DOES COLD BLOOD CARDIOPLEGIA SOLUTION CAUSE DETERIORATION IN CLINICAL PULMONARY FUNCTION FOLLOWING CORONARY ARTERY BYPASS GRAFT SURGERY?

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DECLARATION

I, Tamra Cindy M^{c}Farlane declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, except where due acknowledgement has been made in the text.

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SIGNATURE

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DATE

DEDICATION

This work is dedicated to my father, of blessed memory, who led by example and the maxim "Nil satis sed optima". In so doing, he taught me more than he ever realised.

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Abstract

Pulmonary dysfunction following cardiopulmonary bypass surgery is a widely explored complication and a multitude of factors have been implicated, including but not limited to: operative trauma; the cardiopulmonary bypass circuit; cardioplegia; the type of donor grafts utilised; anaesthesia and fluid administered.

There is a paucity of information regarding the effect of cardioplegia on the lungs. No studies have previously investigated whether allowing cold-blood cardioplegic solution to enter the lung parenchyma, during the period of cardioplegia delivery, has an effect on the clinical outcome of lung function following cardiopulmonary bypass surgery. For this reason an original study was done to determine the effect of preventing cardioplegia from entering the lungs, by evacuating overflow of cardioplegia not drained via the atriocaval cannula, by using a pulmonary artery vent.

A total of 403 patients admitted to undergo full cardiopulmonary bypass were screened and 142 patients who fitted the criteria for inclusion and provided informed consent took part in this prospective double blind randomised clinical trial.

The control group underwent routine cardiopulmonary bypass grafting. The study group had the intervention of a pulmonary artery vent sutured in position at the time the heart was cannulated for bypass. During cardioplegia delivery the cardioplegia was removed via the atriocaval cannula in the control group (A) and via the atriocaval cannula and the pulmonary artery vent in the study group (B). Aside from this difference, the two groups were managed identically intra- and post-operatively.

Outcomes which were compared included eight time measures of arterial blood gases; electrolytes and shunt fraction; bedside lung spirometry measures over five time periods; radiographic measures of atelectasis and effusion over three time points; as well as physiotherapy and hospitalisation requirements. Numerous other potentially extraneous variables were measured and compared in order to monitor homogeneity of the study samples.

The consistency of the results within each group throughout the study provides strong evidence that the measurements taken were accurate. The use of standardised equipment and vigilant adherence to the protocol ensured no extraneous deviation. The internal validity of this study was therefore good and accurate.

The findings of the study however brought into question a previously accepted belief that the pulmonary artery vent prevents the overflow of cardioplegia, not drained from the right atrium, from entering the lungs.

There was no literature or previous studies to confirm or dispute this accepted 'observation' by cardiac surgeons that the cardioplegia does enter the lung parenchyma. To therefore validate the findings of the study a further four original studies were designed and initiated.

The objective of these studies was to establish the efficacy of the pulmonary artery vent and to determine whether cardioplegia indeed circulates through the lung parenchyma or merely accumulates and 'pools'. Technetium (Tc-99m), a radio labelled isotope was added to the cold blood cardioplegia solution prior to delivery in order to determine this.

In the four sub-studies it was confirmed that the pulmonary artery vent is 90-100% effective in retrieving any cardioplegic solution not drained by the atriocaval cannulae, thus confirming the effectiveness of the pulmonary artery vent in preventing cold blood cardioplegic solution from entering the lungs.

The findings of the main study confirmed that respiratory impairment after uncomplicated cardiopulmonary bypass, even in low risk patients, is relatively common, as within each group there was a significant change in outcome measures over time. Inter-group comparisons however showed these changes were not significant, with both groups deteriorating by the same degree post-operatively, therefore establishing that these changes were independent of the intervention of the pulmonary artery vent.

In the control group, the cold blood cardioplegia solution that did not drain from the atriocaval cannula entered the lungs and circulated the lung parenchyma during cardiopulmonary bypass. The study group made certain that none, or very little, of the cold blood cardioplegia solution entered the lungs.

The main findings of this study are therefore that pulmonary function and gas exchange, although markedly reduced following cardiac surgery, are not affected by placement and suctioning via a pulmonary artery vent during the time of cardioplegia delivery intra-operatively.

Furthermore, these studies strongly suggest that cold blood cardioplegia solution is innocuous to the lungs.

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ABBREVIATIONS

α	Alpha receptor blocker
a/A	arterial to Alveolar ratio
AaO_2	Alveolar arterial gradient
α&β	Alpha and Beta receptor blocker
ABG	Arterial blood gas
ACEI	Ace Inhibitor
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
ARDS	Adult respiratory distress syndrome
ATP	Adenosine triphosphate
βB	Beta receptor blocker
BMI	Body mass index
Ca^{2+}	Calcium
CABG	Cardiopulmonary artery bypass graft
CCB	Calcium channel blocker
CI	Confidence interval
CKMB	Creatine kinase myocardium and brain isoenzyme
Cl^-	Chloride
CO_2	Carbon dioxide
COAD	Chronic obstructive airways disease
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
CPK	Creatine phosphokinase
CvO_2	Mixed venous blood
CVP	Central venous pressure
EF	Ejection fraction
FEV_1	Forced Expiratory Volume in 1 second.
FiO_2	Fraction of inspired oxygen
FIV_1	Forced inspiratory volume in 1 second
FIVC	Forced inspiratory vital capacity
Fr	French (size)
FRC	Functional residual capacity
FVC	Forced vital capacity
H^+	Hydrogen ions
Hb	Haemoglobin
HCO_3^-	Bicarbonate
Hct	Haematocrit
ICU	Intensive care unit
IL	Interleukin
INR	International normalising ratio
IQR	Interquartile range
IVC	Inferior vena cavae
K^+	Potassium
LA	Left atrium
LIMA	Left internal mammary artery
LLA	left lung atelectasis
LLE	left lung effusion
Max	Maximum

mCi	Millicuries
Mg^{2+}	Magnesium
MI	Myocardial infarction
Min	Minimum
ml	Millilitres
mmHg	Millimetres of mercury
n	Number
Na^{+}	Sodium
NaCl	Sodium Chloride
NYHA	New York Heart Association Classification
O	Outliers
PA	Pulmonary artery
PaO_2	Arterial partial pressure of oxygen
$PaCO_2$	Arterial partial pressure of carbon dioxide
PEEP	Positive end expiratory pressure
PEFR	Peak Expiratory Flow Rate
PIFR	Peak inspiratory flow rate
PMN	Polymorphonuclear cell
pO_2	partial pressure of oxygen
Postop	Post-operative time period
Pre-op	Pre-operative time period
PTT	Prothrombin time
Q_S/Q_T	Pulmonary shunt fraction
RIMA	Right internal mammary artery
RLA	right lung atelectasis
RLE	right lung effusion
SaO_2	Oxygen saturation
SD	Standard deviation
SE	Standard error
SIRS	Systemic Inflammatory Response Syndrome
SR	Sinus rhythm
SVC	Superior vena cavae
SVG	Saphenous vein graft
Tc-99m	Technetium
TLC	Total lung capacity
TNFα	Tumour necrosis factor α
TXB_2	Thromboxane B_2
μCi	Microcuries
VC	Vital capacity
Vol	Volume
*	Extreme values

DEFINITIONS

Curie Unit for expressing the radioactivity of a radioactive substance, equal to 3.7×10^{10} disintegrations per second

95 % Confidence Interval There is a 95% chance that the "real" difference is between these two limits.

Extreme values Cases with values more than 3 box lengths from the upper or lower edge of the box.

FEV_1 The maximum volume that a subject can exhale in 1 second during a standardised forced expiratory vital capacity manoeuvre.

FIV_1 Maximum volume a subject can inhale in 1 second during a standardised forced inspiratory vital capacity manoeuvre.

FIVC The maximum volume that can be inhaled with maximal effort from a position of maximal expiration.

FVC The maximum volume of air that can be exhaled with a maximally forced effort from the position of maximal inspiration.

Interquartile Range The range between the 25^{th} and 75^{th} percentile

Outliers Cases with values between 1.5 and 3 box lengths from upper or lower edge of the box.

PEFR The first 15-25% of the maximum forced expiratory vital capacity manoeuvre

PIFR The highest inspiratory flow measured during the forced inspiratory vital capacity manoeuvre.

VC Maximum volume of air that can be breathed into or out of the lungs, and is equal to the difference between the total lung capacity and residual volume

PUBLICATIONS

Abstracts

McFarlane T.C., Kleinloog R. The effects of cardioplegia on pulmonary function following coronary artery revascularisation. Cardiovasc J of South Africa 2004; 15:No.5:231-232.

Articles

1. M^{c}Farlane T.C; Kleinloog R; Bennett M. Pulmonary sequestration of cardioplegia administered via the aortic root during aortocoronary bypass surgery. Perfusion 2007; 22: 93-101

2. M^{c}Farlane T.C; Kleinloog R. Does cold blood cardioplegia solution cause deterioration in clinical pulmonary function following coronary artery bypass graft surgery? Perfusion 2007; 22: 103-113

CHAPTER 1

Introduction

"The heart is the source of all movement,
since the heart links the soul with the organs of life"
Aristotle

Elective open heart surgery began in the clinical field in 1953 when Dr F. John Lewis, in Chicago, closed an atrial septal defect using inflow occlusion and moderate systemic hypothermia (28°C) with surface cooling [(1)]. The duration of surgery in this early period was however initially limited by the inability to maintain cerebral circulation. This problem of the need to support the systemic circulation was partially overcome in 1954 when an extra-corporeal heart-lung machine was first used clinically by Dr. J. Gibbon to close an atrial septal defect [(2)].

It was, however, the correction of Fallot's tetralogy using a technique pioneered by Lillehei and colleagues in1954, which introduced the idea of supporting the patient's circulation using controlled cross-circulation from a donor parent to the patient, which initiated the rapid developments in the field of open heart surgery [(3)]. By 1955, the subsequent refinements to the design and function of the extracorporeal pumps and bubble oxygenators had enabled cardiopulmonary bypass to become an integral and routine part of open heart surgery [(3, 4)].

The further evolution of cardiac surgery reflected a conflict between the surgeon's requirement of access to a static, bloodless operating site with sufficient time to complete the intracardiac procedure and the simultaneous need for the myocardium to be protected through a continuous supply of oxygen and substrates. As a result of this dilemma, a number of specialized cardioplegic solutions were formulated to narrow the divide between these two extremes.

1.1 Cardioplegia – Definition and Historical Perspective

Cardioplegia is, by definition, an intentional temporary paralysis of the heart.
This concept was introduced into clinical practice in 1955, by Melrose and colleagues; who produced elective cardiac arrest by occluding the aorta then rapidly injecting a 2.5% solution of potassium citrate in blood into the aortic root [(5)]. Their primary objectives were to improve exposure for surgery by providing surgeons with a quiescent heart and to decrease the incidence of air embolism, which was the prime disadvantage of the inflow occlusion method mentioned above. The most beneficial finding however, which is the main reason for its continued use today, was the protection cardioplegia affords the myocardium.

Concurrent to the development of the Melrose solution, other solutions inducing reversible cardiac arrest after aortic cross clamping were being developed. The use of Acetylcholine as a cardioplegic agent was introduced into clinical practice [(6)], however the technique never became popular because the heart tended to beat when it was touched.

The use of induced cardiac arrest however fell into disrepute after reports by Helmsworth and colleagues[(7)] and later an influential report from the National Heart Institute in Bethesda[(8)] which implicated potassium citrate as potentially toxic and responsible for myocardial necrosis. The outcome was an abandonment of the use of cardioplegia and a swing away for almost fifteen years in English speaking countries, from any discussion or research relating to cardioplegia.

In Germany however, Bretschneider and others continued with more controlled research in this field and during the 1960's developed the "intracellular" cardioplegic solutions [(9)]. So-called because Bretschneider advocated a calcium free, sodium poor, magnesium and procaine solution, equivalent to the intracellular electrolytes.

Bretschneider published the principle of arresting the heart by reducing the sodium and calcium concentrations, in an effort to inhibit the development of an ionic gradient (and consequent action potential) across the membrane. The lack of calcium ions was intended to prevent excitation-contraction coupling. The rationale was to

inhibit the expenditure of energy by decreasing electrophysiological and contractile activity [9].

Kirsch [10], at the University clinic in Hamburg, worked on the theory that a cardioplegic agent should contain no component that would stimulate the breakdown of energy-rich phosphates by activation of phosphorylases. He advocated that it should not contain calcium; potassium or sodium, as adenosine triphosphate (ATP) is used in membrane transport. Local anaesthetics and magnesium, being membrane-stabilizing agents, were thought to slow the decay of organic phosphate in the cell. Procaine was initially included in these "intracellular" solutions, to inhibit the hypothermic induced contraction that occurs when rapidly infusing a cold solution into the heart [9]; however procaine hinders the permeation of H^+ and consequently reduces the effectiveness of potential buffers [11].

Kirsch's magnesium-aspartate-procaine bolus solution was initially used at normothermia, however it was discovered that the efficacy of a high magnesium solution such as Kirsch's, diminishes after 30 minutes normothermia [12]. Hypothermia, previously a popular method on its own, was then reintroduced in conjunction with cardioplegia routinely in the clinical situation [13-15].

In 1976, Hearse and his contemporaries [16] published a study using the working rat heart model in which they experimentally tested various components of the cardioplegic solutions previously used. In contrast to Breschneider and Kirsch, Hearse advocated that the cardioplegic solutions should retain as closely as possible extracellular, rather than intracellular, concentrations of ions, with only those additions shown to be effective and, then, only in their optimal concentrations [16]. He proposed the St. Thomas' solution, the ionic concentration of which is based on the ionic composition of blood, that is, the so-called "extracellular" solution. The first St. Thomas' Hospital solution comprised of Ringer's solution with normal concentrations of sodium and calcium, to which was added16mmol/l potassium chloride (to arrest the heart instantly); 16mmol/l magnesium chloride (for myocardial protection) and 1mmol/l procaine (for membrane stabilisation), to be used at a temperature of about 30°C.

Over the following years, the St. Thomas' Hospital No.1 solution was fully tested and developed further [15, 17, 18]. This solution was used until 1981, when further alterations with a control for pH with the inclusion of bicarbonate as a buffer and reduced sodium for osmotic space, were made. This became known as the St. Thomas' Hospital No.2 solution, which was deemed to be superior to the No.1 solution [19].

By the end of 1978, the use of cardioplegia was fully integrated into clinical practice and discussion was centred not on whether to use cardioplegia, but rather which solution to use.

Buckberg introduced the concept of using blood as the vehicle for potassium infusion into the coronary arteries [20, 21] (Table 1.1). Blood-based cardioplegic solutions have many advantages over crystalloid solutions as there are many intrinsic substances of use to the arrested heart with better oxygenating and buffering capacities [22]. Blood-based solutions have an oxygen carrying vehicle (haemoglobin), which can also carry CO_2, good buffers (histidine, bicarbonate and phosphates), substrates and has the correct ionic composition [23]. The downfalls of blood-based cardioplegic solutions include an increased viscosity at lower temperatures, which may block the vascular bed and prevent complete flushing of the heart [24]. Blood-based cardioplegia which came into existence in the 1980's was therefore succeeded in the early 1990's by the technique of continuous warm blood cardioplegia.

Table 1.1: The Evolution of Cardioplegia

Melrose Solution	Melrose 1955	High K^+ citrate
Intracellular Solutions	Hoelscher 1961	Mg^{2+}/Procaine
	Bretschneider 1964	Low Na^+/ Ca^{2+}free
	Kirsch 1970	Mg^{2+}/ Procaine
Extracellular Solutions	Hearse 1976	High K^+/Mg^{2+}
	Gay-Ebert 1973	High K^+
Blood Cardioplegia	Buckberg 1979	High K^+/blood

Today cardiac surgeons are faced with a multitude of different cardioplegic solutions and cardioplegic techniques being used experimentally and clinically. Cardioplegic solutions are now subdivided into either pure crystalloid (intracellular or extracellular electrolyte equivalent formulations) or blood cardioplegic solutions.

A number of experimental and clinical studies have shown blood cardioplegia to be superior to crystalloid cardioplegic solutions [25-29]. These studies were however conducted a number of years ago, and it may be argued that the advancements made to the present day crystalloid solutions may provide a different answer should they be retested.

It is not in the scope of this text to provide an exhaustive commentary on the types of solutions, merely that the different types exist, and that the solution used in the present clinical trial was to date that considered to be superior, namely the blood cardioplegia solution developed by Buckberg and his colleagues.

1.2 Cardiopulmonary Bypass

Whilst techniques and equipment have been progressively refined, the use of the cardiopulmonary bypass (CPB) circuit and cardioplegia are still essential to most cardiac operations, yet remain an important clinical dilemma [30-32].

The pathophysiology of pulmonary dysfunction following cardiopulmonary bypass surgery, whether total or partial, is complex and multifactorial. The cardiopulmonary bypass circuit has been implicated in provoking a systemic inflammatory response syndrome (SIRS), which can contribute to the development of post-operative complications, including but not limited to pulmonary dysfunction.

In cardiac surgery, this inflammatory reaction is thought to be the result of four main forms of injury [30, 33]:

1. The interaction of blood with the non-physiologic surface of the pump
2. Ischaemia-reperfusion injury
3. Endotoxaemia
4. Operative trauma

Some or all of these may manifest by:

1.2.1 Complement activation

The complement system comprises of twenty plasma proteins, which assist the body in its defence mechanism. Changes to these plasma proteins particularly occur when there is contact of blood with the foreign surface of the circuit, causing activation in a cascade sequence by the classic and alternate pathways. Complement levels fall, and the complement degradation products C3a and C5a are generated during CPB [(34)]. These anaphylatoxins cause histamine release from mast cells, produce pro-inflammatory cytokines and stimulate white blood cells to release oxygen free radicals and lysosomal enzymes. C3a is a potent stimulator of platelet aggregation while C5a stimulates neutrophil aggregation and adherence to endothelial cells [(35)].

The physiological effects of C3a and C5a include vasoconstriction and increased capillary permeability [(36)].

Kirklin [(37)], in a study of 116 consecutive patients undergoing cardiac surgery, of which 41 had pulmonary dysfunction events, related higher levels of plasma C3a, measured 3 hours post cardiopulmonary bypass, to postoperative morbidity. However he noted that the longer the elapsed time of cardiopulmonary bypass and younger the age at operation were also incremental risk factors for post-operative pulmonary dysfunction. Moore [(38)] reported higher levels of C3a in patients requiring prolonged mechanical ventilation. Studies by Tennenburg [(39)] and Bando [(40)] however suggest that although C3a may mediate neutrophil activation, there is no correlation between complement activation and acute lung injury merely that it is one of the many factors in the complex inflammatory reaction.

1.2.2 Polymorphonuclear cell activation

Through contact with the foreign CPB circuit, polymorphonuclear cells (PMNs) are primed and activated. By augmenting PMN activation, pro-inflammatory mediators (cytokines) can promote lung injury [(41)].

Cytokines are endogenous polypeptides produced by a variety of cell types. They serve for signal communication between cells involved in immunity and inflammation

and it is thought their role is essential in the pathogenesis of shock and multiple organ failure during sepsis. The monocytes activated by sepsis or surgical procedures such as cardiopulmonary bypass may release systemic inflammatory cytokines. Several pro-inflammatory cytokines associated with CPB and the promotion of PMN activation, include Tumour Necrosis Factor α (TNF α), Interleukin 1β (IL-1β), Interleukin 6 (IL-6) and Interleukin 8 (IL-8). Once activated, PMNs can release a number of proteolytic enzymes and oxidative chemicals, including oxygen free radicals into the systemic circulation and into local lung tissue [42].

1.2.3 Endotoxins

Endotoxins are lipopolysaccharides originating from the walls of degraded gram-negative bacteria. Once produced, they may activate the coagulation cascade, complement and have the effect of increasing adhesiveness of vascular endothelial cells and increasing the oxidative burst response of neutrophils [43].

These enzymes play a crucial role in the development of post cardiopulmonary bypass lung injury by increasing pulmonary alveolar-endothelial permeability thus consequently affecting lung mechanics and gas exchange [44, 45].

1.2.4 Neutrophil activation

Following the activation of PMNs described above, there is an increased expression of cell adhesion molecules which enhances neutrophil-pulmonary endothelial adhesion, leading to further PMN activation, local pulmonary neutophil recruitment, sequestration and a release of neutrophil proteolytic enzymes, which are a known cause of lung injury [46-48]. To date, there is no feasible way to inhibit this neutrophil release during open heart surgery.

1.2.5 Oxygen free radicals

A free radical is a molecule with an odd number of electrons, and is consequently unstable and chemically reactive [49]. As alluded to above, injured endothelial cells attract and activate polymorhonuclear lekocytes [42], which release proteolytic enzymes and generate oxygen free radicals [50]. Free radicals will in turn result in further endothelial injury [51, 52] by acting on membrane lipids to increase membrane

permeability and may also decrease cardiac and pulmonary function [53]. Although it is difficult to quantify levels of oxygen free radicals in vivo, various methods have indeed shown a significant increase in their activity during and following cardiopulmonary bypass [54-56].

Free radicals are probably formed during ischaemia [49, 57], but in addition are generated to a much greater extent during reperfusion following ischaemia, as their production is dependant on oxygen tension (production of free radicals is greater if the pO_2 is above 150 mm Hg) [58, 59]. Similar findings were made by Ihnken [60], who noted that hyperoxic CPB compared with normoxic CPB, increases oxygen free radical damage to the lung, as reflected by lower vital capacity and FEV_1 levels.

1.2.6 Free radical scavengers

A number of compounds can reduce free radical mediated cellular injury, including but not limited to enzymatic scavengers such as superoxide dismutase, catalase and perioxidase [49]. Of significance, is the fact that one of the salutary effects of blood cardioplegia and reperfusion solutions are the natural oxygen free radical scavengers contained in erythrocytes, which may attenuate the oxygen free radical response[61, 62].

1.3 Operative Trauma

Gu and colleagues[63] investigated to what extent the chest surgical incision contributes to complement activation following cardiopulmonary bypass. Despite having a non-randomized and small (n=22) sample size, they assessed pre- and post-operative biochemical markers of complement activation and systemic inflammatory response (SIRS), in patients undergoing a small chest incision (via anterolateral thoracotomy) and a conventional median sternotomy (representative of a larger tissue injury). Extracorporeal circulation was not used in either group and the surgical intervention techniques were similar in both groups. Their findings suggested there to be a more pronounced inflammatory response with a larger chest incision thus concluding that tissue injury caused by surgical incision contributes to complement activation even in cardiopulmonary bypass patients who are operated on without cardiopulmonary bypass. The conclusions drawn from this research concurred with the findings of other studies [64, 65], that identified the surgical procedure to be the

predominant cause of the acute phase inflammatory response following cardiopulmonary bypass, rather than the historically ascribed CPB procedure. It was conceded however that early neutrophil activation is only evident when extracorporeal circulation is used, but noted that it is uncertain to what extent this early polymorphonuclear cell (PMN) activation is responsible for post cardiopulmonary bypass complications [64, 65].

The reduction in inflammatory response following the minimally invasive technique might be significant enough to be an advantageous technique to employ in those patients with a high degree of comorbidity [66]. The time periods to neutrophil activation before and during cardiopulmonary bypass were investigated and discovered too that neutrophil priming occurs before the commencement of extracorporeal circulation, thus implicating anaesthesia, surgical trauma and other events to neutrophil priming and sensitisation [67].

1.4 Endothelium

The vascular endothelium, comprised of a monolayer of squamous epithelial cells, forms the inner lining of the tunica intima and constitutes the first barrier between the blood stream and the extravascular space. The total surface area of this interface is approximately 1000m^2 and performs a multitude of functions vital for normal homeostasis and without which we could not survive [68].

The current hypothesis is that the endothelium is a key organ, responding to various stimuli not only as a target for injury, but also by altering its structure, function and metabolism thereby influencing secondary responses to injury [69, 70]. Injury to a particular organ will result in concomitant damage to the vascular endothelium of that organ. An important consideration to cardiothoracic surgeons is therefore the function, response to injury and preservation of the endothelium. Of specific importance here, is the effect on the endothelium of the heart and lungs caused by ischaemia and the cardioplegic solution used.

1.4.1 Function of the endothelium

The position of the endothelium between the interstitial tissues and blood allows it to regulate both intravascular and extravascular events. Endothelial cells modulate capillary permeability; inflammation; the immune response; haemostasis and vascular smooth muscle tone [69, 71]. These phenomena are accomplished through maintaining a balance between growth factors and inhibitors that are produced by endothelial cells[72] and through continuous interaction with circulating platelets, leukocytes and vascular smooth muscle cells [73, 74].

The endothelial cell undergoes a change in phenotype, when subjected to cellular stress, be it either oxidative or infectious stress. This so called endothelial cell activation consists of an immediate and a delayed response.

The initial response is a deployment of inflammatory mediators, which on a local level, serves to isolate and neutralise infection and injury [75]. The delayed response, which occurs over several hours, involves transcriptional activation of several genes and new protein expression on the endothelial cell surface. This morphological change of the cytoskeleton produces focal gaps in the endothelial cell monolayer, thus increasing vascular permeability [69]. These activated endothelial cells may in turn become phagocytic, bind circulating immune complexes, attract leukocytes and become procoagulant [42]. Polymorphonuclear leukocytes in turn release smooth muscle relaxant, oxygen free radicals and proteolytic enzymes resulting in further injury [50].

It has been documented that plasma levels of von Willebrand factor (a marker of endothelial injury) are significantly raised in patients undergoing cardiac surgery [76]. The result of this more diffuse endothelial cell injury may therefore be end-organ damage and consequent dysfunction.

1.4.2 Cardioplegia and the endothelium

The primary function of cardioplegia, as discussed earlier, is that of arresting the heart for to provide a quiescent surgical field, while simultaneously limiting myocardial demands and ischaemia. This reversible myocardial electromechanical arrest should therefore be via a solution that is non-toxic to the cells it comes into contact with, namely the myocytes and the endothelium of both the heart and lungs.

It should be stressed that the majority of research into cardioplegia revolves around its function of myocardial protection; there is a paucity of information regarding its effect on the lungs. Relatively few studies have examined the effect of cardioplegic solutions on the endothelium. Carpentier and colleagues [77] were among the first to evaluate the cytotoxic effects on the vascular endothelium that cardioplegic solutions can produce. One of their conclusions, relevant to this study, was that the addition of blood to the more toxic solutions, attenuated their effects. The inclusion of procaine to cardioplegic solutions (mainly intracellular solutions) has also been attributed to being a contributory factor in inducing endothelial damage [78].

After evaluating a number of cardioplegic solutions and their effect on cultured human venous endothelial cells, Von Oppell [79] formulated a model, positively relating cytotoxicity to the following factors:

High concentrations of:

i) Potassium (K^+>20mmol/L)
ii) Chloride Ions and Calcium contents
iii) Calcium–free extracellular electrolyte equivalent formulations (not the intracellular solutions)

Low concentrations of:

i) Magnesium
ii) Amino acid substrates and buffers.

This concurred with earlier findings [80, 81] that highlighted the detrimental effects of cardioplegic solutions in inducing endothelial dysfunction and altered vascular responsiveness and the consequent need for endothelial protective solutions to be found and utilised.

Cold blood cardioplegia has also been implicated in amplifying the inflammatory process through transient plasma iron overload derived from oxidatively damaged haemoglobin by ‘activated’ neutrophils [29].

1.5 Delivery of cardioplegic solutions

The method of delivery of the cardioplegic solution is also as critical as its contents. During the aortic cross clamp period, it is imperative to maintain cardioplegic arrest through a uniform delivery of the solution[82].

The cardioplegic solution may be infused antegrade via the aortic root or retrograde via the right atrium or coronary sinus. The antegrade method, as used in this study will be discussed further.

Buckberg recommended that cardioplegia be infused for 3-5 minutes at 250-350ml/min, citing that duration of infusion is more influential than the volume infused, as the uptake of oxygen is dependant on time and not dose[82]. Additional reperfusions of cardioplegia, every 20 minutes during the cross-clamp period, have been found to be the ideal method of maintaining cardioplegic arrest[82, 83]. During coronary artery bypass surgery, the surgeon's protocol very often includes re-infusion of cardioplegia after every coronary artery anastomosed, which may be between 10 and 20 minutes. On completion of the anastomoses of the coronary arteries, there is a final infusion of a reperfusion solution, which according to the Buckberg protocol should occur 3-4 minutes after re-warming is commenced[84].

1.6 Pulmonary artery vent

On returning to the right atrium via the coronary circulation, the infused cardioplegic solution enters the pulmonary vasculature unless removed by a right atrial or pulmonary artery vent[85]. The amount entering the pulmonary circulation will therefore be dependant upon the volume of cardioplegic solution infused, if not primarily removed by vents.

Coronary sinus flow into the right heart should significantly ebb with aortic cross-clamping except for non-coronary collateral flow (average 48-74ml/min), when cardioplegia (or coronary perfusion) is administered. Most coronary sinus blood including the cardioplegia administered, should therefore be removed if the venous cannulae, or as in the present study, the atriocaval cannula is working correctly [86].

The pulmonary artery (PA) vent inserted 3 to 4cm into the main pulmonary artery safely and simply provides exceptional reduction in left atrial return and decompression of the pulmonary vasculature. During infusion of cardioplegia, the pulmonary artery vent provides an aspiration route in order to discard much of the infused solution as it drains via the coronary sinus, into the right ventricle to the pulmonary artery. [85] The PA vent has been held to be effective in removing excess cardioplegic solution as well as a great deal of blood [87].

In a study of ten patients undergoing cardiopulmonary bypass, the pulmonary artery vent return was measured and found to average 12.5L during the operation [87]. The volume of blood returned through the vent after institution of cardiopulmonary bypass, but before the application of the aortic-cross clamp was 1.1L. During aortic cross-clamp, the average return was 6.4L. The return through the vent following aortic unclamping and up to the time of its removal averaged 5.0L. This study [87] included a scintigraphic analysis, in which the PA vent retrieved 89.9% of a technetium labelled solution placed in the left atrium during aortic cross-clamping.

The reason for there being a high percentage of technetium solution return to the pulmonary artery vent in the above study, was due to injecting it directly into the left atrium and retrieval from the pulmonary artery meant the technetium solution flowed retrograde through the lungs[87].

The topic of pulmonary artery venting has not been well covered in the literature generally. In the few articles covering this subject, pulmonary artery venting has been documented to have the advantages of decreased left heart distension with decreased elevation of end-diastolic pressure, decreased myocardial rewarming and decreased collateral blood return to the operative field, and is an effective means of removing excess cardioplegic solution, particularly in the case of multi-dose cardioplegia, thus maximising operative visibility [87, 88]. During reperfusion, a vent may decrease myocardial oxygen consumption, improve subendocardial blood flow and again avoid the potentially harmful effects of distension [89, 90].

The associated risks of using a pulmonary artery vent are documented to be minimal, particularly when compared to a left ventricular vent, which has been blamed for air embolization with sequelae such as stroke and myocardial infarction [87, 91, 92].

Buckberg [93] advocated the use of a left ventricular vent to be "not only advisable, but an essential component of most operations requiring cardiopulmonary bypass". Since the reported complications on the left ventricular vent however, use of the pulmonary artery vent became favoured, as it is a simple yet effective technique [87].

Today, it appears surgeon's preference dictates whether a vent is used. There is no evidence in the literature to suggest any pulmonary benefits or detriment to using a pulmonary artery or atrial vent.

1.7 Bronchial circulation

In normal anatomy, during cardiopulmonary bypass, blood flow derived from the bronchial arteries has been said to be substantial [94, 95]. This statement is however debatable, as there is dispute of this theory. Assessing the contribution of systemic (bronchial) blood flow to pulmonary gas exchange during cardiopulmonary bypass however, has been negligible[96].

In the normal lung the total bronchial output is estimated to be about 1% of cardiac output, therefore contributing only a small amount to pulmonary capillary blood flow and gaseous exchange [97]. The major portion of this blood flow supplies the bronchial walls and the visceral pleura and is drained into the bronchial veins, i.e. the non-alveolar lung tissue [98]. Bronchial venous return is considerable (ranging from 140ml/min up to 400ml/min^{-1}) in patients with severe coronary artery disease and minimal angina [99, 100].

On measuring blood flow to the left heart, Agostoni [101] found values of 22ml/min for healthy patients, 89ml/min in patients with heart failure; 76ml/min in patients with mitral stenosis [102] and in those patients ventilated with dry air, values of 40ml/min [103]. Baile, [100] who used the same approach, reported much higher values ranging from 8 to 1043 ml/min. Schlensak [104] in a similar study, but using 10 piglets,

reported values of 4.4ml/min during bypass, which was significantly lower than the 40ml/min recorded before cardiopulmonary bypass. They noted that despite adequate perfusion pressure, the bronchial artery blood flow is significantly reduced during cardiopulmonary bypass, and further proposed this low flow when viewed with the ultrastructural changes present at the end of cardiopulmonary bypass to be suggestive of an additional cause of lung ischemia.

Thus it remains unclear from these studies exactly to what extent the bronchial circulation contributes to gaseous exchange during cardiopulmonary bypass. The retrieval of blood by the pulmonary artery vent will however include the returned bronchial artery flow.

1.8 The effect of cardioplegia on the lungs

During cardiopulmonary bypass it has become common practice not to ventilate the lungs, as blood oxygenation by the lungs is performed by the extracorporeal circuit and the movement from mechanical ventilation may interfere with surgical exposure of coronary anatomy.

The development of microatelectasis, hydrostatic pulmonary oedema, poor lung compliance and a higher incidence of infection has been positively correlated with hypoventilation during cardiopulmonary bypass [105, 106]. As the lungs are totally dependant on the bronchial (systemic) blood supply during the period of cardiac arrest, this has led to speculation that mechanical ventilation during the period of bypass may limit postoperative lung injury by preventing these complications [105-107].

Attributing atelectasis as the main causative factor in postoperative respiratory dysfunction, Svennevig [108] and Magnusson [105] compared total lung collapse versus continuous positive airway pressure versus intermittent positive pressure ventilation during cardiopulmonary bypass. From their findings, it appears that mechanical ventilation during cardiopulmonary bypass may actually worsen both intrapulmonary shunting and lung compliance.

Despite a large number of studies designed to investigate this seemingly controversial area, to date the evidence for the benefits of maintaining ventilation alone during cardiopulmonary bypass is inconsistent, with most studies showing no significant preservation of lung function [109-112].

Maintaining ventilation together with pulmonary artery perfusion during cardiopulmonary bypass may however be advantageous. During partial cardiopulmonary bypass (in which some pulmonary artery blood flow remains), an experimental study on the rabbit model demonstrated that the regional blood flow decreases only to 41% of pre bypass value, and tissue adenosine triphosphate (ATP) remain unchanged, whereas during total cardiopulmonary bypass, (during which the lungs are perfused solely by the bronchial arterial system) blood flow decreased to 11% and ATP to 50% of baseline [113]. In a sheep model, Friedman [114] compared total cardiopulmonary bypass (i.e. no ventilation or perfusion; superior and inferior vena cavae snared) with partial cardiopulmonary bypass during which ventilation and perfusion were maintained. Their results suggest a combination of ventilation and perfusion have a beneficial role in the preservation of lung function by limiting platelet and neutrophil sequestration and attenuating the Thromboxane B_2 (TXB_2) response after cardiopulmonary bypass.

Further studies by Friedman [115] clarified the fact that the less the deprivation of pulmonary arterial blood flow during cardiopulmonary bypass the less severe lung injury was provoked.

Based on these findings, Suzuki [116] compared continuous pulmonary perfusion during total cardiopulmonary bypass to conventional bypass on thirty infants requiring surgical correction of congenital defects. The outcome measures were the assessment of PaO_2/FiO_2 and neutrophil counts pre and up to 24 hours after termination of cardiopulmonary bypass. The results from their trial suggest that ischemia-reperfusion injury is an augmenting factor of the lung injury. This growing body of evidence that the lungs are at risk of ischemia-reperfusion injury highlights the need for protective measures.

In a study on neonatal lambs, Nagashima [117] endeavoured to find a method of attenuating the ischemia-reperfusion inflammatory reaction by assessing the effect of continuous high-volume haemofiltration during cardiopulmonary bypass. Their findings were so encouraging that the technique, once investigated further, could have a clinical application in reducing the morbidity rate of cardiopulmonary bypass.

Serraf and associates [118] reported that pulmonary artery perfusion with blood prevented haemodynamic alterations after cardiopulmonary bypass but failed to prevent any of the biochemical disturbances. Sievers [119] demonstrated that short term hypothermic pulmonary artery perfusion with cold oxygenated blood during the period of cardiopulmonary bypass, particularly if combined with ultrafiltration, diminishes the inflammatory response and extent of capillary leakage in the lungs and improves oxygenation. The study however can be criticized for not being randomized; having a small number of patients (n=24) and not comparing standardised surgical procedures. Although able to claim that lung perfusion during cardiopulmonary bypass attenuates alveolar epithelium and endothelial barrier damage, in their findings, they were not able to conclude whether these salutary effects indeed have an effect on clinical events such as long-term respiratory function [119].

Further studies demonstrated that continuous pulmonary perfusion during total cardiopulmonary bypass is an effective means of preventing the lung injury derived from total cardiopulmonary bypass on infants undergoing surgery for congenital heart disease [116].

An experimental study on twelve adult dogs [120], evaluated the effect of right pulmonary artery perfusion with a protective hypothermic anti-inflammatory solution on lung function after cardiopulmonary bypass. Post-operatively, it was found that the non-perfused lung showed diffuse intra-alveolar oedema, haemorrhage and abundant neutrophils, whereas the perfused lung had fewer pathological changes. They were able to concur therefore with the findings of previous studies [121-123] that higher temperature and the inflammatory responses in lung tissue during cardiopulmonary bypass are indeed two major causes of lung injury. Furthermore, the infusion of a hypothermic protective solution into the lungs during cardiopulmonary bypass could reduce the cardiopulmonary bypass induced lung injury.

Lindberg [124] conducted a prospective, randomised clinical investigation to evaluate the consequences of circulating cardioplegic solution through the lungs in comparison to evacuating the solution before it entered the pulmonary circulation. In the relatively small trial (total n=55), haemodynamic, metabolic, haematological and radiographic changes were compared in the early post-operative period. The authors noted a smaller increase in vascular resistance index in the lungs flushed with the cardioplegic solution, alluding to the point that cardioplegic flush of the non-ventilated lung may offer some protection in the immediate (first two hours) post-operative period. Another significant finding from their study was that the right cardiac work increased more in the group without pulmonary flush, thus reflecting a flush-induced reduction of the load on the right ventricle in the early post-operative phase.

Anecdotally, despite reporting of a homogenous group in the Lindberg trial, there was a significant difference ($p=0.04$) in the number of grafts per patient, with the group receiving perfusion having significantly fewer number of grafts than the non-perfused group, which may have been an influential variable. This however did not extend to causing any significant difference in duration of aortic cross-clamp or total bypass time.

Other comments on the Lindberg [124] study relate to the fact that only a single dose of the cardioplegic solution (1L at 4°C) was infused, whereas it is common practice to have multi-dose cardioplegia infusions during the surgery [82, 83]. Of note too, is that the solution is described as a cold, clear solution, but the composition is not described, thus one is not able to classify the solution according to the categories previously discussed.

The conclusions drawn by Lindberg [124] however were that allowing cold, clear cardioplegic solution to pass through the lungs indicated a possible protective action on the lungs.

1.9 Clinical manifestations of lung injury following CPB

Respiratory dysfunction occurs to some degree in the majority of patients undergoing cardiopulmonary bypass. The clinical manifestation of this dysfunction ranges from mild temporary oxygenation defects, atelectasis, and infrequently to the more severe adult respiratory distress syndrome (ARDS) [125, 126]. Although severe lung injury after cardiopulmonary bypass is uncommon, it is a significant cause of morbidity and mortality with a major impact on health care expenditures [127].

Kirklin [123] and colleagues reported a 30% incidence of pulmonary dysfunction after cardiopulmonary bypass, but the methods of quantification, such as measurement of tracheal secretions were subjective, relatively insensitive and non-specific. Prolonged ventilatory support (>48hours) after cardiac operation is necessary in 5% to 22% of patients [126, 128, 129].

After surgery with cardiopulmonary bypass, changes in lung function result from a myriad of factors, including: atelectasis; increased shunt; alterations in chest wall mechanics related to sternotomy or harvest of the left internal mammary artery (LIMA), right internal mammary artery, or both, causing lung trauma; phrenic nerve injury or palsy and changes in the capillary bed and lung parenchyma [130].

1.9.1 Atelectasis

General surgical patients tend to demonstrate hypoxia yet do not have a proportional increase in the alveolar arterial (AaO_2) gradient, whereas following cardiopulmonary bypass surgery there is an increase in the AaO_2 gradient and percentage pulmonary shunt fraction concomitant with hypoxia [126]. The hypoxia following general surgery is attributed to be as a result of a decrease in alveolar oxygen from depressed ventilation, probably as a result of opiate based analgesia. In contrast, the findings following cardiopulmonary bypass are therefore more likely to reflect ventilation-perfusion inequality (blood delivered to non-ventilated alveoli) due to true shunting and therefore atelectasis [126].

Left lower lobe atelectasis is the most common sequelae following cardiopulmonary bypass surgery, with a reported incidence of 68% to 88% [131, 132]. Claims have been

made that radiographic evidence shows atelectasis to be present in as many as 80-90% of patients following cardiac surgery, and predictably that its appearance is exacerbated following extubation of the patient [133].

One contributory mechanism to atelectasis is non ventilation of the lungs during cardiopulmonary bypass. Stimulation of the cellular and humoral immune systems during cardiopulmonary bypass results in the activation of complement and white blood cells [123, 134]. This inflammatory cascade has been found to be at least partially responsible for increased capillary permeability after cardiopulmonary bypass, resulting in flooding of the pulmonary interstitium [135, 136] and leading to intrapulmonary shunting [137].
Hypothermia has been reported to interfere with surfactant production [138]. Interruption of lung surfactant may produce transient alveolar collapse, leading to atelectasis.

Atelectasis therefore contributes to the deterioration of functional residual capacity (FRC); lung compliance; venoarterial admixture and as alluded to above, the alveolar arterial oxygen gradient (AaO_2) following cardiac surgery.

1.9.2 Surgical Incision

A restrictive ventilatory defect follows median sternotomy [139].

As discussed earlier, several studies identified the surgical procedure of median sternotomy to be a predominant cause of the acute phase inflammatory response following cardiopulmonary bypass [64, 65].

Locke [139] tested vital capacity and co-ordination of the rib cage on 16 men following median sternotomy for coronary artery bypass grafting and concluded that the reduced and uncoordinated rib cage expansion that follows the surgery contributes to the restrictive ventilatory defect. A study of the pulmonary function of 18 patients' pre and at 1 and 6 weeks following coronary bypass surgery attributed respiratory muscle weakness to be the main cause of immediate postoperative restrictive lung function

loss and the structural alteration of chest wall mechanics was implicated for the persisting late restrictive pulmonary impairment [32].

Median sternotomy may impair pulmonary function tests by reducing chest wall movement, but this does not explain the changes in PaO_2, AaO_2 gradient or percentage pulmonary shunt fraction [32, 139-141].

1.9.3 LIMA as a conduit

While there is widespread consensus that the internal mammary arteries provide a far superior long term conduit for coronary artery grafting than venous grafts, it is not without drawbacks.

In several clinical studies, internal mammary artery grafting has been identified as increasing the risk of postoperative pulmonary complications [140, 142-145]. Following cardiopulmonary bypass, there is a reduction of at least 25 to 50% in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) and this decrease is much greater in patients who have undergone mobilisation of the internal mammary artery [140, 141, 146].

Reasons suggested for a greater reduction in lung function with internal mammary use compared with saphenous veins, have included post-operative pain, pleurotomy, and the use of a retractor causing chest wall distortion.

Cohen and colleagues [147] have shown that FEV_1 is reduced in all patients with or without harvesting of the internal mammary artery. Differing conclusions were reported from Wimmer-Greinecker [148], whose results (study of 112 patients) indicated a significant reduction of FEV_1 and FEV_1/VC ratio only in patients operated on conventionally, thus implicating the internal mammary artery preparation technique in determining postoperative lung function. The authors of the study were of the opinion the decreases in bedside spirometry were determined, in the early stage, to a large extent by postoperative pain, as there was no difference between the groups by their three month follow up. Matsumoto [145] argued that pleurotomy was not a determinant in reduced FEV_1 postoperatively. It must be emphasised however that in their study they only performed postoperative spirometry 20-30 days following the surgery, thus pain was not an influencing factor.

Cohen and associates [147] demonstrated that patients who underwent coronary artery bypass grafting with the internal mammary artery experienced significantly greater levels of postoperative pain, and further noted that age, smoking and gender had no effect on these postoperative pain levels. Increase in pain levels has therefore predominantly been attributed to the more extensive surgical trauma to the chest wall.

Controversy therefore exists about the effect of pleurotomy on postoperative pulmonary function. Some authors have reported larger decreases in the PaO_2 with internal mammary artery grafting [144, 149], whereas others have reported comparable decreases with both procedures [141, 150].
Singh [151] in a study of the arterial blood gases of 125 patients undergoing bypass surgery noted a large decrease in PaO_2 postoperatively, the nadir occurring on the second postoperative day with significant abnormalities still evident on the eighth postoperative day. The changes in PaO_2 had no significant correlation with age, number of grafts, pump time, smoking history, and duration of anaesthesia or endotracheal intubation. The changes in arterial blood gases in the first days postoperatively were similar in the internal mammary artery graft and saphenous vein graft groups. However, the study showed a significantly longer recovery time in those patients undergoing pleurotomy and internal mammary artery grafting.

In those patients undergoing cauterisation of the internal mammary artery, development of an ipsilateral pleural effusion further prevents alveolar expansion and predisposes patients to the development of atelectasis in the short term [152-154].

Left sided pleural effusions can be detected in 40% of patients after coronary artery surgery, regardless of whether the pleura remains intact or is opened [154]. The findings of Taggart [126] were in accordance and further reported no decrease in pulmonary function whether the internal mammary artery was harvested, or the saphenous vein. Wimmer-Greinecker [148] suggests that opening the pleural space leads to extensive adhesions of the lung, resulting in a decreased Vital Capacity and pulmonary restriction in the long term.

The presence of fluid in the pleural space acts as a space-occupying process and reduces lung volumes. Small to moderate sized pleural effusions however are thought to displace rather than compress the lung and therefore considered to have little effect on pulmonary function [155, 156]. A rationale provided by Vargas [157] for the greater impairment in lung function seen in patients with small pleural effusions or pleural thickening must therefore also be a reflection of the greater thoracic trauma the patient has been subjected to. Their contention is supported by their observation that patients who received intercostal chest drains had greater reductions in FVC (forced vital capacity), FEV_1 and TLC (total lung capacity) when compared with patients who received no pleural drain.

Subxyphoid insertion of the pleural drain results in a significantly lower impairment in pulmonary function and less perceived pain than insertion at the intercostal position, while drainage was equally effective in both positions [158].

Bonacchi [159] demonstrate that the intra pleural chest drains are a supplementary factor inducing painful respiration and greater respiratory dysfunction. The opened pleurae negatively influenced blood arterial gas concentrations, resulting in lower PaO_2 and higher $PaCO_2$ and FiO_2 during mechanical ventilation and in the first few hours following extubation, returning to similar levels by the fifth postoperative day.

The use of bilateral internal mammary artery grafts does not increase the incidence of postoperative pulmonary complications when compared with unilateral internal mammary artery grafting [160].

1.9.4 Phrenic Nerve injury

Diaphragmatic impairment secondary to phrenic nerve injury, particularly that involving the left hemi-diaphragm, is reported to occur in up to 30% of patients and to persist in one third of those patients at one year follow-up following cardiac bypass surgery [132;161-163]. The incidence of diaphragmatic dysfunction varies according to the radiological, electrophysiological or other techniques used for detection [164-167].

The cause of this dysfunction has been attributed to several factors, but most cases report it being due to cold injury or direct, traumatic phrenic nerve damage as a result

of stretching of the nerve during internal mammary artery dissection [163, 168]. The effect of temperature on the phrenic nerve was investigated by Mills [168] who concluded that mild hypothermia affects the diaphragm. The topical use of ice slush for the cooling of the myocardium is considered to be an independent risk factor for phrenic nerve injury, with an eight fold higher incidence according to Dimopoulou and associates [163].

Unilateral damage of the phrenic is more common yet considered to be of little clinical significance in patients with normal preoperative respiratory function [169]. Bilateral phrenic nerve damage has been reported to occur in approximately 2% of cases [163].
In patients with compromised respiratory function preoperatively, the significance of unilateral phrenic nerve injury is far more profound. Studies have found not only an increased number of pulmonary complications and length of hospital stay in those patients with chronic obstructive pulmonary disease (COPD) undergoing coronary artery bypass graft, but in those COPD patients with concomitant phrenic nerve injury, a highly morbid effect was demonstrated [170].

Despite the studies discussed above confirming that coronary artery bypass grafting induces considerable reductions in lung volumes in the early postoperative period, correlating well with reduced respiratory muscle strength, they do not support the view that these abnormalities are solely related to cold induced phrenic nerve injury and subsequent diaphragmatic dysfunction.

1.10 Summary

An extensive literature search has revealed numerous studies examining the physiologic, biochemical and histologic pulmonary alterations following cardiopulmonary bypass surgery. There is however a paucity of information regarding clinical investigation of pulmonary deterioration following cardiopulmonary bypass surgery and cardioplegic solution delivery.

The pathophysiology of pulmonary dysfunction following cardiopulmonary bypass is complex and multifactorial. The extra corporeal circuit has been implicated, through

the interaction of blood with the non-physiologic surface of the pump, to activate a myriad of inflammatory mediators, including but not limited to complement; neutrophils; monocytes; macrophages; platelets and endothelial cells. The production of oxygen free radicals, through their deleterious effect on the alveolar capillary endothelium, leads to interstitial haemorrhage, increased microvascular permeability and miliary atelectasis. Other contributory factors leading to oxidative stress and lung injury include the use of cold blood cardioplegic solution, lung ischaemia and reperfusion injury. It is not known however to what degree each of these factors contributes to lung injury.

The literature abounds with studies on the inflammatory mediators, cascades and by-products produced during cardiopulmonary bypass and cardioplegia delivery, yet relatively few examine the clinical relevance to morbidity. No literature is available directly relating the clinical effect on lung function that cardioplegia delivery may have. The optimal management of the lungs during cardiopulmonary bypass surgery remains to be defined. There is no scientific study regarding the role of cardioplegia in post-operative respiratory dysfunction in patients undergoing cardiac bypass surgery, and in order to accurately delineate those factors most closely related to decreases in pulmonary function, further study is required.

The present study will therefore endeavour to examine whether keeping cardioplegic solution from entering the lungs, through the use of continuous suction via a pulmonary artery vent combined with the application of positive end expiratory pressure (PEEP) and low volume ventilation, during the period of aortic cross-clamp and cardiopulmonary bypass, has a beneficial effect on pulmonary function post-operatively.

CHAPTER 2

Hypothesis and Objectives

Study 1

Hypothesis

This study examines the hypothesis that prevention of the majority of cold blood cardioplegic solution from entering the lungs, by using a pulmonary artery (PA) vent, combined with the application of positive end expiratory pressure (PEEP) and low volume ventilation, during the period of aortic cross-clamp and cardiopulmonary bypass, will result in less deterioration of post-operative arterial blood gases and lung impairment with an earlier return to baseline levels.

Objectives

1. To compare the baseline demographics and health status between the groups to identify whether, despite the randomisation protocol, any baseline differences exist, which may contribute the outcome.

2. To compare all intra-operative and extraneous variables, including confounders to determine whether the two groups studied are homogenous.

3. To compare blood gas results to determine whether the use of a PA vent has clinical significance on blood result changes.

4. To compare bed side spirometry changes to determine whether the use of a PA vent contributes to clinically significant changes in lung function.

5. To compare radiological findings to determine whether the use of a PA vent results in less prevalence of atelectasis and or effusion post-operatively.

6. To determine whether there is any difference in length of hospital or intensive care unit stay following the use of a PA vent and whether the physiotherapy intervention requirements differ when a PA vent is used.

CHAPTER 3

Materials and Methods

A prospective double blind randomised trial was made of 142 patients. This figure was obtained based on a projected 95% confidence interval and 80% power and based on an estimated expected difference of 20% in outcome.

No stratification was used, as there was no demographic information of the patients available beforehand. Patients were randomised in the order in which they came for surgery. Restricted randomisation was used to ensure an even number of patients in both groups.

Group A:
Patients undergoing full cardiopulmonary bypass with cold blood cardioplegic solution allowed entrance into the lungs. (Control group n = 71).

Group B:
Patients undergoing full cardiopulmonary bypass with measures implemented to limit cardioplegic solution from entering the lungs, by continuous suction via a pulmonary artery vent combined with the application of positive end expiratory pressure (PEEP) and low volume ventilation, during the period of aortic cross-clamp and cardiopulmonary bypass. (n = 71).

3.1 Ethical Considerations

Written informed consent was obtained from each patient prior to their participation in the study. Measures were taken at all times to preserve the confidentiality of the data and to ensure anonymity of the volunteers. Only group data is reported.

The study was conducted in Westville Hospital and Entabeni Hospital (Life Healthcare). A proposal was submitted to the Hospitals' Ethics committee and written approval was received on 14 February 2003 to conduct the study in both hospitals. Further Ethics approval was received by the University of Kwa-Zulu Natal.

3.2 Exclusion criteria

The exclusion criteria were as follows:

1. patients undergoing re-do or emergency surgery
2. New York Heart Association (NYHA) Class III or IV
3. congenital or valvular heart disease
4. previous lung surgery
5. history of major parenchymal lung disease
6. bronchial asthma or extensive Chronic Obstructive Airways Disease (COAD)
7. recent chest infection
8. grossly abnormal chest radiograph
9. Ejection fraction (EF) less than 30%
10. pre-operative myocardial infarction (MI) within 2 weeks of surgery or peri-operative MI
11. post-operative low cardiac output state
12. pregnancy
13. Body Mass Index (BMI) exceeding 35 (normal: 21-29).

3.2.1 New York Heart Association Functional Classification

The exclusion criteria prevented those patients undergoing coronary artery bypass grafting with a New York Heart Association Classification (NYHA) of III or IV to participate in the study – namely those patients with cardiac disease resulting in discomfort and marked limitation of physical activity (III); or an inability (IV) to carry on any physical activity without discomfort [171].

Comparison was therefore made between the Class I (patients with cardiac disease but no limitation of physical activity) and II (slight limitation of physical activity).

The researcher was blind as to the patients' surgical group.

3.3 Patient Demographics

Records were made of all demographic details including:

1. age
2. gender
3. height
4. weight
5. Body Mass Index (BMI)
6. angiogram diagnosis
7. Ejection Fraction
8. New York Heart Association (NYHA) Classification
9. medical history
10. smoking history
11. medication
12. allergies
13. all intra–operative details relating to anaesthetic variables and extracorporeal circulation.

3.4 Measures recorded and compared

3.4.1 Arterial Blood Gases

Pulmonary gas exchange was measured by the partial arterial pressure from blood samples drawn from the arterial line placed in the radial artery of the non-dominant arm, when in situ, and from a direct radial arterial puncture for the post-operative Day 5 reading.

The Arterial Blood Gases were measured over 8 time points and analysed using the Bayer Corporation Chiron Diagnostics 865 Ph/Blood Gas/Electrolyte and Metabolite Analyzer (63 North Street; Medfield; Massachusetts;02052-1688).

The time points for analysis were as follows:

1. Pre-operatively whilst the patient was breathing on room air.
2. Intra-operatively, during CPB after the first coronary anastomosis.
3. 1 hour after arrival to the intensive care unit.
4. On T-piece, immediately prior to extubation.
5. 1 hour after endotracheal tube extubation.

A record was made of the patients' FiO_2 for blood taken between time points 2 and 5.

6. Post operative Day 1 (1 reading on room air)*
7. Post operative Day 2 (1 reading on room air)*
8. Post operative Day 5 (1 reading on room air)*

*Arterial blood gases were taken after the patient had been without mask or nasal cannula oxygen for between 15-20 Minutes; at a given time: 09h00.

The patient did not have a nebuliser or physiotherapy treatment within 2 hours before the arterial blood gas was taken.

3.4.2 Shunt Fraction Estimation Measures

Shunt Fraction Estimation was calculated using the a/A ratio (arterial/Alveolar ratio), to determine the extent of intrapulmonary shunting. This method, described in Appendix A, has been deemed the most accurate non-invasive method of determining the extent of a patient's pulmonary shunt.

Measurement of the pulmonary shunt fraction (Q_S/Q_T) is the "gold standard" for quantifying respiratory dysfunction [(172)]. Without an invasive pulmonary artery catheter however, one is not able to obtain the oxygen content of mixed venous blood (CvO_2) value to calculate shunt. There are however widely accepted, simple methods of estimating shunt, of which the arterial-to-alveolar (a/A) ratio is considered the most accurate [(173-175)]. (See Appendix A – for calculation thereof).

3.4.3 Spirometry

Lung function was measured using a portable Spirovit SP-200 Schiller spirometer (Schiller AG; Altgasse 68; CH-6340 Baar/Switzerland).

Spirometry was conducted according to the 2001 Guidelines for Standardised Spirometry in South Africa, as laid down by the South African Thoracic Society Spirometry Standardisation Working Group [(176)].

Patients were always tested in bed, in a high sitting position. As spirometry is an effort dependant test, a standard instruction was issued by the researcher at the start of each test measurement. Each test was performed at least three times and the best results selected for analysis. All tests were performed by the researcher.

A standard analgesic was administered post-operatively, one to two hours prior to spirometry tests. Lung function tests were not conducted within two hours of the patient having had a nebuliser or physiotherapy treatment.

Lung function tests were performed over 5 time points as follows: Pre-operatively, then at a consistent time of day on the first, third, fifth post-operative day and at the patients' one month post-operative follow up appointment.

Measures were taken of Vital Capacity (VC); Forced Vital Capacity (FVC); Forced Expiratory Volume in one second (FEV_1) and FEV_1 as a percentage of Vital Capacity (FEV_1/VC); Peak expiratory flow rate and inspiratory capacities.

3.4.4 Radiographic Measures

One independent radiologist, blind as to the patients' surgical group, was asked to grade atelectasis and effusion on scales of severity and compare three consecutive X-rays.

Atelectasis and Effusion of left and right lung were graded separately by the radiologist and were categorised and defined as follows:

Atelectasis Grading:	Effusion Grading:
0 = No atelectasis	0 = No effusion
1 = Plate-like atelectasis lower lobe	1 = Blunting of costophrenic angle
2 = Sub-segmental atelectasis lower lobe	2 = Level with diaphragm
3 = Segmental collapse lower lobe	3 = Higher than diaphragm
4 = Complete lower lobe collapse	
5 = Other lobe atelectasis – please comment	

The three consecutive X-Rays compared were those taken at the following times:

1. Pre-operatively.
2. on the first post-operative day following the removal of the pericardial and / or mediastinal underwater seal drains.
3. on the fifth post-operative day.

3.5 Standardising of the extraneous variables

The extraneous variables were standardised as follows:

3.5.1 Anaesthetic Technique

A standard drug protocol of Etomidate and Desflurane was used for induction and maintenance of anaesthesia. Sedation consisted of either Propofol or a Morphine/Cyclizine and Midazolam combination, as per the anaesthesiologists' preference. This potential extraneous variable was recorded and as discussed in the results section, the number of patients receiving each medication was similar in the two groups.

In Group B, those patients in whom cardioplegia was prevented from entering the lungs, the lungs were maintained at a Positive end expiratory pressure (PEEP) of 5mmHg during cardioplegia delivery and the time of suctioning via the pulmonary artery vent. Low volume ventilation (Tidal Volume (Vt) = 200ml; rate: 20/min) was administered during cardioplegia delivery.

3.5.2 Surgical Technique

All cases were performed by a single surgeon, blind to the randomisation protocol.
In both groups, standard techniques of full midline sternotomy were performed. After full heparinisation the heart was cannulated (see Cannulation section below) in preparation for cardiopulmonary bypass. Group B patients had the additional intervention of placement of the pulmonary artery vent.

Venous blood was drained from a two stage atriocaval cannula, via gravity, into the membrane oxygenator, temperature was controlled with a heat exchanger incorporated in the oxygenator, and the blood then returned by the cardiopulmonary bypass machine via a cannula inserted into the ascending aorta.

Systemic temperature was lowered and maintained at 32ºC after commencing cardiopulmonary bypass. The aorta was then cross-clamped and blood cardioplegic solution (300ml/min for 3 minutes) was infused via a separate cannula inserted into the aortic root, at a pressure ranging between 180 -250 mmHg.

In addition, the pericardial cavity was irrigated with saline ice slush during each infusion of cardioplegic solution. Multidose maintenance cardioplegia (100 ml/min for 3 minutes) was administered after each anastomosis made throughout the cross clamp period.

Systemic rewarming was commenced during completion of the last distal anastomosis, before the release of the aortic cross clamp and continued throughout the reperfusion period until normothermia was obtained. Patients were then weaned from cardiopulmonary bypass and any necessity for the use of inotropes was documented. Number and type of grafting was recorded as well as cross clamp and theatre time.

3.5.3 Cannulation

The schematic representation (Fig. 3.1) illustrates all the potential cannulation sites used during cardiopulmonary bypass. Not all cannulae depicted here were utilised. The standard cannulae used in this study are as follows:

1. Aortic Cannula: Research Medical Cannula (Edwards Life Sciences Research Medical Inc. 6864 South 300 West – Midvale, Utah 84047 – USA) 24 Fr. Wire reinforced angle tipped aortic cannula.

2. Atriocaval Cannula: A DLP (Medtronic Inc., Minneapolis, MN555432-5406, USA) two-stage atriocaval cannula inserted though the right atrial appendage, to allow the wider portion to sit in the right atrium and the narrower portion in the inferior vena cava. Secured in position with a purse-string suture. Most patients required size 36-46Fr, selected according to patients' body surface area and expected flow rate. Drainage via this cannula was gravity assisted only.

3. Cardioplegia Antegrade Cannula with protection system: (Jostra - Maquet Cardiopulmonary AG, Hechinger Street 38; D-72145 Hirrlingen, Germany) Sidearm vent cardioplegia cannula – Inserted into the aortic root (9 Fr.), with a Y-attachment to the main-line, to enable venting of the aortic root and coronary vascular bed when cardioplegia solution not being delivered.

4. Pulmonary Artery Cannula (*Group B patients only*): DLP (Medtronic Inc., Minneapolis, MN555432-5406, USA) Pulmonary Artery Cannula (Size 16Fr.). Inserted 3 – 4 cm into the main pulmonary artery secured in position via a purse-string suture. During the period of cardioplegia delivery continuous suction was applied via this vent and the contents were returned to the reservoir of the cardiopulmonary bypass circuit. Note: Suction was just within negative range, preventing preferential suctioning and preventing the wall of the pulmonary artery to collapse against the fenestrations of the vent.

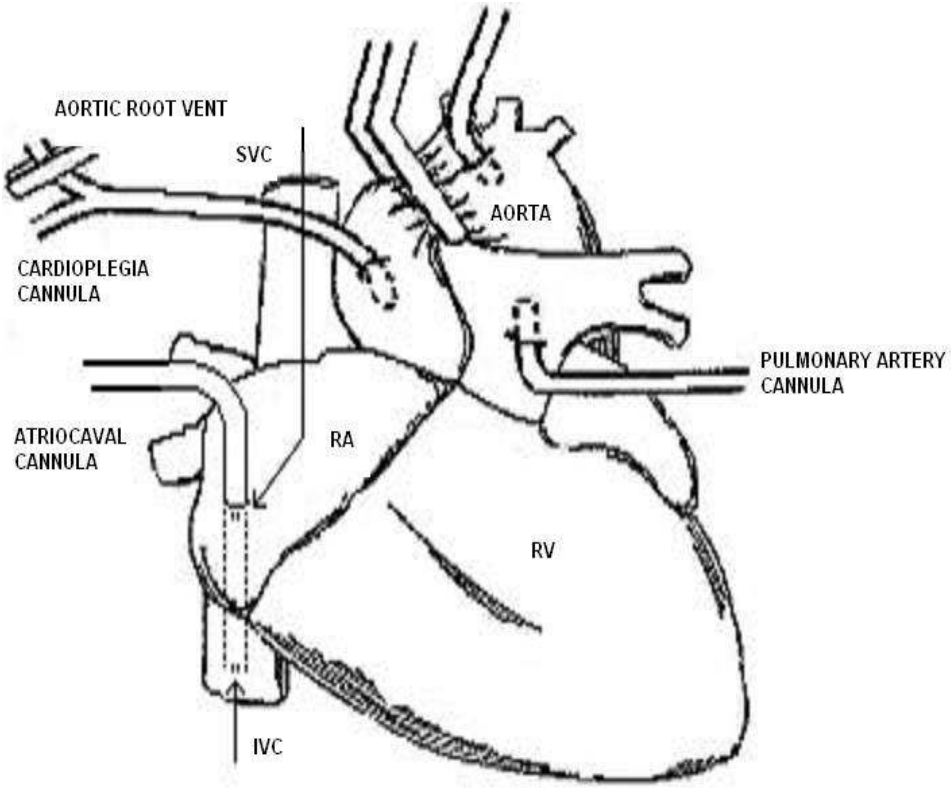


Fig 3.1 Diagram showing cannulae positions during cardiopulmonary bypass

Key: IVC, inferior vena cava; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

3.5.4 CPB Equipment

Conduct of extracorporeal circulation was standard using the COBE Stöckert Roller pump, (München, Germany) with a Hollow fibre Polypropylene Membrane Oxygenator with Avant D903 integrated isolated cardiotomy venous reservoir. Pulsatile flow was instituted in all cases. In each case the optimal flow rate for that patient was maintained.

The arterial filter was standardised in all patients to a Heparin bonded particulate filter.

The level of the bypass reservoir was continually monitored. There were two perfusionists for the study, one of whom monitored the lines at all times to ensure no kinking of the lines occurred at any time.

3.5.5 Cardioplegia Solution

The Medsol (Bodene Pty. Ltd., 6 Gibaud Rd, Korsten, PE, RSA) range of cardioplegia solution was utilised for induction, maintenance and reperfusion. All were combined with blood as per the Buckberg 4:1 Protocol[82,84]. The volume of cardioplegia delivery, as calculated by the volume of flow through the pump, was recorded.

3.5.6 Monitoring of Pressure during CPB

1. Cardioplegia Pressure: The solution was perfused at a rate of 300ml/min. During perfusion, cardioplegia pressure was maintained within the ideally accepted range of 180-250mmHg.

2. Perfusion Pressure: During cardiopulmonary bypass perfusion pressure (Arterial pressure) was maintained within 50-90mmHg.

3. Central Venous Pressure: During cardiopulmonary bypass, CVP was maintained as close to zero as possible.

3.5.7 Analgesia

A standard regime of post-operative analgesia was used, namely a combination analgesic of Ibuprofen 200mg; Paracetamol 250mg; codeine phosphate 10mg, 4-6 hourly in the post-operative period. The protocol prescribed the patient to have analgesia 1-2 hours prior to the spirometry tests being performed post-operatively.

3.5.8 Inotropic Support

Requirement and use of intra-and post-operative inotropes were recorded.

3.5.9 Nebulisation

Standard protocol of medication, the anticholinergic: Ipratropium Bromide was used.*

3.5.10 Physiotherapy

Standard protocol of post-operative care was followed.*

A chart recording the number of physiotherapy sessions required; time taken to return to independent activities and length of hospital stay was kept to compare rate of recovery between the two groups.

* Spirometry tests and blood gases were not taken within two hours of the patient having had a nebuliser or physiotherapy treatment.

3.6 Statistical methodology

Data were captured on an MS Access database and exported into SPSS (SPSS Inc. Chicago, Ill) version 11.5 for analysis. Data were also exported into STATA version 8.0 for GEE analysis.

Fisher's Exact; Chi Square and T-tests were used to compare demographic variables between the two groups. Where the Pearson's Chi-Square assumptions were not violated, these results were reported in preference to Fisher's Exact. However, where >20% of the cells in the cross tabulation had expected counts of <5, Fisher's Exact p-value was reported.

Non-parametric Mann-Whitney tests were used to compare discrete non-normal differences which were measured at one time point between the groups.

Intra and inter-group differences were tested for continuous variables using repeated measures ANOVA. Three hypotheses were tested:

1. The effect of time (was there a significant change in means of both groups over time).
2. The effect of group (was there a significant difference between the groups at all time points).
3. The interaction between time and group (the treatment effect- non parallel profiles of each group over time).

Intra and inter-group differences for discrete variables (e.g. radiology results) were analysed in STATA by ordinal logistical regression. For the spirometry results that categorised patients by diagnosis into one of four groups at each lung testing session, data were analysed using multinominal logistic regression.

All tests were 2-tailed and p-values of ≤ 0.05 defined statistical significance.

CHAPTER 4

Results

Group A

Patients undergoing full cardiopulmonary bypass with cold blood cardioplegic solution allowed to enter the lungs. (Control group n = 71).

Group B

Patients undergoing full cardiopulmonary bypass, with the use of a pulmonary artery vent to limit the cardioplegic solution from entering the lungs. (n = 71).

4.1 Demographics

The quantitative variables were normally distributed (Appendix B) therefore the Parametric T-Test was used.

Patient demographics are shown in Table 4.1 below. There were no significant differences in age, height weight and body mass index (expressed as means) between the two groups, thus the two groups were comparable in baseline demographics.

Table 4.1 T-Test Results of Age; Height; Weight and BMI

	GROUP	N	MEAN	STANDARD DEVIATION ±	STANDARD ERROR	T-VALUE	P-VALUE
Age (years)	A	71	61.58	9.72	1.15	0.144	0.886
	B	71	61.35	8.96	1.06		
Height (m)	A	71	1.73	0.09	0.01	-1.415	0.159
	B	71	1.75	0.09	0.01		
Weight (kg)	A	71	81.94	14.67	1.74	-1.192	0.235
	B	71	84.68	12.56	1.49		
BMI (wt/ht^2)	A	71	27.40	3.75	0.45	-0.564	0.574
	B	71	27.73	3.37	0.40		

4.1.1 Gender

Non-Parametric testing was required to analyse the nominal data for gender comparison between the two groups. As is evident from Table 4.2 below, there were

more males (n=125: 88%) than females (n=17: 12%) in the study, but this distribution was even between the two groups, with Chi-Square Tests showing no difference between the two (Pearson Chi-Square p = 0.438).

Table 4.2 Cross tabulation of gender to group

			GENDER		TOTAL
			F	M	
Group	**A**	Count	7	64	71
		% within group	9.9%	90.1%	100%
	B	Count	10	61	71
		% within group	14.1%	85.9%	100%
Total		Count	17	125	142
		% within group	12.0%	88.0%	100%

Footnote: Pearson Chi-Square value = 0.601; p= 0.438

4.1.2 Race

Race classification, recorded for demographic purposes, showed the majority of patients were Caucasian (n=123: 86.6%) followed by 18 people (12.7%) of Indian descent and one African in Group A (See Table 4.3 below). The Chi-Square Test for this Non-Parametric, Nominal data showed there to be no significant difference in race distribution between groups A and B, with Pearson Chi-Square test showing p= 0.523. This result is representative of the private practice population seen by the surgeon and not a representative sample of the general population sample with cardiovascular disease. However for the purposes of this study, there were no discrepancies in the race ratio between group A and B.

Table 4.3 Cross tabulation of race to group

			Race			Total
			African	Indian	Caucasian	
Group	**A**	Count	1	10	60	71
		Within A	1.4%	14.1%	84.5%	100%
	B	Count	0	8	63	71
		Within B	0.0%	11.3%	88.7%	100%
Total		Count	1	18	123	142
		A and B	0.7%	12.7%	86.6%	100%

Footnote: Pearson Chi-Square value = 0.1.295; p= 0.523.
Note that 33.3% of cells in above table had expected counts <5 thus the assumptions of the chi2 test were violated and the results should be interpreted with caution.

4.2 Baseline Health Status

4.2.1 Angina

On admission to hospital and following randomization into their respective groups, patients' angina status was determined. Due to coincidental factors, despite randomisation procedures, there was a significantly (p=0.032) higher number of patients in group B with unstable angina pre-operatively than group A, as determined by the Pearson Chi-Square Test for Non-Parametric Data. Within Group B, there consisted of a greater number of participants with more severe angina than within Group A.

Table 4.4 Cross tabulation of angina status to group

			Angina			Total
			None	Stable	Unstable	
Group	A	Count	11	49	11	71
		Within A	15.5%	69.0%	15.5%	100%
	B	Count	5	43	23	71
		Within B	7.0%	60.6%	32.4%	100%
Total		Count	16	92	34	142
		A and B	11.3%	64.8%	23.9%	100%

Footnote: Pearson Chi-Square value = 6.877; p= 0.032

4.2.2 Myocardial Infarction History

Despite the slight difference in angina status, there was no significant difference in the incidence of, or time elapsed since myocardial infarction between the two groups. As a result of the exclusion criteria, patients having suffered a recent myocardial infarction (within 2 weeks of surgery) were not invited to participate in the study. As depicted in Table 4.5 below, 76.8% of patients included had no history of myocardial infarction, and there was an identical proportion in the two groups (p=0.843 of Pearson Chi-Square non-parametric Test for Nominal data).

Table 4.5 Cross tabulation of incidence of myocardial infarction to group

			Myocardial Infarction		Total
			No	Yes	
Group	**A**	Count	55	16	71
		Within A	77.5%	22.5%	100.0%
	B	Count	54	17	71
		Within B	76.1%	23.9%	100.0%
Total		Count	109	33	142
		A and B	76.8%	23.2%	100.0%

Footnote: Pearson Chi-Square value = 0.039; p= 0.843

4.2.3 Ejection Fraction

Ejection Fraction, recorded during angiogram procedure or ultrasound test pre-operatively was only available in 134 of the 142 participants. If a left ventriculogram is not performed, or the patient has an abnormal cardiac rhythm during investigation, the ejection fraction is not able to be quantified. The data showed some skewness (Appendix C), being slightly greater than twice its standard error, however the Parametric T-Test was used because it is relatively robust from departures of normality. The Parametric T-Test showed no significant difference in Ejection Fractions between the two groups.

As Table 4.6 below illustrates, the mean Ejection Fraction in group A was 68.2% and 70.2% in Group B. The slight skewness of the data warranted the further tests to determine the equality of variance and equality of the means.

Levene's test for equality of variance and t-test for equality of means (Appendix C) were both not significant between the two groups, thus yielding the T-Test result a valid reflection of the Ejection Fraction data.

Table 4.6 T-test comparing ejection fractions

Group	n	Mean	Standard Deviation	Standard Error Mean
A	67	68.19%	11.49	1.40
B	67	70.22%	10.06	1.23

Footnote: t-Value = 1.086; p= 0.279 * Appendix C

4.2.4 New York Heart Association Functional Classification

Comparison was made between the Class I (patients with cardiac disease but no limitation of physical activity) and II (slight limitation of physical activity). Analysis of this ordinal, categorical data was therefore made using the Non-parametric Chi-Square test.

As evident from Table 4.7 below, there was no significant difference between the groups, with Pearson Chi-Square p=0.263. Of the two groups, 71.8% in total were classified as NYHA I, with a slightly higher number of participants from Group A (n=54) compared to Group B (n=48) with a NYHA Classification of I. This correlates positively to the higher number of patients in Group B with unstable angina.

Table 4.7 Cross tabulation of New York Heart Association functional classification to group

			NYHA Classification		Total
			I	II	
Group	**A**	Count Within A	48 67.6%	23 32.4%	71 100.%
	B	Count Within B	54 76.1%	17 23.9%	71 100.%
Total		Count A and B	102 71.8%	40 28.2%	142 100.%

Footnote: Pearson Chi-Square Value = 1.253 p= 0.263

4.2.5 Angiogram Diagnosis: Number of diseased vessels

Based on angiographic findings, triple vessel disease was the most common diagnosis in both Groups A and B. The medians were reported on and were analysed using the Non-Parametric Mann-Whitney Test, which showed no significant difference (p=0.564) between the two groups in the severity of their coronary artery disease.

Table 4.8 Report of number of diseased coronary arteries by group

Group	n	Median	Minimum	Maximum
A	71	3.00	2	4
B	71	3.00	1	4
Total	142	3.00	1	4

4.2.6 Cardiac Enzymes and Coagulation Studies Pre-Operatively

The Mann-Whitney Non-Parametric Test revealed there to be no significant difference between Group A and B with regards to CPK (p= 0.990); CKMB Isoenzyme (p=0.366); coagulation time (p=0.085); International Normalising Ratio (INR) (p=0.071); PTT (p=0.911) and bleeding time (p=0.520) on the pre-operative routine baseline tests (See Appendix D).

4.2.7 Diabetes

The number of Diabetes sufferers was equal in both groups (Table 4.9 below), with the Pearson Chi-Square showing p=0.559. The majority of patients in the study (n=107: 75.4%) did not have Diabetes Mellitus.

Table 4.9 Cross tabulation of diabetes patients to group

			Diabetes		**Total**
			No	**Yes**	
Group	**A**	Count Within A	55 77.5%	16 22.5%	71 100.%
	B	Count Within B	52 73.2%	19 26.8%	71 100.%
Total		Count A and B	107 75.4%	35 24.6%	142 100.%

Footnote: Pearson Chi-Square value =0.341 p= 0.559

4.2.8 Hypertension

As Table 4.10 below illustrates, there was no significant difference between the groups in the number of patients with hypertension (Pearson Chi-Square p=1.385), although Group B was 10% more prevalent toward suffering from hypertension compared to Group A, with 57.7% of Group B having been diagnosed with hypertension at some stage pre-operatively.

Table 4.10 Cross tabulation of hypertensive patients to group

			Hypertension		Total
			No	Yes	
Group	**A**	Count Within A	37 52.1%	34 47.9%	71 100.%
	B	Count Within B	30 42.3%	41 57.7%	71 100.%
Total		Count A and B	67 47.2%	75 52.8%	142 100.%

Footnote: Pearson Chi-Square value =1.385 p= 0.239

4.3 Risk Factors

4.3.1 Smoking

At the outset of the study, 34.9% of the group had never smoked; 48.6% were ex-smokers and 16.9% current smokers (Table 4.11 below).

The Pearson Chi-Square test comparing Group A and B showed p=0.458 thus there existed no difference in the profiles of smokers between the two groups.

Table 4.11 Cross tabulation of smoking history to group

			Smoking History			Total
			Never	Ex-smoker	Current	
Group	**A**	Count Within A	26 36.6%	31 43.7%	14 19.7%	71 100%
	B	Count Within B	23 32.4%	38 53.5%	10 14.1%	71 100%
Total		Count A and B	49 34.5%	69 48.6%	24 16.9%	142 100%

Footnote: Pearson Chi-Square value = 1.560; p= 0.458

To ascertain whether baseline differences between Group A and B existed with regard to the number of years smoked and the numbers of cigarettes per day, the Medians were calculated and the Non- Parametric Mann-Whitney U Test applied (Appendix E). The median of the number of years patients had been smoking prior to undergoing surgery was 18 years for patients in Group A and 20 years for Group B. The median

of the number of cigarettes per day were 20 per day for Group A and 19 for Group B. The results therefore yielded very similar findings between the groups, with no difference being found in the number of cigarettes smoked per day (p=0.368), nor the duration of smoking prior to admission (p=0.461) (Appendix E).

4.3.2 Allergies

As illustrated in Table 1.10 below, there were similar proportions between group A and B with regard to the number of allergy sufferers and consequently no significant difference with Pearson Chi-Square p=0.688.The majority of patients (77.5%) had no known allergy.

Table 4.12 Cross tabulation of incidence of allergy sufferers to group

			Allergy		Total
			No	Yes	
Group	A	Count	54	17	71
		Within A	76.1%	23.9%	100.0%
	B	Count	56	15	71
		Within B	78.9%	21.1%	100.0%
Total		Count	110	32	142
		A and B	77.5%	22.5%	100.0%

Footnote: Pearson Chi-Square value = 0.161; p=0.688

4.4 Patients Excluded from the Study

A total of 403 patients were screened to assess their suitability to participate in the study. Pre-operatively, 228 patients were immediately excluded (see Appendix F.1 for details).

Of the patients accepted onto the study, 33 fell out or were excluded during the course of the study (Appendix F.2). Randomisation was not affected and the study was continued until the complete data set on 142 patients was obtained.

4.5 Intra-operative Data Results

4.5.1 Sedation

Sedation consisted of either Propofol or a Cyclizine/Morphine and Midazolam combination, as per the anaesthesiologists' preference. This potential extraneous variable was therefore recorded and as evident from Table 4.13 below, the number of patients receiving each medication was similar in the two groups. There was therefore no significant difference between the groups with regard the sedation they received.

Table 4.13 Cross tabulation of sedation type to group

			Sedation		Total
			C+D*	Propofol	
Group	A	Count	12	59	71
		% within group	16.9%	83.1%	100.0%
	B	Count	17	54	71
		% within group	23.9%	76.1%	100.0%
Total		Count	29	113	142
		% within group	20.4%	79.6%	100.0%

Footnote: Pearson Chi-Square value = 1.083; p=0.298
*C+D = Cyclimorph and Dormicum – (Morphine and Midazolam Combination)

4.5.2 Number of Coronary Artery Grafts

The median was preferred to calculate the number of grafts performed as the data is discrete; therefore the non-parametric Mann-Whitney U Test was used. As evident in Table 4.14 below, the distribution was very similar in both groups, with p=0.822.

Table 4.14 Report of number of coronary artery grafts performed by group

Group	N	Median	Min.	Max.	Mean rank	Sum of ranks
A	71	3.00	2	4	72.20	5126.00
B	71	3.00	1	4	70.80	5027.00
Total	142	3.00	1	4		

Footnote: Mann-Whitney U value = 2471.000 p=0.822

4.5.3 Donor Grafts

To ascertain the source of the donor and to compare them between groups A and B, a Cross Tabulation 2x2 was made, using the non-parametric Fisher's Exact Test. From the summarised table below, it is evident that there was no significant difference

between Group A and B with regard to the donor grafts taken, and the number of patients was very similar in both groups. It is also apparent the graft most commonly utilised was the Left Internal Mammary Artery (LIMA) 85.9%, followed by the Right Saphenous Vein Graft, 62%. In the Table 4.15 below, "Long" indicates that the incision went beyond the knee joint, and "Short" refers to either the lower or upper leg alone. Note that total % within study totals to 196.4% as most subjects had more than one donor graft site.

Table 4.15 Comparison of donor graft sites

Donor Graft Site	Total % within study	Total n Within study	Within Group A (n)	Within Group B (n)	Fisher's Exact Test Sig.(2-sided)
LIMA	85.9%	122	58	64	0.227
RSVG (l)	62.0%	88	43	45	0.863
RSVG (s)	22.5%	32	16	16	1.00
LSVG (l)	12.0%	17	8	9	1.00
LSVG (s)	7.7%	11	7	4	0.532
RIMA	4.2%	6	5	1	0.209
RADIAL	2.1%	3	2	1	1.00

KEY: IMA: Internal Mammary Artery: L=left; R=Right
SVG: Saphenous Vein Graft: (s) =Short; (l) =Long
RADIAL: Radial Artery

4.5.4 Total Extracorporeal Pump Time

Skewness of data was recorded as 0.712 compared with the Standard error of skewness 0.203, confirmed the data collected on the duration of extracorporeal circulatory (cardiopulmonary bypass) pump time were slightly skewed.

Calculation of the mean and median were however very similar, with the mean length of time the patient was on extracorporeal circulation being 53.32 minutes and the median at 52 minutes (see Table 4.16 below). Nevertheless, for accuracy, the non-parametric Mann-Whitney Test was performed. The result yielded a non significant difference of p=0.979.

Table 4.16 Cross tabulation of extracorporeal circulation time (min.) to group

Group	n	Median	Min.	Max.	Mean Rank	Sum of Ranks
A	71	52.00	27	94	71.41	5070
B	71	52.00	28	101	71.59	5083
Total	142	52.00	27	101		

Footnote: Mann-Whitney U value= 2514.00; p=0.979

4.5.5 Aortic Clamp Time

As with duration that the patient was on the cardiopulmonary bypass circuit, the data recorded for aortic cross clamp time were slightly skewed (0.752), but the Mann Whitney non-parametric test showed there to be no significant difference p=0.766 between the two groups as Table 4.17 below illustrates. Mean aortic cross clamp time was 35.15 minutes. The median of the cross clamp times was 35 minutes in Group A and 34 minutes in Group B.

Table 4.17 Cross tabulation of aortic cross clamp time (min.) to group

Group	N	Median	Min.	Max.	Mean Rank	Sum of Ranks
A	71	35.00	17	63	72.53	5149.50
B	71	34.00	16	76	70.47	5003.50
Total	142	35.00	16	76		

Footnote: Mann-Whitney U value=2447.500; p=0.766

4.5.6 Haemoconcentration

Haemoconcentration, during cardiopulmonary bypass was used in 76.1% of patients. As the results were in yes/no format, the Chi-Square non-parametric Test was used. The Pearson Chi-Square Test showed the difference to be just within significance, with p=0.049 (Table 4.18 below). Group A contained a higher percentage (83.1%) of patients who had haemoconcentration than group B (69%).

Table 4.18 Cross tabulation of haemoconcentration usage to group

			Haemoconcentration		Total
			None	Yes	
Group	**A**	Count	12	59	71
		Within A	16.9%	83.1%	100.0%
	B	Count	22	49	71
		Within B	31.0%	69.0%	100.0%
Total		Count	34	108	142
		A and B	23.9%	76.1%	100.0%

Footnote: Pearson Chi-Square value = 3.867; p=0.049

4.5.7 Volume of Intravascular Cardioplegia

The data were normally distributed thus the Parametric T-Test was employed. The minimum volume of cardioplegia delivered was 1000ml and the maximum 3200ml. As Table 4.19 below illustrates, the mean volume of cardioplegia delivery between both groups was 2077.99 ml. The difference between the sample mean quantity of cardioplegia delivery in Group A and B was 62.18ml with a 95% confidence interval of the difference from -101.055ml to 225.421 ml; the T-test statistic was 0.753 with 140 degrees of freedom and an associated p value of 0.453. There was therefore no significant difference in the volume of cardioplegia delivered to patients in either Group A or B.

Table 4.19 t-test group statistics for volume of intravascular cardioplegia used

Group	n	Mean (ml.)	Std. Deviation	Std. Error Mean
A	71	2109.08	471.411	55.946
B	71	2046.90	511.657	60.723
Total	142	2077.99		

Footnote: t =0.753; p=0.453

4.5.8 Intra-operative Blood Loss

The degree of blood loss (estimated by surgeon and anaesthesiologist) recorded by the anaesthesiologist, was not significant between the two groups, with p=0.171 calculated using the Non-Parametric Mann-Whitney U Test.

Table 4.20 Report of quantity of blood loss (ml) by group

Group	n	Median	Min.	Max.	Mean Rank	Sum of Ranks
A	69	250ml	0	1000ml	74.54	5143.50
B	70	250ml	0	1000ml	65.52	4586.50
Total	139	250ml	0	1000ml		

Footnote: Mann-Whitney U value=2101.500; p=0.171

4.5.9 Lowest Systemic Temperature

The data collected for the lowest systemic temperature recorded in theatre were slightly skewed. The Mean and Median were very similar at 32.057ºC and 32.1ºC respectively, but the distribution showed a slightly lower temperature in Group B patients when compared with Group A (Table 4.21). With the Non-Parametric Mann Whitney Test however, the Mann-Whitney U value = 2169.5 and p=0.152 yielding this difference to be non significant.

Table 4.21 Cross tabulation of lowest systemic temperature (°C) to group

Group	n	Median	Min.	Max.	Mean Rank	Sum of Ranks
A	71	32.1	28.1	34.5	76.44	5427.50
B	71	32.0	28.1	34.5	66.56	4725.50
Total	142	32.1	28.1	34.5		

Footnote: Mann-Whitney U value=2169.500; p=0.152

4.6 Total Operative Time

The data relating to duration of surgery were not skewed, displaying a normal distribution; therefore the data were analysed using the Parametric T-Test. The mean skin to skin operative time of both groups was 174.03 minutes (Table 4.22). There was no significant difference in total operative time between groups A and B. T-Test confirmed there was no difference in operative time between the groups.

Table 4.22 t-test group statistics for total operation time

Group	n	Mean (min.)	Std. Deviation	Std. Mean Error
A	71	172.52	30.34	3.60
B	71	175.54	27.92	3.31
Total	142	174.03		

Footnote: t = 0.616; p=0.539

4.7 Total Ventilation Time

The data recording the duration of ventilation were very skewed, with the Median in Group B of 462 minutes being higher than Group A by 32 minutes. However as evident in Table 4.23 below, the Median of each group falls within the inter-quartile range of the other. The Non-Parametric Mann Whitney Test confirms this difference as not being significant, with p=0.190.

Table 4.23 Report of total ventilation time (min.) by group

Group	n	Median	Min.	Max.	Mean Rank	Sum of Ranks
A	71	430.00	195	1086	66.97	4755.00
B	71	462.00	260	1180	76.03	5398.00
Total	142	446.50	195	1180		

Footnote: Mann-Whitney U value=2199.000; p=0.190

4.8 Time on T-Piece

The data recording the duration patients were left breathing spontaneously via a T-piece prior to the endotracheal tube being removed were skewed. The results however were similar (Table 4.24 below) between the groups and the median was almost the same between the two groups. Group A patients averaged 40 minutes on T-piece compared with 45 minutes in Group B, before being extubated. Mann Whitney Test however yielded p =0.080 thus showing this difference to be of no significance.

Table 4.24 Report of t-piece duration (min.) by group

Group	N	Median	Min.	Max.	Mean Rank	Sum of Ranks
A	71	40.00	5	200	65.50	4650.50
B	71	45.00	5	230	77.50	5502.50
Total	142	45.00	5	230		

Footnote: Mann-Whitney U value=2094.500; p=0.080

4.9 Time in Intensive Care Unit

The duration patients remained in the ICU was recorded in days. This was almost constantly a number of 2 days in both groups with only one or two outliers. The minimum length of stay in the cardiac ICU was 2 days (48 hours after exit from surgery) and Mann-Whitney U Test Table 4.25 below confirmed any differences between the groups to be not significant with p=0.364.

Table 4.25 Report of duration of ICU stay (days) by group

Group	n	Median	Min.	Max.	Mean Rank	Sum of Ranks
A	71	2.00	2	3	72.95	5179.50
B	71	2.00	2	4	70.05	4973.50
Total	142	2.00	2	4		

Footnote: Mann-Whitney U value=2417.500; p=0.364

4.10 Transfusion Requirement

Exactly half the participants in the study required a blood transfusion within the first 24 hours of surgery. Of these, 53.5% were from group A and 46.5% from group B (Table 4.26 below). There was therefore no significant difference between the two groups in terms of the number of patients undergoing transfusion, with Pearson Chi-Square value = 0.704 and p=0.401.

Table 4.26 Cross tabulation of transfusion requirement to group

			TRANSFUSION		TOTAL
			None	Yes	
Group	**A**	Count	38	33	71
		Within A	53.5%	46.5%	100.0%
	B	Count	33	38	71
		Within B	46.5%	53.5%	100.0%
Total		Count	71	71	142
		A and B	50.0%	50.0%	100.0%

Footnote: Pearson Chi-Square value =0.704; p=0.401

The requirement for quantity of blood transfusion was similar in both groups (see Table 4.27 below) with the median of the quantity of blood products required being 500ml.

As the data were slightly skewed, the non-parametric Mann-Whitney U Test was favoured. The results yielded there to be no difference between Group A and B in terms of the quantity of blood utilized, with p=0.824 (Table 4.27).

Table 4.27 Report of quantity of blood transfusion received (ml) by group

Group	n	Median	Min.	Max.	Mean Rank	Sum of Ranks
A	38	500ml	100ml	1200ml	35.55	1351.00
B	33	500ml	200ml	1100ml	36.52	1205.00
Total	71	500ml	100ml	1200ml		

Footnote: Mann-Whitney U value=610.000; p=0.824

4.11 Potential Confounders

4.11.1 Referring Cardiologist

There were a total of 10 cardiologists who referred the 142 patients for surgery. The Pearson-Chi-Square non-parametric test for this nominal data revealed that there was no significant (p= 0.139) difference between group A and B with regard the referral source of patients (see Appendix G).

4.11.2 Fluid Balance

The Figure 4.1 below depicts the trend of fluid balance which was recorded on an hourly basis by nursing staff, calculated per 24 hour period of the patient's Total Intake less Output. As Table 4.28 below illustrates, the change over time within each group was significant ($p<0.001$) but there were no differences between the two groups ($p=0.108$). The figure below also illustrates that within the first 48 hours, patients' intake of fluid is greater than their output, until the second post-operative day. Also, there was no time by group interaction ($p=0.309$). Thus the change over time was not dependent on group status and the profiles were parallel (Fig.4.1 below).

Table 4.28 Tests of between and within subject effects for fluid balance

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.308	<0.001
Time x Group	Wilks' Lambda	0.974	0.309
Group	F	2.624	0.108

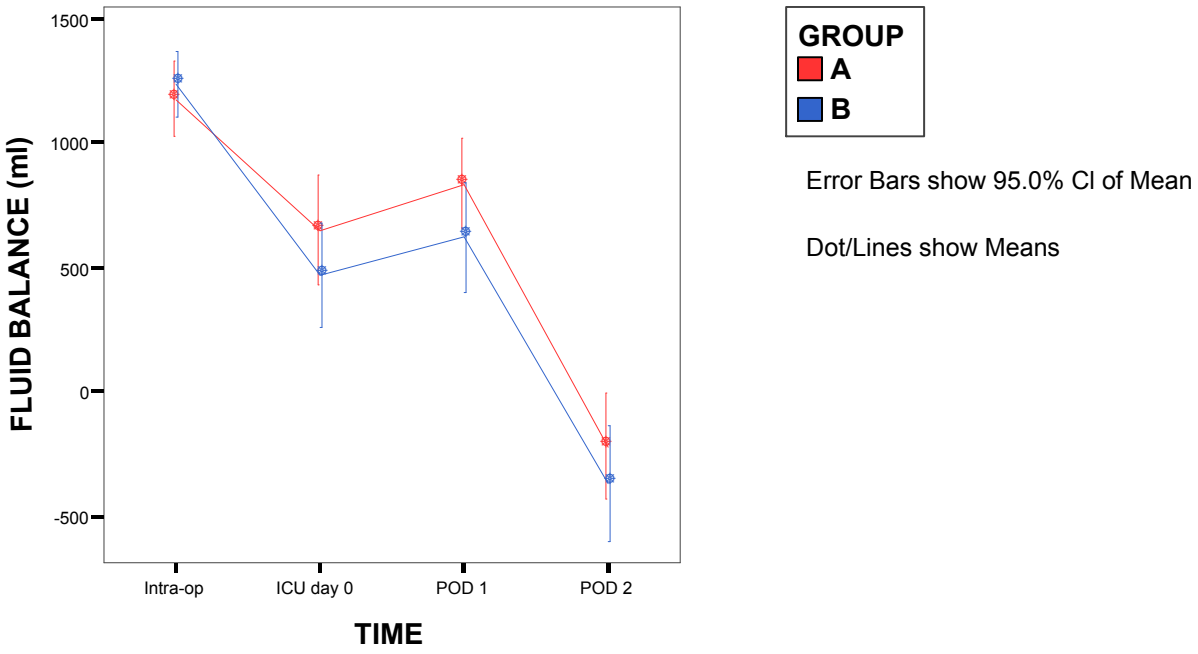


Fig.4.1 Profile plot of daily fluid balance over time by group

4.11.3 Running Fluid Balance

The Figure 4.2 below depicts the trend of running fluid balance which was recorded on an hourly basis by nursing staff, calculated as a running total of patients' total input less total output, recorded as such per 24 hour period. As Table 4.29 below illustrates, the change over time within each group was significant ($p<0.001$) but there were no differences between the two groups ($p=0.225$). The figure below also illustrates that within the first 48 hours, patients' intake of fluid is greater than their output, until the second post-operative day. There was no time by group interaction ($p=0.237$), thus the change over time was not dependent on Group status and the profiles were parallel (Fig. 4.2)

Table 4.29 Tests of between and within subject effects for running fluid balance

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.426	<0.001
Time x Group	Wilks' Lambda	0.970	0.237
Group	F	1.483	0.225

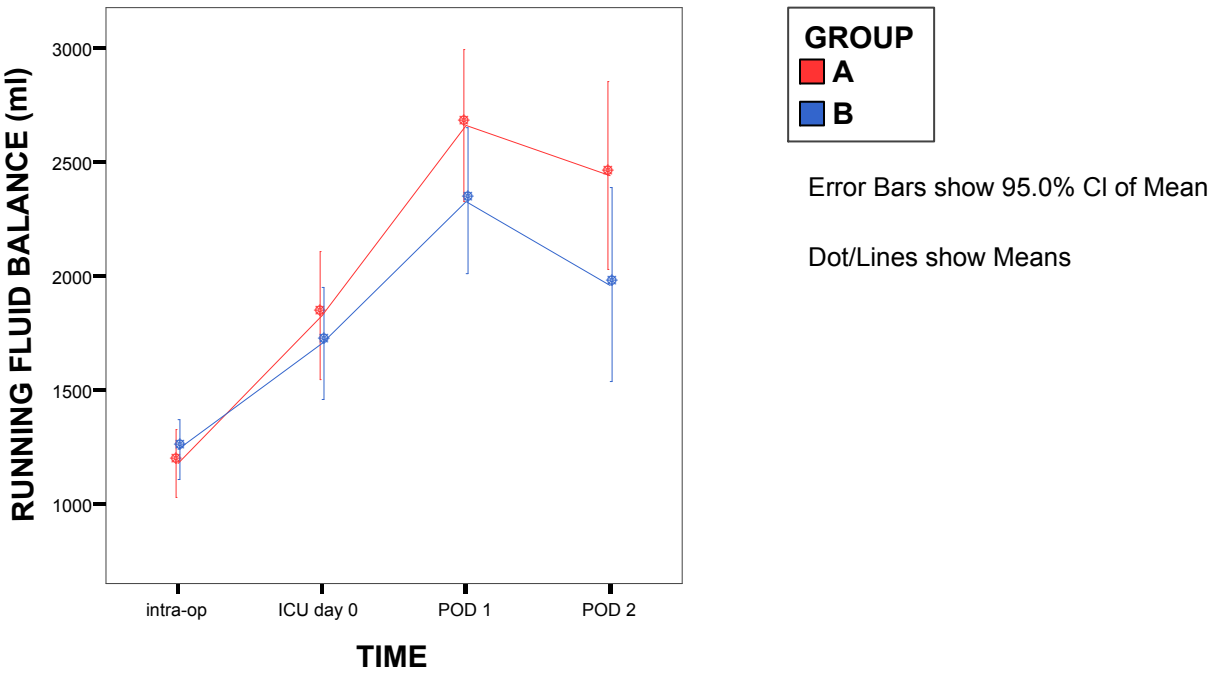


Fig.4.2 Profile plot of running fluid balance over time by group

4.11.4 Heart Rhythm

The Figure 4.3 below illustrates the percentage of patients with an abnormal cardiac rhythm pre- and post-operatively over time. The abnormal rhythm was in the majority of affected patients, atrial fibrillation. Within this classification of abnormal heart rhythm, one patient had a paced (pacemaker generated) rhythm and three had a sinus tachycardia.

Although Group A appeared to have a more abnormal rhythm, both groups followed the same trends of more patients acquiring an abnormal rhythm within the first two days post-operatively before returning toward baseline by the fifth post-operative day.

Cross Sectional analyses were made at each time point and Pearson Chi-Square test revealed that there was no significant difference between Group A and B at any stage with regard to heart rhythm abnormalities (See Appendix H).

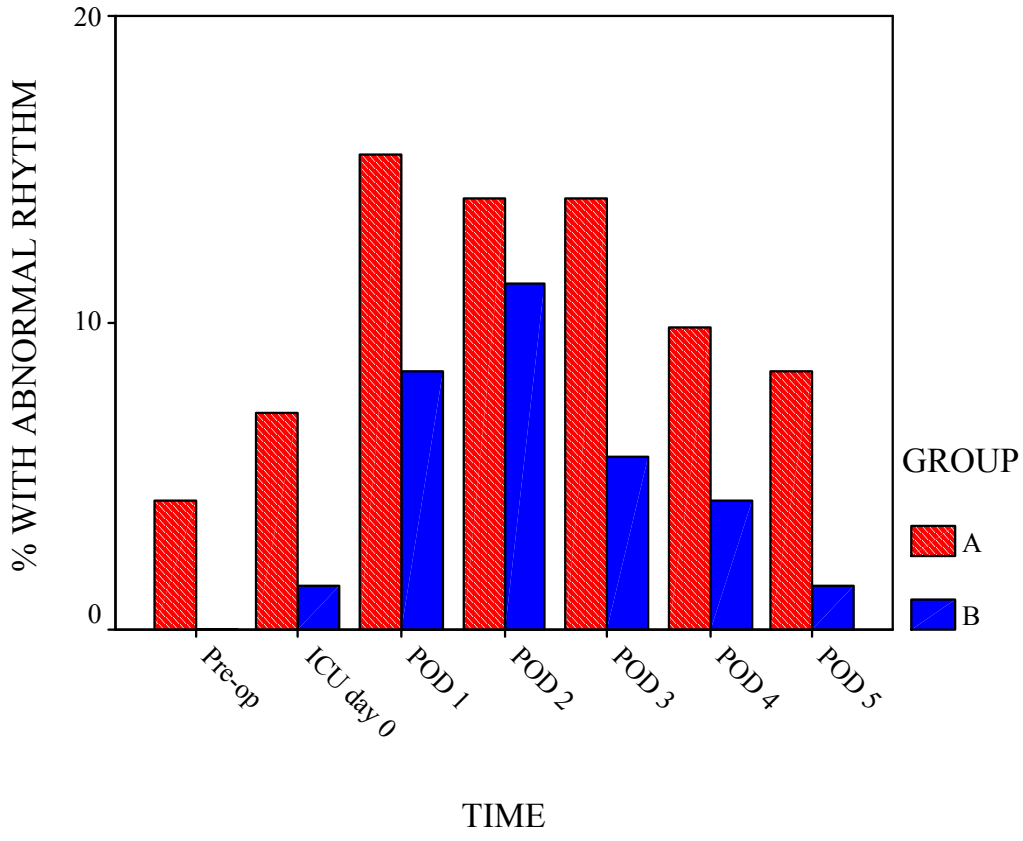


Fig.4.3 Bar graph showing percentage of patients with abnormal heart rhythm over time by group

4.12 Blood Gas Results

Pulmonary gas exchange was measured by Arterial Blood Gas Tests that were taken over 8 time points, as follows:

1. Pre-operatively while patient was breathing room air (FiO_2 .21).
2. Intra-operatively (during anastosmosis of the LIMA)
3. One hour following arrival to the intensive Care Unit
4. On T-Piece, just prior to extubation
5. One hour following extubation
6. The first post-operative day following 15 minutes of room air breathing
7. The second post-operative day following 15 minutes of room air breathing
8. The fifth post-operative day on room air.

Due to the necessity of analysing these repeated measures, the Parametric Test for Repeated Measures ANOVA was utilised.

Initially an intra-group comparison was made to ascertain whether any baseline differences existed between the groups. The results for arterial Oxygen (PaO_2); Carbon Dioxide ($PaCO_2$) and Oxygen Saturation (SaO_2) and shunt fraction estimation yielded similar findings, as discussed below.

4.12.1 paO_2– Arterial Oxygen

Looking at Table 4.30 below, it is evident that the intra-group comparison showed there to be a highly significant change in both Groups A and B over time ($p<0.001$). The interaction of time by group however showed no significance ($p=0.592$), thus indicating no intervention effect. Examination at each time point also revealed no significant difference between the two groups with $p=0.979$ (See Appendix I).

The trend by profile plots is identical in both the group receiving the cardioplegia and that where it was withheld from entering the lung parenchyma.

The high significance of time in each group, yet the non-interaction between the two groups shows that the power is sufficient and the sample size was sufficient to reach these conclusions.

From the profile plots of the estimated marginal means of PaO_2, it is evident that the results from both groups are so similar; the graphs are virtually superimposed at each time point.

Time points 2-5 inclusive were measurements taken whilst the patient was receiving Oxygen. Of interest however neither group has, by post-operative Day 5 (time point 8), reached their baseline levels of arterial Oxygen.

Table 4.30 Tests of between and within subject effects for paO_2

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.031	<0.001
Time x Group	Wilks' Lambda	0.960	0.592
Group	F	0.001	0.979

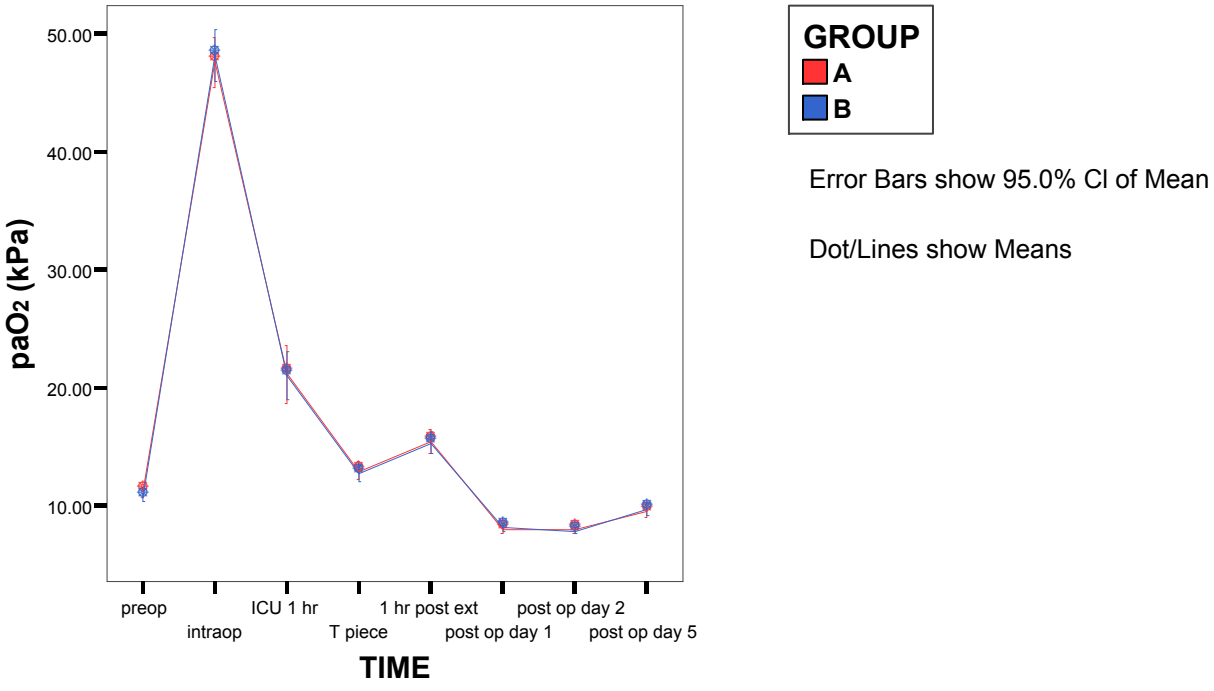


Fig. 4.4 Profile plots of arterial oxygen (paO_2) over time by group

4.12.2 $paCO_2$ – Arterial Carbon Dioxide

Table 4.31 below illustrates that the intra-group comparison showed there to be a highly significant change in both Groups A and B over time ($p<0.001$).

The interaction of time by group however showed no significance ($p=0.702$), thus indicating no effect of the intervention. Examination at each time point also revealed no significant difference between the two groups.

Table 4.31 Tests of between and within subject effects for $paCO_2$

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.226	<0.001
Time x Group	Wilks' Lambda	0.966	0.702
Group	F	0.051	0.821

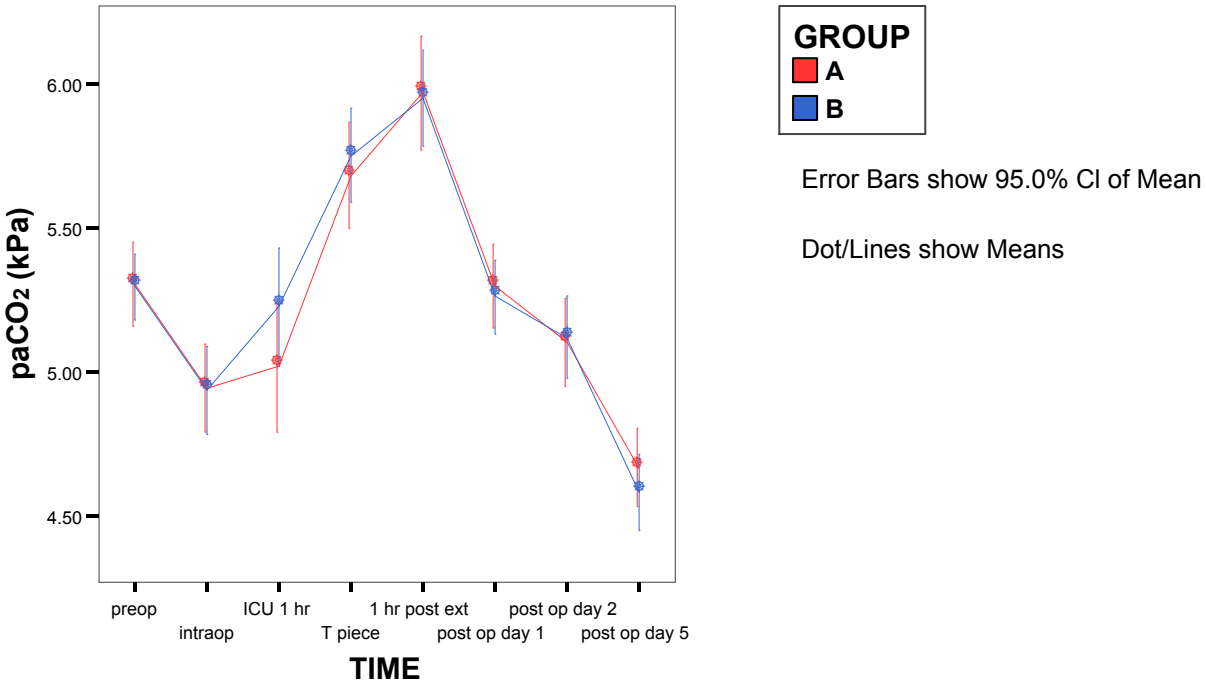


Fig.4.5 Profile plots of arterial carbon dioxide ($paCO_2$) over time by group

As evident from the profile plots in Fig.4.5 above, the highest level of $PaCO_2$ is one hour following removal of the endotracheal tube. This is identical in both groups. Despite the slight visible difference in CO_2 levels between groups A and B at the time points between one hour post-op (ICU 1hr) and on T-piece, this difference was not significant with $p=0.821$.

4.12.3 Estimation of Intrapulmonary Shunting (Q_S/Q_T)

Calculation of and results following statistical analysis of the Shunt Fraction estimation shows a highly significant change ($p<0.001$) over time in Groups A and B. There is however no significant difference in the interaction of time by group, with Wilks' Lambda test showing $p= 0.215$, thus indicating no intervention effect.(Table 4.32 below) Examination at each time point revealed no significant difference between the two groups with $p=0.649$.

It is evident from Fig.4.6 below that following the initial drop from normal preoperative (Time 1) and ventilated (Time 2) levels, a/A ratio takes several days to return to normal (normal = 0.60), but does not reach baseline values after 5 days.

On the Profile Plot Graph (see Fig. 4.6 below), there appears to be a large difference in the groups between time points 3 and 4. For this reason, a Repeated measures analysis was performed between the time points 3 and 4 (Appendix I.2), but there was no significant difference between the groups (p=.292).

Table 4.32 Tests of between and within subject effects for shunt fraction

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.078	<0.001
Time x Group	Wilks' Lambda	0.932	0.215
Group	F	0.208	0.649

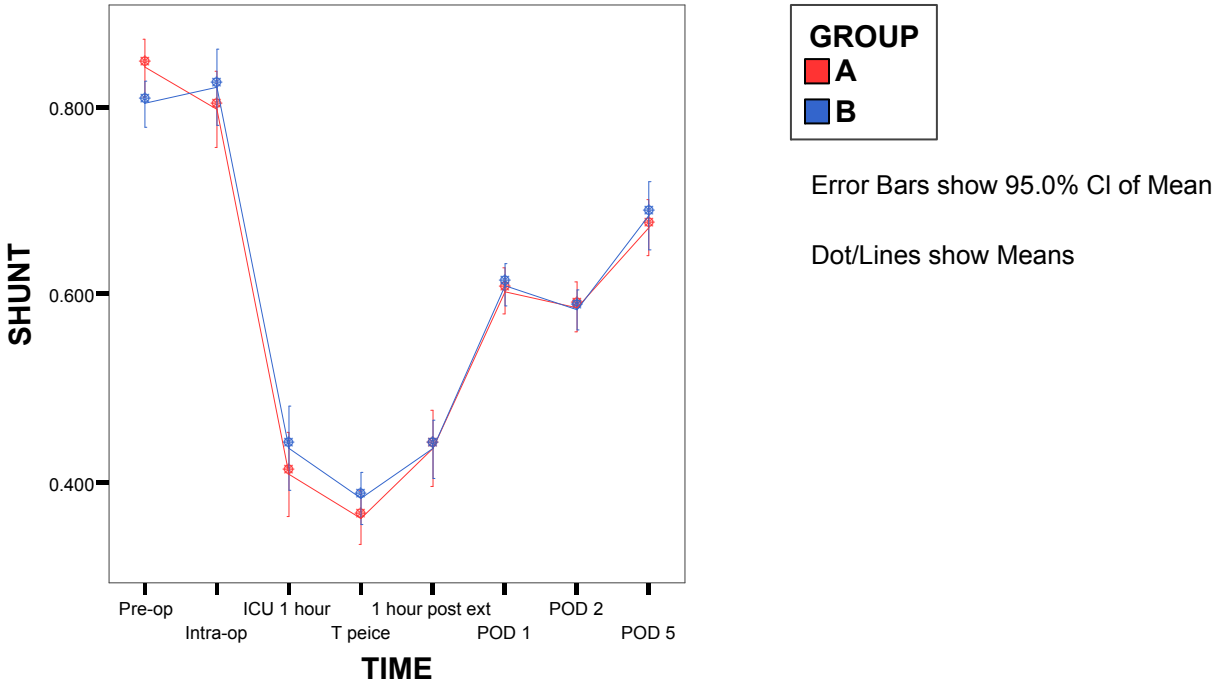


Fig.4.6 Profile plot of shunt fraction estimation over time by group

4.12.4 Oxygen Saturation

As Table 4.33 below illustrates, the intra-group comparison showed there to be a highly significant change in both Groups A and B over time ($p<0.001$).

The interaction of time by group however showed no significance ($p=0.939$), thus showing no effect to Oxygen Saturation by keeping the cardioplegia from entering the lungs. Examination at each time point also revealed no significant difference between the two groups ($p=0.776$).

The trend by profile plots (Fig.4.7) is again virtually identical in both groups.
The high significance of time in each group, yet the non-interaction between the two groups again shows that the power is sufficient and the sample size was sufficient to reach these conclusions.

Table 4.33 Tests of between and within subject effects for oxygen saturation

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.147	<0.001
Time x Group	Wilks' Lambda	0.983	0.939
Group	F	0.081	0.776

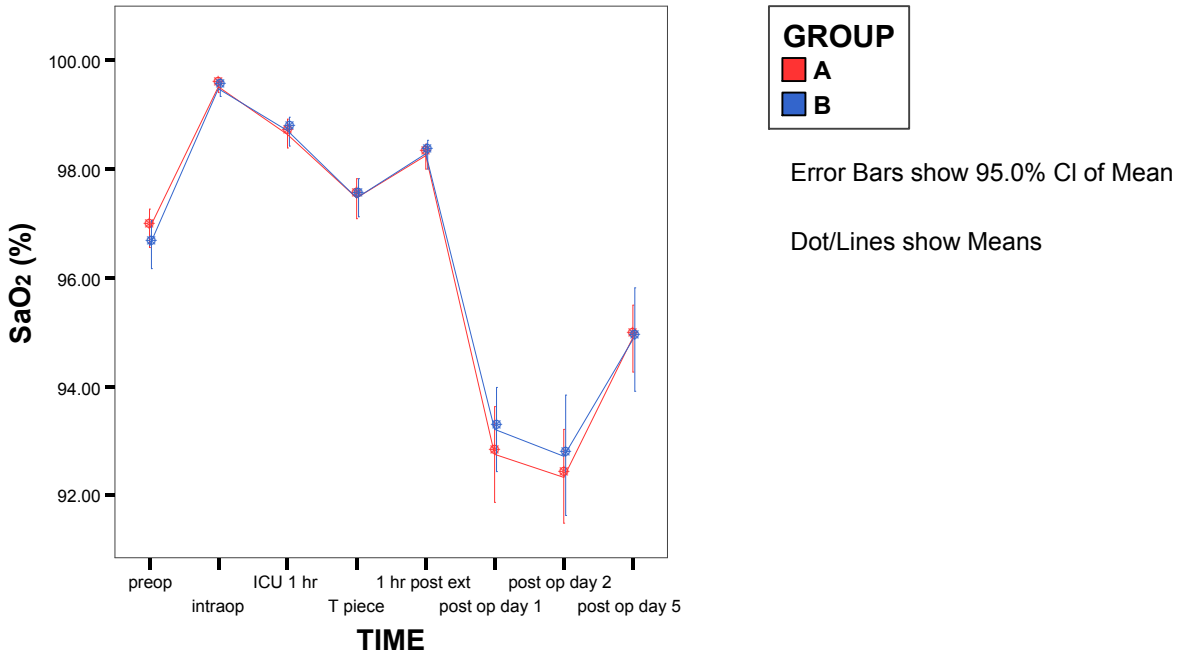


Fig.4.7 Profile plots of oxygen saturation (SaO_2) over time by group

4.12.5 Fraction of Inspired Oxygen

A potential criticism to the above findings may have been that the Oxygen requirement for a certain group may have been greater in order to yield the same Oxygen Saturations or Arterial Oxygen values. For this reason, a record was made of the Fraction of Inspired Oxygen for each participant at each measurement point that was not standardised to the patient breathing room air. This was intra-operatively until one hour following extubation (4 time points).

There was a significant change over time, with patients Oxygen requirements all being reduced ($p<0.001$). There was however no interaction ($p=0.694$) between the two groups, but borderline significance ($p=0.055$) when comparing between subjects effects, with Group A requiring marginally more Oxygen than Group B throughout the ventilated and immediate post-operative period (Table 4.34 below)

Table 4.34 Tests of between and within subject effects for fraction of inspired oxygen

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.190	<0.001
Time x Group	Wilks' Lambda	0.990	0.694
Group	F	3.748	0.055

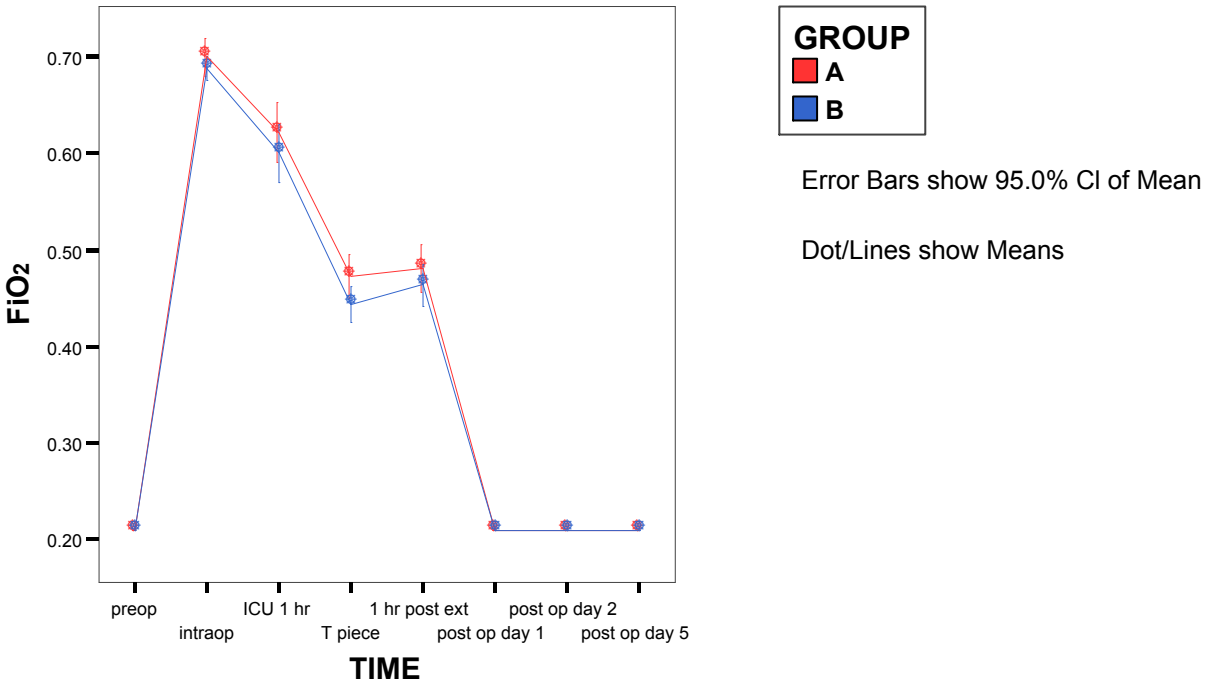


Fig.4.8 Profile plots of Fio_2 requirement over time by group

The above graph shows the weaning from Oxygen as is standard following routine bypass graft surgery.

4.13 Other Blood Results

4.13.1 Haemoglobin

As evident in Table 4.35 below, Haemoglobin (Hb) results altered significantly over time ($p<0.001$). There was however no significant difference between the subjects ($p= 0.688$) and between the two groups over time ($p= 0.708$).

Table 4.35 Tests of between and within subject effects for haemoglobin results over time

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.085	<0.001
Time x Group	Wilks' Lambda	0.966	0.708
Group	F	0.162	0.688

Fig. 4.9 below illustrates both groups show an immediate decrease in Hb, as a result of the intra-operative blood loss and effect of the extracorporeal circuit. The rate at which these levels normalize appear slightly different between the two groups at different times, although these differences were not significant ($p=0.688$). Of note, although the final Day 5 results are increasing to an acceptable post-operative level, they are still below the "normal range" (11.5 -15 g/dl for women and 13.0 – 18.0g/dl for men), and remain well below the baseline levels recorded prior to surgery.

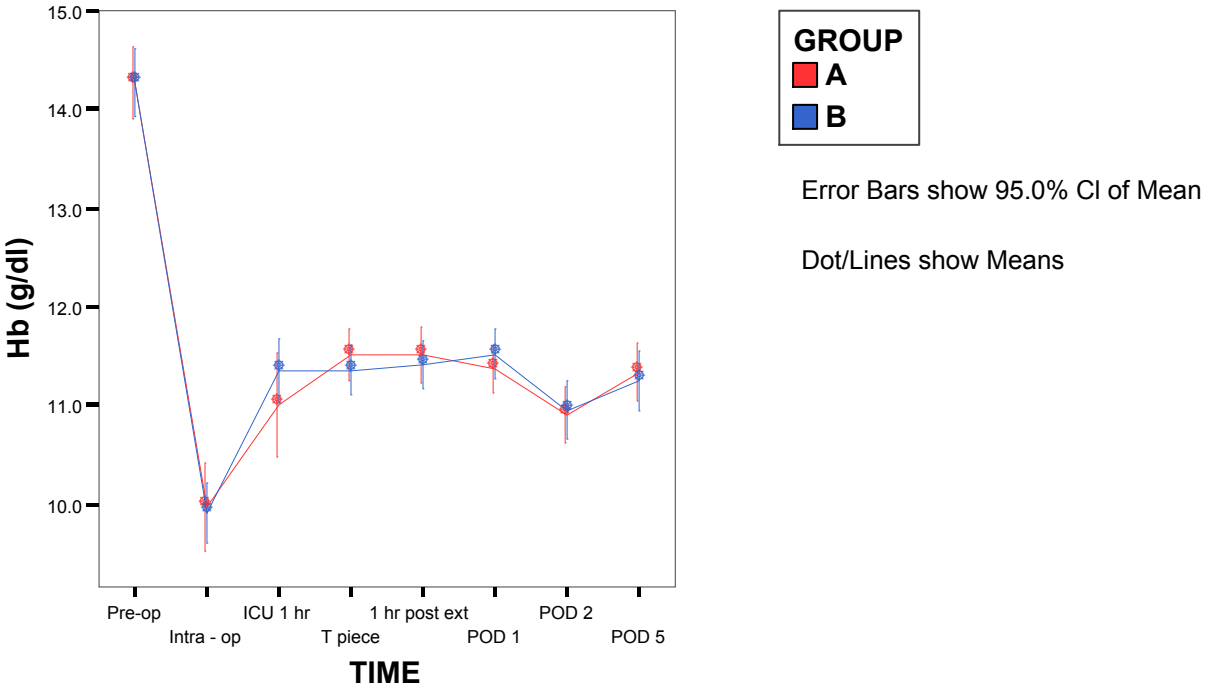


Fig.4.9 Profile plots of Haemoglobin over time by group

4.13.2 Haematocrit (Hct)

As evident in Table 4.36 below, Haematocrit (Hct) results altered significantly over time ($p<0.001$). There was also a significant difference of $p=0.033$ in the time by group interaction.

The Profile Plots in Fig. 4.10 below however show a trend for patients Haematocrit to drop at a faster rate in Group B than Group A, with Group A showing a faster rate of increase in the early stages post-operatively. On Post-operative Day 1 however the Haematocrit levels in Group A dropped whilst Group B increased. By the fifth day post-operatively, both groups were at a similar level. There was therefore no definite trend and the result of a significant difference was merely due to the interaction at two time points where the levels of Haematocrit within the groups were moving in opposite directions.

Table 4.36 Tests of between and within subject effects for Haematocrit results over time

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.136	<0.001
Time x Group	Wilks' Lambda	0.894	0.033
Group	F	0.183	0.669

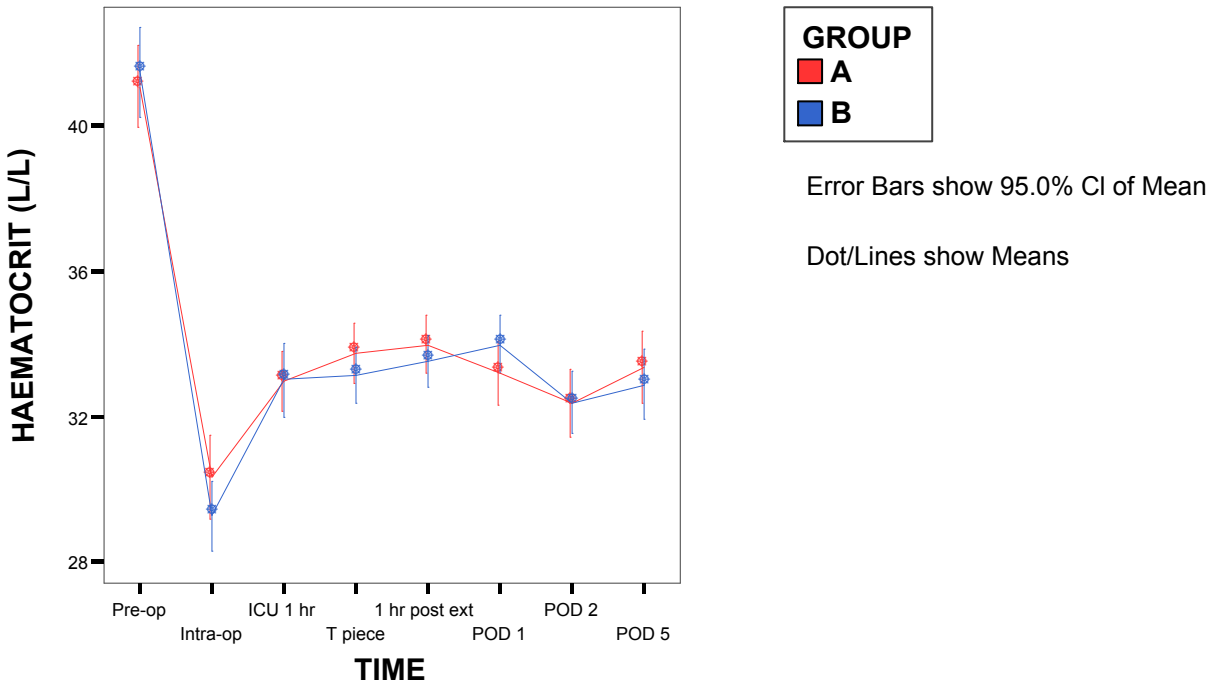


Fig.4.10 Profile plots of Haematocrit over time by group

4.13.3 Bicarbonate ($Hco3^-$); Sodium (Na^+); Potassium (K^+); Glucose and Chloride (Cl^-)

These blood results changed significantly over time, with p <0.001 in each test, however in analysis of each, there was no significant difference between Groups A and B and no significant difference between the two groups over time**.**

Bicarbonate

Table 4.37 Tests of between and within subject effects for levels of Bicarbonate (mmol/l) over time

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.416	<0.001
Time x Group	Wilks' Lambda	0.935	0.236
Group	F	0.165	0.685

Sodium (Na^+)

Table 4.38 Tests of between and within subject effects for sodium (mmol/l) over time

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.174	<0.001
Time x Group	Wilks' Lambda	0.978	0.880
Group	F	0.387	0.535

Potassium (K^+)

Table 4.39 Tests of between and within subject effects for Potassium results (mmol/l) over time

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.241	<0.001
Time x Group	Wilks' Lambda	0.973	0.812
Group	F	3.813	0.053

Glucose

Table 4.40 Tests of between and within subject effects for Glucose results (mmol/l) over time

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.262	<0.001
Time x Group	Wilks' Lambda	0.950	0.425
Group	F	2.105	0.149

Chloride (Cl^-)

Table 4.41 Tests of between and within subject effects for Chloride (mmol/l) results over time

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.369	<0.001
Time x Group	Wilks' Lambda	0.980	0.912
Group	F	0.620	0.432

4.13.4 Urea & Creatinine; Red blood cells; Platelets; White blood cells

There was no significant change over time, no significant differences between the groups and no significant difference between the two groups over time with regards the levels of urea; creatinine; red blood cells; platelets and white blood cells (see Appendix I.

4.14 Lung Function Results

Spirometry was conducted at a set time, according to a standard protocol as set out in the Methods Section (Chapter 3).

The data were complete for all 142 patients.

The time points recorded were:

1. Pre-operatively
2. Post-operative Day 1
3. Post-operative Day 3
4. Post-operative Day 5
5. One month after surgery

4.14.1 Vital Capacity

Vital Capacity refers to the maximum volume of air that can be breathed into or out of the lungs, and is equal to the difference between the total lung capacity and residual volume.

The results of Table 4.42 show there is a significant change ($p<0.001$) over time in Vital capacity. There is no interaction between the two groups, and although there is a significant difference between the two groups ($p=0.021$), this is not a result of the intervention administered.

Pre-operatively and throughout the data collection times, Vital Capacity as alluded to above is significantly higher in group B than A. The slopes of the graph (Fig.4.11 below) do not interact and are parallel throughout, confirming this to be non-significant. Group B had a higher Vital Capacity than Group A throughout, although both groups showed they were recovering to the same extent. This difference between the groups was therefore due to baseline differences, which persisted throughout.

Table 4.42 Tests of between and within subject effects for vital capacity results

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.103	<0.001
Time x Group	Wilks' Lambda	0.989	0.810
Group	F	5.457	0.021

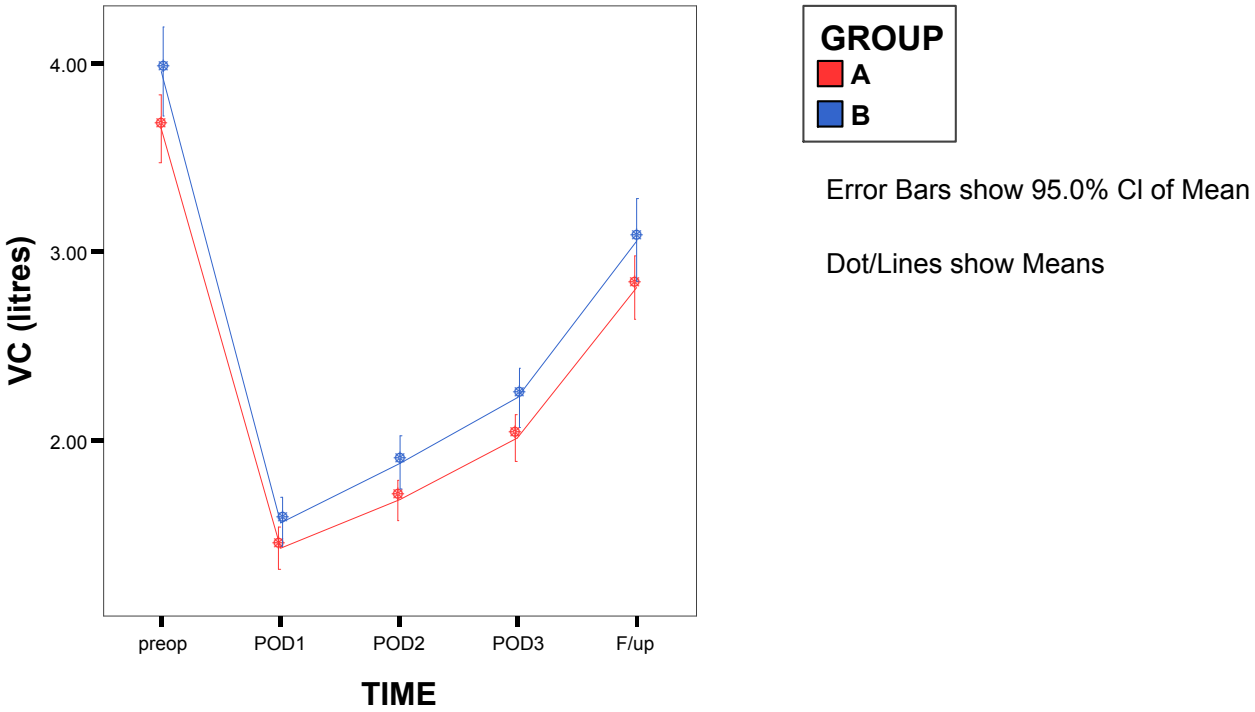


Fig. 4.11 Profile plots of Vital Capacity over time by group

4.14.2 Forced Vital Capacity

Forced (expiratory) vital capacity (FVC) refers to the maximum volume of air that can be exhaled with a maximally forced effort from the position of maximal inspiration.

As with Vital Capacity results above, the Forced Vital Capacity results (Table 4.43) show a significant change over time ($p<0.001$), with Group B significantly above A ($p=0.017$) at all time points from pre-operative assessment (see Fig. 4.12), yet this significance was due to baseline differences and not a result of the intervention to the two groups, as there was no significant difference over time between the two groups ($p=0.876$).

Table 4.43 Tests of between and within subject effects for forced vital capacity results

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.086	<0.001
Time x Group	Wilks' Lambda	0.991	0.876
Group	F	5.875	0.017

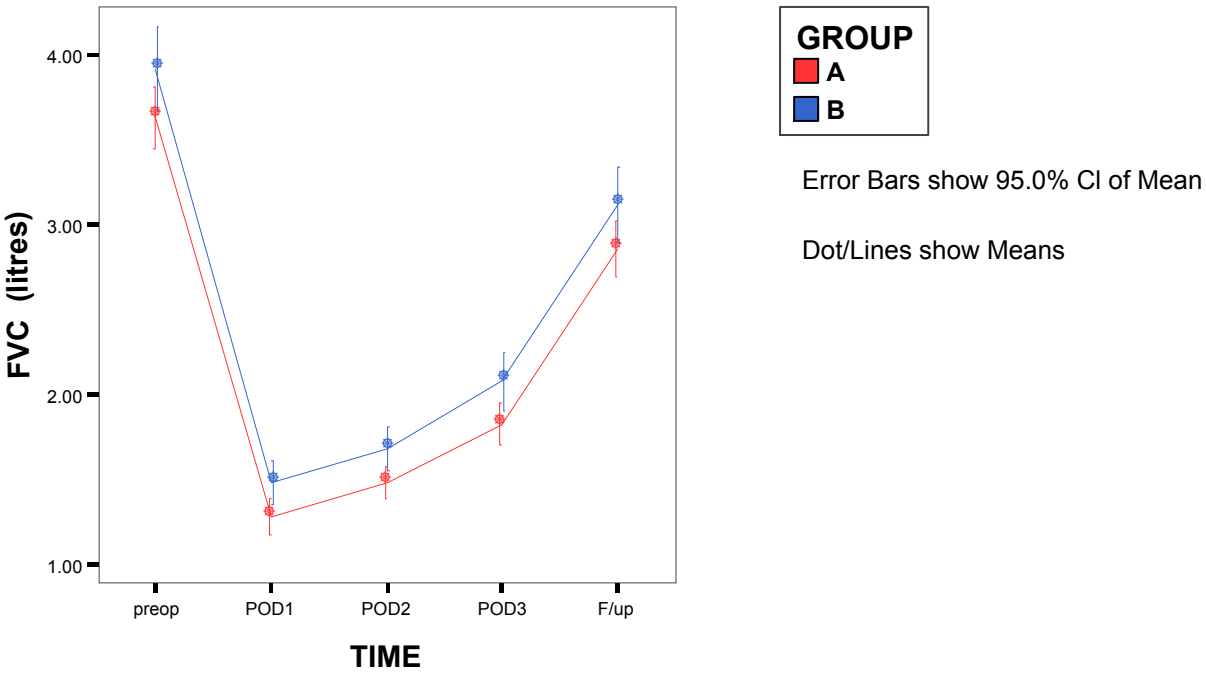


Fig. 4.12 Profile Plots of Forced Vital Capacity over time by group

4.14.3 Forced Expiratory Volume in 1 second (FEV_1)

FEV_1 is the maximum volume that a subject can exhale in 1 second during a standardised forced expiratory vital capacity manoeuvre.

The findings again show the two groups A and B have the same trend (Fig. 4.13), both having a highly significant change over time ($p<0.001$), with group B being marginally higher than A throughout the testing period. This accounts for the significant difference of $p=0.012$ in the Test of between-subjects effects (Table 4.44). There is however no significant difference between the FEV_1 change over time between the two groups ($p=0.894$).

Table 4.44 Tests of between and within subject effects for FEV_1 results

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.094	<0.001
Time x Group	Wilks' Lambda	0.992	0.894
Group	F	6.435	0.012

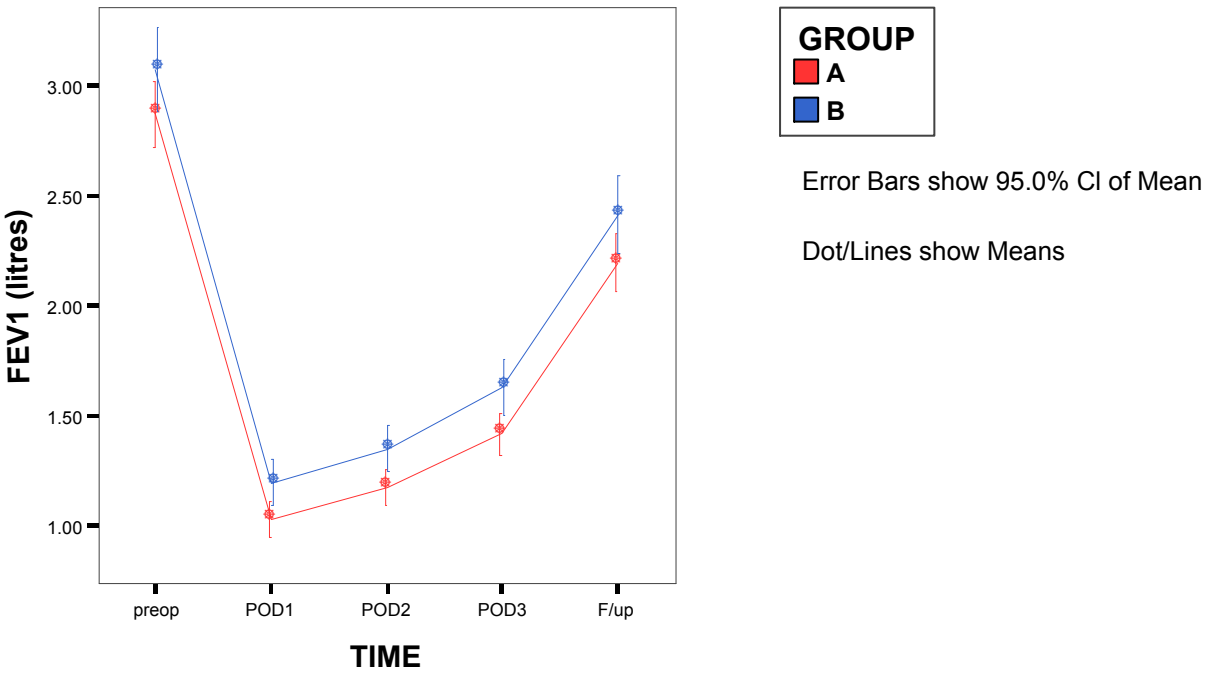


Fig. 4.13 Profile plots of FEV_1 over time by group

4.14.4 Forced Expiratory Volume in 1 second / Forced Vital Capacity (FEV_1/FVC)

The results of the ratio of $FEV_1$1/FVC show a significant change over time post-operatively with $p<0.001$ (Table 4.45), but no significant difference between the two groups. Of note, in Fig 4.14 below, Group A (red group) appears to drop faster until time point 3 (2^{nd} post-operative day) but ends on the same level as Group B. This difference is however not a significant one, thus confirming any changes to be independent of the intervention applied.

Table 4.45 Tests of between and within subject effects for FEV_1/FVC results

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.653	<0.001
Time x Group	Wilks' Lambda	0.974	0.452
Group	F	0.291	0.590

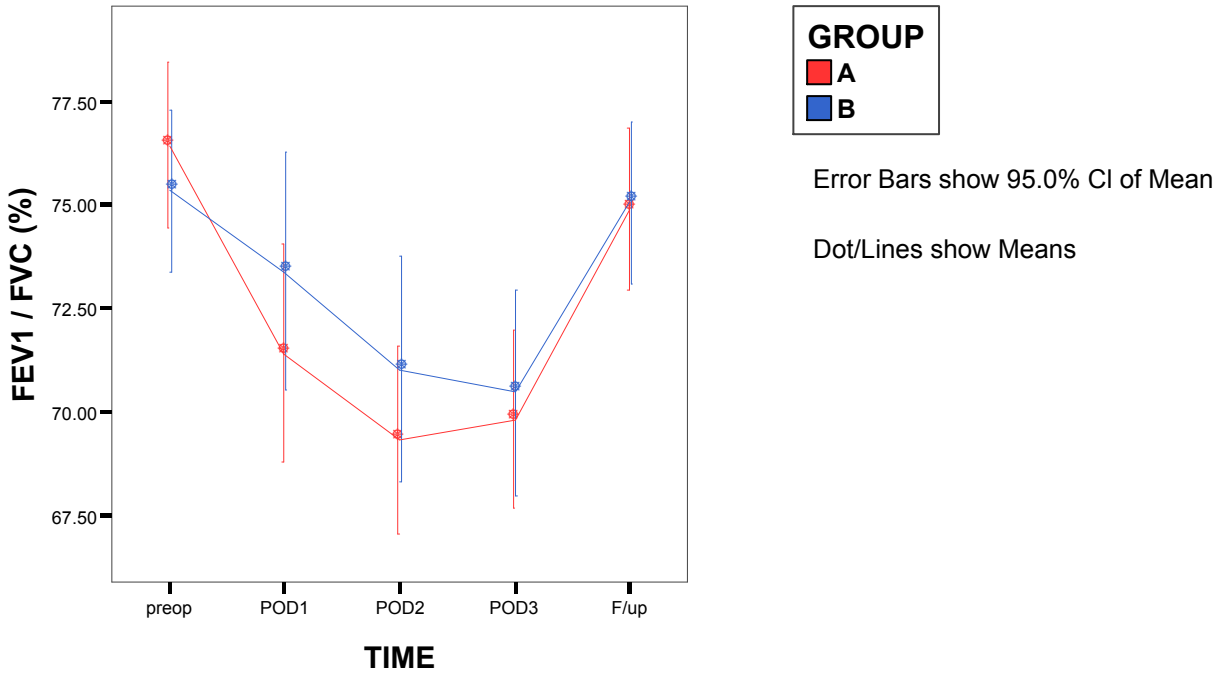


Fig. 4.14 Profile plots of FEV_1/FVC over time by group

4.14.5 Peak Expiratory Flow Rate (PEFR)

PEFR is the highest expiratory flow measured during the forced vital capacity manoeuvre.

The results yielded a significant change over time ($p<0.001$), yet as Table 4.46 illustrates, no significant interaction between Group A and B ($p=0.805$). There was again a significant difference ($p=0.031$) between the two groups all the way through with Group B having slightly higher peak expiratory flows throughout. This was however not an effect due to the intervention, and both groups changed to the same extent over time. Fig.4.15 also clearly shows an overlap of the error bars, signifying the observed differences are not significant.

Table 4.46 Tests of between and within subject effects for PEFR

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.126	<0.001
Time x Group	Wilks' Lambda	0.988	0.805
Group	F	4.740	0.031

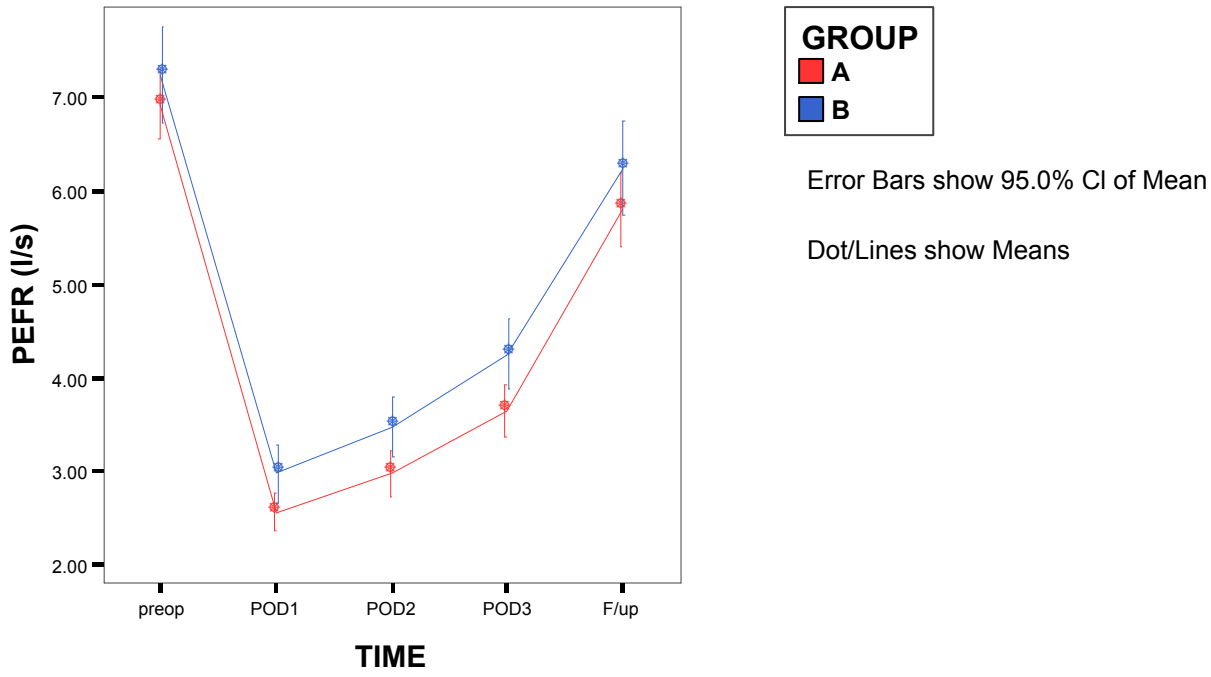


Fig. 4.15 Profile Plots of Peak Expiratory Flow Rate over time by group

4.14.6 Forced Inspiratory Vital Capacity (FIVC)

FIVC is the maximal volume that can be inhaled with maximal effort from a position of maximal expiration.

Table 4.47 below shows there is a significant change in the values from FIVC testing over time ($p<0.001$). The p value close to 1 ($p=0.911$), shows absolutely no evidence of interaction. The parallel lines on the graph confirm this. There was however a significant difference between the two Groups with Group B having a greater FIVC than Group A ($p=0.024$). Again however this was not a difference due to treatment effect. The graph Fig.4.16 also illustrates this change over time but no interaction.

Table 4.47 Tests of between and within subject effects for FIVC

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.107	<0.001
Time x Group	Wilks' Lambda	0.993	0.911
Group	F	5.206	0.024

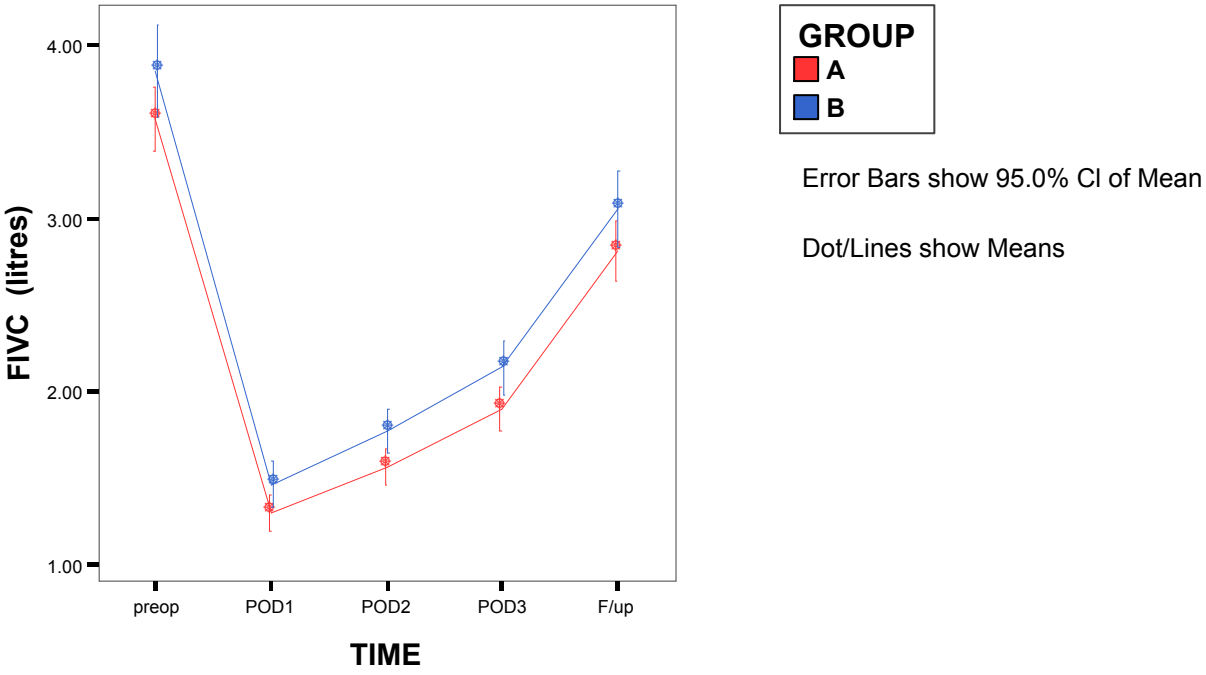


Fig. 4.16 Profile Plots of Forced Inspiratory Vital Capacity over time by group

4.14.7 Forced Inspiratory Volume in 1 Second (FIV_1)

This is the maximum volume a subject can inhale in 1 second during a standardised forced inspiratory vital capacity manoeuvre.

There is a significant change over time, but no interaction (p=0.522) or significant difference between the two groups (Table 4.48).The baseline is identical, but the final reading at the one month post-operative test shows Group B to have recovered somewhat faster than group A (Fig. 4.17). But this is not significant and merely shows a trend toward a possible intervention effect.

Table 4.48 Tests of between and within subject effects for FIV_1

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.213	<0.001
Time x Group	Wilks' Lambda	0.977	0.522
Group	F	0.731	0.394

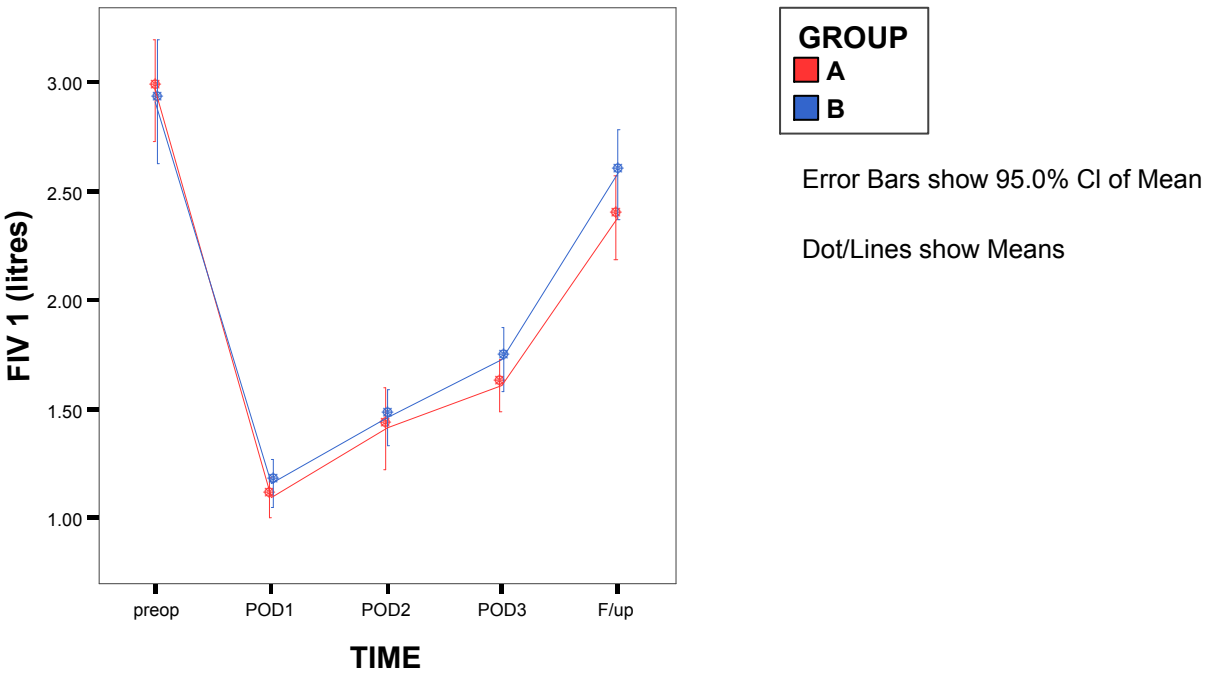


Fig 4.17 Profile Plots of Forced Inspiratory Volume in 1 second over time by group

4.14.8 Ratio of Forced Inspiratory Volume in 1 Second to Forced Inspiratory Vital Capacity ($FIV_1/FIVC$)

There is a significant change over time (P=0.027), but no significant interaction or difference between the two groups. There appears to be a trend for interaction between time points 1-2 and points 4-5 (Fig. 4.18). But the lines are parallel between time points 2-4. It is possible that with a larger sample size there may have been a significant change as group B here appears to be progressing at a faster rate, however this is only based on trends. The statistical tests (Table 4.49) show no significance (p=0.316) between Group A or B from the intervention.

Table 4.49 Tests of between and within subject effects for Ratio of Forced Inspiratory Volume in 1 second to Forced Inspiratory Vital Capacity ($FIV_1/FIVC$)

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.924	0.027
Time x Group	Wilks' Lambda	0.966	0.316
Group	F	1.663	0.199

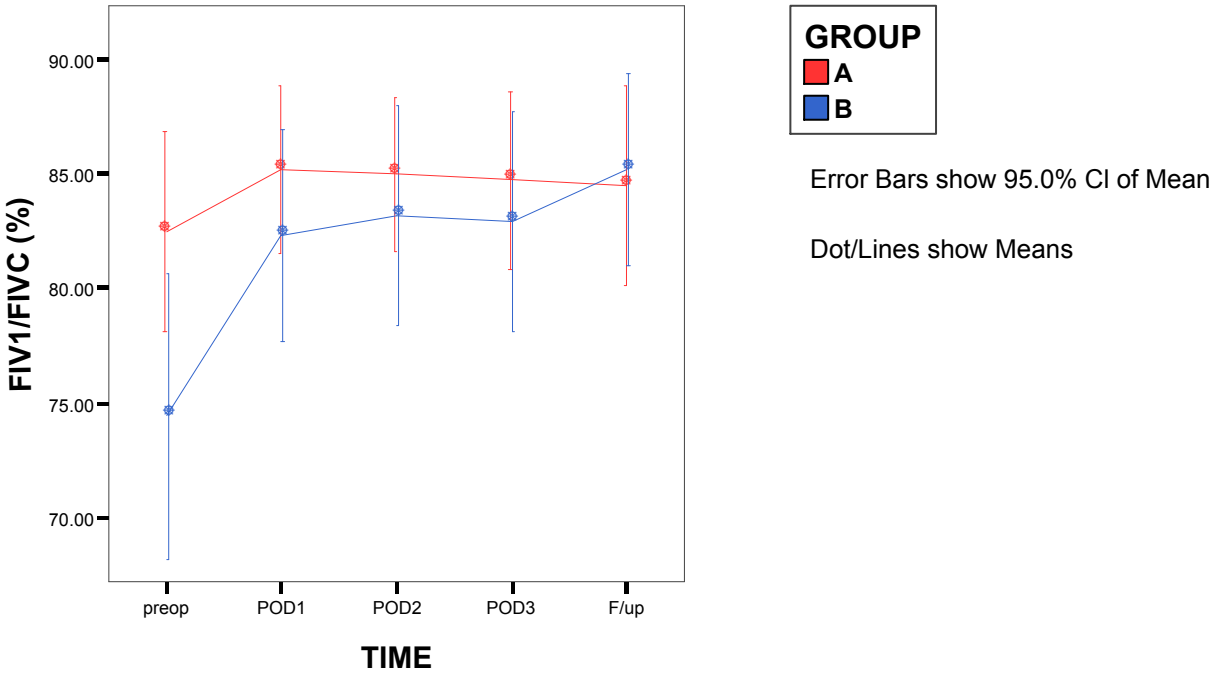


Fig. 4.18 Profile Plots of the Ratio of Forced Inspiratory Volume in 1 second to Forced Inspiratory Vital Capacity ($FIV_1/FIVC$)

4.14.9 Ratio of Forced Inspiratory Volume in 1 Second to Forced Vital Capacity (FIV_1/FVC)

There was a significant change over time in both groups (p=0.10 - Table 4.50), yet this was not significant between the groups (p=0.566), with no interaction occurring. There were no differences at baseline between Groups A and B, but the trend shows B started slightly lower than A and ended at a higher level than A (Fig. 4.19).

Table 4.50 Tests of between and within subject effects for Ratio of Forced Inspiratory Volume in 1 second / Forced Vital Capacity (FIV_1/FVC)

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.908	0.010
Time x Group	Wilks' Lambda	0.979	0.566
Group	F	1.075	0.302

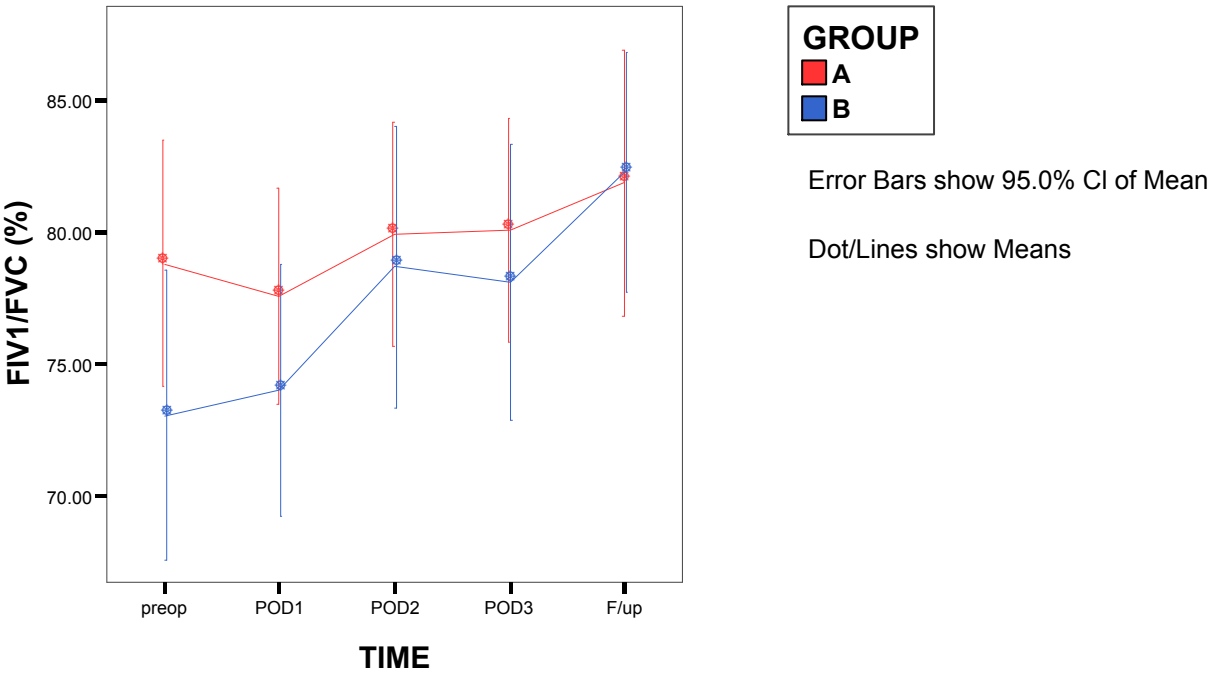


Fig. 4.19 Profile Plots of the Ratio of Forced Inspiratory Volume in 1 second to Forced Vital Capacity (FIV_1/FVC) over time by group

4.14.10 Peak Inspiratory Flow Rate (PIFR)

This is the highest inspiratory flow measured during the forced inspiratory vital capacity manoeuvre.

There is a significant time effect ($p<0.001$), but no significant interaction ($p=0.610$) between the groups (Table 4.51). There is evidence of the same trend as the results of FIV_1 discussed above, where the groups start at the same point (Fig. 4.20), but Group B tends to improve at a slightly faster rate. This however may be due to under powering of the study rather than an effect of the intervention.

Table 4.51 Tests of between and within subject effects for Peak Inspiratory Flow Rate

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.241	<0.001
Time x Group	Wilks' Lambda	0.981	0.610
Group	F	1.868	0.174

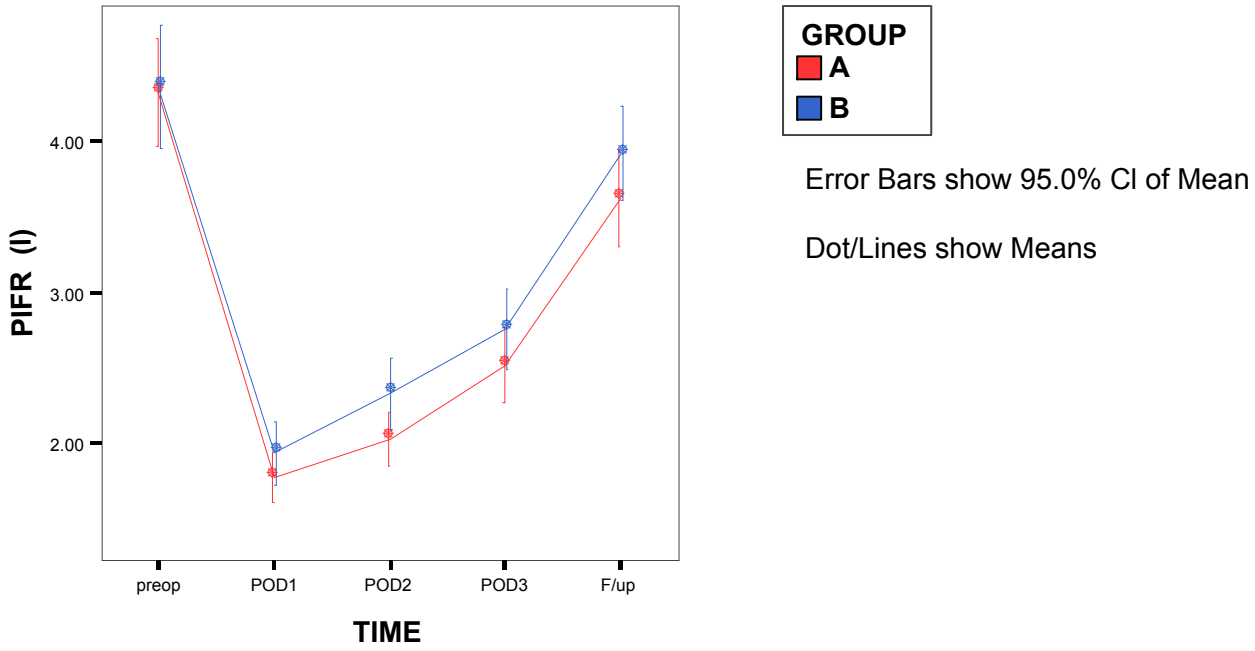


Fig. 4.20 Profile plots of Peak Inspiratory Flow Rate (PIFR) over time by group

The consistency of the results, which measured all aspects of lung function available at the bedside, provides strong evidence that the results are good and valid.

4.14.11 Lung function – Diagnostic Categories

Based on the results following each pulmonary function test, patients were placed into one of four diagnostic categories.

Table 4.52 below illustrates that patients are 1.92 times more likely to encounter a restrictive breathing pattern post-operatively than remain with a normal pattern, and this is diagnosis changes significantly over time, with $p<0.001$. There is however no evidence that this risk is related to the group patients are in, therefore not related to the intervention of whether there is a pulmonary artery vent inserted or not ($p=0.138$).

The presence of an Obstructive pattern was not significant over time ($p=0.385$), therefore patients were more likely over time, to be affected by restrictive patterns of ventilation or a combination of restrictive and obstructive rather than a purely obstructive pattern. The Time by Group interaction (Table 4.52) was not significant for any diagnosis, indicating that Group A and B had equal risk of developing the conditions discussed here.

The bar graphs of Fig. 4.21 below show the percentage of patients with each categorised diagnosis made by lung spirometry. From these trends, it is evident that even at the one month follow up visit, relatively few patients (Group A, 12% and Group B, 17%) had returned to their baseline pulmonary function level of normal.

Although the number that had returned to normal was slightly higher in Group B than A, on cross tabulation at this time point (Appendix J) this was not significant ($p=0.38$).

Many patients tended to exhibit a restrictive breathing pattern or combination of restrictive and obstructive pattern in the early days after surgery and this was similar in both groups A and B.

Table 4.52 Results of ordinal logistic regression analysis of diagnosis from lung function test, by time and group

Diagnosis	Relative risk	p-value	95% C.I.
Restrictive vs Normal	1.92	0.093	0.90-4.10
Time	2.65	0.001	1.46-4.82
Time x Group	0.77	0.138	0.54-1.09
Obstructive vs Normal	1.08	0.931	0.17-6.67
Time	1.57	0.385	0.57-4.31
Time x Group	0.99	0.983	0.55-1.81
Combined vs Normal	1.26	0.524	0.62-2.55
Time	2.26	0.002	1.34-3.82
Time x Group	0.80	0.159	0.59-1.09

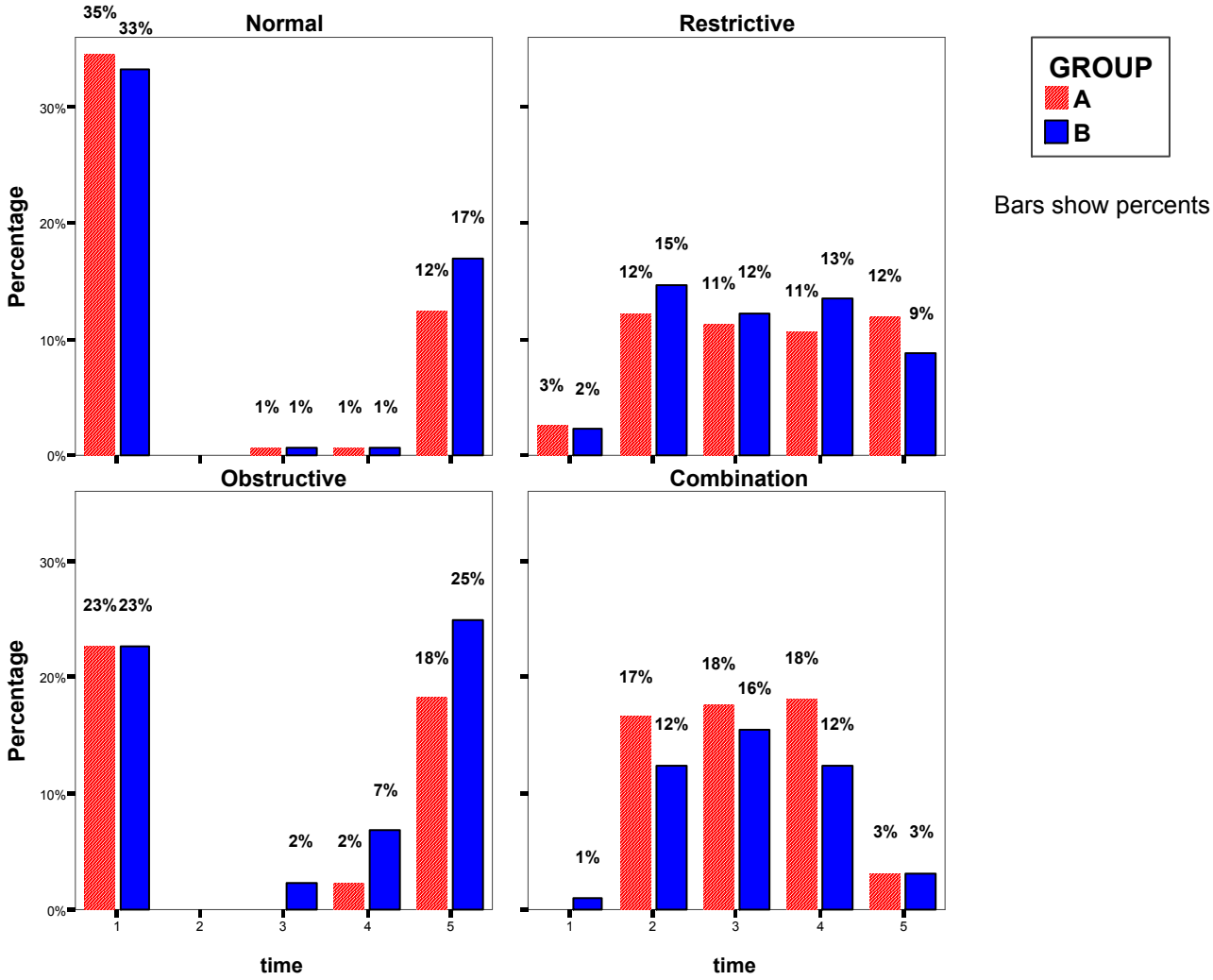


Fig. 4.21 Interactive graph of lung condition diagnoses over time by group
Key: 1. Pre-op 2. Post-op Day 1 3. Post-op Day3
4. Post-operative Day 5 5. One month after surgery

4.15 Radiology Results

Complete data set for all 142 patients were obtained. X-Ray results were collected pre-operatively; on the first post-operative day and 5th post-operative day. Data were analysed using ordinal logistic regression.

Grading was made on a scale of severity (see methods section for greater detail). Summary below:

Atelectasis Grading:	Effusion Grading:
0 = No atelectasis	0 = No effusion
1 = Plate-like atelectasis lower lobe	1 = Blunting costophrenic angle
2 = Sub-segmental atelectasis lower lobe	2 = Level with diaphragm
3 = Segmental collapse lower lobe	3 = Higher than diaphragm
4 = Complete lower lobe collapse	
5 = Other lobe atelectasis – please comment	

4.15.1 Left Lung Atelectasis (LLA)

Table 4.53 below depicts that there was a marginal, albeit not significant difference ($p=0.086$) in the severity of LLA between the two groups. However, Group A tended to have slightly more patients with atelectasis from initial, pre-operative stage right through to the post-operative Day 5 chest radiographs.

Both groups changed significantly over time ($p<0.001$) with a dramatic increase in the severity of LLA and the number of patients affected. The majority of patients acquired left lung atelectasis post-operatively (Fig. 4.22 below). As Table 4.53 displays, as time increased by one unit (i.e. from pre-op to Post-operative Day 1), the risk of an increase in severity by 1 unit (e.g. from 0 to 1) was 6.7 fold. On Post-operative day 1 and Day 5, the median severity of atelectasis in each group was Grade 3, namely segmental collapse of the left lower lobe, in each group (Appendix K1).

There was however no significant difference between patients in Group A or B ($p=0.355$) thus both groups are equally likely to suffer from LLA post-operatively and had equal severity of LLA, and the acquisition and severity of a left lung atelectasis is independent of the treatment received.

Table 4.53 Left lung atelectasis: intra and inter group comparisons

LLA	Odds Ratio	p-value	95% C.I.
Group	0.65	0.086	0.40-1.06
Time	6.72	<0.001	4.09-11.04
Time x Group	1.17	0.355	0.84-1.65

Footnote: Group B versus Group A

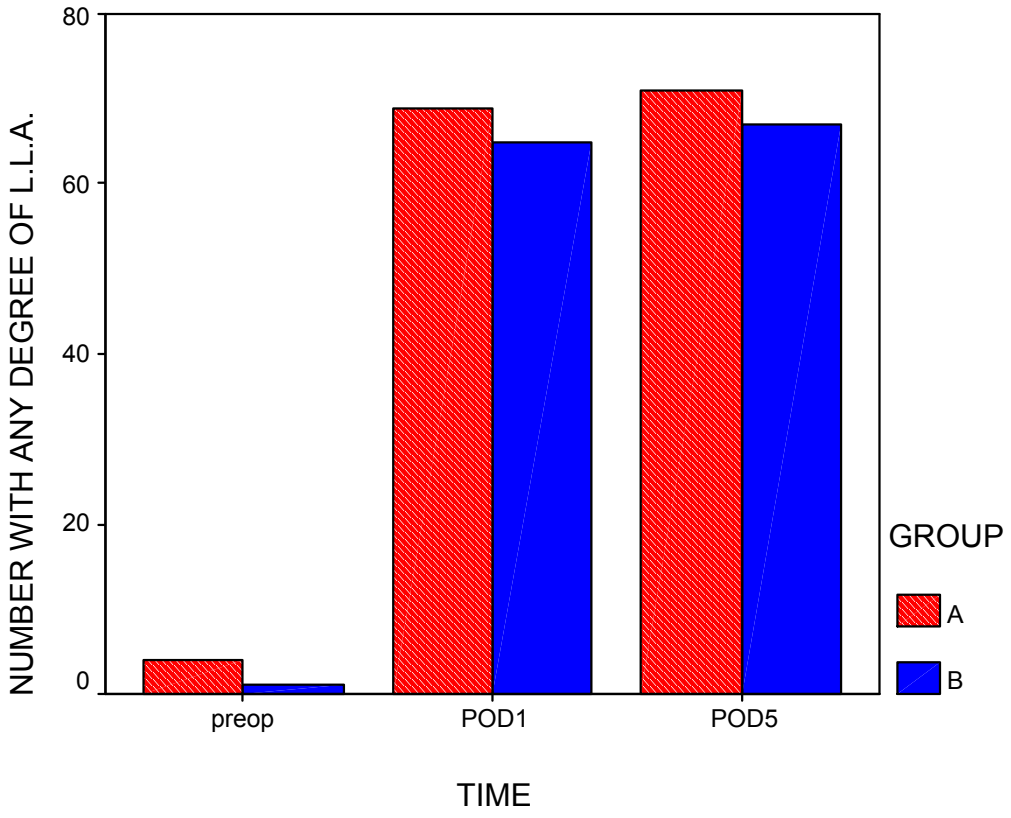


Fig. 4.22 Graph depicting number of patients with any degree of left lung atelectasis

4.15.2 Right Lung Atelectasis (RLA)

Table 4.54 below depicts that there was no significant difference (p=0.866) in the severity of right lung atelectasis between the two groups. Although both groups started with an equal number of patients diagnosed with right lung atelectasis preoperatively, Group A tended to have slightly more patients with atelectasis from the first post-operative day, through to the post-operative Day 5 X-Rays. Both groups increased in severity significantly over time (p<0.001) and increased in the number of patients who acquired right lung atelectasis post-operatively (Fig. 4.23).

As evident in Table 4.54 below, as time increased by one unit, the risk of an increase in severity by one unit was 2.89 times. By contrast to Table 4.53 (the previous table on

LLA) it is apparent that there is a greater risk of acquiring a left side atelectasis compared with right and as evident when one compares the two graphs, there were fewer patients with right lung atelectasis than left. On Post-operative day 1 and Day 5, the median severity of right lung atelectasis in each group was Grade 0, no atelectasis, with both groups showing a similar distribution (Appendix K2).

There was no difference over time between the groups with p=0.821, thus indicating this change was independent of the intervention.

Table 4.54 Right lung atelectasis: intra- and inter-group comparisons

RLA	Odds Ratio	p-value	95%C.I.
Group	0.92	0.866	0.35-2.42
Time	2.89	<0.001	1.64-5.09
Time x Group	0.96	0.821	0.67-1.38

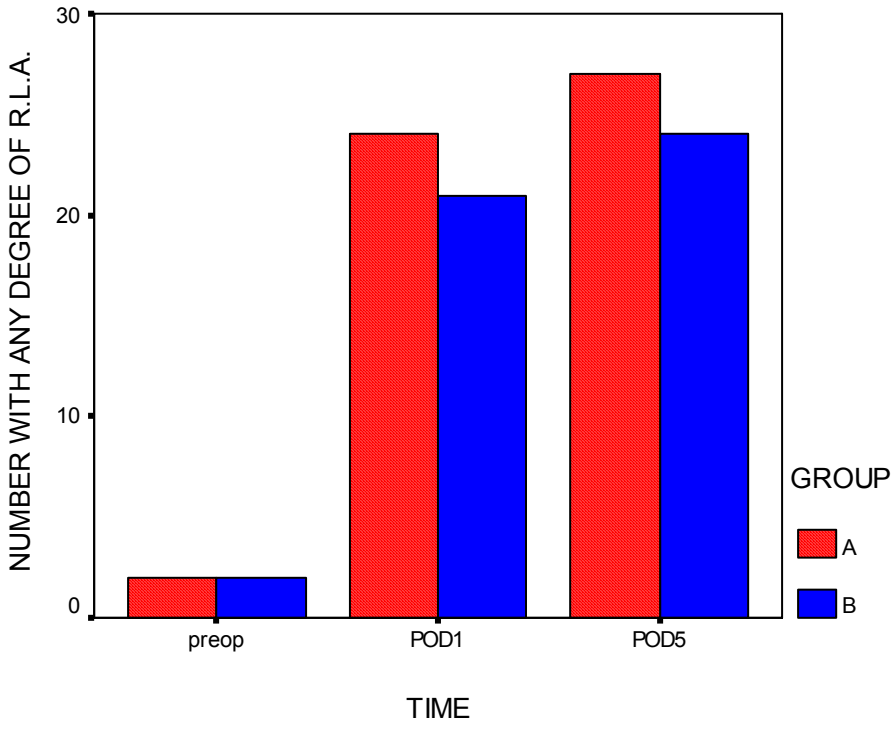


Fig 4.23 Graph depicting number of patients with any degree of right lung atelectasis

4.15.3 Left Lung Effusion (LLE)

Table 4.55 depicts that there was no significant difference (p=0.607) in the severity of left lung pleural effusion between the two groups.

Group A had one patient preoperatively with an effusion, and from initial, pre-operative stage right through to the post-operative Day 5 chest radiographs, tended to have a few more patients diagnosed with a left lung effusion.

Both groups however changed significantly over time (p<0.001) with a dramatic increase in severity and number of patients acquiring left lung effusion post-operatively (Fig.4.24). Of interest, effusion of the left lung tended to progress after the first post-operative chest radiograph was taken. As time increased by one unit, the risk of an increase in severity by one unit was 10.59 fold. The median severity of left pleural effusion in each group on post-operative day 1 was Grade 1 - blunting of the costophrenic angle; and on post-operative day 5 Grade 2, namely effusion level with the diaphragm.
This was similar between the groups (Appendix K3).

There was however no difference over time between the groups with p=0.767, thus indicating these changes to be independent of the intervention administered.

Table 4.55 Left lung pleural effusion: intra- and inter-group comparisons

LLE	**Odds Ratio**	**p-value**	**95% C.I.**
Group	0.80	0.607	0.35-1.84
Time	10.59	<0.001	6.12-18.33
Time x Group	1.06	0.767	0.74-1.51

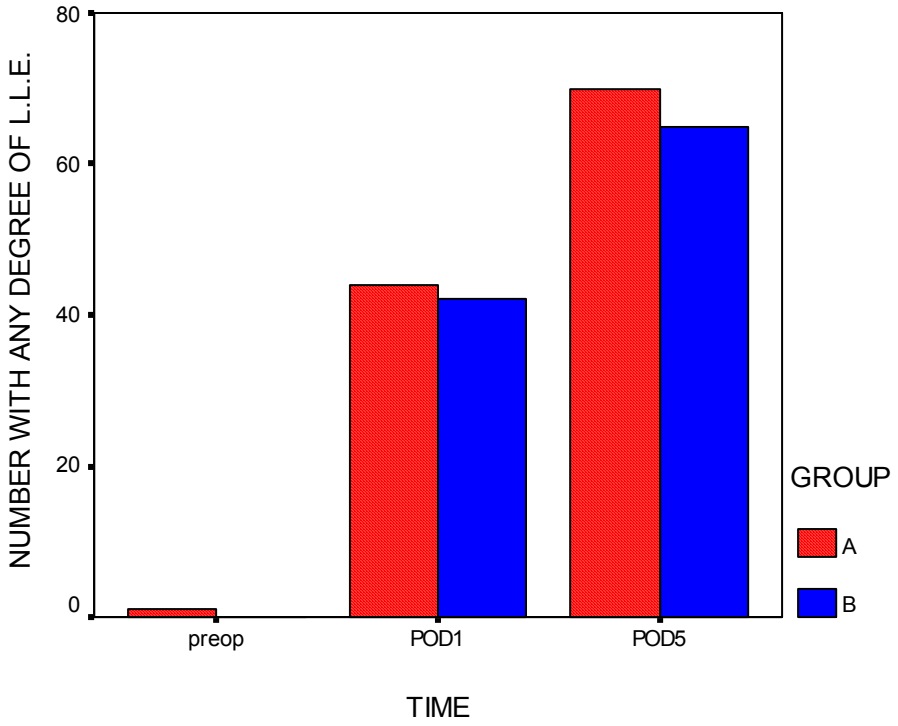


Fig. 4.24 Graph depicting number of patients with any degree of left lung effusion

4.15.4 Right Lung Effusion (RLE)

Table 4.56 below depicts that there was no significant difference (p=0.086) in the severity of right lung effusion between the two groups. Group A commenced with two patients having a right pleural effusion pre-operatively (Fig. 4.25). On the first post-operative day, there were a greater number in Group B with a right pleural effusion than A. The situation reversed by the fifth post-operative day, with a few more patients in Group A than B having been noted to have a right pleural effusion.

Again, as with the trend of left lung effusion, effusion of the right lung tended to progress after the first post-operative chest radiograph was taken. Both groups changed significantly over time, although significance was just reached, (p=0.041) with only a relatively few number of patients within each group (n=3) acquiring a right lung effusion post-operatively (Fig. 4.25). Table 4.56 illustrates that as time increased by one unit, the risk of an increase in severity by one unit of effusion grading was 4.5 times. The median severity of right pleural effusion in each group on post-operative day 1 and 5 was Grade 0 – no effusion. This was similar between the groups (Appendix K4).

There was no difference over time between the groups with p=0.860, thus indicating the change over time to be independent of any intervention effect.

Table 4.56 Right lung effusion: intra- and inter-group comparisons

RLE	Odds Ratio	p-value	95% C.I.
Group	0.7918081	0.855	0.65-9.70
Time	4.5227	0.041	1.06-19.22
Time x Group	1.078571	0.860	0.47-2.49

There was no correlation between harvesting of the right internal mammary artery and evidence of a right pleural effusion (Pearson Chi-Square value = 1.242; p=0.265).

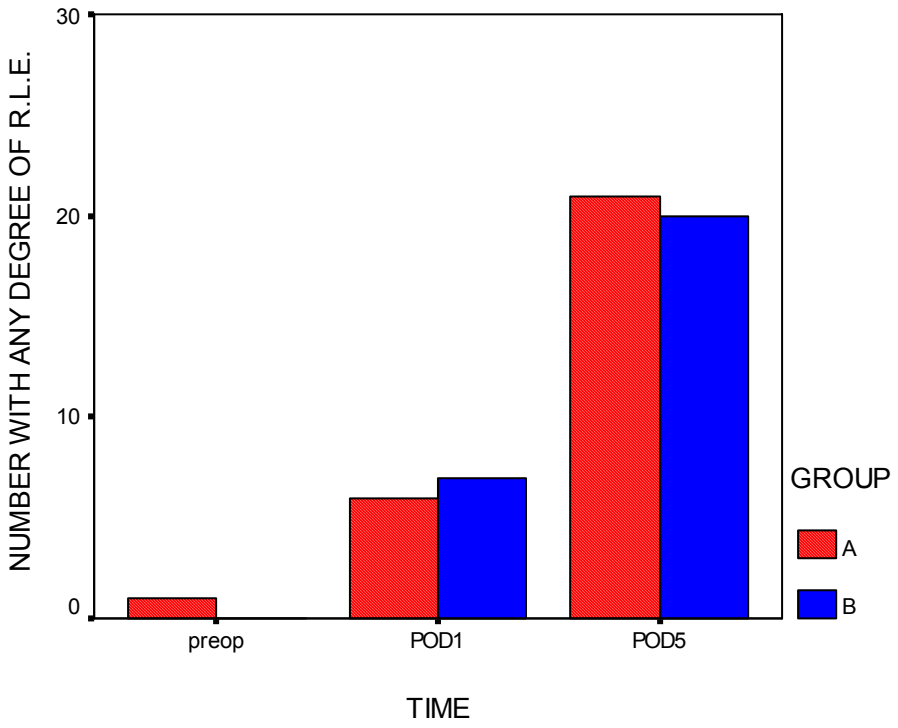


Fig 4.25 Graph depicting number of patients with any degree of right lung effusion

4.16 Physiotherapy and Mobility Results

There was no difference in length of hospital stay between Group A and B, with both groups generally being discharged on the sixth post-operative day (Table 4.57 below).

Table 4.57 Report of length of hospital stay by group

Group	n	Median	Range	Mean Rank	Sum of Ranks
A	71	6	5-10	73.40	5211.50
B	71	6	5-13	69.60	4941.50
n	142	6	5-13		

Footnote: Mann-Whitney U value=2385.500; p=0.557

There was no difference (p=0.279) between the two groups in the number of physiotherapy treatment sessions required (Table 4.58), with both groups averaging a need for ten physiotherapy treatment sessions during the course of their stay.

Table 4.58 Report of physiotherapy requirement to group (no. of treatment sessions)

Group	n	Median	Range	Mean Rank	Sum of Ranks
A	71	10	7-19	75.09	5331.50
B	71	10	8-16	67.91	4821.50
n	142	10	7-19		

Footnote: Mann-Whitney U value=2265.500; p=0.279

The other outcome measures regarding general mobility progress recorded and compared between the two groups were not significant and are therefore merely discussed briefly below. Figures in brackets represent (minimum and – maximum).

On average, patients were transferred to the cardiac high care unit on the second post-operative day (min.2 - max. 4), assisted to sit out in a chair on the third post-operative day (2-6); and commenced walking on this third day (2-9). Most patients were independent with walking on the third post-operative day (2-9).

Generally transfer of patients to the ward took place on the fourth post-operative day (3-8) also the same day that most patients were able to transfer independently from lying in bed to sitting and standing correctly and safely (2-9).

Most patients attempted the stairs with the physiotherapist on the fifth post-operative day (2-10). Physiotherapy treatment for the first supervised phase of in-patient cardiac rehabilitation was on average completed by the fifth post-operative day (4-9). Patients generally received an average of 10 treatment sessions each (initially twice daily) including the pre-operative assessment and counseling session (7-19).

Most patients were discharged from hospital on the sixth post-operative day (5-13).

4.17 Medication

As Table 4.59 below illustrates, the type of medication patients were taking pre-and post-operatively were evenly distributed between the two groups, with no significant difference between groups A or B at any time.

As expected, the requirement for organic nitrates post revascularisation declined in both groups. The requirement for statins for control of hyperlipidaemia and for secondary prevention was greater post-operatively. The need for an antiarrhythmic drug mildly increased in both groups post-operatively.

The usage of night sedation increased post-operatively, as it is a standard medication forming part of the post-operative drug protocol. As drowsiness may influence patients' breathing pattern or lung function, the usage of night sedation between the groups was documented in order to exclude a potential confounder of the results.

Of interest, the prescription of a Platelet Aggregation Inhibitor post-operatively was made in 100% of patients, as is standard protocol following cardiovascular revascularisation surgery.

Facility was made to record the use of prolonged Inotrope support beyond 48 hours, however this was not required in any of the 142 patients, and is therefore not depicted in the table below. Methysergide, prescribed for migraine, was no used in any patients.

Table 4.59 Medication comparisons pre- and post-operatively by group

Medication	Preop A %	Preop B %	Preop p-value	Postop A %	Postop B %	Postop p-value
Antihypertensive	80.3	81.7	0.831	93.0	90.1	0.546
Organic Nitrates	39.4	29.6	0.217	0.0	1.4	0.316
Statins	39.4	39.4	1.000	54.9	49.3	0.502
Antiarrhythmic	0.0	1.4	0.316	1.4	5.6	0.172
Night Sedation	16.9	21.1	0.521	59.2	71.8	0.112
Diuretics	8.5	9.9	0.771	11.3	9.9	0.785
Platelet Inhibit.	71.8	73.2	0.851	100.0	100.0	[a]
Anticoagulants	8.5	8.5	1.000	1.4	0.0	0.316
Fibrinolytics	1.4	0.0	0.316	0.0	0.0	[a]
Periph Vasodilat	1.4	2.8	0.560	0.0	0.0	[a]

Footnote: Pearson Chi-Square Values computed for 2x2 table [a] No statistic computed because constant 0.
Platelet Inhit. = Platelet inhibitors; Periph Vasodilat = Peripheral Vasodilators

4.17.1 Antihypertensive

The majority of patients that were on medication for hypertension were on a Beta-receptor blocker (BB). Table 4.60 shows that 59.2% from Group A and 52.1% of patients in Group B were on this class of antihypertensive. This difference between the groups was not significant, with p=0.398. Post-operatively this figure increased to 74.6% and 84.5% in groups A and B respectively. Again this slight difference between the two groups was not significant.

The other classes of antihypertensives were less popular, but apart from the Calcium channel blockers, in the majority of antihypertensives used, there were no differences between the usages in either group. Of Calcium channel blockers prescribed post-operatively, there were marginally significantly (p=0.042) more patients in Group A than B discharged on Calcium channel blockers.

Of note, the only increase in antihypertensive prescription post-operatively compared with pre-bypass surgery was of the Beta blockers.

Table 4.60 Type of antihypertensive used: pre-and post-operative comparisons by group

Anti-Hypertensive Drug	Pre-op A %	Pre-op B %	Pre-op p-value	Post-op A %	Post-op B %	Post-op p-value
βB	59.2	52.1	0.398	74.6	84.5	0.145
ACEI	18.3	26.8	0.228	14.1	12.7	0.805
CCB	16.9	18.3	0.826	14.1	4.2	**0.042**
ARB	11.3	12.7	0.796	4.2	0.0	0.080
α & β	4.2	2.8	0.649	2.8	0.0	0.154
α	1.4	0.0	0.316	0.0	0.0	[a]

Footnote: Pearson Chi-Square Values computed for 2x2 table

[a] No statistic computed because constant 0.

KEY: βB: Beta blocker; ACEI: Ace Inhibitor; CCB: Calcium channel blocker; ARB: Angiotensin receptor blocker; α & β: Alpha-and Beta-Receptor blocker; α: Alpha receptor blocker

CHAPTER 5

Discussion

5.1 Demographics

As is evident from Table 4.1 in the results section baseline demographics of age; height; weight and body mass index were evenly matched between the two groups.

The exclusion criteria prevented patients with a BMI greater than 35 to participate in the study due to the greater risk this posed upon surgery, ventilation and the technical difficulties involved in performing lung spirometry pre- and post-operatively. During the period of screening and conducting of the study, fifteen (15) patients were excluded as a result of being clinically obese (body mass index exceeding 35) (see Appendix F).

Age is a significant preoperative risk factor for hypoxaemia[178-180]. Octogenarians also have increased mortality and morbidity risks following coronary artery bypass grafting[181; 182]. Advanced age and large body mass index are also associated with postoperative increase of interstitial fluid which can in turn decrease functional residual capacity and alveolar recruitment for gas exchange[183].

5.1.1 Gender

The greater number of males (88%) to females (12%) in the study (Table 4.2) is reflective of the general population with ischaemic heart disease that undergoes coronary intervention procedures[184;185]. This inequality was however evenly matched between the two groups. Despite reports[125] that gender is not a risk factor for postoperative lung complications, the evenly matched groups merely eliminate any potential bias in lung function results due to gender.

5.1.2 Race

As the study took place within two private hospitals, the distribution of Race is not reflective of the general population of patients in South Africa with ischaemic heart

disease requiring coronary revascularisation. The distribution in Table 4.3 is however reflective of the distribution of patients within this surgeon's practice, who have access to private healthcare insurance.

5.2 Baseline Health Status

On the whole, patients' baseline status was homogenous between groups A and B. A coincidental discrepancy was noted in that the number of patients with unstable angina was higher in Group B than A. This did however not translate to any significant physical differences in the incidence of myocardial infarction; ejection fraction; NYHA Classification; or number of diseased coronary vessels, which may have influenced the outcome measures more than the classification of angina alone.

Triple vessel disease was the most common angiographic finding in both groups. This is in accordance with the general population that undergoes coronary artery bypass surgery, as fewer numbers of diseased arteries are usually dealt with through more conservative means, such as coronary angioplasty and coronary stent procedures[186]. Cardiac enzyme levels were matched between the two groups as were the coagulation studies, thus creating a baseline health status that was comparable.

5.2.1 Diabetes

Diabetes is a well known risk factor for cardiac disease[187] and it is widely acknowledged that wound healing in diabetic patients is delayed following any surgical intervention[188-193].

Of the 24.6% of patients with known Diabetes Mellitus (Table 4.9) at the onset of the study, the groups were equally proportioned, thus reducing the likelihood of the outcome of the study being influenced by these extraneous variables.

5.2.2 Hypertension

Table 4.10 in the results section identified the number of patients with known hypertension prior to admission to be 52.8%, which was evenly matched between the two study groups A and B. Of note, 81.0% of patients were on anti-hypertensive medication pre-operatively. The discrepancy between the diagnosis of hypertension

on admission to the higher percentage of patients placed on anti-hypertensive medication prior to surgery, is directly attributed to the fact that the difference of 28.2% of patients on admission were not aware of being hypertensive or had not been previously diagnosed as hypertensive, and were placed on anti-hypertensive medication following admission and prior to surgery.

Uncontrolled hypertension is a significant risk factor in ischaemic heart disease[194]. The two groups were however identical in hypertension status pre-operatively (Table 4.10) and in the number that were prescribed anti-hypertensive medication pre-operatively (Table 4.59).

In those patients that were prescribed anti-hypertensive medication, the class of medication was also evenly matched between the two groups. As certain anti-hypertension medicines may have the side-effect of causing an obstructive breathing pattern[195], this consistency between the two groups translates to the fact that no group was positively or negatively influenced over the other in terms of lung function.

5.2.3 Risk Factors

Only 34.5 % of the participants in the study claimed to have never smoked. Smoking is not only a risk factor in the development of ischaemic heart disease, but also plays a major influential role in compromising breathing and lung function in the early stages following surgery[196]. The results showed that despite a large proportion of the study patients were smokers and ex-smokers, the pack years and number of cigarettes smoked per day were very similar in both group A and B therefore yielding a representative group of the general population that suffer from ischaemic heart disease[197; 198].

The majority of patients (77.5%) had no known allergy, and this was equally distributed between groups A and B. There was therefore no difference in risk factors between the two groups.

As seen above, the similarities in demographics; baseline health status and risk factors show the two groups' potential variables to be comparable at baseline.

5.3 Intra-operative Variables

Due to this being a clinical trial, it was not feasible or ethical to completely standardise the treatment and drugs administered. A standard protocol was followed, but records were made of every potential confounding variable in order to ascertain whether any intervention differences or similarities could be attributed to differences with the intra-operative management besides the intervention given.

5.3.1 Sedation

Propofol was anaesthesiologist's choice of parenteral anaesthetic sedation in the majority (79.6%) of cases. Use of this drug has the advantage that when stopped, it is metabolised quickly and patients are fully awake within a relatively short period.

A Morphine/Cyclizine and Midazolam combination on the other hand is preferred in patients who are at greater risk of cardiovascular events during the induction of anaesthesia as blood pressure tends to fall more dramatically with induction using Propofol. The disadvantage of Morphine/Cyclizine and Midazolam combination is that it takes longer to metabolise once stopped and patients are often more drowsy, with reduced respiratory rates due to the morphine component. For this reason, the anaesthetic medication was compared between the two study groups. There was however no difference between the use of Propofol or Morphine/Cyclizine and Midazolam combination between Groups A and B, with an equal portion receiving each drug.

Potential respiratory differences were therefore not attributable to the type of anaesthetic medication administered.

5.3.2 Number of Grafts and Donor Grafts

As discussed under the baseline health status, section 5.2 above, the majority of patients were diagnosed via angiography as having triple vessel disease (table 4.8). For this reason it therefore follows that the majority of patients underwent triple bypass grafting with no significant difference between groups A or B (Table 4.14).

The conduit of choice for occluded or obstructed left anterior descending artery is usually the left internal mammary artery, due to its long term patency[199-202]. As several studies have implicated this graft to be the cause of pulmonary complications, post-operatively[140-146], a comparison between the two groups was essential in order to establish that any results from spirometry or blood gases were not due to the conduits selected.

There was no difference between the groups (p=0.227) in the number of patients that had their left internal mammary artery utilised for grafting. In fact with regards to every donor site used, the groups were evenly matched, thus so far yielding two homogenous groups at baseline for comparison.

5.3.3 Extracorporeal circulation

The extracorporeal pump as discussed previously has been implicated through complement activation[34-38] to affect the lungs. Rady[203] reported CPB time as one of the only significant factors to predict early post-operative pulmonary dysfunction. For this reason, pump time was recorded. This potential variable is noted to be virtually identical, with both groups averaging a median of 52 minutes on cardiopulmonary bypass, thus one can conclude both groups should have been equally affected by the effects of the bypass pump.

5.3.4 Aortic clamp time

The duration that the aorta was clamped averaged 35 minutes, with no significant difference in either group, thus the effect of aortic cross clamp time was neutral.

5.3.5 Haemoconcentration

Some investigators have identified excessive haemodilution as an important risk factor for the development of pulmonary dysfunction following CPB[204; 205]. In the present study, this risk was reduced through the use of haemoconcentration procedures.

The use of haemoconcentration was just within significance, with slightly greater number of patients in group A receiving haemoconcentration than B. This is however

unlikely to have influenced the post-operative parameters and final lung function results measured.

5.3.6 Volume of Cardioplegia delivery

This averaged 2077.99 ml between the two groups. Neither group had a significantly greater quantity of cardioplegia administered during surgery. Of note however, the majority (if not all) the cardioplegia solution was prevented from entering the lungs in Group B patients, whereas in Group A patients, a large portion of this cardioplegia solution entered the lung parenchyma.

5.3.7 Intra-operative Blood Loss

This was difficult to determine and an estimate of blood loss was made through dialogue between the anaesthesiologist and surgeon. From these estimates, it is apparent that blood loss recorded was virtually identical between the two groups with $p=0.171$. This variable was therefore not an influential factor in the study outcomes.

5.3.8 Lowest systemic temperature

Neither group were influenced by this variable, as all patients were maintained intra-operatively at a median temperature of 32.1°C.

5.3.9 Total operative time and total ventilation time

These potential influential variables on lung function were comparable between the groups, with the mean operating time of 'skin to skin', including anaesthetic time to be 174.03 minutes and total ventilation time to be a median of 446.50 minutes. Total ventilation time was similar between the groups, but it should be borne in mind that the high range in ventilation time is due to the fact that as in many other centres, patients who undergo operation late in the day are more likely to stay intubated overnight purely as a precautionary measure, even though their pulmonary function and clinical status may justify extubation.

5.3.10 T-Piece

To determine whether weaning from ventilation was standardised between the groups and due to the fact that a blood gas reading was taken whilst the patient was breathing via a T-piece (still with endotracheal tube in situ, but breathing spontaneously), the

time each group was on a t-piece was recorded and found to be very similar, with the median being 45 minutes before extubation.

5.3.11 Time in Intensive Care Unit

The period of time spent in the cardiac intensive care unit was comparable between the groups, with the median being 2 days.

5.3.12 Transfusion Requirement

Massive transfusion of blood products have been reported to be a risk factor for pulmonary dysfunction following CPB[128; 206]. However a report by Garber and colleagues[207] disputed this and raised doubt as to the clinical importance of transfusion of blood products as a factor to precipitate acute pulmonary dysfunction, stating the contributory factors were more likely the longer CPB time and surgical trauma than the blood products themselves. Nevertheless, due to the unconfirmed statements one way or another, it was necessary to determine that there were no inter-group differences. The groups were evenly matched on the number that underwent transfusion Table 4.26) as well as the volumes transfused (Table 4.27). There was therefore no influence on lung function with regards to the blood transfusions administered in either group.

5.4 Confounding Variables

5.4.1 Cardiologist referral

There was no bias in the referral source of patients, in that patients from different cardiologists were evenly distributed between the two groups.

5.4.2 Fluid Balance

A greater intake of fluid with less output is a causative factor of pulmonary oedema and thus severely affects respiratory function. For this reason, both daily fluid balance and running fluid balances were monitored and recorded. Despite each group changing significantly over time, there was no difference between the groups in the fluid balance recorded. Running fluid balance results show that the intake of fluid in the first 48 hours increases dramatically and may account for the lung deterioration

post-operatively. The fact however that there is no difference between the two groups shows these results to be independent of the intervention studied.

5.4.3 Heart Rhythm

It has been established that patients who develop atrial fibrillation (AF) post-operatively have a significantly longer hospital stay[208]. Post-operative AF has been recorded in some CABG series to occur in up to 40% of patients[209; 210]. In the present study, 2.1% of patients were in AF pre-operatively. This increased to a maximum of 12.7%, in both groups, by the second post-operative day (Fig 4.3).

That patients in the early post-operative stage (first 48 hours) tend to be at a greater risk of abnormal cardiac rhythm, has been strongly attributed to age and the mere process of opening the pericardium[211], as reviews of the literature have reported inconsistent findings with regard to other hypothesised causes, such as studies implicating the use of cardioplegia; trauma to the right atrium during cannulation and cardiopulmonary bypass[209; 212; 213].

Due to the non-interaction between groups A and B, it is evident that not only did the intervention of the pulmonary artery vent not play a role in influencing AF, but the development of AF was similar in both groups and consequently not a factor in any differences in length of hospital stay between the two groups.

5.4.4 Medication

Both groups of patients were on similar medications and proportions did not differ between the groups, thus this was not an influential variable in the results.

5.5 Comparison of Blood Results and Outcomes

5.5.1 Fraction of Inspired Oxygen

The value of an Arterial Blood Gas is usually highly dependant upon the fraction of inspired Oxygen at the time of measurement. For this reason, a comparison between the two groups' Oxygen consumption at each time measurement interval where the patient was not on room air (FiO_2= .21), was made. Fig.4.8 showed that the patients' Oxygen requirements were highly dependant upon time, yet there was no difference

between Groups A or B in their demand for or use of Oxygen. For this reason therefore, it is feasible to compare the two groups without the influence the effect Oxygen would have played on the results.

5.5.2 Arterial Oxygen

Arterial hypoxaemia is common following cardiac surgery and may persist for several weeks post-operatively[214; 215]. The overall incidence of pulmonary complications in this trial is comparable to those reported elsewhere[126; 151], with a maximal impairment of gas exchange being evident on the second postoperative day. In a study by Taggart and colleagues' [126], one quarter of patients had an arterial oxygen tension of less than 8 kPa while breathing room air (the conventional definition of respiratory failure). The present study also shows the mean arterial oxygen tension on the fifth day to be below baseline levels (Fig.4.4).

There was no discrepancy between the arterial oxygen changes over time between the two groups, thus the pulmonary artery sump was not an influential factor in determining these changes.

5.5.3 Arterial Carbon Dioxide

During CPB, the amount of CO_2 removed from tissues by 1 litre of blood decreases by about 30% and impairment in CO_2 transport persists after the restoration of physiological circulation[216]. This impairment is mainly caused by haemodilution but could be worsened by acidosis[216]. This may account for the decrease in the arterial carbon dioxide levels observed during cardiopulmonary bypass in this study. The peak in carbon dioxide levels following cardiopulmonary bypass is, as expected, one hour following extubation (Fig 4.5) when sedation and analgesia may have played a role in reducing respiratory drive / rate and depth. Levels of arterial carbon dioxide were not influenced by the intervention of the pulmonary artery vent during cardioplegia delivery, as both groups followed the identical trend postoperatively.

5.5.4 Intrapulmonary Shunting (Q_S/Q_T)

As described in the methodology section (Ch. 3), shunt fraction estimation was calculated using the a/A ratio (arterial/Alveolar ratio), to determine the extent of intrapulmonary shunting. This method, described in Appendix A, has been deemed

the most accurate non-invasive method of determining the extent of a patient's pulmonary shunt. Measurement of the pulmonary shunt fraction (Q_S/Q_T) is the "gold standard" for quantifying respiratory dysfunction [172].

As long as the a/A ratio is over 0.60, the intrapulmonary shunt is small. The shunt increases as the a/A ratio decreases. The lower the ratio, the poorer the patient's pulmonary status. The a/A ratio should change by greater than 5% before any assumption of change in (Q_S/Q_T) has occurred. It has not known the extent of change required in order to indicate a clinically significant change.

The results (Fig 4.6) showed the greatest intrapulmonary shunt to occur whilst the patient was on a T-piece, prior to extubation, with a gradual improvement in the first week, but not reaching baseline levels by the fifth post-operative day, similar to the findings of other studies [217; 218].

The use of extracorporeal circulation has been blamed to be responsible for a significant amount of Q_S/Q_T in patients undergoing CABG during the post-operative period after extubation[217]. Other well documented causes of increased shunt are lung atelectasis post-operatively[105; 218; 219]. Of relevance, the findings of the present study show the use of the pulmonary artery vent makes no difference to the changes in shunt post-operatively.

5.5.5 Oxygen Saturation

As for the results of arterial Oxygen and concurring with the findings of other studies[126; 151], the nadir of oxygen saturation occurred on the second post-operative day following cardiopulmonary bypass. These changes were however not influenced at all by the placement and suctioning via a pulmonary artery vent at the time of cardioplegia delivery.

5.5.6 Haemaglobin and Haematocrit

There was an impressive decrease in Haemoglobin and Haematocrit post-operatively in this study, with both remaining well below baseline levels at the final fifth post-operative day test. Taking the intra-operative levels out of the picture, one can see

again the nadir occurring on the second post-operative day, in line with the low of the PaO_2 levels.

5.5.7 Concluding discussion on blood results

Following cardiopulmonary bypass there were significant and substantial changes in the arterial blood gases in both groups. The nadir of paO_2 decrease occurred on the second post-operative day and up until the final test on the fifth post-operative day, there were still significant abnormalities.

There was a substantial increase in intrapulmonary shunting, as evidenced by the decrease in alveolar/arterial ratio. This was most severe in the immediate post-operative period and on T-piece. The second low occurred on the second post-operative day. At final testing, the shunt was still significantly greater than pre-operative levels. A previous study using the multiple inert gas technique established that both ventilation-perfusion mismatching and right-to-left intrapulmonary shunting are responsible for the lower alveolar/arterial ratio in these patients[220].

Alveolar hypoventilation is not responsible for the hypoxaemia since the postoperative values for $PaCO_2$ were less than the pre-operative values.

The decrease in the PaO_2 is particularly noteworthy given the large decline in the haemoglobin and haematocrit noted, again with nadir on the second post-operative day. Patients therefore experience a clinically significant reduction in the oxygen content of their arterial blood, which may compromise the supply of oxygen to the tissues and contribute to tissue ischemia.

The post-operative decreases in ABG's were virtually identical in both groups. Use of a pulmonary artery vent in preventing cardioplegia from entering the lungs is therefore not a factor in the reduction of arterial blood gases in the early and first week following cardiopulmonary bypass.

5.6 Discussion of lung function results

Due to the similar findings throughout the spirometry results, these will be commented upon as a whole.

Despite the recognition in 1962 that restrictive ventilatory defects follow median sternotomy[221], the mechanisms thereof have, to date, not been completely expounded upon. The changes in pulmonary function following cardiopulmonary bypass surgery are the most severe in the first 48 hours[222].

At 24 hours post-operatively, all lung volumes were approximately 36% to 40% of preoperative values in both groups. There was a trend toward improvement by the third post-operative day, with lung volumes at 40-47% of pre-operative values. By the fifth day, lung functions had improved to approximately 50% of baseline. At one month follow up spirometry test, there was still a significant reduction in all lung functions, at levels still averaging between 77% and 80% of pre-operative values.

The degree of impairment observed in the current study is consistent with previous studies, which showed marked reductions in FEV_1 and FVC five days after CABG surgery that persisted for up to six weeks post-operatively[126;132;140;141;144;147;167;170].

In the early stages following coronary artery bypass surgery, pain; atelectasis and the transient increase in lung water that follows extracorporeal circulation would account for a major portion of the fall in Vital Capacity (VC)[144;223;224]. By one week however, all the patients in the present study were independently mobile and uncomplaining of pain whilst performing spirometry. Fluid that accumulates in the lungs after cardiac bypass surgery usually clears by 48 hours post-operatively[223;224]. One study suggests a correlation between pulmonary oedema and low vital capacity and low FEV_1[225]. Postoperative radiography excluded obvious causes of major volume loss, such as lobar collapse, large pleural effusion or consolidation. No patient had dyspnoea or radiographic evidence of pulmonary oedema.

The degree to which the FVC and FEV_1 was reduced in the present study is comparable to that reported in other studies[32;144;226]. The postoperative decrease and

gradual return toward normal levels in this study was similar in the pulmonary artery vent group and the control group. Neither group had reached pre-operative baseline levels one month after the surgery. Previous reports[32;214;221] showed that these severe pulmonary function impairments persist for six weeks. The earlier reports documented more severe pulmonary abnormalities persisting for as long as four months post-operatively[221;227;228]. The fact that there has been improvement in the reduced severity and shorter duration of these abnormalities is likely to be attributed to the refinements in the extracorporeal circulation equipment.

The restrictive ventilatory pattern which dominated the course of post-operative recovery was comparable to previous findings[32;139-141]. The results are therefore attributable to a myriad of factors other than the placement of a pulmonary artery vent for retrieval of cardioplegia solution.

5.7 Discussion of radiology results

The prevalence of atelectasis of the left lung following cardiopulmonary bypass surgery is high[108;165;219;229], with several studies reporting left lung atelectasis to occur in as many as 86-90% of patients[131-133;164;230]. This is due to residual degrees of atelectasis following lung expansion after CPB. Severity varies from microatelectasis, which manifests radiologically as reduced lung volume to complete lobar collapse; which in turn is a major cause of intrapulmonary shunting and hypoxaemia. The majority of the patients in this study were equally diagnosed with some degree of atelectasis postoperatively.

Several postulates for this occurrence of atelectasis include:

1. Trauma to the lung secondary to retraction and subsequent pulmonary contusion[164].
2. The effect of hypothermia on the phrenic nerve, with subsequent paralysis of the left leaf of the diaphragm[231;232]. As the left phrenic nerve is positioned between the pericardium and mediastinal reflection of the left pleura, it is in an exposed and consequently vulnerable position with regard to severe prolonged hypothermia and topical cooling of the heart during coronary artery bypass.
3. CPB time and thus the length of cooling may also contribute to atelectasis.

4. Different surgical technique has been found to be a contributory factor, with varying surgeon's procedures recorded as influencing the degree of atelectasis.

With regard to the present study, the above variables were all controlled through one surgeon and technique performed; similar duration of CPB time in each group and similar volumes of cardioplegia delivery and topical cooling delivered. Yet, as discussed above, the findings correlated precisely to those of prior studies. The primary difference therefore of whether a pulmonary artery vent and the exclusion of most of the cardioplegia overflow from entering the lungs is therefore not a significant contributory factor in the development or prevention of left lung atelectasis, or any of the other radiographic abnormalities reported upon in this study.

The occurrence of a left lung effusion was less prevalent than atelectasis of the left lung, yet occurred in a significant number of patients but was not isolated to one group. The incidence of left effusion was in accordance with other investigative studies[126;154-156].

As with the postulates given for the cause of atelectasis above, postulates as to the cause of effusion include thoracic trauma but also the addition of the thoracic or intercostal drains is thought to be a major factor[157]. Of note, the results of the present study tend to dispute this finding as they show the degree of left and right lung effusion to increase from the first postoperative day to the fifth. This is following the removal of all the drains, which whilst in situ, seem to provide an effective means of limiting pleural effusions.

The conclusion from the radiographic evidence with regard to the objectives of this study however show that the use of a pulmonary artery vent is of no consequence to the degree of effusion witnessed postoperatively.

5.8 Discussion of physiotherapy and mobility results

Physiotherapy treatment in the early post-operative stage following CPB, includes prevention and treatment of atelectasis; pleural effusions (whilst the drains are in situ); retained secretions and immobility.

Prevention and treatment of these pulmonary deteriorations consists of physiotherapy respiratory interventions, including but not limited to: respiratory re-education through deep breathing; percussion; postural drainage (modified) positions; use of incentive spirometry and early mobilisation, in order to mobilise secretions and improve functional residual capacity[233-235].

In this study physiotherapy treatment was standardised and took place at the regular times, but specifically co-ordinated so as not to interfere with the blood gas or spirometry test results.

The findings were that neither group differed in the number of physiotherapy sessions required and the speed at which they returned to normal mobility. Duration of hospital stay was also identical. The intervention of a pulmonary artery vent during cardioplegia delivery therefore does not manifest in any beneficial nor detrimental outcomes with regard to duration of hospital stay or the degree of physiotherapy intervention required.

5.9 Validity of study

Of the larger population from which this sample is drawn, the sample is representative of the distribution of patients within this surgeon's practice, who have access to private healthcare insurance. Whilst race classification in this study appears to be the only discrepant confounding factor the general population as a whole, the other demographic and health variables as described above, are reflective of the general population patients suffering from ischaemic heart disease world-wide. Whether the physiological differences present among the different racial groups is perhaps an area of further study. The external validity of this study may therefore be deemed suitable.

The consistency of the results within each group, throughout the study, which measured all aspects of lung function available at the bedside, blood gas results and radiology results, provides strong evidence that the measurements taken were accurate. The use of standardised equipment and close adherence to the protocol ensured there was no deviation as a result of different equipment. The internal validity and results of this study are therefore good and accurate.

According to the Buckberg protocol[20,21,82-84] the maintenance dose of cardioplegia solutions have a lower, less detrimental quantity of K^+ than the induction dose.

There are no studies to indicate whether these subsequent maintenance doses (performed after each coronary anastomosis is made) provides a cumulative dose of K^+ to the induction, thereby rendering it more damaging to the endothelium or whether it is sequential and each 'relatively low' dose is innocuous to the endothelium.

The Buckberg protocol does result in a more 'dilute' cardioplegia solution as it is merged with four parts blood to one part cardioplegia[20,21], and therefore it may be argued that it is less likely to be damaging to the endothelium in this form. No studies have however, to date, clearly shown the exact quantities of cardioplegia delivered to each patient during coronary artery bypass graft surgery, nor at exactly which quantity it becomes detrimental.

In his study on cardioplegia damage to the endothelial myocardium, Von Oppell[79] noted that whilst studies had been made of venous endothelial cells, "differences do exist between different vascular beds and" and therefore extrapolation of these isolated cellular studies to the human clinical situation should be done with caution.

The current study, despite its documented limitations below, was therefore deemed a unique, valid and appropriate method of determining the clinical relevance of cold blood cardioplegia solution to the pulmonary endothelium.

5.10 Limitations of the study

The inclusion criteria were aimed to select a homogenous group (freedom from lung abnormalities and relatively normal preoperative respiratory ratios). The application of this to the severe COPD patient can therefore not be made without further study.

This study almost certainly underestimates the true incidence and severity of respiratory dysfunction after CPB. The researcher only studied patients at the better

end of the surgical spectrum (mean age 61 years); all in NYHA class I or II with good left ventricular function and no lung disease. Furthermore, 2 patients were excluded from analysis as they required prolonged ventilatory support (> 24hours). Incidentally, each of these patients was from either group in the study, again indicating no intervention effect.

No direct measurement was made of lung ischaemia or endothelial damage as ethical approval to perform lung biopsies was not granted. Consequently, from this clinical study, one is unable to comment on the degree of lung ischaemia or inflammatory response. As far as the inflammatory response is concerned however, both groups were exposed to the same type of extracorporeal circuit for a similar time period, underwent the same extent of operative trauma, and received comparable amounts of blood, thus the degree of inflammation should be considered very similar.

A criticism of the exceptionally close correlation in many of the results between Group A and B is that perhaps despite numerous authors[85-90] stating that the PA vent retrieves most of the spill over from the blood entering the right atrium not collected by the atriocaval cannula, it may be argued and postulated that the results of this study show the PA vent is perhaps either:

i) Superfluous as a cardioplegia retrieval method – as all blood and cardioplegia may be drained via the atriocaval cannula, leaving nothing to be collected by the PA vent.
Or
ii) not that effective in eliminating all the cardioplegia, thus allowing much of the cardioplegia to enter the lung parenchyma, and that any amount of cardioplegia rather than increased quantity may be the causative factor of damage.

The criticisms above, pertaining to the efficacy of the pulmonary artery vent thus required further investigation prior to reaching any definitive conclusions with regard the use of the pulmonary artery vent upon clinical outcomes.

CHAPTER 6

Hypothesis and Objectives

Hypothesis

This study was instituted to determine whether the cold blood cardioplegia solution is completely evacuated by the right atrium drainage, via the atriocaval cannula, or whether there is spill over and part of the solution is circulated through the lungs during cardioplegia administration.

Objectives

The study was four-fold, with the objectives as follows:

1. To identify whether the pulmonary artery vent (drainage) retrieves any cardioplegia solution.

2. To identify whether without the pulmonary artery vent in situ, the cardioplegia passes through the pulmonary vasculature and is retrieved by the left atrium vent.

3. To simultaneously retrieve left atrium and pulmonary artery vent return whilst the superior and inferior vena cave are snared, to determine the presence or absence of the cardioplegia solution at these points.

4. Without the pulmonary artery vent in situ, the superior and inferior vena cavae snared, does the left atrium retrieve the technetium labelled cardioplegia solution i.e. does the cardioplegia solution pass through the lungs or merely accumulate and 'pool' within?

6.1 Ethical Considerations of Technetium Studies

Ethics approval for these further studies was applied for and permission obtained from the University of KwaZulu-Natal as well as Westville Hospital and Entabeni Hospital (Life Healthcare), in which hospitals the studies were conducted. Written informed consent was obtained from each patient prior to their participation in the study.

CHAPTER 7

Clinical Study on the performance of the Pulmonary Artery Vent

"Because it is easy to measure it makes it important
Because it is difficult to measure it makes it unimportant."
Anon.

7.1 Introduction

As cardioplegia is a clear solution which is combined with blood in a ratio of one part cardioplegia to four parts blood according to the Buckberg method[20-21], it is impossible in this form to trace its pathway. By adding an isotope to the cardioplegia solution however one is effectively able to "label" the cardioplegia with the radioactive tracer and thus determine the precise exit points of the cardioplegia solution. No direct studies have been made of this flow pattern.

This chapter presents data of a prospective study to determine whether the pulmonary artery vent retrieves any spill over of the cardioplegia and blood solution not drained from the coronary sinus into by atriocaval cannula of the bypass circuit.

The presence of any Technetium-labelled cardioplegia in the solution retrieved by the pulmonary artery vent will therefore be a compelling argument that without the pulmonary artery vent, cardioplegia "spill over" would enter the lung parenchyma.

7.2 Materials and Methods

The first five patients admitted for coronary artery bypass grafting that fitted the inclusion criteria identical to that of the initial study and consented to this study were included.

7.2.1 Surgical Technique

The standard technique of midline sternotomy was performed. After full heparanisation the heart was cannulated (see Cannulation section below) in

preparation for cardiopulmonary bypass. Management of the cardiopulmonary bypass equipment was also standard as per the initial study.

Temperature was controlled with a heat exchanger incorporated in the oxygenator. Systemic temperature was lowered and maintained at 32ºC after commencing cardiopulmonary bypass. The aorta was then cross-clamped and blood cardioplegic solution (300ml/min for 3 minutes) was infused via a separate cannula inserted into the aortic root, at a pressure ranging between 180 -250 mmHg.

The patients in this first Technetium study were managed identically to those patients in Group B, described in the initial study above, namely those patients that had the addition of a pulmonary artery vent.

The method of anaesthesia and drug administration was standardised according to the protocol of the initial study.

7.2.2 Cannulation

Cannulae were used, as follows:

1. Aortic Cannula: Research Medical Cannula (Edwards Life Sciences Research Medical Inc. 6864 South 300 West – Midvale, Utah 84047 – USA) 24 Fr. Wire reinforced angle tipped aortic cannula.

2. Atriocaval Cannula: A DLP (Medtronic Inc., Minneapolis, MN555432-5406, USA) two-stage atriocaval cannula inserted though the right atrial appendage, to allow the wider portion to sit in the right atrium and the narrower portion in the inferior vena cava. Secured in position with a purse-string suture. Most patients required size 36-46Fr selected according to patients' body surface area and expected flow rate. Drainage via this cannula was gravity assisted.

3. Cardioplegia Antegrade Cannula with protection system: (Jostra - Maquet Cardiopulmonary AG, Hechinger Street 38; D-72145 Hirrlingen, Germany) Sidearm vent cardioplegia cannula – Inserted into the aortic root (9 Fr.), with

a Y-attachment to the main-line, to enable venting of the aortic root and coronary vascular bed when cardioplegia solution not being delivered.

4. Pulmonary Artery Cannula: DLP (Medtronic Inc., Minneapolis, MN555432-5406, USA) Pulmonary Artery Cannula (Size 16Fr.). Inserted 3 – 4 cm into the main pulmonary artery secured in position via a purse-string suture. During the period of cardioplegia delivery continuous suction was applied via this vent and the contents were not returned to the reservoir of the cardiopulmonary bypass circuit, but instead were collected in a separate marked collection bag. Note: Suction was just within negative range, preventing preferential suctioning and preventing the wall of the pulmonary artery to collapse against the fenestrations of the vent.

7.2.3 Isotope management

Two syringe samples of Technetium Isotope material (Tc-99m), a radioactive tracer, were obtained, measured and the time thereof recorded. Each sample contained approximately 15mCi of Technetium Isotope within a 3ml sample of Sodium Chloride (NaCl) (exact measures per patient recorded). The contents of each syringe were introduced into the induction cardioplegia, and maintenance cardioplegia solutions respectively. Volumes of cardioplegia used were recorded and any remaining, unused volumes were recorded and collected for analysis.

The outflow from the pulmonary artery vent during cardioplegia delivery was retrieved in a separate bag, thus prevented from returning to the bypass circuit. The volume remaining in all the cardioplegia bags in contact with the Technetium was recorded post-operatively and the quantity of Technetium within each bag was determined by a nuclear medicine radiographer with the use of a 'Curimentor' dose calibrator. The radiographer was blind as to the surgical technique used.

The amount of Technetium (Tc-99m) in the collection bags and the introductory bags, as well as the 'empty' syringes was recorded and double checked by the independent radiographer and observed by the researcher. The time of analysis was recorded in order to account for decay. Decay was then factored into the results, and calculated according the Isotope Decay Table [177].

In order to assess with greater specificity and to establish the accuracy of the above dose calibrator measures, thereby ensuring internal validity and reproducibility of the results, further analysis was made of the quantities of Tc-99m in each sample. A pipette was used to obtain a 1ml sample from each bag. These samples were then transferred into heparinised glass vacutainers. To further ensure the validity of these results, two vacutainers from each sample were obtained and compared.

The Tc-99m tracer samples were analysed 24 hours after collection using Gamma Acquisition and Analysis on the Genie 2000vdm Well Counter. The 1ml samples were counted for 60 seconds and the integral counts for that one minute were compared. Of note, the reason for the deliberate delay in testing of samples was due to the fact that high doses of Tc-99m saturate the well counter, rendering readings inaccurate.

The difference between amount of Tc-99m introduced and retrieved for the induction and maintenance cardioplegia deliveries were calculated and the retrieval Tc-99m expressed as a percentage of the quantity introduced (after decay factor calculated). The paired samples were then statistically analysed. The volumes of cardioplegia introduced and volumes of blood and cardioplegia solution retrieved were also recorded and analysed.

These ratios of the well counter measures were checked against the dose calibrator measures to validate and confirm the consistency of the findings.

Due to the small sample size, data were analysed with SPSS statistical software, using Non-Parametric tests and descriptive analysis.

7.3 Results

The patient group comprised of five men, with a median age of 60y (range 54 - 63y). All five patients underwent triple bypass grafting.

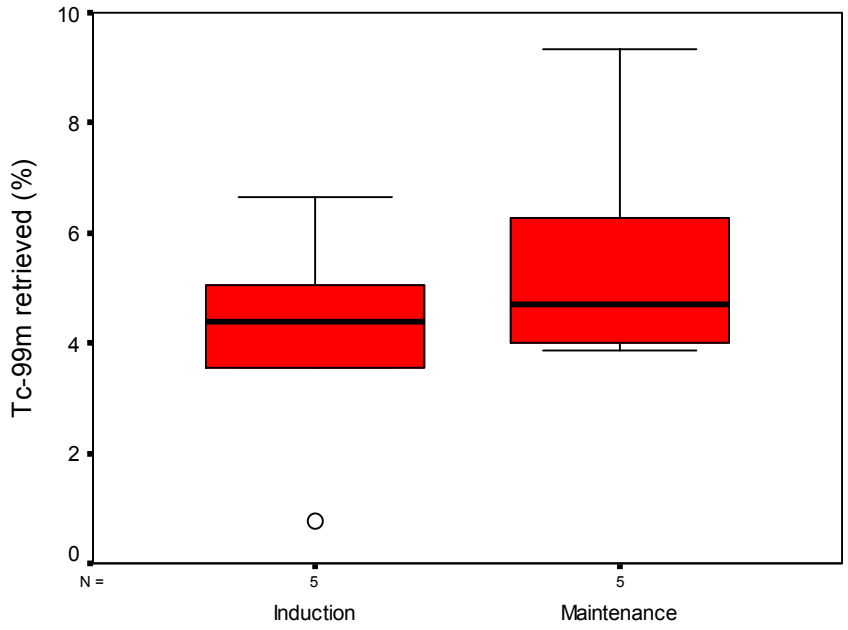
7.3.1 Retrieval of Technetium

Due to the small sample size and skewing of the data from the retrieval of the maintenance dose of cardioplegia, the paired samples were analysed using the Non-Parametric Wilcoxon Signed Ranks Test.

Tc-99m was present in every sample (100%) of induction and maintenance retrieval from the Pulmonary Artery vent (PA). For the purpose of clarification and interest, the quantities thereof will be expounded upon. The well counter measures obtained confirmed the dose calibrator ratios. For concise reporting however only the results from the dose calibrator are reported on in this section.

The results of the analysis of the Technetium (Tc-99m) retrieved from the PA vent is shown as the percentage retrieved of the amount that was introduced. In Fig.7.1 below, it is seen that the percentage of Tc-99m retrieved from the pulmonary artery vent was similar in both the deliveries of induction and maintenance doses of cardioplegia, but with the maintenance dose showing a higher percentage of retrieval (median 4.7% - the IQR - Interquartile range : 4.0-7.8%) to the induction (median 4.4% - IQR: 2.2-5.9%).

The Wilcoxon Signed Ranks Test revealed that although the sum of ranks was marginally higher in the maintenance delivery, the difference was not significant, with p=0.5. (See Appendix L.1).



Percentage of Tc-99m retrieved from PA vent

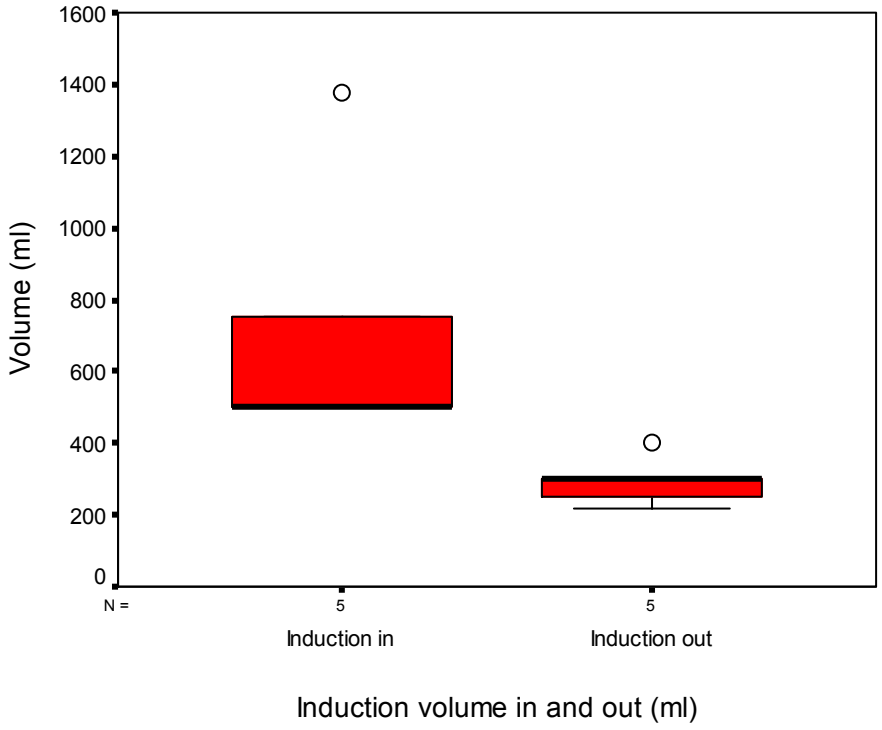
Key: O = Outlier

Fig. 7.1 Percentage of Technetium Retrieved by Induction and Maintenance delivery phases

7.3.2 Volume of Delivery and Retrieval

The median total volume of Induction cardioplegia solution administered using the Buckberg (4:1) protocol was 500ml (IQR: 500-1063ml). The median retrieval volume from the PA vent was 300ml (IQR: 235-350ml). This resulted in a statistically significant difference of a greater volume introduced than retrieved, with p=0.043 (Appendix L.2).

During the maintenance dose administration, the median total volume introduced was 1500ml (IQR: 725-1500ml), whilst the pulmonary artery vent retrieved a median of 500ml (IQR: 435-650ml), resulting in no significant change with p=0.080 (Appendix L.2). Figure 7.2 below shows the trends that a higher volume of solution was delivered than retrieved during induction phase of cardioplegia delivery. Figure 7.3 shows the same trend during the maintenance phase.



Key: O = Outlier

Fig. 7.2 Volume of cardioplegia solution administered and retrieved from the pulmonary artery vent by induction delivery phase

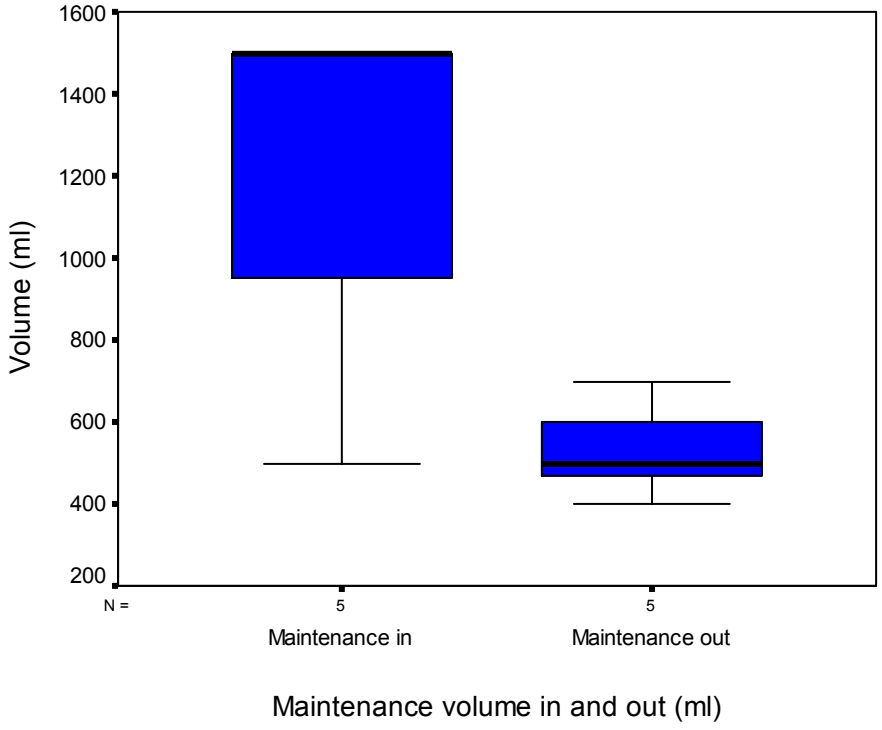
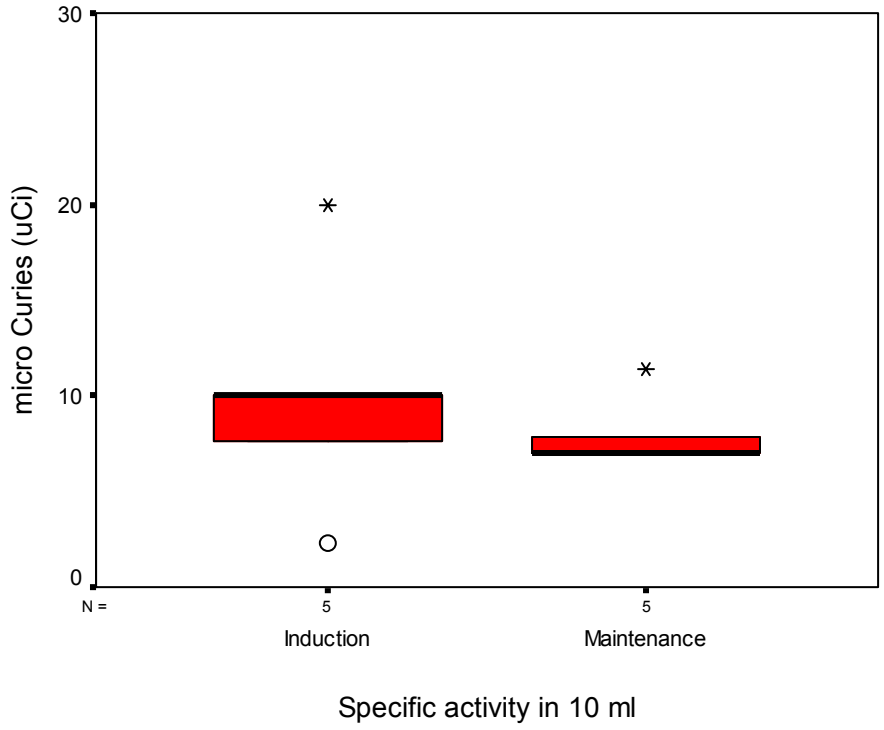


Fig. 7.3 Volume of cardioplegia solution administered and retrieved from the pulmonary artery vent by maintenance delivery phase

7.3.3 Specific Activity of Tc-99m in a 10ml sample

A 10ml representative sample of the total retrieval from the pulmonary artery vent was analysed to determine the specific level of radioactivity within each standardised volume of 10ml.

Background radiation was measured at 0µCi. The median of the specific activity in the induction sample from the PA vent was 10µCi (IQR: 4.97-15µCi). The specific activity median of the maintenance retrieval was 7µCi (IQR: 7 - 9.6µCi), with Wilcoxon Signed Ranks test yielding no statistically significant difference between the two (p=0.892 - Appendix L.3). The Figure 7.4 below illustrates the similar levels of specific activity of Technetium retrieved by the pulmonary artery vent at both induction and maintenance delivery time points.



Key: O = Outlier
* = Extreme value

Fig. 7.4 Specific Activity of Technetium in a 10ml sample, retrieved from the pulmonary artery vent, by induction and maintenance delivery phases

7.4 Discussion

The pulmonary artery vent has been accepted in the literature to be an effective route for aspiration and drainage of cardioplegic solution[85]. Prior to this study, it may have been argued that the requirement of a pulmonary artery vent in preventing cardioplegia from entering the lungs, in the light of present day efficacious atriocaval cannulae, is superfluous.

This study by yielding a positive result in 100% of the patients has therefore shown that without a pulmonary artery vent in situ, cardioplegia, albeit a small percentage would have entered the lung parenchyma.

As seen from the results above, the maintenance dose of cardioplegia retrieved a marginally greater percentage of the Tc-99m than induction. This is however likely to be related to the significantly far larger volumes of maintenance cardioplegia delivered to induction.

The specific activity of Tc-99m in a 10ml sample, within the induction dose was marginally greater than within the maintenance sample.

The relatively small percentage of Tc-99m retrieved, as well as low volumes of blood retrieved indicate that the pulmonary artery vent merely collects the excess cardioplegia solution that the atriocaval cannula is not able to deal with during the time of cardioplegia delivery.

7.5 Limitations of this study

The small sample size limits the power of the study.

There is the possibility of a Type 2 error existing, as despite not being statistically significant, the absolute differences may be clinically important. This particular study was however not necessarily powered to detect whether significant differences existed as this was not the primary objective of the study.

This study has conclusively fulfilled the primary objective and shown that the PA vent retrieves spillover from the right ventricle which would have otherwise entered the lungs. It is however unable to conclude that all the cardioplegia administered is retrieved by the atriocaval cannula and the PA vent and that nothing enters the lungs. It is unlikely that the small quantity of cardioplegia that may escape the final exit point of the pulmonary artery vent is sufficient to be of consequence.

In an endeavour to clarify this point however, further investigations were necessary to determine whether cardioplegia is present in the left atrium. This will be detailed in the next chapter.

CHAPTER 8

Clinical Study on the retrieval of Isotope labelled cardioplegia solution from a left atrium vent during cardioplegia delivery

8.1 Introduction

This chapter presents data of a prospective study which aims to identify whether without the pulmonary artery vent in situ (as in Ch 7), the Technetium-labelled cardioplegia solution passes through the pulmonary vasculature and is retrieved by the left atrium vent.

8.2 Materials and Methods

The first five patients admitted for coronary artery bypass grafting that fitted the inclusion criteria identical to that of the initial study and consented to this study were included.

8.2.1 Surgical Technique

The standard technique of midline sternotomy was performed. After full heparanisation the heart was cannulated (see Cannulation section below) in preparation for cardiopulmonary bypass. Management of the cardiopulmonary bypass equipment was also standard as per the initial study.

Temperature was controlled with a heat exchanger incorporated in the oxygenator. Systemic temperature was lowered and maintained at 32ºC after commencing cardiopulmonary bypass. The aorta was then cross-clamped and cardioplegic solution (300ml/min for 3 minutes) was infused via a separate cannula inserted into the aortic root, at a pressure ranging between 180 -250 mmHg.

The patients in this second Technetium study were managed in a similar manner to those patients in Group A, described in the initial study, with the exception that these five patients that had the addition of a left atrium vent inserted at the time of cannulation.

The method of anaesthesia and drug administration was standardised according to the protocol of the initial study.

8.2.2 Cannulation

Cannulae were used, as follows:

1. Aortic Cannula: Research Medical Cannula (Edwards Life Sciences Research Medical Inc. 6864 South 300 West – Midvale, Utah 84047 – USA) 24 Fr. Wire reinforced angle tipped aortic cannula.

2. Atriocaval Cannula: A DLP (Medtronic Inc., Minneapolis, MN555432-5406, USA) two-stage atriocaval cannula inserted though the right atrial appendage, to allow the wider portion to sit in the right atrium and the narrower portion in the inferior vena cava. Secured in position with a purse-string suture. Most patients required size 36-46Fr selected according to patients' body surface area and expected flow rate. Drainage via this cannula was gravity assisted only.

3. Cardioplegia Antegrade Cannula with protection system: (Jostra - Maquet Cardiopulmonary AG, Hechinger Street 38; D-72145 Hirrlingen, Germany) Sidearm vent cardioplegia cannula – Inserted into the aortic root (9 Fr.), with a Y-attachment to the main-line, to enable venting of the aortic root and coronary vascular bed when cardioplegia solution not being delivered.

4. Left Atrium Cannula: DLP (Medtronic Inc., Minneapolis, MN555432-5406, USA). Inserted into the left atrium via the left superior pulmonary vein and secured into position via a purse-string suture. During the period of cardioplegia delivery continuous suction was applied via this vent and the contents were not returned to the reservoir of the cardiopulmonary bypass circuit, but instead were collected in a separate marked collection bag. Note: Suction was just within negative range, preventing preferential suctioning and preventing the wall of the pulmonary vein to collapse against the fenestrations of the vent.

8.2.3 Isotope management

Two syringe samples of Technetium Isotope material (Tc-99m), a radioactive tracer, were obtained, measured and the time thereof recorded. Each sample contained approximately 15mCi of Technetium Isotope within a 3ml sample of Sodium Chloride (NaCl) (exact measures per patient recorded). The contents of each syringe were introduced into the induction cardioplegia, and maintenance cardioplegia solutions respectively. Volumes of cardioplegia used were recorded and any remaining, unused volumes were recorded and collected for analysis.

The outflow from the left atrium vent during cardioplegia delivery was retrieved in a separate bag and thus prevented from returning to the bypass circuit. The volume remaining in all the cardioplegia bags in contact with the Technetium was recorded post-operatively and the quantity of Technetium within each bag was determined by a nuclear medicine radiographer with the use of a 'Curimentor' dose calibrator, in the same manner as the study of the pulmonary artery vent, discussed in Chapter 7. The radiographer was blind as to the surgical technique used.

The amount of Technetium (Tc-99m) in the collection bags and the introductory bags, as well as the 'empty' syringes was recorded and double checked by the independent radiographer and observed by the researcher. The time of analysis was recorded in order to account for decay. Decay was then factored into the results, and calculated according the Isotope Decay Table [177].

In order to assess with greater specificity and to establish the accuracy of the above dose calibrator measures, thereby ensuring internal validity and reproducibility of the results, further analysis was made of the quantities of Tc-99m in each sample. A pipette was used to obtain a 1ml sample from each bag. These samples were then transferred into heparinised glass vacutainers. To further ensure the validity of these results, two vacutainers from each sample were obtained and compared.

The Tc-99m tracer samples were analysed 24 hours after collection using Gamma Acquisition and Analysis on the Genie 2000vdm Well Counter. The 1ml samples were counted for 60 seconds and the integral counts for that one minute were compared. Of note, the reason for the deliberate delay in testing of samples was due to

the fact that high doses of Tc-99m saturate the well counter, rendering readings inaccurate.

The difference between amount of Tc-99m introduced and retrieved for the induction and maintenance cardioplegia deliveries were calculated and the retrieval Tc-99m expressed as a percentage of the quantity introduced (after decay factor calculated).

The paired samples were then statistically analysed. The volumes of cardioplegia introduced and volumes of blood and cardioplegia solution retrieved were also recorded and analysed.
These ratios of the well counter measures were checked against the dose calibrator measures to validate and confirm the consistency of the findings.

Due to the small sample size, data were analysed with SPSS statistical software, using Non-Parametric tests and descriptive analysis.

8.3 Results

The patient group comprised of three men and two women, with a median age of 69y (range 51-73y). Four of the five patients underwent triple bypass grafting and one patient a double bypass graft.

8.3.1 Retrieval of Technetium

Due to the small sample size, the paired samples were analysed using the Non-Parametric Wilcoxon Signed Ranks Test.

Tc-99m was present in every sample (100%) of induction and maintenance retrieval from the LA vent. For the purpose of clarification and interest, the quantities thereof will be elaborated upon.

The results of analysis of the Technetium (Tc-99m) retrieved from the left atrium vent is calculated and reported as the percentage recovered of the amount that was introduced.

The left atrium vent retrieved a median of 2.7% (the IQR - Interquartile range: 0.9 - 9.3%) of the induction dose whereas the maintenance dose showed the retrieval median to be 17% (IQR: 9.6 - 28%). The Wilcoxon Signed Ranks Test revealed that although the sum of ranks was markedly higher in the maintenance delivery, the difference was not significant, with p=0.08 (see Appendix M.1).

In Fig.8.1 below, it is evident that the percentage of Tc-99m retrieved from the left atrium vent (LA) despite not being of significance in this sample of five patients, is visibly greater following the delivery of the maintenance dose of cardioplegia than induction dose.

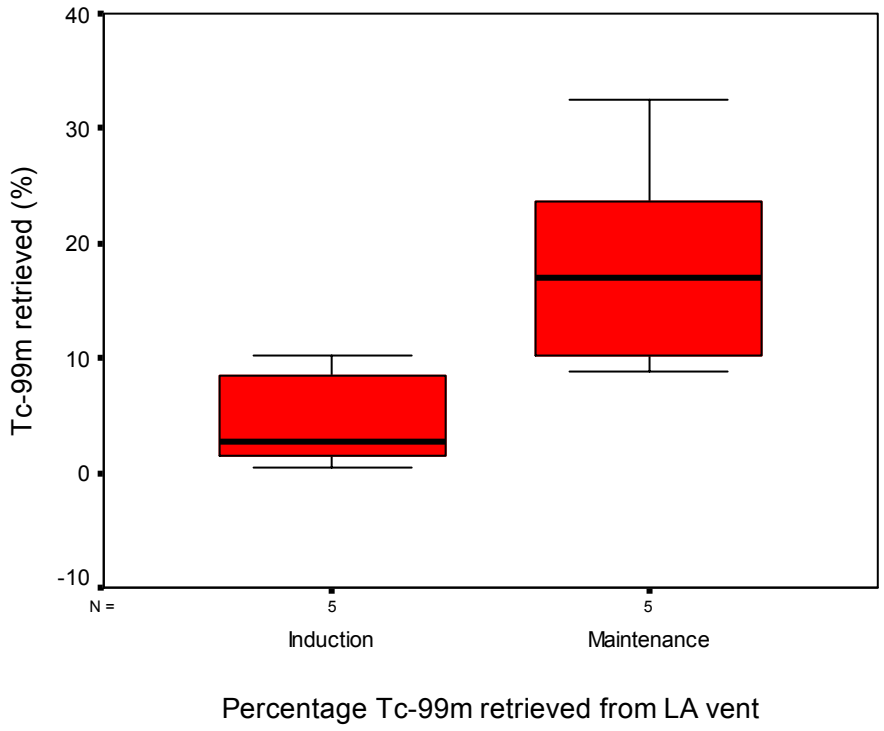


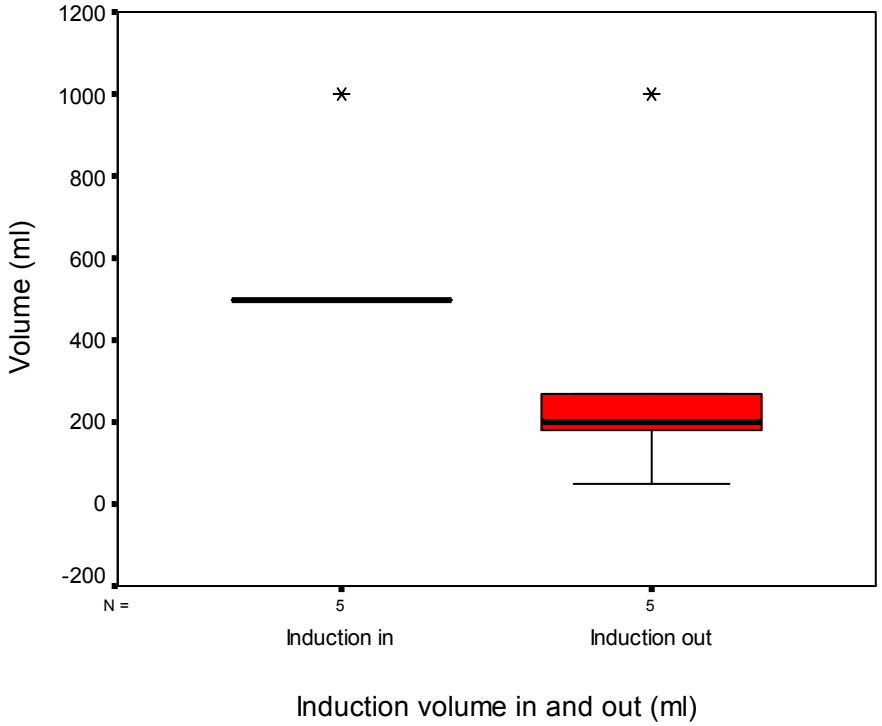
Fig. 8.1 Percentage of Technetium retrieved from the left atrium vent by induction and maintenance delivery phases

8.3.2 Volume of Delivery and Retrieval

The median total volume of induction cardioplegia solution administered using the Buckberg (4:1) protocol was 500ml (IQR: 500-750ml). Despite a median of only 200ml (IQR: 115-635ml) being retrieved from the left atrium vent, the Wilcoxon Signed Ranks Test showed this difference to be of no statistical significance, with p=0.345 (see Appendix M.2).

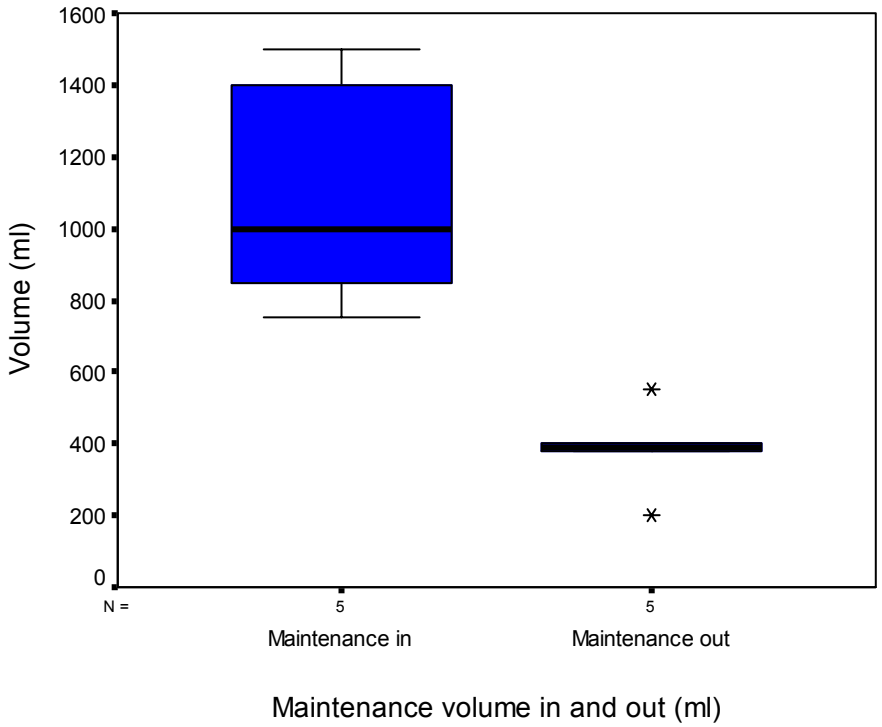
During the maintenance dose administration, the median total volume introduced was 1000ml (IQR: 800-1450ml), whilst the left atrium vent retrieved a median of 390ml (IQR: 290-475ml), which according to the Wilcoxon Signed Ranks Test, resulted in a significant decrease with p=0.043 (see Appendix M.2).

Figures 8.2 and 8.3 below illustrate these trends and differences during cardioplegia induction delivery phase and the maintenance delivery phase respectively.



Key: * = Extreme value

Fig. 8.2 Volume (ml) of cardioplegia solution administered and retrieved from the left atrium vent by induction delivery phase



Key: * = Extreme value

Fig. 8.3 Volume (ml) of cardioplegia solution administered and retrieved from the left atrium vent by maintenance delivery phase

8.3.3 Specific Activity of Tc-99m in a 10ml sample

A 10ml representative sample of the total retrieval from the pulmonary artery vent was analysed to determine the specific level of radioactivity within each standardised volume of 10ml.

Background radiation was measured at 0µCi. The median of the specific activity of Tc-99m in the induction sample from the LA vent was 11.56µCi (IQR: 5.65-28.68µCi). The specific activity median of the maintenance retrieval was 23.9µCi (IQR: 17.39-35.89µCi). The Wilcoxon Signed Ranks Test yielded no statistically significant difference between the two (p=0.345 – see Appendix L.3). Figure 8.4 below illustrates the similar levels of specific activity of Technetium retrieved by the left atrium vent at both induction and maintenance delivery time points.

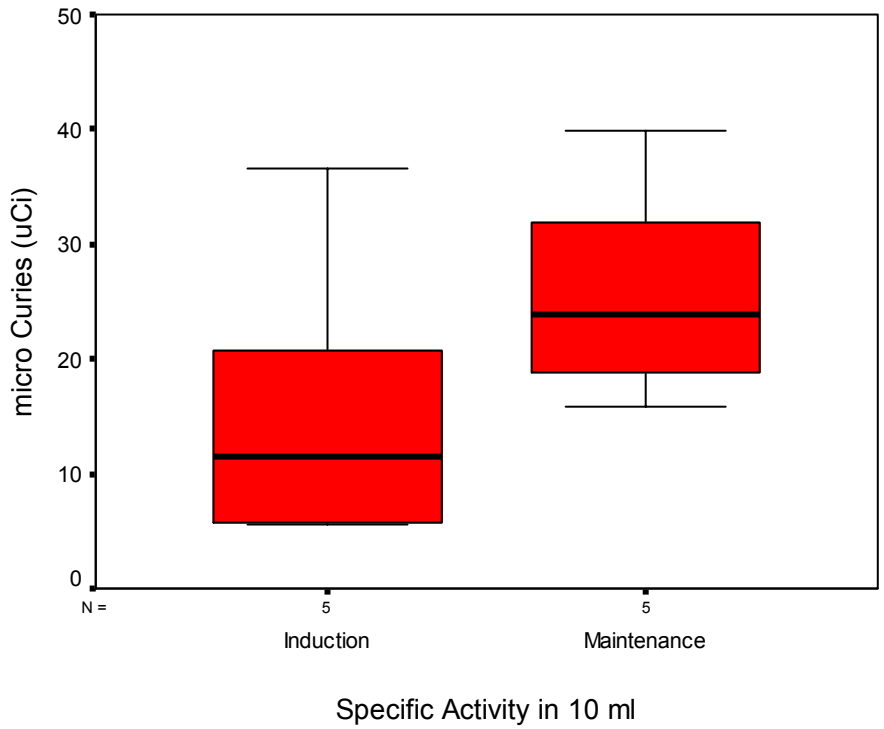


Fig. 8.4 Specific Activity of Technetium in a 10ml sample, retrieved from the left atrium vent, by induction and maintenance delivery phases

8.4 Discussion

This study by yielding a positive result in 100% of the patients has shown that without a pulmonary artery vent in situ, cardioplegia is retrieved by the left atrium vent, therefore suggesting that cardioplegia has circulated through the lungs.

As seen from the results above, following the maintenance dose of cardioplegia a greater percentage of the Tc-99m was retrieved than following the induction dose. Although this difference was not significant in this small group it demonstrates a potential trend, which perhaps with a larger sample size, would reach significance.

It may be speculated that the larger quantity of Technetium retrieved by the maintenance dose collection may be attributed to the following:

1. There was a larger volume of maintenance dose of cardioplegia solution delivered compared to induction. The specific activity of Tc-99m within a 10ml sample of the maintenance dose was however only marginally greater than that within the induction sample, implying that merely the volume of cardioplegia solution delivered and retrieved was larger.
2. As collection of the cardioplegia solution took place during the time of cardioplegia delivery, it is possible that there was an accumulation of the residual Tc-99m from the induction delivery, particularly as there is further "dead space" in terms of the pulmonary vascular bed, to travel through to reach the LA vent.
3. As cardioplegia solution was primarily drained by the atriocaval cannula to the bypass circuit, Technetium entered the bypass circuit and subsequently the systemic circulation. This may have accounted for the greater volume of blood retrieved during the maintenance dose, as it is likely to have included the bronchial and pulmonary vein return, which opens into the left atrium[236].

The relatively small percentage of Tc-99m retrieved, as well as the relatively low volumes of blood retrieved indicate again that the atriocaval cannula primarily collects the majority of cardioplegia solution. There is also a strong probability that much of the Tc-99m was "lost" in many areas which are difficult to quantify, such as

the cardiopulmonary bypass circuit; tubes between the CPB circuit and the patient; cannulae; coronary arteries; and lung parenchyma.

8.5 Limitations of this study

The small sample size limits the power of the study, thus implying some weakness of the statistical results. This is clearly as a result of the single surgeon design of the clinical trial, which on the other hand, guarantees the uniform peri-operative management of the patient population throughout the trial.

Despite the positive finding of Technetium in the left atrium of every patient in this study, it is difficult to establish what degree the return from the pulmonary and bronchial circulation contributed to this finding, as Tc-99m had not been prevented from returning to the cardiopulmonary bypass circuit and accordingly, the systemic circulation.

The bronchial arteries originate in the descending thoracic aorta or the upper intercostal arteries and supply the bronchial wall as far as the respiratory bronchioles. They communicate with branches of the pulmonary artery and anastomose with branches of the pulmonary arteries in the visceral pleura and walls of the smaller bronchi, thereafter draining into the pulmonary veins[236]. It is thought however that these anastomoses are more prevalent in the newborn and are later obliterated to a distinct degree[237]. It is therefore plausible that the finding of Tc-99m in the left atrium was merely the return of systemic, "Tc-99m contaminated" blood via the cardiopulmonary bypass circuit.

To validate this finding, the cardioplegia would need to be prevented from reaching the cardiopulmonary bypass circuit and hence the systemic circulation.

As alluded to above, the small percentage of Tc-99m retrieved is fundamentally due to a large quantity of technetium being left in the tubes, CPB circuit and coronaries. In an attempt to reduce this "loss" to extraneous factors, the method of Tc-99m delivery was modified slightly, by direct injection into the aortic root at the time of cardioplegia delivery.

CHAPTER 9

Study on the simultaneous retrieval of Isotope labelled cardioplegia solution from the pulmonary artery and left atrium with superior and inferior vena cavae snared

9.1 Introduction

The aim of the present study is to determine, through the simultaneous collection from the pulmonary artery and the left atrium vent, whether there is spill over of cardioplegia solution from the pulmonary artery vent, which then passes through the pulmonary vasculature and is collected by the left atrium vent. By snaring the vena cavae, it is ensured that any return to the left atrium vent is not from the cardiopulmonary bypass circuit, nor therefore from the systemic circulation, but has to have been via the lung parenchyma.

9.2 Materials and Methods

The first five patients admitted for coronary artery bypass grafting that fitted the inclusion criteria identical to that of the initial study and consented to this study were included.

9.2.1 Surgical Technique

The standard technique of midline sternotomy was performed. After full heparanisation the heart was cannulated (see Cannulation section below) in preparation for cardiopulmonary bypass. Management of the cardiopulmonary bypass equipment was also standard as per the initial study.

Coronary artery return was prevented from being drained from the heart to the CPB by snaring of the superior and inferior vena cavae immediately prior to the institution of CPB.

Temperature was controlled with a heat exchanger incorporated in the oxygenator.

Systemic temperature was lowered and maintained at 32ºC after commencing cardiopulmonary bypass. The aorta was then cross-clamped and cardioplegic solution (300ml/min for 3 minutes) was infused via a separate cannula inserted into the aortic root, at a pressure ranging between 180 - 250 mmHg.

9.2.2 Cannulation

Cannulae were used, as follows:

1. Aortic Cannula: Research Medical Cannula (Edwards Life Sciences Research Medical Inc. 6864 South 300 West – Midvale, Utah 84047 – USA) 24 Fr. Wire reinforced angle tipped aortic cannula.

2. Cardioplegia Cannula: DLP (Medtronic Inc., Minneapolis, MN555432-5406, USA). Sidearm vent cardioplegia cannula – Inserted into the aortic root (9 Fr.), with a 3 way tap attachment to the main-line, to enable introduction of the Technetium directly as a bolus, via a syringe, at time of cardioplegia delivery and also to enable venting of the aortic root and coronary vascular bed when the cardioplegia solution was not being delivered.

3. Pulmonary Artery Cannula: DLP (Medtronic Inc., Minneapolis, MN555432-5406, USA) Pulmonary Artery Cannula (Size 16Fr.). Inserted 3 – 4 cm into the main pulmonary artery secured in position via a purse-string suture. During the period of cardioplegia delivery continuous suction was applied via this vent and the contents were not returned to the reservoir of the cardiopulmonary bypass circuit, but instead were collected in a separate marked collection bag. Note: Suction was just within negative range, preventing preferential suctioning and preventing the wall of the pulmonary artery to collapse against the fenestrations of the vent.

4. Left Atrium Cannula: DLP (Medtronic Inc., Minneapolis, MN555432-5406, USA). Inserted into the left atrium via the left superior pulmonary vein and secured into position via a purse-string suture. During the period of cardioplegia delivery continuous suction was applied via this vent and the contents were not returned to the reservoir of the cardiopulmonary bypass

circuit, but instead were collected in a separate marked collection bag. Note: Suction was just within negative range, preventing preferential suctioning and preventing the wall of the pulmonary artery to collapse against the fenestrations of the vent.

5. Two caval cannulae: (Medtronic Inc., Minneapolis, MN555432-5406, USA). Inserted in the superior and inferior vena cavae respectively, distal to the snares.

The diagram below illustrates the positions of the snares and cannulae during this study. Note, the left atrium vent is not shown.

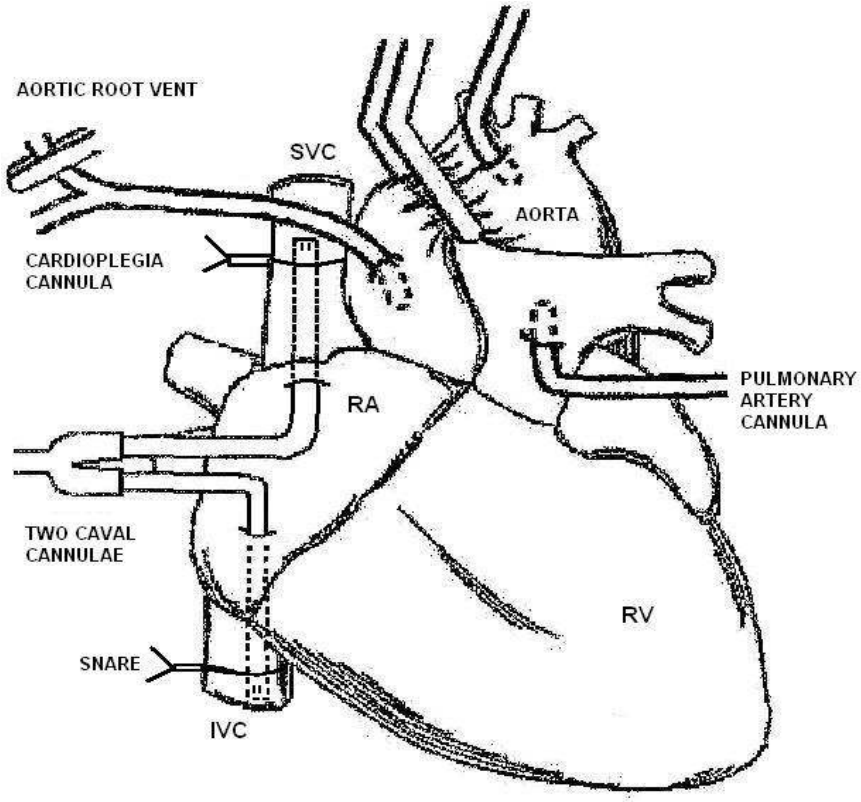


Fig 9.1 Diagram showing cannulae positions during cardiopulmonary bypass with vena cavae snared

Key: IVC, inferior vena cava; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

9.2.3 Isotope management

One syringe sample of Technetium Isotope material (Tc-99m), a radioactive tracer, were obtained, measured and the time thereof recorded. The sample contained approximately 5mCi of Technetium Isotope made up to 3ml volume with Sodium Chloride (NaCl) (exact Tc-99m measures per patient recorded).

The contents of the syringe were introduced as a bolus into the patient at the time of induction cardioplegia delivery via the 3-way connector on the cardioplegia cannula.

The retrieval of blood from the pulmonary artery vent and left atrium vent was collected in separate, labelled reservoirs and analysed in the same manner as the previous studies, wherein the volume remaining in the collection bags was recorded post-operatively and the quantity of Technetium within each bag was determined by a nuclear medicine radiographer with the use of a 'Curimentor' dose calibrator.

During cardioplegia delivery, a syringe sample of blood returning to the CPB circuit was obtained and analysed to determine whether any cardioplegia was escaping the snares on the vena cavae and entering the CPB circuit.

The radiographer was again blind as to the surgical technique used and any anticipated outcomes.

The amount of Technetium (Tc-99m) in the collection bags and the 'empty' introductory syringes was recorded and double checked by the independent radiographer and observed by the researcher. The time of analysis was recorded in order to account for decay. Decay was then factored into the results, and calculated by the researcher, according the Isotope Decay Table [177].

In order to assess with greater specificity and to confirm the accuracy of the above dose calibrator measures, thereby ensuring internal validity and reproducibility of the results, a further analysis was made of the quantities of Tc-99m in each sample. A pipette was used to obtain a 1ml sample from each bag and the sample of blood collected at the CPB circuit. These samples were then transferred into heparinised glass vacutainers. To ensure the validity of these results, two vacutainers of each sample were obtained and compared.

The Tc-99m tracer samples were analysed after collection using Gamma Acquisition and Analysis on the Genie 2000vdm Well Counter. The 1ml samples were each counted for 60 seconds and the integral counts for that one minute were compared.

The difference between amount of Tc-99m introduced and retrieved for the induction cardioplegia delivery was calculated and the retrieval Tc-99m was expressed as a percentage of the quantity introduced (after decay factor calculated). The paired samples were then statistically analysed. The volume of blood and cardioplegia solution retrieved from the pulmonary artery vent and left atrium vent were also recorded and analysed.

These ratios of the well counter measures were checked against the dose calibrator measures to validate and confirm the consistency of the findings.

Data were analysed with SPSS statistical software. Due to the limited study size and possible skewness resulting from the small sample size, Non-Parametric tests and descriptive analysis were utilized.

9.3 Results

The patient group comprised 3 men and 2 women, with a median age of 67y (range 64-76y). Four of the five patients underwent triple bypass grafting; one patient underwent a double bypass graft.

9.3.1 Retrieval of Technetium

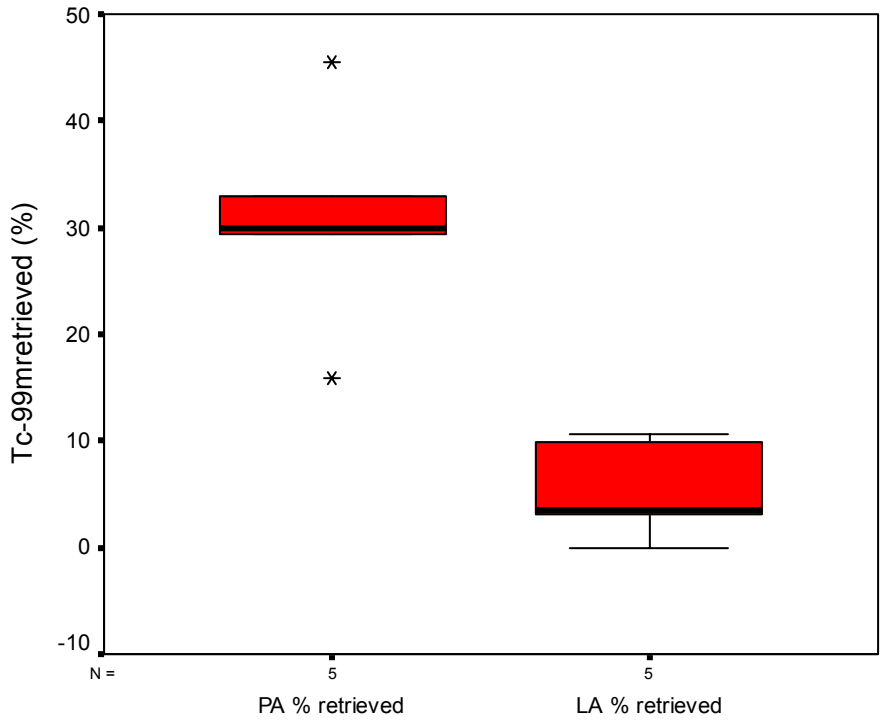
There was no evidence of Technetium in the samples of blood returning to the cardiopulmonary bypass circuit during cardioplegia delivery.

Tc-99m was present in all five samples obtained from the pulmonary artery vent. One of the five samples of retrieval from the LA vent did not contain any technetium and hence any cardioplegia solution, indicating the PA vent was 100% effective. In the other four, there minimal quantities were retrieved from the LA vent, indicating the PA vent was greater than 90% effective. For the purpose of clarification and interest, the quantities thereof will be illustrated.

Due to the small sample size, the paired samples were analysed using the Non-Parametric Wilcoxon Signed Ranks Test. The results of analysis of the Technetium (Tc-99m) retrieved from the pulmonary artery vent and left atrium vent is calculated and reported as the percentage recovered of the amount that was introduced.

The pulmonary artery vent retrieved a median of 29.9% (the IQR - Interquartile range: 22.6-39.2%) of the induction dose whereas the left atrium vent retrieved a median of 3.6% (IQR: 1.6-10.3%). The Wilcoxon Signed Ranks test revealed this to be a significant difference with p=0.043 (see Appendix N.1).

In Fig.9.2 below, it is evident that the percentage of Tc-99m retrieved from the pulmonary artery vent (PA) was greater than the left atrium vent (LA) following the delivery of cardioplegia.



Key: * = Extreme value

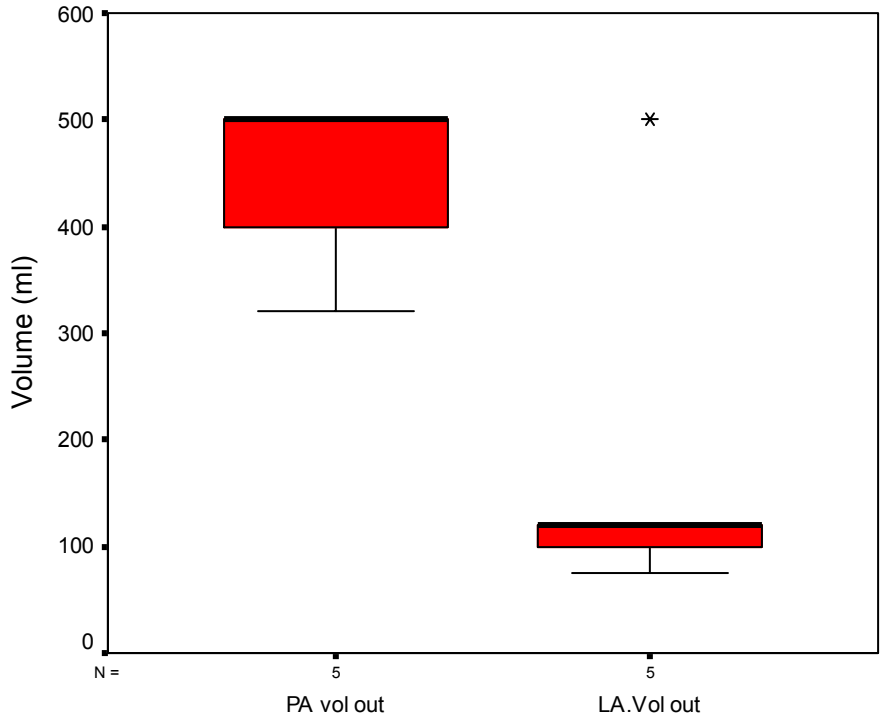
Fig.9.2 Percentage of Tc-99m retrieved from pulmonary artery and left atrium vent

9.3.2 Volume of Delivery and Retrieval

Cardioplegia delivery was standard in all patients, with duration of delivery being equal.

The median total volume of induction cardioplegia solution retrieved from the pulmonary artery vent was 500ml (IQR: 360-500ml). The median left atrium vent return was 120ml (IQR: 87.5-310ml). Despite the observed difference in volume retrieved, this was not of statistical significance, with p=0.068 (see Appendix N.2).

Figure 9.3 below shows the trend that a higher volume of cardioplegia solution was retrieved by the pulmonary artery vent compared with the left atrium vent, but this is of no statistical significance.



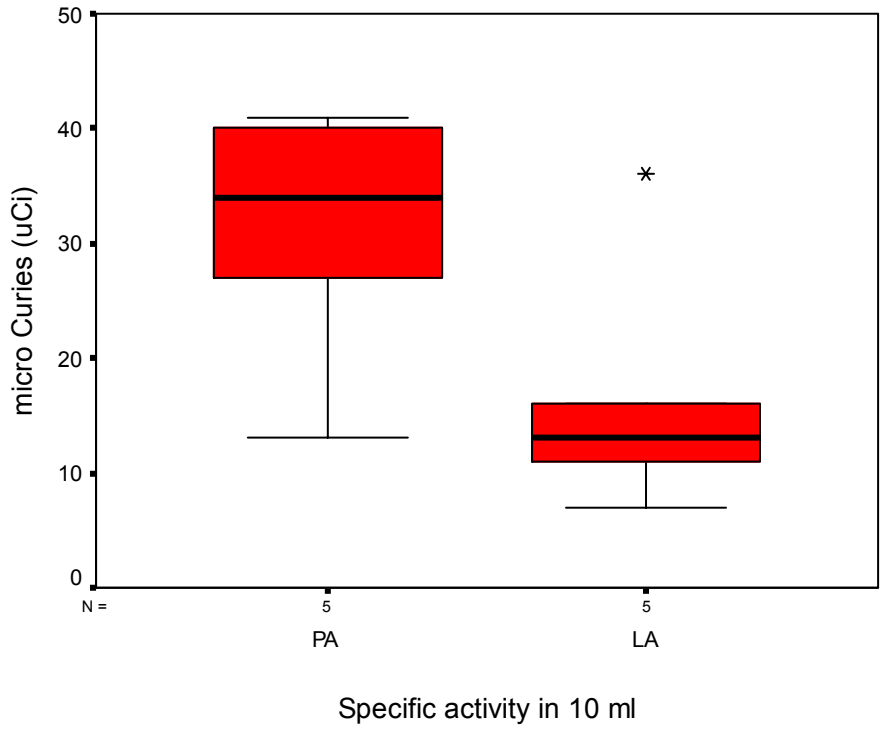
Key: * = Extreme value

Fig. 9.3 Volume of cardioplegia solution retrieved from the pulmonary artery vent and left atrium vent during induction of cardioplegia

9.3.3 Specific Activity of Tc-99m in a 10ml sample

A 10ml representative sample of the total retrieval from the pulmonary artery vent and left atrium vent was analysed to determine the specific level of radioactivity within each standardised volume of 10ml.

The median of the pulmonary artery vent sample was 34µCi (IQR: 20-41µCi). The specific activity median of the left atrium vent retrieval was 13µCi (IQR: 9-26µCi). The Wilcoxon Signed Ranks test yielded a statistically significant difference between the two (p=0.043 – see Appendix N.3). The Figure 9.4 below illustrates this large difference.



Key: * = Extreme value

Fig. 9.4 Specific Activity of Technetium in a 10ml sample, retrieved from the pulmonary artery vent and left atrium vent during induction of cardioplegia

9.4 Discussion

In the above study cardioplegia solution was prevented from entering the cardiopulmonary bypass circuit through snaring of the superior and inferior vena cavae, and effectively so, as evidenced by the Technetium-free sample taken at the CPB circuit mid-way through cardioplegia delivery. *The cardioplegia solution was therefore 'forced' to enter the right ventricle and subsequently the pulmonary artery.* It is evident that the majority of cardioplegia solution was removed by the pulmonary artery vent.

It appears that the PA vent, working in isolation, was not 100% effective in eliminating all the CP solution in every patient, as a small quantity was retrieved by the LA vent in 4 of the 5 patients and none in the 5th patient. It should however be borne in mind that in the original study, the pulmonary artery vent was merely used as a secondary removal point to collect the "overflow", where most of the cardioplegia solution had primarily been evacuated by the atriocaval cannula. Had the snares not been in place, and the cardioplegia not been drawn away from the heart in the usual manner, but had been prevented from entering the systemic circulation, it is feasible that the pulmonary artery vent would have collected the remaining solution and nothing, or very little, would have escaped it and entered the lung parenchyma.

9.5 Limitations of this study

Firstly, it must be emphasised that although statistical significance was reached in the percentage of Tc-99m retrieved and the volume retrieved, it may be merely from the small sample size. There was a great degree of overlapping range in the results of the specific activity of Tc-99m in the study, with no statistical significance detected, emphasizing the small sample size as insufficient to reach a firm quantitative conclusion. As the power is limited due to the study size, the non-parametric test was used. The p-value is highly dependant upon sample size. As a result of this, any composite conclusions are unable to be made.

As indicated above, the heart and lungs during cardiopulmonary bypass are not a completely isolated system and it is not feasible to isolate the return from the

atriocaval cannulae so that the Tc-99m does not ‘contaminate’ the findings and lead to “false positive” readings elsewhere.

A further study was undertaken to determine whether cardioplegia circulates through the lungs or merely accumulates and ‘pools’ in the pulmonary vasculature.

CHAPTER 10

Clinical Study to determine whether, by assessing LA vent retrieval, cardioplegia circulates through the lungs or merely accumulates in the pulmonary vasculature

10.1 Introduction

This study arose due to the question that the samples of left atrium vent return (in Chapter 8) were possibly positive for cardioplegia as they were 'contaminated' with Tc-99m, as a result of entering the systemic circulation after passing through the bypass circuit and entering the bronchial circulation, which ultimately drains into the left atrium.

The second question was whether if forced to enter the pulmonary artery, the cardioplegia would indeed circulate through the pulmonary vasculature to the left atrium or merely pool and accumulate in the pulmonary artery and right side of the heart.

In an endeavour to isolate the findings as best as possible from the systemic circulation and consequently eliminate the likelihood of 'contamination' of Tc-99m, this final study was instituted.

10.2 Materials and Methods

The first five patients admitted for coronary artery bypass grafting that fitted the inclusion criteria identical to that of the initial study and consented to this study were included.

10.2.1 Surgical Technique

The standard technique of midline sternotomy was performed. After full heparanisation the heart was cannulated (see Cannulation section below) in preparation for cardiopulmonary bypass. Management of the cardiopulmonary bypass equipment was also standard as per the initial study.

Coronary artery return was prevented from being drained from the heart to the CPB by snaring of the superior and inferior vena cavae immediately prior to the institution of CPB.

Temperature was controlled with a heat exchanger incorporated in the oxygenator. Systemic temperature was lowered and maintained at 32ºC after commencing cardiopulmonary bypass. The aorta was then cross-clamped and cardioplegic solution (300ml/min for 3 minutes) was infused via a separate cannula inserted into the aortic root, at a pressure ranging between 180 -250 mmHg.

10.2.2 Cannulation

Cannulae were used, as follows:

1. Aortic Cannula: Research Medical Cannula (Edwards Life Sciences Research Medical Inc. 6864 South 300 West – Midvale, Utah 84047 – USA) 24 Fr. Wire reinforced angle tipped aortic cannula.

2. Cardioplegia Antegrade Cannula with protection system: (Jostra - Maquet Cardiopulmonary AG, Hechinger Street 38; D-72145 Hirrlingen, Germany) Sidearm vent cardioplegia cannula – Inserted into the aortic root (9 Fr.), with a 3 way tap attachment to the main-line, to enable introduction of the Technetium directly as a bolus, via a syringe, at time of cardioplegia delivery and also to enable venting of the aortic root and coronary vascular bed when the cardioplegia solution was not being delivered.

3. Left Atrium Cannula: DLP (Medtronic Inc., Minneapolis, MN555432-5406, USA). Inserted into the left atrium via the left superior pulmonary vein and secured into position via a purse-string suture. During the period of cardioplegia delivery continuous suction was applied via this vent and the contents were not returned to the reservoir of the cardiopulmonary bypass circuit, but instead were collected in a separate marked collection bag. Note: Suction was just within negative range, preventing preferential suctioning and preventing the wall of the pulmonary artery to collapse against the fenestrations of the vent.

4. Two caval cannulae: (Medtronic Inc., Minneapolis, MN555432-5406, USA). Inserted in the superior and inferior vena cavae respectively, distal to the snares.

10.2.3 Isotope management

One syringe sample of Technetium Isotope material (Tc-99m), a radioactive tracer, were obtained, measured and the time thereof recorded. The sample contained approximately 5mCi of Technetium Isotope made up to 3ml volume with Sodium Chloride (NaCl) (exact Tc-99m measures per patient recorded).

The contents of the syringe were introduced as a bolus into the patient at the time of induction cardioplegia delivery via the 3-way connector on the cardioplegia cannula.

The retrieval of blood from the left atrium vent was collected in a separate, labelled reservoir and analysed in the same manner as the previous studies, wherein the volume remaining in the left atrium collection bag was recorded post-operatively and the quantity of Technetium within the bag was determined by a nuclear medicine radiographer with the use of a 'Curimentor' dose calibrator.

During cardioplegia delivery, a syringe sample of blood returning to the CPB circuit was obtained and analysed to determine whether any cardioplegia was escaping the snares around the vena cavae and entering the CPB circuit.

The radiographer was again blind as to the surgical technique used and any anticipated outcomes.

The amount of Technetium (Tc-99m) in the collection bag and the 'empty' introductory syringe was recorded and double checked by the independent radiographer and observed by the researcher. The time of analysis was recorded in order to account for decay. Decay was then factored into the results, and calculated according the Isotope Decay Table [177].

In order to assess with greater specificity and to confirm the accuracy of the above dose calibrator measures, thereby ensuring internal validity and reproducibility of the results, a further analysis was made of the quantities of Tc-99m in each sample. A

pipette was used to obtain a 1ml sample from the bag and from the sample of blood taken at the CPB circuit. These samples were then transferred into heparinised glass vacutainers. To ensure the validity of these results, two vacutainers of each sample were obtained and compared.

The Tc-99m tracer samples were analysed after collection using Gamma Acquisition and Analysis on the Genie 2000vdm Well Counter. The 1ml samples were each counted for 60 seconds and the integral counts for that one minute were compared.
The difference between amount of Tc-99m introduced and retrieved for the induction cardioplegia delivery was calculated and the retrieval Tc-99m was expressed as a percentage of the quantity introduced (after decay factor calculated). The paired samples were then statistically analysed. The volume of blood and cardioplegia solution retrieved from the left atrium vent was also recorded and analysed.

These ratios of the well counter measures were checked against the dose calibrator measures to validate and confirm the consistency of the findings.

Data were analysed with SPSS statistical software. Due to the limited study size and possible skewness resulting from the small sample size, Non-Parametric tests and descriptive analysis were employed.

10.3 Results

The patient group comprised 5 men, with a median age of 63y (range 51-73y). All of the five patients underwent triple bypass grafting.

10.3.1 Retrieval of Technetium

There was no evidence of Technetium in the samples of blood returning to the cardiopulmonary bypass circuit during cardioplegia delivery.

Tc-99m and hence cardioplegia was present in all five samples obtained from the left atrium vent (100%). For the purpose of clarification and interest, the quantities thereof will be presented.

Due to the single study design and the small sample group, the data were analysed using descriptive statistics only. The results of analysis of the Technetium (Tc-99m) retrieved from the left atrium vent is calculated and reported as the percentage recovered of the amount that was introduced.

The left atrium vent retrieved a median of 31% (the IQR - Interquartile range: 5.9-43.9%) of the induction dose.
In Table 10.1 below, it is evident that the percentage of Tc-99m retrieved from the left atrium vent (LA) following the delivery of cardioplegia ranges from 3.3% to a maximum of 47% of that introduced.

Table 10.1 Statistics from left atrium vent study with vena cavae snared.

N=5		% Retrieved	Volume Out (ml)	Specific Activity (μ)
Median		31.02	380	30.00
Minimum		3.3	190	8
Maximum		47.2	440	45
Percentiles	25	5.94	255	10.50
	50	31.02	380	30.00
	75	43.97	425	43.50

10.3.2 Volume of Delivery and Retrieval

Cardioplegia delivery was standard in all patients, with duration of delivery being equal.

The median total volume of induction cardioplegia solution retrieved from the left atrium vent was 380ml (IQR: 255-425ml) (See Table 10.1).

10.3.3 Specific Activity of Tc-99m in a 10ml sample

A 10ml representative sample of the total retrieval from the left atrium vent was analysed to determine the specific level of radioactivity within a standardised volume of 10ml.

The specific activity median of the left atrium vent retrieval was 30μCi (IQR: 10.5-43.5μCi) See Table 10.1.

10.4 Discussion

In this study cardioplegia solution was prevented from entering the cardiopulmonary bypass circuit through snaring of the superior and inferior vena cavae, and effectively so, as evidenced by the Technetium-free sample taken at the CPB circuit mid-way through cardioplegia delivery. The cardioplegia solution was therefore 'forced' to enter the right ventricle and subsequently the pulmonary artery and lung parenchyma. The retrieval of blood and technetium labelled cardioplegia, in every patient, from the left atrium vent proves that cardioplegia passes through the pulmonary circulation and does not merely accumulate and 'pool' in the lung parenchyma as may have been argued prior to this study.

10.5 Limitations of this study

The small sample size limits the validity of the findings somewhat, as descriptive statistics only were able to be employed to analyse the findings.

Nevertheless, the study was not planned for statistical analysis and achieved the aim of determining that cardioplegia can and does circulate the lung parenchyma, if not collected by vents and cannulae in the right side of the heart.

CHAPTER 11

Conclusion

Lung deterioration following cardiopulmonary bypass surgery is a widely explored complication and a myriad of factors have been held responsible, including but not limited to: the surgical incision; the cardiopulmonary bypass circuit; cardioplegia; the type of donor grafts utilised; anaesthesia and fluid administered. No studies have previously investigated whether allowing cold-blood cardioplegic solution to enter the lung parenchyma during the period of cardioplegia delivery has a beneficial or detrimental effect on the clinical outcome of lung function following cardiopulmonary bypass surgery.

The initial section of this research work consisted of a double blind randomised clinical trial on 142 patients admitted to undergo full cardiopulmonary bypass. A total of 403 patients were screened for admission to this study. Patients were subject to strict exclusion criteria and were excluded if they possessed any other medical condition which may have influenced the outcome of the results. The homogeneity of the two groups is evident by the fact that patient demographics; baseline health status and risk factors were very similar between the two groups.

The control group underwent routine cardiopulmonary bypass grafting. The study group had the intervention of a pulmonary artery vent sutured in position at the time the heart was cannulated for bypass. During cardioplegia delivery the cardioplegia was removed via the atriocaval cannula in the control group (A) and via the atriocaval cannula and the pulmonary artery vent in the study group (B). Aside from this intervention in the study group, the two groups were managed identically intra- and post-operatively. This is evident in the comparable findings between the two groups regarding anaesthetic technique; donor grafting and number; cardiopulmonary bypass time; aortic clamp times; volume of cardioplegia delivered; operative time and ventilation time as well as transfusion requirements.

The findings of the study confirmed that respiratory impairment after uncomplicated cardiopulmonary bypass, even in low risk patients, is relatively common.

Arterial Oxygen and Oxygen Saturation, as established with previous studies[126;151], shows the nadir to occur on the second post-operative day following cardiopulmonary bypass. By the last recorded reading of Arterial blood samples taken, on the fifth post-operative day, it was evident that the levels were still significantly below those of the baseline.

There are considerable reductions in lung volumes, particularly in the early postoperative period. The impairment in respiratory function, which is often severe and still marked in a large number of patients by the end of the fifth post-operative day has often not returned to baseline levels in many patients by their one-month follow-up appointment.

Radiology findings showed significant abnormalities in the form of atelectasis and pleural effusions following bypass surgery.

The consistency of the results within each group throughout the study provides strong evidence that the measurements taken were accurate. The use of standardised equipment and vigilant adherence to the protocol ensured no extraneous deviation. The internal validity of this study was therefore good and accurate.

The outcome measures discussed above all recorded a significant change within each group over time. Inter-group comparisons however showed these changes were not significant, with both groups deteriorating by the same degree post-operatively, therefore establishing that these changes were independent of the intervention of the pulmonary artery vent.

Pulmonary function and gas exchange, although markedly reduced following cardiac surgery, is therefore not affected by the insertion of a pulmonary artery vent during the time of cold blood cardioplegia delivery in order to prevent the solution from entering the lung parenchyma. There is therefore no advantage to clinical pulmonary function by placing a pulmonary artery vent in the pulmonary artery during cardiopulmonary bypass.

The initial study was however unable to definitively confirm that the similar outcomes were reflective of the control group having had cardioplegia enter and circulate the lung parenchyma and the study group having had cardioplegia prevented from entering the lungs. As a result of this query and limitation, it was necessary to establish the efficacy of the pulmonary artery vent and to determine whether cardioplegia indeed circulates through the lung parenchyma or merely accumulates and 'pools'.

As there are no related studies in the literature answering these questions, a method of determining the efficacy of the pulmonary artery vent and the pathway of cold blood cardioplegia solution was formulated and investigated.

By labelling the cold blood cardioplegia solution with a radio labelled isotope, it was established in the first sub-study that despite drainage from the atriocaval cannula, the pulmonary artery vent does collect a moderate amount of "spill over" that would have otherwise entered the lung parenchyma.

A further sub-study investigated whether, without a pulmonary artery vent in situ, cardioplegia solution is retrieved at the left atrium. The findings were positive that cardioplegia is retrieved at the left atrium. This study was however flawed as the return to the left atrium included the return from the systemic circulation (return from the cardiopulmonary bypass circuit) via the bronchial and pulmonary circulation. The likelihood of a 'false positive' finding was therefore high and further study was necessary.

The simultaneous retrieval of isotope labelled cardioplegia solution from the pulmonary artery and the left atrium whilst the superior and inferior vena cave were snared, tested the efficacy of the pulmonary artery vent and ensured that any cardioplegia retrieved from the left atrium must have circulated the lungs. This third sub-study confirms the efficacy of the pulmonary artery vent as one patient had 100% retrieval from the pulmonary artery vent. Of the remaining four patients, the pulmonary artery vent was effective in retrieving over 90% of the cardioplegia that reached the pulmonary artery. This study however did not conclusively show whether

cardioplegia blood solution circulates the lungs or merely accumulates and "pools" within.

The final sub-study conclusively proved that when cold blood cardioplegia enters the pulmonary artery and lung parenchyma, it indeed circulates the lungs and does not merely accumulate, as may have been initially argued.

It may be argued that the small sample size in each of these follow up studies disputes the validity of the findings, however the studies were not employed to ascertain statistical significance or quantities, merely the presence or absence of cardioplegia at specific points. This has been successfully established.

The relevance of these sub-studies to the original study therefore allows one to reach more definitive conclusions, namely that:

1. In the control group, the cold blood cardioplegia solution that did not drain from the atriocaval cannula would have entered the lungs and circulated the lung parenchyma during cardiopulmonary bypass.

2. It is highly likely that in the study group, the pulmonary artery vent ensured that no or very little cold blood cardioplegia entered the lung parenchyma.

3. It can therefore be stated that cold blood cardioplegia solution is innocuous to the lungs, as evidenced in the identical clinical findings between the two groups.

As ethical approval to perform lung biopsies was not granted, no direct measurement was made of lung ischaemia. Consequently, from this study, one is unable to comment on the degree of ischaemia or inflammatory response.

As far as the inflammatory response is concerned however, both groups were exposed to the same type of extracorporeal circuit for a similar time period, underwent the same extent of operative trauma, and received comparable amounts of blood, and thus the degree of inflammation should be considered approximately the same.

It has been established that allowing cardioplegia to enter and circulate the lungs does not have a detrimental effect on clinical lung function. As alluded to in the opening paragraph of this chapter, a multitude of factors have been implicated in the deteriorations in lung function noted following cardiopulmonary bypass, but from this study it is evident that cold blood cardioplegia is not a source of lung deterioration and therefore should no longer be included as a causative factor.

The mere fact that cardioplegia solution is innocuous to the lungs and the fact it does circulate through the lungs during cardiopulmonary bypass could mean that the insertion of an endothelial "protective" solution may provide an improvement in clinical lung function. A recent study[238], initiated after the present study, has evaluated the effect on piglets of perfusion with oxygenated blood during aortic cross clamping. Their preliminary findings are that continuous perfusion is effective in preventing lung injury, but to date no studies have been commenced to determine the clinical significance of their findings.

It is possible that the introduction of a protective solution during the period of cardiopulmonary bypass will be more beneficial on clinical lung function than merely allowing or excluding cold blood cardioplegia solution from going through the lungs. Further study in this area is required, although research into the other causative factors of lung deterioration, such as the cardiopulmonary bypass circuit, should continue.

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Appendix A

Shunt Fraction Estimation Calculation (Q_S/Q_T)

Arterial /alveolar ratio: PaO_2 / PAO_2

NORMAL VALUE > 60%

The alveolar level is calculated as follows:

$PAO_2 = FiO_2$ (PB x PH_20) – $PaCO_2$ /r

Assuming: 1. PB (barometric pressure) is 760mmHg
2. PH2O (Water vapour pressure) is 47;
3. r (respiratory quotient) is 0.8

These assumptions are generally accurate at sea level.
Therefore the equation is calculated:

$PAO_2 = FiO_2$ (713) – $PaCO_2$/ 0.8

As long as the a/A ratio is over 0.60, the intrapulmonary shunt is small.
If the shunt increases, the a/A ratio decreases.
The lower the ratio, the worse the patient's pulmonary status.

The a/A ratio should change by greater than 5% before any assumption of change in (Q_S/Q_T) has occurred.

It is not known the extent of change required in order to indicate a clinically significant change.

Appendix B

Demographics

Test for Skewness of Data

Frequencies:

Statistics

		AGE	HEIGHT	WEIGHT	BMI
N	Valid	142	142	142	142
	Missing	0	0	0	0
Skewness		-.202	-.311	-.055	.091
Std. Error of Skewness		.203	.203	.203	.203

Data between the groups were therefore evenly distributed.

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
AGE	Equal variances assumed	1.411	.237	.144	140	.886	.23	1.569	-2.877	3.327
	Equal variances not assumed			.144	139.073	.886	.23	1.569	-2.877	3.328
HEIGHT	Equal variances assumed	.080	.777	-1.415	140	.159	-.0208	.01473	-.04997	.00828
	Equal variances not assumed			-1.415	139.507	.159	-.0208	.01473	-.04997	.00828
WEIGHT	Equal variances assumed	1.199	.275	-1.192	140	.235	-2.73	2.292	-7.264	1.799
	Equal variances not assumed			-1.192	136.772	.235	-2.73	2.292	-7.264	1.800
BMI	Equal variances assumed	1.753	.188	-.564	140	.574	-.3374	.59871	-1.52110	.84625
	Equal variances not assumed			-.564	138.462	.574	-.3374	.59871	-1.52121	.84636

Appendix C

Ejection Fraction

Statistics

EjectionFraction

N	Valid	134
	Missing	8
Mean		69.206
Median		70.500
Skewness		-.429
Std. Error of Skewness		.209

Independent Samples T-Test for Ejection Fraction

	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
EQUAL VARIANCES:								Lower	Upper
ASSUMED	.722	.397	-1.086	132	.279	-2.027	1.8664	-5.7188	1.6650
NOT ASSUMED			-1.086	129.740	.280	-2.027	1.8664	-5.7194	1.6656

Appendix D

Cardiac Enzymes and Coagulation Studies

Mann-Whitney Test: Ranks

	Group Numeric	N	Mean Rank	Sum of Ranks
CPK Pre-op	A	30	34.03	1021.00
	B	37	33.97	1257.00
	Total	67		
CKMB Isoenzyme Pre-op	A	24	30.75	738.00
	B	32	26.81	858.00
	Total	56		
Coagulation Control Pre-op	A	30	25.82	774.50
	B	28	33.45	936.50
	Total	58		
INR PRE-OP	A	62	64.65	4008.50
	B	56	53.79	3012.50
	Total	118		
PTT PRE-OP	A	63	58.31	3673.50
	B	53	58.73	3112.50
	Total	116		
Bleeding time Pre-op	A	55	54.29	2986.00
	B	49	50.49	2474.00
	Total	104		

Test Statistics (a)

	CPK Pre-Op	CKMB Isoenzyme Pre-op	Coagulation Control Pre-op	INR Pre-op	PTT Pre-op	Bleeding Time Pre-op
Mann-Whitney U	554.00	330.00	309.50	1416.50	1657.50	1249.00
Asymp. Sig. (2-tailed)	0.990	0.366	0.085	0.071	0.947	0.520

a Grouping Variable: group numeric

Appendix E

Smoking Behaviour

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
No. of years smoked * GROUP	93	65.5%	49	34.5%	142	100.0%
No. of cigs per day * GROUP	93	65.5%	49	34.5%	142	100.0%

Report

GROUP		No. of years smoked	No. of cigs. per day
A	Median	18.00	20.00
	Minimum	5	5
	Maximum	47	60
B	Median	20.00	19.00
	Minimum	1	2
	Maximum	50	70
Total	Median	20.00	20.00
	Minimum	1	2
	Maximum	50	70

Mann-Whitney U Test: Ranks

	group numeric	N	Mean Rank	Sum of Ranks
No. of years smoked	A	45	44.88	2019.50
	B	48	48.99	2351.50
	Total	93		
No. of cigs. per day	A	45	49.54	2229.50
	B	48	44.61	2141.50
	Total	93		

Test Statistics (a)

	No. of years smoked	No. of cigs. per day
Mann-Whitney U	984.500	965.500
Asymp. Sig. (2-tailed)	.461	.368

a Grouping Variable: group numeric

Appendix F

Patients excluded from the study

Table F.1 Pre-Operative Exclusions

REASON	NO.
OPCAB	68
M.I. Pre-op	51
Emergency	39
Re-do Bypass	20
BMI > 30	15
Lung Impairment	9
MIDCAB	7
Low E.F.	7
Hybrid procedure	5
Refusal to participate	5
Renal Impairment	2
TOTAL	**228**
Other Institution (not screened)	142

Table F.2 Exclusions after admission to study

REASON	NO.
IABP required	7
Surgery too late in day	6
Protocol Violation	6
Peri-Operative M.I.	3
No forms completed	3
Confused post-op	2
Too low paO_2	2
DNA 1 month follow-up appt.	2
Refusal to participate	2
TOTAL	**33**

Appendix G

Referring cardiologists

Table G.1 Cross tabulation of Group to Cardiologist

			Cardiologist										Total
			1	2	3	4	5	6	7	8	9	10	
group	A	No.	5	12	25	2	1	7	12	3	1	3	71
		A %	7.0	16.9	35.2	2.8	1.4	9.9	16.9	4.2	1.4	4.2	100.0
	B	No.	3	14	11	2	0	13	23	3	0	2	71
		B %	4.2	19.7	15.5	2.8	0	18.3	32.4	4.2	0	2.8	100.0
Total		No.	8	26	36	4	1	20	35	6	1	5	142
		A+B	5.6	18.3	25.4	2.8	0.7	14.1	24.6	4.2	0.7	3.5	100.0

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	13.555[a]	9	.139
Likelihood Ratio	14.568	9	.103
N of Valid Cases	142		

a. 12 cells (60.0%) have expected count less than 5. The minimum expected count is .50.

Appendix H

Heart Rhythm Analyses

Table H.1 Summary of Cross-sectional analyses at each time point for heart rhythm

Time Period:		Pre-op		ICU Day 0		Post-op Day 1		POD 2	
		NR	AR	NR	AR	NR	AR	NR	AR
A	Count	68	3	66	5	60	11	61	10
	% within group	95.8	4.2	93.0	7.0	84.5	15.5	85.9	14.1%
B	Count	71	0	70	1	65	6	63	8
	% within group	100	0	98.6	1.4	91.5	8.5	88.7	11.3%
Total Count		139	3	136	6	125	17	124	18
% within group		97.9	2.1	95.8	4.2	88.0	12.0	87.3	12.7%

Where: NR= Normal Rhythm AR = Abnormal Rhythm

Table H.1 continued

Post- Operative Day: (table continued)		POD 3		POD 4		POD 5	
		NR	AR	NR	AR	NR	AR
A	Count	61	10	64	7	65	6
	% within group	85.9	14.1	90.1	9.9	91.5	8.5
B	Count	67	4	68	3	70	1
	% within group	94.4	5.6	95.8	4.2	98.6	1.4
Total Count		128	14	132	10	135	7
% within group		90.1	9.9	93.0	7.0	95.1	4.9

Where: NR= Normal Rhythm AR = Abnormal Rhythm

Table H.2 Pearson Chi-Square Tests

Pearson Chi-Square	Value	Deg. Of freedom	Asymp. Sig. (2-sided)
Pre - Op	3.065(a)	1	.080
ICU Day 0	2.784(b)	1	.095
POD 1	1.671(c)	1	.196
POD 2	.254(d)	1	.614
POD 3	2.853(e)	1	.091
POD 4	1.721(f)	1	.190
POD 5	3.757(g)	1	.053

a 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.50.
b 2 cells (50.0%) have expected count less than 5. The minimum expected count is 3.00.
c 0 cells (.0%) have expected count less than 5. The minimum expected count is 8.50.
d 0 cells (.0%) have expected count less than 5. The minimum expected count is 9.00.
e 0 cells (.0%) have expected count less than 5. The minimum expected count is 7.00.
f 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.00.
g 2 cells (50.0%) have expected count less than 5. The minimum expected count is 3.50.

Appendix I

Blood Test Analyses

I.1 paO_2– Arterial Oxygen Analyses between groups at every time point

Table I.1 Tests of Between-Subjects Effects by group at each time-point

Measure: PAO_2
Transformed Variable: Average

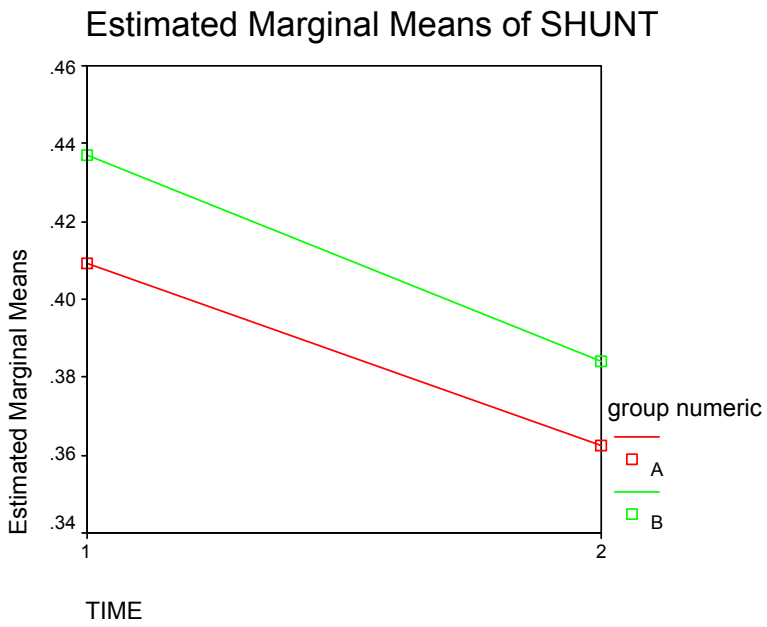
Source	Type III Sum of Squares	Mean Square	F	Sig.
Intercept	317553.263	317553.263	7221.727	.000
Group n	.030	.030	.001	.979
Error	6156.070	43.972		

I.2 Estimation of Intrapulmonary Shunting (Q_S/Q_T) between groups between time points 3 (ICU 1 hour) and 4 (T-piece)

Table I.2 Tests of between-subjects effects between ICU 1 hour and T-piece analysis

Measure: SHUNT
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	45.024	1	45.024	1172.915	.000
GROUPN	.043	1	.043	1.118	.292
Error	5.374	140	.038		



Where: Time 1: 1hour ICU and time 2: T-piece

Appendix I Blood Test Analyses continued

Table I.3 Urea results

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.990	0.299
Time x Group	Wilks' Lambda	0.998	0.626
Group	F	0.072	0.789

Table I.4 Creatinine results

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.995	0.456
Time x Group	Wilks' Lambda	0.996	0.494
Group	F	1.178	0.280

Table I.5 Red blood cell results

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.494	0.021
Time x Group	Wilks' Lambda	1.000	0.964
Group	F	0.090	0.771

Table I.6 Platelet results

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.995	0.536
Time x Group	Wilks' Lambda	0.989	0.330
Group	F	0.513	0.476

Table I.7 White blood cell results

Effect	Statistic	Value	p-value
Time	Wilks' Lambda	0.959	0.063
Time x Group	Wilks' Lambda	0.995	0.515
Group	F	0.791	0.376

Appendix J

Lung Function Test Analyses

Table J.1 Cross tabulation of group by diagnosis at one month follow up appointment (final time point)

			Diagnosis at one month follow-up appointment				Total
			Normal	Restrictive	Obstructive	Combination	
Group	A	Count	19	38	8	6	71
		% within group	26.8	53.5	11.3	8.5	100.0
	B	Count	26	28	11	6	71
		% within group	36.6	39.4	15.5	8.5	100.0
Total		Count	45	66	19	12	142
		% within group	31.7	46.5	13.4	8.5	100.0

Footnote: Pearson Chi-Square value =3.078; p=0.380

Appendix K

Radiology Results

K.1

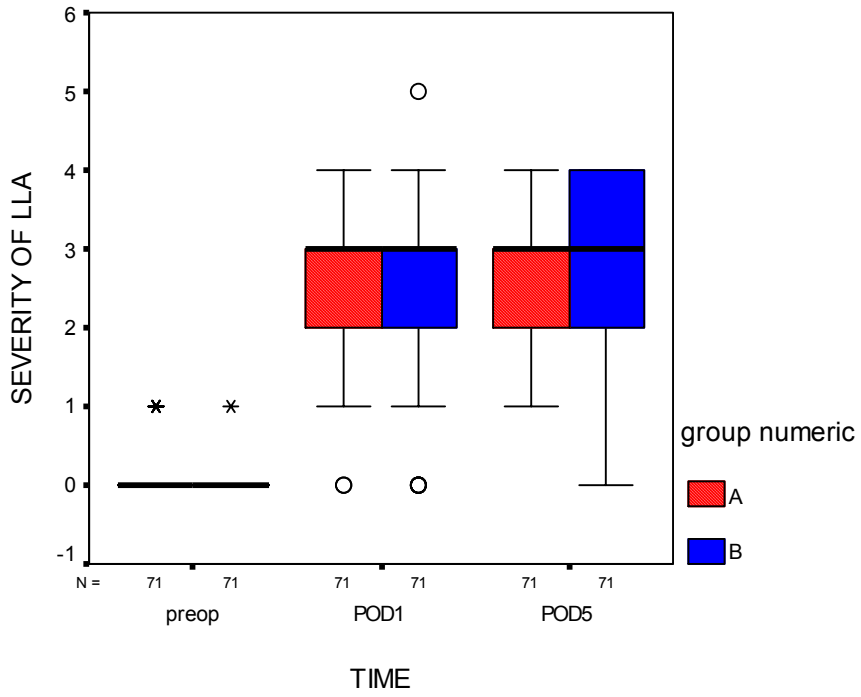


Fig. K.1 Graph depicting severity of left lung atelectasis by group over time

K.2

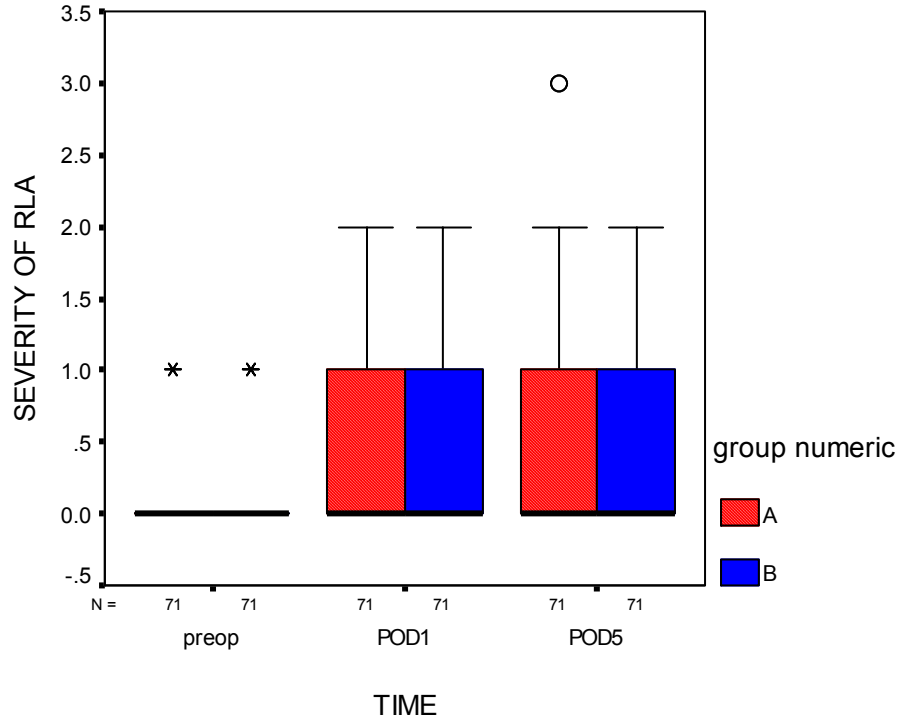


Fig. K.2 Graph depicting severity of right lung atelectasis by group over time

K.3

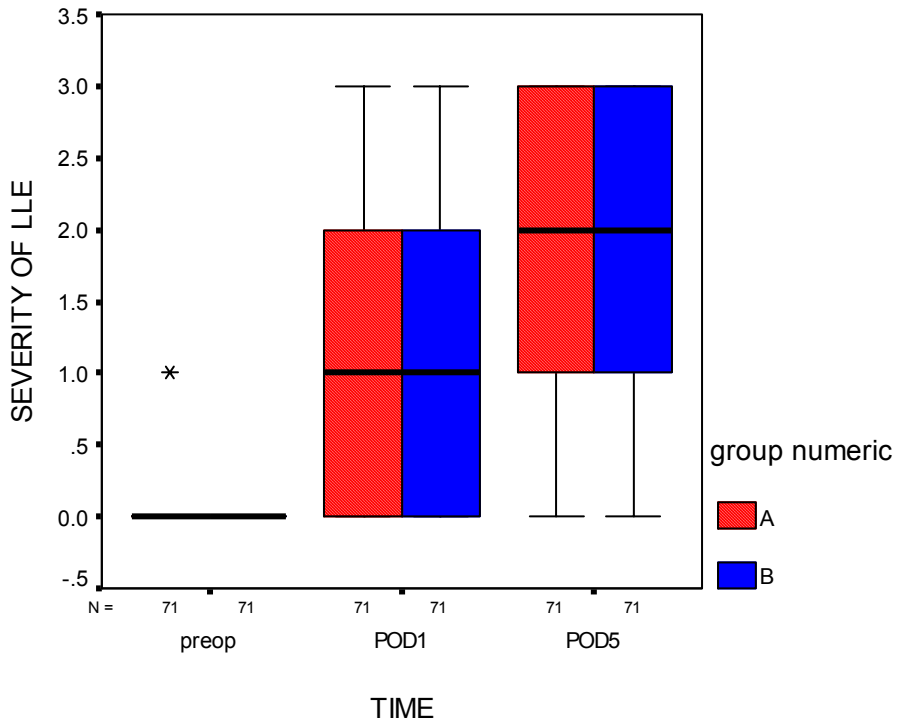


Fig. K.3 Graph depicting severity of left lung effusion by group over time

K.4

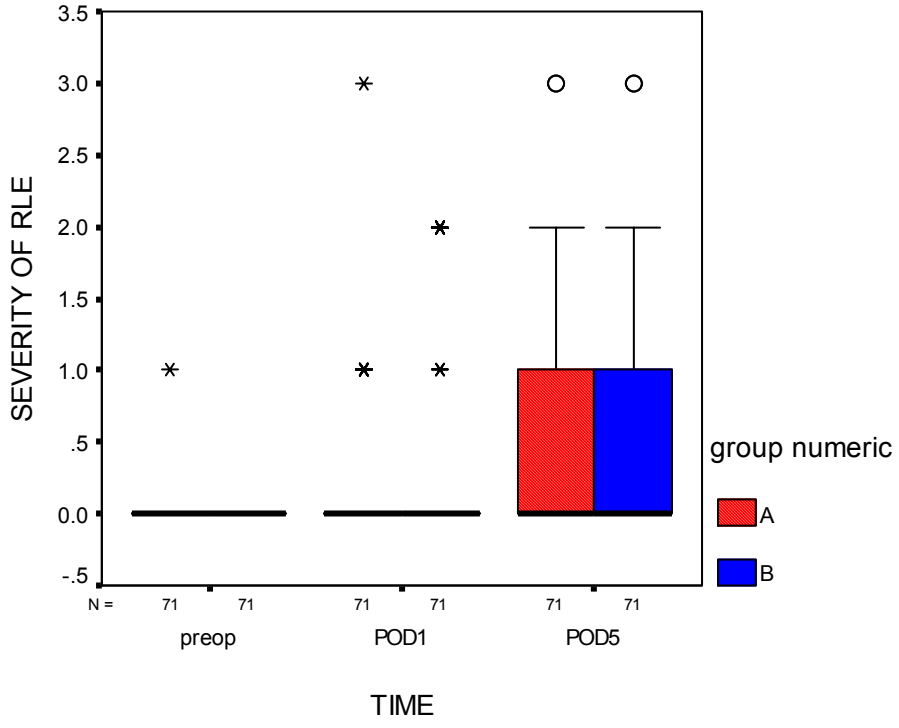


Fig. K.4 Graph depicting severity of right lung effusion by group over time

Appendix L

Technetium Studies of PA Vent

Table L.1 Wilcoxon Signed Ranks Test of Percentage Retrieval from PA Vent

		N	Mean Rank	Sum of Ranks
Maintenance % retrieved - Induction % retrieved	Negative Ranks	2(a)	2.50	5.00
	Positive Ranks	3(b)	3.33	10.00
	Ties	0(c)		

a Maintenance % retrieved < Induction % retrieved
b Maintenance % retrieved > Induction % retrieved
c Maintenance % retrieved = Induction % retrieved

Test Statistics: Significance(2-tailed) p=0.500

Table L.2 Wilcoxon Signed Ranks Test of volume introduced and volume retrieved from PA Vent

		N	Mean Rank	Sum of Ranks
Induction volume out - Induction total volume in	Negative Ranks	5(a)	3.00	15.00
	Positive Ranks	0(b)	.00	.00
Maintenance volume out - Maintenance total volume in	Negative Ranks	4(c)	3.50	14.00
	Positive Ranks	1(d)	1.00	1.00

a Induction volume out < Induction total volume in
b Induction volume out > Induction total volume in
c Maintenance volume out < Maintenance total volume out.
d. Induction Maintenance volume out > Maintenance total volume in

Test Statistics: Significance(2-tailed) Induction: p=0.043
Test Statistics: Significance(2-tailed) Maintenance: p=0.080

Table L.3 Wilcoxon Signed Ranks Test of Specific Activity of Tc-99m in a 10ml sample from PA Vent

		N	Mean Rank	Sum of Ranks
Specific Activity Maintenance - Specific Activity induction	Negative Ranks	3(a)	2.67	8.00
	Positive Ranks	2(b)	3.50	7.00
	Ties	0(c)		
	Total	5		

a Specific Activity Maint < Specific Activity induct
b Specific Activity Maint > Specific Activity induct
c Specific Activity Maint = Specific Activity induct

Test Statistics: Significance(2-tailed): p=0.892

Appendix M

Technetium Studies of LA Vent

Table M.1 Wilcoxon Signed Ranks Test of Percentage Retrieval from LA Vent

		N	Mean Rank	Sum of Ranks
Maintenance % retrieved - Induction % retrieved	Negative Ranks	1(a)	1.00	1.00
	Positive Ranks	4(b)	3.50	14.00
	Ties	0(c)		
	Total	5		

a Maintenance % retrieved < Induction % retrieved
b Maintenance % retrieved > Induction % retrieved
c Maintenance % retrieved = Induction % retrieved

Test Statistics: Significance(2-tailed): p=0.080

Table M.2 Wilcoxon Signed Ranks Test of volume introduced and volume retrieved from LA Vent

		N	Mean Rank	Sum of Ranks
Induction volume out - Induction total volume in	Negative Ranks	4(a)	2.75	11.00
	Positive Ranks	1(b)	4.00	4.00
Maintenance volume out - Maintenance total volume in	Negative Ranks	5(c)	3.00	15.00
	Positive Ranks	0(d)	.00	.00

a Induction volume out < Induction total volume in
b Induction volume out > Induction total volume in
c Maintenance volume out < Maintenance total volume in
d Maintenance volume out > Maintenance total volume in

Test Statistics: Significance(2-tailed) Induction: p=0.345
Test Statistics: Significance(2-tailed) Maintenance: p=0.043

Table M.3 Wilcoxon Signed Ranks Test of Specific Activity of Tc-99m in a 10ml sample from LA Vent

		N	Mean Rank	Sum of Ranks
Specific Activity Maintenance - Specific Activity induction	Negative Ranks	2(a)	2.00	4.00
	Positive Ranks	3(b)	3.67	11.00
	Ties	0(c)		
	Total	5		

a Specific Activity Maintenance < Specific Activity induction
b Specific Activity Maintenance > Specific Activity induction
c Specific Activity Maintenance = Specific Activity induction

Test Statistics: Significance(2-tailed): p=0.345

Appendix N

Technetium Studies of PA and LA Vent simultaneously

Table N.1 Wilcoxon Signed Ranks Test of % Retrieval from PA and LA Vents

		N	Mean Rank	Sum of Ranks
LA % retrieved - PA % retrieved	Negative Ranks	5(a)	3.00	15.00
	Positive Ranks	0(b)	.00	.00
	Ties	0(c)		
	Total	5		

a LA % retrieved < PA % retrieved
b LA % retrieved > PA % retrieved
c LA % retrieved = PA % retrieved

Test Statistics: Significance(2-tailed): p=0.043

Table N.2 Wilcoxon Signed Ranks Test of volume retrieved from PA and LA Vents

		N	Mean Rank	Sum of Ranks
LA.Vol out - PA vol out	Negative Ranks	4(a)	2.50	10.00
	Positive Ranks	0(b)	.00	.00
	Ties	1(c)		
	Total	5		

a LA.Vol out < PA vol out
b LA.Vol out > PA vol out
c LA.Vol out = PA vol out

Test Statistics: Significance(2-tailed): p=0.068

Table N.3 Wilcoxon Signed Ranks Test of Specific Activity of Tc-99m in a 10ml sample from PA and LA Vents

		N	Mean Rank	Sum of Ranks
LA Specific Activity - PA Activity Induction	Negative Ranks	5(a)	3.00	15.00
	Positive Ranks	0(b)	.00	.00
	Ties	0(c)		
	Total	5		

a LA Specific Activity < PA Activity induct
b LA Specific Activity > PA Activity induct
c LA Specific Activity = PA Activity induct

Test Statistics: Significance(2-tailed): p=0.043