biochemical properties that are augmented when heparin molecules are immobilized onto surfaces (Wahba, Philipp, Behr and Birnbaum, 1998).

The primary function of soluble heparin is to inhibit the later stage of the coagulation cascade via antithrombin III-mediated interactions with thrombin and factor Xa. It has been postulated that surface bound heparin, because of its location being at the sites of

activation, may more effectively inhibit contact activation. Recent experimental and clinical results do, indeed, show that heparin-coated circuits inhibit factor XIIa *in vitro* and reduce the levels of kallikrein-C1 inhibitor complexes in patients undergoing cardiac operations. The inhibition of contact activation prevents the subsequent activation of the intrinsic coagulation system and may have a profound effect in attenuating other associated inflammatory responses (Sanchez, Elgue, Riesenfeld and Olsson, 1998).

Some studies reported reduced blood loss and blood transfusion requirements when heparin-coated circuits were used in conjunction with reduced systemic heparin (von Segesser, Weiss, Pasic, Garcia and Turina, 1994). Similar findings were observed by Ovrum, Holen, Tangen, Brosstad, Abdelnoor, Ringdal, Qystese and Istad (1995). Aldea and Shemin (1998) conducted a clinical study that employed an integrated blood conservation strategy that included maximal cell saving, use of heparin-coated low prime circuits with closed venous reservoirs, minimal use of cardiotomy suckers, use of large-bore directional arterial cannulae, normothermic bypass, precise heparin-protamine titration, and routine use of epsilon-aminocaproic acid. Patients in the study group were treated with the heparin-coated circuit and a reduced systemic anticoagulation (ACT > 280 s), whereas patients in the control group were exposed to the uncoated circuit and full-systemic anticoagulation (ACT > 480 s). Significant reductions in blood loss and blood transfusion requirements, length of intensive care unit and hospital stays, duration of ventilator support, morbidity and postoperative complications were observed in the study group when compared to those in the control group.

When the functions of heparin are preserved on the surface, the immobilized heparin plays multiple roles in attenuating the systemic inflammatory response. These include the ability to attenuate contact activation, coagulation activation, complement activation and, directly or indirectly, platelet and leukocyte activation. The heparin-coated circuits also substantially reduces the release of other inflammatory mediators. The heparinized surfaces render the CPB circuits protein resistant and augment lipoprotein binding. The

multifunctional nature of the heparinized surface is believed to contribute to the overall biocompatibility of the surface (Hsu, 2001).

2.2.4.3 Autotransfusion

Autotransfusion includes any technique in which the patient's own blood is collected, processed and stored, followed by reinfusion when circumstances dictate. In the peri-operative period of cardiac surgery, a number of techniques are recognized as useful in this context. Preoperative autologous donation, with or without erythropoietin supplementation, intraoperative acute normovolemic haemodilution, intraoperative cell salvage, postoperative cell salvage (reinfusion of shed mediastinal blood) and platelet rich plasmapheresis are all techniques which are used with more or less enthusiasm to reduce the need for an allogenic blood transfusion (Goodnough et al., 1999). Although autotransfusion is not the answer to every problem, there is no doubt that it should play a significant part in the strategy of blood conservation (Goodnough et al., 1999).

2.2.4.4 Pre-operative autologous blood donation

This particular technique is rarely used except for patients who may have particularly difficult antibodies for homologous cross matching and female patients with childbearing potential in whom sensitization to homologous transfusion that may be reflected in haemolytic disease of the newborn child. Pre-operative autologous donation (PAD) is a technique of blood conservation in which the patient who is scheduled for surgery in the near future donates his own blood on a number of occasions, depending upon the number of units required. The blood is screened and stored and is then available for reinfusion during the peri-operative period. It is generally accepted as safe and effective blood conservation measure provided that the technique is applied in a logical way. Central to the principle of PAD is the fact that red cell regeneration in the patient receiving oral iron supplementation takes approximately 2 weeks per unit of blood removed. If any shorter time period is allowed to elapse between donations or between donation and surgery, the effectiveness of PAD is reduced. In fact, the patient will

instead have undergone a form of normovolaemic haemodilution, a technique which is often performed safely, more effectively and with less expense at the time of surgery (Cross, 2001).

Patients undergoing cardiac surgery that are unsuitable for PAD

Patients undergoing cardiac surgery that are not suitable for PAD include patients: who cannot wait for two weeks for surgery; with unstable or crescendo angina; with symptomatic left main stem disease; with congestive heart failure and aortic stenosis; who have active endocarditis; patients with sickle cell traits and patients who present with preoperative anaemia who's Hct is less than 34%. Old age is not considered a contraindication to PAD because the incidence of adverse reactions to donation is similar to the general population. (Popovsky, Whitaker and Arnold, 1995).

Preoperative autologous donation should commence at a time prior to surgery such that the selected number of units of blood can be collected with full red cell regeneration prior to surgery. If less than 2 weeks elapses between donations prior to surgery, the Hct at the time of surgery will be lower than it would have been without PAD. The time period between the first donation and surgery is limited by the maximum storage time for blood. In general, this is 42 days. The maximum number of units of blood that can be removed with full red cell regeneration is therefore three, assuming that surgery is scheduled exactly 42 days after the first donation. From the time of commencing PAD, oral iron supplementation should always be given together with vitamin C to increase gastrointestinal absorption of iron. Any variability in time for red cell regeneration appears to depend on the iron stores of the patient when PAD commences. Parenteral iron has been proposed as a method of increasing the speed of red cell regeneration. Although this may increase the speed of red cell regeneration, the incidence of anaphylaxis is too high for it to be a technique which is used regularly. Erythropoietin therapy in combination with PAD has been shown to be an effective method of reducing the time for red cell regeneration. A dose of 600 U/kg on days 7 and 14 pre-operatively allows 2 units of blood to be removed during this period while still having the Hct return

to baseline at the time of surgery. The safety of this treatment is well established but the main objection to a much wider use of the technique is the cost involved (Cross, 2001).

The risks of transfusion of autologous blood and blood products are significantly less than those associated with allogenic transfusion. For this reason, there is a tendency to reduce the threshold for reinfusion of PAD blood. However, there are risks associated with any transfusion. The risks are mainly due to clerical error, resulting in the transfusion of the incorrect unit. Other risks such as bacterial contamination of the unit, air embolus or volume overload must also be considered. The threshold for transfusion should be based on clinical need rather than influenced by the increased safety of PAD blood and availability (Birkmeyer, Aubuchon, Littenberg, O'Connor, Nease Jr, Nugent and Goodnough, 1994).

Different protocols have been developed for pre-donation programmes at numerous centres. Availability of adequate liquid and frozen storage techniques allow donors to deposit one to eight units of blood in the pre-operative period. Weekly phlebotomies performed for as many weeks as required with the last donation no fewer than 72 hours prior to surgery is the usual practice, resulting in a few units stored in CPD (short shelf-life). Other more complicated regimes exist for use in special circumstances. The major drawback to this technique is logistical, particularly for those hospitals serving a large regional population.

The spider diagram in figure 1 represents the benefits to pre-depositing blood for autologous transfusion.

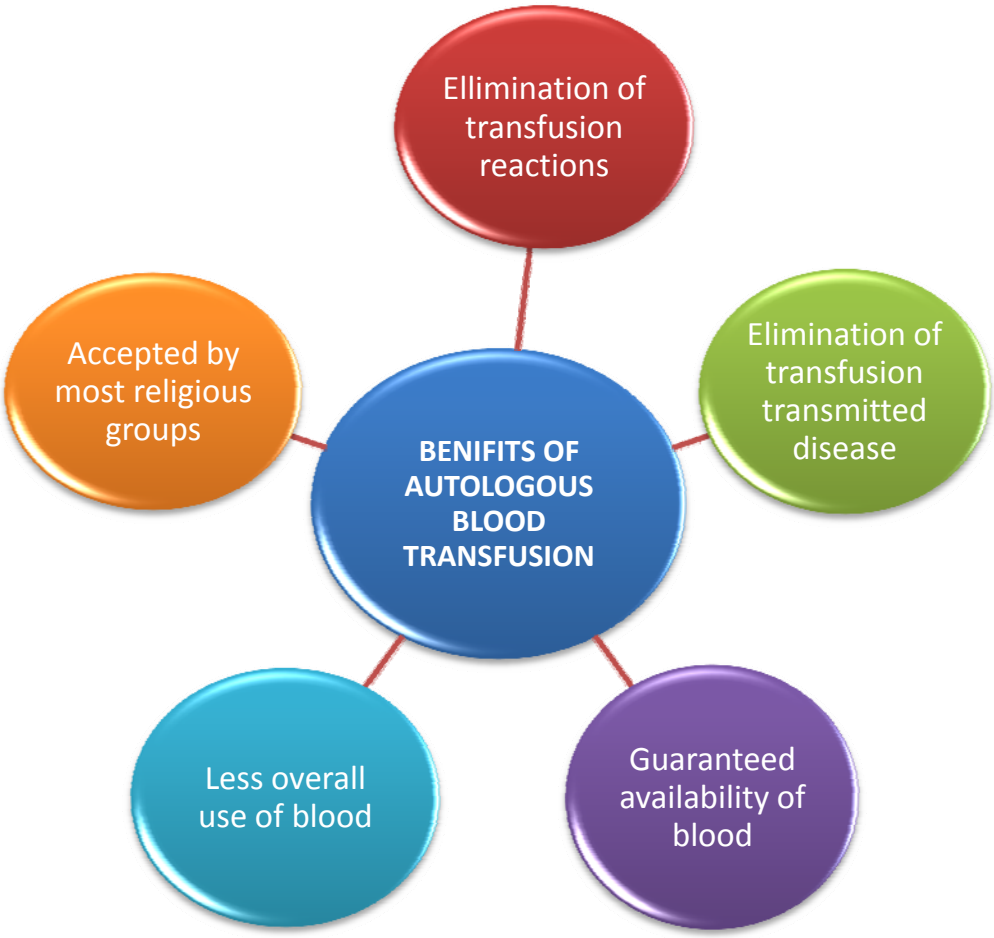


Figure 1: The benefits of autologous blood transfusion

2.2.4.5 Acute normovolemic haemodilution (ANH) and pre-operative autologous blood salvaging

Historically, the use of haemodilution was first reported by Panico and Neptune (1959). Their report was an anecdotal experience with low Hct that occurred when it was necessary to return to CPB emergently and there was insufficient time to obtain donor blood to prime the heart-lung machine. However, it was the work of Cooley, Beall and Grondin (1962) that led to the widespread use of haemodilution during CPB.

The technique of autologous blood salvaging involving the withdrawal of one or more units pre-bypass, has become standard for most open-heart units. Blood is removed from the patient during the early stages of an operation (before any significant blood loss) with simultaneous replacement with a non-blood fluid to maintain normovolemia. The autologous blood, which contains a full complement of clotting factors and effective platelets, can be re-infused when the operation is complete or sooner, if clinically indicated. In cardiac surgery, blood is removed during the pre-bypass period and generally re-infused at the end of the operation (Groom, 2002).

The degree of haemodilution and the amount of autologous blood salvaged depends on pre-operative Hct and the calculated pack cell volume (PCV) drop. The target haematocrit was approximately 24 % and the replacement fluids used is either Gelufusine (Gel)®, Ringers Lactate® or Hesterile® solution. The lower haematocrit results from a considerable decrease in the number of red blood cells lost during surgery due to trauma of the CPB circuit. Animal and clinical studies have demonstrated that the diminished oxygen-carrying capacity of the red cell depleted blood is offset by the increased capillary flow rates achieved as a result of lowered viscosity (Kessler and Messmer, 1975).

Large volume additions of crystalloid fluid result in low colloid oncotic pressures. This prompted the use of colloids such as Gel and human albumin as a volume expander to replace salvaged blood in this study. This was used with the intention of preventing water diffusion into the interstitial space during CPB. This water load may lead to postoperative complications, particularly in children and patients with compromised renal function and those with functional or metabolic pulmonary impairment. Failure to reduce this water load significantly during the first 48 hours post-bypass may be due to the high plasma level of antidiuretic hormone (ADH) during crystalloid haemodilution and non-pulsatile flow (Philbin et al., 1979). This massive release of ADH may be caused by the abrupt reduction in blood pressure registered by the aortic and left atrial baroreceptor at the start of bypass. The additional fluid (crystalloid and colloids) that were added to the circuit at the initiation of CPB in order to replace the autologous blood

that was salvaged was removed with the use of haemofiltration post operatively.

Patients who are deemed unsuitable for PAD for medical reasons will, in general, be unsuitable for ANH. The time for red cell regeneration is not an issue for ANH and, therefore, patients who might have been excluded from PAD purely on grounds of time will be suitable for ANH (Popovsky, Whitaker and Arnold, 1995). Patients presenting for cardiac surgery are always required to have a central venous cannula inserted. The side-arm of a pulmonary artery catheter introducer is a suitable route for removal of blood. Even with a pulmonary artery catheter *in situ*, an 8.5 F introducer is generally large enough to allow drainage by gravity to occur at a reasonable rate of 10 – 15 minutes per unit, with the aim of completion prior to heparinization. Concerns that heparin may impair platelet function in the collected blood means that most clinicians will now aim to complete ANH prior to this point (Gillon, Desmond and Thomas, 1999).

Guidelines have recently been produced covering many of the concerns about collection, labelling, storage and reinfusion or disposal of autologous blood. Blood is collected into a standard collection bag identical to those used by the Blood Transfusion Service. Ideally, a rocker scale should be used so that the correct volume of blood can be added to each bag to maintain the correct anticoagulant ratio so that complete mixing occurs. The collection line is knotted twice before removal of the integral needle and the bag is labelled so that it can be checked prior to reinfusion. Storage of autologous salvaged blood should be in the operating room so that the risk of a clerical error leading to an incorrect reinfusion is kept to a minimum. Storage of platelets at room temperature is optimal for preservation of function and the short time period that the blood is stored means that the risk of bacterial contamination or replication is minimum (Napier, Bruce, Chapman, Duguid, Kelsey, Knowles, Murphy, Williamson, Wood, Lee, Contreras, Cross, Desmond, Gillon and Lardy Williams, 1997).

If ANH and autologous blood salvaging is to be effective, it is important that an optimal volume of blood is removed. If 50 ml of blood is removed from a 70-kg patient presenting for cardiac surgery, it is unlikely that any benefit of ANH will be

demonstrated, in terms of Hct level at discharge or allogenic blood transfusion. The maximum volume of blood that can be safely removed should always be removed if the technique is to be an effective one. It is important to decide what the transfusion threshold should be both prior to and during CPB. A transfusion threshold of 30% prior to CPB and 18% during CPB is often acceptable. Using these figures and by estimating the blood volume of the patient and knowing the priming volume of the CPB circuit, it is possible to calculate the volume of blood that can be withdrawn without exceeding either of the transfusion thresholds. In practice, only whole units of blood are removed so that the anticoagulant / blood ratio is correct (Cross, 2001).

Reinfusion of ANH blood should be during CPB if the Hct falls to an unacceptably low level (below 18%). This should only occur after blood that may have been collected by cell salvage is returned to the CPB circuit and all blood available by cardiotomy suction from the mediastinum and pleural spaces are also returned. The bag of ANH blood that has been collected last with the lowest concentration of platelets and clotting factors should be used first (Napier et al., 1997).

Following CPB, blood should not be re-infused until administration of protamine is complete, unless a low Hct at this time makes it obligatory. When blood is returned, it should be given in the reverse order to that in which it was collected. It will reduce the chance of a clerical error if all the autologous blood salvaged is re-infused prior to the end of surgery or at least connected to the patient by this time (Cross, 2001).

2.2.4.6 Intra-operative platelet rich plasmapheresis (PRP)

The success of PRP in limiting exposure to allogenic blood transfusion has been mixed. Early studies published in the late 1980's by Giordano, Rivers, Chung, Mammana, Marco, Raczkowski, Sabbagh, Sanderson and Strug (1988), indicated that PRP was a technique that could be used in the pre-CPB period to reduce the need for allogenic blood transfusion. The aim of the procedure was to minimize the post-CPB bleeding by providing the patients with autologous functional platelets and coagulation factors that

have not been exposed to the CPB circuit. The technique involved the removal of blood from the patient via a large bore central line and mixing it with an anticoagulant. The blood then passed into a centrifuge where it was spun to separate the red cells from the plasma and the platelets. The red cells were returned to the patient and the platelet rich plasma was stored ready for reinfusion after CPB.

The technique of intra-operative platelet rich plasmapheresis was not one of preserving red cells, but one of reducing the coagulopathy that often follows CPB. If the tendency to bleed was reduced, so likelihood of an allogenic transfusion is reduced. The storage of platelets in certain anticoagulants may damage the platelet membrane and the platelet-pheresis process itself may activate platelets making them less effective when rein-fused (Ford, Unsworth, Aziz, Tooze, Besouw van, Bevan and Treasure, 1999). The process, which often takes an hour to complete, should be finished before heparinization of the patient. If performed effectively this may actually prolong the operation. The removal of blood must be matched by an infusion of colloid or crystalloid to maintain normovolemia. The infusion must be varied, depending upon whether the PRP process is removing or re-infusing blood. The complex nature of the technique means that a dedicated technician always performs it. Close coordination between anaesthetist and technician is essential if the technique is to be performed safely (Rubens, Fergusson, Wells, Huang, McGowan and Laupacis, 1998). The PRP product should be stored at room temperature in the operating room and re-infused at the end of the operation after reversal of heparin (Cross, 2001).

2.2.4.7 Intra-operative cell salvage devices (ICD)

During the early 1960's when interest in all forms of autologous transfusion resurfaced, it was inevitable that intra-operative salvage would attract attention. Cell salvage was introduced initially as a technique that could be used in circumstances when homologous blood was not available, but its use by the armed forces was soon widespread. Despite the technical difficulties with the early techniques, which included haemolysis, disseminated intravascular coagulation, in addition to fat and air embolism

the concept of blood salvage and re-infusion still seemed worthwhile. However, although there were substantial technical advances from the s1960's to 1980's, the ideal auto transfusion system as outlined by Gilcher and Orr (1975) in Table 7 could not be developed.

Table 7: Properties of an ideal autologous blood cell saver

1. Rapid assembly
2. Ease of operation
3. Low cost equipment and software
4. In-line filtration
5. Minimal blood/air interface
6. Simplified and non systemic anticoagulation
7. Red cell concentration facility
8. Removal of cellular, fluid contaminants and other extraneous debris
9. Rapid return to the patient
10. Safety from air emboli and coagulopathy

It was only in the 1980's, with the discovery that AIDS could be transmitted by homologous blood transfusion, that cell salvage was adopted by all surgeons who were using a significant amount of homologous blood. Between 1960 and 1990 little was seen in the way of development of cell salvage, although significant refinement had taken place (Hall, Schweiger and Finlayson, 1990). Today technology, with the aid of biomedical engineering, has provided us with devices that conform to all the requirements outlined by Gilcher and Orr (1975). Intraoperative cell savage (ICS) has been widely used during cardiac surgery for the last 28 years (Cross, 2001).

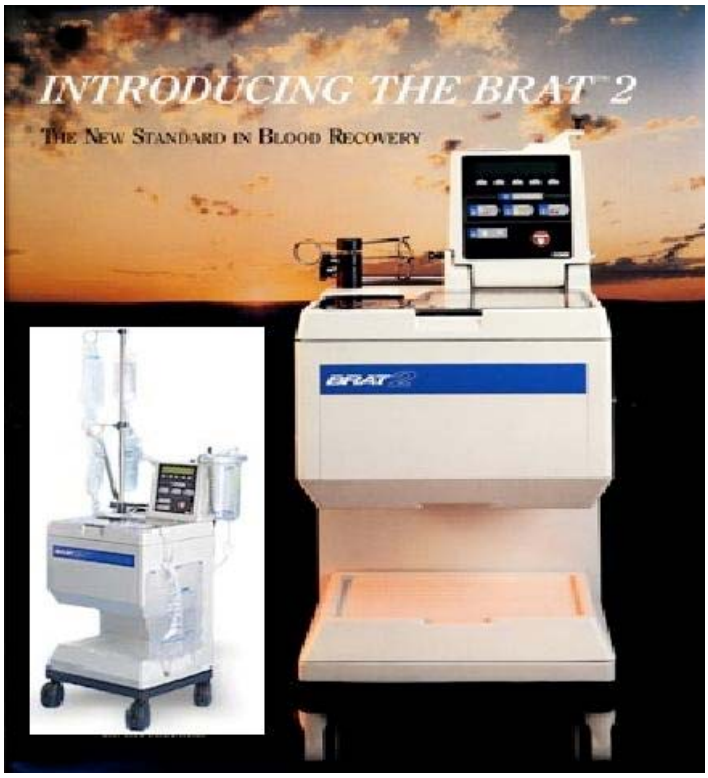


Figure 2: Brat 2 cell-saver device used at the NWAFH

As illustrated in figure 2 the cell saver device consists of a vacuum pump which aspirates blood and air into a hard-shell cardiotomy reservoir. The negative pressure within the reservoir is controlled by automatic adjustment of a negative air pressure relief valve. Initially the system was designed to be used with systemic anticoagulation of the patient but it is now used with the addition of local anticoagulant at the suction tip. Thirty thousand international units of heparin is added to one litre of 8% normal saline and titrated physically by the end user depending on the amount of bleeding and anticoagulation status.

Filtration and de-foaming takes place within the reservoir and the salvaged product is then infused by a roller pump into a centrifugal bowl where separation and washing takes place. The products are removed serially through a centrally placed channel (Figure 2) starting with the lightest component which is the plasma, and ending with the heaviest component which is the red cells. After washing, the bagged blood is removed

from the machine and hung up for transfusion to the patient via an intra-venous line.
The three stages required to wash blood using an autologous cell saver device is outlined below and illustrated in figure 3.

Stage 1

Blood is collected from the operative site (or from the CPB machine) using large-bore suction and tubing which contains heparinized saline. It passes through a 25 – 40 µm filter and then collects in a reservoir. After collection of 500 – 1000 ml of blood in the reservoir, the blood is pumped into the spinning Latham bowl (approximate volume 225 ml).

Stage 2

By differential centrifugation, the red cells are concentrated. As the bowl fills with red cells the supernatant containing plasma, free haemoglobin and other soluble components, pass into a waste bag. The buffy coat, which should contain the majority of platelets and white cells, is the final part of the supernatant to pass into the waste bag before the bowl is full of red cells.

Stage 3

This stage of the process consists of washing the concentrated red cells with approximately 1000 ml of 0.9% saline to further remove unwanted soluble substances. The final product should consist of red cells (Hct 50 – 60%) suspended in saline with few or no platelets, leukocytes, clotting factors or humoral substances (Cross, 2001).

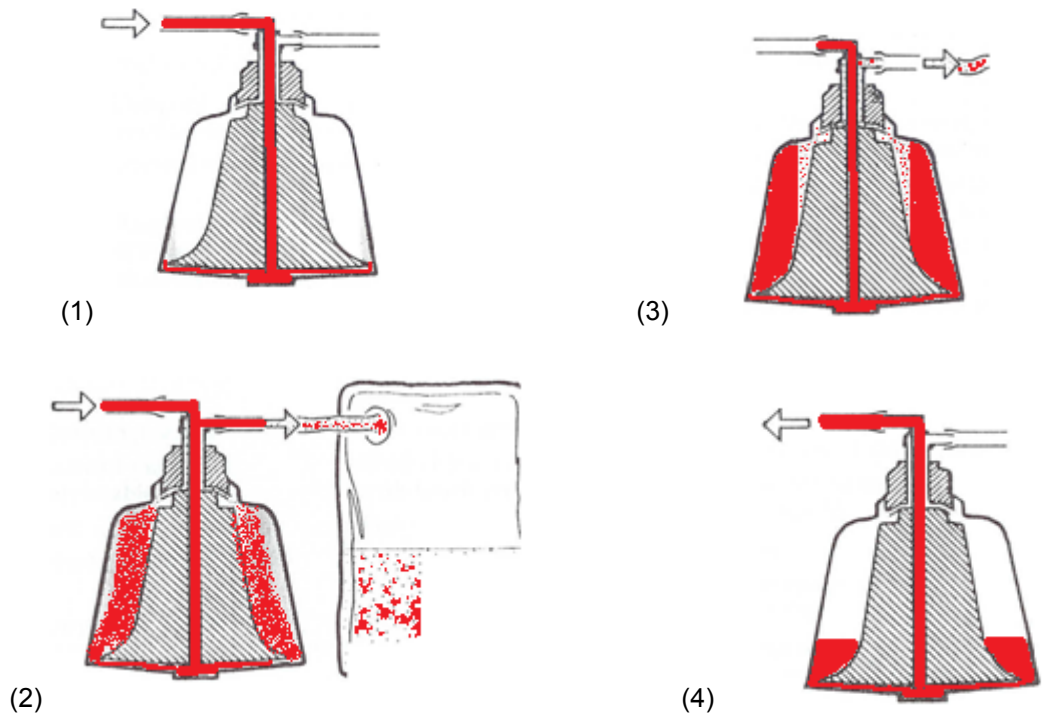


Figure 3: Step-by-step illustration of the cell saver while "washing" blood

1) Diluted blood being pumped into spinning centrifuge bowl.

2) Centrifugal force holds red cells in suspension while supernatant is expelled to the waste bag.

3) Saline "wash" is introduced while cell circulation is maintained against the flow of wash solution.

4) Washed cells are returned to perfusion circuit or to transfusion bag.

These systems provide a final product of high Hct (70%) consisting of washed red cells suspended in saline, free from particulate matter, vasoactive substances and contaminants. Thus, this decreases the chances of coagulation abnormalities. The final product is re-infused by gravity and therefore air embolism is not a concern. Virtually all contaminants are removed. There is no limit to the number of salvaged units that could be re-infused with this system, provided that fresh frozen plasma is given to the patient for coagulation support.

However, one should remember that not only the heparin is removed by the washing process, but so are all the clotting factors and platelets. The red cells which are collected have a survival rate which is equal to that of the patient's own or homologous blood. Their morphology is unchanged. The levels of 2,3-DPG are higher than homologous blood and the osmotic fragility is unchanged (Cross, 2001). All evidence suggests that the washed product from a cell salvage system is equal or superior to homologous blood. Cell salvage can also be used to concentrate the residual blood left in the CPB machine (Reents, Babin-Ebell, Misoph, Schwarzkopf and Elert, 1999). The cost of cell salvage per case now costs little more than the cost of a single unit of concentrated red cells. Using this fact alone, ICS should be used for all cases where the median blood loss intra-operatively and blood use post-operatively is in excess of one unit (Reents et al., 1999).

Possible complications associated with the use of a cell salvage device which occurred in the past, although refinement of the cell salvage technique has taken place to reduce the risks, include the following:

Air embolism

Some cell salvage systems will allow direct reinfusion of the cell salvage product and without air detectors and an automatic pump, cut off circuit and software.

Bacterial contamination

Skin contaminants can be detected in the cell salvage product, but this has not been reported to be clinically significant. Because of these concerns, cell salvage is sometimes avoided in the immune compromised population, for example cardiac transplantation. Of much greater concern is the possibility of bacterial replication in the cell salvage product prior to reinfusion and to limit this possibility, blood should be re-infused within 6 hours.

Heparin contamination

Although most evidence suggest that heparin is adequately removed by washing of the cell salvage product, this may be of importance if no monitoring of heparin effect is being used, for example activated clotting time measurement.

Topical antibiotics

Neomycin or Bacitracin, are used during some surgical procedures. Some of these substances may be aspirated into the cell saver and although the amount returned to the patient is small compared with systemic absorption, this is sometimes of concern.

Topical haemostatic agents

Surgicel, if aspirated into the cell saver may not be adequately removed by cell washing and, in an animal model, it may promote clotting of the system.

Fat embolism

Fat particles may be aspirated into the cell saver, especially during orthopaedic or cardiac surgery (from the sternal edges). Not all fat particles will be removed by cell salvage and those that are less than 40 μm will pass through many fine screen filters.

Tumour cell contamination

Contamination of cell salvage blood by tumour cells has been a concern for many years and has often been considered to be a reason to avoid cell salvage during cancer surgery However, tumour cell removal or inactivation by leukofiltration or gamma irradiation has changed this attitude.

Patient misidentification

Patient misidentification can be a potential problem, especially when cell salvage blood moves with a patient prior to reinfusion, for example on transfer from the operating room to the intensive care unit.

Sickling of red cells during cell salvage

Although cell salvage has been used successfully in patients who have been transfused to reduce the HB to 25%, cell salvage is best avoided in this population in order to reduce the chance of reinfusion of sickled cells.

Coagulopathy

The process of large volumes of cell salvage blood will lead to a coagulopathy as there is significant removal of clotting factors and platelets (Cross, 2001).

2.2.4.8 Retrograde autologous priming of the CPB circuit

Retrograde autologous priming (RAP) or prime displacement of the CPB circuit is a technique employed to reduce the priming volume of the circuit. The reduced haemodilution which, therefore, occurs at the onset of CPB, allows a higher Hct to be maintained throughout CPB. Alternatively, more effective ANH may be performed prior to CPB, while still maintaining an adequate Hct during CPB. After CPB, a higher Hct means that the patient is less likely to reach a transfusion threshold and therefore, receive a blood transfusion. Although a method of priming the CPB circuit using an autologous technique was first described in 1960, the technique did not prove popular until much later. In the 1990s numerous authors published modifications of the technique of priming the CPB circuit. Reductions in homologous blood usage as a result of this modification have recently been demonstrated (Cromer and Wolk, 1998).

The technique of RAP in adult cardiac surgery can differ between cardiac centres as pump configurations and CPB circuit designs are not standardized. However, whatever method is used, the primary aim is to displace the clear fluid prime with autologous blood and reduce haemodilution at the onset of bypass (Rousou, Engelmon, Flack, Deaton, Garb and Owen, 1999). After termination of CPB and removal of the cannulae, the prime solution is returned to the circuit, displacing the patient's blood which is then collected for reinfusion by the anaesthetist. Alternatively, cell salvage may be used to

concentrate the blood remaining in the CPB circuit at the end of CPB (Rousou et al., 1999).

Using this technique prime displacement is achieved in less than 2 minutes, reducing the priming volume from 1600 ml to approximately 600 ml in the smaller anaemic patient with a pre-CPB Hct of 30%. Using a normal prime would have an Hct of 20% on CPB. However, using the RAP technique, the Hct would be 25%. With a larger patient or with a higher Hct prior to CPB, the technique should be combined with ANH to prevent a high Hct during CPB. The Hct (%) should be maintained at less than the patient's core temperature so that the viscosity of the blood, when hypothermic, is not excessive (Cross, 2001).

Retrograde autologous priming will be particularly effective when the patient has a low circulating blood volume and the dilution at the commencement of CPB is more significant. Rosengart, De Bois, O'Hara, Helm, Gomez, Lang, Altorki, Hartman, Isom and Krieger (1998) demonstrated a fall in requirements for allogenic blood from 53% to 27%. This study has been repeated recently and even without ICS, transfusion requirements following primary coronary bypass grafting fell from 47.5% to 20%.

2.2.4.9 Re-infusion of shed mediastinal blood

This is a post-operative blood conservation technique (post-operative cell savage). The collection of shed mediastinal blood (SMB) is usually performed using a collection chamber designed for the purpose. This is often the cardiotomy reservoir from the CPB circuit. Blood is allowed to drain into this from the chest drains. From there it is either continuously re-infused using a pump or it is intermittently emptied into a collection bag and then re-infused into the patient. The use of a continuous system means that precautions must be taken to avoid an air embolus. A maximum volume for reinfusion of 500 – 750 ml or time for reinfusion of 6 hours is usually stipulated when using the technique (Body, Birminhan, Parks, Ley, Maddi, Shernan, Siegel, Stover, D'ambra, Levin, Mangano and Spiess, 1999).

Although the main aim of reinfusion of SMB is to reduce exposure to homologous blood and blood products, it may do this with a risk of increased post-operative bleeding and abnormalities of coagulation. Shed mediastinal blood is a thrombocytopenic, defibrinogenated product with an Hct of approximately 20%. The Hct may vary, depending on the rate of bleeding. Red cell haemolysis is common and plasma-free haemoglobin levels as high as 4 g/l may be found. Although this is high, the total exposure to plasma-free haemoglobin is not enough to cause renal failure. Tissue plasminogen activator (TPA) and fibrin degradation products are both elevated in SMB and although raised levels may be found systemically following reinfusion of SMB, this is unlikely to be a reflection of a systemic response. Some studies have demonstrated bacterial contamination of SMB, although this has not been associated with evidence of sepsis (Huet, Salmi, Fergusson, Koopman-van Gemert, Rubens and Laupacis, 1999).

2.2.4.10 Surgical Technique

In cardiac surgery today source of surgical bleeding is found in approximately two-thirds of patients post operatively. Common sites of ongoing haemorrhage include side branches of the internal mammary artery and saphenous vein grafts, mammary arterial harvest sites, graft anastomoses, cannulation sites, insertion sites of pacing wires, and around sternal closure wires. Meticulous surgical haemostasis is the basis of any blood conservation program. Careful haemostasis before heparinization and CPB is as important as after administration of protamine. Another surgical blood conservation measure includes aiming to achieve optimal coagulation status by full and sustained re-warming of the patient, minimal homologous transfusion using strict transfusion guidelines and early return to the operating room in cases of excessive bleeding.

2.2.4.11 Pharmacological strategies for blood conservation in cardiac surgery

Individualized dosing of heparin is recommended to improve control of the heparin dosage and to prevent prolonged activated clotting times (ACT) that may occur if a standard dose is given routinely. Heparin titration has so far shown efficacy in reducing

blood loss after bypass in comparison with standard heparin anticoagulation (Shore-Lesserson, 2000).

Macfarlane (1937) noted that blood removed from a patient, immediately after cholecystectomy, clotted normally but was “quite fluid” when inspected the following day. This occurred due to increased perioperative fibrinolytic activity that has been recognized to occur in surgical operations without CPB. Prevention of transfusion has become possible by manipulation of the control of coagulation and inflammatory processes and by the introduction of pharmacologic agents (Porte and Leebeek, 2002). Non-surgical factors that may affect blood loss include the function of the haemostatic system, vascular abnormalities (e.g. connective tissue disorders), and arterial and venous blood pressure. In general, diffuse bleeding from the surgical field, which cannot be attributed to detectable bleeding vessels, is usually referred to as non-surgical bleeding. The pathogenesis of non-surgical bleeding is often multi-factorial and the exact mechanisms may remain unidentified in the individual patient. The normal haemostatic system consists of a complex and delicate interaction of cellular blood components (platelets, leukocytes), endothelial and sub-endothelial layers, and plasmatic proteolytic enzymes and protease inhibitors (Porte and Leebeek, 2002).

Ideally, pharmacological agents with a specific working mechanism should be used in those situations where a specific defect in the haemostatic mechanism has been identified and where it can be corrected by this drug. In daily practice, however, several of these specific agents (such as anti-fibrinolytics) have been shown to be effective in controlling bleeding even in the absence of a detectable specific haemostatic defect (Porte and Leebeek, 2002). Excessive bleeding after surgery involving CPB is attributable to the size of the surgical wound required for these procedures and by the activation of both coagulation and fibrinolysis by the passage of blood through the CPB circuit. This stimulation of the formation and dissolution of clots results in excessive consumption of coagulation factors and predisposes patients to prolonged and excessive bleeding (Royston, 1995).

Transfused blood products are used extensively in patients undergoing cardiac surgery, but recent concern over the availability and safety of these products has prompted much interest in methods of minimizing peri-operative transfusion requirements. These include autologous blood donation, intra- and post-operative cell salvage, normovolemic haemodilution and pharmacological methods. Drug therapy is easy to use and allows the complex and time-consuming measures associated with autologous blood transfusion to be avoided (Barrons and Jahr, 1996). Pharmacological options primarily consist of topical agents, antifibrinolytics, and agents that may enhance platelet function and improve primary haemostasis such as desmopressin (Lanpacis and Fergusson, 1997).

2.3 SUMMARY OF BLOOD CONSERVATION (according to ATS guidelines)

There are definite benefits to the patient if any or all these methods of blood conservation could be performed in combination during cardiac surgery. However, the indications, limitations and risks are different for each patient. In summary, the main objectives and aim as clinicians in the attempt to conserve blood in cardiac surgery with CPB should ideally be to:

- **Minimize blood loss**
  1) Use heparin-coated circuits
  2) Improve surgical techniques to restrict bleeding
  3) Infuse blood from the operative field into a cell saver instead of the waste suction.

- **Maximize blood salvage**
  1) Implement the use of auto transfusion systems
  2) Encourage the patients to accept pre-operative autologous blood donation
  3) Use autologous blood salvaging techniques before CPB
  4) Promote the use of intraoperative cell salvage devices (icd) during cardiac surgery

- **Maximize blood generation**
    1) Adopt the use of erythropoietin – to encourage production of red blood cell
    2) Use Vitamins / minerals e.g. – iron and vitamin C to strengthen blood components

- **Optimize coagulation status**
    1) Use of aprotinin to improve coagulability thereby reducing bleeding
    2) Avoid the use of Aspirin® < 5 days before the date of the operation
    3) Plavix® , which is also an anticoagulant should be stopped < 5 days before the operation
    4) Heparin® stopped < 48 hrs before the operation to prevent bleeding during surgery
    5) Individualized dosing of heparin to prevent hyper anticoagulation during CPB
    6) Intra-operative platelet rich plasmapheresis will promote coagulation status

- **Avoid unnecessary blood transfusion**
    1) Aim to re-infuse most of the shed mediastinal blood during surgery
    2) Use retrograde autologous priming (RAP) to prime the CPB circuit instead of blood

2.4 DIFFERENT PERFUSION TECHNIQUES OF PERFORMING CARDIAC SURGERY

There are three major aproaches to cardiac perfusion systems during cardiac surgery. One approach is, off pump coronary artery bypass grafting (OPCABG), The second is conventional cardiopulmonary bypass and the third is mini bypass.

2.4.1 Off pump coronary artery bypass grafting (OPCABG)

Figure 4 represents an off pump surgery technique which is performed without the aid of a heart lung machine as the name suggests. In this type of surgery the sugeon relies on small retractors, physical manipulation of the heart muscle and drug therapy in order to perform this procedure.

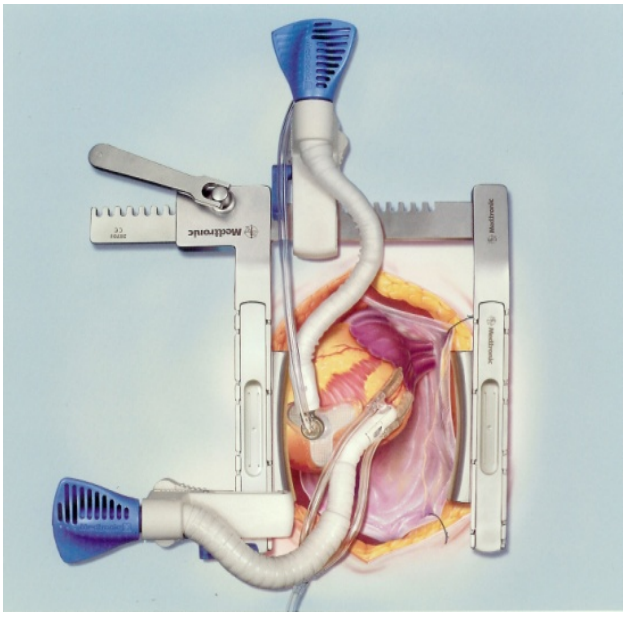


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Figure 4: Off pump surgery/ OPCABG

2.4.1.1 Advantages off pump surgery

- Minimal haemodilution
- No contact with foreign surfaces
- Reduced inflammation
- Lower levels of ACT required (200 sec)
- No cross-clamp required
- Continuous coronary myocardial perfusion

2.4.1.2 Limitations of off pump surgery

- Can only be used in closed cases
- Pressure drop during manipulation
- More demanding on the anaesthetist and surgeon
- Crash on bypass when OPCAB fails
- Studies show ↓ long term graft patency as compared to conventional CPB
- Requires a more experienced surgeon
- Relies on the ability of perfusionists to crash onto CPB if the procedure fails

Figure 5 below shows a surgical opening of the sternum during an off pump surgery

Figure 5: Surgical opening of the sternum during off pump surgery

2.4.2 Conventional CPB

Figure 6 represents a typical conventional CPB circuit.

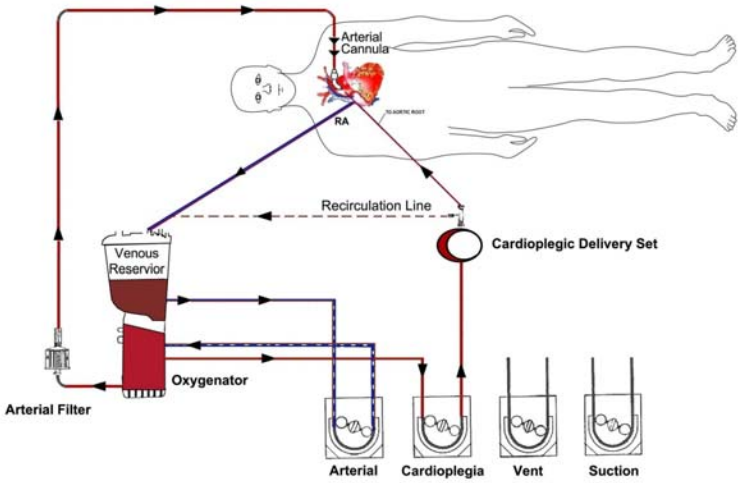


Figure 6: Diagram of a CPB circuit

2.4.2.1 Advantages of conventional CPB

- Cardiotomy reservoir – open system
- Easy to control macro-venous emboli
- Reservoir used to control blood volume
- Less demanding
- Can be used in all cardiac cases

2.4.2.2 Limitations of conventional CPB

- High priming volume (1700 ml)
- Excessive haemodilution
- Lower haematocrit level
- Higher ACT levels required (> 480 sec)
- Greater surface contact
- Open system (blood air interface)
- Increased inflammatory mediators

Figure 7 shows a picture of a conventional CPB circuit on a Jostra HL 30 heart lung machine in an operating room while on bypass

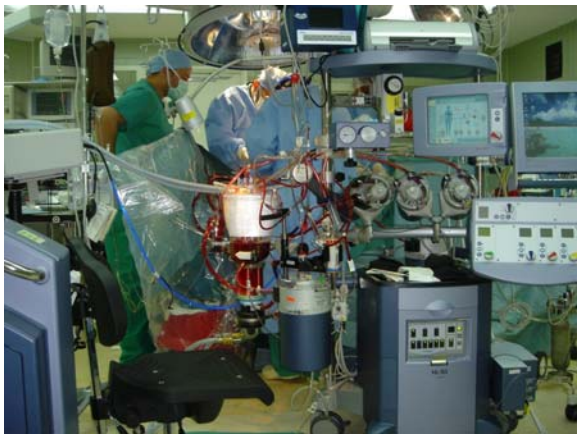


Figure 7: A conventional CPB set-up in the operating room

2.4.3 Mini bypass

Figure 8 represents a typical mini bypass circuit and cardioplegic pump used to arrest the heart. A cell saver device is commonly used with these procedures.

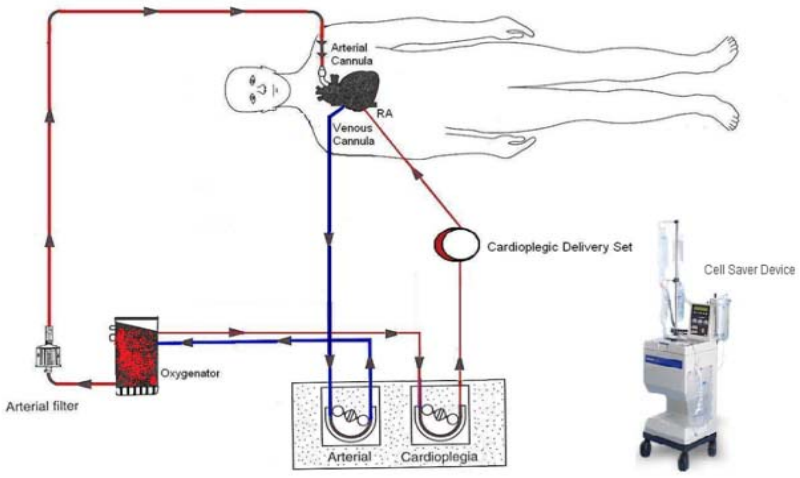


Figure 8: Diagram of a mini bypass system

2.4.3.1 Advantages of mini bypass

- ↓ priming volume
- ↓ haemodilution
- ↓ need for donor blood
- ↓ foreign surface
- no blood-air contact
- less haemolysis
- less blood activation
- reduced anticoagulation
- transportation ease
- ECMO, left ventricular assist device (LVAD) and right ventricular assist device (RVAD)
- compact design
- easy set-up
- closed circuit
- no suction
- no reservoir
- minimal components

2.4.3.2 Limitations of mini bypass surgery

- Commonly used in closed cases
- More careful with cannulation
- Requires a centrifugal pump
- Requires co-operation of entire team
- Requires more experienced staff

2.4.3.3 Different types of mini bypass available on the market today

The pictures contained in figures 9 to 14 represent the latest heart lung machines available on the market today and the corresponding mini bypass circuit on the right. The Jostra HL 30 is unique in its ergonomic design (Figure 9). The pump can be configured according to user preference or patient's requirements. Figure 10 represents the Jostra mini extracorporeal circulation (MECC) system.

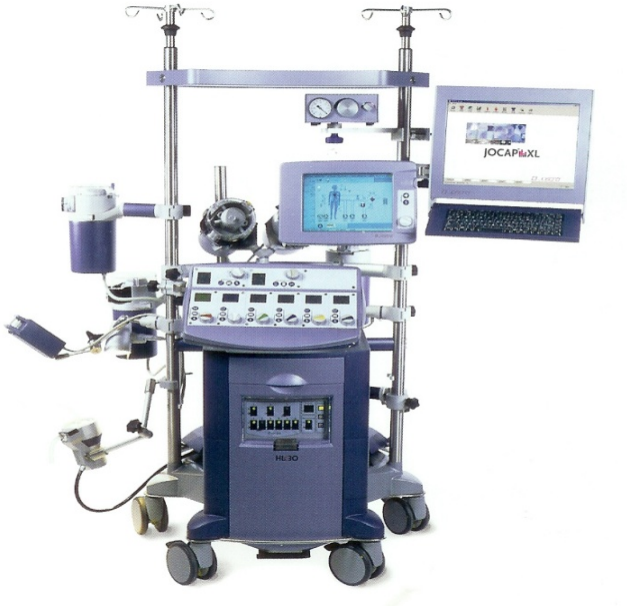


Figure 9: Jostra HL 30

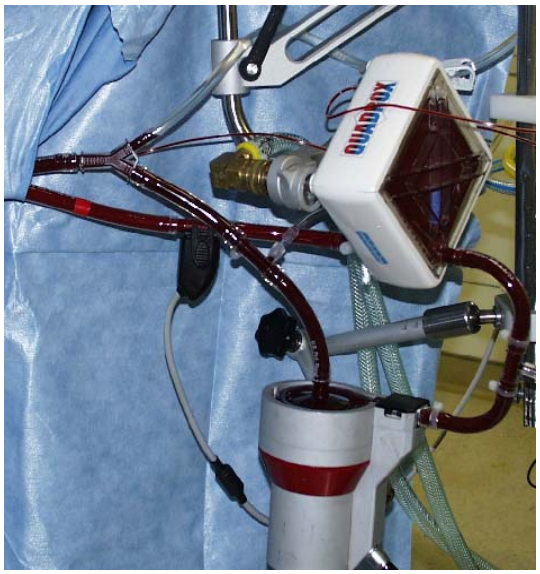


Figure 10: MECC system by Jostra

Figure 11 represents the Stockert S5 heart lung machines and the corresponding extracorporeal circulation optimized (ECCO) mini bypass circuit in Figure 12. The S5 "direct driven" pump heads makes it accurate and reliable.

Figure 11: Stockert S5

Figure 12: ECCO system by Dideco

The picture contained in Figure 13 represents the Performer heart lung machine by Medtronic and its corresponding Resting Heart mini bypass circuit Figure 14. The performer's portable design that was based on a dialysis machine is an advantage.

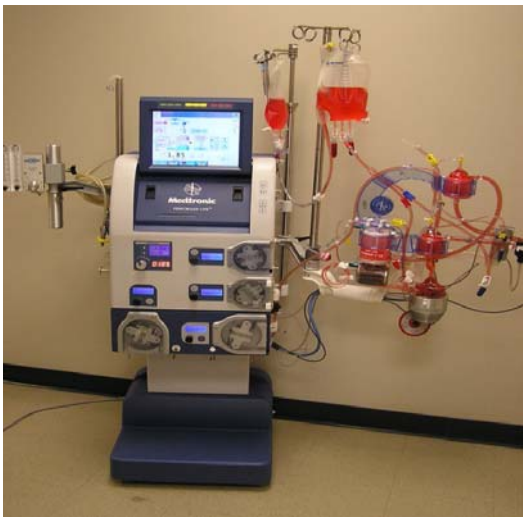


Figure 13: Medtronic Performer

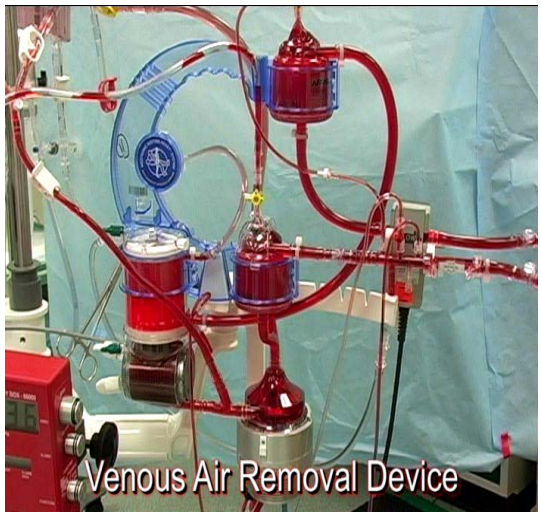


Figure 14: Resting Heart system by Medtronic

2.5 CHOICE OF PRIMING FLUIDS FOR CPB

2.5.1 Introduction

The topic of an ideal combination for priming constituents in the bypass circuit to initiate CPB during cardiac surgery remains to be argumentative. Homologous blood, autologous blood, crystalloids, synthetic colloids and human albumin are some of the additives used at most centres around the world but with different combination protocols. Since this is dependent on hospital protocol, surgeon preference, perfusionist preference and anaesthetic influence, there still remains no consensus as to what constitutes the ideal prime.

The purpose of this section is to:

(a) Outline the rationale behind the shift away from whole blood towards the utilization of clear fluid primes in the extracorporeal circuit.
(b) Illustrate the behaviour of crystalloid and colloid solutions in the circulation with reference to changes in hydrostatic, crystalloid and colloid osmotic pressures as well as Hct and viscosity.
(c) Review the literature concerning associated clinical research and indicate future lines of development.

2.5.2 History of priming constituents of a CPB circuit

During the early period of open-heart surgery, heart-lung machines were primed with fresh heparinized homologous blood. The original film oxygenators required large priming volumes (3-5litres). The problem of providing an adequate supply of fresh donor blood soon forced clinicians to switch to routinely collected banked blood, in spite of fears that this might provoke citrate intoxication (Zuhdi, McCollough, Carey and Greer, 1960). These fears proved groundless and it is instructive to recall that in those early days of open-heart surgery, it was also considered a fundamental error to administer

more than the barest minimum of clear fluids intra-operatively. Even the volume of heparinized saline required to flush the pressure catheter was suspected of causing the pulmonary oedema sometimes observed (Trede, 1969).

The disadvantages of perfusing patients with large volumes of genetically heterogeneous blood soon became manifest. These included the 'homologous blood syndrome' (Dow, Dickson, Hamer and Gadboys, 1960), where plasma migrated from the intravascular compartment in an unpredictable fashion, causing a shock like state with pooling of blood in the splanchnic circulation. Hepatic congestion and portal hypertension ensued, accompanied by increasing metabolic acidosis, coagulopathy and renal failure. Obstruction of the pulmonary vascular bed with platelet aggregates (McNamara, Burran, Larson, Omiya, Suchiro and Yamase, 1972) and immunologically triggered opening of pulmonary shunts (Melrose, Nahas, Alverez, Todd and Dempster, 1965) helped to produce post-operative pulmonary congestion and hypoxia ('perfusion lung').

A significant reduction in pulmonary surfactant activity followed whole blood perfusion, accompanied by reduced lung compliance, increased surface tension and microscopic changes akin to those seen in infantile respiratory distress syndrome. (Gardner, Finlay and Tooley, 1962). Proctor (1966) postulated that the homologous blood syndrome was precipitated by incompatibility reactions occurring not only between recipient and donor blood, but also between individual pooled donor elements.

Circulation of total blood primes through the early oxygenator/roller pump systems also produced damage to red blood corpuscles (haemolysis) and to plasma proteins (denaturation) and made extravagant demands upon transfusion services. Viral hepatitis remained a serious late complication even after screening donors for the presence of Australia antigen. The reported incidence following transfusion varies between 0.16% and 6% (Doenicke, Grote and Lorenz, 1977) and has not been reduced by the introduction of frozen washed cells.

2.5.3 Haemodilution during bypass

In an attempt to conserve blood, Panico and Neptune (1959) designed a pump oxygenator in which a largely saline prime was layered on top of the patient's blood. This development introduced the concept of haemodilution and promoted experimental and clinical work at various centres (Cooley, Beall and Grondin, 1962; Greer, Carey and Zudhi, 1962). Only partial haemodilution was possible with most early large-volume oxygenators in order to guarantee delivery of a solution of adequate oxygen-carrying capacity to the patient. Litwak, Gadboys, Khan and Wisoff (1965) utilized partial ACD blood/albumin/crystalloid primes and noted a reduction in pulmonary and coagulation complications as well as a linear increase in urine production with increasing haemodilution. McGrath, Gonzalez-Lavin and Neary (1989) used dextran or albumin to improve the flow characteristics of blood and to avoid the capillary blockage produced by intravascular aggregates (sludging). Experimentation with total non-haemic primes followed, which used low volume primes of 5% dextrose in water and perfused at low flow rates (20 ml/kg/min) to minimize mechanical damage to erythrocytes (Zuhdi, McCollough, Carey, Krieger and Greer, 1961).

More recently higher volume primes utilizing more physiological flow rates have been employed. Some authors have advocated electrolyte solutions only (Laver and Buckley 1972; Lilleaasen Froysaker and Stokke, 1978) and others crystalloid colloid mixtures (Lee, Rubin and Huggins, 1975; Zubiate Kay, Mendez, Krohn, Hockman and Dunne, 1974) sometimes supplementing with autologous blood transfusion post-bypass (Hardesty, Bayer and Bahnson, 1968). Universal agreement exists that high-volume dilution reduces intra-operative and post-operative blood requirements. Verska, Ludington and Brewer (1974), were able to show a total peri-operative blood requirement of 1500 ml using a non-haemic prime compared with 3500 ml using a partial blood prime. Hallowell, Bland, Buckley and Lowenstein (1972), demonstrated that a further reduction averaging 860 ml per case could be achieved by employing autologous blood transfusion. Platelet counts were consistently higher and there was less postoperative bleeding in patients treated with total haemodilution and autologous

blood transfusion compared with patients receiving part-blood primes (Lilleaason, 1977).

Haemodilution has also shown to produce a remarkable absence of metabolic acidosis, interpreted as an index of good tissue perfusion with concomitant absence of peripheral vasoconstriction or cyanosis, stable electrolyte pattern, excellent urinary output and minimal renal problems (Roe, Swenson, Hepps and Bruns, 1964).

Finally, haemodilution has been shown to: minimize the increase in pulmonary compliance in dogs during whole-blood perfusion (Camishion, Fraimow, Kelsey, Tokunaga, Davies,,Joshi, Cathcart and Pierucci, 1968); to reduce post-perfusion pulmonary complications in humans (Hepps, Roe, Wright and Gardner, 1963) and to oppose the adverse effects of hypothermia on cerebral cortical flow (Utley et al., 1981).

2.5.4 Blood viscosity

The viscosity of blood depends mainly upon its haematocrit and the latter drops markedly when using non-haemic primes during CPB. Systemic vascular resistance varies with viscosity and arteriolar vasodilation (Smith and Crowell, 1967). Calculations for changes in systemic vascular resistance usually ignore the effect of viscosity on the assumption that this remains constant. However, the fall in blood pressure frequently seen when going on bypass using crystalloid primes, has been shown by Gordon, Ravin, Rawitscher and Daicoff (1975) to be substantially due to the acute reduction in viscosity produced by haemodilution.

2.5.5 Factors influencing hypotension at the commencement of bypass

The factors contributing to the occurrence of hypotension at the commencement of bypass include:

a) Acute reduction in viscosity produced by haemodilution (Gordon et al., 1975).

b) Reflex vasodilation of capacitance and resistance vessels during partial bypass, possibly caused by triggering of the baroreceptor system due to pulse generation by the beating heart during continuous fluid infusion from the arterial line (Boulanger, 1977).
c) Alteration in baroreceptor perception as blood flow changes from a pulsatile to a non- pulsatile mode (Dunn, Kirsch, Harness, Carroll, Straker and Sloan, 1974).
d) Dilution of circulating catecholamines by the extracorporeal priming volume (Balasaraswathi, Glisson, El-Etr and Azad, 1980).

2.5.6 Conclusion of priming fluids for CPB

The selection of the blood and blood products, crystalloids fluids or synthetic colloids used in priming the CPB circuit should conform to the basic physiological principals. Ideally the priming concoction should be of a similar osmotic and oncotic pressure as plasma in order to attempt to reduce the water component of the circulating blood volume from passing across the capillary walls into interstitial spaces. Blood viscosity plays a significant role in a drop in blood pressure during the initiation of CPB due to an acute haemodilution resulting from blood mixing with priming solution. It was, therefore, imperative that the drop in circulating haematocrit was calculated before going onto CPB using the following formula for adults and infants:

$$\text{PCV DROP in Adults} = \frac{\text{BV (Patients weight in kg x 70) + Patients HCT}}{\text{BV + Circuit Prime (Fluids)}}$$

Ideally approximately = 24 %

$$\text{PCV DROP in Infants} = \frac{\text{BV (Patients weight in kg x 80) + Patients HCT}}{\text{BV + Circuit Prime (Fluids)}}$$

Ideally approximately = 24 %

2.6 HAEMOFILTRATION

2.6.1 Haemofiltration compared to renal haemodialysis in general

Haemofiltration is a technique which was developed as an alternative to conventional haemodialysis for the treatment of patients in renal failure (Henderson, Livoti, Ford, Kelly and Lysaght, 1973). Its application in cardiac surgery relates to its principal ability to remove excess fluid from the circulation.

Haemofiltration differs from dialysis in that the membranes used are constructed in a different manner and from different materials. Furthermore, a dialysate fluid is not employed. Solutes of different molecular size and diffusivity are cleared at the same rate as each other by pure convection which is generated by applying a vacuum to the dialysate side of the membrane and a positive pressure to the blood side. High flux dialysers as well as haemofilters can be used for haemofiltration. These membranes have a filtration rate of up to 40% of the blood flow. In order to maintain patient fluid balance, a corresponding volume of physiological solution has to be re-infused. The advantages of haemofiltration over conventional dialysis are that the removal of substances of molecular weight between 2000 Daltons and 20 000 Daltons is more efficient and the rate of fluid removal is far greater.

This has important implications both with respect to dialysis quality and to the time required to perform adequate dialysis. In addition, haemofiltration patients have been shown to be much more stable haemodynamically (Chaignon, Aubert, Martin, Lucsko and Guedon, 1982). High flux dialysis and haemofiltration attracted the attention of open-heart teams primarily because both techniques may be used to haemoconcentrate CPB circuit contents (Hopeck, Lane and Schroeder, 1981). Most centres use dialysis for a number of years as an adjunct to CPB for those patients who underwent open-heart surgery with known renal insufficiency (Intonti, Alquati, Schiavello and Alessandrini, 1981).

Renal insufficiency in association with cardiac disease can occur in patients with rheumatic fever which causes renal disease as well as cardiac valvular lesions. Dialysis patients frequently develop severe coronary artery disease (Lansing, Leb and Berman, 1968), (Raggi, Boulay, Taber, Amin, Dillon, Burke and Chertow, 2002) and are prone to a form of infective endocarditis (Lowrie, Lazarus, Hampers and Merrill, 1974). Patients with bacterial endocarditis can develop renal failure as a result of circulating antibodies and mycotic emboli. Improvements in perfusion and oxygenation management have encouraged the submission of such patients, even with very severe renal dysfunction, to corrective cardiac surgery.

Haemodilution to a haematocrit of 20 - 30% is now almost a universal practice for CPB. This fluid load of 20 - 40 ml/kg is poorly tolerated immediately after bypass by patients in renal failure. The use of conventional haemodialysis in the immediate pre-operative and post-operative period may be limited in these patients due to their reduced cardiac reserve. Intra-operative haemofiltration or high flux dialysis can therefore play a very useful role in the treatment of these patients, by both removing toxic metabolites and by controlling the fluid load.

The other major reason for interest in haemofiltration results from the use of multiple dose cardioplegia for myocardial preservation (Hearse, Braimbridge and Jynge, 1981). This practice frequently leads to further haemodilution, together with an inappropriately high concentration of certain ions, particularly potassium and magnesium.

2.6.2 Historic perspective of haemofiltration in cardiac surgery

The use of haemofiltration as a means of removing fluid from oedematous patients dates back to the early 1900's when patients with renal failure were placed on ultra porous membrane devices. In the 1970’s the implementation of haemofiltration was used for open heart surgery (Henderson et al., 1973). At first the use of haemofiltration to concentrate blood in the extracorporeal circuit was restricted to severely haemodiluted patients. Haemofiltration under these conditions was found to be

particularly helpful in producing higher postoperative haemoglobin concentrations (Breckenridge, Digerness and Kirklin, 1970). During the 1980's it was recognized that this procedure could not only be applied to patients in renal failure but also to over-hydrated patients for volume control during open heart surgery.

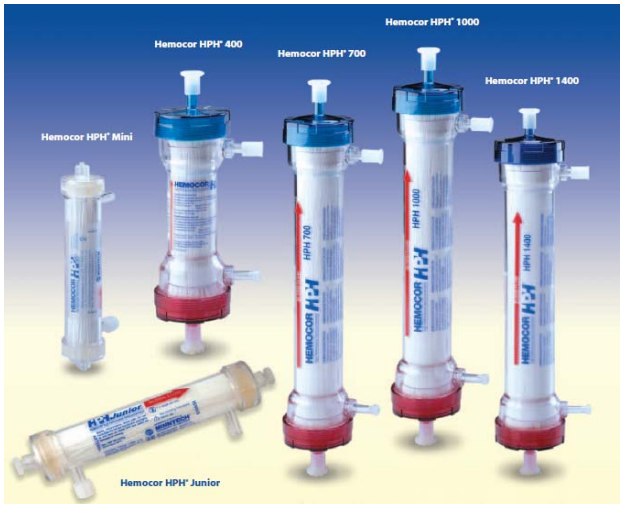
Today, haemofiltration, or haemoconcentration, has found widespread application as a means of volume control and blood preservation in cardiac surgery on adults as well as children. Stored homologous blood is associated with several potentially hazardous substances, which include: the release of emboli made up of non viable platelets; leukocycytes and fibrin (Reul, Beal and Greenberg, 1974; Liu, Su and Ding, 1992); post-transfusion thrombocytopenia (Bareford, Chandler, Hawker, Jackson, Smith and Boughton, 1987); fibronectin depletion (Pourrat, Sié, Desrez, Bernies, Diana, Ferrand and Fournial, 1985); the transmission of viral infections such as Cytomegalovirus and HIV (Gould, Graham, Freeman and Holden, 1987) and immunosuppressive effects (George and Morello, 1986). However, special variations of haemofiltration are used with patients undergoing open heart surgery, one of these specialized techniques is known as modified ultrafiltration (MUF) (Naik, Knight, Elliott, 1991).

2.6.3 Basic physiological principles of haemofiltration

The primary purpose of haemofiltration is to selectively separate excess plasma water and low molecular weight solutes and plasma proteins from blood using a semi-permeable membrane. The driving force for haemofiltration is hydrostatic transmembrane pressure, unlike haemodialysis which uses oncotic forces. Haemofiltration is accomplished by applying resistance to the exit side of the haemofilter to increase the transmembrane pressure within the haemofilter thereby, facilitating fluid removal across its semi- permeable membrane. Ultrafiltration rate can be increased by increasing the blood flow through the filter, thereby increasing the positive transmembrane pressure in the filter. The rate is also increased by increasing the resistance at the outlet of the haemofilter, thereby increasing the transmembrane

pressures which facilitate higher ultrafiltrate volumes and increase in the negative pressure on the effluent side of the filter (Richard, 1994).

Figure 15 depicts examples of different types of haemoconcentrators that were used at the NWAFH during the study. The picture shows the blood inlet ports at the bottom and an outlet ports on the top of the photograph. The ports on the right side are used as a waste drainage ports.



®

Figure 15: Picture of Hemocor haemofilters ® used at NWAFH

The size of the patient dictated the appropriate size of haemofilter that was used, the smallest filter (HPH mini®) in figure 15 was used for the smallest sized patients and the HPH 1400® was used in the largest size patients. Ultrafiltration is dependent on transmembrane pressures (TMP). Pressures of 100 - 500 mmHg are usually suggested by most manufacturers. However, other factors, such as the rate of blood flow through the haemofilter, blood temperature, viscosity of the blood and serum protein levels may affect fluid removal. Trans-membrane pressure can be mathematically expressed as:

$$TMP = (Pa + Pv) / 2 + Ps$$

(TMP = Total trans-membrane pressure; Pa = Arterial or inlet blood pressure; Pv = Venous or outlet blood pressure and Ps = Amount of negative pressure applied to the effluent side of the membrane)

General recommendation from the manufacturer and the most commonly used systems for the placement of the haemoconcentrator in the CPB circuit, is that the inlet tube leading to the ultrafiltration device may be placed as a branch connection from the arterial line filter. The outflow from the device is then returned to the cardiotomy reservoir. Another method may be to use the recirculation line in the circuit as the inlet line to the filter and again, return the outflow to the cardiotomy. In either case, only a single pump need be employed, that being the patient's main arterial pump. Some disadvantages to this method may be that, as the patient's pressures and flows change, the flow through the ultrafilter will also change. Another disadvantage is that the pump head flow rates may need to be increased to compensate for the shunt created by the ultrafilter. The filtrate may drain in to a collection bag either passively using gravity as an aid or actively by the use of a vacuum.

Other variations on these basic hook-up procedures are adopted and applied at some centres. The most important points that should be considered when using a haemoconcentrator in a CPB circuit are: the pressure head driving the flow to the filter; the filter return path to return the blood to the extracorporeal circuit and the collection of ultrafiltrate.

2.6.4 Technical considerations with the use of a haemofilter

Historically, ultrafiltration devices have either been made as parallel membrane sheets or of hollow fibre construction. The hollow fibre design due to its less bulky nature, smaller priming volume and simplicity of use, has become the most practical choice for haemoconcentrators. The hollow fibres are filled with thousands of hollow polysulfone, polyacrylolite or cellulose acetate fibres with each fibre having an internal diameter of about 200 microns.

2.6.5 Factors affecting the ultrafiltration rate

The rate of ultrafiltration per minute is dependent on:

- Blood supply by a dedicated blood pump or shunt
- Degree of haemodilution or gross fluid overload
- Blood viscosity
- Pressure difference between the hydrostatic and the osmotic pressure
- Pore size of the membrane within the haemoconcentrator
- Membrane surface area of the haemoconcentrator
- Structure of the membranes used in the haemofiltration.
- Transmembrane pressure

(Information summarized from user manual – Medtonic - Minntech Hemocor)

2.6.6 Haemofiltration circuit

It is possible to place a haemofilter anywhere in the circuit where a convenient shunt can be established. From a safety standpoint, it is preferred to return filtered blood to an area of the circuit which can deal with micro-bubbles. The placement of the ultrafilter in the extracorporeal circuit really depends on the application for that procedure i.e., will haemoconcentration be employed after the procedure or will it be employed throughout?

If the use of ultrafiltration is decided upon prior to the initiation of bypass, the inlet tube leading to the ultrafiltration device may be placed as a branch connection from the arterial line filter. The outflow from the device is then returned to the cardiotomy reservoir. Another method may be to use the recirculation line in the circuit as the inlet line to the haemofilter and again, return the outflow to the cardiotomy. In either case,

only a single pump needs to be employed, that being the main arterial pump head. Some disadvantages to this method may be that, as the patient's pressure and flows change, the flow through the haemofilter will also change. Another disadvantage is that the pump head flow rates may need to be increased to compensate for the shunt created by the haemofilter.

Other variations on these basic hook-up procedures may certainly be applied. Some of the main considerations when using this device in the bypass circuit is the pressure head driving the flow to the filter, the filter return path to return the blood to the extracorporeal circuit, and the collection of the effluent. Once primed, introduction of air into the system should be avoided since this will reduce the efficiency of the device. Blood may therefore be drawn from the following ports of the CPB circuit:

(a) A port in the venous line
(b) The arterial reservoir (via the coronary perfusion port if available)
(c) The arterial line

Filtered blood may be returned to the venous line, cardiotomy reservoir or to the 'quick prime' port of a hardshell oxygenator. Blood flow through the circuit may be controlled using a low flow pump or alternatively, and more simply, by using a controlled resistance applied to a shunt off the arterial line incorporating a flowmeter of the kind used in dialysis circuits. It is also possible to install the device in a parallel circuit in the arterial line as long as an arterial line filter or bubble trap is employed.

When designing the circuit it is worthwhile to bear in mind that a convenient means of collecting the remaining CPB circuit volume at the end of bypass is desirable. This may involve making a modification to the circuit at the end of bypass, e.g., transferring the remaining volume to the cardiotomy reservoir by forming a small re-circulating circuit. The remaining circuit volume may be displaced into this re-circulating circuit using a standard electrolyte solution so that bypass can be re-established safely and quickly, if necessary.

2.6.7 Operation

The haemofilter may be set up with the rest of the CPB circuit or added at a later time during the procedure. For instance, a team may elect to use one of these devices only if particular problems of fluid loading occur during the procedure. In this case it will probably be worthwhile to modify the routine circuit in a way which makes this addition safe and simple. On the other hand, other teams may decide to use one of these devices on a routine basis, in which case the device will be set up and primed along with the rest of the circuit. Some of these devices require to be rinsed prior to connection to the patient.

When priming initially with asanguinous fluid, it is helpful to produce a positive pressure (by restricting the outflow) of about 300 mmHg (40 kPa) once the air has been displaced. The vacuum line should be left open to the atmosphere at this stage. This fills the ultrafiltration compartment of the device. If the filter is added at a later stage, perhaps when the bypass has been established for some time or even at the end of the bypass, then the blood pathway should be filled slowly with the vacuum port open to the atmosphere.

Once most of the air has been removed the blood flow may be increased and vacuum applied according to the desired rate of fluid removal. Once primed with blood it is preferable to maintain a slow flow through the device to avoid sludging.

2.6.8 Fluid control

If the haemofilter is being used purely for the control of fluid load then it will probably be used only towards the final stages of the perfusion. In patients with a pre-operatively expanded blood volume (typically patients with chronic right-sided heart failure) it may be preferable to store the excess volume of blood until the end of the procedure, depending on the haematocrit. Ideally the perfusate should have a haematocrit of

around 25% during hypothermia in order to provide optimum viscosity consistent with adequate oxygen carriage.

However, if the haemofilter is being used to clear metabolites, ultrafiltration may be carried out during the entire bypass period with volume replacement using one of the standard haemofiltration solutions. The clearance of metabolites is related directly to the filtration rate multiplied by the ratio of filtrate concentration to plasma concentration. Since all substances below the cut-off of the membrane are filtered by haemofiltration the filtrate has basically the same concentration in the lower molecular weight range as the filtered medium. Hence, clearance by haemofiltration is directly proportional to filtration rate which means that fairly large volumes of ultrafiltration require to be processed in order to remove metabolites from patients with established renal failure. Haemofilters can concentrate down to a haematocrit of 70%. However, it is seldom practical and haematocrits of 45% to 55% fulfils most practical requirements.

2.6.9 Heparin removal by ultrafiltration

Heparin is a very heterogeneous substance which, depending on its source, may be made up of molecules ranging in molecular weight between 6000 and 22 000 Daltons (Goodman and Gillman, 1970). As such, at least a proportion of the heparin in the CPB circuit will be removed by ultrafiltration. Therefore, when employing haemofiltration during CPB heparin monitoring is even more important than usual.

2.6.10 Haemofiltration techniques

There is ongoing research in haemofiltration techniques, i.e. MUF, dilutional ultrafiltration (DUF) and "zero-balance" ultrafiltration (ZBUF) (Journois, Israel-Biet, Pouard, Rolland, Silvester, Vouhe and Safran, 1996). The latter two included the adult population and were off-shoots of MUF from paediatric cardiac surgery. Modified ultrafiltration consists of a circuit that allows removal of plasma water from the extracorporeal circuit as well as the patient, primarily at the end of the bypass

procedure. Dilutional ultrafiltration consists of haemodiluting the patient with a calculated crystalloid volume in the warming phase of bypass. This haemodilution is then reversed in order to enhance the removal of complement activated inflammatory mediators that are expressed in high levels at this time. "Zero-balance" ultrafiltration is similar to DUF in its haemodilution process and inflammatory mediator removal. However, it also removes excess of volume from the patient in order to increase plasma proteins and haematocrit.

2.7 MODIFIED ULTRAFILTRATION

2.7.1 History of modified ultrafiltration

It is just over 18 years since Elliot, Naik and Knight introduced the technique of modified ultrafiltration to paediatric cardiac surgery. The year 2001 represented a very good time for Elliot et al. to look back on the work done, to consider the position of modified ultrafiltration in the practice of cardiac surgery and to imagine the work that needed to be done in the future (Elliot, 2001).

Ultrafiltration began as a response to the observation of an accumulation of total body water associated with open heart surgery. This accumulation of total body water was first studied in detail by Tadaki Maehara from Tokyo while working with Martin Elliot and colleagues, after pioneering work by Ivan Novak from Prague (Maehara, Novak, Wyse and Elliot, 1991). Cardiopulmonary bypass with hypothermia and haemodilution is associated with a dramatic accumulation of water in the body and with tissue oedema. This tissue oedema causes organ dysfunction (Kern, Morana, Sears and Hickey, 1992). In the late 1980's and early 1990's, Elliot (1993) hypothesised that removal of water from the body towards the end of CPB would result in improved organ function and perhaps better outcomes. In that early era a series of experiments were carried out in which they were able to demonstrate that ultrafiltration performed during bypass (conventional ultrafiltration) was less consistent a technique than modified ultrafiltration (performed just after bypass) in the removal of total body water. A subsequent

prospective randomised trial by Naik, Knight and Elliott (1991) confirmed these changes in total body water and concomitantly demonstrated dramatically improved systolic blood pressure and elevation in haematocrit during ultrafiltration.

Further investigation of the elevation of blood pressure by Naik, Balaji and Elliott (1993) and later by Davies, Nguyen, Gaynor and Elliott (1998) using microsonometric crystals and pre-load recruitable work index demonstrated that the improved blood pressure was due to improved myocardial contractility and cardiac index and not to elevation of systemic vascular resistance. A serendipitous finding was a fall in pulmonary vascular resistance. Subsequently modified ultrafiltration spread rapidly as a technique throughout the world and most paediatric units are currently using modified ultrafiltration to support their cardiac practice.

Recently, MUF had been applied in adults and many have replicated the findings that were observed in children, in adults (Onoe, Magara, Nojima, Yamamoto, Hong, Uga, Kiguchi, Minamoto and Sasai, 1999). Ellliot (2001) outlined a policy or guide for future MUF researchers which states that a researcher should:

- Use a higher haematocrit during bypass
- Operate using moderate hypothermia
- Keep full flow on CPB wherever possible
- Use CUF during re-warming to ↑oxygen supply to meet increased demand
- Use MUF after CPB to optimise haemodynamic, modulate the inflammatory response and treat components of the injury caused by haemodilution and hypothermic cardiopulmonary bypass.

(Presented by Martin M.J Elliott at the 1215th UK Meeting on June 25, 2001)

Naik, Knight and Elliott (1991) introduced the technique of modified ultrafiltration to paediatric cardiac surgery at the Great Orlmond Street Hospital (GOSH) in 1991. Early studies demonstrated that ultrafiltration performed during bypass (CUF) was a less

consistent technique than MUF (performed just after bypass) in the removal of total body water (Elliot, 1993).

Subsequently, MUF has spread rapidly as a technique throughout the world. Today many centres are using MUF to support their cardiac practice in an aim to reduce haemodilution and homologous blood use.

2.7.2 Overview of previous studies

Table 8 is an overview of previous studies and includes the authors of the publication, the year of publication, the total number of patients included in the study, the title of the study and the clinical outcome.

Table 8: An overview of effects of MUF from previous studies

Author	Year	N	Title of Study	Clinical outcome
Naik, Knight and Elliott	1991	50	A successful modification of ultrafiltration for cardiopulmonary bypass in children.	↑ BP, ↑CO, ↓ blood loss, ↓ TBW, ↓ transfusion requirements, ↓ PVR ↓Vent. time, ↓ ICU stay
Naik, Knight and Elliot	1991	50	A prospective randomized study of a modified technique of ultrafiltration during paediatric open-heart surgery.	↓ Blood loss, ↓ blood transfused, ↓ TBW, ↑ arterial blood pressure, ↑ systolic BP, ↑ diastolic BP
Skaryak, Kirshbom, DiBernardo, Kern, Greeley, Ungerleider and Gaynor	1995	26	MUF improves cerebral metabolic recovery after circulatory arrest	↑cerebral oxygen delivery, ↑ metabolic recovery
Ad, Snir, Katz, Birk and Vidne	1996	80	Use of the modified technique of ultrafiltration in paediatric open-heart surgery: a prospective study.	↑ systemic BP, ↑ Haematocrit, ↓ Postoperative blood loss ↓ blood transfusion

Author	Year	N	Title of Study	Clinical outcome
Koutlas et al.	1997	41	Modified Ultrafiltration Reduces Postoperative Morbidity After Cavopulmonary Connection	↓ Postoperative bleeding ↓ transfusion requirements, ↓ hospital stay
Draasima et al.	1997	198	Modified Ultrafiltration After CPB in Paediatric Cardiac Surgery	↓ blood loss, ↓ transfusion requirements
Friesen, Campbell, Clarke and Tornabene	1997	20	Modified Ultrafiltration attenuates dilutional coagulopathy in paediatric open heart operations	↑ fibrinogen, ↑ plasma proteins, ↑ prothrombin time
Wang, Huang, Zhu, Chen, Su and Ding	1998	40	Modified Ultrafiltration in Paediatric Cardiopulmonary bypass	↓ TNF, ↓ IL-8 ↓ excess tissue fluid ↓ cytokines.
Davies, et al.	1998	21	Modified Ultrafiltration Improves Left Ventricular Function In Infants after Cardiopulmonary Bypass	↑ contractility, ↓ inotropic support
Bando, Turrentine, Vijay, Sharp, Sekine, Lalone, Szekely and Brown	1998	100	Effects of Modified Ultrafiltration in high risk patients undergoing operations for congenital heart failure	↓ transfusion requirements, ↓Ventilation time, ↓ ICU stay
Bando, Vijay, Turrentine, Sharp, Means, Ensing, Lalone, Sekine, Szekely and Brown	1998	24	Dilutional and Modified Ultrafiltration Reduces Pulmonary Hypertension After Operation for Congenital Heart Disease	↓Ventilation time, ↓ ICU stay
Daggett, Lodge, Scarborough, Chai, Jaggers and Ungerleider	1998	18	Modified Ultrafiltration versus conventional ultrafiltration in piglets	↑ contractility, ↑ BP, ↑ myocardial oedema, ↓ TBW
Pearl, Manning, McNamara, Saucier and Thomas	1999	34	Effects of MUF on plasma thomboxane B2, leukotriene B4, endothelin-1 in infants undergoing CPB	↑↓ TXB2, ET-1, LTB 4
Gaynor	1998 2003	R	Use of modified ultrafiltration after repair of congenital heart defects. The effect of MUF on the post operative cost in patients with congenital heart disease	↑ systolic blood pressure, ↑ cardiac index, ↑ haematocrit

Author	Year	N	Title of Study	Clinical outcome
Larustovskii et al.	1998	61	The use of modified ultrafiltration in correcting complex congenital heart defects in newborn and nursing infants.	↑ haematocrit, ↓ donor blood, ↓ inflammation mediators ↓ cytokines.
Schlunzen, Pedersen, Hjortholm, Hansen and Ditlevsen	1998	138	Modified ultrafiltration in paediatric cardiac surgery.	↑ Haematocrit, ↑ systolic arterial pressure, ↑ arterial oxygenation ↓ Heart rate.
Aeba, Katogi, Omoto, Kashima and Kawada	2000	29	MUF improves Carbon Dioxide Removal After CPB in Infants	↑ CO2 removal
Onoe et al.	1999	41	Application of modified ultrafiltration to cardiac surgery in adults.	↑ haematocrit, ↑ systolic blood pressure
Yndgaard, Andersen, Andersen, Petterson and Baek	2000	20	The effects of MUF on circulating endotoxins in children undergoing CPB	↓ endotoxin
Boga, Islamoglu, Badak, Cikirikcioglu, Bakalim, Yagdi, Buket and Hamulu	2000	40	Effects of MUF on inflammatory mediators and cardiac performance in CABG's	↑ CI, ↑ SVR
Grunenfelder, Zund, Schoeberlein, Maly, Schurr, Gunti, Fischer, Turina, Fragata, Wan and El-Gamel	2000	97	MUF lowers adhesion molecules and cytokine levels after CPB without clinical relevance in adults	↓ cytokines, ↓ ICAM, ↓ E-selectin, ↓ IL 6-8, ↓ Adhesion Molecules
Kameyama, Ando, Okamoto, Hanada, Yamanaka, Sasahashi, Hirose, Matsuno and Matsuura	2000	R	The effect of modified ultrafiltration in pediatric open heart surgery.	↓ intubation time, ↓ respiratory index ↑ pulmonary function
Onoe, Oku, Kitayama, Matsumoto and Kaneda	2001	24	Modified ultrafiltration may improve postoperative pulmonary function in children with ventricular septal defect	↑ BP, ↑ oxygenation, ↑ Systolic blood pressure ↑ haematocrit, ↑ pulmonary function
Luciani, Menon, Vecchi, Auriemma and Mazzucco	2001	R	MUF reduces morbidity after adult cardiac operation	↓ neurological, GIT and respiratory complications

Author	Year	N	Title of Study	Clinical outcome
Leyh, Bartels, Joubert-Hubner, Bechtel and Sievers	2001	48	Influence of modified ultrafiltration on coagulation, fibrinolysis and blood loss in adult cardiac surgery	↓ postoperative blood loss, ↓ blood transfusion
Kiziltepe, Uysalel, Corapcioglu, Dalva, Akan and Akalin	2001	40	Effects of combine conventional and modified ultrafiltration in adult patients	↑ haematocrit, ↓ blood loss, ↑ MAP, ↑ CI, ↑ oxygenation
Kamada, Niibori, Akimoto, Yokayama, Tofukuji, Iguchi, Ohmi, Tabayashi, Kikuchi and Matsuura	2001	20	Efficacy of modified ultrafiltration in coronary artery bypass grafting.	↑ haematocrit, ↓ Postoperative blood loss
Onoe, Magara, Yamamoto and Nojima	2000	9	Modified ultrafiltration removes serum interleukin-8 in adult cardiac surgery.	↑ haematocrit, ↑ systolic blood pressure ↓ serum IL-8.
Ootaki, Yamaguchi, Oshima, Yoshimura and Oka	2002	7	Effects of modified ultrafiltration on coagulation factors in paediatric cardiac surgery.	↑ haematocrit, ↑ platelet count , ↑ total plasma proteins, ↑ albumin, ↑ Fibrinogen, ↑ prothrombin, ↑ factor VII
Hiramatsu, Imai, Kurosawa, Takanashi, Aoki, Shin'oka and Nakazawa	2002	22	Effect of dilutional and modified ultrafiltration in plasma endothelin-1 and pulmonary vascular resistance after the Fontan procedure.	↓ endothelin-1, low PVR post operatively
Liu, Long, Feng, Ji and Li	2004	30	Comparative study of pulmonary function after CUF or MUF during cardiac surgery of infants	MUF improves pulmonary function post CPB in low weight infants
Sever, Tansel, Basaran, Kafali, Ugurlucan, Alisayin, Alpgut, Dayioglu and Onursal	2004	27	The benefits of continuous ultrafiltration in paediatric cardiac surgery.	↓ inflammatory mediators ↓ inflammatory response ↓ ventilatory support & ICU stay
Li, Hoschtitzky, Allen, Elliott and Redington	2004	16	An analysis of oxygen consumption and oxygen delivery in euthermic infants after CPB with MUF.	↓ systemic oxygen consumption ↓ cytokines

Author	Year	N	Title of Study	Clinical outcome
Fujita, Ishihara, Kusama, Shimizu, Kimura, Iizuka, Ozaki, Muraoka, Morimoto, Takeshima, Kikuchi and Maehara	2004	30	Effect of modified ultrafiltration on inflammatory mediators, coagulation factors, and other proteins in blood after an extracorporeal circuit	↑ haematocrit, ↑ number of red cells, ↑ albumin, ↑coagulation Factor VII ↑ X, ↑ platelet factor (PF)-4, ↑ antithrombin (AT-) III.
Mahmoud, Burhani, Hannef, Jamjoom, Al-Githmi and Baslaim	2005	40	Effect of modified ultrafiltration on pulmonary function after cardiopulmonary bypass.	↑ lung compliance ↑ gas exchange capacity
Sahoo, Kiran, Kapoor, Choudhary and Choudhury	2007	50	Effects of combined conventional ultrafiltration and a simplified modified ultrafiltration in adult cardiac surgery	↑ MAP ↑ haematocrit ↑ oxygenation parameters ↑↓ postoperative blood loss ventilation, ICU stay and hospital stay
Aggarwal, Das, Sharma and Kiran	2007	30	Efficacy of combined modified and conventional ultrafiltration during cardiac surgery in children	↑ posterior wall thickness ↑ haematocrit, ↑ systolic BP ↑↓ ICU stay
Medlin and Sistino	2006	5	Cerebral oxygen saturation changes during modified ultrafiltration	↑ Cerebral oxygen saturation
Wang , Zhu, Huang, Cai, Xu, Jlang and Shen	2007	80	Effect of flow rate, negative pressure, and duration of modified ultrafiltration on hemodynamics and inflammatory mediators	↓ hemodilution ↑ cardiac function ↓ inflammatory mediators
Takabayashi, Shimpo, Yokoyama, and Iwata	2007	30	Relationship between increased blood pressure and hematocrit during modified ultrafiltration for pediatric open heart surgery	↑ haematocrit, ↑ systolic BP and ↑ diastolic BP
Perez	2008	125	ICU outcomes in adult cardiac surgery patients in relation to ultrafiltration type	Ultrafiltration was considered a safe and reliable technique.

↑ - Increases, ↓ - Decreases, ↑↓ - No change, BP - Blood Pressure, TBW - Total body water, CO -Cardiac output, IL – Interleukin, PVR - Pulmonary vascular resistance, CI - Cardiac index, SVR - Systemic vascular resistance, ICU - Intensive care unit, R – Review, Vent. Time – Ventilation Time, CUF- Conventional ultrafiltration and MUF- Modified ultrafiltration

2.8 Summary: The role of MUF during cardiac surgery

Modified ultrafiltration entails haemoconcentrating the patient's excess circulating blood volume, deeming this technique important in the treatment of post-operative oedema and increasing the Hct (Naik, Knight and Elliott, 1991). This reduces the need for donor blood thereby, reducing the complications associated with homologous blood transfusion. Reduction in positive fluid balances increases the contractility of the myocardium (Davies et al., 1998).

Modified ultrafiltration reduces pulmonary vascular resistance, reducing intubation periods and thus, causing a decrease in the total costs of the post surgical care (Koutlas et al. 1997). It is beneficial in removing inflammatory mediators, Interleukin IL - 8, IL - 6 and tumour necrosis factor (TNF) (Wang, Chiu, Hsu, Wang, Lin, Chang, Huang and Chu, 1996). If all these factors are not corrected they pose as formidable threats that are responsible for a number of post cardiac surgical complications worldwide. Off pump surgery may be a solution but this cannot be instituted for all types of cardiac surgical procedures. Therefore, the task of finding a technique that is most efficient in countering these problems needs to be investigated.

The benefits of the MUF during CPB surgery has been established. The task now is to explore the effectiveness of the different types of MUF systems used at majority of the large cardiac centres in the world and to determine which of these methods is the most effective and the safest technique for the continuation and progress of MUF on a global platform in the future. Most cardiac patients undergoing CPB surgery at the Northwest Armed Forces Hospital undergo MUF. This is performed after CPB. It is performed using an artificial kidney (haemoconcentrator) and involves removing the extra fluid that is infused into the patient in order to perform CPB. This reduces the need for homologous blood transfusions which reduces the complications associated with it, i.e., MUF helps in removing harmful inflammatory mediators (IL - 8, IL - 6 and TNF) produced by the body during CPB. This decreases organ damage, thus resulting in a shorter recovery time. Modified ultrafiltration also increases the blood pressure which

reduces the need for certain anotropic drugs (Naik, Knight and Elliott, 1991; Wang et al., 1996; Fujita et al., 2004).

Recent studies show that the use of a combination of CUF on bypass and MUF after bypass yields the best results (Sahoo et al., 2007; Aggarwal et al., 2007). Many new systems such as AVMUF are being developed and tried at centres all over the world today. However, no trials have been done with VAMUF (Choudhary, Talwar, Airan, Yadav and Venugopal, 2007). All MUF systems work by pumping blood in reverse through either the bypass circuit or the body (from aorta to right atrium). The difference in this technique is that blood will flow through the bypass circuit and body in a forward direction (from right atrium to aorta) following the normal blood flow dynamics of CPB and the blood flow of the body as opposed to the reverse in AVMUF. The purpose of this study is to ascertain the safest, most effective and physiologically correct method to perform MUF.

CHAPTER THREE: METHODOLOGY

3.1 PRELIMINARY STUDIES

After determining that studies of this technique (venoarterial modified ultrafiltration) had not been done or published before, extensive work had to be undertaken before performing this new method in human studies. Preliminary studies of this novel technique included the following steps:

3.1.2 Literature survey for modified ultrafiltration in 2003

Although the first successful attempts to perform modified ultrafiltration (MUF) occurred in the early 1990's, it only began to become an area of interest among perfusionists and cardiac surgeons during the early 2000. It was during this era that stimulated vast interest on this technique. This interest prompted a literature survey to be carried out using perfusion text books, cardiothoracic journals and the information from the internet as a guide. After studying the information and brainstorming at a department level, an agreement was reached that the technique seemed theoretically viable as a possible solution to alleviate part of the deleterious effects of cardiopulmonary bypass, thereby improving patient recovery. Information gathering, brainstorming and an agreement to pursue this subject began at the Northwest Armed Forces Hospital situated in a military city known as Tabuk, in the Kingdom of Saudi Arabia.

3.1.3 National survey for MUF in the kingdom of Saudi Arabia

A survey regarding MUF was carried out in the Kingdom using the Arabian Perfusion website (www.sasect.sa). The Saudi Arabian Society for Extracorporeal Technology (SASECT) was contacted for a member list and relevant emails and contact details together with permission to contact registered members. Once permission was granted and the list was received, a survey was emailed to the respective members and the response was overwhelming. Support regarding any further information or assistance

with regards to MUF was also offered by many Saudi and international perfusionists (expatriates) employed within the Kingdom. The questionnaire that was posted on perfusion websites and emailed directly to numerous hospitals is attached as Appendix 2.

3.1.4 International survey for modified ultrafiltration

A similar survey was carried out on a larger scale using worldwide web (WWW) on the internet as this was the quickest method of communication considering the large perfusionist population globally. The following perfusion web sites were consulted: www.perfusion.com, www.perflist.com, www.middleastperfusion.com and www.amsect.com. The questionnaire was emailed to all the members located across the world. Replies were received from numerous perfusionists from hospitals situated in various countries e.g. Germany, America, Canada, Europe, India, Australia, and Netherlands. Some were selected and attached as Appendix 3.

3.1.5 Consensus on the most common types of MUF practice worldwide

All relevant information and diagram depictions of MUF were collected and reviewed intensely. All positive data regarding MUF were pooled in one category and all negative data in another (Appendix 4). Techniques were grouped into the different approaches of performing MUF. All the techniques gathered from the response to the survey were studied intensely in order to determine the advantage and disadvantages of the each technique. As a result of evaluation of these techniques a criteria for the ideal MUF technique was derived (Appendix 5).

Preliminary studies of circuit diagrams were performed to ascertain which of the MUF techniques were the most effective, user friendly, safe and required the least amount of changes to the CPB circuit. It was established that some techniques required too many changes to the MUF circuit to convert from conventional ultrafiltration on bypass to a MUF circuit post bypass.

Some AVMUF systems required blood from the aorta to flow retrogradely through the arterial filter while others used the recirculation line to bypass the arterial filter. Some techniques required a separate circuit to be employed that was dedicated to MUF only. This increased exposure to a foreign surface area thereby attenuating CPB's negative effects. Some had no heat exchanger capabilities and this contributed to heat loss after CPB and during MUF, especially in infants. Some techniques were not safe as they had no bubble trap or other in-line air-bubble safety device to trap any foreign particles or air generated within the MUF circuit. Some of the venovenous modified ultrafiltration (VVMUF) circuits and techniques that were investigated proved to be unpractical. The blood was drawn from the RA and redirected back to the RA after passing through the MUF system. This would result in high degrees of recirculation of the same blood.

After analysing and studying various methods of performing MUF a circuit was designed that seemed to fulfil all the criteria required for an ideal MUF system in accordance with appendix 5. It was unique since blood flow was from the RA to the Aorta after passing through the MUF circuit. This technique was referred to as the venoarterial modified ultrafiltration (VAMUF) indicative of the direction blood flow. The VAMUF circuit that was designed and final accepted as the method of choice is depicted in Figure 16.

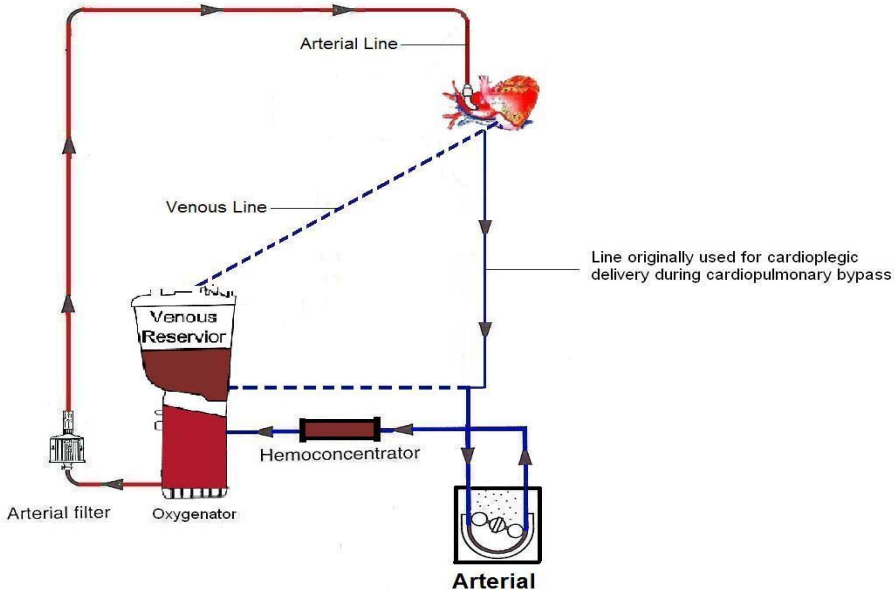


Figure 16: Basic VAMUF circuit diagram

3.1.6 Department presentation and permission to experiment on MUF circuits

The circuit diagram of the technique together with a detailed power-point presentation was presented to the Department of Cardiac Surgery at the NWAFH in Tabuk (Kingdom of Saudi Arabia) in order to obtain permission to carry out “dry” (cardiotomy reservoir circuit without priming fluid) and later “wet” circuit (primed with fluid) assimilation studies. The presentation was attended by the Chief of Cardiac services department, adult and paediatric cardiac surgeons and their registrars, the cardiologists and their registrars, the cardiac head nurse and the nursing team. The concept and technique was widely accepted resulting in support and permission being granted to carry out “dry” and “wet” circuit experiments.

3.1.7 “Dry” and “wet” circuit experimentation and assimilations

Many variants to the original design was studied and experimented on, in “dry” circuits for the next few months. This was a cost saving measure since no fluids were used in the circuit tubing allowing them to be altered and re-used in numerous investigations. After establishing which circuit was the appropriate one for this study, “wet” circuit (circuits primed with solution) investigations were initiated. This was performed at a later date due to the increased cost factor of using fluid in disposable bypass circuits. All perfusionists that intended to perform this technique on human subjects, during CPB, were trained on all aspects of this system. They also carried out individual “wet” circuit assimilations training.

3.1.8 Practical presentation of customized circuit

The final VAMUF circuit was presented at a practical seminar. The entire operating team were enlightened on the specifics of the technique as well as how it would affect their role in the operation. The surgeons were enlightened on the changes in cannulation after CPB. The anaesthetist and registrar were briefed on the protomine initiation time and time of MUF and the nursing team were provided with a system

readiness plan as well as the details of the complete blood gas and laboratory analysis. This study was submitted for ethical approval on animal subjects after all members of the cardiac team were enlightened regarding the technique and agreed that it was safe.

3.1.9 Ethical approval

In order to obtain ethical approval from the NWAFH ethical board, a veterinary surgeon (vet) was contacted and briefed on the entire process. On confirmation that the study appeared ethically safe for animal studies, a report was then submitted by the vet to the ethical board. Animal studies commenced on approval from the ethical board.

3.1.10 Animal studies

The breed of animal selected, based on the advice from the vet were goats (Capra Hircus). These goats were purchased with funds obtained from sponsors and the principal investigator. The venue allocated for the animal studies was the operating rooms at the department of post graduate studies at the NWAFH. The cleaning personnel were financially compensated for the services by the principal investigator. The animal studies were invaluable and provided important insight into the VAMUF technique and helped resolve minor faults. It aided the medical team to become more familiar and confident in the practical aspect of performing VAMUF. A photograph of an animal study carried out at the NWAFH animal laboratory is depicted in Appendix 6.

3.1.11 Presentation of findings of animal studies

The result of the animal studies was presented in the form of a digital power-point presentation to the appropriate heads of department and was open to constructive criticism. Laboratory results of the animal studies are attached as appendices 7; 8 and 9. Feedback was documented and taken into consideration when performing human studies. It was unanimously accepted that this new technique was a formidable one and was safe to perform in cardiac surgery patients. The relevant heads of departments

were supportive and recommended that a proposal to conduct the VAMUF study on human subjects be forwarded to the ethical board for ethical approval.

3.1.12 Modified ultrafiltration study on human subjects

It is generally very difficult for one to get ethical approval for any type of invasive medical study in the Kingdom of Saudi Arabia particularly on human subjects. This is due to the nature of Saudi judicial system which is based on “Muslim Shari’a Law” (According to the Quran). Medical staff and specialist surgeons can be placed on house arrest if investigations occur from a result of loss of life, during or after surgery. As an expatriate he or she is not allowed to leave the country until the case is resolved. This could possibly take years to get closure on. Thanks to the efforts of the heads of departments and their full support and co-operation official permission was obtained from the Ethical committee for the study to proceed.

3.1.13 Ethical concerns

Arteriovenous modified ultrafiltration and VVMUF are performed at numerous centres worldwide. Venoarterial modified ultrafiltration has not been undertaken before and there are no studies performed and published prior to this trial. Venoarterial modified ultrafiltration follows all the rules of conventional bypass. Blood is drawn from the venous side and infused in the aorta and into systemic circulation. The flow through the VAMUF circuit is pro-grade and mimics the flows of cardiopulmonary bypass. Blood flow through the coronary arteries increases while the workload on the myocardium should decrease due to decreased volume of blood entering the heart. This should offer the same advantages as the Intra Aortic Balloon Pump. A valid point of argumentation is that, if VAMUF is unsafe then one would also have to deem conventional cardiopulmonary bypass and the use of an Intra Aortic Balloon Pump (which is an emergency left ventricular assist device) as unsafe as well, because they follow the same principals as the VAMUF.

3.1.14 Research question

The research question that needs to be answered in this study is as follows: How does the VAMUF compare to the conventional AVMUF systems with regards to, set up, learning curve; lab results; performing the procedure; physiology of the procedure; haemodynamic changes in the patient and clinical outcome?

3.1.15 Rationale for study

Modified ultrafiltration during cardiac surgery is relatively new but has proven its importance in numerous studies (Sahoo et al., 2007). This progress is due to the exploration of new techniques on cardiopulmonary bypass and re-exploration of original MUF techniques. Most cardiac medical professionals have accepted the idea of MUF but hesitate to practise it due to complicated set ups, alterations required in the CPB circuit, reversal of blood flow through the CPB circuit, use of the cardioplegic circuit, use of a second pump, increased surgery time and use of additional PVC bypass circuit lines. This study aims to outline a more effective method of performing MUF with regards to, setting up the circuit, performing the process, maintaining haemodynamic stability during and after CPB and reducing ventilation time, reducing stay in the intensive care unit and decreasing hospital stay.

3.1.16 The use of MUF on adults and paediatric patients

History of MUF shows that the MUF technique was developed in the 1990's at the Hospital for Sick Children in London, U.K. by Naik, Knight and Elliot (1991). Because this study was performed at a hospital that specialised in children, concurrent studies at other centres seemed to follow this trend. However, recent studies do show that modified ultrafiltration reduces morbidity after adult cardiac operations (Luciani et al., 2001).

The priming volume of the CPB circuit in adult patients and paediatric patients are directly related to the weight of the patient. Therefore haemodilution is significant in both groups of patients. From calculations it can be extrapolated that haemodilution is very significant in both adults and paediatric patients alike (Appendix 11). Since MUF reduces haemodilution it could be used in adults as well as paediatric patients (Naik, Knight and Elliott, 1991).

Modified ultrafiltration improves systolic blood pressure and elevates haematocrit (Hct) levels (Draaisma et al., 1997). This results in haemodynamic stability and also reduces the need for donor blood. Thus reducing the undesirable effects associated with donor blood. This is beneficial to both adult and paediatric patients.

Modified ultrafiltration removes inflammatory mediators, IL-8, IL-6 and TNF that have a negative effect on patient's recovery time (Wang et al., 1996). It is crucial to adopt techniques that reduces ICU and hospital stay in patients.

Therefore, in this study MUF was performed on paediatric and adult patients as well to ensure that all patients benefited from its effect post CPB and cardiac surgery.

3.2 HUMAN STUDIES

3.2.1 Introduction

The location of the study was confined to a tertiary care facility at the Northwest Armed Forces Military hospital in Tabuk, Saudi Arabia. Tabuk is located in the northwest region of Saudi Arabia which is surrounded by Iraq, Jordan, Israel and Egypt as illustrated in Figure: 17. The Saudi Arabian Bedouin way of life is still a very important part of Saudi culture even though the country has become more westernized. Tea (Chai) made from roasted cardamom is a very important past time together with smoking the Hoka ("hubbly bubbly") (Figure 18).

Figure 17: Geographical location **Figure 18: Study population**

(The following pictures were presented to the principal investigator by the Saudi Arabian photographic association (Friends of light) for his contribution to medicine in Saudi Arabia and to be used in this study)

A Saudi Bedouin roasting nuts to consume as an important source of protein. Note that the Bedouin still use fire produced from wood as their source of heat for cooking. Their traditional Arabic coffee and tea plays a very important role in their daily lives.

Figure 19: Traditional way of life

The harsh Arabian natural environment has extreme weather conditions. The temperature in the Northwest region of Saudi Arabia ranges from a maximum of 50º C in summer (Figure 20), to a minimum of - 8º C in winter (Figure 21).

Figure 20: Sand dunes in summer

Figure 21: Snowfall in winter

3.2.2 Study design

The protocol for the study was approved by the hospital's ethical committee in advance. This study was a prospective, randomised clinical controlled study of 60 cardiac surgical patients that required life support by a heart lung machine. The patients were categorised into two groups. Group 1 the (AVMUF group) was the control group and consisted of 30 patients (*n* = 30). Group 2 was the experimental group which consisted of 30 VAMUF patients (*n* = 30). For uniformity and consistency all 60 patients underwent blind randomisation on the morning of the procedure by an independent member of staff.

3.2.3 Methodology

A clinical evaluation of the patients was carried out by the surgeons pre-operatively. Patients who met the inclusion criteria where provided with a letter of information for participation in the study, in English and Arabic (Appendix 12 and 13). Those who agreed signed an informed consent in English or Arabic (Appendix 14 and 15). In addition to this, they were also required to sign a letter of consent for operation/investigation that was required by the hospital (Appendix 16).

Patients were randomly allocated into one of the two study groups. Both study groups underwent conventional ultrafiltration (CUF) during CPB and MUF (AVMUF or VAMUF) for 10 to 15 minutes after separation from cardiopulmonary bypass (CPB). Two surgeons conducted all the surgical corrections during cardiopulmonary bypass. One was an adult surgeon and the other a paediatric surgeon. They have been working together for the past four years and are qualified consultant in their respective fields. One consultant anaesthetist together with his registrar put the patient off to sleep, intubated, and inserted all monitoring lines and assisted with the pharmacological control of blood pressure during the procedures. The principal investigator performed the MUF process after termination of cardiopulmonary bypass. He was responsible for ensuring that all blood samples were collected at the appropriate times, analysed and

recorded for final comparison. If MUF was performed by a second perfusionist, it was under the direct supervision of the principal investigator.

Demographic data, length of CPB, length of CSU stay and length of hospital stay, the use of hypothermic arrest, complications, haemodynamic support, use of peritoneal dialysis catheters for the relief of abdominal compression, creatinine levels, body weights and duration of intubation were also recorded by the principal investigator.

3.2.4 Patients selection criteria

Patients who participated in the study were selected according to following criteria:

3.2.4.1 Inclusion criteria

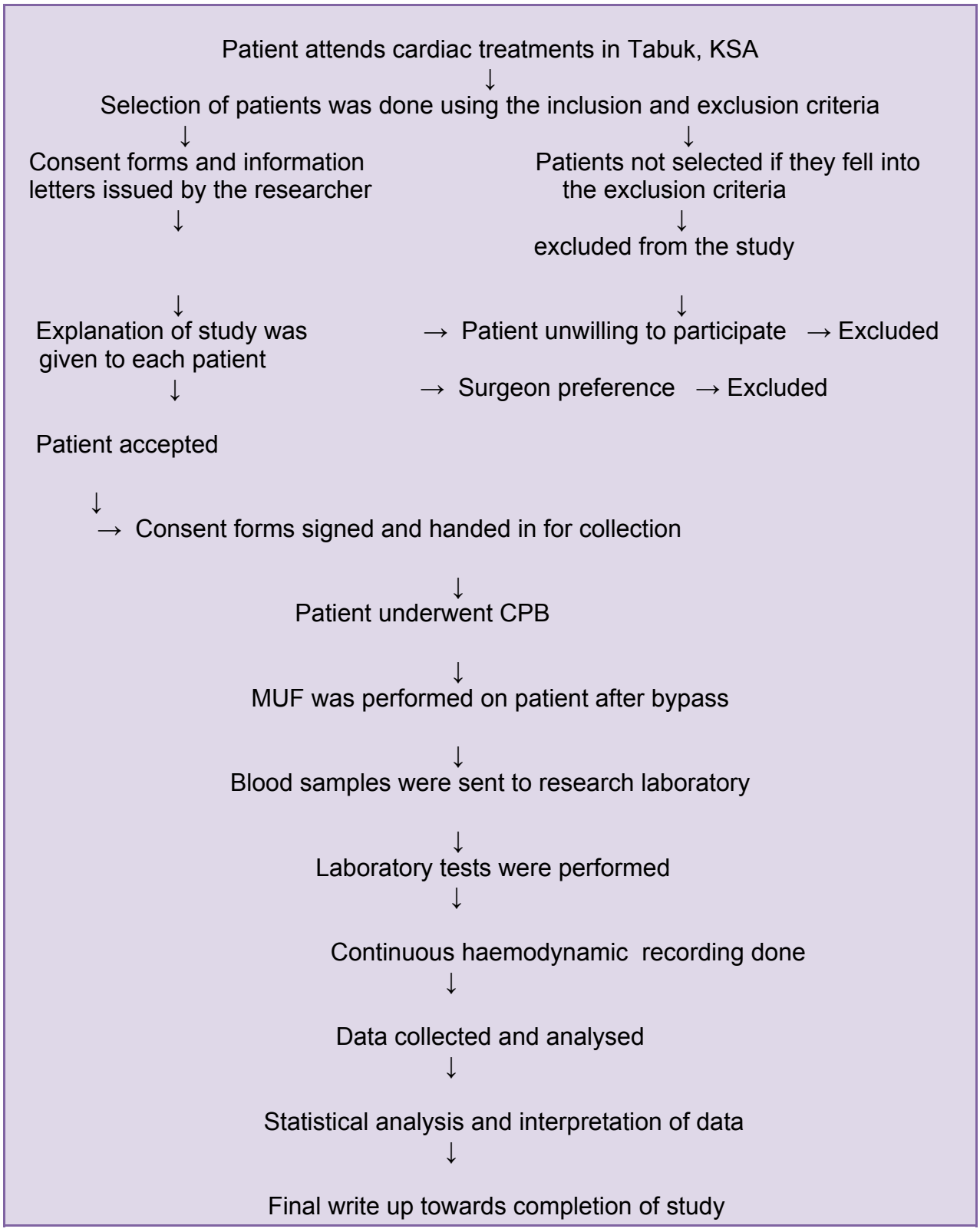
- Required life support by a heart lung machine.
- Infants/Paediatrics congenital cardiac surgical cases that required CPB.
- Only patients that were stable enough to perform MUF on.
- All adult Coronary artery bypass and valve cases on CPB.
- All patients between the ages of 1 week to 75 years.
- All patients with an ejection fraction of 25% and more.
- Reside or work in Saudi Arabia.
- Only patients operated at the NWAFH.

3.2.4.2 Exclusion criteria

- Off-pump Coronary Artery Bypass Grafting (OPCABG) patients.
- Patients that were haemodynamically unstable after termination of CPB.
- Patients with a low positive fluid balance post CPB.
- Patients that the operating surgeons did not prefer to perform MUF on.
- Surgeon preference

A flow chart summarising the research process is contained in Table 9.

Table 9: Flow Chart – Summary of the research process



3.2.5 Brief description of techniques of performing AVMUF and VAMUF

3.2.5.1 Conventional arteriovenous MUF

The conventional AVMUF technique was performed after termination of CPB. Blood was removed from the heart retrogradely from the aortic cannula that was originally placed in the aorta during CPB. It was then circulated through a pump-head that was dedicated for MUF, where it was haemoconcentrated before being re-infused into the patients via the RA. This technique is known as arteriovenous modified ultrafiltration (AVMUF). Positive fluid balance was calculated and MUF terminated when sufficient filtrate was obtained in the ultrafiltrate waste bag. Patients were always left with a reasonable positive fluid balance in both types of MUF to encourage postoperative urine output.

3.2.5.2 Venoarterial MUF

Venoarterial modified ultrafiltration was also performed after termination of cardiopulmonary bypass. In VAMUF, blood was removed from the right atrium of the heart from a venous cannula that was originally placed in the RA during CPB. This blood is then circulated through the main pump head where it is haemoconcentrated before being infused into the patients via the arterial cannula that was placed in the aorta during routine CPB. This is known as venoarterial modified ultrafiltration (VAMUF). Positive fluid balance was calculated and VAMUF was terminated when sufficient filtrate was obtained in the ultrafiltrate waste bag. Patient's pressure was observed and controlled at all times by the principal investigator in consultation with the anaesthetist.

3.2.6 Parameters measured during the MUF study

The results of the parameters measured were categorized under two major headings i.e., primary and secondary outcomes. The primary outcomes included the data of parameters that had a bearing on patient outcome and important in establishing which

method of MUF is the most effective. The secondary outcome is important as a reference of data surrounding the study.

3.2.6.1 Primary outcomes

The primary outcomes measured included the following:

- Post operative variables – Included: ventilation time, ICU stay, hospital stay and discharge day
- Fluid management data – Total fluid input, total fluid output and fluid balance
- Haemodynamic variables data analysis:
  a.) Arterial pressure : Systolic
  Diastolic
  Mean
  b.) Central venous pressure
  c.) Heart rate (beats per min)
- Blood gas analysis data - pO_2, pCO_2 and blood saturation
- Haematological value data analysis – Hct, HB, RBC, WBC, platelets and Albumin
  Hct: High - Improved haemodynamic stability (↓) need for donor blood
  Low - Compromised haemodynamic stability (↑) need for donor blood
- Electrolyte data analysis – Serum concentration of sodium, potassium, calcium, serum phosphate and magnesium
- Renal related markers data analysis – serum BUN, creatinine and uric acid
- Cardiac markers data analysis - CK, CK-MB and serum lactate
  Lactate**:** High – Signifies inadequate tissue perfusion
  Low – Signifies good tissue perfusion

3.2.6.2 Secondary outcomes

The secondary outcomes measured were as follows:

- Modified ultrafiltration demographic data - Patient's mean age, gender, height, weight, BSA and type of operation
- Cardiopulmonary bypass (CPB) data - CPB and cross clamp time
- CUF and MUF ultrafiltration data

  Total CUF volume = Ultrafiltrate removed from the circuit during CPB.

  Total MUF volume = Ultrafiltrate removed from the patient & CPB.

3.3 CARDIOPULMONARY BYPASS

3.3.1 The extracorporeal circuit

The general trend in modern day cardiopulmonary bypass (CPB) during cardiac surgery is to reduce the CBP circuit as much as safely possible. This primary reason behind reducing the length of the CPB circuit is to reduce the priming volume required to prime the circuit. This reduction in priming volume facilitates a decrease in the degree of haemodilution of the patient's intravascular blood volume.

Another important factor dictating the design of the bypass circuit is the need to reduce increased surface contact of blood and its components to a foreign surface. This reduction in exposure results in a reduced production of harmful inflammatory mediators. Conventional CPB requires the use of a cardiotomy reservoir which is usually opened to the atmosphere. This results in blood air interface and an increase in the production of inflammatory mediators. Length of the circuit, priming volume and an open circuit are the primary detrimental factors that affect the patient during bypass. In this research these factors were taken into consideration when selecting a method to set-up and perform CPB at the research centre. The philosophy of the NWAFH perfusion department was that no two patients are alike. Therefore, no patients should be treated with exactly the same equipment based on convenience. Therefore, each patient who underwent CPB had a circuit custom made to suit the individual requirements.

3.3.2 The heart lung machine (COBE Century)

Modern day heart lung machines have come a long way since the inception of the first machine in cardiac surgery in the early 1950's by Gibbon (1954) The heart lung machine is still the basis upon which most cardiac surgical operations are possible today. This technology together with the knowledge and skill of a professionally trained perfusionist allows the surgeon to operate safely on a bloodless operative field.

3.3.3 Back-up heart lung machine

One of the two heart lung machines used in this study was the COBE Century (USA) (Figure 22). This basic traditional heart lung machine consisted of 4 belt driven pump heads mounted on a metal base with wheels. These pumps are connected to a central processing unit (CPU) and a control panel. Conventional pumps have their control knobs located on the front panel of each individual pump head. There are usually two metal masts that form an integral part of the machine that can be used as a drip stand and as a holder to attach accessories upon. It was used once in each MUF group.

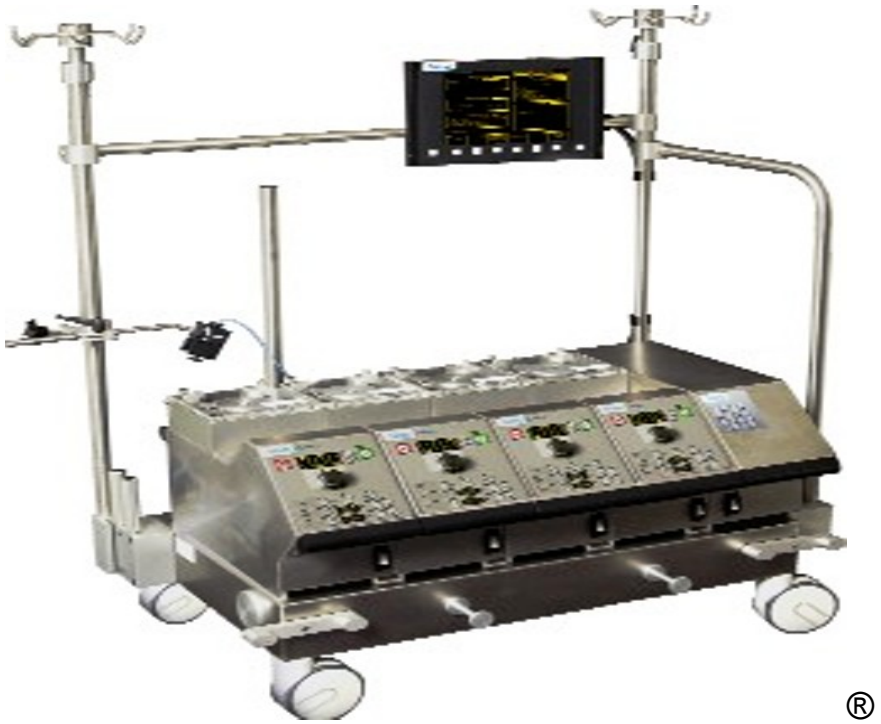


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Figure 22: The COBE Century heart lung machine

The COBE Century heart lung machine was also fitted with a Sechrist blender that was mounted onto one of the two drip stands. This apparatus allowed for accurate control of mix air and FiO_2 gases entering the oxygenator during CPB.

A vacuum assisted venous drainage (VAVD) system by Marquet (Germany) was also attached to the machine to assist with venous drainage when CPB was initiated. The pump was also fitted with two safety devices. The level sensor was connected to a level sensor pad that was placed on the venous reservoir before bypass. This ensured that the pump would first alarm and then be automatically switched off if the blood level in the reservoir dropped below the sensor level. This ensured that no air would be pumped into the patient as the reservoir is an open system. The second safety device was a bubble detector that was connected to the arterial line post arterial filter. This was the last line of defence that would switch the main pump off in the event that air passed the level sensor and the arterial filter. This machine was used as a secondary pump as it was the older of the two machines and was therefore not used routinely.

3.3.4 Primary heart lung machine (JOSTRA HL 30)

The second heart lung machine that was used was the HL 30 made by Jostra and marketed by Marquet (Germany) (Figure 23). The HL 30 was the primary pump that was used for majority of the cases that MUF was performed in. This machine was equipped with all the hardware and software technology that present day could offer including an online Jocap recording system.

Figure 23 reveals the ergonomic design of the HL 30. The main pump head was completely mobile and allowed the perfusionist to align the pump head as close to the patient as possible while still ensuring the sterility of the operating environment. This proximity to the operating table allowed for reduction in the length of the CPB circuit's PVC tubing facilitating a lower priming volume. Individual pump heads delegated for use

as a cardiotomy sucker, vent, intra-cardiac sump and cardioplegic pump could also be placed closer to the patient due to its smaller size and mounting abilities when compared to other machines. This allowed for a reduction in dead space within the tubing, and hence reducing unnecessary surface contact of blood to the tubing surface and thereby reducing systemic inflammatory response.

The VAVD system was also used on the HL 30 to assist with venous drainage. This allowed for the venous reservoir to be placed higher up than normally possible and much closer to the patient. These advantages reduced the priming volume from 1700 ml to 1000 ml when compared to a conventional system used in adults. The Jocap online computer recording system stored all the pumps activities for reviewing and future reference.

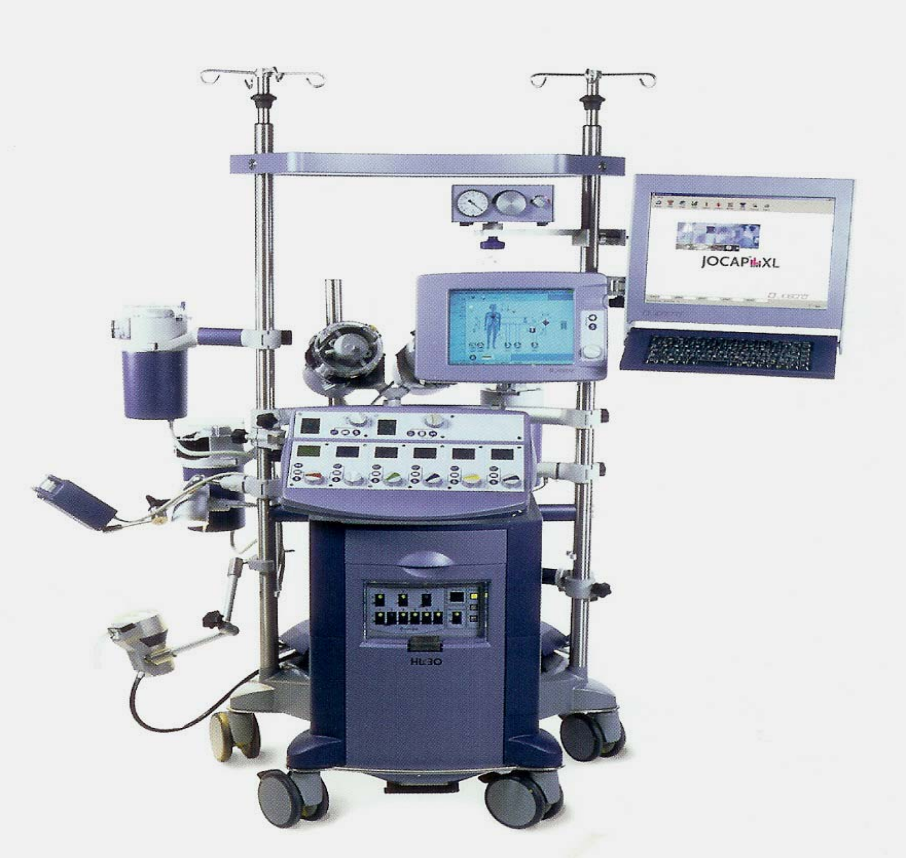

Figure 23: Jostra HL 30 heart lung machine ®

3.3.5 CPB protocol

A Jostra HL 30 heart lung machine was used to support most patients during cardiopulmonary bypass surgery. Various oxygenators were used in both adults and paediatric cases. Adult oxygenators included the: Quadrox by Jostra, Avant by Dideco and the Affinity which was supplied by Medtronic. The neonate, infant and paediatric oxygenators consisted of the Safe Micro & Mini by Polystan and the D 901, D 902 & D 905 manufactured by the Dideco group. The Gish Vision cardioplegic delivery set was used for all groups.

3.3.6 Selection criteria for suitable oxygenators

All circuits were set up after patients were wheeled into theatre. The selection of oxygenators and appropriate circuits were based on the patient's BSA. Table 10 outlines the oxygenator, size of custom pack and the priming volume required for patients based on their BSA.

Table 10: Appropriate oxygenator size chart

Body Surface Area	Oxygenator	Custom Pack	Priming Volume
0.1 - 0.29	Safe Micro (D 901)	Neonate	300 ml
0.3- 0.95	Safe Mini (D 902)	Infant	500 ml
0.96 – 1.65	D 905	Paediatric	800 ml
> 1.65	Quadrox Avant Affinity	Adult	1500 ml

3.3.7 Priming solutions

Table 11 outlines the priming solutions and drugs used on the different age groups

Table 11: Priming solution

Additives	Neonates	Infants	Paediatric	Adult
Fluids				
Plasmalyte A	50 ml	100 ml	250 ml	1000 ml
Albumin	50 ml/ 20 %	100 ml/ 20 %	100 ml/ 20 %	250 ml/ 5 %
Gelofusine	50 ml	100 ml	250 ml	250 ml
Blood	1 Unit of PRBC	1 Unit of PRBC	1 Unit of whole blood	Unless required
Drugs				
Heparin	3000 IU	3000 IU	5000 IU	10000 IU
Dexamethozone	2 mg	4 mg	8 mg	8 mg
Mannitol	2.5 ml/kg body weight	2.5 ml/kg body weight	2.5 ml/kg body weight	-
Lasix	-	-	-	40 mg
Zinacef	325 mg	750 mg	750 mg	1.5 g
NaHCO3	10 ml/ 4 %	20 ml/ 4 %	20 ml/ 8 %	
CaCl	200 mg	200 mg	250 mg	

3.3.8 Priming constituents

In the adult patient group, 1000 ml of Plasmalyte-A was introduced into the CPB circuit. Another 250 ml of 5% albumin was added to the prime in order to coat the lumen of the tubing in order to reduce platelet adhesion whilst also assisting in maintaining oncotic pressures during CPB. Gelofusine (250 m) was used as a volume expander and to

complete priming of the cardioplegic and MUF circuit. This resulted in a total of 1500 ml of prime to which heparin (anti-coagulant), Dexamethozone (anti-inflammatory), Lasix (diuretic) and Zinacef (antibiotic) was added.

The neonate, infant and paediatric circuits were initially primed with 500 ml of Plasmalyte - A before the addition of 100 ml of 20% albumin. After infusion of heparin into circulating prime, homologous donor blood was then introduced to the circuit. The prime was circulated through the haemoconcentrator and washed (filtered) in order to reduce some of the deleterious effects associated with donor blood as well as to decrease the lactate value. Gelofusine was added as a volume expander as required during the “washing” process. The gas blender was adjusted during circulation in order to stabilize the pO_2 & pCO_2 levels.

Blood samples that were taken from the prime were analysed following. Thereafter, electrolytes, oximetry and ACT were corrected accordingly. The haemofilter has a membrane pore size that allows most drugs to pass through it. Therefore, drugs were added to the prime just before going onto bypass i.e., after the washing process was complete. This was to prevent any drugs from being washed out together with the ultrafiltrate.

3.4 Perfusion

3.4.1 Perfusion records

An accurate perfusion record was completed for each case which included the following patient information: hospital ID; name; age; gender; height; weight; BSA; allergies; blood type; pre-op laboratory data and diagnosis/history. Additional procedure information included: date; procedure; perfusionist(s); surgeon; surgical registrars; anaesthesia personnel; nursing staff and comments/events. The following disposables were used and lot numbers were recorded: oxygenator; cardiotomy reservoir; tubing

pack/arterial filter; cardioplegia set; ultrafiltration set; vacuum assisted venous drainage set and cell saver set.

The following patient parameters were documented at 25 minute intervals: blood flow rates; arterial line pressure; arterial blood pressure; central venous pressure; arterial blood gases results and activated clotting times (ACT) results. Patient temperatures which included: oesophageal and rectal. Additional temperature included: venous blood; arterial blood; cardioplegic solution; myocardium and heat exchanger settings and gradient were also recorded. Additional information recorded included: gas flow settings on the blender; oxygen and sweep rate.

Fluid input volume consisted of the CPB prime, blood products, colloids and cardioplegic solution. Fluid output volumes included: pre-operative autologous prime (PAP), retrograde autologous prime (RAP), urine output, conventional ultrafiltrate (CUF), modified ultrafiltrate (MUF) and the volume of contents in the drains. The name and dosage of medications administered via extracorporeal circuit and the inhalational anaesthetic agent (sevofluorane) dosage on the bypass circuit were recorded. The perfusion records were signed by the primary perfusionist and retained as part of the patient's medical record. Additional copies of the perfusion record were retained in the perfusion department and patient database. An electronic copy was also stored in the Jocap software system of the HL 30 heart lung machine.

3.4.2 CPB checklist

A checklist was completed and signed for each case before initiating CPB. The checklist was co-signed by the second perfusionist assigned to the case. It was thereafter retained in the perfusion department records (Appendix 17).

3.4.3 Safety devices employed during CPB

The safety devices that were employed during CPB on the bypass circuit included the, arterial filter; bubble detector; level sensor; anaesthetic gas scavenge, line pressure alarms and a bubble trap.

3.4.4 Appropriate blood flow rate during CPB.

The calculated blood flow rate for each patient was determined prior to CPB using the patient's BSA times the cardiac index. The appropriate blood flow rate during CPB was calculated by evaluation of a combination of measurements which included: venous oxygen saturation, body surface area, arterial blood pressure and temperature. The additional parameters that guided blood flow rate included levels of arterial pO_2, venous pO_2, oxygen consumption, base excess, circuit volume, physician request, stage of the operation and level of anaesthesia.

3.4.5 Set-up of CPB circuit

Cardiopulmonary bypass was conducted with an appropriate membrane oxygenator (Dideco or Polystan Safe) and a Jostra HL 30 or COBE Century cardiopulmonary bypass machine. The CPB and cardioplegic circuits were flushed with CO_2 gas for 5 minutes before plasmalyte-A solution was introduced into the circuit.

Since this system of MUF and conventional ultrafiltration requires no changes to be made to the circuit, the haemoconcentrator was connected to the cardioplegic circuit upon set-up. Flushing of the haemoconcentrator together with the cardioplegic circuit resulted in easy priming and eradication of air bubbles from within the haemoconcentrator. A paediatric haemoconcentrator the Dideco D 02 was used for all paediatric patients and the Dideco D 04 for all adults. The priming volume of the D 02 haemoconcentrator was 25 ml and the D 04 was 50 ml. This required a reasonable amount of priming volume to prevent excessive haemodilution. Although these are regarded as paediatric haemoconcentrators they allowed adequate flows through it in order to facilitate the performance of MUF in all groups from Neonates to Adult patients.

3.4.6 Basic CPB procedure

Prime was maintained at 30°C in order to ensure rapid cooling whilst ensuring not to

exceed a temperature gradient of 10-12°C between the prime and the patient's blood. This reduced the risk of cerebral tissue injury. Priming solution was pre-circulated through a 5 μm prebypass filter (Dideco) before cannulation. Cardiopulmonary bypass was employed with core temperature of 30°C to 33°C. Non-pulsatile flow of BSA x 2.4 (adults) and BSA x 2.6 (infants) and BSA x 2.8 (neonates) was used at normothermia. A minimum of 70 % of the patient's full flows were maintained at 30°C. Mean arterial blood pressure was maintained between 50 and 80 mmHg in adults depending on the stage of the procedure. Oxygen inflow from the gas blender into the oxygenator was adjusted for normal oxygenation in accordance with the patient's temperature.

3.5. ANAESTHETIC PROTOCOL

3.5.1 Anaesthetic regime for CPB and cardiac surgery

All patients were kept "nil per mouth" from midnight. Lorazepam was given orally 2 – 3 mg (0.03 – 0.05 mg/kg) at sleeping time. Two hours before surgery, lorazepam was given in the same dose. Morphine 0.1 - 0.15 mg/kg intra muscular was given one hour before surgery. Intravenous maintenance fluid, lactated Ringer's solution (100 ml/hr), was started after insertion of a 14 - G venous cannula with the aid of local anaesthetic infiltration.

Upon arrival in the operative room, patients received sedation dose of midazolam 1 - 3 mg (0.01 - 0.1 mg/kg) IV according to the age. Insertion of arterial catheter 20 - G was inserted under local anaesthesia in the non-dominant hand unless otherwise indicated. Anaesthesia was induced using fentanyl 3 – 5 mg/kg IV and thiopental sodium (3 - 5 mg/kg) IV. Muscle relaxation was achieved with pancuronium bromide (0.1 - 0.15 mg/kg) IV. Following relaxation and endotracheal intubation, patients were ventilated to normocapnia with a 50% oxygen air mixture.

Anaesthesia was maintained with isoflurane, intermittent doses of fentanyl and muscle relaxation, as needed. Following which, a central venous line was inserted via the

internal jugular vein (IJV) route (commonly the right IJV) with Seldinger technique and insertion of balloon-tipped pulmonary artery floatation catheter was inserted when needed only.

3.5.2 Administration of Aprotinin (Trasylol)

Intravenous infusion of 2 million kallikrein inactivating units of aprotinin (Trasylol, Bayer, AG, Leverkusen, Germany, 10,000 KIU/ml, 50 ml vials of pure aprotinin in a preservative-free isotonic solution) was administered through the CVP catheter over 20 minutes after induction of anaesthesia and before skin incision.

Subsequently, half a million KIU/hour of aprotinin was administered by continuous intravenous infusion throughout the operation until skin closure. Before the institution of CPB, 2 million KIU of aprotinin was added to the priming solution of the circuit. During bypass, the drug was infused in the same infusion rate through the venous port of the CPB machine. A test dose of aprotinin (1 ml) was administered through the central venous catheter to the patient to help detect any allergic responses before the administration of the initial loading dose. The prime dose was not added to the CPB prime solution until the patient had safely received the loading dose.

3.5.3 Anticoagulation and activated clotting time (ACT)

Preoperatively, patients were anticoagulated with 300 – 400 IU/kg heparin sodium. After 3 minutes, 2 ml whole blood sample, withdrawn from the arterial cannula, were injected in ACT tube (Hemochron, Edison, NJ, USA seen below). The ACT tube is kaolin-activated, non-evacuated glass test tube with flip-top for needleless blood sample transfer. The ACT test was performed with the aid of the Hemochron 401 portable coagulation instrument (Hemochron, USA). The first heparin dose was supplemented by 50 to 100 IU/kg top-up doses if needed to maintain an ACT greater than 450 seconds. During CPB, blood samples for ACT were obtained from the arterial port of the bypass machine.

The Hemochron Jr. Signature® Micro-coagulation System as shown in Figure 21, was one of the machines that was used at the NWAFH cardiac surgery department to measure and monitor ACT's. It performed rapid coagulation tests in the operating room with just one drop (.015cc) of fresh blood sample which was withdrawn directly from the patient or the heart-lung machine

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Figure 24: Hemochron ACT machine

3.6 SURGICAL PROCEDURE

3.6.1 Cardiac surgical techniques

The surgical technique included full median sternotomy approach. All procedures included in this study were performed using CPB established by aortic inflow cannulation. For outflow cannulation, the bi-caval technique was used for valve operations, and single two-stage cannula was used for aortic valve and coronary artery bypass grafting (CABG) surgery.

Left ventricular venting was performed through aortic root needle for CABG and through left ventricle cannula for valve surgery. All coronary anastomosis and valve surgery were performed under cardiac arrest using cold blood antegrade or retrograde cardioplegia, or both. Boston's children cardioplegic solution was used in all patients. The surgeons were made aware of which type of MUF was to be performed before initiation of bypass. There were no changes required on the surgical side for conventional ultrafiltration (CUF) to be performed in both groups.

In the AVMUF group, the surgeon was required to unclamp the arterial line and clamp off the venous line proximal to the venous reservoir side. At the termination of AVMUF the arterial cannula was removed first and the circuit was emptied into the patient via the line in the RA. In the VAMUF technique, the surgeon was asked to connect the outlet of the cardioplegic line into an insertion point in the RA. During termination of VAMUF the venous line was removed first and the circuit was emptied via the arterial cannula in the aorta.

3.6.2 Temperature regulation during CPB

The patients were cooled using a Jostra HCU 30 heater-cooler unit (Figure 25). Adult patients were cooled to 32^0C and paediatric to 30^0C during the entire procedure, before re-warming commenced. The HCU 30 heater cooler unit has three water outlets which can control the oxygenator temperature and the cardioplegic temperature independently. This machine has the ability for rapid cooling or warming while not exceeding a temperature gradient of 10-12 º C.

Figure 25: Jostra HCU 30 ® digital remote interface and heater-cooler unit

3.7 CONVENTIONAL CPB BYPASS

3.7.1 CPB perfusion technique

During CPB deoxygenated blood was removed from the heart via an arterial cannula which was placed in the RA before institution of bypass. As seen in Figure 26, blood flow was directed to a venous reservoir through a venous line. This flow generally results from negative pressure created in the venous line by the force of gravity. In this study an alternate method of venous drainage was performed, which made use of a vacuum assisted venous drainage (VAVD) system (Appendix 18). Blood from the venous reservoir was then pumped to an oxygenator by an arterial roller pump head. Gaseous exchange occurred in the oxygenator (artificial lung) after which blood then moved through an arterial filter, which trapped air bubbles and micro emboli that may have entered the bypass circuit. Blood then re-entered the heart via an arterial cannula that was placed in the aorta before CPB. The cardioplegic delivery circuit mixed blood with cardioplegic solution which was then infused into the aortic root to accomplish cardiac arrest by destabilization of the sodium potassium pump in the myocardial tissue of the heart.

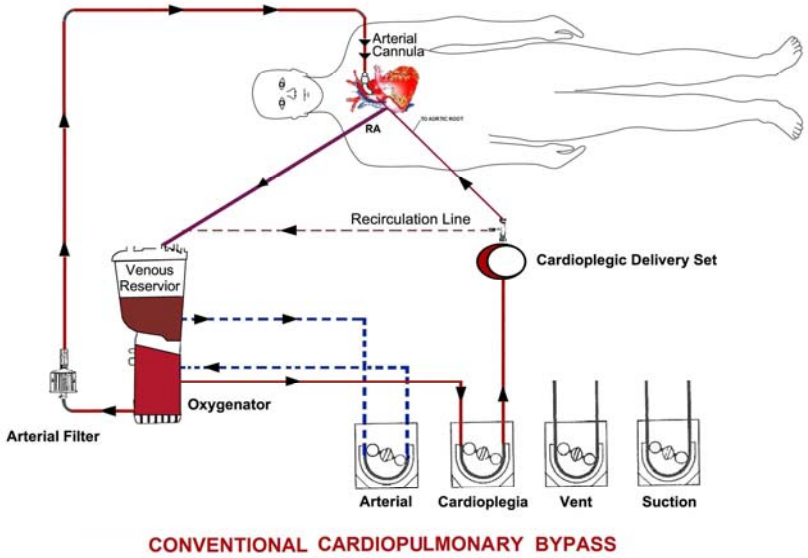


Figure 26: Conventional CPB circuit

3.7.2 Cardioplegic solution

Boston's Cardioplegic Solution (Plasmalyte A - 1000 ml; mannitol 20% - 16ml; lidocaine 1% - 13ml; magnesium sulphate 8 mmol; potassium chloride 26 mmol and sodium bicarbonate 8.4% - 13 mmol) was used to attain arrest. This was administered with 1 portion of blood to 4 portions of cardioplegia (1:4), unlike most conventional blood cardioplegia which has a ratio of 4:1.

3.7.3 Cardioplegia temperature control

Cardioplegia solution temperature was controlled with a HCU 30 dual cooler/heater unit (Figure 22). The cooler portion of the unit is set at 3°C for cold cardioplegia delivery. The heater portion of the unit is set at 39°C for warm re-perfusion blood delivery.

3.7.4 Cardioplegia delivery technique

The Vision blood cardioplegic delivery (BCD) manufactured by Gish biomedical set (Figure 27) was used routinely for all case. It has a priming volume of 45 ml and could accommodate a maximum flow rate of 600 ml/min. The housing material was polycarbonate with a stainless steel heat exchanger.

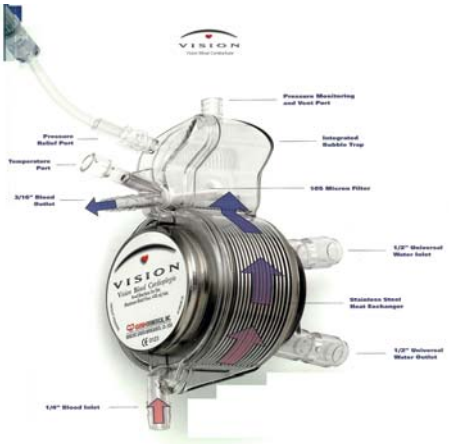


Figure 27: Vision blood cardioplegic delivery set by Gish biomedical

3.7.5 Cardioplegia

Three doses of cardioplegia were administered as follows:

a) Cold induction cardioplegic solution

Following the initiation of CPB, cold induction cardioplegia was administered after the aorta was cross clamped. Upon the surgeon's request, cold induction solution was "dribbled" and then delivered at a pressure not exceeding 120 mmHg. The pressure was measured with a pressure isolator connected to a transducer on the HL 30 heart lung machine. A total dose of 20 - 25 ml/kg was ideally delivered over a 2 - 4 minute period. At 10 ml/kg intervals, the amount of cardioplegia solution delivered was announced to the surgeon by the perfusionist. The myocardial temperature was also announced to the surgeon provided it was being monitored. The target myocardial temperature range was 10 – 15°C. The perfusionist continued with cardioplegic solution delivery until cardiac asystole and calculated infusion full dose was achieved.

b) Maintenance cardioplegic solution

The perfusionist notified the surgeon when 25 minutes had elapsed since the last dose of cardioplegia solution or when the myocardial temperature exceeded 15ºC. Generally with Boston's children cardioplegia, one dose of cardioplegia was administered for the entire duration for most cases, unless activity resumed before removal of the aortic cross-clamp, or if the procedure required a cross-clamp time of more than 1½ hours. Regardless, maintenance cardioplegia is delivered at the surgeon's discretion together with the advice of the principal perfusionist.

c) Warm reperfusion cardioplegia ("Hot Shot")

The surgeon informed the perfusionist in advance of the intended time for the delivery of the dose of warm reperfusion blood. This allowed the perfusionist time to re-warm the

bypass circuit as well as the cardioplegic circuit and infuse the necessary drugs. The HCU 30 dual heater-cooler was set at 37 ºC and circulated. After the delivery line was flushed, a 15 - 20 ml/kg dose of warm reperfusion solution (blood only) was delivered just prior to the release of the aortic cross-clamp, over a 3 minute period, at a pressure of 120 mmHg, which was measured on a transducer on the HL 30 heart lung machine.

Regitine was administered during the re-warming phase to ensure adequate re-warming of the peripheral vascular beds. Re-warming was also performed at a rate that ensured that a gradient of 10-12 ^{o} C between the prime and the patient's blood was maintained. A "hot-shot" of only blood was administered through the cardioplegic delivery set just before the removal of the aortic cross-clamp. The blood entering the coronaries ensured wash-out of metabolites from the myocardium whilst carrying O_2 to the myocardial cells and CO_2 away from it. Reperfusion of the coronary tree with warm blood also ensured wash-out of excess intravascular K^+ levels. Thereby, encouraging the re-establishment of the sodium–potassium pump, that was previously offset by the infusion of cardioplegic solution. This also aided in de-airing of the coronary arteries. The temperature of the "hot-shot" also increased the myocardial temperature. Thus contributing to the re-instatement of a normal metabolic rate of myocardial tissue and facilitating increased electrical activity for a normal heart rate. Blood samples were analyzed towards the end of the re-warming phase and the necessary adjustments were made to the gas blender to correct the pO_2 & pCO_2 levels. Furthermore, sodium bicarbonate ($NaHCO_{3)}$, K^+ and Ca^+ were administered as required.

3.8 CONVENTIONAL ULTRAFILTRATION PROTOCOL

Conventional ultrafiltration was performed during the re-warming phase of CPB, provided there was sufficient blood volume in the cardiotomy reservoir. This was dependant on the degree of urine output, priming volume and cardioplegic volume that were administered throughout the peri-operative period. The same circuits that were initially used to perform CUF were also used to perform MUF post CPB in both groups.

3.8.1 CUF protocol in the AVMUF group

Figure 28 shows a circuit diagram of CUF in the AVMUF group. Blood was removed from the oxygenator through a connector placed at one of the outlet ports. Blood was pumped through the haemofilter and after filtration was re-infused into the cardiotomy reservoir through a recirculation port in the venous line (Figure 28). This reduction in systemic flow volume reaching the patient through the arterial line was compensated by a calculated increase in the difference in the inline pressure reading.

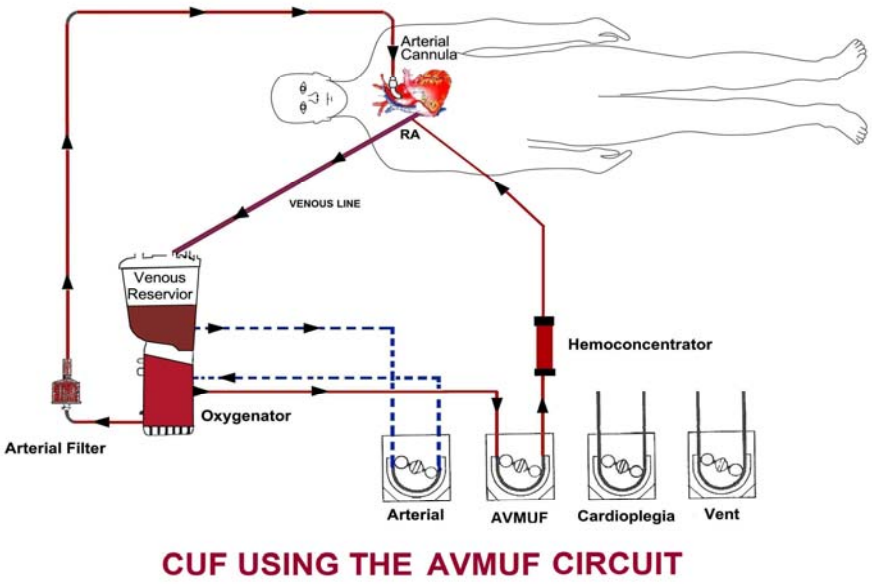


Figure 28: CUF technique in the AVMUF group

3.8.2 CUF protocol in the VAMUF group

Figure 29 illustrates a circuit diagram of CUF in the VAMUF group. Blood was removed from the venous reservoir post pump and pre-oxygenator through a connector placed at the proximal end of the line closer to the pump head. Filtered blood re-entered the same line at the distal end, closer to the oxygenator, after passing through the haemofilter. There was no reduction in systemic flow volume reaching the patient using this system, as all blood flow was redirected to the arterial side again after passing through the haemoconcentrator. Therefore, arterial flow remained constant during the ultrafiltration.

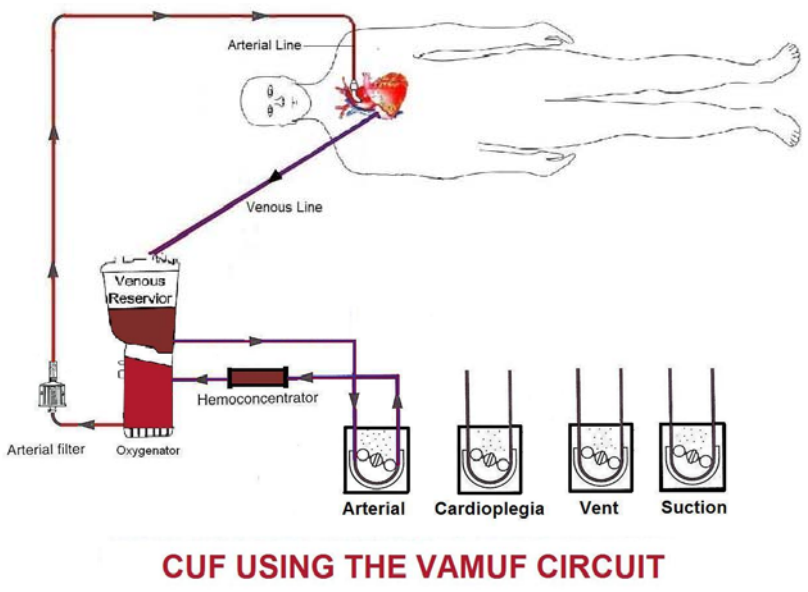


Figure 29: CUF technique in the VAMUF group

3.9 Termination of CPB

Heparin neutralization after termination of CPB was performed by slow intravenous administration of a 10 mg/ml solution of protamine sulphate in a peripheral line at a dose of 1 mg for every 100 IU of initial heparin dose. Activated clotting time was monitored after protamine administration, until it returned to near pre-heparinization level i.e., not greater than 10% above baseline. If the ACT was greater than 10% of the pre-heparinization level, then additional protamine (20 – 50 mg) was administrated. Post surgery, blood was transfused when the haematocrit value was less than 24% and if the haemoglobin was less than 8 gm/dl.

The indication for administering postoperative platelet, fresh frozen, or cryoprecipitate transfusion was the presence of a platelet count of less than 150 000 platelets per microlitre; prothrombin time or partial thromboplastin time more than 1½ times the control value; fibrinogen level less than 100 mg/dl; and elevated bleeding time.

3.10 MODIFIED ULTRAFILTRATION PROTOCOLS

3.10.1 Perfusion during MUF and cardiac surgery

- CPB and MUF were conducted by the principal investigator.
- Perfusion data was recorded with the aid of an assistant perfusionist.
- Perfusion department maintained a policy and procedures manual which included:
    - Routine and emergency procedures
    - Departmental policies, procedures and guidelines
    - Catastrophic perfusion event management
- Policy and procedures were reviewed and revised on a periodic basis and on arrival of new staff to the perfusion department.
- All results were recorded on a MUF data collection sheet (Appendix 19).

3.10.2 AVMUF technique

Arteriovenous modified ultrafiltration was performed after termination of CPB. Figure 30 illustrates the AVMUF circuit. The arterial and venous lines were clamped off after termination of CPB and before institution of MUF. These clamps prevented blood from draining out the patient and entering the main CPB circuit. During MUF, blood was removed from the heart retrogradely through the arterial cannula that was placed in the aorta in order to perform CPB. The flow through the MUF circuit in both groups was 10 – 15 % of the calculated bypass flow rate. Blood bypassed the arterial filter and flowed retrogradely through the oxygenator and into the AVMUF circuit. Blood was then pumped by a roller pump through a haemoconcentrator (artificial kidney) where positive pressure caused haemofiltration to occur and the ultrafiltrate (waste product) was collected in a separate measured bag. Blood that left the haemoconcentrator entered the right atrium via a separate line that was connected to the venous line in order to perform MUF. This process was termed as arteriovenous modified ultrafiltration (AVMUF) since blood was removed from the aorta and was pumped actively into the

right atrium (Naik, Knight and Elliott, 1991). Positive fluid balance in the patient and the CPB circuit was calculated. Modified ultrafiltration was terminated when sufficient filtrate was obtained in the ultrafiltrate waste bag. Patients were always left with a reasonable positive fluid balance in both types of MUF to encourage postoperative urine output. The patient's pressure was observed and controlled at all times by the principal investigator in coordination with the anaesthetist and surgeon.

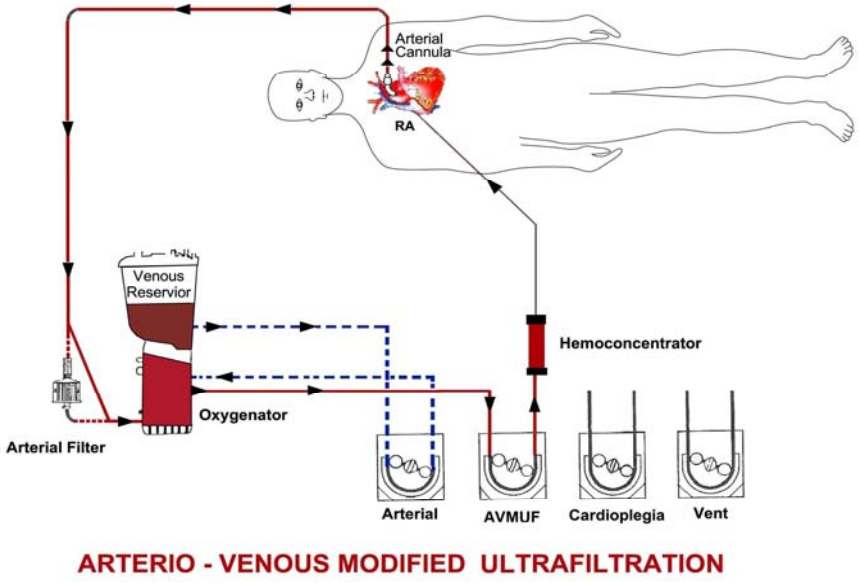


Figure 30: AVMUF technique

3.10.3 VAMUF technique

Venoarterial modified ultrafiltration was also performed after termination of CPB. The difference with VA-MUF was that blood was removed from the Right Atrium of the heart through a cardioplegic line that was connected to the venous cannula that was originally placed in the RA during CPB. Figure 31 illustrates that blood was circulated through the main pump head and through a haemoconcentrator where ultrafiltration occurred before it entered the oxygenator. Thereafter oxygenated blood left the oxygenator and passed through an arterial filter (Pal auto vent) where air bubbles were trapped and displaced into the atmosphere. It then entered the patient through the arterial cannula that was placed in the aorta during routine CPB. A maximum flow of 200 ml/min passed through the haemoconcentrator at any given time. This ensured sufficient transmembrane

pressure within the membranes of the filter to facilitate ultrafiltration. Blood leaving the VAMUF circuit was warmed by the stainless steel heater exchanger that was incorporated into the oxygenator connected to the Jostra HCU 30 Heater- cooler unit. This was imperative in preventing heat-loss while performing VAMUF, especially in neonate, infant and paediatric patients. Positive fluid balance was calculated and VAMUF was terminated when sufficient filtrate was obtained in the ultrafiltrate waste bag. Patient's pressure was observed and controlled at all times by the principal investigator in coordination with the anaesthetist and surgeon.

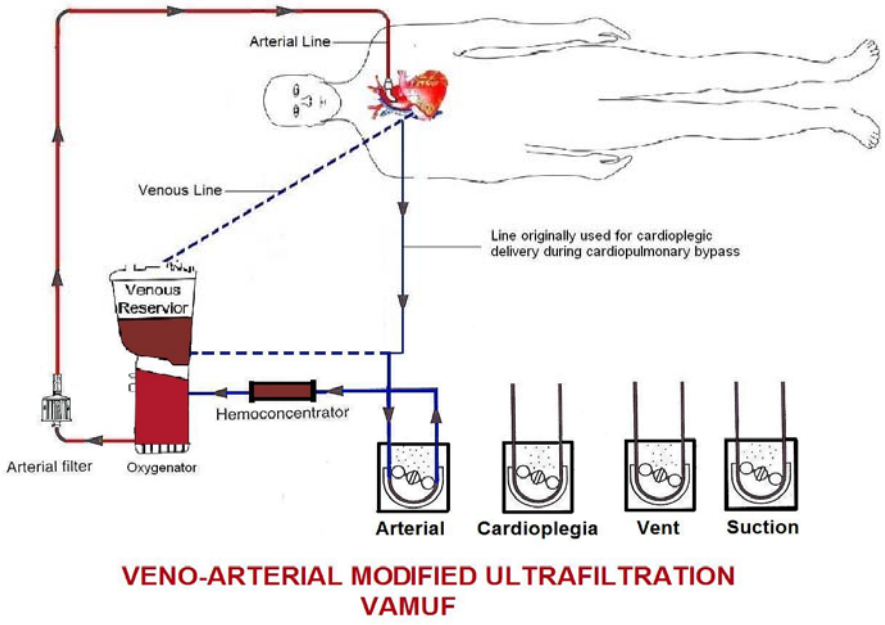


Figure 31: VAMUF technique

3.10.4 Termination of AVMUF and VAMUF

It was ensured that a positive fluid balance of 10 % of the calculated blood volume remained in the patient. MUF was terminated upon achieving this residual fluid volume. Residual fluid volume in the patient was calculated using the following formula:

Residual fluid volume = Total fluid input – Total fluid output
Total Fluid input = *Anaesthetic fluid input + Prime + cardioplegia +fluid added on CPB*
Total Fluid output = *Pre-CPB urine output + urine output on CPB + ultrafiltrate volume*

This residual fluid volume would encourage continuous glomerular filtration by ensuring that a hypotonic solution passed through the nephrons of the kidneys. The excess residual fluid volume also compensated for post operative urine output as well. This was imperative to prevent dehydration and re-infusion of fluid immediately after post-op. The patient's pressure was controlled throughout MUF by infusion of blood volume simultaneously from the reservoir and lines until the arterial filter was emptied and simultaneously chased with prime. The primed circuit ensured re-institution of bypass with ease, if required. Before bypass, the total volume of fluid contained from the outlet of the reservoir until post arterial filter was calculated while priming the circuit. This allowed the perfusionist to precisely empty that calculated volume of blood occupying that area of the circuit thus, resulting in the entire blood volume in the bypass circuit and cardioplegic circuit being infused into the patient in order to complete MUF.

After completion of MUF and stabilisation of the patient, post MUF, blood samples were extracted and some was analyzed using the blood gas analyzer whereas the rest were sent to the laboratory for haematological and biochemical analysis. Haemodynamic parameters where taken from the monitor and recorded as post MUF readings for comparison against preMUF results.

3.10.5 Summary of the VAMUF procedure

The sequence of events required to perform VAMUF is summarized in Table 12.

Table 12: VAMUF sequence of events

3.10.6 Protocols for blood samples collected for analysis

Blood samples were collected at various intervals during the procedure. Blood was sent to the laboratory (lab) for haematological and biochemical measurements of (serum creatinine; calculated creatinine clearance; BUN; uric acid; sodium; phosphorus; calcium and lactate levels). Blood-gas analysis was also performed in the operating room. Data from the blood-gas analyzer was recorded immediately while the results from the lab were captured from the hospitals “Sener” computer information system.

3.10.6.1 On admission in the Cardiac Care Unit (CCU)

A routine blood sample was taken by the relevant nurse in charge of the patient and sent to the lab for biochemical analysis. The principal investigator over-looked the collection of the sample and later downloaded, analyzed and stored all data.

3.10.6.2 During CPB

Routine monitoring and recording of urine output was done by the principal investigator and anaesthetic nurse. Conventional ultrafiltration was performed when the cardiotomy reservoir blood volume was sufficient. The amount of ultrafiltrate and filtration rate was recorded. Routine blood gas analysis was performed every 25 minutes on CPB.

3.10.6.3 After CPB but prior to institution of MUF

A blood sample was taken by the anaesthetist and sent to the lab by the principal investigator for biochemical analysis and measurements. Part of the blood sample that was taken was introduced into the Blood Gas analyser for routine parameter measurements. Arterial pressure, central venous pressure, saturation and heart rates were also recorded.

3.10.6.4 After commencement of MUF

A blood sample was drawn by the anaesthetist and sent immediately to the laboratory by the principal investigator for biochemical measurements. Part of the blood sample that was drawn introduced into the blood gas analyser for routine parameter measurements. Arterial pressure, central venous pressure, saturation as well as the heart rate was recorded. The amount of ultrafiltrate and rate of filtration was recorded.

3.10.6.5 On admission in Cardiac Surgical Unit (CSU)

A nurse recorded routine total urine output measurements. Measurement and recording of cardiac output tests were performed after the patient was stabilized. A routine blood sample was collected by the respiratory therapist and handed over to the principal investigator to be sent to the lab for analysis.

3.10.6.6 In CSU after 24 hour

Total urine output for the last 24 hours was measured and recorded. Arterial pressure, central venous pressure, saturation and heart rate were recorded. A blood sample was aspirated and sent to lab for biochemical analysis.

3.11 MEASURES TAKEN TO OVERCOME COMMON COMPLICATIONS ASSOCIATED WITH MUF

One must realize that there are risk factors involved in any surgical procedure no matter how small it may seem. After contacting the Perfusion community on the worldwide web and identifying the common problems associated with MUF, solution to these problems were overcome by the follows methods:

3.11.1 Cavitation in the arterial or venous line

Cavitation in the arterial or venous line could occur if the blood flow rate was too high thereby creating excessive negative pressure within the lumen of the tubing. This could result in air being drawn out of solution (in this case air would be drawn out of blood) by the occlusive roller pump if it is not noticed for a prolonged period of time. Cavitation was rectified by reducing the flow rate on the pump console. The air posed no threat to the patient in VAMUF as there was an arterial filter in place that trapped the air bubble that manages to pass through the oxygenator.

The oxygenator is designed in such a manner that it allowed blood to pass through while trapping most of the air at the top of the oxygenator. This is due to the fact that the inlet of the oxygenator is at the top and the outlet at the bottom. Since air has a lighter molecular weight than blood, it rose to the top of the oxygenator and remained there, until displaced with very high flows and macro emboli. The conventional AVMUF system had no safety mechanisms in place to trap air emboli, although most perfusionist were not too concerned with this as they were pumping blood into the right atrium. No cavitation within the venous line was experienced with the both techniques, as the flow that was required to facilitate ultrafiltration was continuously monitors and adjusted accordingly.

3.11.2 Drop in arterial pressure

Possible drop in arterial pressure was regulated by pump flow rates. However, a high rate of extraction of volume from the systemic flow causes the blood pressure to drop. During AVMUF the arterial blood pressure drops due to blood being removed from the aorta. This reduces the volume of blood entering the systemic circulation. The drop in pressure does not occur in VAMUF because blood is infused into the aorta which causes the blood pressure to increase while also increasing coronary perfusion during diastole (same advantages as with the use of an Intra Aortic Balloon Pump). The patient's pressure was monitored continuously by the perfusionist, anaesthetist and

surgeon. Any drop in arterial pressure was prevented during VAMUF by slow infusion of blood from the CPB circuit into the patient in order to compensate for the volume lost through ultrafiltration.

3.11.3 De-cannulation.

This is a possible due to human error on the surgical side. De-cannulation is unlikely to occur from the perfusion side unless the circuit has no monitor and pressure cut off systems in place. The over pressurising of the MUF circuit was prevented by pressure isolators that were connected to the central processing unit mainframe of the heart-lung machine. These pressure isolators were connected to transducers that would have first alarmed when the pressure reaches 200 mmHg and the computer software would then stop the pump-head when it exceeds 250 mmHg. This system prevented the line from rupturing due to excessive pressures during MUF. During VAMUF this problem was alleviated by connecting the cardioplegic line directly to the existing venous cannula that was used during CPB. This eliminated the need for the cardioplegic needle (which is generally small and flimsy when compared to the venous cannula) to be re-inserted into the right atrial appendage.

3.11.4 Increased time for blood to be exposed to a foreign surface.

The time period for MUF ranges from 10 – 15 minutes. This is considered as a minor factor when compared to the advantages that MUF has to offer as proven by previous studies. The red blood cell damage was minimal because the roller pump head rotated at low speeds (200 ml/min) as compared to CPB (1 – 5 l /min).

3.11.5 Over-pressurization of haemoconcentrator

This was prevented by the use of pressure isolators connected at the inlet of haemoconcentrator (pre-membrane) and at the outlet of haemoconcentrator (post - membrane) prior to institution of CPB. A maximum inlet pressure of 200 mmHg

(according to manufactures specifications) was maintained. The transmembrane pressure (TP) was calculated by mathematical derivation as follows:

TP = *Premembrane Pressure – Post membrane Pressure*

3.11.6 Air in circuit.

Any air that may have entered the circuit possibly from the haemoconcentrator was trapped by the bubble trap of the cardioplegic delivery set that was used to perform VAMUF. This air was eradicated via the recirculation line into the venous reservoir and vented into the atmosphere. During AVMUF air was of no major concern as blood was re-infused into the right side of the heart.

3.11.7 Recirculation through circuit.

Both the VAMUF and the AVMUF circuits did have the ability to re-circulate blood in order to eradicate air, should the need arise. This could be achieved with ease if and when it was required, due the use of a re-circulation line connected from the arterial filter to the venous reservoir during CPB for the purpose of de-airing.

3.11.8 Heat loss.

A drop in temperature is a phenomenon that commonly occurs in MUF circuit where a completely separate circuit from the CPB circuit is used for the sole purpose of performing MUF. The drop in temperature is more defined and pronounced in the paediatric population because of their small body surface area. The oxygenator used during VAMUF and AVMUF had a stainless steel heat exchanger incorporated within. This allowed for continuous manipulation of the patients body temperature and the ability to re-warm blood, if required, as it passed the MUF circuit and entered the patient.

3.12 Statistical analysis

The SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA) was used to analyse the data. A *p* value <0.05 was considered as statistically significant. All quantitative variables were checked for normality using the skewness statistic. Quantitative normally distributed data were compared between the two arms of the trial using independent t-tests, while non normal data were compared using Mann- Whitney tests. Pearson's chi square tests were used when the variables were categorical and Fisher's exact test in the case of binary variables. Comparison of the difference between pre and post values between the treatment arms was achieved by calculating the difference between pre and post MUF values in each arm and comparing this difference by means of independent t-tests. Percentage differences were calculated by dividing the difference by the baseline value and multiplying by 100. Profile plots were generated to visually examine the changes over time by treatment arm.

CHAPTER FOUR: RESULTS OF STUDY

4.1. Clinical variable – secondary outcomes

4.1.1 Demographic Data

Tables 13 and 14 represent demographic data and type of operations expressed as a mean, standard deviation and percentage of all patients included in this clinical experimental study. The data suggests that there were no significant difference in any of the demographic variables or type of procedure by treatment arm.

Table 13: Modified ultrafiltration demographic data

Variables	AVMUF *Mean (±SD)*	VAMUF *Mean (±SD)*	*p* value
Age (mean ±SD)*	37.01 (±28.8)	43.37 (±26.7)	**0.382**
Gender (M:F)	19:11	23:7	**0.260**
Height (cm)*	132.9 (±38.8)	144.0 (±34.9)	**0.253**
Weight (kg)*	50.6 (±33.1)	53.6 (±26.9)	**0.706**
BSA (m^2)*	1.24 (±0.7)	1.38 (±0.6)	**0.419**
BMI (kg/m^2)*	23.36 (±8.0)	22.77 (±6.5)	**0.763**

Table 14: Types of operation performed

Type of operation	AVMUF *Mean (±SD)*	VAMUF *Mean (±SD)*	*p* value
CABG	16 (±53.3%)	16 (±53.3%)	**0.791**
Valve	3 (±10.0%)	6 (±20.0%)	
ASD	3 (±10.0%)	3 (±10%)	
VSD	4 (±13.3%)	3 (±10%)	
ASD+VSD	1 (±3.3%)	0 (±0%)	
Rastelli operation	1 (±3.3%)	0 (±0%)	
Other congenital	2 (±6.7%)	2 (±6.7%)	

4.1.2 CPB and cross-clamp time

Table 15 represents the CPB data expressed as a mean of all patients CPB and cross clamp times. All values are expressed as mean ± standard deviation. The results reflect that neither CPB time nor cross-clamping time showed any difference between the two treatment arms of the study.

Table 15: CPB and cross-clamp time in the AVMUF and VAMUF groups

Variables	AVMUF *Mean (±SD*	VAMUF *Mean (±SD*	*p* value
CPB time (min)	106.07 (±41.6)	107.07 (±43.8)	*0.928*
Cross-clamp time (min)	79.23 (±33.2)	76.70 (±33.6)	*0.770*

CPB time (min) - Total time a patient was supported by the heart lung machine.
Cross-clamp time (min) – Total anoxic time when there is no blood flow to heart muscles.

4.1.3 Electrolyte balance data

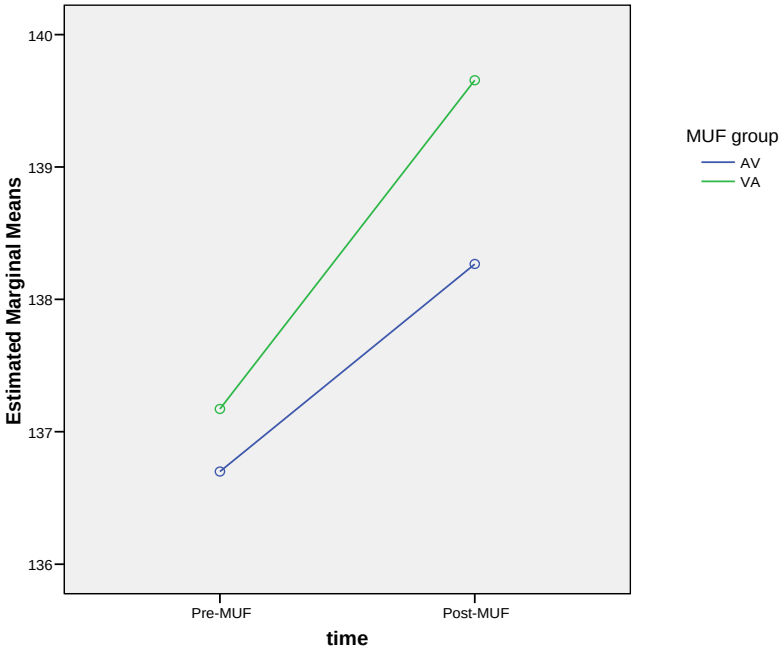
Table 16 demonstrates that there were no significant differences in the changes in any of the electrolyte variables between pre and post between the treatment arms. The rate of change was similar in both arms, Graphs 1 to 5 further demonstrate that the slopes of the lines in the two arms are similar for both groups for all variables, with the exception of phosphorous. However, the change in phosphorus was very small.

Table 16: Electrolyte concentrations in the AVMUF and VAMUF groups

Variables	AVMUF		VAMUF		*p* value
	Pre – MUF *Mean (±SD)*	*Post – MUF* *Mean (±SD)*	*Pre – MUF* *Mean (±SD)*	*Post – MUF* *Mean (±SD)*	
Na^+ (mmol/l)	136.7 (±3.0)	138.27 (±3.2)	137.17 (±3.5)	139.67 (±4.9)	**0.271**
K^+ (mmol/l)	4.04 (±0.6)	3.87 (±0.5)	4.09 (±0.6)	3.86 (±0.6)	**0.590**
Ca^{2+} (mmol/l)	1.36 (±0.4)	1.26 (±0.3)	1.35 (±0.3)	1.25 (±0.3)	**0.990**
PO_4^- (mmol/l)	0.97 (±0.4)	0.97 (±0.4)	1.00 (±0.3)	1.03 (±0.4)	**0.640**
Mg^{2+} (mmol/l)	1.23 (±0.3)	1.16 (±0.3)	1.12 (±0.3)	1.01 (±0.2)	**0.388**

4.1.3.1 Effects of MUF on serum sodium (Na^+)

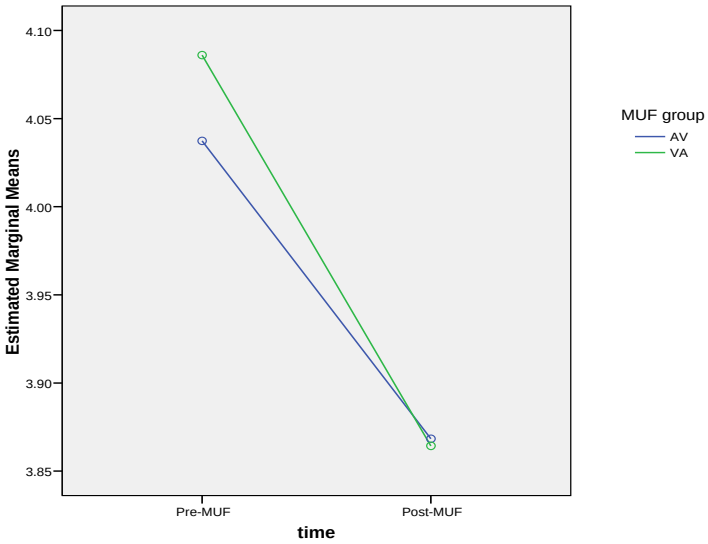
Table 16 shows that there were no significant differences in both groups. The Na^+ in the AVMUF group increased from 136.7 mmol/l ± 3.0 to 138.27 mmol/l ± 3.2, with a mean difference of 1.57 mmol/l and the Na^+ in the AVMUF increased from 137.17 mmol/l ± 3.5 to 139.67 mmol/l ± 4.9, with a mean difference of 2.48 mmol/l. The results of Graph1 demonstrate that both groups are efficient in maintaining Na^+ stability after MUF (*P* = 0.271).



Graph 1: Profile plot of mean sodium (Na^+) over time by treatment arm

4.1.3.2 Effects of MUF on serum potassium (K^+)

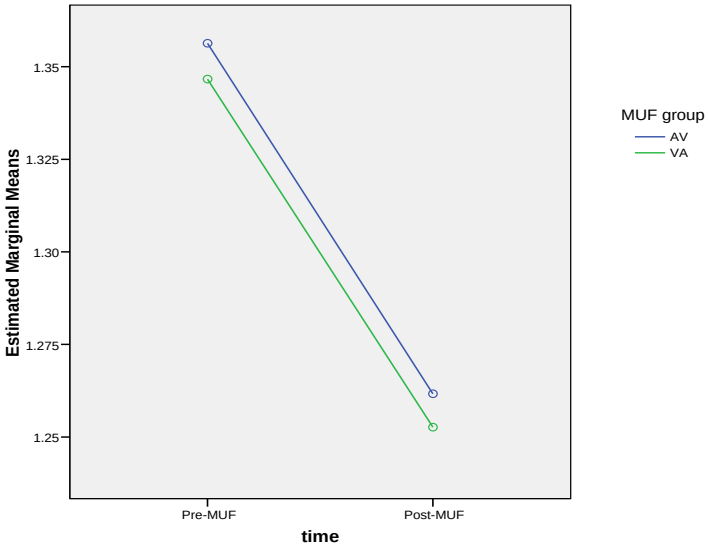
In Table 16 the K^+ in the AVMUF group decreased from 4.04 mmol/l ± 0.6 to 3.87 mmol/l ± 0.5 with a mean difference of -0.17mmol/l, whereas the K^+ in the VAMUF group dropped from 4.09 mmol/l ± 0.6 to 3.86 mmol/l ± 0.6, with a mean difference of -0.22 mmol/l. Although there were no significant differences the in change of mean serum potassium for both groups (Graph 2). Both groups demonstrated that they did not have a negative impact on the K^+ balance in the body.



Graph 2: Profile plot of mean potassium (K^+) over time by treatment arm

4.1.3.3 Effects of MUF on serum calcium (Ca^{2+})

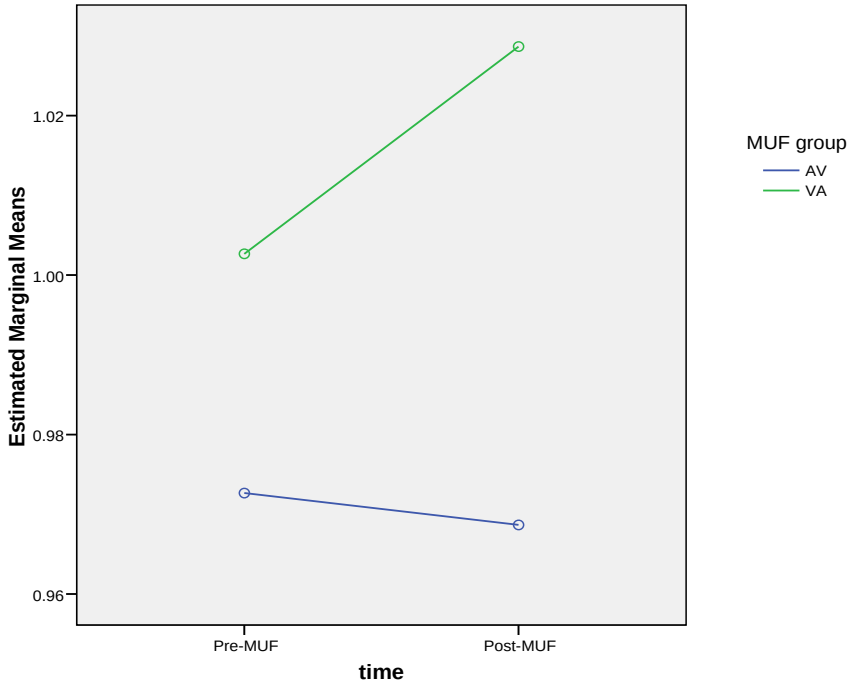
According to Table 16 there was a decrease in (Ca^{2+}) in the AVMUF group. The Ca^{2+} decreased from 1.36 mmol/l ± 0.4 to 1.26 mmol/l ± 0.3, with a difference of - 0.9 mmol/l. In the VAMUF group it decreased from 1.35 mmol/l ± 0.3 to 1.25 mmol/l ± 0.3 with a difference of - 0.9 mmol/l. Although no significant differences in Ca^{2+} levels were noted between the MUF groups (Graph 3), both groups reduced the Ca^{2+} levels to the normal range.



Graph 3: Profile plot of mean calcium (Ca^{2+}) over time by treatment arm

4.1.3.4 Effects of MUF on serum phosphate (PO_4^-)

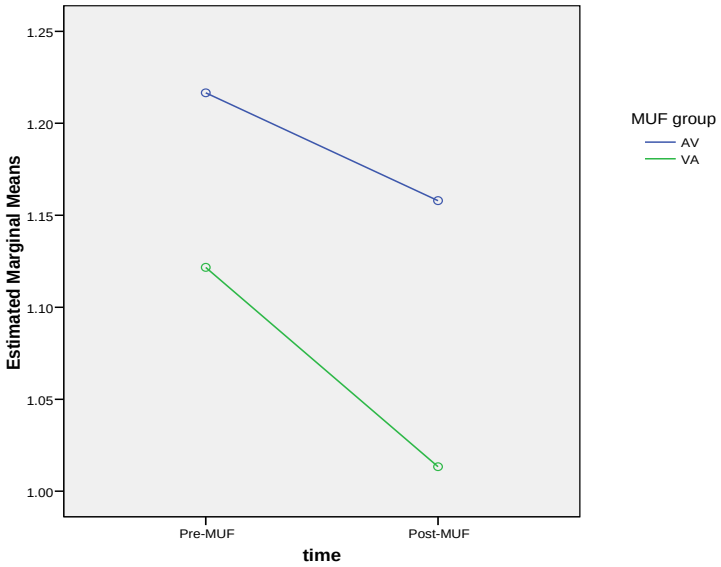
The serum phosphate levels in the AVMUF group remained at 0.97 mmol/l ± 0.4 after MUF, whereas in the VAMUF group PO_4^- increased from 1.00 mmol/l ± 0.3 to 1.03 mmol/l ± 0.4, with a difference of 0.3 mmol/l (Table 16) . Graph 4 demonstrates that PO_4^- in both groups was kept within the normal range. The results proved that both groups were successful in maintaining PO_4^- stability after MUF.



Graph 4: Profile plot of mean serum phoshate (PO_4^-) over time by treatment arm

4.1.3.5 Effects of MUF on serum magnesium (Mg^{2+})

The serum Mg^{2+} in the AVMUF group decreased from 1.23 mmol/l ± 0.3 to 1.16 mmol/l ± 0.3, with a difference of -0.6 mmol/l and in the VAMUF group the Mg^{2+} decreased from 1.12 mmol/l ± 0.3 to 1.01 mmol/l ± 0.2, with a mean difference of -0.11 mmol/l (Table 16). From Graph 5 it is clearly evident that both groups headed towards reaching the target normal range although there are no significant differences between both groups. Both techniques proved their importance in re-stabilizing Mg^{2+} levels in the body after MUF.



Graph 5: Profile plot of mean Magnesium (Mg^{2+}) over time by treatment arm

4.2 CLINICAL VARIABLE – PRIMARY OUTCOMES

4.2.1 Anaesthetic, perfusion and clinical data

Table 17 represents anaesthetic, perfusion and clinical data expressed as a mean and ± standard deviation of all patients included in the study. The results of Table 17 confirm that was a statistically significant difference in the ventilation time between the two arms of the study (p< 0.001). The VAMUF group showed a much lower ventilation time than the AVMUF group. Intensive care unit stay, Hospital stay and discharge days were significantly lower in the VAMUF group as well.

Table 17: Anaesthetic, perfusion and clinical data

Variables	AVMUF (n=29) *Mean (±SD)*	VAMUF (n=29) *Mean (±SD)*	*p* value
Ventilation time (hr)	15.14 (±5.1)	10.21 (±2.6)	***<0.001***
ICU stay (hr)	46.38 (±25.7)	30.14 (±11.0)	***0.003***
Hospital stay (d)	8.76 (±1.9)	7.41 (±1.8)	***0.007***
Discharge days (POD)	7.86 (±1.9)	6.48 (±1.8)	***0.007***

Ventilation time (hr) – Total time the patient is on the ventilator post operatively in ICU.
ICU stay (hr) – Reflects total time patient was brought to ICU post bypass until they leave the unit.
Hospital stay (d) - Reflects total number of days the patient spends in the hospital until discharge.
Discharge days (POD) - Includes days from the date of surgery until the day of discharge.

4.2.2 Conventional and modified ultrafiltration data

Table 18 represents conventional and modified ultrafiltration data expressed as median and inter-quartile range. It demonstrates that there was a statistically significant difference in median CUF volume between the two arms (p=0.043), with the VAMUF arm having the greater volume. There was no difference between the arms with regards to MUF volume (p=0.275).

Table 18: CUF and MUF data in the AVMUF and VAMUF groups

Variables	AVMUF *Mean (±SD)*	VAMUF *Mean (±SD)*	*p* value
CUF volume (ml)	150 (±363)	325 (±700)	***0.043***
MUF volume (ml)	900 (±438)	825 (±613)	***0.275***

Total CUF *(conventional ultrafiltration)* **=** Ultrafiltrate removed from the circuit during CPB.
Total MUF (*modified* ***ultrafiltration)*** **=** Ultrafiltrate removed from the patient & circuit post CPB.

4.2.3 Fluid management data

Table 19 represents the fluid management data expressed as a mean percentage ± standard deviation of the patients total fluid input.

Table 19: Fluid management data

Group	Total fluid input	Standard deviation	Total fluid output	Standard deviation	Fluid balance	Standard deviation
AVMUF	2702.67	1282.02	2118.67	1028.11	598.33	410.41
AVMUF (%)	100 %	0	79.49%	9.1%	20.81%	9.1%
VAMUF	2947.33	1362.89	2481.17	1187.50	449.17	280.59
VAMUF (%)	100 %	0	84.25%	8.8%	15.11%	6.9%

Total Fluid Input **=** Preoperative fluid input + CPB Fluid Prime + Cardioplegia + Fluid added on CPB.
Total Urine Output **=** Urine output pre-CPB + urine output during-CPB + urine output post-CPB
Total Fluid Output **=** Total CUF + Total MUF + Total Urine Output + Total in drains
Total Fluid Balance **=** Total Fluid Input - (Total CUF + Total MUF + Total Urine Output)

The results of Table 19 suggest that there was a statistically significant difference in mean percentage of fluid output between the two arms (p=0.044), with the VAMUF arm having a greater percentage output than the AVMUF arm. There was also a statistically significant difference in fluid balance between the two arms (p=0.008), with the VAMUF arm having a lower percentage fluid balance than the AVMUF arm. The VAMUF group had a remaining fluid balance of 15.11% of the total fluid input while the AVMUF group had a higher remaining fluid balance of 20.81% of the total fluid input.

4.2.4 Haemodynamic data

Table 20 represents the haemodynamic data expressed as mean ± standard deviation with the exception of diastolic pressure. The results of all the haemodynamic variables showed that the change between pre and post MUF was statistically significantly different between the two study arms.

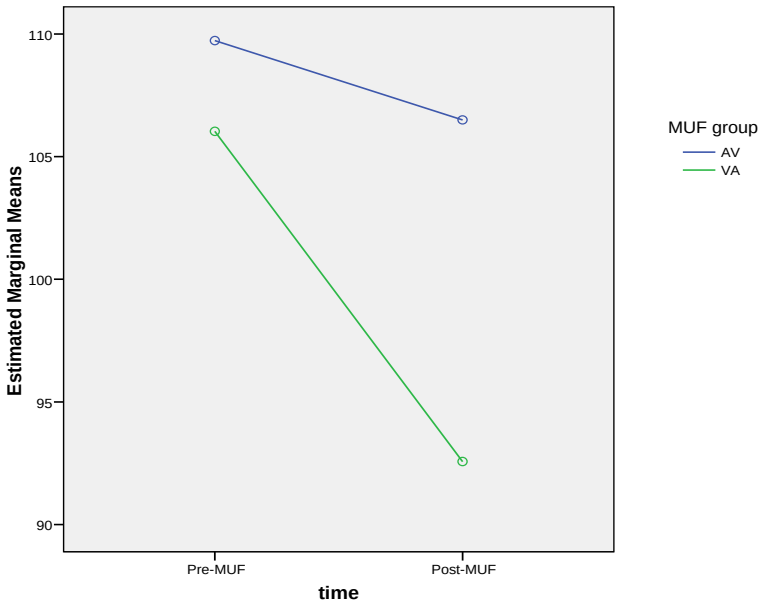
Table 20: Haemodynamic variables in the AVMUF and VAMUF groups

Variables	AVMUF		VAMUF		*p* value
	Pre – MUF Mean (±SD)	*Post – MUF Mean (±SD)*	*Pre – MUF Mean (±SD)*	*Post – MUF Mean (±SD)*	
HR (bpm)	109.73 (±19.1)	106.5 (±19.2)	106.03 (±17.3)	92.57 (±17.1)	<0.001
HR (%)	100	97.07 (6.4)	100	87.45 (±8.6)	<0.001
SP (mmHg)	99 (±13.4)	108.3 (±10.8)	93.07 (±12.6)	114.6 (±12.5)	<0.001
SP (%)	100	110.18 (±8.3)	100	124.07 (±11.1)	<0.001
DP (mmHg)	51.37 (±10.4)	59.00 (±10.2)	50.07 (±7.1)	56.57 (±7.0)	0.533
DP (%)	100	116.90 (±18.0)	100	113.88 (±11.9)	0.447
MP (mmHg)	65.83 (±8.7)	71.76 (±6.6)	61.60 (±7.9)	74.93 (±7.5)	<0.001
MP (%)	100	109.78 (±10.4)	100	122.93 (±16.4)	<0.001
CVP (cmH_2O)	12.13 (±3.8)	10.43 (±3.2)	12.3 (±3.4)	9.53 (±3.7)	0.002
CVP (%)	100	86.5 (±8.8)	100	76.12 (±13.2)	**0.001**

The VAMUF group showed the largest decrease in heart rate (HR) and CVP. The mean pressure also increased more in the VAMUF group than in the AVMUF group.

4.2.4.1 Effects of MUF on heart rate

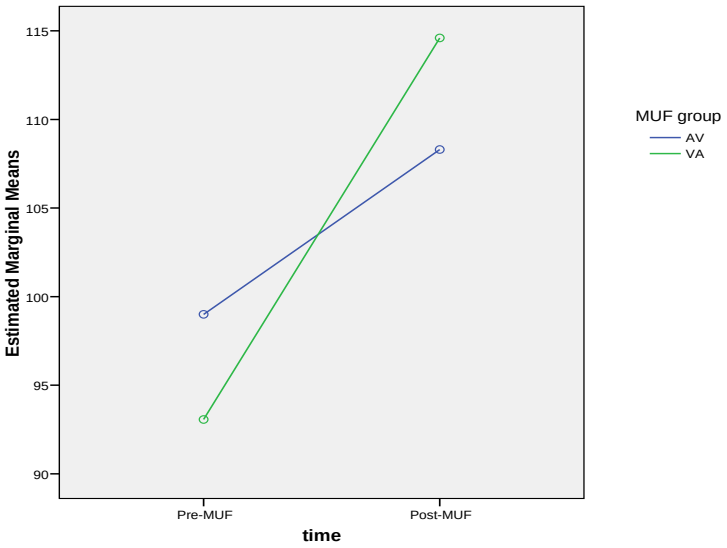
Table 20 and Graph 6 demonstrate that there was a more significant drop in heart rate in the VAMUF group (106.03 beats per minute (bmp) ±17.3 to 92.57 bmp ±17.1 with a difference of – 12.55) as compared to the AVMUF group (109.73 bmp ± 19.1 to 106.5 bmp ±19.2, with a difference of -3.23). The mean HR in the AVMUF group dropped by 2.93 % of the pre-MUF HR, whereas the mean HR in the VAMUF group dropped by 12.55 % of the pre-MUF HR.



Graph 6: Profile plot of mean heart rate over time by treatment arm

4.2.4.2 Effects of MUF on the patients' systolic pressure

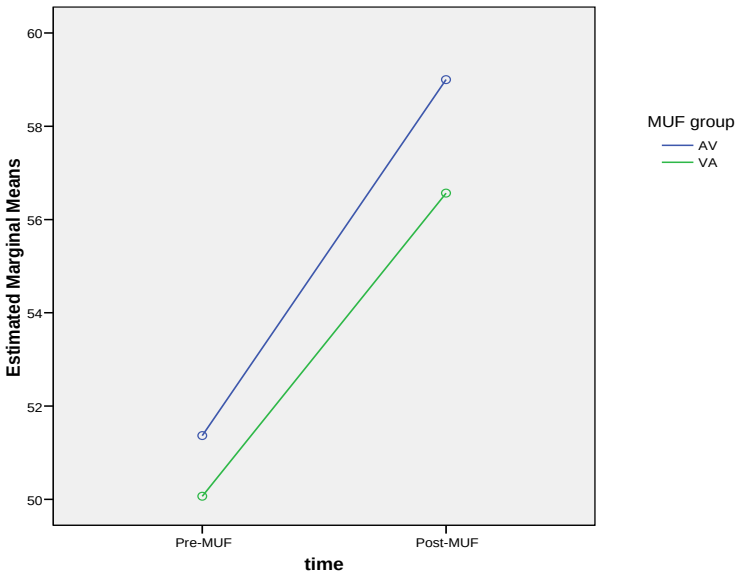
Table 20 shows the mean systolic pressure in the AVMUF increased from 99 mmHg ±13.4 to 108.3 mmHg ± 10.8, with a difference of 9.30 mmHg. The systolic pressure in the VAMUF group increased from 93.07 mmHg ± 12.6 to 114.6 mmHg ± 12.5, with a difference of 12.53 mmHg. Graph 7 illustrates that the VAMUF group had a more significant rise in mean systolic blood pressure of 24.07 % as compared to the AVMUF group which had a 10.18 % rise in mean systolic BP ($p < 0.001$).



Graph 7: Profile plot of mean systolic pressure over time by treatment arm

4.2.4.3 Effects of MUF on the patients' diastolic pressure

Table 20 shows that diastolic pressure in the AVMUF group increased from 51.37 mmHg ±10.4 to 59.00 mmHg ± 10.2, with a difference of 7.63 mmHg. Diastolic pressure in VAMUF group increased from 50.07 mmHg ±7.1 to 56.57 mmHg ±7.0, with a difference of 6.50 mmHg.

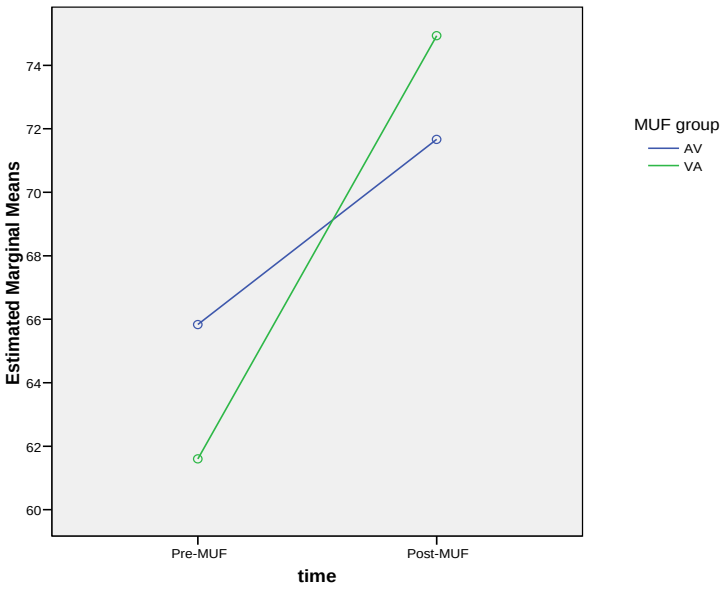


Graph 8: Profile plot of mean diastolic pressure over time by treatment arm

Graph 8 demonstrates that the VAMUF group displayed a lower increase in mean diastolic pressure of 13.88 % (reflects a greater degree of ventricular emptying) where as the AVMUF group had a 16.89 % increase in mean diastolic pressure (reflects a lower volume of ventricular emptying).

4.2.4.4 Effects of MUF on the patients' mean arterial blood pressure (MAP)

Mean arterial pressure in the AVMUF group increased from 65.83 mmHg ± 8.7 to 71.76 mmHg ± 6.6, with a difference of 5.83 mmHg, whereas in the VAMUF group it increased from 61.60 mmHg ± 7.9 to 74.93 mmHg ± 7.5, with a difference of 13.33 mmHg (Table 20). Graph 9 demonstrates that the VAMUF group had a more significant rise in BP, i.e., a 22.93% elevation in MAP whereas the AVMUF group had a 9.78 % increase.

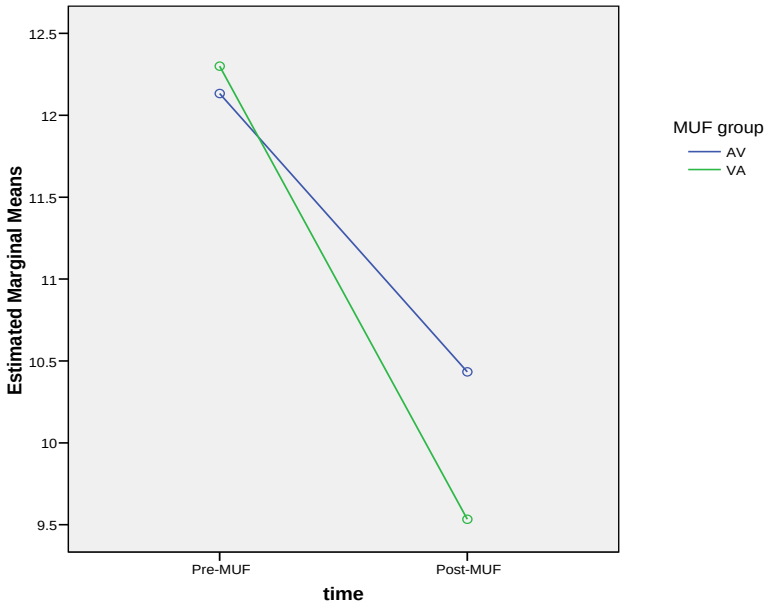


Graph 9: Profile plot of mean blood pressure over time by treatment arm

4.2.4.5 Effects of MUF on the patients' mean CVP

In the AVMUF group, mean CVP decreased from 12.13 mmHg ± 3.8 to 10.43 mmHg ± 3.2, with a difference of - 1.7 mmHg. In the VAMUF group it decreased from 12.3 mmHg ± 3.4 to 9.53 mmHg ± 3.7, with a difference of -2.77 mmHg (Table 20).

Graph10 demonstrates that CVP in the AVMUF group decreased by 13.5% of the preMUF CVP, whereas the VAMUF group had a more significant reduction of 23.88 % of the pre-MUF CVP.



Graph 10: Profile plot of mean central venous pressure over time by treatment arm

4.2.5 Gas exchange and acid base status

Table 21 represents the gas exchange and acid base status data expressed as mean ± standard deviation.

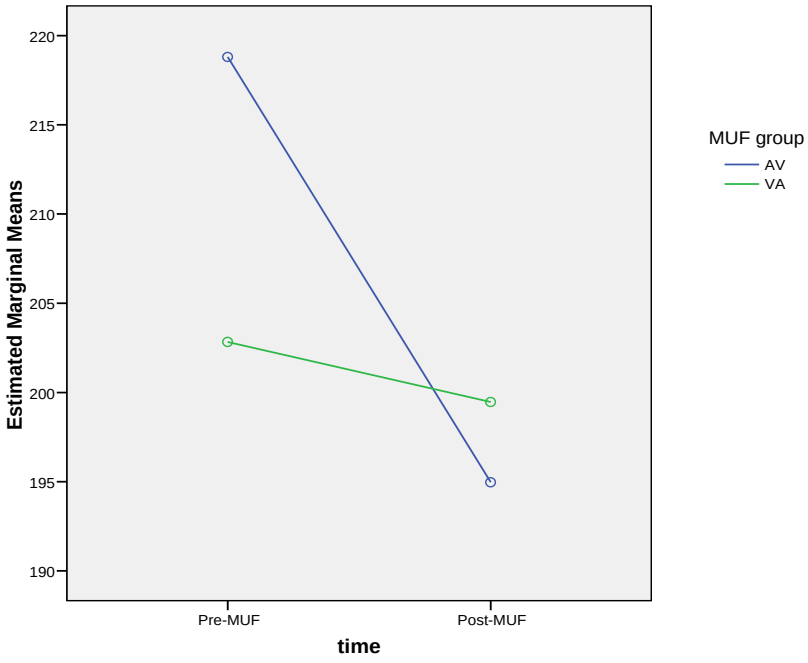
Table 21: Blood gas analysis data

Variables	AVMUF		VAMUF		*p* value
	Pre – MUF *Mean (±SD)*	*Post – MUF* *Mean (±SD)*	*Pre – MUF* *Mean (±SD)*	*Post – MUF* *Mean (±SD)*	
pO_2 (mmHg)	218.8 (±102.0)	194.97 (±72.1)	202.83 (±89.6)	199.47 (±81.9)	**0.287**
pO_2 (%)	100	96.67 (±27)	100	105.80 (±42.2)	**0.322**
pCO_2 (mmHg)	36.7 (±4.9)	37.17 (±5.9)	35.30 (±5.7)	34.66 (±2.5)	**0.488**
pCO_2 (%)	100	103.08 (±26.6)	100	100.10 (±14.1)	**0.590**
SaO_2 (%)	99.03 (±1.6)	99.37 (±1.1)	99.00 (±2.4)	99.83 (±0.7)	**0.191**

The results demonstrate that there were no significant differences between the two treatment arms with regards to the change in blood gas variables. This is also illustrated in Graphs 11 to 13.

4.2.5.1 Effects of MUF on the partial pressure of oxygen (pO_2) in blood

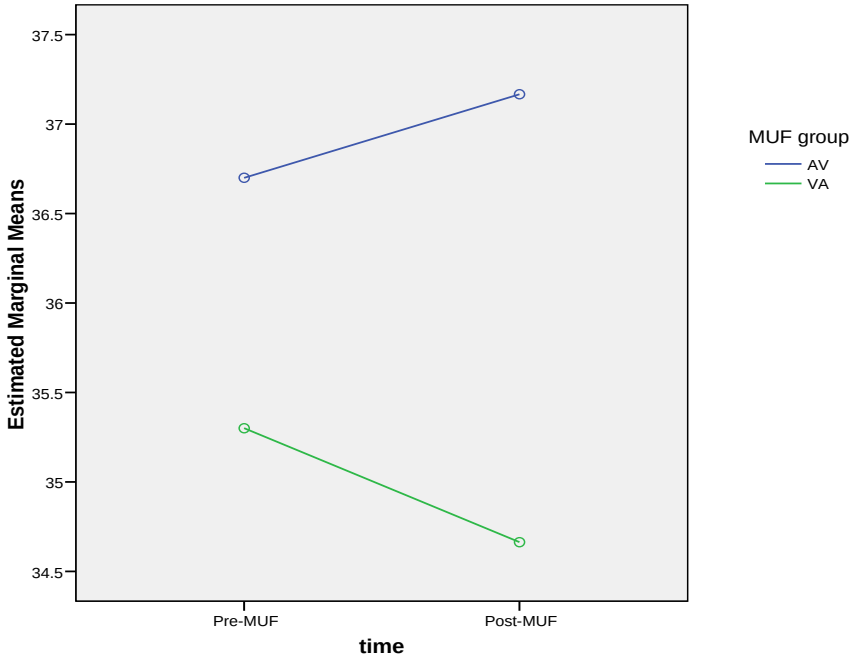
The normal value of pO_2 for arterial blood gas is 75-100 mmHg. In Table 21 the AVMUF group tends to have a rapid drop in pO_2 levels after MUF from 218.8 mmHg ± 102.0 to 194.97 mmHg ± 72.1, with a difference of - 28.83 mmHg. The VAMUF group had a gentle drop in pO_2 levels post MUF i.e., from 202.83 mmHg ± 89.6 to 199.47 mmHg ± 81.9, with a difference of -3.37 mmHg. The reason for this was that the VAMUF technique oxygenated blood as MUF was being performed. The AVMUF technique, on the other hand had no oxygenator in the circuit. Graph 11 demonstrates that the VAMUF group has more control over post bypass serum oxygen transition rate, with a percentage drop of +5.8 %, while the AVMUF has a pO_2 drop of -3.3%.



Graph 11: Profile plot of mean partial pressures of oxygen (pO_2) over time

4.2.5.2 Effects of MUF on partial pressure of carbon dioxide (pCO_2) in blood

The normal range of pCO_2 in an adult is 35 - 45 mmHg and 33 - 43 mmHg in children. Table 21 shows that pCO_2 in the AVMUF group increased from a mean of 36.7 mmHg ± 4.9 to a mean of 37.17 mmHg ± 5.9 with a difference of 0.47 mmHg, whereas the VAMUF group had a drop in pCO_2 levels from 35.30 mmHg ± 5.7 to 34.66 mmHg ± 2.5, with a mean difference of -0.64 mmHg. Both the AVMUF group and the VAMUF group remain within the normal range for pCO_2 level. The AVMUF group tends to move towards respiratory acidosis while the VAMUF group tended to move towards respiratory alkalosis. The pCO_2 in the AVMUF groups increased by 3.08 %, while the VAMUF group had a post MUF difference of 0.1 %. Graph 12 demonstrates that there were no significant changes in the pCO_2 levels from pre-MUF to post- MUF in both the groups.

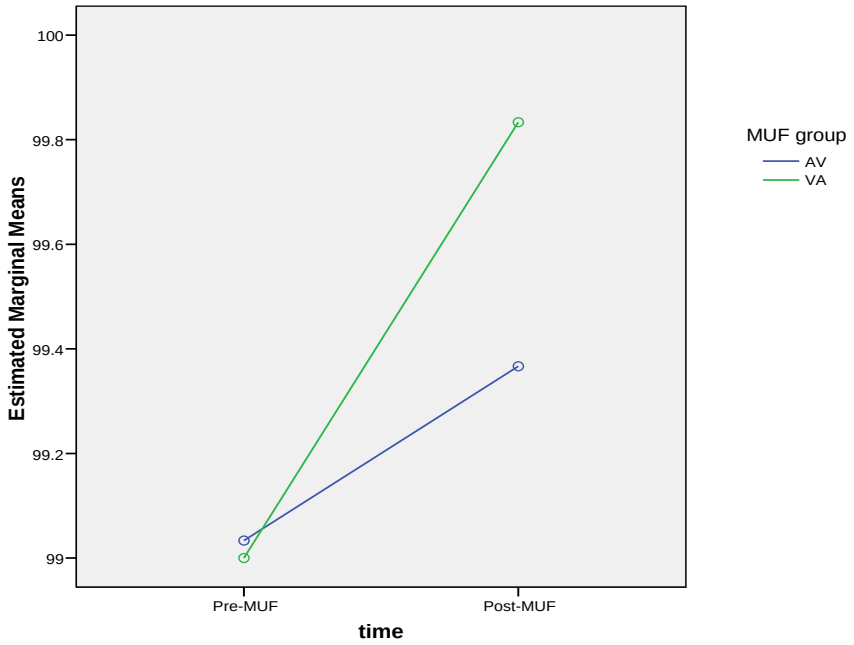


Graph 12: Profile plot of mean pCO_2 over time by treatment arm

4.2.5.3 Effects of MUF on the oxygen saturation (SaO_2) in blood

The SaO_2 in the AVMUF group increased marginally from 99.03 % ± 1.6 to 99.37% ± 1.1, with a mean difference of 0.33% and the VAMUF study group also increased

marginally from 99% ± 2.4 to 99.83% ± 0.7, with a mean difference of 0.83% (Table 21). The results in Graph 13 show that pre and post MUF arterial oxygen saturation remain stable and within normal ranges while MUF was being performed, making both procedures safe with regards to oximetry parameters.



Graph 13: Profile plot of mean saturation over time by treatment arm

4.2.6 Haematological data

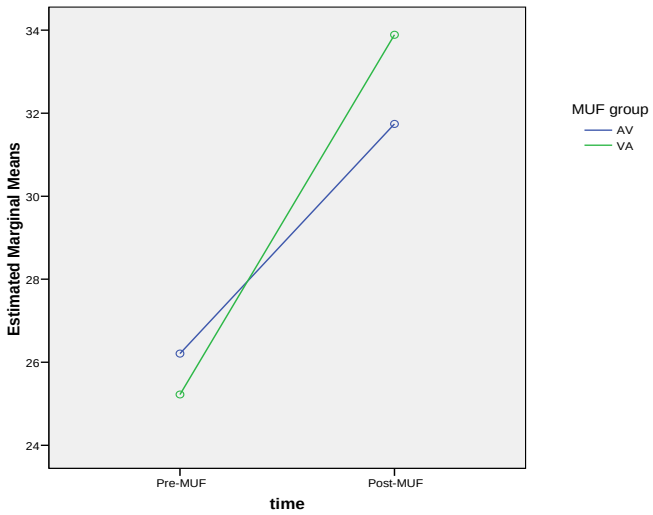
Table 22 represents the haematological data expressed as mean ± standard deviation. The Hct, HB, RBC, and albumin concentrations showed significant differences from pre to post treatment between the two treatment arms. All values increased over time, to a greater extent in the VAMUF arm.

Table 22: Haematological data analysis

Variables	AVMUF		VAMUF		*p* value
	Pre – MUF *Mean (±SD)*	***Post – MUF*** *Mean (±SD)*	***Pre – MUF*** *Mean (±SD)*	***Post – MUF*** *Mean (±SD)*	
Hct (%)	26.21 (±2.9)	31.74 (±5.7)	25.22 (±3.5)	33.89 (±4.0)	**0.006**
Hb (g/dl)	8.88 (±0.9)	10.83 (±1.4)	8.47 (±1.1)	11.34 (±1.3)	**0.001**
Hb (%)	100	122.51(±15.3)	100	134.55 (±12.4)	**0.001**
RBC (M/µL)	3.38 (±1.1)	3.74 (±0.6)	3.11 (±1.4)	3.86 (±0.7)	**0.056**
RBC (%)	100	114.57 (±15.9)	100	124.32 (±18.0)	**0.030**
WBC (K/µL)	15.06 (±7.3)	16.12 (±9.6)	16.26 (±6.3)	16.91(±6.2)	**0.781**
WBC (%)	100	109.48 (±51.0)	100	103.99 (±31.0)	**0.927**
PLT (K/µL)	165.27(±37.1)	172.20(±47.9)	193.70(±56.5)	198.67(±54.5)	**0.919**
PLT (%)	100	104.58 (±23.7)	100	104.51 (±21.2)	**0.999**
Alb (g/L)	22.93 (±5.4)	29.2 (±6.6)	22.33 (±4.5)	32.27(±4.7)	**<0.001**
Alb (%)	100	128.26 (±15.5)	100	156.18 (±19.8)	**<0.001**

4.2.6.1 Effects of MUF on the patients' Hct

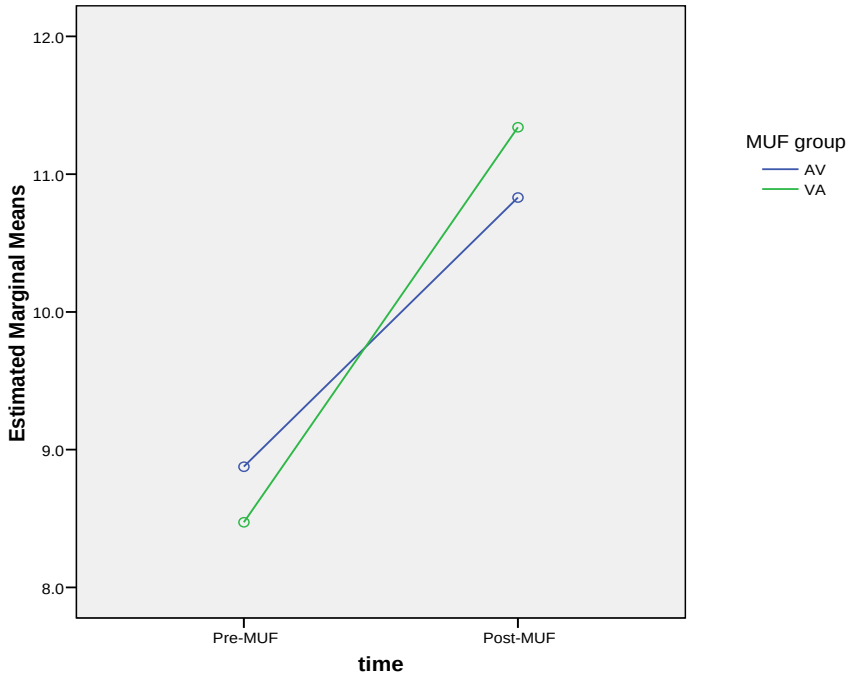
Table 22 shows that the mean Hct in the AVMUF group increased from 26.21% ± 2.9 to 31.74% ± 5.7, with an increase of 5.53%. In Graph 14 the VAMUF group had a more significant increase in mean Hct, i.e., from 25.22% ±3.5 to 33.89% ± 4.0, with an increase of 8.66 %. (Graph 14)



Graph 14: Profile plot of mean Hct over time by treatment arm

4.2.6.2 Effects of MUF on haemoglobin (Hb)

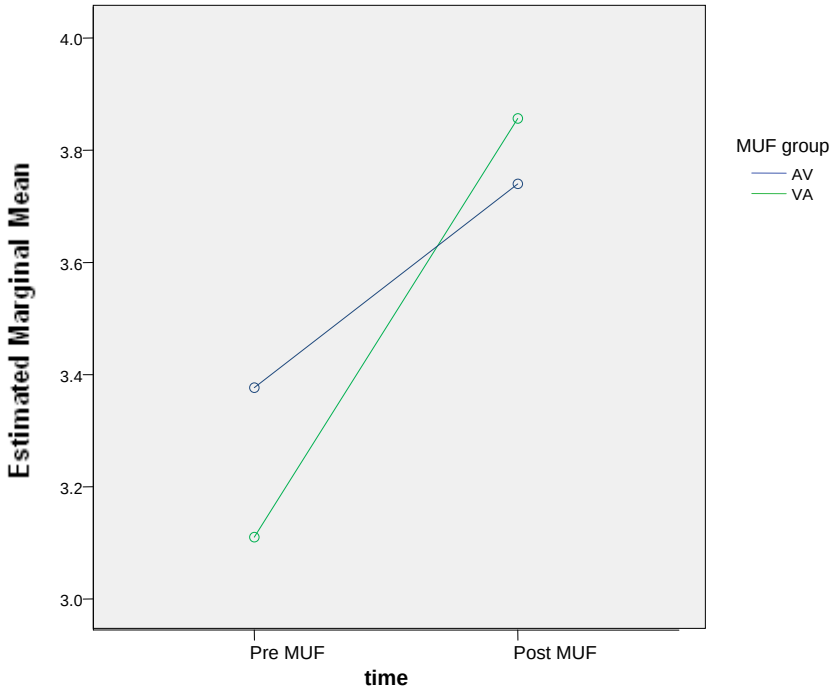
In the AVMUF group Hb levels increased from 8.88 g/dl ± 0.9 to 10.83 g/dl ± 1.4, with a difference of 1.95 g/dl. In the VAMUF group, Hb increased from 8.47 g/dl ± 1.1 to 11.34 g/dl ± 1.3, with an increase of 2.87 g/dl (Table 22). Graph 15 illustrates that the VAMUF study group had a more significant rise in Hb, with an increase of 34.6 %, when compared to the AVMUF group which had a 22.5 % increase in Hb.



Graph 15: Profile plot of mean Hb over time by treatment arm

4.2.6.3 Effects of MUF on red blood cell (RBC) count

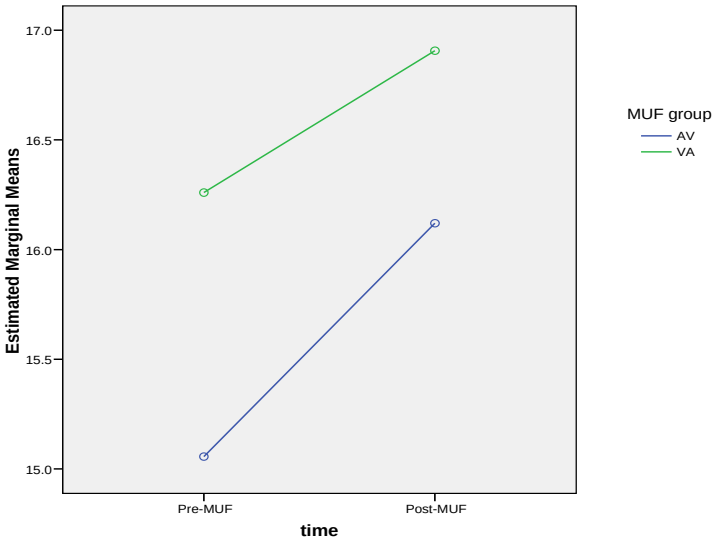
In the AVMUF group the RBC count increased from 3.38 M/µl to 3.74 M/µl, with a mean difference of 0.36 M/µl. The VAMUF group had a more significant increase of RBC count from 3.11 M/µl to 3.86 M/µl, with a difference of 0.75 M/µl (Table 22). Graph 16 illustrates that the VAMUF study group's RBC count increased by 24.3 %, whereas in the AVMUF group RBC count increased by 14.6 %.



Graph 16: Profile plot of mean RBC over time by treatment arm

4.2.6.4 Effects of MUF on white blood cell (WBC) count

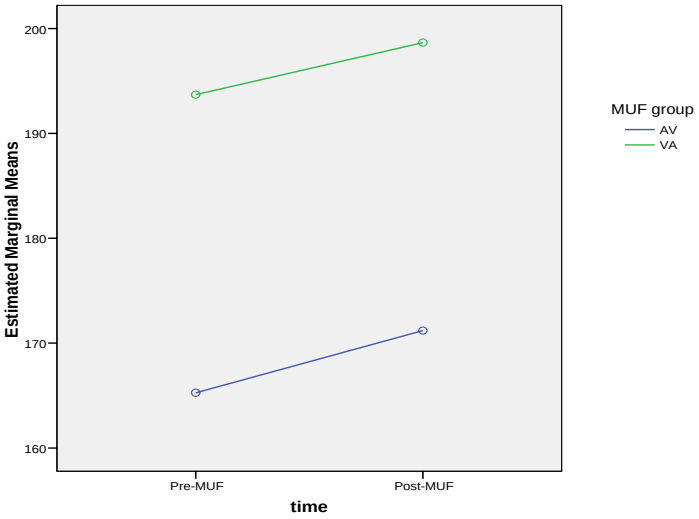
The normal range for white blood cell (WBC) in adults is 3.8 - 10.8 K/µl with an optimal reading of 7.3 K/µl. Higher ranges are found in children, newborns and infants. In Table 22 the WBC in the AVMUF group increased from 15.06 K/µl ± 7.3 to 16.12 K/µl ± 9.6, with a difference of 1.06 K/µl. The VAMUF group had a less significant rise in WBC from 16.26 K/µl ± 6.3 to 16.91 K/µl ± 6.2, with a difference of 0.65 K/µl. Graph 17 shows that WBC in the AVMUF group increased by 9.5 % while in the VAMUF group it increased by 4.0 %.



Graph 17: Profile plot of mean WBC over time by treatment arm

4.2.6.5 Effects of MUF on the patients' platelet count (PLT)

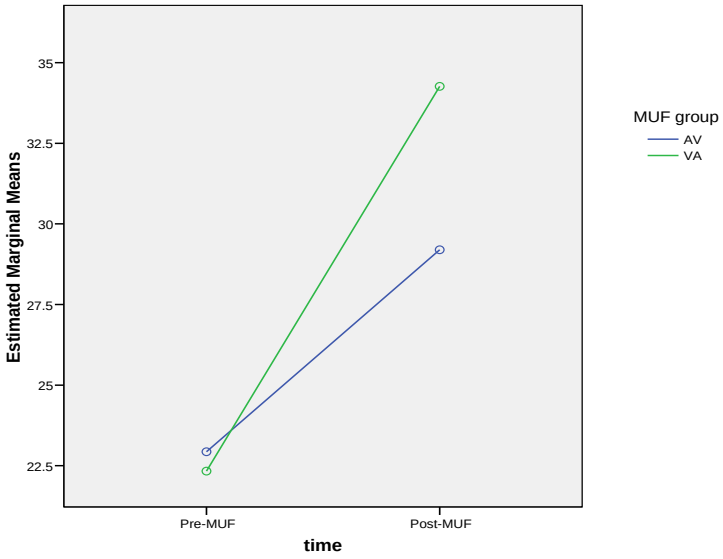
The normal range for PLT in an adult is 130 - 400 K/µl with an optimal reading of 265 K/µl. Higher ranges are found in children, newborns and infants. The PLT count in the AVMUF group increased from 165.27 K/µl ± 37.1 to 172.20 K/µl ±47.9, with a difference of 5.93 K/µl (Table 22). In the VAMUF group it rose from 193.70 K/µl ± 56.5 to 198.67 K/µl ± 54.5, with a difference of 4.97 K/µl. Both the AVMUF group (4.6 %) and the VAMUF group (4.5 %) showed positive increase in PLT count (Graph 18).



Graph 18: Profile plot of mean platelets over time by treatment arm

4.2.6.6 Effects of MUF on serum albumin (alb) concentration

Serum albumin in the AVMUF group increased from 22.93 g/l ± 5.4 to 29.2 g/l ± 6.6, with a difference of 6.27 g/l. In the VAMUF group serum albumin increased from 22.33 g/l ± 4.5 to 32.27 g/l ± 4.7, with a difference of 11.93 g/l (Table 22). Serum alb in the AVMUF group increased by 28.3%, while the VAMUF study group demonstrated a more significant increase of 56.2%. The results in Graph 19 suggests that the VAMUF group had a more significant impact on increasing the serum proteins like albumin ($P < 0.001$



Graph 19: Profile plot of mean albumin over time by treatment arm

4.2.7 Metabolites and renal related markers

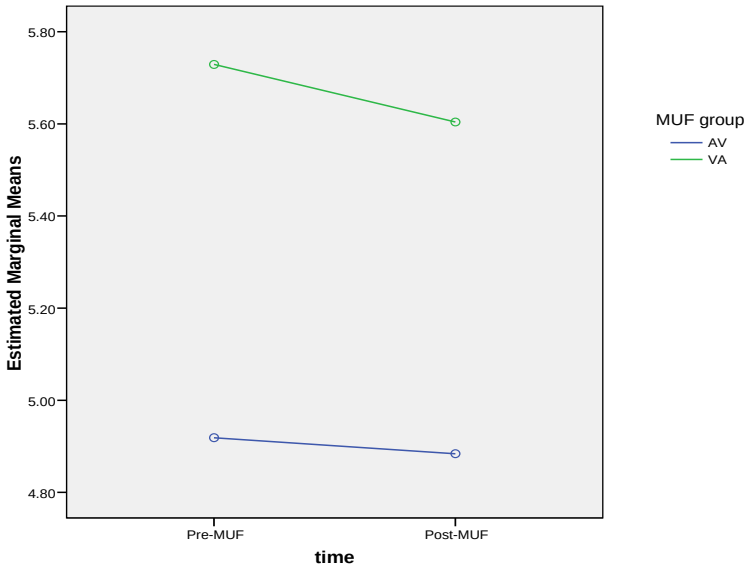
In Table 22 the metabolites and renal markers are expressed as mean ± standard deviation. Creatinine and uric acid showed a significantly greater decrease over time in the VAMUF group than the AVMUF group ($p<0.001$ and $p<0.027$ respectively). The ratio of urea to creatinine also showed significant differences between the treatment arms. The VAMUF group showed a greater increase over time than the AVMUF group. This is also represented in the Graphs 20 to 22.

Table 23: Renal related markers in the AVMUF and VAMUF groups

Variables	AVMUF		VAMUF		*p* value
	Pre – MUF *Mean (±SD)*	*Post – MUF* *Mean (±SD)*	*Pre – MUF* *Mean (±SD)*	*Post – MUF* *Mean (±SD)*	
B.U.N - (mmol/L)	4.92 (±2.3)	4.88 (±2.1)	5.73(±3.5)	5.60 (±3.4)	**0.520**
B.U.N - (%)	100	102.64 (±15.6)	100	98.39 (±10.5)	**0.221**
S-Creat-(mmol/L)	67.90(±37.2)	67.17(±38.1)	71.17 (±25.1)	59.83 (±26.0)	**0.001**
S-Creat-(%)	100	98.78 (±17.4)	100	82.81(±18.7)	**0.001**
Uric acid (mmol/L)	272.2(±85.2)	268.9(±77.8)	276.57(±76.9)	258.10(±65.8)	**0.027**
S – Uric acid (%)	100	99.98 (±10.4)	100	94.13 (±9.2)	**0.025**

4.2.7.1 Effects of MUF on blood urea nitrogen (BUN) after CPB

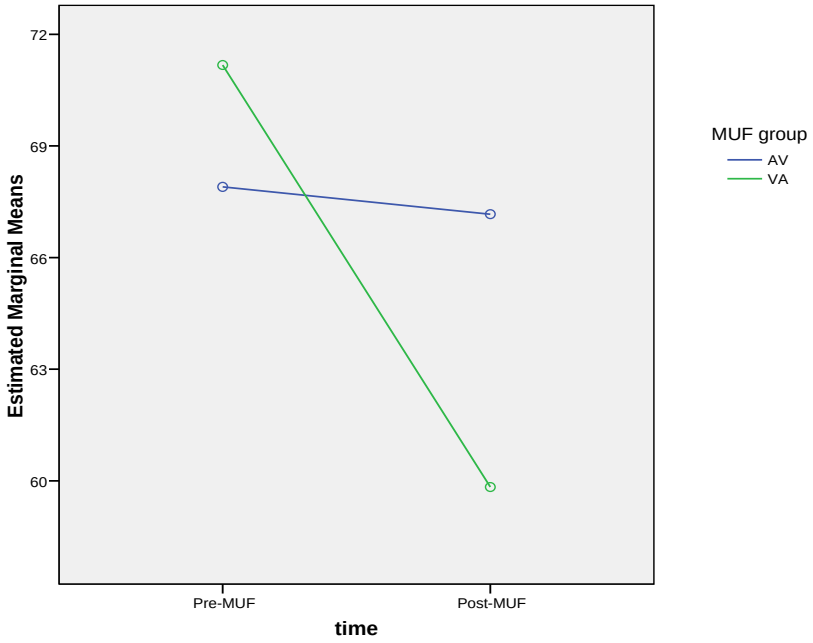
In the AVMUF group BUN decreased from 4.92 mmol/l ± 2.3 to 4.88 mmol/l ± 2.1, with a difference of - 0.04 mmol/l. In the VAMUF study group it decreased from 5.73 mmol/l ± 3.5 to 5.60 mmol/l ±3.4, with a difference of - 0.13 mmol/l (Table 23). The AVMUF demonstrated an increase of 2.64 % while the VAMUF group demonstrated a significant decrease of - 1.61% (Graph 20).



Graph 20: Profile plot of mean urea over time by treatment arm

4.2.7.2 Effects of MUF on the patients' serum creatinine

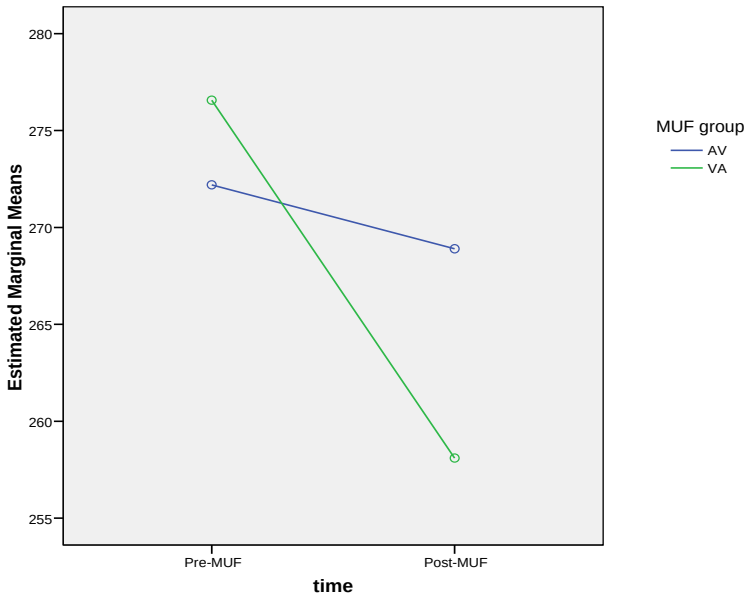
Serum creatinine decreased in the AVMUF group from 67.90 mmol/l ± 37.2 to 67.17 mmol/l ± 38.1, with a mean difference of -0.73 µmol/l (Table 23). There was a more significant decrease of serum creatinine in the VAMUF group which decreased from 71.17 µmol/l ± 25.1 to 59.83 mmol/l ± 26.0, with a mean difference of -11.34 µmol/l. Graph 21 illustrates that there was a significant difference in the ability of the VAMUF study group to reduce creatinine, which dropped by 17.2%. The AVMUF group had a smaller percentage decrease of 1.22%.



Graph 21: Profile plot of mean creatinine over time by treatment arm

4.2.7.3 Effects of MUF on the patients' serum uric acid

Serum uric acid decreased in the AVMUF group from 272.2 µmmol/l ± 85.2 to 268.9 µmmol/l ± 77.8, with a mean difference of - 3.30 µmmol/l (Table 23). In the AVMUF group it decreased from 276.57 µmmol/l ± 76.9 to 258.10 ± 65.8, with a mean difference of -18.47 µmmol/l. The VAMUF group showed a significant difference of 5.87 % in serum uric acid after cardiac surgery and CPB while the AVMUF group showed a decrease of 0.02% (Graph 22).



Graph 22: Profile plot of mean uric acid over time by treatment arm

4.2.8 Cardiac markers

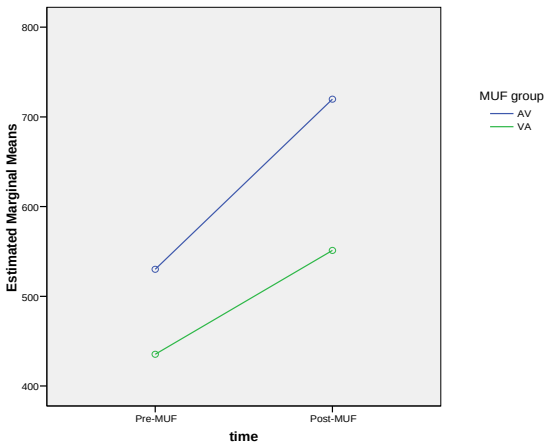
Table 23 represents an analysis of cardiac markers expressed as mean ± standard deviation. Only serum lactate showed a significant difference over time between the treatment arms, (p < 0.001). The VAMUF arm showed a larger decrease between preMUF and postMUF than the AVMUF arm. The change in the other variables did not differ significantly between treatment arms. This is also represented in the Graphs 23 to 25.

Table 24: Cardiac markers in the AVMUF and VAMUF group

Variables	AVMUF		VAMUF		*p* value
	Pre – MUF *Mean (±SD)*	*Post – MUF* *Mean (±SD)*	*Pre – MUF* *Mean (±SD)*	*Post – MUF* *Mean (±SD)*	
CK (U/L)	541.00 (±334.9)	719.69 (±436.1)	435.33 (±219.9)	551.1 (±242.1)	**0.140**
CK-MB (IU/L)	16.84 (±12.2)	16.88 (±5.9)	16.99 (±6.9)	22.63 (±13.8)	**0.062**
CK – MB (%)	4.29 (±3.6)	3.97 (±3.6)	5.03 (±3.4)	4.79 (±2.9)	**0.825**
S – Lact (mmol/L)	3.64 (±1.4)	3.22 (±1.3)	3.99 (±1.0)	2.53 (±0.9)	**<0.001**
S – Lact (%)	100	88.73(±12.9)	100	62.13(±14.7)	**<0.001**

4.2.8.1 Effects of MUF on creatinine kinase (CK)

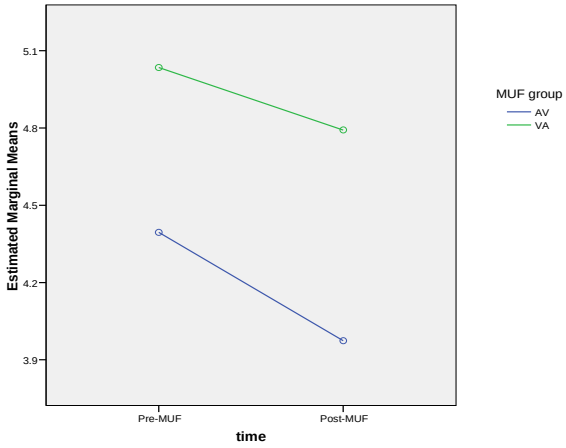
Table 24 demonstrates that CK values in the AVMUF group increased from 541.00 U/l ± 334.9 to 719.69 U/l ± 436.1, with a mean difference 189.6 U/l. In the VAMUF group CK increased from 435.33 U/l ± 219.9 to 551.1 U/l ± 242.1, with a mean difference of 115.8 U/l. Graph 23 illustrates that there was a more significant increase in CK in the AVMUF group compared to the VAMUF study group.



Graph 23: Profile plot of mean creatinine kinase (CK)

4.2.8.2 Effects of MUF on creatinine kinase myocardial band (CK-MB)

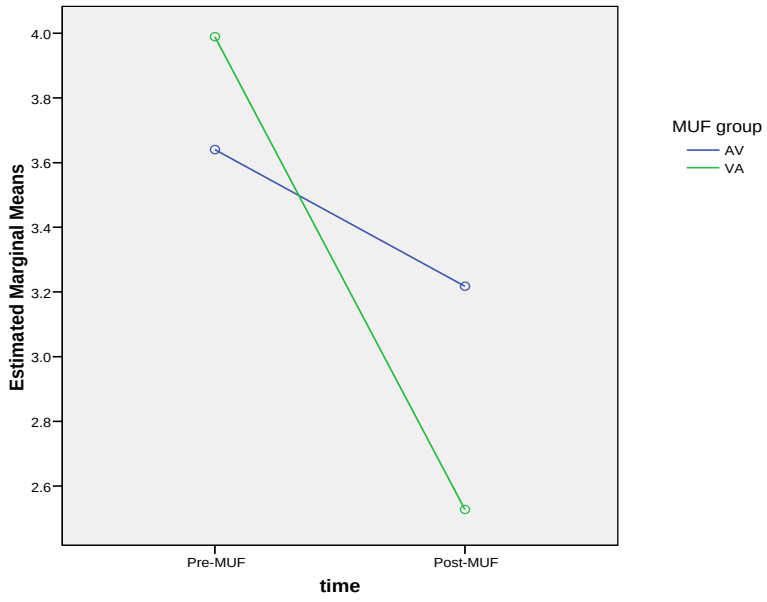
Graph 24 demonstrates there was no significant difference in the two groups. In the AVMUF group the CK-MB decreased from 4.29 % ± 3.6 to 3.97 % ± 3.6, with a difference of 0.42 % and in the VAMUF group it decreased from 5.03 % ± 3.4 to 4.79% ± 2.9, with a mean difference of 0.24%.



Graph 24: Profile plot of mean CK-MB percent by treatment arm

4.2.8.3 Effects of MUF on mean serum lactate

Table 24 demonstrates that serum lactate levels decreased in the AVMUF group from 3.64 mmol/l ± 1.4 to 3.22 mmol/l ± 1.3, with a mean difference of 0.42. In the VAMUF group it decreased from 3.99 mmol/l ± 1.0 to 2.53 mmol/l ± 0.9, with a mean difference of 1.46 mmol/l. There was a more significant decrease in serum lactate in the VAMUF study group (37.87%) than the AVMUF control group which had a decrease (11.2%) after MUF post CPB (Graph 25).



Graph 25: Mean serum lactate (s-lact)

4.3 CONCLUSION OF RESULTS

The results indicate that there were no significant differences in any of the mean demographic variables, CPB or cross-clamping times. There were highly statistically significant differences in the ventilation times. The VAMUF group showed a much lower ventilation time than the AVMUF group ($p < 0.001$). Intensive care unit stay, hospital stay and discharge days were all significantly lower in the VAMUF group as well ($p = 0.007$). There was a borderline statistically significant difference in mean

CUF volume with the VAMUF having the greater volume (p = 0.043). Venoarterial modified ultrafiltration had a statistically significant percentage fluid output than the AVMUF (p = 0.044). Venoarterial modified ultrafiltration also showed a lower percentage positive fluid balance in patients than the AVMUF, (15.11% compared to 20.81%). The heart rate (p < 0.001), systolic blood pressure (p < *0.001)*, mean blood pressure (p < 0.001) and central venous pressure (CVP) (p = 0.002) were statistically significantly higher after VAMUF. There were no significant differences in gas exchange and acid base status. Creatinine (p =0.001) and uric acid (p = *0.*027) showed a significantly greater decrease over time in the VAMUF group. VAMUF arm showed a more significant decrease in serum lactate than AVMUF (p <*0.001)*.

inCHAPTER FIVE : DISCUSSION

Medical professionals routinely explore new ideas and techniques in an attempt to reduce post operative bleeding and decrease ICU and hospital stay. This entails the invention of new ideas and techniques and the re-exploration of old ones. Modified ultrafiltration is one of those techniques.

There are numerous adverse effects that are associated with the use of CPB in patients (Butler, Parker, Pillai, Westaby, Shale, and Rocker, 1993). These adverse effects include: an increase in capillary permeability which leads to an overall increase in total body water and oedema formation (Maehara et al., 1991); pulmonary compliance and gas transfer being decreased and myocardial oedema which may result in diastolic dysfunction (Bando et al., 1998). Several studies have previously established that the implementation of MUF decreased post operative oedema arising from haemodilution. Hence, MUF reduced the need for donor blood, thus reducing the complications associated with homologous blood transfusion. MUF also reduced complement activation by removing tumour necrosis factor (TNF), interleukin-6, interleukin-8, cytokines and endothelin-1 (Grunenfelder et al., 2000). This arguably resulted in decreased organ damage and hence quicker recovery times.

Numerous types of MUF were investigated during the preliminary studies of this research. One of them included the conventional AVMUF used by Naik Knight and Elliott (1991). Some were circuits taken from publications while a few were selected from the feedback acquired from other hospitals. All these various techniques of MUF were compared to the VAMUF circuit that was designed uniquely by the principle investigator for the purpose of this study.

A survey that was carried out on the worldwide web of various cardiac institutes revealed that none of them had performed VAMUF. Until then, no literature had suggested that VAMUF had been attempted or published at other centres worldwide. During the VAMUF, the blood that was removed from the RA via the venous cannula flowed through the haemoconcentrator. The filtrated blood was then returned to the

aorta through the aortic cannula. This method followed the same physiology as CPB and the body's normal blood flow pattern.

To terminate MUF, different centres used different criteria. Some terminated MUF when the CPB circuit contents were completely salvaged (Chaturvedi, Shore, White, Scallan, Gothard, Redington and Lincoln, 1999), some used a time-based criterion (Naik, Knight and Elliott, 1991), others used a haematocrit end point (Daggett et al., 1998) while a few used an ultrafiltrate volume end point (Journois et al., 1996). Although the use of varying techniques and end point criteria made the interpretation of published results difficult, the beneficial effects of MUF have still been independently reproduced at many institutions. The VAMUF incorporated all of these criteria while taking into consideration optimal haematocrit, volume constrains, calculated excess fluid volume as well as the blood flow dynamics.

Previous studies have raised concerns regarding the potential risks and complications of MUF (Hanley, 2000; Elliott, 1999). The initial concern was that MUF would lead to haemodynamic instability if blood was drawn from the arterial cannula immediately after separation from CPB. Nevertheless, the converse proved true and MUF resulted in increased arterial blood pressure, decreased filling pressures and improved cardiac performance. However, one could still argue that the increase in arterial blood pressure during AVMUF was due to the increased oncotic pressures which resulted from the increased total proteins and haematocrit after removal of excess fluid from the blood and not from the blood flow dynamics. Furthermore, during AVMUF, systolic and diastolic pressure increased without a change in vascular tone. This suggested that the pre-load and after-load of the heart increased. This increased the workload of the heart during diastole. During VAMUF there was an increase in systolic pressure and a small decrease in diastolic pressure in comparison to AVMUF. This suggested that there was a decrease in workload for the ventricles. In the VAMUF technique, blood was removed from the RA and this allowed the RA, RV, lungs, LA and LV an opportunity to recover from the anoxia caused during cross clamping on CPB. Blood was eventually re-infused into the aorta where it increased coronary flow during diastole. The VAMUF therefore increased the supply of blood to the heart while decreasing the demand.

The introduction of the IABP in cardiac surgery benefited patients with poor myocardial function (Golding, Loop, Peter, Cosgrove, Taylor and Philips, 1980). The principle and blood flow dynamics of the VAMUF is similar to that of the IABP. The IABP primarily increases diastolic pressure in the aortic root and thereby coronary perfusion. However, this increase in organ perfusion is entirely dependent on myocardial function (Bolooki, 1984). The VAMUF on the other hand, increased both diastolic pressure in the aortic root (hence ↑coronary perfusion) and systolic pressures (↑arterial blood flows) thereby increasing organ perfusion as well. However, this increase in organ perfusion was based on the mechanical pump flow produced by the designated MUF pump-head on the heart lung machine and not on myocardial function.

There are various mechanisms by which MUF produces the beneficial effects seen after CPB. These mechanisms are still not yet fully understood. Previous studies hypothesized that MUF improved organ function by simply reducing excess TBW and tissue oedema (Naik, Knight and Elliott, 1991; Naik, Balaji and Elliott, 1993). Subsequent studies, however, demonstrated that substantial amounts of inflammatory mediators and vasoactive substances were found in the ultrafiltrate. These included tumor necrosis factor α, interleukins 6, 8, and 10, and endothelin- 1. Hence, this could have also contributed to the improved organ function. (Bando et al.,1998; Journois et al., 1996; Li et al., 2004; Elliott, 1999; Wang et al., 1996; Hiramatsu et al., 2002). According to Bando et al. (1998) and Journois et al. (1996), it was possible that a combination of CUF and MUF would allow CUF to initiate the removal of mediators early in the inflammatory cascade during the re-warming period of CPB and thus decrease the severity of the inflammatory response. According to Naik, Knight and Elliott (1991), it was most likely that a combination of both these procedures would possibly contribute to a favourable outcome which included: reduction of tissue oedema, removal of inflammatory mediators (Larustovskii et al., 1998); increase in haematocrit (Schlunzen et al., 1998); total proteins (Ootaki et al., 2002); decreased homologous blood transfusion (Koutlas et al., 1997; Draasima et al., 1997) and improved cerebral metabolism after circulatory arrest (Skaryak et al., 1995). Previous reviews documented by Bando et al. (1998) speculated that the removal of mediators diminished the inflammatory response to CPB, thus,

ameliorating some of the adverse sequelae. No study has yet established a definite relationship between removal of inflammatory mediators and improved outcome.

Daggett et al. (1998) concluded that MUF was superior to CUF in reducing the total body weight gain, reducing myocardial oedema, increasing mean arterial pressure, and improving left ventricular contractility in neonatal piglets undergoing CPB. The volume of filtrate removed was significantly greater with MUF than with CUF. Therefore, the removal of mediators was correspondingly greater although the concentration of inflammatory mediators in the filtrate did not differ between CUF and MUF (Wang et al., 1996). Kiziltepe et al., (2001) hypothesized and proved that these benefits could be achieved if a combination of MUF plus CUF was performed post operatively on adult patients undergoing cardiac surgery with the aid of CPB.

The evidence of these previous studies suggested that the optimal benefits of ultrafiltration in patients undergoing cardiac surgery with CPB would result from a combination of both CUF and MUF techniques. This study used the data from these previous studies as logic and performed CUF and MUF in combination for whichever cases it was possible.

One could argue that the Cell Saver is a good formidable alternative to haemoconcentrating the blood in the oxygenator post operatively. Solem, Tengborn, Steen, and Lührs (1987) performed an investigation where concentration of superfluous blood in the oxygenator after the termination of a cardiopulmonary bypass was studied. One group of patients were treated with a centrifugation system while another group was treated with a hollow fibre haemofilter. Although both methods functioned well, the products differed greatly as centrifugation revealed highly concentrated red cells in saline solution while haemofiltration produced protein-rich concentrated whole blood. The haemoconcentrator provides whole blood which is important to maintain oncotic pressures post CPB. It is also superior to the cell saver because it has the ability to concentrate the patient's circulating blood volume during MUF. The dilution or eradication of plasma proteins by a cell saver device increases water transfer to extravascular compartments and attenuates blood loss as a result of clotting disturbances (Utley et al., 1981; Kirklin, Blackstone and Kirklin, 1987; Kern et al., 1992). Dilution of plasma proteins in blood increases water

transfer to extravascular compartments which is a major cause of capillary leak and organ failure. Therefore, a combination of CUF and MUF are formidable techniques in reducing the effects of haemodilution during CPB, thereby reducing the effects of capillary leak on end organs.

From the exploration of publications it was concluded that the effectiveness of MUF had been established in numerous studies over the past few years. It was for this reason that too much emphasis was not placed on re-confirming or disputing the results of previous studies once again. Instead, efforts were concentrated on attempting to find the most efficient and physiological method of performing MUF. The VAMUF approach was the chosen technique for this comparative study against the conventional AVMUF technique.

This experimental study explored the difference in the method of performing MUF on a total of 60 patients (30 VAMUF and 30 AVMUF) in order to establish which technique was more physiological and followed the normal physiological blood flow pathway of the body and the CPB circuit. The different parameters that were measured were used as indicators to confirm which technique was more physiological. In the AVMUF technique, blood that was removed from the aorta flowed retrograde through the bypass circuit and through a separate MUF circuit. Here it was haemoconcentrated and returned to the patient via the RA. In the VAMUF technique, the blood that was removed from the RA flowed pro-grade through the CPB circuit where it was haemoconcentrated and re-infused into the aorta. The results of this prospective clinical study established that there were significant differences between the results obtained from patients who underwent the conventional AVMUF technique and patients who underwent the VAMUF technique.

When compared to the AVMUF group, the VAMUF group demonstrated significant improvement in immediate postoperative arterial oxygenation in patients. This is probably due to the fact that the VAMUF had an oxygenator as part of the circuit. This could be an advantage to maintain adequate saturation immediately after separating from CPB but it possibly also increases the length of the CPB circuit thereby increasing surface contact. The VAMUF also resulted in higher arterial pressures. Moreover, the VAMUF patients required less homologous blood

transfusion and had shorter ventilatory support time than the AVMUF. Shorter ventilation time as a result of MUF was documented by Meliones et al. (1995) and may have been due to the removal of free water and the use of fewer transfusions that may have contributed to improved pulmonary mechanics after CPB (Meliones et al., 1995). This is probably what caused earlier extubation in the VAMUF patient group. Removal of small molecule inflammatory agents, including endothelin-1 (a potent pulmonary vasoconstrictor) (Bando et al., 1998) and other cytokines, may have also played a significant role in lowering postoperative pulmonary arterial pressure and reducing lung injury after reperfusion (Journois, Pouard, Greeley, Mauriat, Vouhe and Safran, 1994).

It was also suggested that intra-myocardial air could have been a contributing factor for myocardial dysfunction after paediatric cardiac surgery (Bell, Rimar and Barash, 1989; Greeley et al., 1990). Therapy for myocardial air embolism was directed at increasing perfusion pressure to propel air through the arterioles and capillary bed. Patients with intramyocardial air demonstrated dramatic haemodynamic and echocardiographic improvements after the administration of phenylephrine or reperfusing the heart with high pump flow rates and high perfusion pressures on CPB (Greeley et al., 1990). The VAMUF increased coronary blood flow and BP in the arteries. According to Greeley et al. (1990), this assisted in eradicating air bubbles that were possibly in the coronaries. On the other hand, AVMUF decreased diastolic perfusion pressures during the process as blood was removed from the aortic root, thereby decreasing coronary blood flow.

The final results, as documented in chapter five, suggest that there were no significant differences in any of the demographic variables or type of procedures included in this study. There were no significant differences with regards to the CPB and cross-clamp times between the AVMUF and VAMUF groups. The results of the study also confirmed that there was a statistically significant difference in the ventilation time between the two arms of the study ($p < 0.001$). The VAMUF group showed a much lower ventilation time than the AVMUF group. Previous MUF studies also showed a decrease in ventilation time in patients who underwent MUF as was demonstrated in this study (Naik, Knight and Elliott, 1991; Bando et al., 1998;

Sever et al., 2004; Kameyama et al., 2000; Mahmoud et al., 2005). Intensive care unit stay, hospital stay and discharge days were reduced in both groups as noted by Naik, Knight and Elliott (1991), Bando et al. (1998) and Sever et al. (2004). However, these values were significantly lower in the VAMUF group.

Electrolyte variables in this study demonstrated that there were no significant differences in the changes in any electrolyte between pre MUF and post MUF in both groups. The changes on serum sodium (Na^+), serum potassium (K^+), serum calcium (Ca^{2+}), Serum Phosphate (PO_4^-), Serum Magnesium (Mg^{2+}), after MUF were insignificant. However, although there were no significant difference in change between electrolytes in pre MUF and post MUF, both groups demonstrated that they did not have a negative impact on electrolyte balance.

Fluid management data revealed that there was a statistically significant difference in fluid output between the two groups ($p = 0.044$) with the VAMUF arm having a greater percentage output than the AVMUF. There was also a statistically significant difference in the fluid balance between the two arms ($p = 0.008$) with the VAMUF arm having a lower percentage fluid balance than the AVMUF arm. After MUF, the VAMUF patients had a remaining fluid balance of 15.11% of the total fluid input while the AVMUF patients had a higher remaining fluid balance of 20.81% of the total fluid input. The AVMUF group ended up more fluid positive compared to the VAMUF group, based on the differences in volume removal during the CUF rather than the MUF phase. It is possible that the results could reflect differences in total fluid balance regardless of technique. This decrease in TBW after MUF was also documented in studies by Naik, Knight and Elliott (1991) and Daggett et al. (1998).

Haemodynamic data showed that the change between pre MUF and post MUF was significantly different between the two groups in terms of heart rate and CVP. The VAMUF group showed a larger decrease. This group also demonstrated a greater increase in terms of systolic and mean pressure as compared to the AVMUF group. There was a more significant drop in heart rate in the VAMUF group as compared to the AVMUF group ($p = 0.001$) with an increase in mean blood pressure. The advantages of a decrease in heart rate with an increase in mean blood pressure post MUF was also documented by Schlunzen et al. (1998).

The VAMUF group showed a more significant rise of 24.07 % in the mean systolic blood pressure in comparison to the AVMUF group which had a 10.18 % rise in the mean systolic BP ($p < 0.001$). The rise in systolic BP was published in previous studies (Naik, Knight and Elliott, 1991; Ad et al., 1996; Gaynor, 1998; Daggett et al., 1998; Schlunzen et al., 1998; Onoe et al., 1999 and Onoe et al., 2001). The VAMUF group displayed a more significant rise in mean BP with a 22.93% elevation in mean arterial blood pressure whereas the AVMUF group displayed a 9.78 % increase in mean BP. The AVMUF group demonstrated a CVP decrease of 13.5% whereas the VAMUF group demonstrated a more significant reduction of 23.88 % of the pre MUF CVP, with an increase in mean pressure.

The VAMUF group had more control over post bypass serum oxygen transition rate with an increase of +5.8 % while the AVMUF had a pO_2 drop of -3.3%. This increase in pO_2 post MUF was documented by Aeba et al., (2000) and Sahoo et al. (2007). There were no significant changes in the pCO_2 levels from pre MUF to post MUF in both the groups although as related to other studies both groups showed an improvement in pCO_2 levels after MUF (Aeba et al., 2000; Sahoo et al., 2007). There were no significant changes in preMUF and post MUF arterial oxygen saturation which remained stable and within normal ranges, thus making these procedures safe with regards to oximetry parameters.

Haematological data which included Hct, HB, RBC and albumin showed significant differences in change from pre MUF to post MUF between the two groups. The VAMUF group had a more significant increase in mean Hct from 25.22% ±3.5 to 33.89% ± 4.0 with an increase of 8.66 %. This increase in Hct was documented in previous trials (Naik, Knight and Elliott, 1991; Ad et al, 1996; Larustovskii et al., 1998; Onoe et al., 1999; Onoe, 2001; Kiziltepe et al., 2001). The VAMUF group had a more significant rise of 34.6 % in HB as compared to the AVMUF group which had a 22.5 % increase in HB. This rise in HB was in keeping with previous studies (Kamada et al., 2001; Ootaki et al., 2002; Fujita et al., 2004; Sahoo et al., 2007; Aggarwal et al., 2007).

Haematological results indicated that the RBC count in the VAMUF group increased by 24.3 % while it only increased by 14.6 % in the AVMUF group. Fujita et al. (2004) also published a study that documented that RBC count increased post MUF. White blood cells increased by 4.0 % in the VAMUF group while it increased by 9.5 % in the AVMUF group. This significant difference (p - 0.781) suggested that VAMUF caused less WBC activation. The effects of MUF on patient's platelet count, was first documented by Ootaki et al. (2002) and Fujita et al. (2004). Both the AVMUF group and the VAMUF group showed a positive increase of 4.6 % and 4.5 % respectively in platelet count. Hence, this improved clotting factors which assisted in reducing post operative bleeding.

The VAMUF group demonstrated a more significant increase of 56.2% in serum albumin while the AVMUF group only increased by 28.3%. These results suggested that the VAMUF group had a more significant impact on increasing the serum proteins like albumin ($p < 0.001$) and thereby increasing blood viscosity and oncotic pressures which could have possibly encouraged tissue perfusion post cardiac surgery (Ootaki et al., 2002; Fujita et al., 2004).

The effects of MUF on metabolites and renal related markers were illustrated by creatinine and uric acid which showed a significantly greater decrease over time in the VAMUF group ($p< 0.001$ and $p< 0.027$ respectively). The ratio of urea to creatinine also showed significant differences between the treatment arms, but the VAMUF group showed a greater increase over time than the AVMUF group. However, it is not clear if removal of these markers actually signify end organ improvement after MUF. More studies will have to be carried out in order to prove their association in the future.

The VAMUF patients had a significant decrease of 1.61% on their serum blood urea nitrogen (BUN) after CPB while the patients who underwent AVMUF demonstrated an increase of 2.64 %. This suggested that VAMUF was more effective in removing BUN than AVMUF. However, a study performed by Williams and team in 2006 noted that urea measurement 48 hours post operatively showed no signs of any difference between DUF and MUF (Williams, Ramamoorthy, Chu, Hammer, Kamra, Boltz, Pentcheva, McCarthy and Reddy, 2006).

A limitation with the VAMUF circuit was that it required a greater volume of blood to remain in the CPB/MUF circuit while the AVMUF circuit used smaller size tubing from the haemoconcentrator to the patient. Nevertheless, this did not pose as a serious problem since all the blood from the circuit volume was returned to the patient at the end of MUF in both groups.

In this study, serum creatinine decreased more significantly in the VAMUF group. This result suggested that VAMUF had a greater ability to reduce the metabolite creatinine, which dropped by 17.2% as compared to the AVMUF group which only decreased by 1.22%. Williams et al. (2006) also found that MUF decreased serum creatinine postoperatively. However, their study showed that 48 hours post-operatively, there was no difference in creatinine between DUF and MUF.

Serum uric acid in the VAMUF group showed a significant difference of 5.87 % in comparison to the AVMUF group, which decreased by only 0.02%. This significant reduction of metabolites in the VAMUF group contributed positively to patient recovery in the post operative phase.

Measurement of cardiac markers revealed that only serum lactate showed a significant difference ($p < 0.001$) with VAMUF showing a larger decrease between pre and post readings. The change in the results for the removal of other variables like CK and CK-MB post MUF was noticeable when compared to pre MUF but did not differ significantly between the treatment arms. It is still not fully understood whether the removal of these cardiac markers actually contributed to faster cardiac and end organ recovery and whether a lower reading after MUF signified better cardiac myocardial function or hospital outcome. This is probably a good avenue to be explored in future MUF studies.

Figure 32 is an illustration of the AVMUF blood flow dynamics. Blood was removed retrograde via a new cannula or connector that was attached to the arterial line of the aorta cannula used for CPB. It was then actively removed by a designated MUF roller pump after which it flowed through a haemoconcentrator before it was infused into the RA by another new cannula, connector or cardioplegic stick. The results of this study indicated that the AVMUF group had a less significant increase in haemodynamic variables. Theoretically, this could have possibly arisen from the fact that blood was removed from the aorta at near the aortic root. This decreased systemic flow to the head vessels and to the descending aorta which in turn decreased cerebral circulation and resulted in decreased end organ perfusion. The removal of blood from the aorta also decreased flow into the coronary arteries during diastole when the aortic valve closed. This decreased myocardial perfusion. Blood was then re-infused into the body via the RA and this resulted in an increase in blood volume in the RA, RV, pulmonary circulation, and left side of the heart. This increased blood volume resulted in an increased work load on the myocardium which was already receiving decreased coronary perfusion. The AVMUF thus increased the workload on the heart whilst it decreased blood supply to the myocardium. This affected the paediatric patients more than the adult patients because of their small BSA.

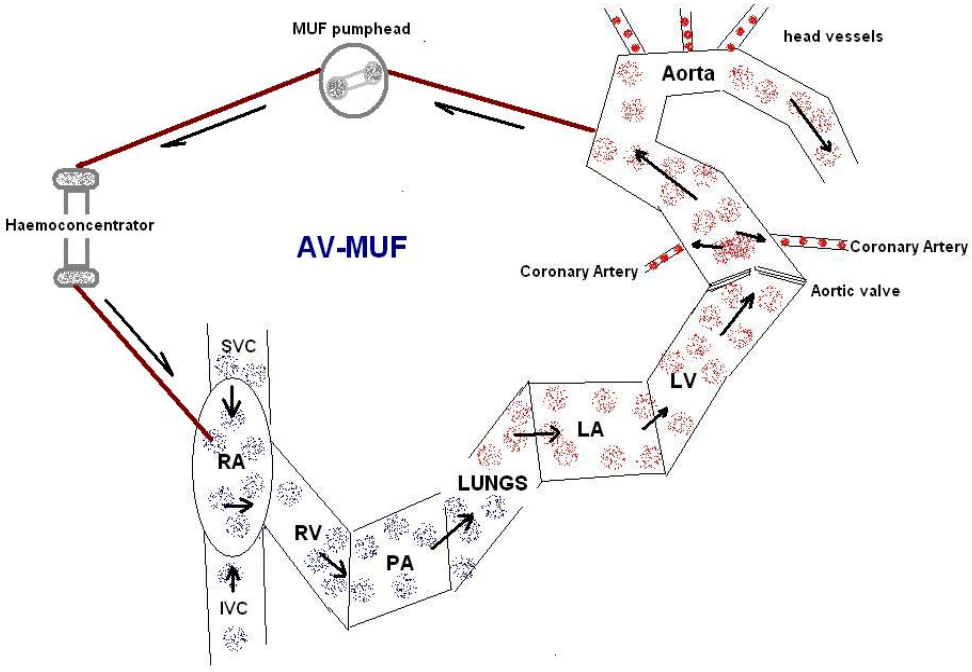


Figure 32: AVMUF blood flow dynamics diagram

Figure 33 is an illustration of the VAMUF blood flow dynamics. Blood was removed pro-grade and actively from the RA by the main pump used for CPB. It then flowed through the oxygenator where it was oxygenated before passing through the haemoconcentrator. The blood was then re-infused into the aorta through the same aortic cannulae that was used for CPB. The results of this study indicated that the VAMUF group had a more significant increase in haemodynamic variables. Theoretically, this could have possibly arisen from the fact that blood was removed from the RA during VAMUF, resulting in a decrease in blood volume in the RA, RV, pulmonary circulation and the left side of the heart. This decreased blood volume resulted in a decreased work load on the myocardium. Blood was then re-infused into the aorta near the aortic root thus, increasing blood systemic flow to the head vessels and to the descending aorta. This increased cerebral circulation and also increased end organ perfusion. The re-infusion of blood into the aorta increased blood flow into the coronary arteries during diastole when the aortic valve closed. This increased myocardial perfusion. The VAMUF thus increased blood supply to the heart whilst it decreased myocardial demand. Further studies still need to be carried out regarding measurement of flows in each of the major vessels during MUF.

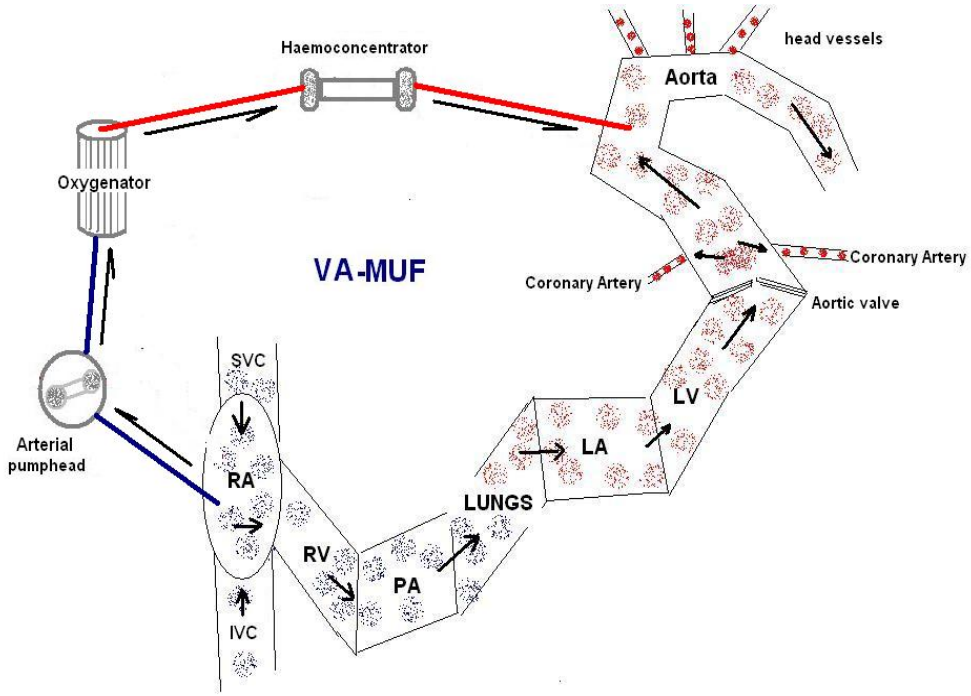


Figure 33: VAMUF blood flow dynamics diagram

Table 25 illustrates a general comparison between AVMUF and VAMUF from the time it was set-up until the procedure was completed. It was based on circuit requirements, changes that had to be made to accommodate the process, difference in flow patterns through the CPB circuit and changes in blood flow dynamics within the patient as illustrated in Figures 31 and 32.

TABLE 25: Comparison between AVMUF and VAMUF

AVMUF	VAMUF
1.) Blood flow was circulated through a separate MUF circuit	Blood flow was circulated through a normal CPB circuit in order to perform MUF
2.) Required flushing of the MUF circuit	No additional flushing was required
3.) Blood was drawn from the aorta and infused into the RA	Blood was drawn from the RA and infused into the Aorta
4.) Retrograde blood flow path in the patient (Arterial to venous)	Pro-grade blood flow path in the patient (Venous to Arterial)
5.) Blood flow was retrograde through the CPB circuit	Blood flow was pro-grade through the CPB Circuit
6.) Decreased systemic blood flow	Increased systemic blood flow
7.) Decreased coronary perfusion	Increased coronary perfusion
8.) Increased blood volume in cardiac cycle	Decreased volume blood in cardiac cycle
9.) Increased work load on the left and right heart	Decreased work load on the left and right heart
10.) Patient's temperature dropped during MUF	Patient's temperature was controlled by a heater-c unit
11.) Longer PVC lines increased surface contact of blood to a foreign body	Shorter PVC lines reduced surface contact since the MUF circuit was incorporated into the existing conventional bypass set.
12.) Required additional cannulae	No additional cannulae was required

CHAPTER SIX: SUMMARY, CONCLUSION AND FUTURE WORK

6.1 SUMMARY

The role of MUF in removing inflammatory mediators, reducing the need for homologous donor blood and decreasing pulmonary vascular resistance during CPB surgery had already been established. Different types of MUF systems performed at cardiac centres in the world were evaluated in order to determine which methods were the most effective and safe. All the data that was received illustrated that none of the MUF techniques that were performed followed the normal venous to arterial blood flow dynamics.

This study compared the conventional AVMUF system that was used at majority of the centres worldwide to the VAMUF system that was designed by the principal investigator. This technique of VAMUF was designed to mimic the normal pro-grade blood flow pattern of the body and CPB circuit in comparison to the conventional retrograde AVMUF systems.

A total of 60 patients who underwent MUF where divided into two groups of 30 each for the AVMUF and the VAMUF. Modified ultrafiltration was performed for a mean time of 12 minutes in both groups. In the AVMUF the blood was removed from the aorta, haemoconcentrated and then infused into the RA, using a separate pump head. In the VAMUF the blood was removed from the RA, haemoconcentrated and then infused into the patient via the aorta, using the main pump head and following the body's natural blood flow pattern. No technical complications were encountered during CUF or MUF in both groups.

The results obtained indicated that there were no significant differences in any of the mean demographic variables, CPB or cross-clamping times. There were statistically significant differences in the ventilation times with the VAMUF group showing a much lower ventilation time than the AVMUF group. Intensive care unit stay, hospital stay and discharge days were all significantly lower in the VAMUF group as well. There was a statistically significant difference in mean CUF volume with the VAMUF having a greater volume. When compared to the AVMUF, the VAMUF presented a

statistically significant percentage fluid output. The VAMUF also showed a lower percentage positive fluid balance in the patient in comparison to the AVMUF. The haemodynamic variables were significantly higher after VAMUF. There were no significant differences in oximetry. The renal markers indicated a significantly greater decrease over time in the VAMUF group. The VAMUF arm showed a more significant decrease in serum lactate than the AVMUF. Table 26 summarizes the results of this study giving a general comparison between the AVMUF and the VAMUF with regards to the criteria of an ideal MUF technique**.**

Table :26 Criteria for an Ideal MUF Technique

CRITERIA	AVMUF	VAMUF
Reduced the excess fluid volume in the patient	✓	✓
Concentrated the volume left in the CPB circuit after bypass	✓	✓
Increased the HB/HCT in the patient	✓	✓
Reduced the need for donor blood	✓	✓
Did not require additional tubing for the MUF circuit	X	✓
Proved to be a safe system	✓	✓
Simulated the patient's normal blood flow pathway	X	✓
Required minimum or no changes to the CPB circuit	✓	✓
Did not interfere or reduce the patient's systemic blood volume	X	✓
Does not reduce the patients' arterial pressures	✓	✓
Did not reduce the systemic blood flow	X	✓
Had an acceptable learning curve	✓	✓
Is user friendly	✓	✓
Was able to abandon the procedure at any stage to reinstitute CPB	✓	✓
Required the use of one pump head for bypass and MUF	X	✓
Was able to oxygenate blood if required while on MUF	X	✓
Had heat exchanging capabilities incorporated	X	✓
Entire MUF circuit had ¼ inch tubing	✓	X
Had the ability to be used for conventional ultrafiltration as well	✓	✓
Allowed for the entire volume in the CPB circuit to be infused into the patient before termination of the procedure.	✓	✓
Allowed for the circuit to remain primed after termination of MUF in order to re-initiate CPB if required.	✓	✓

6.2 CONCLUSION

This study hypothesized that an ultrafiltration strategy using the VAMUF instead of the AVMUF would maximize physiological benefits and would provide an optimal outcome for patients undergoing cardiac surgery. The study found that a combination of the CUF and the VAMUF provided more benefits in terms of haemodynamics, haematology, fluid balance and patient outcome in comparison to a combination of the CUF and the AVMUF. The VAMUF was not only comparable to the AVMUF regarding clinical parameters but it was also practically more physiological with regards to the blood flow dynamics through the patient and the CPB circuit. Systemic blood flow to the major organs and the heart increased with the VAMUF while the work load of the heart decreased. From this study, it can therefore be concluded that the VAMUF is a more physiological technique than the AVMUF and is a formidable alternative to the conventional techniques of performing MUF in cardiac surgery post CPB.

6.3 FUTURE WORK

Cardiopulmonary bypass has been around for many years and may still be around for the near future, at least. This holds an opportunity to advance this field of medicine in order to try to achieve the highest possible degree of patient care.

The various mechanisms by which MUF produces the beneficial effects are still not yet fully understood. It was hypothesized that MUF improved organ function by simply removing inflammatory mediators, reducing excess TBW and tissue oedema, vasoactive substances which included TNF α, interleukins 6, 8, and 10, and endothelin-1. It is still not fully understood whether the removal of these cardiac markers actually contributed to faster cardiac and end organ recovery, or whether a lower reading after MUF signified better cardiac myocardial function or hospital outcome. This uncertainty is motivation enough and probably a good avenue to be explored in future MUF studies. Further studies still need to be carried out regarding measurement of flows in each of the major vessels during MUF. That should provide more clarity on which method of performing MUF should be the technique of choice.

eleCHAPTER SEVEN: REFERENCES

Ad, N., Snir, E., Katz, J., Birk, E. and Vidne, B.A. 1996. Use of the modified technique of ultrafiltration in pediatric open-heart surgery: a prospective study. *Isr J Med Sci,* 32(12): 1326–1331.

Aeba, R., Katogi, T., Omoto, T., Kashima, I. and Kawada, S. 2000. Modified ultrafiltration improves carbon dioxide removal after cardiopulmonary bypass in infants. *Artifi Organs,* 24(4): 300–304.

Agarwal, M.B. 2007. The ideal transfusion trigger in critically ill patients. *Indian J Crit Care Med,* 11: 173-175.

Aggarwal, N.K., Das, S.N., Sharma, G. and Kiran, U. 2007. Efficacy of combined modified and conventional ultrafiltration during cardiac surgery in children. *Ann Card Anaesth,* 10(1): 27-33.

Aldea, G.S. and Shemin, R.J. 1998. Heparin-bonded circuits improve clinical outcomes in patients undergoing CABG: A new 'gold standard'? *ACC Current J Rev,* March/April: 45–48.

Anand, K.J. and Hickey, P.R. 1992. Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. *N Engl J Med,* 326: 1.

Baker, E.J., Olinger, G.N. and Baker, J.E. 1991. Calcium content of St. Thomas' II cardioplegic solution damages ischemic immature myocardium. *Ann Thorac Surg,* 52: 993-999.

Balasaraswathi, K., Glisson, S.N., El-Etr, A.A. and Azad, C. 1980. Effect of priming volume on serum catecholamines during cardiopulmonary bypass. *Canadian Journal of Anesthesia,* 27(2): 135–139.

Bando, K., Turrentine, M.W., Sharp, T.G., Sekine, Y., Aufiero, T.X., Sun, K., Sekine, E. and Brown, J.W. 1996. Pulmonary hypertension after operations for congenital heart disease: analysis of risk factors and management. *J Thorac Cardiovasc Surg,* 112: 1600-1609.

Bando, K., Turrentine, M.W., Vijay, P., Sharp, T.G., Sekine, Y., Lalone, B.J., Szekely, L. and Brown, J.W. 1998. Effect of modified ultrafiltration in high-risk patients undergoing operations for congenital heart disease. *Ann Thorac Surg,* 66: 821-828.

Bando, K., Vijay, P., Turrentine, M.W., Sharp, T.G., Means, L.J., Ensing, G.J., Lalone, B.J., Sekine, Y., Szekely, L. and Brown, J.W. 1998. Dilutional and modified ultrafiltration reduces pulmonary hypertension after operations for congenital heart disease: A prospective randomized study. *J Thorac Cardiovasc Surg,* 115: 517-527.

Bannan, S. and Martin, P.G. 1998. Aprotinin complements heparin bonding in an in vitro model of cardiopulmonary bypass. *British Journal of Haematology,* 101(3-1): 455–461.

Bareford, D., Chandler, S.T., Hawker, R.J., Jackson, N., Smith, M. and Boughton, B.J. 1987. Splenic platelet-sequestration following routine transfusion is reduced by filtered/washed blood products. *British Journal of Haematology,* 67(2): 177-180.

Barrons, R.W. and Jahr, J.S. 1996. A review of post-cardiopulmonary bypass bleeding, aminocaproic acid, tranexamic acid, and aprotinin. *American Journal of Theraputics,* 3: 821–838.

Bell, C., Rimar, S. and Barash, P. 1989. Intraoperative ST-segment changes consistent with myocardial ischemia in the neonate: A report of three cases. *Anesthesiology,* 71(4): 601-603.

Berdat, P.A., Eichenbergera, E., Ebella, J., Pfammatter, J., Pavlovic, M., Zobrist, C., Gygaxa, E., Nydegger, U. and Carrel, T. 2004. Elimination of proinflammatory cytokines in pediatric cardiac surgery. *The American Association for Thoracic Surgery*. 127(6): 1688-1696.

Bigelow, W.G., Callaghan, J.C. and Hopps, J.A. 1950. General hypothermia for experimental intracardiac surgery: the use of electrophrenic respirations, an artificial pacemaker for cardiac standstill and radio-frequency rewarming in general hypothermia. *Ann Surg*, 132(3): 531-539.

Birkmeyer, J.D., Aubuchon, J.P., Littenberg, B., O'Connor, G.T., Nease Jr, R.F., Nugent, W.C. and Goodnough, L.T. 1994. Cost-effectiveness of preoperative autologous donation in coronary artery bypass grafting. *Ann Thorac Surg,* 57: 161–168.

Blauth, C., Smith, P., Newman, S., Arnold, J., Siddons, F., Harrison, M.J., Treasure, T., Klinger, L. and Taylor, K.M. 1989. Retinal microembolism and neuropsychiatric deficit following clinical CPB: comparison of a membrane and a bubble oxygenator. A preliminary communication. *Eur J Cardio-thoracic Surgery,* 3: 135-138.

Blundell, J. 1818. The transfusion of blood by the syringe. Available at: http://en.wikipedia.org/wiki/James_Blundell_(physician) [accessed 9 January, 2008].

Body, S.C., Birminhan, J., Parks, R., Ley, C., Maddi, R., Shernan, S.K., Siegel, L.C., Stover, E.P., D'ambra, M.N., Levin, J., Mangano, D.T. and Spiess, B.D. 1999. Safety and efficacy of shed mediastinal blood transfusion after cardiac surgery. *J Thorac Cardiovasc Anesth,* 13: 410–416.

Boga, M., Islamoglu, F., Badak, I., Cikirikcioglu, M., Bakalim, T., Yagdi, T., Buket, S. and Hamulu, A. 2000. The effects of modified hemofiltration on inflammatory mediators and cardiac performance in coronary artery bypass grafting. *Perfusion,* 15(2): 143-150.

Bolooki, H. 1984. Clinical application of Intra-Aortic Balloon Pump. New York: Futura Publishing.

Boulanger, M. 1977. Levels of circulating norepinephrine and epinephrine before, during and after cardiopulmonary bypass in man. *Survey Anesthesiology,* 21: 48-53.

Breckenridge, I.M., Digerness, S.B. and Kirklin, J.W. 1970. Increased extracellular fluid after open intracardiac operation. *Surg Gynecol Obstet,* 131(1)-53-6.

Butler, J., Parker, D., Pillai, R., Westaby, S., Shale, D.J. and Rocker, G.M. 1993. Effect of cardiopulmonary bypass on systemic release of neutrophil elastase and tumor necrosis factor. *The Journals of Thoracic and Cardiovascular Surgery*, 105: 25–30.

Camishion, R.C., Fraimow, W., Kelsey, D.M., Tokunaga, K., Davies, A.L., Joshi, P., Cathcart, R.T. and Pierucci, L. 1968. Effect of partial and total cardiopulmonary bypass with whole blood or hemodilution priming on pulmonary surfactant activity. *J Surg Res,* 8(1): 1-6.

Chai, P.I., Williamson, J.A., Lodge, A.J., Daggett, C.W., Scarborough, J.E., Meliones, J.N., Cheifetz, I.M., Jaggers, J.J. and Ungerleider, R.M. 1999. Effects of ischemia on pulmonary dysfunction after CPB. *Ann Thorac Surg,* 67: 731-735.

Chaignon, M., Aubert, P., Martin, M.F., Lucsko, M. and Guedon, J. 1982. Haemodynamic effects of haemodialysis and hemofiltration. *Artif Organs,* 6(1): 27-30.

Chaturvedi, R.R., Shore, D.F., White, P.A., Scallan, M.H., Gothard, J.W.W., Redington, A.N. and Lincoln, C. 1999. Modified ultrafiltration improves global left ventricular systolic function after open-heart surgery in infants and children. *Eur J Cardiothorac Surg,* 15: 742-746.

Cheung, A.T., Cruz-Shiavone, G.E., Meng, Q.C., Pochettino, A., Augoustides, J.A., Bavaria, J.E. and Ochroch, E.A. 2007. Cardiopulmonary bypass, hemolysis, and nitroprusside-induced cyanide production. *Anesth Analg,* 105: 29-33.

Choudhary, S.K., Talwar, S., Airan, B., Yadav, S. and Venugopal, P. 2007. A simplified circuit of modified ultrafiltration. *Heart, Lung and Circulation,* 16(2): 113-115.

Chu, S.H., Huang, T.S., Hsu, R.B., Wang, S.S. and Wang, C.J. 1991. Thyroid hormone changes after cardiovascular surgery and clinical implications. *Annals of Thoracic Surgery,* 52: 791-796.

Clark, R.E., Dietz, D.R. and Miller, J.G. 1976. Continuous detection of microemboli during cardiopulmonary bypass in animals and man. *Circulation,* 54(6suppl): III74-78.

Cooley, D.A., Beall, A.C. and Grondin, P. 1962. Open-heart operations with disposable oxygenators, 5 per cent dextrose prime and normothermia. *Surgery,* 52: 713-719.

Corno, A.F., Bethencourt, D.M., Laks, H., Haas, G.S., Bhuta, S., Davtyan, H.G., Flynn, W.M., Drinkwater, D.C., Laidig, C. and Chang, P. 1987. Myocardial protection in the neonatal heart. A comparison of topical hypothermia and crystalloid and blood cardioplegic solutions. *The Journal of Thoracic and Cardiovascular Surgery,* 93: 163-172.

Cromer, M.J. and Wolk, D.R. 1998. A minimal priming technique that allows higher circulating hemoglobin on cardiopulmonary bypass. *Perfusion,* 13(5): 311–313.

Cross, M.H. 2001. Autotransfusion in cardiac surgery. *Perfusion,* 16(5): 391–400.

Daggett, C.W., Lodge, A.J., Scarborough, J.E., Chai, P.J., Jaggers, J. and Ungerleider, R.M. 1998. Modified ultrafiltration versus conventional ultrafiltration:

A randomized prospective study in neonatal piglets. *J Thorac Cardiovasc Surg,* 115: 336-342.

Darling, E., Harris-Holloway, S., Kern, F.H., Ungerleider, R., Jaggers, J., Lawson, S. and Shearer, I. 2000. Impact of modifying components and fluid administration using miniaturized circuitry in neonatal cardiopulmonary bypass. *Perfusion*, 15(1): 3-12.

Davies, M.J., Nguyen, K., Gaynor, J.W. and Elliott, M.J. 1998. Modified ultrafiltration improves left ventricular systolic function in infants after cardiopulmonary bypass. *J Thorac Cardiovasc Surg,* 115: 361–370.

Dennis, C., Spreng, D.S., Nelson, G.E., Karlson, K.E., Nelson, R.M., Thomas, J.V., Eder, W.P. and Varco, R.L. 1951. Development of a pump-oxygenator to replace the heart and lungs: An apparatus applicable to human patients and application to one case. *Ann Surg*, 134(4): 709-721.

Doenicke, A., Grote, B. and Lorenz, W. 1977. Blood and blood substitutes. *Br J Anaesth,* 49: 681-688.

Dow, J.W., Dickson, J.F., Hamer, N.A. and Gadboys, H.L. 1960. Anaphylactic shock due to homologous blood exchange in the dog. *J Thorac Cardiovasc Surg*, 39:449–456.

Draasima, A.M., Hazekamp, M.G., Frank, M., Anes, N., Schoof, P.H. and Huysmans, H.A. 1997. Modified ultrafiltration after cardiopulmonary bypass in pediatric cardiac surgery. *Ann Thorac Surg,* 64: 521-525.

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

Edmunds, L.H. 1999. Blood conservation. In Buxton, B., Frazier, O.H. and Westaby, S. (eds.) *Ischemic Heart Disease Surgical Management.* London: Mosby International.

Elliot, M.J. 1993. Minimising the bypass circuit: rational step in development of paediatric perfusion. *Perfusion,* 8: 81-86.

Elliott, M.J. 1993. Ultrafiltration and modified ultrafiltration in pediatric open heart operations. *Ann Thorac Surg,* 556: 1518–1522.

Elliott, M. 1999. Modified ultrafiltration and open heart surgery in children. *Paediatr Anaesth,* 9:1-5.

Elliott, M.J. 2001. Modified Ultrafiltration. 12th 15th UK, 25 June.

Engelman, R.M., Haag, B., Lemeshow, S., Angelo, A. and Rousou, J.H. 1983. Mechanism of plasma catecholamine increases during coronary artery bypass and valve procedures. The *Journal of Thoracic and Cardiovascular Surgery,* 86: 608-615.

Ferry, P.C. 1987. Neurologic sequelae of cardiac surgery in children. *Am J Dis Child,* 141(3): 309-312.

Fessatidis, I.T., Thomas, V.L., Shore, D.F., Sedgwick, M.E., Hunt, R.H. and Weller, R.O. 1993. Brain damage after profoundly hypothermic circulatory arrest: correlations between neurophysiologic and neuropathologic findings. An experimental study in vertebrates. *The Journal of Thoracic and Cardiovascular Surgery*, 106: 32-41.

Ferraris, V.A., Ferraris, S.P., Saha, S.P., Hessel, E.A., Haan, C.K., Royston, B.D., Bridges, R., Higgins, R., Despotis, G. and Brown, R. 2007. Perioperative Blood Transfusion and Blood Conservation in Cardiac Surgery. *The Annals of Thoracic Surgery*. 83(5), Supp 1: S27-S86.

Finn, A, Naik, S., Klein, N., Levinsky, R.J., Strobel, S. and Elliott, M. 1993. Interleukin-8 release and neutrophil degranulation after pediatric cardiopulmonary bypass. *The Journal of Thoracic and Cardiovascular Surgery,* 105: 234–241.

Flaim, S.F., Minteer, W.J., Clark, D.P. and Zelis, R. 1979. Cardiovascular response to acute aquatic and treadmill exercise in the untrained rat. *Journal of Applied Physiology,* 46(2): 302-308.

Ford, S.M.S., Unsworth, M.J., Aziz, T., Tooze, J., Besouw van, J. P. Bevan, D. and Treasure, T. 1999. Haemostatic function of pheresed platelets during cardiac surgery. *British Journal of Anaesthesia,* 82(suppl 2): A64.

Friesen, R.H, Campbell, D.N., Clarke, D.R. and Tornabene, M.A. 1997. Modified ultrafiltration attenuates dilutional coagulopathy in pediatric open heart operations. *Ann Thorac Surg,* 64: 1787–1789.

Fujita, M., Ishihara, M., Kusama, Y., Shimizu, M., Kimura, T., Iizuka, Y., Ozaki, S., Muraoka, M., Morimoto, Y., Takeshima, S., Kikuchi, M. and Maehara, T. 2004. Effects of modified ultrafiltration on inflammotry mediators, coagulation factors and other proteins in blood after an extracorporeal circuit. *Artif Organs,* 28(3): 310-313.

Gardner, R.E., Finlay, T.N. and Tooley, W.H. 1962. The effect of cardiopulmonary bypass on surface activity of lung extracts. *Bull. Soc lilt. Chir,* 21: 542-551.

Gaynor, J.W. 1998. Use of modified ultrafiltration after repair of congenital heart defects. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu,* 1: 81–90.

Gaynor, J.W. 2003.The effect of modified ultrafiltration on the postoperative course in patients with congenital heart disease. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu,* 6: 128-139.

George, M.D. and Morello, P.J. 1986. Immunological effects of blood transfusion upon renal transplantation, tumour operations and bacterial infections. *Am J surg,* 152(3): 329-337.

Gibbon, J.H, 1954. Application of mechanical heart and lung apparatus to cardiac surgery. *Minn Med*, 37(3): 171-185.

Gilcher, R.O. and Orr, M.D. 1975. Intra-operative autotransfusion. *Transfusion,* 15(5): 520.

Gillon, J., Desmond, M. and Thomas, M.J. 1999. Acute normovolaemia haemodilution. *Transfus Med* 9(3): 259–264.

Giordano, G.F., Rivers, S.L., Chung, G.K., Mammana, R.B., Marco, J.D., Raczkowski, A.R., Sabbagh, A., Sanderson, R.G. and Strug, B.S. 1988. Autologous platelet-rich plasma in cardiac surgery: effect on intraoperative and postoperative transfusion requirements. *The Annals of Thoracic Surgery,* 46: 416–419.

Golding, L.A., Loop, F.D., Peter, M., Cosgrove, D.M., Taylor, P.C and Philips, D.F. 1980. Late survival following use of intraaortic balloonpumping in revascularization surgery. *Ann Thorac Surg,* 30(1): 48-51.

Goodman, L.S. and Gillman, A. 1970. *The Pharmacological Basis of Therapeutics.* 4th ed. London: Macmillan.

Goodnough, L.T., Brecher, M.E., Kanter, M.H. and Aubuchon, J.P. 1999. Transfusion medicine. Blood transfusion. First of two parts. *N Engl J Med,* 340(6): 438–447.

Gordon, R., Ravin, M., Rawitscher, R.E. and Daicoff, G.R. 1975. Changes in arterial pressure, viscosity and resistance during cardiopulmonary bypass. *The Journal of Thoracic and Cardiovascular Surgery,* 69: 552-556.

Gott, V.L. and Daggett, R.L. 1999. Serendipity and the development of heparin and carbon surfaces. *Ann Thorac Surg,* 68(3 Suppl): S19–22.

Gould, F.K., Graham, T.R., Freeman, R. and Holden, M.P. 1987. Cytomegalovirus as a cause of immunosuppression following aortic valve replacement. *Perfusion, 2(3)*: 181-183.

Greeley, W.J., Kern, F.H., Ungerleider, R.M. and Kisslo, J.A. 1990. Intramyocardial air causes right ventricular dysfunction after repair of a congenital heart defect. *Anesthesiology,* 73(5): 1042-1046.

Greer, A.E., Carey, J.M. and Zudhi, N. 1962. Haemodilution principle of hypothermic perfusion. A concept obviating blood priming. *J Thorac.Cardiovasc Surg,* 43: 640-648.

Groom, R.C. 2002. High or low hematocrit during cardiopulmonary bypass for patients undergoing coronary artery bypass graft surgery? An evidence-based approach to the question. *Perfusion,* 17(2): 99–102.

Grunenfelder, J., Zund, G., Schoeberlein, A. Maly, F.E., Schurr, U., Guntli, S., Fischer, K., Turina, M., Fragata, J., Wan, S. and El Gamel, A.M. 2000. Modified ultrafiltration lowers adhesion molecule and cytokine levels after cardiopulmonary bypass without clinical relevance in adults. *Eur J Cardiothorac Surg,* 17: 77-83.

Hall, R.I., Schweiger, I.M. and Finlayson, D.C. 1990. The benefit of the Hemonetics Cell Saver apparatus during cardiac surgery. *Can J Anaesth,* 37(6): 618–623.

Hallowell, P., Bland, J.H., Buckley, M.J. and Lowenstein, E. 1972. Transfusion of fresh autologous blood in open-heart surgery. *J Thorac Cardiovasc Surg,* 64(6): 941-948.

Hanley, F.L. 2000. Surgery for congenital heart disease. *J Thorac Cardiovasc Surg,* 119:506-507.

Hardesty, R.L., Bayer, W.L. and Bahnson, H.T. 1968. A technique for the use of autologous fresh blood during open-heart surgery. *J Thorac Cardiovasc Surg,* 56(5): 683-688.

Harker, L.A., Malpass, T.W., Branson, H.E., Hessel, E.A. and Slichter, S.J. 1980. Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: acquired transient platelet dysfunction associated with selective alpha-granule release. *Blood,* 56: 824-834.

Hearse, D.J., Braimbridge, M.V. and Jynge, P. 1981. Protection of the ischaemic myocardium. New York: Raven Press.

Hebert, P.C., Wells, G. Blajchman, M.A., Marshall, J., Martin, C., Pagliarello, G., Tweeddale, M., Schweitzer, I. and Yetisir, E. 1999. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med,* 340(13): 1056.

Henderson, L.W., Livoti, L.G., Ford, C.A., Kelly, A.B. and Lysaght, M.J.1973. Clinical experience with intermittent hemodiafiltration. *Trans Am Soc Artif Intern Organs,* 9: 119-123.

Hepps, S.A., Roe, B.B., Wright, R.R. and Gardner, R.E. 1963. Amelioration of the pulmonary postperfusion syndrome with hemodilution and low molecular weight dextran. *Surgery,* 54: 232-243.

Hetzer, R., Warnecke, H., Wittrock, H., Engel, H.J., Borst, H.G. 1980. Extracoronary collateral myocardial blood flow during cardioplegic arrest. *J Thorac Cardiovasc Surg,* 28(3): 191-196.

Hiramatsu, T., Imai, Y., Kurosawa, H., Takanashi, Y., Aoki, M., Shin'oka, T. and Nakazawa, M. 2002. Effects of dilutional and modified ultrafiltration in plasma endothelin-1 and pulmonary vascular resistance after the Fontan procedure. *Ann Thorac Surg,* 73:862–865.

Hopeck, J.M., Lane, R.S. and Schroeder, J.W. 1981. Oxygenator volume controlled by parallel ultrafiltration to remove plasma water. *J Extracorp Technol,* 13: 267–271.

Hsu, L. 2001. Heparin-coated cardiopulmonary bypass circuits: current status. *Perfusion,* 16(5): 417–428.

Huet, C., Salmi, L.R., Fergusson, D., Koopman-van Gemert, A.W.M.M., Rubens, F. and Laupacis, A. 1999. A meta-analysis of the effectiveness of cell salvage to minimize perioperative allogenic blood transfusion in cardiac surgery. *Anesth Analg,* 89: 861–869.

Intonti, F., Alquati, P., Schiavello, R. and Alessandrini, F. 1981. Ultrafiltration during open heart surgery in chronic renal failure. *Scandinavian Cardiovascular Journal,* 15(2): 217-220.

Jaggers, J.J., Neal, M.C., Smith, P.K., Ungerleider, R.M. and Lawson, J.H. **1**999. Infant cardiopulmonary bypass: a procoagulant state. *Ann Thorac Surg,* 68: 513-520.

John, R. and Lee, S. 2008. The biological basis of thrombosis and bleeding in patients with ventricular assist devices. *Journal of Cardiovascular Translational Research,* 2(1): 63-70.

Journois, D., Israel-Biet, D., Pouard, P., Rolland, B., Silvester, W., Vouhe, P. and Safran, D. 1996. High-volume, zero-balanced hemofiltration to reduce delayed inflammatory response to cardiopulmonary bypass in children. *Anesthesiology,* 85(5): 965-976.

Journois, D., Pouard, P., Greeley, W.J., Mauriat, P., Vouhe, P. and Safran D. 1994. Hemofiltration during cardiopulmonary bypass in pediatric cardiac surgery. Effects on hemostasis, cytokines, and complement components. *Anesthesiology,* 81(5): 1181–1189.

Kamada, M., Niibori, K., Akimoto, H., Yokayama, H., Tofukuji, M., Iguchi, A., Ohmi, M., Tabayashi, K., Kikuchi, S. and Matsuura, T. 2001. Efficacy of modified ultrafiltration in coronary artery bypass grafting. *Japanese Journal of Thoracic Surgery,* 54(6): 463-467.

Kameyama, T., Ando, F., Okamoto, F., Hanada, M., Yamanaka, K., Sasahashi, N., Hirose, K., Matsuno, S. and Matsuura, S. 2000. The effect of modified ultrafiltration in pediatric open heart surgery. *Ann Thorac Cardiovasc Surg,* 6: 19–26.

Kaza, A.K., Cope, J.T., Fiser, S.M., Long, S.M., Kern, J.A., Kron, I.L., Tribble, C.G. 2003. Elimination of fat microemboli during cardiopulmonary bypass. *Ann Thorac Surg,* 75: 555-9

Keenan, H.T., Thiagarajan, R., Stephens, K.E., Williams, G., Ramamoorthy, C. and Lupinetti, F.M. 2000. Pulmonary function after modified venovenous ultrafiltration in infants: a prospective, randomized trial. *J Thorac Cardiovasc Surg,* 119: 501-505.

Kern, F.H., Morana, N.J., Sears, J.J. and Hickey, P.R. 1992. Coagulation defects in neonates during cardiopulmonary bypass. *The Annals of Thoracic Surgery,* 54: 541-546.

Kern, F.H., Ungerleider, R.M., Reves, J.G., Quill, T., Smith, L.R., Baldwin, B., Croughwell, N.D. and Greeley, W.J. 1993. Effect of altering pump flow rate on cerebral blood flow and metabolism in infants and children. *The Annals of Thoracic Surgery,* 56: 1366-1372.

Kessler, M. and Messmer, K. 1975. Tissue oxygenation during haemodilution in intentional hemodilution. *Bibliotheea Haematologica,* 41: 16.

Kirklin, J.K., Blackstone, E.H. and Kirklin, J.W. 1987. Cardiopulmonary bypass: studies on its damaging effects. *Blood Purif,* 5(2): 168-178.

Kirklin, J.K., Westaby, S., Blackstone, E.H., Kirklin, J.W., Chenoweth, D.E. and Pacifico, A.D. 1983. Complement and the damaging effects of cardiopulmonary bypass. *The Journal of Thoracic and Cardiovascular Surgery*, 86: 845-857.

Kirklin, J.W. and Barratt-Boyes, B.G. 1993. *Cardiac surgery.* 2nd ed. New York: Churchill Livingstone.

Kirklin, J.W., DuShane, J.W., Patrick, R.T., Donald, D.E., Hetzel, P.S., Harshbarger, H.G. and Wood, E.H. 1955. Intracardiac surgery with the aid of a mechanical pump - oxygenator system (Gibbon type): report of eight cases. *Proc Staff Meet Mayo Clin,* 30(10): 201.

Kirshbom, P.M., Page, S.O., Jacobs, M.T., Tsui, S.S.L., Bello, E., Ungerleider, R.M., Schwinn, D.A. and Gaynor, J.W. 1997. CPB and circulatory arrest increase endothelin-l production and receptor expression in the lung. *J Thorac Cardiovasc Surg,* 113(4): 777-783.

Kirshbom, P.M., Tsui, S.S., DiBernardo, L.R., Meliones, J.N., Schwinn, D.A., Ungerleider, R.M. and Gaynor, J.W. 1995. Blockade of endothelin-converting enzyme reduces pulmonary hypertension after cardiopulmonary bypass and circulatory arrest. *Surgery,* 118(2): 440-445.

Kiziltepe, U., Uysalel, A., Corapcioglu, T., Dalva, K., Akan, H. and Akalin, H. 2001. Effects of combined conventional and modified ultrafiltration in adult patients. *Ann Thorac Surg,* 71: 684-693.

Koutlas, T.C., Gaynor, J.W., Nicolson, S.C., Steven, J.M., Wernovsky, G. and Spray, T.L. 1997. Modified ultrafiltration reduces postoperative morbidity after cavopulmonary connection. *Ann Thorac Surg,* 64: 37-42.

Kraft, L.F., Katholi, R.E., Woods, W.T. and James, T.N. 1980. Attenuation by magnesium of the electrophysiologic effects of hyperkalemIa on human and canine heart cells. *The American Journal of Cardiology,* 45: 1189-1195.

Kronon, M.T., Allen, B.S., Hernan, J., Halldorsson, A.O., Rahman, S., Buckberg, G.D., Wang, T. and Ilbawi, M.N**.** 1999. Superiority of magnesium cardioplegia in a neonatal myocardial protection. *Ann Thorac Surg,* 68: 2285-2291.

Kucuk, O., Kwaan, H.C., Frederickson, J., Wade, L. and Green, D. 1986. Increased fibrinolytic activity in patients undergoing cardiopulmonary bypass operation. *American Journal of Hematology,* 23(3): 223 – 229.

Lanpacis, A. and Fergusson, D. 1997. International study of perioperative transfusion investigators. Drugs to minimize perioperative blood loss in cardiac surgery. *Anesth Analg,* 85: 1258–1267.

Lansing, A.M., Leb, D.E. and Berman, L.B. 1968. Cardiovascular surgery in end stage renal failure. *J Am Med Assoc,* 204: 682-686.

Larustovskii, M.B., Ll'in, V.N., Abramian, M.V., Grigor'iants, R.G., Vedernikova, L.A., Mikhailova, I.L., Samsonova, N.N. and Shelepova, V.M. 1998. The use of modified ultrafiltration in correcting complex congenital heart defects in newborn and nursing infants. *Anesteziol Reanimatol*, 1: 41-47.

Lassnigg, A., Schmidlin, D., Mouhieddine, M., Bachmann, L.M., Drum, W., Bauer, P. and Hiesmayr, M. 2004. Minimal Changes of Serum Creatinine Predict Prognosis in Patients after Cardiothoracic Surgery. *J Am Soc Nephrol*, 15: 1597-1605

Laver, M.B. and Buckley, M.J. 1972. Extreme hemodilution in the surgical patient. In Messmer, K. and Schmid-Schonbein, H. (eds.) *Hemodilution: theoretical basis and clinical application.* Basel: S. Karger. pp. 215-255.

Lawrence, H. and Cohn, M.D. 2003. Fifty years of open-heart surgery. *Circulation,* 107: 2168-2170.

Lee, W.H., Rubin, J.W. and Huggins, M.P. 1975. Clinical evaluation of priming solutions for pump oxygenator perfusion. *The Annals of Thoracic Surgery,* 19: 529-536.

Lewis, F.J. and Taufic, M. 1953. Closure of atrial septal defects with the aid of hypothermia: experimental accomplishments and the report of one successful case. *Surgery*, 33(1): 52-59.

Leyh, R.G., Bartels, C., Joubert-Hubner, E., Bechtel, J.F.M. and Sievers, H.H. 2001. Influence of modified ultrafiltration on coagulation, fibrinolysis and blood loss in adult cardiac surgery. *Eur J Cardiothorac Surg,* 19: 145–151.

Li, J., Hoschtitzky, A., Allen, M.L., Elliott, M.J. and Redington, A.N. 2004. An analysis of oxygen consumption and oxygen delivery in euthermic infants after cardiopulmonary bypass with modified ultrafiltration. *Ann Thorac Surg,* 78: 1389-1396.

LiIleaason, P. 1977. Moderate and extreme haemodilution in open-heart surgery: blood requirements, bleeding and platelet counts. *Scand J Thorac Cardiovasc Surg, 77*: 97-103.

Lilleaasen, P., Froysaker, T. and Stokke, O. 1978. Cardiac surgery in extreme haemodilution without donor blood, blood products or artificial macromolecules. *Scand J Thorac Cardiovasc Surg,* 12(3): 249-51.

Lillehei, C.W. 1955. Controlled cross circulation for direct-vision intracardiac surgery; correction of ventricular septal defects, atrioventricularis communis and tetralogy of Fallot. *Postgrad Med, 17(5): 388-396.*

Lillehei, C.W., Varco, R.L., Cohen, M., Warden, H.E., Patton, C. and Moller, J.H. 1986. The first open-heart repairs of ventricular septal defect, atrioventricular communis and tetralogy of Fallot using extracorporeal circulation by cross-circulation: a 30-year follow-up. *Annals of Thoracic Surgery*, 41: 4-21.

Limperopoulos, C., Majnemer, A., Shevell, M.I., Rohlicek, C., Tchervenkov, C. and Gottesman, R. 1999. Neurologic status of newborns with congenital heart defects before open heart surgery. *Pediatrics,* 103: 402-409.

Litwak, R.S., Gadboys, H.L., Kahn, M. and Wisoff, B.G. 1965. High flow total body perfusion utilizing diluted perfusate in a large prime system. *J Thorac Cardiovasc Surg,* 49: 74-90.

Liu, J.P., Long, C., Feng, Z.Y., Ji, B.Y and Li, C.H. 2004. Comparative study of pulmonary function after conventional ultrafiltration or modified ultrafiltration during cardiac surgery of infants. [Abstract]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao,* 24(4): 364–366.

Liu, J.F., Su, Z.K. and Ding, W.X. 1992. Quantification of particulate microemboli during cardiopulmonary bypass: experimental and clinical studies. *The Annals of Thoracic Sugery,* 54: 1196-1202.

Lodge, A.J., Chai, P.J., Daggett, C.W., Ungerleider, R.M. and Jaggers, J. 1999. Methylprednisolone reduces the inflammatory response to cardiopulmonary bypass in neonatal piglets: timing of dose is important. *J Thorac Cardiovasc Surg,* 117: 515-522.

Lodge, A.J., Undar, A., Daggett, C.W., Runge, T.M., Calhoon, J.H. and Ungerleider, R.M. 1997. Regional blood flow during pulsatile cardiopulmonary bypass and after circulatory arrest in an infant model. *Ann Thorac Surg,* 63(5): 1243-1250.

Lorusso, R., Cicco, G., Totaro, P. and Gelsomino, S. 2009. Effects of phosphorylcholine coating on extracorporeal circulation management and postoperative outcome. *Interact CardioVasc Thorac Surg*, 8: 7-11.

Lowrie, E.G., Lazarus, J.M., Hampers, C.L. and Merrill, J.P. 1974. Cardiovascular disease in dialysis patients. *New Engl J Med,* 290: 737-738.

Luciani, G.B., Menon, T., Vecchi, B., Auriemma, S. and Mazzuco, A. 2001. Modified ultrafiltration reduces morbidity after adult cardiac operations: A prospective, randomized clinical trial. *Circulation,* 104(Suppl 1): 253–259.

MacDonald, P.M., Hutchinson, J.E., Herring, W., McAfee, T. and Briseno, S. 1982. Utilization of donor blood. *J Extracorp Technol,* 14: 4.

Macfarlane, R.G. 1937. Fibrinolysis following operation. *Lancet,* 1: 10-12.

Maehara, T., Novak, I., Wyse, R.K. and Elliott, M.J. 1991. Perioperative monitoring of total body water by bio-electrical impedance in children undergoing open heart surgery. *European Journal of Cardio-Thoracic Surgery,* 5: 258–264.

Mahmoud, A.B.S., Burhani, M.S., Hannef, A.A., Jamjoom, A.A., Al-Githmi, I.S. and Baslaim, G.M. 2005. Effect of modified ultrafiltration on pulmonary function after cardiopulmonary bypass. *Chest,* 128(5): 3447-3453.

Malm, J.R., Manger, W.M., Sullivan, S.F., Papper, E.M. and Nahas, G.G. 1966. The effect of acidosis on sympatho-adrenal stimulation. Particular reference to cardiopulmonary bypass. *JAMA,* 197(2): 121-125.

Mastoraki, A., Karatzis, E., Mastoraki, S., Kriaras, L., Sfirakis, P. and Geroulanos, S. 2007. Postoperative jaundice after cardiac Surgery. *Hepatobiliary Pancreat Dis Int,* 6(4): 383-387.

McGiffin, D.C. and Kirklin, J.K. 1994. Cardiopulmonary bypass, deep hypothermia and total circulatory arrest. In Maroudis, E.C. and Backer, C.L (eds.) *Pediatric cardiac surgery.* 2nd ed. St Louis: Mosby. pp. 115-129

McGrath, L.B., Gonzalez-Lavin, L. and Neary, M.J. 1989. Comparison of dextran 40 with albumin and Ringer's lactate as components of perfusion prime for cardiopulmonary bypass in patients undergoing myocardial revascularization. *Perfusion,* 4(1): 41-49.

McLeish, M.J. and Kenyon, G.L. 2005. Relating structure to mechanism in creatine kinase. *Critical Rev Biochem Molec Biol,* 40(1): 1–20.

McNamara, J.J., Burran, E.L., Larson, E., Omiya, G., Suchiro, G. and Yamase, H. 1972. Effects of debris in stored blood on pulmonary microvasculature. *Ann Thorac Surg,* 14(2): 133-9.

Medlin, M. and Sistino, J. 2006. Cerebral oxygen saturation changes during modified ultrafiltration. *Perfusion*, 21(6): 325-328.

Meliones, J.N., Gaynor, J.W., Wilson, B.G., Kern, F.H., Schulman, S.R., Shearer, I.R. 1995. Modified ultrafiltration reduces airway pressures and improves lung compliance after congenital heart surgery. *J Am Coll Cardiol, 25:* 271A.

Melrose, D.G., Nahas, R., Alverez, D., Todd, I.A. and Dempster, W.J. 1965. Post operative hypoxia after extracorporeal circulation: a possible graft against host reaction. *Experientia,* 15(21): 47–50.

Mitchell, I.M., Pollock, J.C., Jamieson, M.P., Donaghey, S.F., Paton, R.D. and Logan, R.W. 1992. The effects of CPB on thyroid function in infants weighing less than five kilograms. *The Journal of Thoracic and Cardiovascular Surgery,* 103: 800-805.

Moat, N.E., Shore, D.F. and Evans, I.W. 1993. Organ dysfunction and cardiopulmonary bypass: the role of complement and complement regulatory proteins. *European Journal of Cardio-Thoracic Surgery,* 7: 563-573.

Murphy, P.J., Connery, C., Hicks Jr, G.L. and Blumberg, N. 1992. Homologous blood transfusion as a risk factor for postoperative infection after coronary artery bypass graft operations. *The Journal of Thoracic and Cardiovascular Surgery*, 104: 1092-1099.

Naik, S.K., Balaji, S. and Elliott, M.J. 1993. Modified ultrafiltration improves hemodynamics after cardiopulmonary bypass in children. [abstract]. *J Am Coll Cardiol,* 19: 37.

Naik, S.K., Knight, A. and Elliott, M. 1991. A prospective randomized study of a modified technique of ultrafiltration during pediatric open-heart surgery. *Circulation*, 84(Suppl III): 422-431.

Naik, S.K., Knight, A. and Elliott, M.J. 1991. A successful modification of ultrafiltration for cardiopulmonary bypass in children. *Perfusion,* 6(1): 41-50.

Napier, J.A., Bruce, M., Chapman, J., Duguid, J.K., Kelsey, P.R., Knowles, S.M., Murphy, M.F., Williamson, L.M., Wood, J.K., Lee, D., Contreras, M., Cross, N., Desmond, M.J., Gillon, J., Lardy, A. and Williams, F.G. 1997. Guidelines for autologous transfusion II. Perioperative haemodilution and cell salvage. British Committee for Standards in Haematology Blood Transfusion Task Force. Autologous Transfusion Working Party. *Br J Anaesth,* 78: 768–771.

Onoe, M., Magara, T., Nojima, T., Yamamoto, Y., Hong, S., Uga, H., Kiguchi, T., Minamoto, T. and Sasai, S. 1999. Application of modified ultrafiltration to cardiac surgery in adults. *Japanese Journal of Thoracic Surgery,* 52(6): 451–454.

Onoe, M., Magara, T., Yamamoto, Y. and Nojima, T. 2000. Modified ultrafiltration removes serum interleukin-8 in adult cardiac surgery. *Perfusion,* 16(1): 37–42.

Onoe, M., Oku, H., Kitayama, H., Matsumoto, T. and Kaneda, T. 2001. Modified ultrafiltration may improve postoperative pulmonary function in children with a ventricular septal defect. *Surgery Today,* 31(7): 586–590.

Ootaki, Y., Yamaguchi, M., Oshima, Y., Yoshimura, N. and Oka, S. 2002. Effects of modified ultrafiltration on coagulation factors in pediatric cardiac surgery. *Surgery Today,* 32: 203–206.

Ovrum, E., Holen, E.A., Tangen, G., Brosstad, F., Abdelnoor, M., Ringdal, M.L., Qystese, R. and Istad, R. 1995. Completely heparinized cardiopulmonary bypass and reduced systemic heparin: Clinical and hemostatic effects. *Ann Thorac Surg,* 60: 365–371.

Panico, F.G. and Neptune, W.B. 1959. A mechanism to eliminate the donor blood prime from the pump oxygenator. *J Am Med* Assoc *Surg,* 170(6): 664-669.

Pearl, J. M., Manning, P.B., McNamara, J.L., Saucier, M.M. and Thomas, D.W. 1999. Effect of modified ultrafiltration on plasma thromboxane B2, leukotriene B4 and endothelin-1 in infants undergoing cardiopulmonary bypass. *Ann thorac Surg,* 68(4): 1369-1375.

Pérez-Vela, J.L., Ruiz-Alonso, E., Guillén-Ramírez, F., García-Maellas, M.T., Renes-Carreño, E., Cerro-García, M., Cortina-Romero, J. and Hernández-Rodríguez, I. 2008. ICU outcomes in adult cardiac surgery patients in relation to ultrafiltration type. *Perfusion,* 23: 79-87.

Philbin, D.M., Coggins, C.H., Emerson, C.W., Levine, F.H. and Buckley, M.J. 1979. Plasma vasopressin levels and urinary sodium excretion during cardio-pulmonary bypass. Comparison of halothane and morphine anaesthesia. *J Thorac Cardiovasc Surg,* 77(4): 582-585.

Philbin, D.M., Levine, F.H., Emerson, C.W., Coggins, C.H., Buckley, M.J. and Austen, W.G. 1979. Plasma vasopressin levels and urinary flow during cardiopulmonary bypass in patients with valvular heart disease: effect of pulsatile flow. *J Thorac Cardiovasc Surg,* 78(5): 779-783.

Popovsky, M.A., Whitaker, B. and Arnold, N.L. 1995. Severe outcomes of allogenic and autologous blood donation: Frequency of characterization. *Transfusion,* 35(9): 734–737.

Porte, R.J., Leebeek, F.W.G. 2002. Pharmacological strategies to decrease transfusion requirement in patients undergoing surgery. *Drugs,* 62(15): 2193–2211.

Pourrat, E., Sié, P.M., Desrez, X., Bernies, M., Diana, C., Ferrand, C. and Fournial, G. 1985. Changes in plasma fibronectin levels after cardiac and pulmonary surgery. *Scand J Cardiovasc Surg,* 19(1): 63-67.

Proctor, E. 1966. Closed chest circulatory support by pump-oxygenator in experimental ventricular fibrillation at normal temperature. *Thorax,* 21(4): 385–390.

Raggi, P., Boulay, A., Taber, S.C., Amin, N., Dillon, M., Burke, K. and Chertow, G.M., 2002. Cardiac calcification in adult hemodialysis patients: A link between end-stage renal disease and cardiovascular disease? *Journal of the American College of Cardiology* 39(4): 695-701.

Ratcliffe, J.M., Wyse, R.K.H., Hunter, S., Alberti, K.G. and Elliott, M.J. 1988. The role of the priming fluid in the metabolic response to cardiopulmonary bypass in children of less than 15 kg body weight undergoing open-heart surgery. *J Thorac Cardiovasc Surg,* 36(2): 65-74.

Rebeyka, I.M., Diaz, R.M., Waddell, J.F., Coles, J.G. and Williams, W.G. 1992. Magnesium-based blood cardioplegia in a neonatal heart model. *Circulation,* 86: 361.

Reents, W., Babin-Ebell, J., Misoph, M.R., Schwarzkopf, A. and Elert, O. 1999. Influence of different autotransfusion devices on the quality of salvaged blood. *Ann Thorac Surg,* 68: 58–62.

Reul, G., Beal, A.C. and Greenberg, S. 1974. Protection of the pulmonary vasculature by fine screen filtration. *Chest,* 66: 4-9.

Richard, A. 1994. *Principals of ultrafiltration, cardiopulmonary bypass in neonate, infants and young children.* 159-163.

Roe, B.B., Swenson, E.E., Hepps, S.A. and Bruns, D.L. 1964. Total body perfusion in cardiac operations with perfusate of balanced electrolytes and low molecular weight dextran. *Arch Surg,* 88(1): 128-134.

Rosengart, T.K., De Bois, W., O'Hara, M., Helm, R., Gomez, M., Lang, S.J., Altorki, N., Ko, W., Hartman, G.S., Isom, O.W. and Krieger, K.H. 1998. Retrograde autologous priming for cardiopulmonary bypass: a safe and effective means of decreasing hemodilution and transfusion requirements. *J Thorac Cardiovasc Surg,* 115: 426–439.

Rousou, J.A., Engelmon, R.M., Flack, J.E., Deaton, D.W., Garb, J.L. and Owen, S.G. 1999. The 'primeless pump': a novel technique for intraoperative blood conservation. *Cardiovascular surgery (London, England),* 7(2): 228–235.

Royston, D. 1995. Blood-sparing drugs: aprotinin, tranexamic acid and epsilon-aminocaproic acid. *Int Anesthesiol Clin,* 33: 155– 179.

Rubens, F.D., Fergusson, D., Wells, P.S., Huang, M., McGowan, J.L. and Laupacis, A. 1998. Platelet-rich plasmapheresis in cardiac surgery: a meta-analysis of the effect on transfusion requirements. *J Thorac Cardiovasc Surg,* 116: 641–647.

Sahoo, T.K., Kiran, U., Kapoor, P.M., Choudhary, S.K. and Choudury, M. 2007. The effects of combind conventional ultrafiltration and a simplified modified ultrafiltration in adult cardiac surgery. *Ind J Thorac and Cardiovasc Surg,* 23: 116-124.

Sanchez, J., Elgue, G., Riesenfeld, J., and Olsson, P. 1998. Studies of adsorption, activation, and inhibition of factor XII on immobilized heparin. *Thrombosis Res,* 89: 41–50.

Schlunzen, L., Pedersen, J., Hjortholm, K., Hansen, O.K., Ditlevsen, E. 1998. Modified ultrafiltration in paediatric cardiac surgery. *Perfusion,* 13(2): 105–109.

Seghaye, M., Duchateau, J., Grabitz, R.G., Nitsch, G., Marcus, C., Messmer, B.J. and von Bernuth, G. 1994. Complement, leukocytes and leukocyte elastase in full-term neonates undegoing cardiac operation. *J Thorac Cardiovasv Surg,* 108: 29-36.

Sever, K., Tansel, T., Basaran, M., Kafali, E., Ugurlucan, M., Alisayin, O., Alpqut, U., Dayioglu, E.and Onursal, E. 2004. The benefits of continuous ultrafiltration in pediatric cardiac surgery. *Scand Cardiovasc J,* 38(5): 307–311.

Shen, Y. and Frenkel, E. 2004. Acquired platelet dysfunction. *Hematology/Oncology Clinics of North America*, 21(4): 647-661.

Shore-Lesserson, L. and Gravlee, G.P. 2000. Anticoagulation for cardiopulmonary bypass. In Gravlee, G.P., Davis, R.F., Kurusz, M. and Utley, J.R. (eds.) *Cardiopulmonary bypass: principles and practice.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins. pp. 435–472.

Skaryak, L.A., Kirshbom, P.M., DiBernardo, L.R., Kern, F.H., Greeley, W.J., Ungerleider, R.M. and Gaynor, J.W. 1995. Modified ultrafiltration improves cerebral metabolic recovery after circulatory arrest. *J Thorac Cardiovasc Surg,* 109: 744–752.

Smith, C.R. 1998. Management of bleeding complication in redo cardiac operations. *Ann Thorac Surg,* 65(4Suppl): S2–8.

Smith, E.E. and Crowell, J.W. 1967. Role of an increased hematocrit in altitude acclimatization. *Aerospace Med,* 38: 39-43.

Solem, J.O., Tengborn, L., Steen, S. and Lührs, C. 1987. Cell saver versus hemofilter for concentration of oxygenator blood after cardiopulmonary bypass. *The Thoracic and cardiovascular surgeon*, 35(1): 42-47.

Sonntag, J., Dahnert, I., Stiller, B., Hetzer, R. and Lange, P.E. 1998. Complement and contact activation during cardiovascular operations in infants. *Ann Thorac Surg,* 65: 525-531.

Spiess, B.D., Ley, C., Body, S.C., Lawrence, C. Siegel, E., Stover, P., Maddi, R., D'Ambra, M., Jain, U., Liu, F., Herskowitz, A., Mangano, D.T. and Levin, J. 1998. Hematocrit value on intensive care unit entry influences the frequency of q-wave myocardial infarction after coronary artery bypass grafting. *J Thorac Cardiovasc Surg,* 116: 460–467.

Steinberg, J.B., Kapelanski, D.P., Olson, J.D. and Weiler, J.M. 1993. Cytokine and complement levels in patients undergoing CPB. *J Thorac Cardiovase Surg,* 106: 1008.

Takabayashi, S., Shimpo, H., Yokoyama, K. And Iwata, H. 2007. Relationship between increased blood pressure and hematocrit during modified ultrafiltration for pediatric open heart surgery. *General Thoracic and Cardiovascular Surgery,* 55:12–18

Thuribeck, W.M. and Angus, G.E. 1975. Growth and aging of the normal human lung. *Chest,* 67(suppI2): 3S-7S.

Tobias, M.A. 1986.Choice of priming fluids. In Taylor, M.K. (ed.) Cardiopulmonary bypass: Principals and Management.Gt Britain: Cambridge University Press. 237.

Trede, M. 1969. Experimental investigations into the behaviour of coagulation and renal function during high dilutional perfusions with glucose, Haemaccel and Rheomacrodex. *Bibl Haematol,* 33: 553–68.

Turley, K., Roizen, M., Vlahakes, G.J., Graham, B. and Ebert, P. A. 1980. Catecholamine response to deep hypothermia and total circulatory arrest in the infant lamb. *Circulation,* 62: 1175-1179.

Ungerleider, R.M. 1955. Congenital heart disease. In Sabiston, D.C. (ed.) *Atlas of Cardiothoracic Surgery,* Philadelphia: WB Saunders.

Ungerleider. R.M., 1998, Effects of cardiopulmonary bypass and the use of modified ultrafiltration. *Ann Thoracic Surgery*, 65: S35–S38.

Utley, J.R., Wachtel, C., Cain, R.B., Spaw, E.A., Collins, J.C. and Stephens, D.B. 1981. Effects of hypothermia, hemodilution and pump oxygenation on organ water content, blood flow and oxygen delivery, and renal function. *Annals of Thoracic Surgery,* 31: 121-133.

Van der Linden, J., Lindvall, G. and Sartipy, U. 2005. Aprotinin decreases postoperative bleeding and number of transfusions in patients on clopidogrel undergoing coronary artery bypass graft surgery. *Circulation,* 112(1): 276- 280.

Vanvakas, E.C. 2002. Possible mechanisms of allogenic blood transfusion-associated postoperative infection. *Transfusion Medicines Reviews,* 16: 144–160.

Verska, J.J., Ludington, L.G. and Brewer, L.A. 1974. A comparative study of cardiopulmonary bypass with non-blood and blood prime. *The Annals of Thoracic Surgery,* 18(1): 72-80.

Von Segesser, L.K., Weiss, B.M., Pasic, M., Garcia, E. and Turina, M.I. 1994. Risks and benefit of low systemic heparinization during open heart operations. *The Annals of Thoracic Surgery,* 58: 391–397.

Wahba, A., Philipp, A., Behr, R., Birnbaum, D.E. 1998. Heparin-coated equipment reduces the risk of oxygenator failure. *Ann Thorac Surg,* 65(5): 1310–1312.

Wang, M., Chiu, I., Hsu, C., Wang, C., Lin, P., Chang, C.I., Huang, C. and Chu, S. 1996. Efficacy of ultrafiltration in removing inflammatory mediators during pediatric cardiac operations. *Ann Thorac Surg,* 61: 651-656.

Wang, W., Huang, H.M., Zhu, D.M., Chen, H., Su, Z.K. and Ding. W.X. 1998. Modified ultrafiltration in pediatric cardiopulmonary bypass. *Perfusion,* 13(5): 304-310.

Wang, W., Zhu, D.M., Huang, H.M., Cai, X.M., Xu, C., Jlang, L.M. and Shen, L.S. 2007. Effect of flow rate, negative pressure, and duration of modified ultrafiltration on hemodynamics and inflammatory mediators. *ASAIO J*, 53(1):41-5.

Wheeldon, D. and Bethune, D. 1990. Haemofiltration during cardiopulmonary bypass. *Perfusion,* 5: 39-51.

Williams, G.D., Ramamoorthy, C., Chu, L., Hammer, G.B., Kamra, K., Boltz, M.G., Pentcheva, K., McCarthy, J.P. and Reddy, V.M. 2006. Modified and conventional ultrafiltration during pediatric cardiac surgery: Clinical outcomes compared. *J Thorac Cardiovasc Surg,* 132: 1291-1298.

Wilson, J.D. and Taswell, H.F. 1968. Autotransfusion: historical review and preliminary report on a new method. *Mayo Clin Proc,* 43(1): 26-35.

Yndgaard, S., Andersen, L.W., Andersen, C., Petterson, G. and Baek, L. S. 2000. The effect of modified ultrafiltration on the amount of circulating endotoxins in children undergoing cardiopulmonary bypass. *J Cardiothorac Vasc Anesth,* 14(4): 399–401.

Young, J.A., Kisker, C.T. and Doty, D.B. 1978. Adequate anticoagulation during CPB determined by activated clotting time and the appearance of fibrin monomer. *Ann Thome Surg,* 26(3): 231-240.

Yung, T., Leung, M., Chan, B., Mok, C., Lee, J., Chiu, C., Cheung, H. and Sudhaman, D. 1993. Phrenic nerve palsy after surgery for congenital heart diseases: The Hong Kong experience. *J Hk Coll Cardiol*, 1: 66- 69.

Zubiate, P., Kay, J.H., Mendez, A.M., Krohn, B.G., Hockman, R. and Dunne, E.F. 1974. Coronary artery surgery: A new technique with use of little blood, if any. *The Journal of Thoracic and Cardiovascular Surgery,* 68(2): 263-267.

Zuhdi, N., McCollough, B., Carey, J., and Greer A. 1960. The use of citrated banked blood for open heart surgery. *Anaesthesiology,* 21(5): 496-501.

Zuhdi, N., McCollough, B., Carey, J., Krieger, C. and Greer, A. 1961. Hypothermic perfusion for open-heart surgical procedures: report on the use of a heart-lung machine primed with 5% dextrose in water inducing hemodilution. *J Int Coll Surg,* 35: 319-326.

APPENDIX 1

A SUPERIOR ARTERIO - VENOUS MODIFIED ULTRAFILTRATION (MUF) TECHNIQUE

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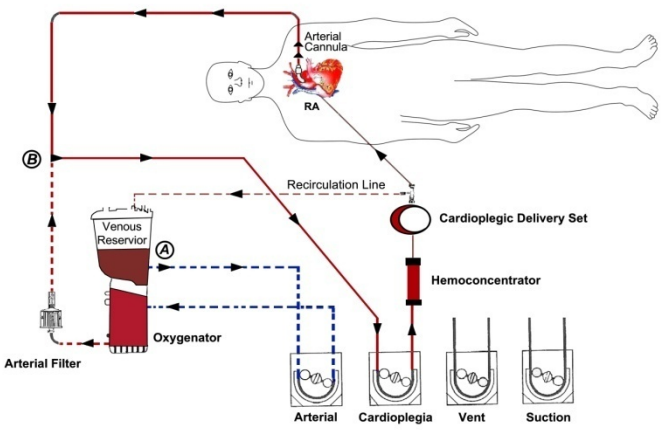
Background We have modified the cardiopulmonary bypass circuit to perform MUF in a safe effective and efficient manner in both adult and paediatric cardiac patients.

Method At the end of bypass, blood is removed retrogradely via the arterial line and circulated through the cardioplegic circuit and a haemoconcentrator before being returned to the patient via cardioplegic line connected directly to right atrium or to a side port of the venous cannula. A recirculation line connects the cardioplegic circuit to the venous reservoir via a 3-way stop-cork. This system eliminates the use of an additional pump head and lines required by other MUF systems. During MUF blood flow is post oxygenator and arterial filter. This allows simultaneous filtration of blood from the patient and the reservoir (A) until point B of the CPB circuit. Haemodynamic status of the patient is kept stable by infusing volume from the venous reservoir to replace the volume ultrafiltered. Additional safety features include a bubble trap and heat exchanger that is incorporated in the cardioplegia delivery set .



ARTERIO - VENOUS MODIFIED UL TRAFILTRATION

Results

	Pediatric (n–10)		*Adult (n-15)*	
	Pre MUF	Post MUF	Pre MUF	Post MUF
MAP (mmHg)	61 ± 13	74 ± 5	67 ± 8	76 ± 9
HCT (%)	25 ± 3	35 ± 3	27 ± 4	30 ± 8
S-ALB (g/L)	26 ± 4	41 ± 7	20 ± 4	26 ± 7
S-LACT (mmol/L)	3.0±0.5	2.7 ±0.7	4.5 ±1.7	4.1 ±2.0
+ve Fluid Bal (ml)	1336 ± 506	154 ±122	3600 ± 707	607 ±409

Conclusions

- The results of this study showed that this technique of AV-MUF is effective in reducing fluid overload, improving haemodynamics and biochemical parameters.
- MUF was completed successfully in all patients without any complication.
- One circuit is used from the beginning of CPB to the end of MUF with no changes to the circuit.
- Enhanced safety of the system due to incorporated bubble trap and heat exchanger which allows for the re-warming of blood during MUF.
- This is a simple, efficient and safe system of MUF which can be used in all patients.

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APPENDIX 2

Good day

Greetings to all fellow Perfusionists in Saudi and Abroad.

I am conducting a survey on how many centres are practicing MUF (Modified ultrafiltration) on patients post cardiac surgery. It would be highly appreciated if you could please answer the following questions to be used in a proposed MUF study in the near future:

1.) What type of MUF do you perform? (AVMUF | VVMUF | VAMUF or AAMUF).

2.) Do you use it routinely and in all cases?

3.) Do you perform it on Paediatrics only or Adult and Paediatric cases?

4.) Which pump head or heads do you use to perform MUF?

5.) Do you do conventional ultrafiltration on bypass.

6) Do you need to make changes in order to perform MUF?

7.) If it is possible can you explain the route of blood flow thru your MUF circuit?

8.) May I have the pleasure to know name and which hospital you are from?

Thank you in advance for your assistance with this MUF survey and your response will be appreciated.

*** NB**: *This is for a MUF trial and your answers may be used in the submission of a dissertation/thesis and/or publication*

APPENDIX 3

This is Gopal Naidu from Fortis hospital, Vasantkunj, Newdelhi, INDIA. Previously I had worked in Narayana Hrudayalaya, Bangalore. At present this centre I am not performing MUF for any cases. Only for neonates and sick adult cases we are conducting CUF (conventional ultrafiltration). My previous place we used to do MUF for all neonates, some infants and sick adult cases.

1. We used to perform AV-MUF.

2. Postcross clamp,cardioplegia puncture site will be used for deairing vent as well as Arteio-venous shunt.

3. Cardioplegia roller pump head will be used AVMUF

4. Take blood from aorta through BCD in Clock wise direction (reverse).CP pump out let(clock wise) hemofilter will be placed by placing two luer lock connectors. (Hemofilter will be deaired proper before performing MUF).Fiter outlet line will be shunted towards venousline by placing clamps in appropriate position. With this technique along with MUF we can maintain temperature also.

Regards

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Mr Mohanlall

We perform AVMUF on our adult and pediatric patients

Presently we use it routinely on all our pediatric patients and on about 50% of our adult patients We use a roller head on our pediatric patients and a centrifugal pump on our adult patients We perform ultrafiltration on CPB. If we perform MUF, our cardioplegia system is pre-adapted for MUF

I can send you a copy of my presentation if you would like after the I present at the Wisconsin Perfusion Society meeting.

Tom Steffens

University of Wisconsin Hospital & Clinics

Madison Wisconsin USA

tsteffens@uwhealth.org

---

1. AVMUF
2. Only pediatric cases (We do all populations)
3. Peds
4. Cardioplegia pump head. Arterial pump head used to propel oxygenator blood forward as needed
5. ZBUF on all Peds. We do alter the two positions of the hemoconcentrator to the cardioplegia/muf circuit before MUF
6. Aortic line to recirculation port out to cardioplegia line thru cardioplegia set up and to venous line to venous cannulae

Bill Harris CCP

Ochsner Foundation Clinic,

New Orleans

Mr. Mohanlall

We mainly do pedi's and muf all cases.
Usually AV muf.
Adults we do not see a difference unless you just take the fluid off on the bypass side and give back in a bag 2-300 cc only.

Our set up is such that we have our h/c inline with our pleg system so we use this as a bubble trap.
I'll send you our specs if you want.

At the end of the case, we flush our plegia out of the circuit and go forward thru our h/c which takes the blood from the arterial cannula back thru the hc and cardioplegia set and returns thru a LL in the venous cannula, (we use ll connectors on the venous side so the plegia line in inserted there and the line clamped below.).

Clamp out your arterial filter and use the bypass loop.

IF volume is necessary we just go forward on the arterial pump, continue giving the volume out of the oxygenator side, flush with crystalloid until the circuit is clear,

They pull the arterial cannula and place in saline bucket so we give all blood back, yet keep our circuits primed at all times.

If by chance the pt can't take all the volume we send it to the cell saver……. Really is the simplest circuit and safe way..You must of course continue to watch the arterial pressure monitor and if you see a negative, immediately stop the muff as you have either a kink or sucking on the heart and pull air…Make sure when you do go forward on the arterial cannula there is no air..make the table watch also…

Group effort on the case!
Hope this helps.
Mary

MARY E MENSCH RN CCP LP
Pediatric Perfusion
Methodist Healthcare

Dear Rakesh

“Marhabaa” and nice to hear from you.

Answering your survey:

1. We are using AV-MUF

2. For all neonatal cases and

3. Peadiatric smaller than 30 kg no MUF for Adult

4. We have to dis-engaged pump from CUF and MUF.

5. Yes we do conventional ultrafiltration during bypass, yes before start MUF at the end of bypass small modifications needed by placing clamps.

6. My own way of AVMUF (not a center protocol)

   From:

   Aortic cannula-art filter - purgeline - stopcock - MUF pump - Heomfilter-line to proximal Pleg delivery system- Pleg system - pleg line to connected to lurlock in the Venous cannuli.==.

Best wishes

ENAD ALANAZI

King Faizal Specialist Hospital

Riyadh

Kingdom of Saudi Arabia

APPENDIX 4

The table below depicts the positive and negative comments from perfusionists that were received following a survey carried out over the internet as part of the preliminary study.

Positive Comments	Negative Comments
Decrease fluid overload post surgery	Increases work load
Increases blood pressure after MUF	Increases bypass procedure time
Increases ventricular function	Increases exposure to new circuit
Decreases ventilation time	Increases chances for human error
Reduces inflammatory mediators	Arterial blood pressure drops during MUF
Decreases ICU stay	Central venous pressure drops during MUF
Decreases hospital stay	Increased equipment costs
Decreases overall costs	Air cavitation
	De-cannulation during the procedure
	Over pressurization of the haemoconcentrator
	Air in the CPB lines or MUF circuit
	Heat loss to the patient

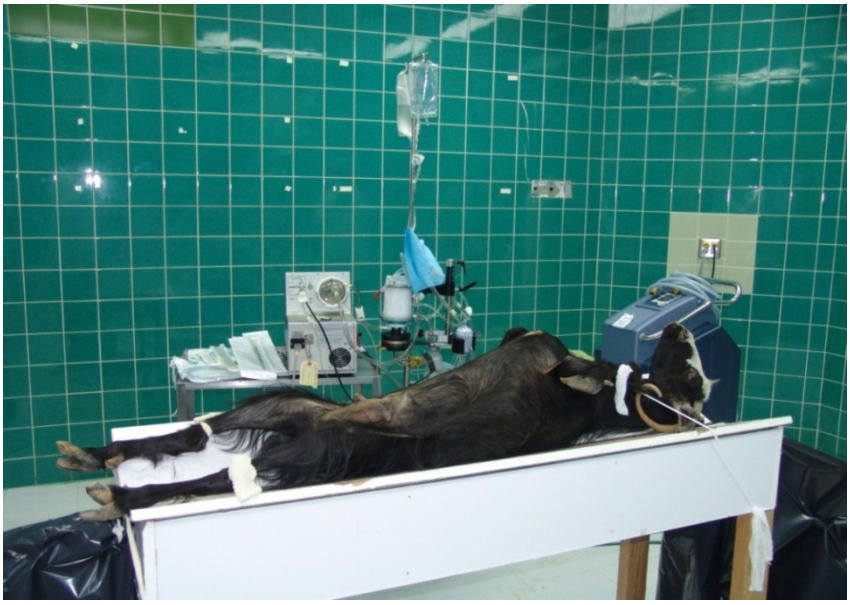
APPENDIX 5

Criteria for an Ideal MUF Technique:

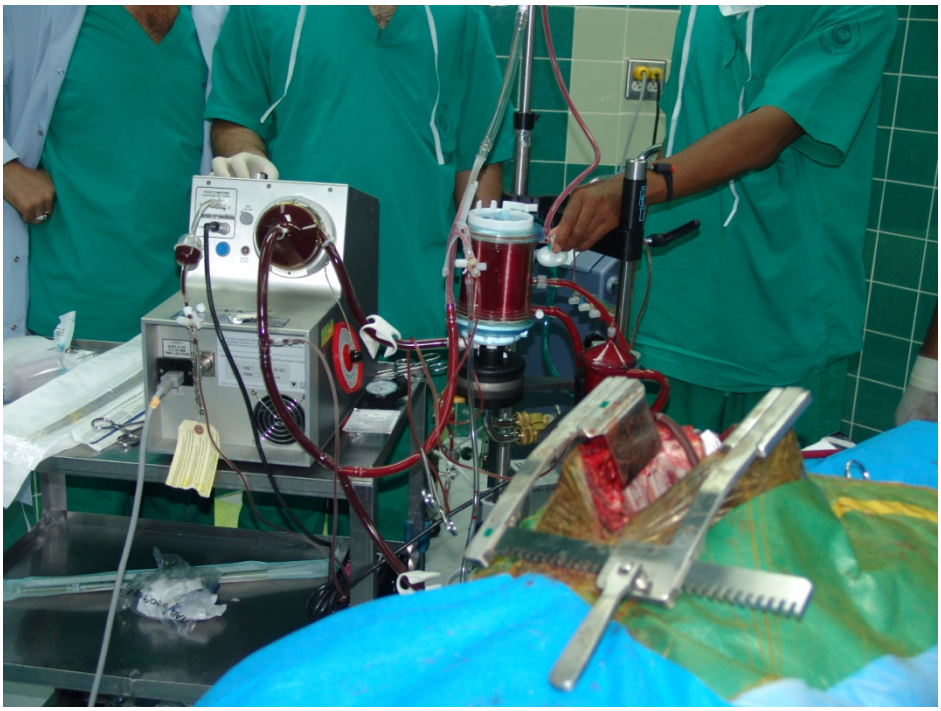
- *It should reduce the excess fluid volume of the patient*
- *It should concentrate the volume left in the CPB circuit after bypass*
- *It should increase the HB/HCT in the patient*
- *It should reduce the need for donor blood*
- *It should be financially viable*
- *It must be a safe system*
- *Must be done with minimum amount of changes to the system*
- *Should follow the normal physiological blood path of the CPB circuit*
- *Should require minimum or no changes to the CPB circuit to perform it*
- *Should not interfere or reduce the patients systemic circulation*
- *Should not reduce the patients arterial pressures*
- *It should simulate the patients normal blood pathway*
- *Should require minimum or no changes to the CPB circuit on the surgical side*
- *It should have an acceptable learning curve*
- *It should be user friendly*
- *One must be able to abandon the procedure at stage to reinstitute CPB*
- *It should require the use of one pump head*
- *It should be able to oxygenate blood if required*
- *It should have a heat exchanging capabilities incorporated*
- *Ideally should have the ability to be used for conventional ultrafiltration as well*
- *It should allow for the entire volume in the CPB circuit to be infused into the patient before termination of the procedure.*
- *It should allow for the circuit to remain primed after termination of MUF in order to re-initiate CPB if required.*

APPENDIX 6

The pictures below depicts early periods of an animal study carried out at the Northwest Armed Forces Hospital's animal laboratory



A Capra Hircus (goat) being prepared for MUF study at the NWAFH animal lab.



Animal on bypass without the use of a cardiotomy reservoir

APPENDIX 7

ANIMAL STUDY DEMOGRAPHIC DATA

The table below describes relevant animal (capra hircus – goat) information & operative details of the goats used for the preliminary study. They were all subjected to veno-arterial modified ultrafiltration (VAMUF). The animal was brought into the animal laboratory early in the morning and prepared by the vet and assisting staff members. The animal was weighed and measured as well as check for abnormalities. The average age was estimated by the vet and from information rendered by the farmer upon purchased. Each animal was subjected to VAMUF until calculated target volume was reached.

Est. Average Age (Yrs)	**Average Weight (Kg)**	**Average BSA (m2)**	**Average Arterial Cannula size (FR)**	**Average Venous Cannula size (FR)**	**Average Bypass Time (min)**	**Average AVMUF Time (min)**
3.3	39.9	11.93	17.2	30	39	13.4

APPENDIX 8

Data analysis for fluid management during VAMUF animal trials

The table below reflects the mean and standard deviations for the fluid management table. The fluid balance after performing VAMUF is acceptable to this study considering that the animal will have a small positive volume left. This positive volume will be beneficial as it will encourage urine output postoperatively.

Fluids	Total number	Mean (Average)	Standard deviation
Fluid input (ml)	10	2805	± 296.69
CUF (ml)	10	312	± 52.02
VAMUF (ml)	10	646	± 124.38
Urine output (ml)	10	951	± 112.98
Fluid Balance (ml)	10	896	± 220
MUF time (min)	10	13.4	± 0.966

Total Fluid Input = Anaesthetic fluid input + CPB Fluid Prime + Cardioplegia + Fluid Added on CPB.

Total CUF *(Conventional Ultrafiltration)* ***=*** Total ultrafiltrate removed from the circuit during CPB.

Total VAMUF *(Modified Ultrafiltration)* ***=*** Total ultrafiltrate removed from the patient & circuit post CPB.

Total Urine Output = Urine output pre-CPB + urine output during-CPB + urine output post-CPB

Total Fluid Balance = Total Fluid Input - (Total CUF + Total MUF + Total Urine Output)

APPENDIX 9

Haemodynamic and arterial blood gas analysis

The table below reflects haemodynamic parameters that were measured invasively before and after VAMUF using catheters and transducers and connected to a monitor.

Haemodynamics	Pre-MUF (Mean)	Post-MUF (mean)	Diff
HR (bpm)	76	69	– 7
BP (syst.,mmHg)	105	115	+ 10
BP (diast.,mmHg)	65	62	– 3
BP (mean,mmHg)	67	77	+ 10
CVP	7	6	– 1

Laboratory measurements of haematocrit and haemoglobin content in blood

The table below reflects the mean haematocrit (HCT) and haemoglobin (HgB) results before and after VAMUF was performed. The results show a significant increase in HCT and HgB.

Variable	Pre-MUF (mean)	Post-MUF (mean)	Diff
HgB (g/dl)	7.8	9.6	+ 1.8
Hct (%)	23.4	28.8	+ 5.4

APPENDIX 10

A comparison of the percentage haemodilution in adult CPB as compared to paediatric

The priming volume of the CPB circuit in adult patients and paediatric patients are directly related to the weight of the patient.

Therefore haemodilution is significant in both groups of patients, eg:

Paediatric patient : Estimated average weight = 7 kg (WT)

Calculated blood volume = 7 kg (weight) x 80 (constant) = 560 ml (BV)

Estimated average prime = 360 ml (Crystalloid Prime)

- Prime for a 7 kg patients will be calculated according to the design of the NWAFH CPB circuit. A complete ¼ inch CPB circuit would be suitable for a patient in this weight group.
- Total crystalloid prime = *Total volume in CPB circuit – donor blood + cardioplegia (Boston's Children's Cardioplegic Solution) – albumin*

(20% in 50ml x 2 Bottles)(20ml Albumin (Alb.) + 80ml Fluid)

= 500ml – 200ml – 20ml + 80ml

= 360 ml (Crystalloid Prime)

Haemodilution that occurs in paediatric patients upon initiation of bypass:

Paediatric = $\frac{\text{Crystalloid Prime}}{\text{Blood Volume}} \times \frac{1}{100} = \frac{360}{560} \times \frac{1}{100} =$ *64 %*

Average Adult patient : Estimated average weight = 70 kg (WT)

Calculated blood volume = 70 kg (weight) x 70 constant) = 4900 ml (BV)

Estimated average prime = 2350 ml (Crystalloid Prime)

- Prime for a 75 kg patients will be calculated according to the design of the CPB circuit use at the authors centre(Northwest Armed Forces Hospital). A ½ inch venous line and a 3/8 arterial line would in the CPB circuit would be suitable for a patient in this weight group.
- Total crystalloid prime = Total volume in CPB circuit + cardioplegia (Boston's Children's Cardioplegic Solution) – Albumin(4 % in 250ml)(10ml Alb. + 240 fluid)

= 1600ml + 1000ml – 10 ml + 240ml

= 2830 ml (Crystalloid Prime)

Haemodilution that occurs in adult patients upon initiation of bypass

Adults = $\frac{\text{Crystalloid Prime}}{\text{Blood Volume}} \times \frac{1}{100} = \frac{2830}{4900} \times \frac{1}{100} =$ *58 %*

* From the above calculations one can extrapolate that haemodilution is very significant in both adults and paediatric patients alike.

APPENDIX 11

Rakesh Mohanlall

B Tech Clinical Technology (Cardiovascular Perfusionist)
Registered Clinical Technologist (Perfusion)
King Abdul Aziz Hospital Cardiac Services Department
Northwest Armed Forces Programme
Tel: + 966444 11088 ext 85937
Email: rakeshmohanlall@hotmail.com

DURBAN INSTITUTE OF TECHNOLOGY

INFORMATION FOR PARTICIPATION IN STUDY

TITLE: Continuous Modified Ultrafiltration In Comparison with Conventional Modified Ultrafiltration Systems

INTRODUCTION

You are invited to be a volunteer for a research study. The information in this letter will help you understand what the research is about and how it will benefit your quality of bypass .If there is any questions, which are not clearly explained in this letter, do not hesitate to ask the perfusion staff or investigator.

PURPOSE OF THIS STUDY

Several studies have previously established that the implementation of Modified ultrafiltration (MUF) decreases post-operative oedema thus reducing the need for donor blood (thereby reducing the complications associated with homologous blood transfusion). It also reduces complement activation resulting in decreased organ damage and hence quicker recovery times. Ideally all cardiac patients undergoing cardiopulmonary bypass surgery at the North West Armed Forces Hospital will undergo (MUF). In this study different techniques of performing the same procedure will be analyzed to attempt to ascertain which is the most effective, efficient and safest technique to use to perform this valuable procedure. The process of MUF will be carried out by the principal perfusionist in co-ordination with the surgeon and anaesthetist. The patient will be carefully monitored during this procedure to ensure patient's safety at all times.

REQUIREMENTS OF THE PATIENT

As a candidate in this research, you will undergo routine corrective surgery on a cardiopulmonary bypass machine before MUF can be performed on you. It will be performed under general anaesthesia so it will not cause you any discomfort.

MUF helps reduce your positive fluid balance, increase your haematocrit level, increases your blood pressure, reduces the need for donor blood and may decrease your ventilation period. It may therefore reduce hospital stay. To qualify to be in this research, the following is required:

- Live or work in Saudi Arabia
- Be between 1 week and 85 years of age
- Undergo life support by a heart lung machine
- Must have pathologies that require heart surgery on bypass
- Only patients that are stable enough to perform MUF on
- All patients between the ages of 1 week to 85 years
- Have an ejection fraction of more than 25%
- Be operated at the NWAFH only

PATIENTS RIGHT TO PARTICIPATE

Your participation in this trial is entirely voluntarily. Your withdrawal at any time will not affect your medical treatment. There are no risks involved.

CONFIDENTIALITY

All information obtained in this trial will be strictly confidential.
Data that may be reported in scientific journals or published will not include information that will identify you as a patient in this study.

APPENDIX 12

إقرار موافقة على المشاركة في دراسة

عنوان الدراسة:
الترشيح المستدق المعدل (من الوريد إلى الشريان) مقارنة مع أنظمة الترشيح المستدق المعدل (من الشريان إلى الوريد)
مقدمة:
ندعوك للتطوع والمشاركة في هذه الدراسة. ستساعدك المعلومات التي تجدها في هذه المقدمة على فهم موضوع الدراسة وكيف يمكن أن تستفيد من ناحية جودة عملية تحويلك على جهاز القلب والرئة الإصطناعي. إذا كانت لديك أي أسئلة لم يتم الإجابة عنها بوضوح في هذه المقدمة فلا تتردد في طرحها على أحد فنيين تروية القلب أو الفني الأساسي الذي يجري الدراسة. تجرى عملية الترشيح المستدق المعدل من طرف فني تروية القلب الأساسي بالتنسيق مع الجراح وطبيب التخدير. وستكون مراقبا بشكل فائق لضمان سلامتك كل الوقت. وبصفتك متطوعا لهذه الدراسة ستجرى لك عملية قلب مفتوح بشكل روتيني وذلك باستخدام جهاز القلب والرئة الإصطناعي قبل أن يجرى لك الترشيح المستمر المعدل. وسيجرى هذا تحت تأثير تخدير كلي ولن تشعر بأي ألم.

الهدف من هذه الدراسة:
يجرى الترشيح المستمر المعدل لمعظم مرضى القلب بمستشفى القوات المسلحة بالشمالية الغربية الذين تجرى لهم عملية قلب مفتوح باستخدام جهاز القلب والرئة الإصطناعي. يجرى الترشيح باستخدام كلية صناعية وذلك لإزالة السوائل الإضافية التي تحقن في المريض عندما يتم تحويله على جهاز القلب والرئة الإصطناعي. يقلل هذا الإجراء من الحاجة إلى نقل الدم للمريض وبالتالي يقلل من المشاكل المرتبطة بنقل الدم. يساعد الترشيح في إزالة المواد الضارة التي يفرزها الجسم أثناء فترة التحويل على جهاز القلب والرئة الإصطناعي. وهذا يقلل من إحتمال حصول تلف في أعضاء الجسم وبالتالي يقصر من الفترة الضرورية للشفاء. بالإضافة إلى هذا فهو يرفع ضغط الدم وبالتالي يلغي الحاجة إلى استخدام بعض الأدوية. تعمل كل أنظمة الترشيح العادية بضخ الدم عكس إتجاه الدورة الدموية الخاصة بجهاز القلب والرئة الإصطناعي. أما الفائدة في التقنية المتبعة في هذه الدراسة فتتجلى في كون الدم يجري عبر جهاز القلب والرئة الإصناعي وعبر الجسم متحركا إلى الأمام وهذا بخلاف الأنظمة العادية التي يجري فيها الدم عكسيا. إن الهدف من هذه الدراسة هو التحقق من الطريقة الأكثر سلامة وفعالية والأصح فيزيولوجيا لإجراء الترشيح المستمر المعدل.

الشروط الأساسية المطلوب أن تتوفر في المريض
للترشيح المريض لهذه الدراسة يجب أن تتوفر فيه الشروط التالية:

- أن يعيش ويعمل المريض في المملكة العربية السعودية
- أن يستعمل معه جهاز القلب والرئة الإصطناعي
- ان يعاني من أمراض تحتاج إلى إجراء عملية قلب مفتوح باستخدام جهاز القلب والرئة الإصطناعي
- أن يكون وضع المريض مستقرا بشكل يسمح بإجراء الدراسة.
- كل المرضى الذين يتراوح عمرهم بين الأسبوع و75 سنة.
- أن تكون قوة انقباض وانبساط عضلة القلب أكثر من 25%.
- أن تجرى عملية المريض في مستشفى القوات المسلحة بالشمالية الغربية.

حق المريض في المشاركة في الدراسة:
إن مشاركتك في هذه الدراسة تطوعية بكل معنى الكلمة، ولن يؤثر تراجعك عن قرارك على علاجك. ولاتوجد هناك أية مخاطر.
السرية والخصوصية:
ستكون كل المعلومات المحصلة من هذه الدراسة سرية.
إن أي معلومات قد تذكر في المجلات العلمية أو تنشر لن يذكر فيها إسمك كمريض أجريت عليه الدراسة.

الطالب صاحب الدراسة: راكش موهانلال (فني تروية قلب أول)
المشرف : الدكتور آرتو نيملاندر (رئيس قسم جراحة القلب بمستشفى القوات المسلحة بالشمالية الغربية)
المشرف: الدكتور ج. آدامز (مساعد مدير التكنولوجيا الإكلينيكية / معهد دوربن للتكنلوجيا)

APPENDIX 13

Rakesh Mohanlall

B Tech Clinical Technology (Cardiovascular Perfusionist)
Registered Clinical Technologist (Perfusion)
King Abdul Aziz Hospital Cardiac Services Department
Northwest Armed Forces Programme
Tel: + 966444 11088 ext 85937
Email: rakeshmohanlall@hotmail.com

Informed Consent Form

Date:

Title of research study: *Venoarterial modified ultrafiltration versus conventional arteriovenous modified ultrafiltration in cardiac surgery*

Names of supervisors: Dr Nemlander and DR J.K. ADAM
Telephone: (0966) 44411088 ext 85423 (031) 2085291

Name of research student : Rakesh Mohanlall
Mobile Phone : + 966 501749391

PLEASE CIRCLE THE APPROPRIATE ANSWER:

1. Have you read the research information sheet? YES/NO
2. Have you had the opportunity to ask questions regarding this study? YES/NO
3. Have you received satisfactory answers to your questions? YES/NO
4. Have you had the opportunity to discuss this study? YES/NO
5. Have you received enough information about this study? YES/NO
6. Do you understand the implications of your involvement in this study? YES/NO
7. Do you understand that you are free to withdraw from this study?
   a) At any time? YES/NO
   b) Without having to give a reason for withdrawing? YES/NO
   c) Without affecting your future health cares? YES/NO
8. Do you agree to voluntarily participate in this study? YES/NO
9. Whom have you spoken to? _____

Please ensure the researcher completes each section with you.
If you have answered NO to any of the above, please obtain the necessary information before signing.

Please print in block letters:

PATIENT Name_____ Signature_____

WITNESS Name_____ Signature_____

RESEARCH Name_____ Signature_____

APPENDIX 14

نموذج موافقة عن علم واطلاع

التاريخ:

عنوان الدراسة:
الترشيح المستدق المعدل (من الوريد إلى الشريان) مقارنة مع أنظمة الترشيح المستدق المعدل (من الشريان إلى الوريد)

أسماء المشرفين: الكتور نملاندر / والدكتورة ج. ك. آدمز

الهاتف: 44411088 (00966) تحويلة 85423 / 2085291 (031)

إسم الطالب صاحب الدراسة: راكش موهانلال

رقم الجوال: 501749391 (966)

ضع دائرة على الإجابة الملائمة:

1. هل قمت بقراءة النشرة الخاصة بالدراسة؟	**نعم / لا**
2. هل سنحت لك الفرصة أن تطرح أسئلة بخصوص الدراسة؟	**نعم / لا**
3. هل حصلت على إجابات مقنعة لأسئلتك؟	**نعم / لا**
4. هل أعطيت فرصة لمناقشة الدراسة؟	**نعم / لا**
5. هل أعطيت لك معلومات كافية عن الدراسة؟	**نعم / لا**
6. هل فهمت المقتضى من مشاركتك في هذه الدراسة؟	**نعم / لا**
7. هل تعرف أنه لديك الحرية في التراجع عن قرارك في المشاركة في هذه الدراسة؟	**نعم / لا**
أ. في أي وقت؟	**نعم / لا**
ب. دون أن تكون ملزما بتبرير قرارك؟	**نعم / لا**
ج. دون أن يؤثر هذا على عنايتك الصحية في المستقبل؟	**نعم / لا**
8. هل توافق على التطوع للمشاركة في هذه الدراسة؟	**نعم / لا**
9. إسم الشخص الذي تكلمت معه بخصوص هذه الدراسة؟_____	

احرص على أن يقوم الشخص المسؤول عن الدراسة بالتطرق إلى كل المواضيع السابقة معك.
إذا أجبت بـ "لا" على أي من الأسئلة التي ذكرت فوق، الرجاء التأكد من الحصول على المعلومات الضرورية قبل التوقيع.

الرجاء الكتابة بخط واضح:

المريض : الإسم:_____ **التوقيع: -**
_____

الشاهد : الإسم:_____ **التوقيع: -**
_____

صاحب الدراسة : الإسم:_____ **التوقيع: -**
_____

APPENDIX 15

بسم الله الرحمن الرحيم

NORTH WEST ARMED FORCES
HOSPITALS PROGRAM
TABUK, SAUDI ARABIA

برنامج مستشفيات القوات المسلحة
بالمنطقة الشمالية الغربية / تبوك
المملكة العربية السعودية

Name: _____

MRN: _____

Age: _____

Sex: _____

"PATIENT IDENTIFICATION"

CONSENT TO OPERATION / INVESTIGATION

إقرار بالموافقة على إجراء عملية / فحص

Date: _____

Department/Ward: _____

Consultant Name: _____

Number: _____

I _____
(Name of Patient)

hereby authorize the performance of

_____
(Description of Procedure)

under local or general anesthesia upon me by/under the supervision of Dr _____.

A description of the procedure, the reasons for its performance and the serious risks and side effects that may occur as a result of this procedure have been explained to me. This information was provided to me by Dr _____.

I understand that no guarantee or assurance has been given as the results that may be obtained.

I also consent to such further or alternative operative measures as may be found to be absolutely necessary during the course of the procedure and to administration of a local or other anesthetic for the purpose of the same

I consent to staff in training attending procedures.

I consent to the disposal by the Hospital of any tissue (internal organs) which may be removed from my body.

_____
Signature of Patient

_____
Date

_____
Signature of Guardian

_____
Date

_____
Signature of Witness

_____
Signature of Witness

التاريخ _____

القسم/ المعطة :_____

إسم الإستشاري :_____

الرقـــــم :_____

أقر أنا :_____
(اسم المريض)

بالموافقة على عمل _____
(طبيعة الإجراء)

تحت تأثير التخدير الموضعي أو العام بواسطة أو تحت إشـراف الطبيب _____.

وقد تلقيت إيضاحات عن طبيعة الإجراء ، أسباب القيام به المخـاطر والأعراض الجانبية التي تترتب عن هذا الإجراء وقد تم تزويـدي بـهذه المعلومـات مـن قبـل الطبيب:_____.

وأنني أدرك أنه لم يتم تقديم أي ضمان أو تعهد بخصوص النتائج المترتبة على هذه العملية.

واوافق أيضاً على عمل أي إجراءات جراحية أخرى أو بديلة قـد تصبح ضرورية جداً أثناء الجراحة كما أوافق على الإجـراءات الخاصة بالتخدير الموضعي أو أي تخدير لنفس هذا الغرض.

أوافق على حضور العاملين تحت التدريب للإجراءات الطبية.

أوافق على قيام المستشفى بالتخلص مـن أي نسـيج (أعضـاء داخلية) قد يتم إزالتها من جسدي.

_____
توقيع المريض

_____
التاريخ

_____
توقيع ولي الأمر

_____
التاريخ

_____
توقيع الشاهد الأول

_____
توقيع الشاهد الثاني

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APPENDIX 16

Name: _____

MRN: _____

Age: _____

Sex: ❒ **Male** ❒ **Female**

"PATIENT IDENTIFICATION"

CARDIAC SERVICES DEPARTMENT
PERFUSIONIST PRE –BYPASS SAFETY CHECKLIST

Procedure: _____ ***Date:*** _____

PATIENT		**GAS SUPPLY**		**SAFETY MECHANISMS**	
Chart reviewed		Gas supply verified		Operational & engaged	
Procedure reviewed		Gas line securely connected & not kinked		Arterial filter/bubble trap de-aired	
		Flow meter / blender functional		Cardiotomy reservoir vented	
STERILITY		Hoses securely plugged to wall & leak-free			
Components checked for package integrity/expiration date		Gas exhaust unobstructed		**ANTICOAGULATION**	
No cracks on oxygenator & arterial line filter		**LINES /PUMP TUBING**		Heparin time & dose verified	
		Connections secure		Anticoagulation tested & reported	
PUMP		Tubing direction traced & correct			
Speed controls functional		No kinks noted		**SUPPLIES**	
Roller heads smooth & quiet		One-way valve(s) in correct direction		Tubing clamps counted & available	
Occlusions set		AV loop & Art line filter de-aired & leak free		Drugs available & properly labeled	
Flow rate indicator correct for patient and/or tubing size		Patency of art. Line/cannula verified		Solutions available	
Pump direction correct		Recirculation & art. filter purge lines closed.		Blood available	
Holders secure		**MONITORING**		Sampling syringes & act tubes available	
		Temperature probes in place & calibrated			
CARDIOPLEGIA		Pump pressure monitors calibrated		**BACK-UP**	
Solution checked for composition/exp date		In-line monitoring device calibrated		Hand cranks available	
System de-aired /leak free		Blood gas analyzer functional & calibrated		Emergency lighting available	
		Machines' date & time verified		Duplicate circuit components available	
TEMPERATURE CONTROL				UPS functional	
Heat exchanger(s)connected & water flow direction verified		**ELECTRICAL**			
Heat exchanger(s)leak tested		Power cord(s) securely connected			
		Power available			

Perfusionist : _____ **Double-checked by :** _____

APPENDIX 17

JOSTRA VACUUM ASSISTED VENOUS DRAINAGE

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Controller specifications

Dimension	183 (W) x 87 (H) x 158 (D) mm
Weight	3.3 kg
Tube connection to vacuum source	1/4" barbed connector
Tube connection to reservoir	1/4" barbed connector
Vacuum source requirement	-200 to +760 mmHg, min. ?ow 11 stl/min.
Vacuum regulation limits	0 to -100 ± 10 mmHg
Vacuum regulation tolerance	± 10 mmHg if airflow within ± 10 stl/min
Pressure meter	Mechanical, Class 1.6, 0 to -120 mmHg
Negative pressure relief valve	Factory set at -100 ± 10 mmHg
Positive pressure relief valve	Factory set at 3 ± 2 mmHg

The Jostra VAVD controller

The vacuum applied to the venous reservoir was switched on when the controller was turned on. The level of vacuum applied was regulated. The controller had pressure relief valves that protected the venous reservoir from a pressure above +3 mmHg or a pressure below -100 mmHg.

Simple tubing set

The sterile tubing set with moisture trap provided easy connection between the controller and the reservoir and was used with the controller. The moisture trap has a self-adhesive pad to enable it to be attached to the reservoir surface, no special holder was required.

APPENDIX 18

Modified ultrafiltration study data collection sheet

Patient Name: Patient Number:
Type of procedure: MUF Type:
Weight: Height: Age / Sex:
Date: Surgeon:
Perfusionist: Anaesthetist:
X- Clamp Time: Bypass Time:

PARAMETER	BEFORE MUF	AFTER MUF
Arterial Pressure		
CVP		
Arterial saturation (Monitor)		
Heart rate		
Blood analysis from blood gas machine		
pO2		
pCO2		
HB		
HCT		
Sodium		
Potassium		
Lactate		
Calcium		
Ultrafiltration Amount		
Ultrafiltration Time		
Ultrafiltration Rate		
Blood Results from the lab		
Platelet Count		
RBC Count		
WBC Count		
Serum Creatinine		
Blood Urea		
Serum Uric Acid		
Phosphorus		
MMB %		
MMB		
CK		
Mg		
Albumin		
Blood		
Blood Products		
Urine Output	12 hrs - ml	24 hrs - ml

Fluid Input - Fluid Output - Fluid Balance –
ICU Stay - Hospital Stay -