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Perioperative Organ Dysfunction in Patients undergoing Coronary Artery Bypass Grafting either with Cardiopulmonary Bypass and Cardioplegic Arrest or Without

By

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Dedicated to my wife Beena Varghese

Fool me once, shame on you. Fool me twice, shame on me

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Abbreviations Used

α - GST:	Alpha glutathione-s-transferase
ABP:	Arterial blood pressure
ADH:	Anti-diuretic hormone
AF:	Atrial fibrillation
ALP:	Alkaline phosphatase
ALT:	Alanine aminotransferase
AST:	Aspartate transaminase
ATP:	Adenosine triphosphate
AXC:	Aortic cross-clamp
B-FABP:	Brain type fatty acid binding protein
BPI:	Bactericidal permeability increasing protein
CABG:	Coronary artery bypass grafting
CaO_2:	Arterial blood oxygen content
CB:	Conjugated bilirubin
CC16:	Clara cell secretory protein
CCF:	Congestive cardiac failure
CCO:	Continuous cardiac output
CCS:	Canadian Cardiovascular Society
CI:	Cardiac Index
CO:	Cardiac output
CO_2gap:	Gastric minus arterial carbon dioxide tension
CPB:	Cardiopulmonary bypass
cTnI:	Cardiac troponin I
CVA:	Cerebro-vascular accident
CvO_2:	Mixed venous oxygen content
CVP:	Central venous pressure
DB:	Double blind
DO_2:	Whole-body (global) oxygen delivery
EDTA:	ethylene-diamine-tetra-acetic acid
EEP:	Energy equivalent pressure
EGF:	Epidermal growth factor

GIT:	Gastrointestinal
Hb:	Haemoglobin
H-FABP:	Heart type fatty acid binding protein
HNP:	Human Neutrophil Peptides
HR:	heart rate
IABP:	Intra-aortic balloon pump
ICU:	Intensive care unit
I-FABP:	Intestinal type fatty acid binding protein
IL:	Interleukin
IQR:	Inter quartile range
LAD:	Left anterior descending
L-FABP:	Liver type fatty acid binding protein
LFTs:	Liver function tests
LIMA:	Left internal mammary artery
LV:	Left ventricular
LVEF:	Left ventricular ejection fraction
MAP:	mean arterial blood pressure
MBL:	Mannose Binding Lectin
MEGX:	Mono-ethyl-glycine-xylidide
MI:	Myocardial infarction
MIDCABG:	Minimally Invasive Direct Coronary Artery Bypass Grafting
mPAP:	mean pulmonary artery pressure
NAD:	Noradrenaline
NAG:	N-acetyl glucosaminidase
NGAL:	Neutrophil gelatinase associated lipocalin
NO:	Nitric oxide
NOS:	Nitric oxide synthase
OFR:	Oxygen-free radicals
OM:	Obtuse marginal
ONCAB:	On-pump coronary artery bypass grafting
OPCAB:	Off-pump coronary artery bypass grafting

$PaCO_2$: Partial pressure of carbon dioxide in arterial blood

PAF: Platelet-activating factor

PaO_2: Partial pressure of oxygen in arterial blood

PAP: Pulmonary artery pressure

PAR: pressure adjusted rate

pCO_2: Partial pressure of carbon dioxide

PCI: Percutaneous coronary intervention

PCV: Packed cell volume

PDA: Posterior descending artery

PE: Phenylephrine

PG: Prostaglandin

$PgCO_2$: Partial pressure of carbon dioxide in gastric lumen

pHi: Intra-mucosal pH

Pi-GST: Pi glutathione-s-transferase

pO_2: Partial pressure of oxygen

PvO_2: Partial pressure of oxygen in mixed venous blood

PVR: Pulmonary vascular resistance

RCA: Right coronary artery

RIMA: Right internal mammary artery

RV: Right ventricle, right ventricular

S100 β: S100 beta

SaO_2: Arterial blood oxygen saturation

SD: Standard deviation

SHE: Surplus hemodynamic energy

SIELI: Severe ischemic early liver injury

SIRS: Systemic inflammatory response syndrome

SP – D: Surfactant protein D

SVI: Stroke Volume Index

SvO_2: Mixed venous blood oxygen saturation

SVRI: Systemic Vascular Resistance Index

TB: Total bilirubin

TGF-alpha: Transforming growth factor alpha

TNF-α:	Tumour necrosis factor alpha
TSH:	Thyroid-stimulating hormone
TxA2:	Thromboxane A2
VO_2:	Whole-body (global) oxygen consumption
*	Symbol for multiplication
X-clamp:	Aortic cross-clamp

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Abstract

Background

This was a pilot study to evaluate the changes in the concentration of a novel range of biomarkers in patients undergoing coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB) and cardioplegic arrest referred to as ONCAB or without OPCAB. It has been suggested that the avoidance of the deleterious effects of CPB and ischaemic arrest can reduce perioperative organ dysfunction. In this thesis, a prospective randomised controlled study was undertaken to evaluate the changes in biomarker profile between the two groups.

Methods

Forty-three patients were randomized to either ONCAB (n=20) or OPCAB (n=23). Blood samples were collected after anaesthetic induction, at the end of operation and 4,8,12 hours postoperatively. Urine specimens were also collected at similar time points. In addition all patients were monitored with a Swan Ganz and gastric tonometer catheter. Arterial blood gas analysis was measured preoperatively, postoperatively and hourly for the first 12 hours postoperatively. Biochemical markers used to assess myocardial dysfunction were cardiac troponin I (TnI) and heart type fatty acid binding protein (H-FABP). Physiological function was assessed using electrocardiography (ECG), cardiac index (CI), and the pressure adjusted rate (PAR) concept. Pulmonary dysfunction was assessed by means of release of Clara cell 16 protein and surfactant protein D. The respiratory index (PaO_2/FiO_2) and time to extubation were used as indicators of physiological dysfunction. Renal dysfunction was assessed by release of neutrophil gelatinase associated lipocalin (NGAL), rate of excretion of alpha glutathione-s-transferase (α-GSH) and pi glutathione-s-transferase (π-GSH). Gastrointestinal function was assessed by measuring the partial pressure of CO_2 in the stomach ($PgCO_2$), the CO_2 gap ($CO_2gap = PgCO_2 – PaCO_2$) and calculation of gastric intra-mucosal acidosis or pHi ($pHi = 6.1 + Log\ 10\ (arterial\ HCO_3/PgCO_2)*K$). Gastro-intestinal damage was assessed by measuring the release of intestinal type fatty acid binding protein (I-FABP), bactericidal permeability increasing protein (BPI), defensins (HNP), antibodies to endotoxin (IgG EndoCab & IgM EndoCab). Liver dysfunction was assessed by release of hepatic alpha glutathione-s-transferase (Hα-GSH); blood lactate levels and liver type fatty acid binding protein (L-FABP). Complement activation was measured by release of mannose binding lecithin (MBL). Stress hormone release was measured by release of cortisol. Whole body

oxygen extraction was calculated as follows Arterial blood oxygen content (CaO_2) = Hb * SaO_2*1.39 + (0.003*PaO_2) ml/dL, Hb is haemoglobin concentration in g/dL, SaO_2 is the percentage of oxygen saturation of arterial blood, PaO_2 is the partial pressure of oxygen in the arterial blood. In the above equation the factor 0.003PaO_2 is negligible and was not calculated for the purposes of our study. Whole body oxygen delivery DO_2 (ml/min/m^2)=$Ca0_2$*CI*0.1. The mixed venous oxygen content (CvO_2) = $HbSvO_2$ 1.39 + (0.003 * PvO_2) ml/dL, SvO_2 is the percentage of oxygen saturation of mixed venous blood PvO_2 is the partial pressure of oxygen in mixed venous blood. The factor 0.003*PvO_2 is negligible and was not calculated in this study. Whole body oxygen consumption (VO_2) = (CaO_2 – CvO_2)*Cardiac index * 0.1 ml/min/m^2. Extraction fraction = (VO_2/DO_2)*100. Neurological dysfunction was assessed by release of brain type fatty acid binding protein (B-FABP) and S-100 beta.

Results

The total amount of troponin-I released postoperatively was 107 +/- 22 μg/l in the ONCAB group vs. 53.4 +/- 23.6 μg/l in the OPCAB group (p=0.001). Troponin-I levels were significantly higher in the ONCAB group postoperatively (p<0.001) and at 4 hours (p=0.003). The total amount of H-FABP released postoperatively was 498.9 +/- 262.7 ng/ml in the ONCAB group vs. 478.3 +/- 914.7 ng/ml in the OPCAB group (p=NS). H-FABP levels were significantly higher in the ONCAB group immediately postoperatively (p<0.001). The coefficient of determination R^2 was 0.69 for H-FABP and cTnI. The average amount of dopamine used per hour was 2.3μg/Kg/minute in the ONCAB group vs. 1.4μg/Kg/minute in the OPCAB group (p<0.001). The average amount of noradrenaline used per hour was 1.8μg/Kg/minute in the ONCAB group and 1.18μg/Kg/minute in the OPCAB group. There was no significant change in cardiac index post operatively (p=0.81). There was no group procedure interaction (p=0.81). There was a significant and similar decline in SvO_2 postoperatively (p=0.004) in both groups. There was no significant difference between OPCAB and ONCAB (p=0.86). The average pressure adjusted rate score per minute was 10.8 (ONCAB) vs. 9.1 (OPCAB) p=0.07. There was no statistically significant change in CC16 levels over time (p=0.08). There was no significant time procedure interaction (p=0.35). There was no significant procedure interaction (p=0.97). There was no significant difference in the AUC between groups p=0.874. SP-D concentrations changed with time (p=0.001) but

not in a linear fashion. The change was dependent on the preoperative value (p=0.001). There was no time procedure interaction (p=0.11) or procedure interaction (p=0.91). AUC between groups p=0.30. There were no significant differences in extubation times (p=0.97). There was no difference in respiratory index (p=0.58). There was no significant change over time (p=0.33). There was a significant time procedure interaction (p=<0.001). There was greater release of NGAL post operatively in the ONCAB group than the OPCAB group (p=<0.001). There was no significant difference in the AUC between the two groups (p=0.32). Release rate of α-GST showed that the changes were related to time. Release rates changed in a linear fashion (p=0.01). There was also a time procedure interaction (p=0.05). The release rate of α-GST was statistically significantly higher at 4 hours in the ONCAB group (p=0.05). Release rate of π-GST showed a significant change over time (p=0.001) and that this was linear (p=0.01). There was no significant time procedure interaction (p=0.29). There were no significant differences between procedures (p=0.69). There was a similar and significant decline in pHi in both groups over time but no difference between groups (p=0.69). The CO_2 gap showed significant interaction with time (p=<0.001). There was no difference between groups (p=0.80). There was a significant (p<0.001) negative Spearman's correlation Rs -0.84 between pHi and CO_2 gap. There was a similar and significant rise in $PgCO_2$ in both groups but no difference between groups (p=0.58) There was a significant positive Spearman correlation between the $PgCO_2$ and CO_2 gap, Spearman's rho =0.844; p<0.001. There was a significant negative Spearman correlation between the $PgCO_2$ and the pHi, Spearman's rho = 0.928; p<0.001. There was a similar rise in cortisol in both groups but no difference between groups (p=0.89). There was a similar decline in levels of endotoxin antibody in both groups for both classes of immunoglobulin. There was no difference between groups For IgG EndoCAB (p=0.59) or IgM EndoCAB (p=0.81). I-FABP release was similar between both groups (p=0.55). However the area under the curve (AUC) was greater in the ONCAB group (p=0.001). Release of BPI was dependent on the preoperative levels (p=0.016). There was a greater release of BPI in the ONCAB group postoperatively (p=0.001) and at 4 hours (p=0.031). Release of defensins was greater in the ONCAB group post operatively (p=0.001) and at 4 hours (p=0.031). Release of MBL showed a significant time (p=0.002) interaction. The post-operative levels were affected by preoperative levels (p=0.023). There was no difference between the groups (p=0.66). There were no significant differences in oxygen extraction (p=0.49) between the two groups. For Hepatic α GST there was a significant time

($p<0.001$) interaction and this relationship was linear ($p<0.001$). There was no difference between groups ($p=0.74$). For L-FABP there was no significant time ($p=0.70$) interaction. There was no difference between groups ($p=0.26$). There was no significant difference in serum lactate between groups ($p=0.96$). Release of S100 beta showed a significant time interaction ($p<0.001$). There was a significant difference between procedures ($p=0.003$). There was greater release of S100 beta in the ONCAB group for all time points: post operatively ($p=0.001$), 4 hours ($p=0.004$), 8 hours ($p=0.05$) and at 12 hours ($p=0.008$). Release of B-FABP showed no significant time interaction ($p=0.46$), no significant time procedure interaction ($p=0.67$) and no significant difference between procedures ($p=0.73$). B-FABP showed an initial decline in both groups. The maximal decline occurred about 4 hours postoperatively. Subsequently there was a dramatic rise in the ONCAB group at 4 hours and at 8 hours in the OPCAB group. Thereafter there was a decline to baseline.

Conclusions

In this pilot study elimination of CPB did not result in any superior clinical outcomes. However it was not designed or adequately powered to do so. In this study there was no difference in length of stay, use of blood products or incidence of postoperative atrial fibrillation between the two groups. However OPCAB did result in lower release of markers of myocardial injury and reduced inotropic requirements. Levels of CC16 and SP-D, which are effectors of the inflammatory response, changed appropriately in a similar fashion within the two groups. There were no significant changes in the respiratory index or the time to extubation. This study has not found any advantages for OPCAB surgery over conventional surgery using CPB for hepatocellular injury in patients who have no pre-existing evidence of liver dysfunction. The pattern of renal injury is quite interesting. The ONCAB group fared worse immediately postoperatively as suggested by the greater release of NGAL and at 4 hours as suggested by the greater release of αGST. Of note is that OPCAB seemed to offer no added benefit to the distal tubular system, as there were no differences in πGST between the two groups. There was greater blood brain barrier dysfunction in the ONCAB group as suggested the greater release of S100 beta. The changes in release of B-FABP are more complex. Both groups suffered similar levels of CNS injury and this occurred earlier in the ONCAB group commensurate with the embolic load associated with establishment of CPB. There was a similar decline in gastrointestinal function as measured by changes in pHi, $PgCO_2$, CO_2 gap, DO_2, VO_2 and extraction fraction in both groups but not between the two

groups. However there was a greater cumulative release of I-FABP in the ONCAB group. This suggests mucosal disruption that facilitates bacterial permeation. This may explain why the levels of BPI and HNP were also higher in the ONCAB group.

Authors Statement

This is to confirm that this thesis is entirely my own work with the sole exception of those areas indicated in the text and or the acknowledgement section

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Presentations and Publications arising from Thesis

A prospective randomized study to evaluate changes in human neutrophil defensins as a surrogate marker of intestinal damage in patients at high-risk of renal injury undergoing coronary revascularization with and without cardiopulmonary bypass preliminary results.
Book of Abstracts 4th EACTS/ESTS joint meeting, Barcelona 2005
D Varghese, M Hanson, P Wood, D Hett, T Velissaris, SK Ohri.

A prospective randomized study to evaluate changes in B-FABP as novel mark of neurological injury in patients under going coronary revascularization with and with out cardio pulmonary by pass.
6th Biennial Conference of Pakistan Society of Cardiovascular & Thoracic Surgeons, 2006.
D Varghese, M Pelsers, M Hanson, P Wood, D Hett, T Velissaris, SK Ohri.

Prospective randomized study to evaluate changes in EndoCab as a surrogate marker of endotoxemia in patients under going coronary revascularization with and with out cardiopulmonary bypass.
6th Biennial Conference of Pakistan Society of Cardiovascular & Thoracic Surgeons, 2006
D Varghese, M Pelsers, M Hanson, P Wood, D Hett, T Velissaris, SK Ohri.

Neutrophil gelatinase associated lipocalin as novel marker of renal injury in patients under going coronary revascularization with and without cardio pulmonary bypass.
6th Biennial Conference of Pakistan Society of Cardiovascular & Thoracic Surgeons, 2006
D Varghese, M Pelsers, M Hanson, P Wood, D Hett, T Velissaris, SK Ohri.

A prospective randomized study to evaluate changes in B-FABP as novel marker of neurological injury in patients undergoing coronary revascularization with and without cardiopulmonary bypass – preliminary results.
18th Annual Meeting of the Mediterranean Association of Cardiology and Cardiac Surgery, Cyprus, 2006. D Varghese, M Pelsers, M Hanson, P Wood, D Hett, T Velissaris, SK Ohri.

A prospective randomized study to evaluate changes in H-FABP as a novel marker of myocardial necrosis in patients undergoing coronary revascularization with and without cardiopulmonary bypass.
18th Annual Meeting of the Mediterranean Association of Cardiology and Cardiac Surgery, Cyprus 2006. D Varghese, M Pelsers, M Hanson, P Wood, D Hett, T Velissaris, SK Ohri.

A prospective randomized study to evaluate changes in surfactant protein-d as a marker of pulmonary dysfunction in patients undergoing coronary revascularization with and without cardiopulmonary bypass.
18th Annual Meeting of the Mediterranean Association of Cardiology and Cardiac Surgery, Cyprus, 2006. D Varghese, M Pelsers, M Hanson, P Wood, D Hett, T Velissaris, SK Ohri.

Neutrophil gelatinase associated lipocalin as a novel marker of renal injury in patients undergoing coronary revascularization with and without cardiopulmonary bypass.
18th Annual Meeting of the Mediterranean Association of Cardiology and Cardiac Surgery, Cyprus, 2006. D Varghese, M Pelsers, M Hanson, P Wood, D Hett, T Velissaris, SK Ohri.

A prospective randomized study to evaluate changes in cardiac troponin-I as a marker of myocardial necrosis in patients undergoing coronary revascularization with and without cardiopulmonary bypass.
18th Annual Meeting of the Mediterranean Association of Cardiology and Cardiac Surgery, Cyprus, 2006. D Varghese, M Pelsers, M Hanson, P Wood, D Hett, T Velissaris, SK Ohri.

A prospective randomized study to evaluate changes in alpha-GST as a novel marker of hepatocellular necrosis in patients at high-risk of renal injury undergoing coronary revascularization with and without cardiopulmonary bypass.
18th Annual Meeting of the Mediterranean Association of Cardiology and Cardiac Surgery, Cyprus 2006. D Varghese, M Pelsers, M Hanson, P Wood, D Hett, T Velissaris, SK Ohri.

International Presentations As First Presenter

A prospective randomised study to evaluate changes in bactericidal permeability increasing (BPI) protein as a surrogate marker of gram-negative bacteraemia in patients undergoing coronary revascularization with and without cardiopulmonary bypass.

Presented at the 5th EACTS/ESTS joint meeting, Sweden, 2006

D Varghese, M Pelsers, M Hanson, P Wood, D Hett, T Velissaris, SK Ohri.

A prospective randomised study to evaluate changes in human neutrophil defensins in patients undergoing coronary revascularisation with and without cardiopulmonary bypass.

Presented at the 4th EACTS/ESTS joint meeting, Spain, 2005

D Varghese, M Pelsers, M Hanson, P Wood, D Hett, Theo Velissaris, SK Ohri.

Chapter 1 Introduction

The Burden Of Coronary Artery Disease

There are many pathological disorders that affect the heart but the most common cause of cardiac morbidity and mortality in developed countries is ischaemic coronary artery disease [(3)]. Coronary atherosclerosis is a diffuse, heterogeneous process that affects most of the arteries in the body and is the primary cause of coronary artery disease. It is a chronic inflammatory condition that leads to the sub-endothelial accumulation of lipid and subsequent formation of a fatty streak on the arterial surface [(4)]. This process begins in childhood and its rate of progression is affected by over 200 known factors including age, hyperlipidaemia, hypertension, gender, heredity, diabetes and cigarette smoking [(5)]. By the end of the second decade of life, fatty streaks are evident in the lumen of the aorta, and coronary and cerebral arteries. The proximal portion of the left anterior descending coronary artery (LAD) is particularly susceptible to the deposition of fatty streaks, and by the third decade these have developed into fibrous plaques, called atheroma, with necrotic, lipid rich cores. Such plaques can significantly narrow the arteries and impair the blood supply to the surrounding tissues. The activation of genes that induce arterial calcification changes the mechanical characteristics of the arterial wall and predisposes the friable, fibrous cap overlying the plaque to develop cracks and fissures. This exposes the flowing blood to high levels of the potent coagulant, tissue factor, which leads to formation of platelet mural thrombi and stenosis of the arterial lumen. The subsequent ischaemic necrosis in the surrounding tissue can cause myocardial infarction, stroke or gangrene depending on the location of the obstructed artery. Thus, ischaemic heart disease (IHD) is generally characterised by a prolonged silent phase followed by the onset of either stable angina, unstable coronary syndromes, myocardial infarction or death. IHD was the cause of death in 105,842 people for the year 2004 in the United Kingdom: approximately 21% of deaths in men and 15% of deaths in women. The morbidity due to IHD is even higher with an estimated 2 million people suffering from angina. The economic burden is around £3,500 million a year in treatment costs with an estimated loss to the UK economy of about £4,400 million because of days lost to death, illness and infirmity.

There are three main approaches to the management of IHD. The least invasive of these is medical therapy, which aims to simultaneously reduce myocardial oxygen

requirements and prevent thrombosis. If this treatment proves ineffective, the alternative is to restore blood flow to the myocardium via interventional cardiac revascularisation. The most common methods of achieving this are the catheter-based approaches of either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

A Surgical Treatment For Symptomatic Coronary Artery Disease

The development of open-heart surgery has been achieved in incremental steps by numerous investigators from many diverse fields. Outlined below is a brief overview of the most significant milestones that together have resulted in the development of one the most successful treatments ever. Jenner first elucidated the relationship between coronary artery stenosis and angina in 1777 on his friend the eminent surgeon Hunter [(6)]. Early surgical attempts to treat angina can be classified into 3 main groups: (1) denervation of the heart; (2) reduction of myocardial workload; (3) increase blood supply to ischaemic areas. Some of the most notable landmarks are shown in the table below.

Table 1-1. Evolution of CABG [(6)]

Surgeon	Method	Date
Charles Emile Francois-Frank	Thoraco-Cervical Sympathectomy (did not actually carry out procedure)	1899
Charles Mayo	Cervical sympathectomy	1913
Gastineau Earle & Strickland Goodall	Posterior rhizotomy (did not actually carry out procedure)	1913
Elliot Cutler	Sub-total thyroidectomy	1932
Beck & Tichy	Epicardial scarification	1934
Beck	Pectoral muscle grafting	1935
O'Shaughnessey	Omental pedicled grafts	1936
Thompson	Pericardial talc poudrage	1938
Beck	Pericardial asbestos poudrage	1939
Vineberg	Intra-myocardial implantation of left internal mammary artery	1948

Rene Favaloro developed the concept of aortic coronary saphenous vein bypass grafts in 1967. That same year Kolessov performed the first direct anastomosis of the internal mammary artery (IMA) to an obstructed coronary artery (LAD). These first operations paved the way for a new treatment that now benefits over 800,000 people worldwide. Currently about 28,000 CABG operations are performed annually in the UK. The mortality for primary

CABG ranges from 1% to 2%. It should be noted that despite the increasing morbidity of the population undergoing CABG the mortality has fallen from 6-7% in the 1970s. There is a strong scientific basis for CABG in multi-vessel and left main stem disease. This is summarized in the meta-analysis by Yusuf and colleagues of seven randomized trials of CABG versus medical therapy, involving 2650 patients followed-up for 10 years, which was published in *The Lancet* in 1994 [7]. The trials showed that there was a survival advantage and marked improvement in symptom relief in patients undergoing CABG who had left main stem disease or triple-vessel disease, especially when it involved proximal left anterior descending artery (LAD), and that the benefits were magnified in patients with severe symptoms, a positive exercise electrocardiogram, or impaired left ventricular function, or a combination of these. The popularisation of CABG would not have been feasible without concomitant developments in cardiopulmonary bypass (CPB) technology, techniques of myocardial preservation and an array of supporting technologies some of which are detailed below.

The Development Of Cardiopulmonary Bypass

In 1916, Jay McLean, a student at Johns Hopkins School of Medicine, entered the laboratory of Professor WH Howell, the leading haematologist of his age. Using ether as a solvent, McLean extracted a compound from ox heart, which he termed "courin" that had anticoagulant properties. Professor Howell named the anticoagulant "heparin", but later work showed that McLean had extracted phospholipids with anticoagulant properties. Thus, McLean did not discover heparin, but his paper initiated an intensive search for an anticoagulant and showed that one existed. Professor Howell himself, using aqueous extraction and acetone precipitation of dog liver, produced a different anticoagulant, which he also named "heparin". This was the real thing and probably similar or identical to a substance Doyon and colleagues extracted from dog liver in 1911. In 1933, Charles and Scott developed a technique to extract non-toxic heparin from beef lung in commercial quantities. This was just in time for the Gibbons' studies. Shortly thereafter, Chargaff and Olson reported that protamine neutralized heparin *in vitro*. In 1939, Jorpes used protamine to neutralize heparin.

These developments made possible the development of extracorporeal circulation by

John Gibbon Jr. Gibbon performed the first total bypass of the heart and lungs in experimental animals in 1937. In 1951 Dennis described the first use of CPB in a human. Though the patient a 6 year old succumbed this was due to an uncorrected congenital abnormality at operation and not the newly invented heart lung machine.

Whilst the development of extra-corporeal circulation allowed procedures to be carried out on the heart without the threat of haemodynamic collapse it soon became apparent that a beating heart made repairs technically more difficult and remained metabolically active which led to adverse post-operative complications. The development of modern cardioplegic techniques can be traced back to 1878 when Boehm working at the Pharmacological Institute of the University of Dorpat. Boehm studied the resuscitation of cats whose hearts had been stopped by a range of noxious chemicals including potassium salts. He found that he could successfully resuscitate those animals whose hearts had been stopped with the use of potassium. In 1883 Sidney Ringer working at University College London showed that an excess of potassium salts in fluid bathing an isolated heart, would stop it beating. In 1904 Martin who worked at John Hopkins University arrested the isolated hearts of terrapins for periods of up to 35 minutes by infusing potassium chloride solution. When the solution was washed out normal cardiac activity resumed. Melrose working at the Royal Postgraduate Medical School, Hammersmith Hospital carried out experimental work on dogs and in isolated hearts, which convinced him of the potential for use in humans. In 1955 at the Hammersmith hospital the first elective cardiac arrest on the operating table was performed. With the patient on CPB the aorta was cross-clamped and potassium citrate was injected directly into the aortic root. This produced cardiac arrest in the flaccid, diastolic phase and allowed the operation to be carried out in a dry motionless heart. On release of the aortic cross clamp, reperfusion of the coronary circulation washed out the potassium citrate and restored normal cardiac function in a very short time to the elation of the surgical team. Cardioplegic solutions and the technique have continued to evolve. The repertoire now includes both antegrade and retrograde techniques via the coronary sinus, warm and cold solutions, and crystalloid or blood cardioplegia.

Hypothermia has been applied therapeutically since antiquity. The Roman citizen Hippocrates advocated the packing of wounded soldiers in snow and ice. Napoleonic surgeon Baron Dominque Larrey recorded those officers, who were kept closer to the fire, survived less often than the minimally pampered infantrymen. In modern times the first medical article

concerning hypothermia was published in 1945.This study focused on the effects of hypothermia on patients suffering from severe head injury. In the 1950's hypothermia received its first medical application, being used in intra-cerebral aneurysm surgery to create a bloodless field. Most of the early research focused on the applications of deep hypothermia, defined as a body temperature between 20-25 °C (68-77 °F). Such an extreme reduction in body temperature is associated with numerous side effects. Making the use of deep hypothermia is impractical in most clinical situations. This period also saw sporadic investigation of more mild forms of hypothermia, with mild hypothermia being defined as core body temperature between 32-34°C (89.6-93.2°F). In the 1950's Rosomoff demonstrated in dogs the positive effects of mild hypothermia after brain ischemia and traumatic brain injury.

The cellular processes responsible for the therapeutic effect of hypothermia are due mainly due to reduced cellular metabolism. For every drop in body temperature of a degree Celsius, the rate of cellular metabolism decreases by 5-7%. Furthermore, it is notable that even a small drop in temperature enhances cell membrane stability during periods of hypoxia. For this reason, hypothermia prevents an influx of unwanted ions during an ischaemic insult. By reducing cell membrane permeability, hypothermia ameliorates the cascade of reactions triggered by hypoxia. Even moderate reductions in temperature support the integrity of the cellular membrane, helping to minimize any disruption to the cellular environment. By limiting the disruption of homeostasis caused by ischemia, many now postulate that hypothermia minimizes tissue injury by increasing free radical protection [(8)]. The therapeutic effect of hypothermia does not confine itself to metabolism and membrane stability. Another school of thought focuses on hypothermia's ability to prevent damage that occurs after circulation is restored to tissues and organs, or what is termed reperfusion injury. An individual suffering from an ischaemic insult continues to sustain damage well after circulation is restored. In rats it has been shown that neurons often necrose a full 24 hours after blood flow has been restored. Some theorize that this delayed cell death is mediated by various inflammatory immune responses that occur during reperfusion. Within the cranium, these inflammatory responses can cause a rise in intracranial pressure, which may lead to further neuronal injury and in some situations cell death. Hypothermia has been shown to help moderate intracranial pressure rise and the harmful effect of a patient's inflammatory immune responses during reperfusion. Beyond this, reperfusion also increases free radical

production. Many now suspect it is because hypothermia reduces both intracranial pressure and free radical production that hypothermia improves patient outcome following a reduction of blood flow to the brain. Bigelow pioneered the concept of hypothermia in cardiac surgery. Further developments led to the first successful purely hypothermic repair of a patient with an atrial septal defect in 1952 by Lewis and colleagues. However it was 1960 before it was considered safe to combine hypothermia and CPB. Furthermore some surgeons combined CPB with topical cardiac cooling with cold saline or ice chips in the pericardium. This so called technique of "ice-chip arrest" is still used by some surgeons today.

Whilst the development of CPB has been responsible for the explosion in cardiac surgery over the last 50 years the technique causes a range of damaging effects that has been termed the "post perfusion syndrome" (PPS). It is the magnitude and severity of this response that are fiercely debated. In it's most severe form, a spectrum of injury may be observed that includes one or more of the following clinical manifestations: pulmonary, renal, gut, neurological and myocardial dysfunction; coagulopathy; vasoconstriction; capillary permeability; vasodilatation; accumulation of increased interstitial fluid; haemolysis; pyrexia; and increased susceptibility to infections and leucocytosis. Hornick and Taylor have suggested a more suitable term for this condition designated the systemic inflammatory response after bypass or SIRAB [(9)].

The potential range of complications arising from CPB may be classified as either due to haemodynamic changes or related to SIRAB.

The Systemic Inflammatory Response To Cardiopulmonary Bypass (SIRAB)

Inflammation is a system of the defensive reactions of the vascularized tissues of the organism to the pathogenic insult of any origin. The goal of inflammation is to eliminate the cause, to eliminate destroyed tissue and, through regeneration or repair, to restore metabolism and function of the organs to the state of dynamic balance. The insult may be classified according to nature of the noxious stimulus: biologic (micro-organisms), physical (mechanical insult, radiation), chemical (poisons, acids), metabolic (hypoxia, malnutrition), immunologic (autoimmune diseases), endogenic disorders of neuro-humoral regulation. The response to the noxious stimulus is to trigger an endogenous defensive reaction.

CPB is associated with an inflammatory response due to extensive contact between anti-coagulated blood and the synthetic surfaces of the extracorporeal circuit. Blood cell interactions and plasma protein alterations prolong the bleeding time, increase postoperative blood loss, and trigger a chemical and cellular whole body inflammatory response. Extracorporeal circulation has been associated with both qualitative and quantitative alterations of platelets, neutrophils and complement and contact systems.

The Contact System

The contact system consists of four proteins: factor XII, pre-kallikrein, high-molecular-weight-kininogen (HMWK) and factor XI. Adsorption of factor XII (Hageman factor) onto a foreign surface in the presence of pre-kallikrein and HMWK changes the three-dimensional geometry of the protein to produce active proteases factors XIIa and XIIf. In a feedback loop, factor XIIa cleaves pre-kallikrein to produce kallikrein and HMWK to produce bradykinin, a short acting vasodilator. Factor XIIa in the presence of kallikrein and HMWK also activates factor XI to factor XIa. Factor XIa activates the intrinsic coagulation cascade, which proceeds through factor IX to activate factor X and form thrombin. Kallikrein is a major agonist for neutrophils; factor XIIa is a weak agonist.

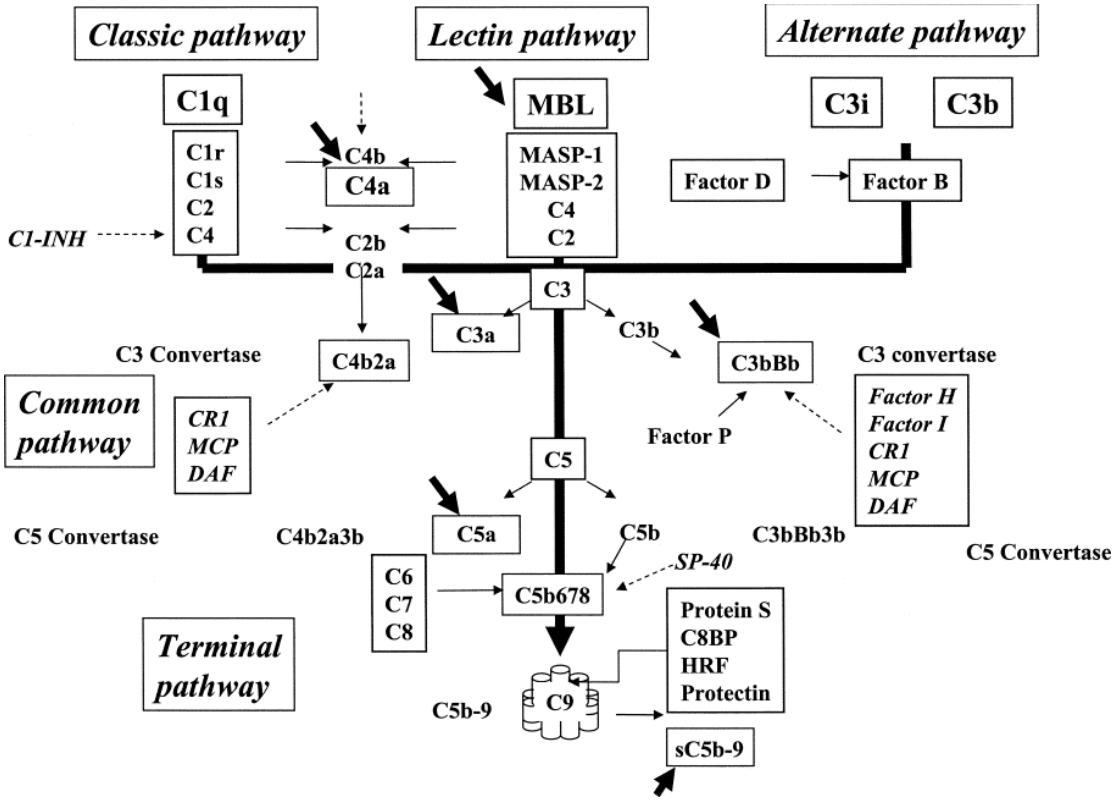
The contact proteins are activated during in vitro recirculation of heparinized blood in a perfusion circuit and during CPB and open-heart surgery.

The Complement System

The complement system is a complex cascade involving proteolytic cleavage of serum glycoproteins often activated by cell receptors. This cascade ultimately results in the induction of the inflammatory response, phagocyte chemotaxis and opsonisation and cell lysis. Complement factors C3a, C5a and C4 can induce vasodilatation, increased capillary permeability and expression of leukocyte adhesion molecules. Complements C3a and C4b are opsonins that attach phagocytes to microorganisms. Complements C3a and C4a promote phagocyte chemo-taxis. Complement C3b may be an opsonin for antigen-antibody complexes which helps prevent damage from the formation of large, insoluble immune aggregates. Complement C5a, like C3a is an anaphyla-toxin, and is a chemo-attractant for induction of neutrophil release of antimicrobial proteases and oxygen radicals. A complex of complements C5b, C6, C7, and C8 mediates the polymerization of up to eighteen C9

molecules into a tube-like membrane attack complex that is inserted into the plasma membrane of an unwanted organism such as of gram-negative bacteria and viral infected cells. This channel through the lipid bilayer results in lysis of the cell. Ischaemic infarction may also cause initiation of the complement cascade. Excessive deposits of membrane attack complexes in tissues may occur following ischaemic injury. Other deleterious effects of complement activation include, degranulation of neutrophils, basophils and mast cells, unwanted release of the neutrophil products elastase and oxygen radicals. Three pathways have been elucidated through which the complement cascade can be initiated; classical, alternate and lectin pathways. All three pathways merge at common intersection, complement C3. The classical pathway mediates specific antibody responses. The classical pathway is initiated by the binding of antibodies to cell surface antigens. Subsequent binding of the antibody to complement C1q subunits of C1 result in catalytically active C1s subunits. The two activated C1s subunits are then able to catalyse the assembly of the C3 convertase (complement C4b2a) from complements C2 and C4. The alternate pathway does not require the action of antibodies to initiate the cascade, but is initiated by foreign cell surface components. In the alternate pathway complement C3 undergoes spontaneous cleavage resulting in complement B binding to C3b. Diffusion of the Ba subunit results in an active alternate pathway C3 convertase (C3bBb). C3bBb is stabilized by binding to properdin prior to merging into the common pathway and conversion of C3. The lectin pathway is similar to the classical pathway. C1q is not involved in the lectin pathway. Instead an opsonin, mannan-binding protein (MBP), is involved in the initiation process. To our knowledge this process has not been studied in patients undergoing OPCAB.

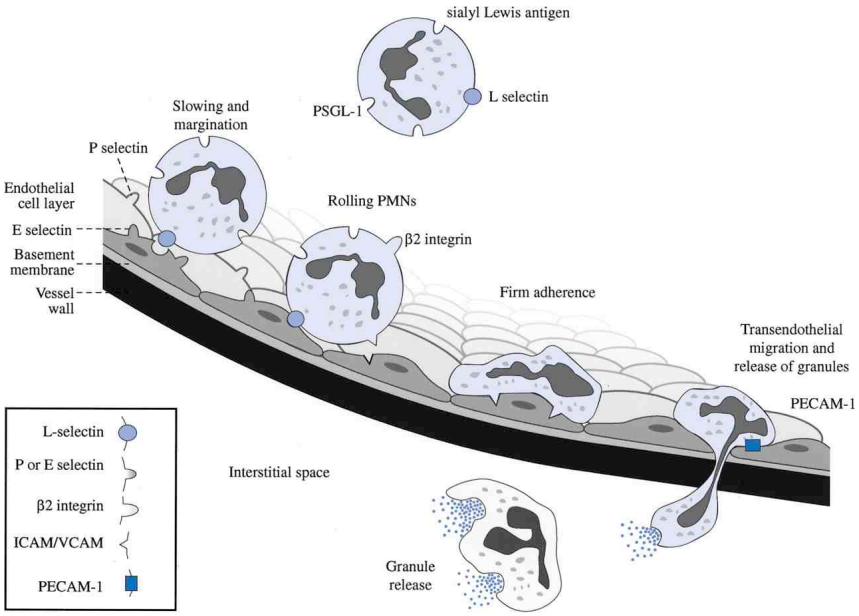
Figure 1-1 The lecithin pathway of complement activation [10]



Neutrophils and Endothelial Cells

Complement activation is one of the most important factors for leukocyte activation and leucocytosis during cardiac surgery and it is considered to be a "trigger" of the CPB-induced inflammatory response. CPB initiates a humoral cascade that also results in the activation of the vascular endothelium. This results in the expression of adhesion molecules that promote adhesion of neutrophils to the vascular endothelium. This causes the neutrophils to roll along the endothelium; a process mediated by selectin interaction with carbohydrate ligands. Activation of the neutrophils results in activation of integrin molecules on the neutrophil surface. This results in firm adhesion of the neutrophils to activated endothelium through receptors belonging to the immunoglobulin (Ig) family. Activated adherent neutrophils extra-vasate through the endothelium into the tissue interstitial space. This process of neutrophil activation, firm adhesion and sequestration can lead to obstruction of capillaries and local ischemia. In addition these activated cells release a variety of cytotoxic products, which can cause direct cellular injury. These cyto-toxins include both preformed agents that are present in the granules of neutrophils and newly synthesized molecules. To our knowledge the role of one such agent termed 'human neutrophil peptide' has not been investigated in the context of CABG.

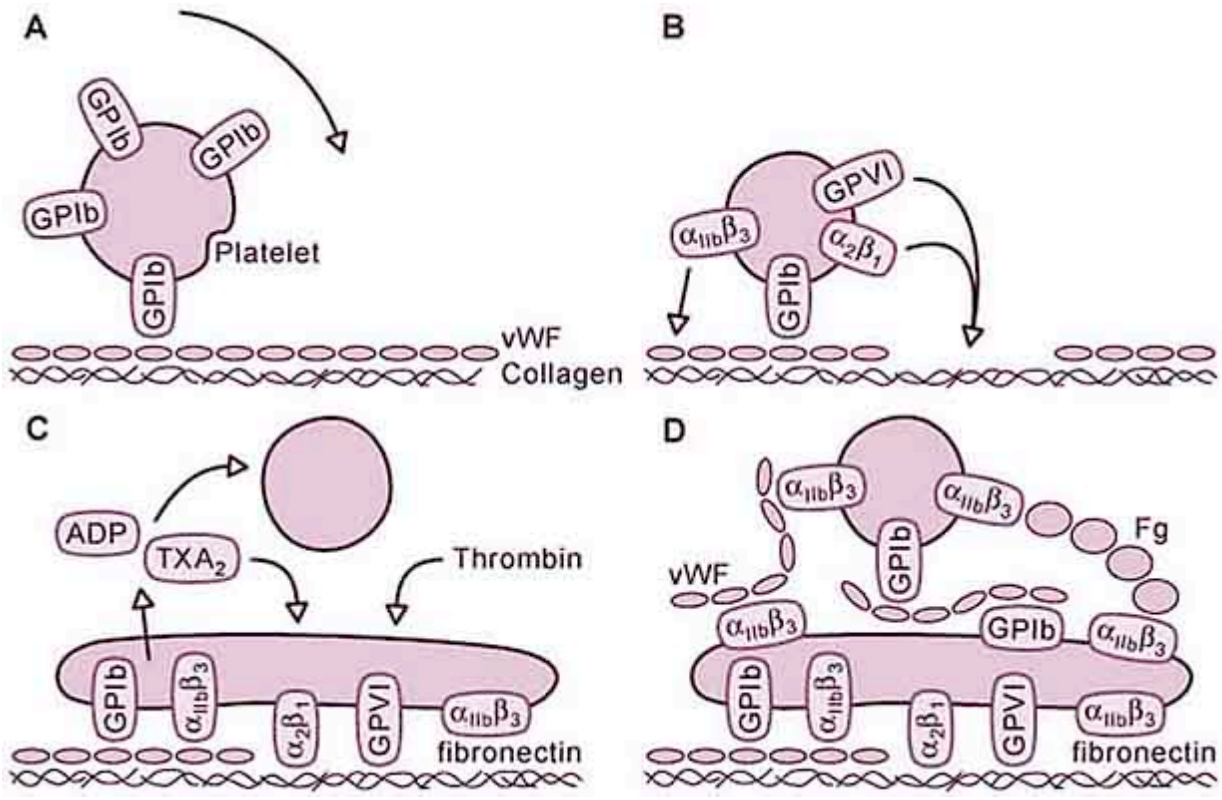
Figure 1-2. Neutrophil Activation [11]



Platelets

Platelets are discoid cell fragments, derived from megakaryocytes in the bone marrow that circulate freely in the blood. Under normal conditions they neither adhere to each other nor to other cellular surfaces. However, when blood vessels are damaged at the luminal surface, platelets adhere to the exposed sub-endothelium. Rheological factors such as shear stresses, turbulence and areas of stagnant flow have less effect on platelets than red cells. The most platelet destructive components of the CPB circuit are the oxygenator & cardiotomy suction. Cardiotomy suction exposes platelets to air-blood & tissue-blood interfaces resulting in platelet activation. The amount of blood aspirated by cardiotomy sucker directly correlates with platelet loss. Filters also provide a surface for platelets to aggregate. The large surface area of synthetic surface of membrane oxygenators accounts for rapid decline in platelet count. However, bubble oxygenators have a greater effect in reducing platelet numbers. Dilution is responsible for most of the thrombocytopenia during CPB, while platelet adhesion, aggregation & destruction are responsible for the remainder. Hypothermia also causes thrombocytopenia by a reversible sequestration of platelets in the portal circulation. Among the main stimuli, able to induce full platelet activation, including shape change, secretion and aggregation, are collagen, thrombin, ADP and thromboxane A_2 (TXA_2). Collagen acts primarily through integrin a2b1 and glycoprotein VI, whereas thrombin, ADP and thromboxane A2 (TXA_2) function through hepta-helical, G-protein-coupled receptors. Most platelet activators function directly or indirectly through G-protein-coupled receptors and induce several intracellular signalling pathways, which eventually lead to secretion of granule contents, change of shape and inside-out activation of GP-IIb/IIIa (integrin aIIbb3). Activation of GP-IIb/IIIa allows fibrinogen (Fb) or vWF to cross-bridge adjacent platelets. The main pathway that leads to platelet activation involves the Gq/phospholipase C-b (PLC-b)-mediated formation of inositol 1,4,5 triphosphate (IP3) and diacyl glycerol (DAG). This in turn results in the release of Ca^{2+} from intracellular stores and the activation of protein kinase C (PKC) isoforms. This adhesion is mediated by collagen and von Willebrand factor (vWF) both of which are exposed at the sub-endothelial surface. Adherent platelets release various factors, which activate other nearby platelets resulting in the recruitment of more platelets at the site of vascular injury. Initially, activated platelets change their shape, an event immediately followed by the secretion of platelet granule contents (including ADP, fibrinogen and serotonin) as well as by platelet aggregation.

Figure 1-3. Platelet Activation [12]



A – rolling of platelets over collagen bound vWF mediated by GPIb

B – attachment mediated by alpha (2) beta (1) and glycoprotein VI (GP VI) binding to collagen, and by alpha (IIB) beta (3) binding to collagen-bound vWF.

C – activation, secretion and spreading

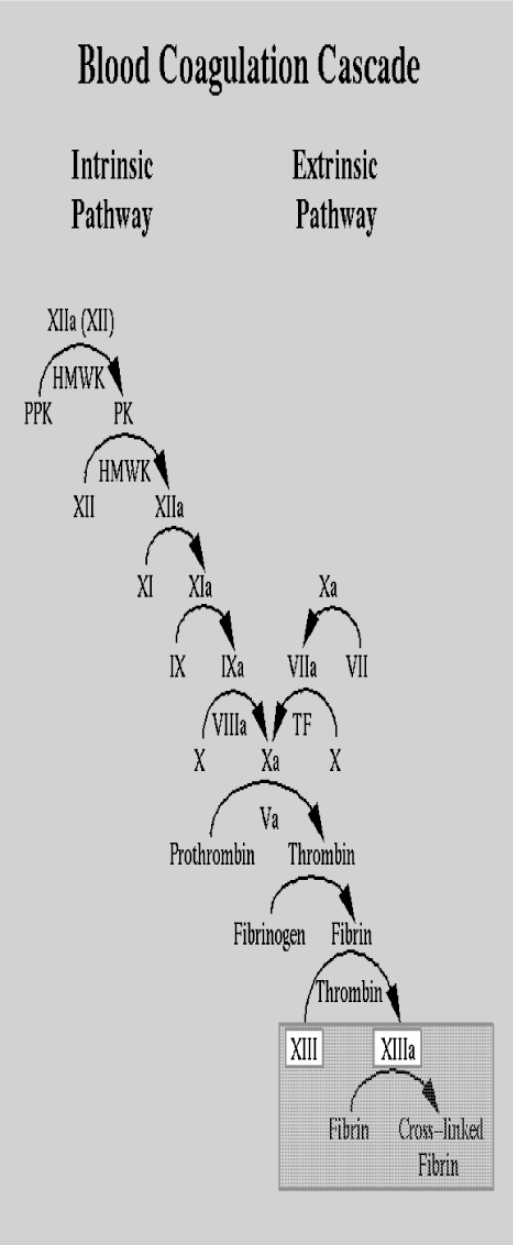
D – Aggregate formation

Aggregation of platelets is mediated by fibrinogen or vWF. They connect platelets by bridging complexes of glycoprotein IIb/IIIa (integrin aIIbb3) on adjacent platelets, forming a platelet aggregate. Each platelet contains about 50,000 to 80,000 glycoprotein IIb/IIIa (GP-IIb/IIIa) molecules on its surface. In order to bind fibrinogen and vWF, GP-IIb/IIIa has to be converted from a low affinity/avidity state to a high affinity/avidity state by a process described as inside-out signalling that is initiated during platelet activation. The rapid formation of a 'platelet plug' at sites of vascular injury is the main mechanism of primary haemostasis. This is followed by a strengthening of the primary thrombus due to the formation of fibrin fibrils by the coagulation cascade.

The Coagulation System

The coagulation cascade of haemostasis has two pathways, the contact activation pathway (formerly known as the intrinsic pathway) and the tissue factor pathway (formerly known as the extrinsic pathway) that lead to fibrin formation. It was previously thought that the coagulation cascade consisted of two pathways of equal importance joined to a common pathway. It is now known that the primary pathway for the initiation of blood coagulation is the tissue factor pathway. The pathways are a series of reactions, in which a zymogen (inactive enzyme precursor) of a serine protease and its glycoprotein co-factor are activated to become active components that then catalyse the next reaction in the cascade, ultimately resulting in cross-linked fibrin. The coagulation factors are generally serine proteases. There are some exceptions. For example, factor VIII and factor V are glycoproteins and factor XIII is a trans-glutaminase. Serine proteases act by cleaving other proteins at specific sites. The coagulation factors circulate as inactive zymogens. Tissue Factor pathway: the main role of the tissue factor pathway is to generate a 'thrombin burst,' thrombin being the single most important constituent of the coagulation cascade in terms of its feedback activation roles. Factor VIIa (FVIIa) circulates in a higher amount than any other activated coagulation factor. Following damage to the blood vessel, endothelium tissue factor (TF) is released, forming a complex with FVIIa (TF-FVIIa), which activates FIX and FX. FVII itself is activated by thrombin, FXIa, plasmin, FXII and FXa. The activation of FXa by TF-FVIIa is almost immediately inhibited by tissue factor pathway inhibitor (TFPI). FXa and its co-factor FVa form the pro-thrombinase complex, which activates prothrombin to thrombin. Thrombin then activates other components of the coagulation cascade, including FV and FVII (which activates FXI which in turn activates FIX), and activates and releases FVIII from being bound to vWF. FVIIIa is the co-factor of FIXa and together they form the tenase complex, which activates FX, and so the cycle continues. Contact Activation pathway: There is formation of the primary complex on collagen by high molecular weight kininogen (HMWK), pre-kallikrein and FXII (Hageman factor). Pre-kallikrein is converted to kallikrein and FXII becomes FXIIa. FXIIa converts FXI into FXIa. Factor XIa activates FIX, which with its co-factor FVIIIa form the tenase complex, which activates FX to FXa. The minor role that the contact activation pathway has in initiating clot formation can be illustrated by the fact that patients with severe deficiencies of FXII, HMWK and pre-kallikrein do not have a bleeding disorder.

Figure 1-4. The Clotting Cascade [13]



Number and/or name	Function
I (fibrinogen)	Forms clot (fibrin)
II (prothrombin)	Its active form (IIa) activates I, V, VIII, XI, XIII, protein C, platelets
Tissue factor	Co-factor of VIIa (formerly known as factor III)
Calcium	Required for coagulation factors to bind to phospholipid (formerly known as factor IV)
V (proaccelerin, labile factor)	Co-factor of X with which it forms the prothrombinase complex
VI	*Unassigned* – old name of Factor Va
VII (stable factor)	Activates IX, X
VIII (antihemophilic factor)	Co-factor of IX with which it forms the tenase complex
IX (Christmas factor)	Activates X: forms tenase complex with factor VIII
X (Stuart-Prower factor)	Activates II: forms prothrombinase complex with factor V
XI (plasma thromboplastin antecedent)	Activates IX
XII (Hageman factor)	Activates factor XI and prekallikrein
XIII (fibrin-stabilizing factor)	Crosslinks fibrin

Thrombin has a large array of functions. Its primary role is the conversion of fibrinogen to fibrin, the building block of a haemostatic plug. In addition, it activates Factors VIII and V and their inhibitor protein C (in the presence of thrombomodulin), and it activates Factor XIII, which forms covalent bonds that crosslink the fibrin polymers that form from activated monomers.

Following activation by the contact factor or tissue factor pathways the coagulation cascade is maintained in a pro-thrombotic state by the continued activation of FVIII and FIX

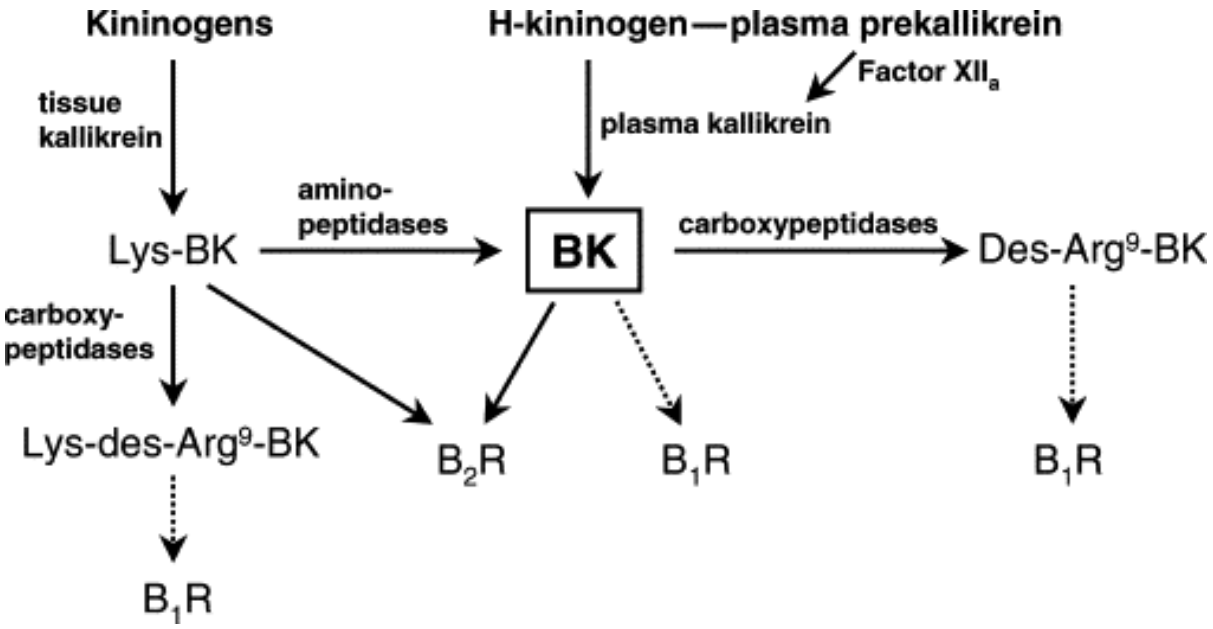
to form the tenase complex, until it is down regulated by the anticoagulant pathways.

The Kinin-Forming System

The kinins, bradykinin and lysylbradykinin, are important mediators of inflammatory responses. They are liberated from precursor molecules, kininogens, by the action of various proteases, collectively known as kininogenase. Three types of kininogen have been identified: high- and low-molecular weight kininogen (HMWK and LMWK respectively), and T-kininogen. These molecules are synthesized by hepatocytes and are released into the plasma, where in addition to releasing kinins, they function as (i) cofactors in the coagulation pathway; (ii) inhibitors of cysteine protease enzymes; and (iii) part of the acute phase response. The kinins are potent vasoactive basic peptides and their properties are wide ranging, including the ability to increase vascular permeability, cause vasodilation, pain, and the contraction of smooth muscle, and to stimulate arachidonic acid metabolism. Three different pathways may lead to kinin formation during inflammation: (i) the generation of bradykinin as a result of activation of the Hageman factor and the production of plasma kallikrein; (ii) the production of lysylbradykinin by tissue kallikreins; and (iii) the action of cellular proteases in kinin formation. In brief, HMWK and pre-kallikrein circulate in plasma as a 1:1 stoichiometric complex. This complex, together with the Hageman factor, binds to negatively charged surface or collagen. Once they are exposed by tissue damage, the Hageman factor is activated, pre-kallikrein is converted to kallikrein, and HMWK itself is digested to release bradykinin, a nine amino acid peptide. As bradykinin is such a potent vasoactive peptide, its activity and its formation must be carefully controlled. Activation of the pathway is controlled internally by the presence of inhibitors for each of the active components. C1 inhibitor controls the activity of the activated Hageman factor, while α2-macroglobulin and C1 inhibitor act as kallikrein inhibitors. There are a variety of enzymes in plasma that control bradykinin activity, including carboxypeptidase N, which removes the C-terminal arginine residue, thus inactivating the peptide. Kallikrein also act directly on the complement pathway with direct cleavage of the chemo-tactically active peptide C5a from the complement component C5. Cleavage of fibrinogen by plasmin results in a number of products including fibrino-peptide B, which potentiates the action of bradykinin and has also chemotactic activity for phagocytic cells. The mechanism of bradykinin formation in plasma

and in tissues is shown below.

Figure 1-5. The Kallikrein System[14]



Abbreviations: B_1R, B_1 receptor; B_2R, B_2 receptor; BK, bradykinin.

Pulsatile Cardiopulmonary Bypass

Physiological blood flow is 3.0-3.2 L/min/m^2 at rest and is pulsatile in character. With the added protection of hypothermia flow rates of 2.0 – 2.4 L/min/m^2 are practical at 32°C. The body response to reduced flow is progressive peripheral vasoconstriction. Despite this the vast majority of CPB is conducted in a non-pulsatile manner. In this study we used non-pulsatile CPB. To date, we do not have a common definition or precise quantification of pulsatile flow, without which direct and meaningful comparisons of different perfusion modes are impossible. Investigators who focus on the topic of pulsatile vs. non-pulsatile flow need a definition because it is commonly believed that pulse pressure is sufficient for direct comparisons. Quantification of pulsatility in terms of pulse pressure is inadequate because the generation of pulsatile flow depends on an energy gradient. Therefore, the pump flow and arterial pressure must be included in quantification of different perfusion modes. The Energy Equivalent Pressure formula (EEP) [15] is based on the ratio between the area beneath the haemodynamic power curve (fpdt) and the area beneath the pump flow curve (fdt) during each pulse cycle

$$EEP = (\int fpdt) / (\int fdt)$$

Where f is the pump flow rate, p is the arterial pressure (mm Hg), and dt indicates that the integration is performed over time (t). The unit of the EEP is millimetres of mercury. Therefore, it is possible to compare the EEP with the mean arterial pressure (MAP). The difference between the EEP and MAP is the extra energy generated by each pulsatile or non-pulsatile device. The difference between EEP and MAP in the normal human heart is approximately 10%. The Surplus Haemodynamic Energy (SHE) [16] formula is calculated by multiplying the difference between the EEP and the MAP by 1332. The SHE equals the extra energy in terms of energy units.

$$\text{SHE (ergs/cm}^3\text{)} = 1332[((\int fpdt) / (\int fdt)) - MAP]$$

Thus pulsatile flow contains higher energy, which may be beneficial for vital organ perfusion during cardiopulmonary bypass. EEP is higher even in a pulsatile roller model than in non-pulsatile roller pumps.

The beneficial effects of pulsatile perfusion occur at the level of the microcirculation, and the extra energy required to produce pulsatile flow is distributed into the microcirculation where it maintains capillary bed patency. Undar et al [16] found considerable evidence that pulsatile flow is superior to non-pulsatile flow during CPB. Several results indicated that some forms of pulsatile flow are no more damaging to red blood cells and platelets than non-pulsatile flow. Some studies reported significantly lower pulmonary vascular resistance with pulsatile CPB than with non-pulsatile flow and also showed that pulsatile flow generates more haemodynamic energy that improves microcirculation and metabolism when compared with non-pulsatile flow and inhibits oedema formation. Pulsatile flow was associated with decreased levels of thyroid hormone, plasma vasopressin, adrenocortical hormone, cortisol, catecholamines, rennin, angiotensin II and thromboxane. Pulsatile flow significantly improves blood flow of the vital organs including the brain, heart, liver, pancreas, kidney, and gastrointestinal system; preserves lung function; reduces the systemic inflammatory response syndrome; and decreases the incidence of postoperative deaths in paediatric and adult patients [16]. Whilst detractors of pulsatile CPB have only ever claimed that there is no difference between the pulsatile and non-pulsatile system in terms of end-organ recovery none of them has documented that pulsatile flow is worse than non-pulsatile flow.

Haemodilution

Haemodilution represents is one of the most significant advances in CPB. Even John Gibbon had decided that a perfusion technique employing a prime of normal composition (blood) with "normal" flow rates (70 to 80 ml/kg/minute) and normal blood pressure should be the way forward. However research by Panico [17], Neptune [18] and Cooley [19] showed that the use of asanguineous prime was safe and practical. It reduced the considerable strain on hospital blood banks. Crystalloid priming solutions are the norm in the present day practice of adult cardiac surgery. On commencement of CPB the haematocrit falls to between 20 - 25%. This reduces blood viscosity, improves regional blood flow, improves oxygen delivery to the tissues and reduces exposure to homologous blood products.

Prediction of initial haematocrit during cardiopulmonary bypass

$$\text{Predicted Hct during CPB} = \frac{\text{Patients red blood cell volume before CPB}}{\text{Patients estimated blood volume+ CPB prime volume+ pre-CPB intravenous fluid volume}}$$

The estimated blood volume can be calculated by multiplying the patients weight in kilograms by 7% (female patients) and 7.5% (male patients). If use of the intended prime volume will cause unacceptable haemodilution then packed red blood cells can be added to the CPB circuit to compensate [9].

Theoretical Adverse Effects Of Cardiopulmonary Bypass And Adverse Clinical Complications[20]

Though somewhat alarming the incidence of appreciable clinical complications is quite uncommon. This is felt by many to be counter intuitive as CPB does cause a more profound disturbance of the "milieu intérieur" as suggested by the release of markers of organ injury

1. Complement and neutrophil activation, vasoconstriction, with increase in capillary permeability, leading to fluid shift into the interstitial compartment.

2. Platelet damage and release of vasoactive substances increase capillary permeability, leading to further fluid shift into the interstitial compartment and impaired haemostasis.

3. Haemodilution leading to lowered colloidal oncotic pressure with resultant intravascular interstitial oedema (including pulmonary oedema)

4. Alteration in fluid balance, urine output, and increase in interstitial renal perfusion volume, increase or decrease in urine output, and increase or decrease in intravascular volume

5. Coagulopathies: caused by inadequate heparin reversal, heparin rebound, consumption of clotting factors and platelets, and platelet dysfunction.

6. Increase in catecholamine release, which can lead to stress on suture sites and subsequent bleeding

7. Increase in levels of renin, angiotensin, aldosterone and antidiuretic hormone with subsequent sodium and water retention.

8. Serum dilution; intracellular-extracellular electrolyte disturbances (e.g. hypokalaemia, and alteration in endocrine function and hypernatremia), fluid shifts and acid-base disequilibrium.

9. Metabolic disturbances: alteration in electrolyte disturbances, carbohydrate metabolism with concomitant stimulation of glycogenolysis by increase in adrenaline secretion.

10. Hypothermia increases systemic vascular resistance due to vasoconstriction; decrease in myocardial contractility and heart rate, resulting in decreased cardiac output and perfusion pressure (including renal perfusion, with subsequent decrease in urine output); hyperglycaemia due to impairment of release of insulin by pancreatic islet cells and altered glucose transport across the cell membrane.

11. Alteration in cardiac function with decreased cardiac output, cardiac arrhythmias (prolonged cardioplegic arrest of >60minutes can result in prolonged ischaemic periods with tissue hypoxia, acidosis, sub-endocardial necrosis, release of myocardial enzymes, and compromised cardiac performance).

12. Alteration in central nervous system function due to emboli (gas, atheromatous debris from aorta, fat and biological emboli) or ischaemic events.

13. Alteration in pulmonary function Pulmonary oedema; acute respiratory distress syndrome (ARDS); atelectasis (alveolar collapse and retention of secretions; predisposition to micro thrombi, which can increase pulmonary shunting, interstitial pulmonary oedema and anoxia.

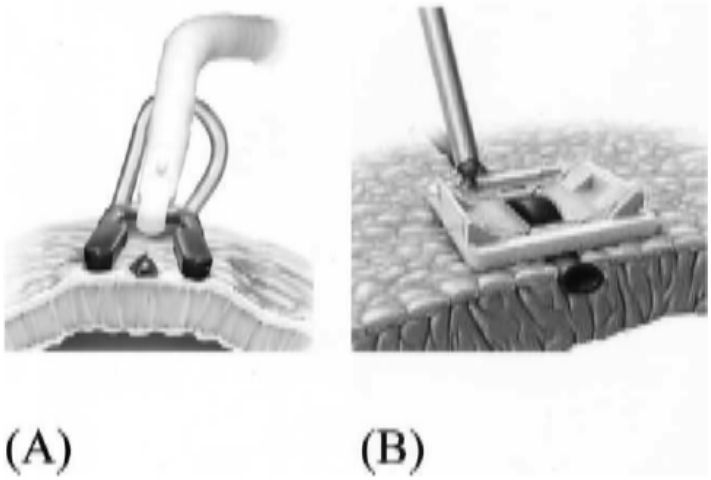
14. Alteration in gastrointestinal (GI) function with splanchnic vasoconstriction leading to bowel ischaemia; gastritis and frank GI haemorrhage.

History Of Off-Pump Coronary Artery Bypass Grafting (OPCAB)

On 25th February 1964 Koselov performed the first successful CABG on a beating heart. In a study of artificial circulation Kolesov concluded that while cardiopulmonary bypass is safe and reliable for use during open-heart surgery, the global inflammatory response following the extracorporeal circulation is too great to justify its use for CABG. Kolesov continued to perform CABG without extracorporeal circulation, believing in the superiority of the off-pump technique. However he did use CPB in 18% of his CABG procedures from 1964 to 1974 [(21)]. Other proponents of OPCAB at this time included Ankeney and Trapp. In 1975, Trapp [(22)] and Ankeney [(23)] presented their landmark reports of operations, performed without CPB, for disease of the right and left anterior descending coronary arteries. In 2004, Ankeney published a review of his extensive clinical experience with off-pump coronary bypass from 1969 through 1985 in 733 patients. This is a remarkable report, because it represents both an early pioneering achievement and a two-decade experience with the OPCAB approach. The series includes patients with both single and double vessel disease who underwent CABG of the right coronary artery (RCA) and/ or the left anterior descending coronary artery (LAD). The author describes his methods for stabilization of the heart by means of traction sutures [(24)]. Buffolo reported CABG by simple interruption of coronary flow in selected cases [(25)]. Benetti also described OPCAB in selected cases [(26)]. Inspired by such reports there was a tremendous resurgence of interest in OPCAB. In 1995 the medical products industry launched a series of innovative products to enable coronary revascularization on the beating heart. The aim of all these devices is to reduce the degree of motion at the site of anastomosis. These devices are commonly suction based though non-suction devices have also been used. The Octopus™ stabilizer (Medtronic Inc., USA) has proved particularly popular as it is mounted on a flexible arm that facilitates grafting of lateral vessels. Complete revascularization of the heart by accessing all coronary territories requires adequate exposure and stabilization of target coronary arteries. The LAD and proximal right coronary arteries can be exposed with minimal cardiac displacement and haemodynamic compromise using surgical packs. The circumflex, diagonal, posterior descending artery and distal right coronary artery are more difficult to expose. The application of slings, pericardial sutures and the placement of surgical packs help to displace

and elevate the heart anteriorly providing adequate exposure.

Figure 1-6. Stabilizers Used In OPCAB [27]



(A) The Octopus™ tissue stabilizer system (Medtronic Inc., USA) achieving local stabilisation by suction onto the heart surface. The malleable suction pods assure easy application, such that the site is lifted and not depressed, thus avoiding impairment of ventricular filling. (B) The Immobilizer stabilisation platform (Genzyme Inc., USA) achieving stabilisation by capturing the target vessel loops

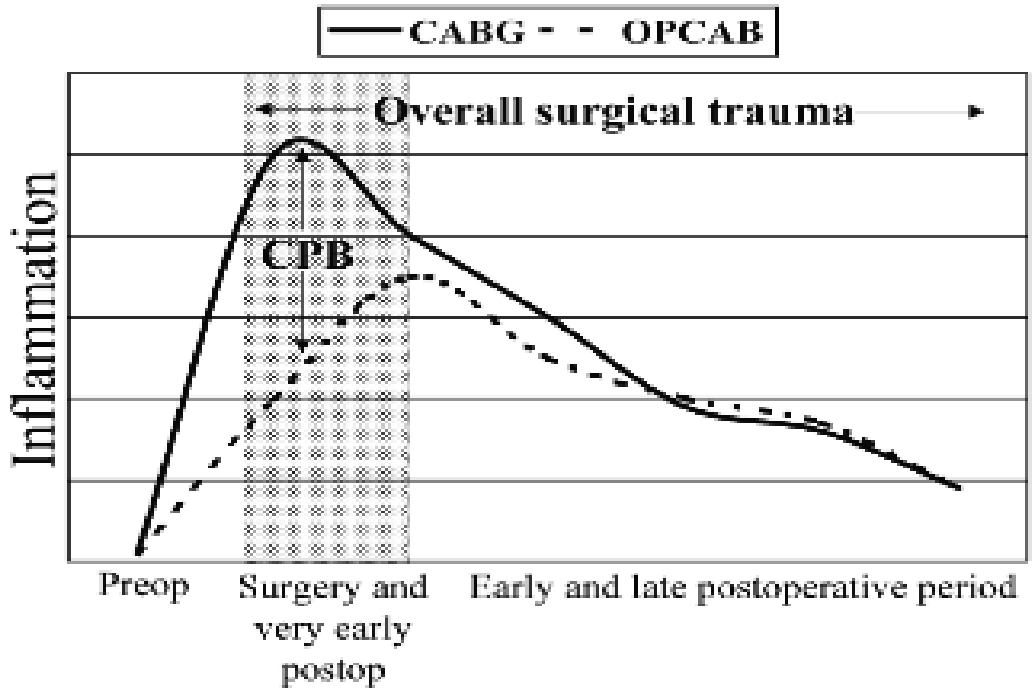
A Trendelenburg tilt with rotation of the operating table to the right and opening the right pleura reduces haemodynamic compromise due to compression of the heart against the right pleura, while performing anastomosis on the posterior and lateral walls. Exposure of the posterior descending artery may require a steep Trendelenburg tilt. Intra-coronary shunts are now commonly used during construction of anastomoses to maintain distal perfusion, display the suture line and reduce back bleeding. The main causes of hemodynamic instability during OPCAB surgery are the impairment of venous return due to chamber compression and abnormal positioning; and pump failure due to direct ventricular compression and or ischemia during occlusion of the target arteries. Mitral valve and tricuspid valve distortion can contribute significantly to hemodynamic instability, and cardiac displacement increases the risk of intraoperative arrhythmia. The extent of the hemodynamic compromise depends on the coronary artery being anastomosed, the greatest being the circumflex artery and its branches on the lateral/ posterior aspect of the heart. It is therefore prudent to graft vessels on the anterior aspect of the heart (i.e. LIMA to LAD is usually first), before any lifting (PDA,

distal RCA) or rotation (diagonal, circumflex) occurs. Changes in arterial pressure and cardiac output may occur rapidly with cardiac manipulation and the anesthetist must pre-empt these to maintain hemodynamic stability. The use of the Trendelenburg position to optimize preload, and the use of vasopressors, inotropes, or repositioning of the heart may improve cardiac output. If adequate hemodynamic parameters cannot be maintained it will be necessary to convert to an on pump technique. Patients with certain patterns of coronary artery disease (diffuse disease, calcification, intra-myocardial, small targets) may also need conversion to CPB. Nevertheless the intuitive concept that avoiding CPB should lead to better clinical outcomes has led to the resurgence of OPCAB.

Chapter 2 Organ damage

The graph below shows the current thinking on the differences between the two techniques. During surgery and the very early hours of the postoperative period, some pro-inflammatory mediators peak to significantly higher levels in CABG than OPCAB patients. However, during the following postoperative period, the differences in terms of the inflammatory state progressively fade and finally cancel out.

Figure 2-1 Potential advantage of OPCAB [28]

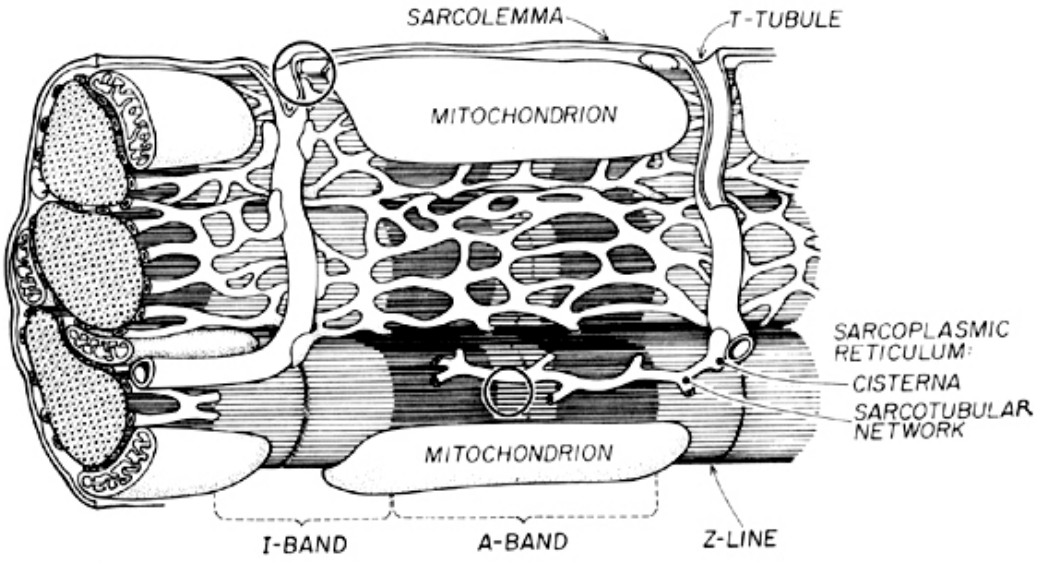


Myocardial Injury

Since the first report in 1967 by Taber and colleagues [29] of the devastating development of the "stone heart" [30, 31] in patients dying after cardiac operations, clinicians have realised that myocardial protection is the key to successful outcome in cardiac surgery.

Myocardial Structure

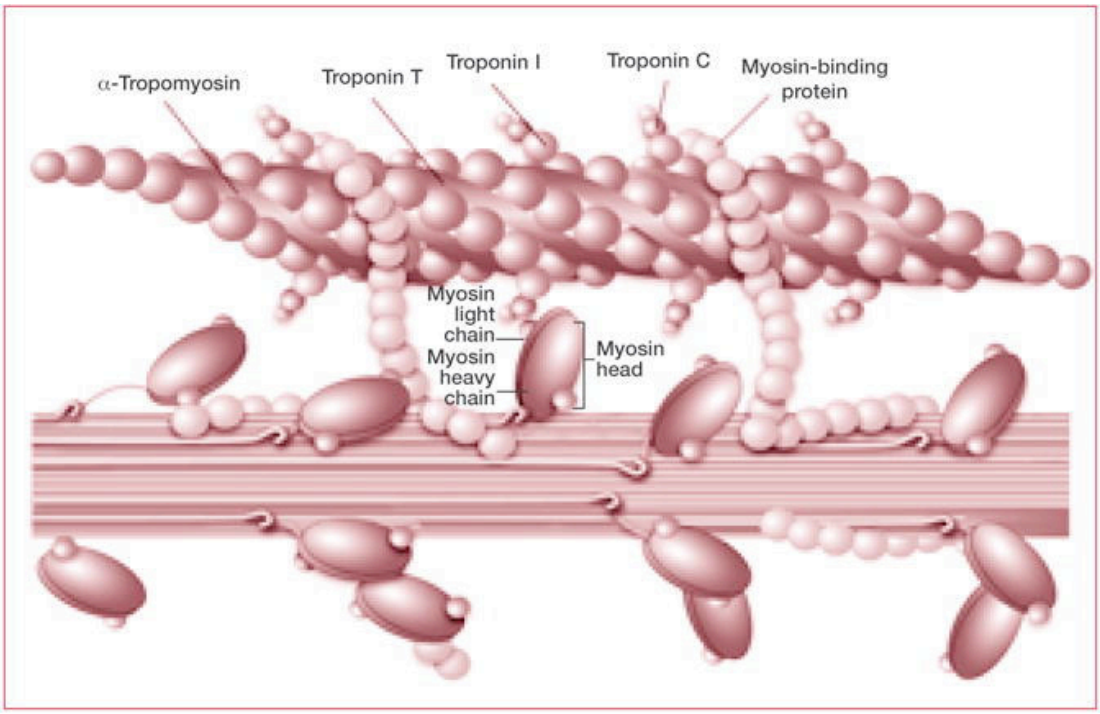
Figure 2-2 Ultrastructure Of Cardiomyocyte [32]



During embryonic development, the splanchnic mesoderm cells of the primitive heart tube align into chain like arrays. Cardiac cells form complex junctions between their extended processes. Cells within a chain often bifurcate and bind to cells in adjacent chains. Consequently, the heart consists of tightly knit bundles of cells, interwoven in a fashion that provides for a characteristic wave of contraction that leads to a 'wringing out' of the ventricles. Mature cardiomyocytes are about 15 μm in diameter and from 85 to 100 μm in length. Each cardiomyocyte has one or two centrally located nuclei, which make up about 2% of the cell's volume. Surrounding the cells is a delicate sheath of endomysial connective tissue containing a rich capillary network. Cardiomyocytes contain numerous mitochondria, which account for about 40% or more of cytoplasmic volume. Fatty acids, transported to the cardiomyocytes by lipoproteins are the major fuel to the myocardium [33]. Fatty acids are

stored as triglycerides in numerous lipid droplets within the cardiomyocytes. A small amount of glycogen is present and can be broken down to glucose and used for oxidation during periods of stress. The contractile machinery of the cardiomyocyte is the sarcomere. About 50 sarcomeres in tandem make up a myofibril; there are about a bundle of 50 to100 myofibrils per cardiomyocyte. Each sarcomere is made up of thick and thin filaments (mostly myosin and actin, respectively) that interact via cross-bridges that extend from the myosin filaments. Six actin filaments are arranged in a hexagonal array around each myosin filament. Troponin is a component of thin filaments along with actin and tropomyosin), and is the protein to which calcium binds to accomplish this regulation. Troponin has three subunits, TnC, TnI, and TnT. When calcium is bound to specific sites on TnC, tropomyosin rolls out of the way of the actin filament active sites, so that myosin (a molecular motor organized in muscle thick filaments) can attach to the thin filament and produce force and/or movement. In the absence of calcium, tropomyosin interferes with this action of myosin, and therefore muscles remain relaxed. Myosin filaments are arranged in trigonal arrays relative to each other. So, there is a 2:1 ratio of actin to myosin throughout the cell. The sarcoplasmic reticulum (SR) makes up about 0.1% of the cell's volume. It functions to store, release and re-sequester the free calcium involved in triggering contraction/relaxation. T-tubules (invaginations of the outer cell membrane) carry the electrical depolarization of the membrane toward the calcium storage area of the SR, effectively triggering the release of that calcium

Figure 2-3 Structure Of Troponin [34]



Contractile proteins in the cardiac sarcomere. The top chain represents actin; the bottom chain represents myosin. Contraction occurs when calcium binds the troponin complex, allowing myosin to bind to actin with the production of force: "Myosin rows the actin sea".

Biomarkers of Myocardial Injury

The development of assays for the detection of cardiac-specific enzymes such as troponin I has been shown to be a sensitive and specific serum marker of myocardial injury following CPB [35, 36] and after CABG [37]. Fatty acid binding proteins (FABP) are a class of cytoplasmic proteins with a molecular weight of 15KDa that bind long chain fatty acids. The FABP content of human heart muscle (H-FABP) is markedly high, comprising about 10 to 20 mol% of cytoplasmic proteins[38]. Several studies have suggested that OPCAB is associated with a lower release of a variety of cardiac markers. The aim of this study was to investigate a novel marker termed heart type fatty acid binding protein as a marker of myocardial injury

and correlate its release with that of cardiac troponin I. Pelsers and colleagues have shown that H-FABP is rapidly released following acute myocardial infarction[38]. Significantly elevated levels are found within 3 hours after AMI and generally return to basal levels after about 12 to 24 hours. Liu[39] et al noted that compared with cTnI and CK-MB, H-FABP was an earlier and potentially useful marker in the rapid evaluation of myocardial damage following valve replacement surgery with CPB. Furthermore elevation of H-FABP has been shown to be associated with an increased risk of death and major cardiac events in patients presenting across the spectrum of acute coronary syndromes and was independent of other established clinical risk predictors and biomarkers[40]. H-FABP plasma concentrations have also been shown to directly correlate with the amount of necrotic myocardium[41]. Petzold et al[42] studied patients undergoing CABG and concluded that H-FABP was a rapid marker of perioperative myocardial damage, which peaks earlier than CKMB or TnI. H-FABP has a peak as early as 3 hours after acute myocardial infarction and 2 hours after reperfusion after CABG[43]. Epema et al noted in their study of patients undergoing ONCAB that plasma H-FABP started to rise directly after aortic clamp release, reaching peak values after 1.23 hours (95% confidence interval [CI], 0 to 2.66 hours), which was significantly earlier ($p < 0.001$) than the peak values of cTnI and CK-MB (cTnI: mean, 14.1 hours; 95% CI, 6.36 to 21.84 hours; CK-MB: mean, 16.35; 95% CI, 9.23 to 23.47 h). There is general agreement that OPCAB results in reduced release of CKMB, cardiac troponin T and troponin C. The aim of this study was to elucidate if there were any changes in H-FABP levels and to see how they correlated with the current gold standard troponin I.

The development of OPCAB allows us to study in detail the relative magnitude of the stress of CPB and cardioplegic arrest on myocardial injury. Table 1[20] summarizes some of the literature to date on this topic.

Table 2-1. Comparison Of Myocardial Injury In Patients Undergoing OPCAB Or ONCAB [20]

Study	*CABG + CPB (number of cases)*	*OPCAB (number of cases)*	*Main Outcome*
Selvanayagam, 2004	30	30	OPCAB resulted in significantly better LV function early after surgery but did not reduce the incidence or extent of irreversible myocardial injury.
Vedin, 2003	29	29	Immediately after surgery, there was better CV performance and less release of markers of myocardial damage after OPCAB.
Sahlman, 2003	26	24	Less CK-MB release and better myocardial preservation in OPCAB patients.
Baker, 2001	14	12	TnT release was reduced in the OPCAB patients at all time points (repeated measures ANOVA P=0.043), reaching statistical significance at 8 (P=0.033), 10 (P=0.038), and 12 (P=0.019) hours.
Czerny, 2001	40	40	Clinical and hospital outcomes were comparable between the 2 groups with no deaths or new MIs. Three OPCAB patients had successful PTCA.
van Dijk, 2001	139	142	Release of CK-MB was 41% less in the OPCAB group (P <0.01). In both groups, 4% of patients had recurrent angina. Survival free of CV events was 93% (OPCAB) and 94.2% (CABG) (P=0.06).
Pentilla, 2001	11	11	Maximum myocardial lactate production (P=0.02), transcardiac pH difference (P=0.007), peak postoperative CK-MB mass (P <0.001) and Tn I (P=0.008) were high in CABG.
Gulielmos, 2000	20	20	TnT and CK-MB levels were significantly higher after CPB procedures (P <0.0056).
Wildhirt, 2000	13	13	OPCAB reduced myocardial cell damage and lipid peroxidation and was associated with a reduced activation of endothelin.
Ascione, 1999	40	40	No deaths or intraoperative MIs in either group. TnI release was consistently lower in the OPCAB group and was significant at 1, 4, 12, and 24 hours postoperatively. Arrhythmias were significantly lower in the OPCAB group (P <0.05).
Krejca, 1999	25	13	CABG without aortic cross-clamping and without CPB offered superior myocardial protection.

Assessment Of Myocardial Function

Recordings of heart rate (HR), central venous pressure (CVP), blood pressure and mean arterial pressure (MAP) were recorded from the patient monitors and logged by a computer every 5 seconds postoperatively for 12 hours. This data was used to determine the pressure adjusted rate (PAR). The concept is part of the Multiple Organ Dysfunction Score (MODS)[44] that has been extensively validated in a general intensive care setting. It is described by the formula: PAR=(PULSE CVP)/MAP. The actual PAR is calculated and then scored accordingly.

PAR SCORE	0	1	2	3	4
PAR	</=10	10.1-15	15.1-20	20.1-30	>30

Pulmonary Injury

The incidence of postoperative pulmonary complications following cardiopulmonary bypass (CPB) ranges from 20% to 95% [45]. Complications that occur include [46] pleural effusion (27%-95%), atelectasis (16.6%-88%), phrenic nerve paralysis (30%-75%), prolonged mechanical ventilation (6%- 58%), diaphragmatic dysfunction (2%- 54%), pneumonia (4.2% to 20%), diaphragmatic paralysis (9%), pulmonary embolism (0.04% to 3.2%), aspiration (1.9%), pneumothorax (1.4%), chylothorax (18 case reports), trapped lung syndrome (single case report) and acute respiratory distress syndrome (ARDS). The incidence of acute respiratory distress syndrome (ARDS) ranges from 0.5% to 1.7% with attendant mortality rates of 91.6% [47]. ARDS was first described in 1967 by Ashbaugh et al [48]. ARDS is defined as the ratio of arterial partial oxygen tension (PaO_2) as fraction of inspired oxygen (FiO_2) below 27 KPa in the presence of bilateral alveolar infiltrates on the chest x-ray. These infiltrates may appear similar to those of left ventricular failure, but the cardiac silhouette appears normal in ARDS. Also, the pulmonary capillary wedge pressure is normal (less than 18 mmHg) in ARDS, but raised in left ventricular failure. A PaO2/FiO_2 ratio between 27KPa

and 40 KPa with bilateral infiltrates indicates acute lung injury (ALI). Although formally considered different from ARDS, ALI is usually a precursor to ARDS [49, 50].

Table 2-2. Risk factors for Lung dysfunction [46]

Preoperative	Intraoperative	Postoperative
• Chronic obstructive pulmonary disease • Obesity • Age:>60 years, >70years, >80years • Diabetes • History of smoking • Chronic heart failure • Emergency surgery • Previous cardiac surgery • Immobility	• Respiratory depression • Neurologic injury • Lung deflation • Cardiopulmonary bypass • Topical cooling • Internal mammary artery dissection • Sternotomy incision • Increased number of bypass grafts • Increased duration of CPB • Lower core temperature	• Respiratory depression associated with non-reversal of anaesthesia • Phrenic nerve dysfunction • Diaphragmatic dysfunction • Pain • Constant tidal volumes/short shallow respiration • Reduced compliance • Reduced vital capacity and functional residual capacity • Ventilation-perfusion mismatch and physiological shunt • Fluid imbalance • Immobility and position • Chest tubes • Nasogastric tubes • Impaired mucociliary clearance • Ineffective cough • Pleural effusion • Atelectasis • Pulmonary oedema • Aspiration

Pulmonary Structure

The alveoli form the gas exchange surface. They are sac-like evaginations about 200μm in diameter. There are over 700 million alveoli present in the human lungs representing a total surface area of 70 – 90 m^2. The wall of each alveolus is 0.1μm thick. The air in the alveolus is separated from capillary blood by three components referred to collectively as the blood-air barrier: the surface lining and cytoplasm of the alveolar cells, the fused basal laminae of the closely apposed alveolar and endothelial cells and the cytoplasm of the endothelial cells. The total thickness of these layers varies from 0.1 to 1.5μm.

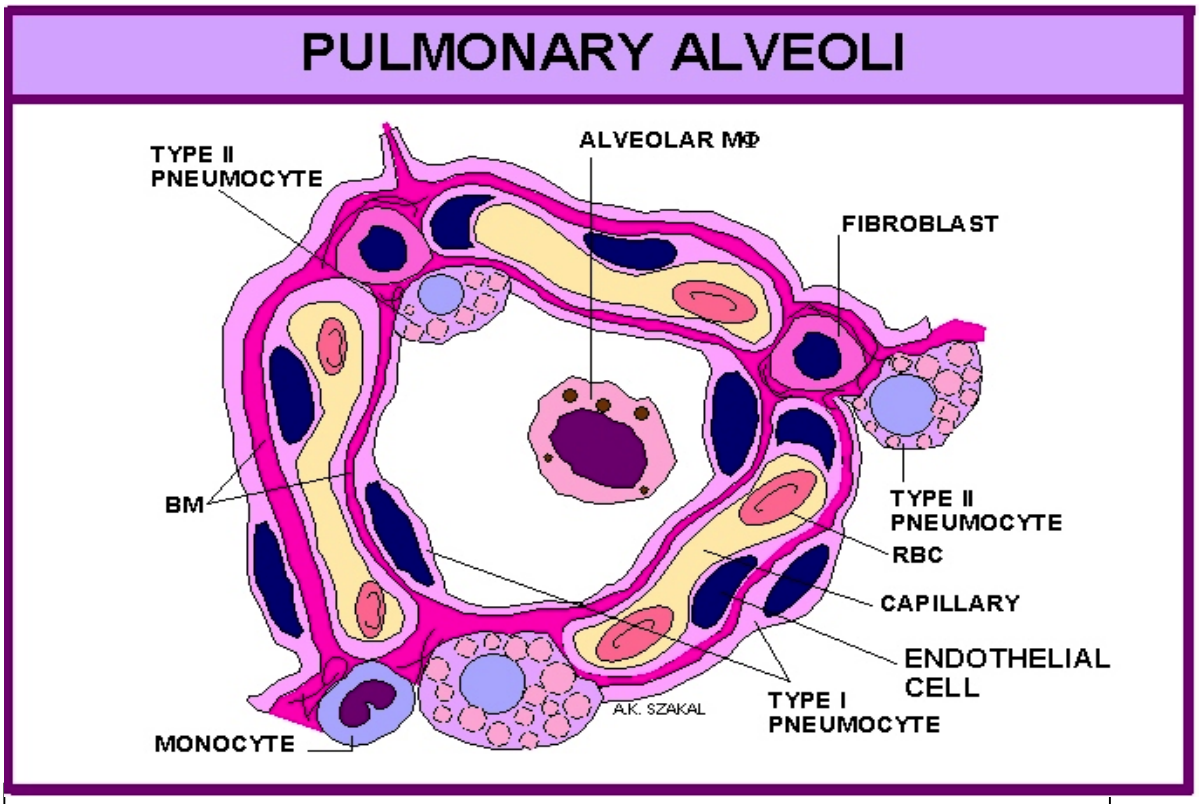


Figure 2-4. Pulmonary Alveolus [1]

Capillary endothelial cells are extremely thin. The endothelial lining of the capillaries is continuous and not fenestrated. Type 1 pneumocytes also known as squamous alveolar cells

are extremely attenuated cells that line the alveolar surfaces. Type 1 cells make up 97% of the alveolar surfaces. They have desmosomal and occluding junctions that prevent the leakage of tissue fluid into the alveolar air spaces. Type 2 pneumocytes make up 3% of the alveolar surface. These are interspersed among the type 1 cells with which they have occluding and desmosomal junctions. These cells secrete and manufacture pulmonary surfactant, which lowers alveolar surface tension, preventing alveolar collapse and thereby reducing the work of breathing. The surfactant layer consists of an aqueous, proteinaceous layer covered with a monomolecular phospholipid film that is primarily composed of dipalmitoyl phosphatidylcholine and phosphatidylglycerol. Surfactant also contains several types of proteins.

Biomarkers Of Lung Injury

The lung epithelium secretes several specific proteins into the air spaces of the respiratory tract. These include the major secretory product of Clara cells termed Clara cell protein (CC16) and the alveolar surfactants A to D. Small amounts of CC16 and SP-D are detectable in the circulation. This can only be explained by leakage into the vascular compartment following parenchymal damage [51, 52]. This has been termed pneumoproteinaemia [52]. Clara cell protein 16 plays an important immunosuppressive and anti-inflammatory role in the lung. It also prevents degradation of lung surfactant phospholipids. Surfactant Protein D belongs to the collectin family. These proteins are oligomeric proteins composed of carbohydrate recognition domains (CRD) attached to collagenous regions. The highest concentrations of CC16 are found in pulmonary fluids such as the epithelial lining fluid (ELF), the broncho-alveolar lavage-fluid (BALF), and the sputum. In serum the normal range in healthy non-smokers is between 10 and 15 μg/ L that is

a value about 10,000 times lower than the ELF. Thus there is a huge concentration gradient probably provides the driving force for the movement of CC16 from the lung into the blood. The lung is the major site of synthesis of SP-D where the molecules are produced and secreted onto the epithelial surfaces by type 2-pneumocytes. SP-D is a 42-kDa (monomeric) protein. SP-D is an important factor in the pulmonary antimicrobial defence. The anti-microbial defence mechanisms of SP-D are direct opsonization, neutralization and agglutination thus enhancing the clearance of pulmonary pathogens by alveolar macrophages. SP-D synthesis and secretion significantly increase during inflammatory stress.

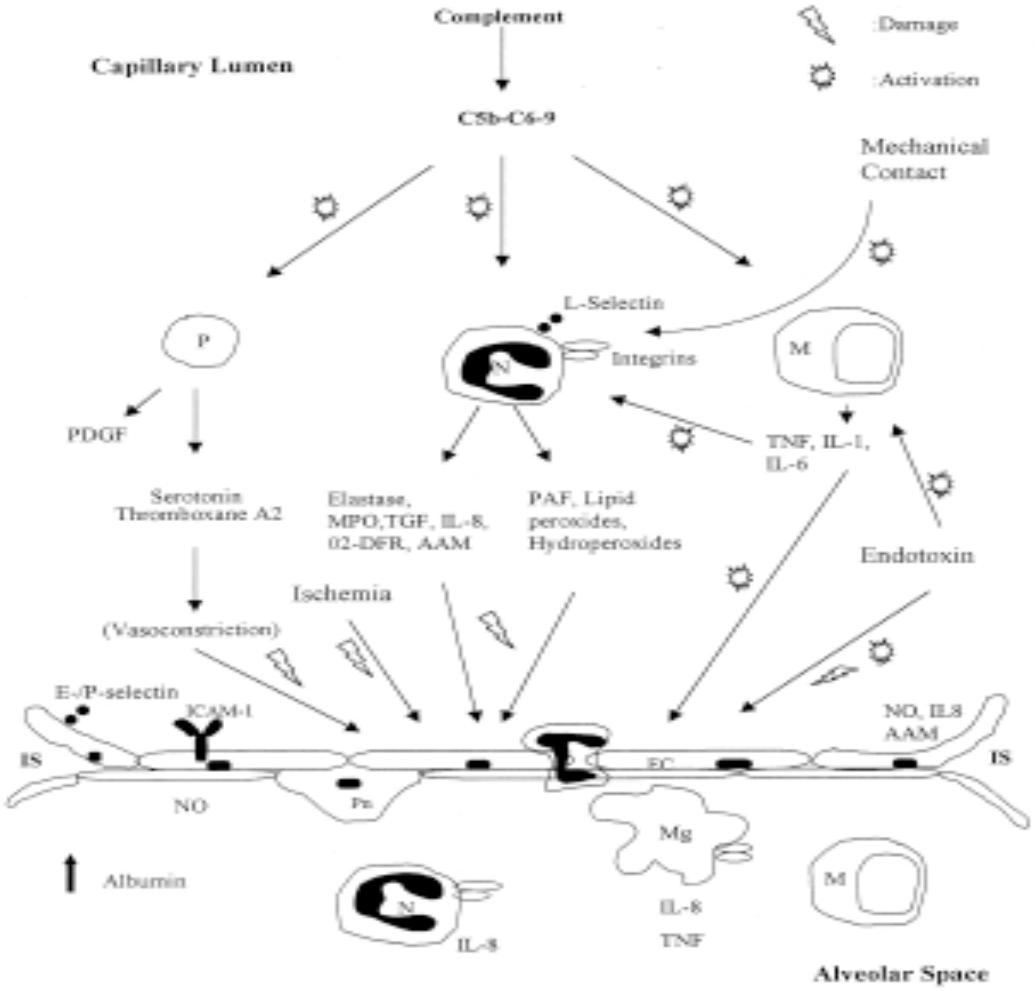
Both CC16 and SP-D have already been validated as blood markers of lung hyper permeability in a variety of lung disorders caused by lung toxicants and other insults [(53)]. To our knowledge only Van Boven [(54)] has investigated the role of CC16 in patients undergoing CABG and a Medline search revealed no prior investigations on SP-D [(54)].

Pathophysiology Of Lung Dysfunction

Pulmonary dysfunction is very common after operations involving CPB. This may present as a spectrum of manifestations, from mild postoperative dyspnoea to florid adult respiratory distress syndrome (ARDS) in 2% of cases, which, in itself, carries a 50% mortality rate [(55)]. Acute lung injury (ALI) after CPB results from sequential priming and activation of neutrophils. Activated neutrophils release neutral serine, elastase, and matrix metallo-proteinases (MMPs) and oxygen radical species, which damage alveolar-capillary basement membranes and the extracellular matrix, resulting in an ALI clinically defined as ARDS [(56)]. Whilst several trials have shown no clinically significant difference with the elimination of CPB we sought to investigate whether these novel biochemical markers of 'pneumo-proteinaemia', could potentially serve as early and highly sensitive peripheral markers for cellular injury, epithelial leakage at different levels and thus lung injury.

Pulmonary dysfunction results from a plethora of insults including cardioplegic solution, foreign mechanical surfaces, and shearing forces. Injury to the pneumocytes leads to loss of epithelium integrity, decreased surfactant production, and altered ion transport, resulting in oedema accumulation within the alveoli. Because of the damage to the epithelium, hyaline membranes - a collection of damaged cells that result in thickening of the epithelium - form, and progressive fibrosis occurs. Continued endothelial damage leads to altered permeability and movement of protein-rich fluid into the alveolar airspace, further impairing alveolar gas exchange. As a result, diffuse lung injury occurs and acute respiratory failure follows. This causes a widespread increase in capillary permeability, with resultant exudation of protein rich fluid into the interstitium and alveoli. In addition, there is a deficiency of surfactant, and the wet soggy lungs become less compliant and have a tendency to collapse (in dependent zones). CT scan of the lungs displays heterogeneous injury, with damaged lung tissue surrounded with normal looking tissue. The functional residual capacity falls, and the work of breathing increases.

Figure 2-5. Alveolar Inflammation [47]



(AAM 5 arachidonic acid metabolites; ICAM-1 5 intercellular adhesion molecule-1; IL 5 interleukin; IS 5 interstitial space; LPS 5 lipopolysaccharide; M 5 monocyte; Mg 5 macrophage; MPO 5 myeloperoxidase; N 5 neutrophil; NO 5 nitric oxide; O2-DFR 5 oxygen-derived free radicals; P 5 platelet; PAF 5 platelet-activating factor; PDGF 5 platelet-derived growth factor; Pn 5 pneumocyte; TGF 5 tumour growth factor; TNF 5 tumour necrosis factor.)

Measurement Of Respiratory Function

Acute lung injury (ALI) is a diffuse heterogeneous lung injury characterized by hypoxemia, non-cardiogenic pulmonary oedema, low lung compliance and widespread capillary leakage. ALI is caused by any stimulus of local or systemic inflammation, principally sepsis. Acute Lung Injury (ALI) and ARDS are defined as: Bilateral pulmonary infiltrates on chest x-ray; Pulmonary capillary Wedge Pressure < 18 mmHg (2.4 KPa); PaO_2/FiO_2 =27KPa to 40 KPa = ALI; PaO_2/FiO_2 <27KPa = ARDS. (FiO_2 = fractional inspired oxygen; PaO2 = arterial oxygen tension.) Primary ALI is caused by a direct injury to the lung (e.g. pneumonia). Secondary ALI is caused by an indirect insult (e.g. SIRS). There are two stages – the acute

phase characterized by disruption of the alveolar-capillary interface, leakage of protein rich fluid into the interstitium and alveolar space and extensive release of cytokines and migration of neutrophils. In patients undergoing CABG it is possible to have both primary and secondary ALI. A later reparative phase is characterized by fibro-proliferation, and organization of lung tissue. The patient has low lung volumes, atelectasis, loss of compliance, ventilation-perfusion mismatch (increased dead space) and right to left shunt.

Gastrointestinal injury

The incidence of GI complications among 2.7 million patients undergoing coronary artery bypass grafting (CABG) was 4.1% with inpatient mortality 12.0% [57]. Reported complications include bleeding (24% to 61%), pancreatitis (2% to 34%), perforated ulcer ((2% to 8%), mesenteric ischemia (5% to 36%), ileus/obstruction (3% to 21%), cholecystitis (5% to 14%), diverticulitis (25 to 3%) and hepatic failure (5% to 10%).

Table 2-3. Risk Factors For GI Complications [57]

Predictors	Odds ratio	95% Confidence interval
Age		
18 – 40	1.0	-
41 – 49	1.0	0.94 – 1.11
50 – 64	1.5	1.38 – 1.62
65 – 74	2.1	1.98 – 2.32
>75	2.6	2.41 – 2.83
Charlston Comorbidity Index		
0	1.0	-
1	1.0	1.03 – 1.06
2	1.1	1.06 – 1.12
3	1.5	1.47 – 1.59
Operation		
Multi vessel CABG	1.2	1.17 – 1.26
Internal mammary use	0.9	0.90 – 0.94
CABG & Valve	1.5	1.45 – 1.52
Intra-aortic balloon pump	1.6	1.59 – 1.65
Admission type		
Elective	1.0	-
Urgent	1.2	1.15 – 1.19
Emergency	1.5	1.44 – 1.49
Comorbidity		
Renal failure	1.2	1.09 – 1.25
Haemodialysis	3.4	3.24 – 3.50

Despite these recent findings cardiopulmonary bypass (CPB) is still recognized as the main culprit[58, 59]. Mack et al[58] state that the use of cardiopulmonary bypass (odds ratio 2.08, confidence interval 1.52-2.83) is an independent predictor of gastrointestinal complications. The advent of CABG without the use of CPB (OPCAB) allows interrogation of this phenomenon in detail

The arterial inflow to the splanchnic region is via the coeliac, superior and inferior mesenteric arteries. The major organs contained include the stomach, small and large

intestines, pancreas, spleen, liver and gall bladder. The venous efflux via the portal vein is the sum of all splanchnic arterial influx, except the hepatic arterial flow. The anatomy of the blood flow of the small intestinal villus is particularly important. Each villus has an artery and a vein that run in parallel but their blood flows are in opposite directions. This counter current arrangement allows for the exchange of oxygen from the artery to the vein along their course within the villus. This results in a descending gradient of tissue pO_2 from the base of the villus to its tip. Consequently the lower pO_2 at the tip makes the villus more susceptible to tissue hypoxia[60]. The splanchnic circulation receives 25-30% of the cardiac output and contains more than 20% of the circulating blood volume.

The Gastrointestinal Mucosal Barrier

The gastrointestinal mucosa forms a barrier between the body and a luminal environment, which contains nutrients, potentially hostile microorganisms and toxins. The challenge is to allow efficient transport of nutrients across the epithelium while rigorously excluding passage of harmful molecules and organisms into the animal. The barrier properties of the gastric and intestinal mucosa are referred to as the 'gastrointestinal barrier'. The gastrointestinal barrier is often discussed as having two components:

The intrinsic barrier is composed of the epithelial cells lining the digestive tube and the tight junctions that tie them together.

The extrinsic barrier consists of secretions and other influences that are not physically part of the epithelium, but which affect the epithelial cells and maintain their barrier function.

The alimentary canal is lined by sheets of epithelial cells that form the mucosal surface. With few exceptions, epithelial cells in the stomach and intestines are circumferentially tied to one another by tight junctions, which seal the para-cellular spaces and thereby establish the basic gastrointestinal barrier. Throughout the digestive tube, maintenance of an intact epithelium is thus critical to the integrity of the barrier. In general, toxins and microorganisms that are able to breach the single layer of epithelial cells have unimpeded access to the systemic circulation.

Different types of epithelial cells have different and specific barrier functions. For example, the apical plasma membranes of gastric parietal and chief cells have atypically low permeability to protons, which aids in preventing damage due to back diffusion of acid into

the cells. Small intestinal epithelial cells lack this specialized ability and thus are much more susceptible to acid-induced damage.

Tight junctions encircling gastrointestinal epithelial cells are a critical component of the intrinsic barrier and provide protection of the intercellular spaces[61]. These structures used to be viewed as passive structures akin to welds, but recent studies indicate that they are much more dynamic than previously thought, and their permeability may be regulated by a number of factors that affect the epithelial cells[62].

The gastrointestinal epithelium is populated by a variety of functionally mature cells derived from proliferation of stem cells. Most of the mature epithelial cells, including mucous cells in the stomach and absorptive cells in the small intestine, show rapid turnover rates, and die within a few days of their formation. Maintenance of epithelial integrity thus requires a precise balance between cell proliferation and cell death.

Stem cells that support continual replenishment of gastrointestinal epithelium reside in the middle of the gastric pits and within the crypts of the small and large intestine. Epithelial cell dynamics of the small intestine have been particularly well studied. These stem cells proliferate continually to supply cells that then differentiate into absorptive enterocytes, mucus-secreting goblet cells, entero-endocrine cells and Paneth cells. Except for Paneth cells, which remain in the crypts, the other cells differentiate into their mature forms as they migrate up from the crypts to replace cells extruded from the tips of the villi. This migration takes approximately 3 to 6 days.

The entire gastrointestinal epithelium is coated with mucus, which is synthesized by cells that form part of the epithelium. Mucus serves an important role in mitigating shear stresses on the epithelium and contributes to barrier function in several ways. The abundant carbohydrates on mucin molecules bind to bacteria, which aids in preventing epithelial colonization and, by causing aggregation, accelerates clearance. Diffusion of hydrophilic molecules is considerably lower in mucus than in aqueous solution, which is thought to retard diffusion of a variety of damaging chemicals, including gastric acid, to the epithelial surface. In addition to being coated with a mucus layer, gastric and duodenal epithelial cells secrete bicarbonate ion on their apical surfaces. This serves to maintain a neutral pH along the epithelial plasma membrane, even though highly acidic conditions exist in the lumen.

Normal proliferation of gastric and intestinal epithelial cells, as well as proliferation in response to such injury as ulceration, is known to be affected by a large number of

endocrine and paracrine factors. Several of the enteric hormones are known to enhance rates of proliferation. Different forms of injury to the epithelium can lead to either enhanced or suppressed rates of cell proliferation. For example, it has been demonstrated that resection of a portion of the canine small intestine is followed by epithelial cell hyperplasia and increased villus length in animals fed orally. Animals fed parenterally failed to show the same compensatory hyperplasia, indicating that, among other factors, local nutrients play an important role in cell dynamics.

Prostaglandins, particularly prostaglandin E2 and prostacyclin have long been known to have cyto-protective effects on the gastrointestinal epithelium. A common clinical correlate in many mammals is the use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin synthesis is commonly associated with gastric erosions and ulcers. Dogs are particularly sensitive to this side effect. Prostaglandins are synthesized within the mucosa from arachidonic acid, through the action of cyclooxygenases. Their cyto-protective effect appears to result from a complex ability to stimulate mucosal mucus and bicarbonate secretion, to increase mucosal blood flow and, particularly in the stomach, to limit back diffusion of acid into the epithelium.

Two peptides that have received attention for their potential role in barrier maintenance are epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-alpha). EGF is secreted in saliva and from duodenal glands, whilst TGF-alpha is produced by gastric epithelial cells. Both peptides bind to a common receptor and stimulate epithelial cell proliferation. In the stomach, they also enhance mucus secretion and inhibit acid production. Other cytokines such as fibroblast growth factor and hepatocyte growth factor have been shown to enhance healing of gastrointestinal ulcers in experimental models.

Trefoil proteins are a family of small peptides that are secreted abundantly by goblet cells in the gastric and intestinal mucosa, and coat the apical surface of the epithelial cells. Their distinctive molecular structure appears to render them resistant to proteolytic destruction. A number of studies have demonstrated that trefoil peptides play an important role in mucosal integrity, repair of lesions, and in limiting epithelial cell proliferation. They have been shown to protect the epithelium from a broad range of toxic chemicals and drugs. Trefoil proteins also appear to be a central player in the restitution phase of epithelial damage repair, where epithelial cells flatten and migrate from the wound edge to cover denuded areas. Mice with targeted deletions in trefoil genes showed exaggerated responses to mild

chemical injury and delayed mucosal healing.

Another molecule that plays a crucial role in mucosal integrity and barrier function is nitric oxide (NO). Paradoxically, NO also contributes to mucosal injury in a number of digestive diseases. This molecule is synthesized from arginine through the action of one of three isoforms of nitric oxide synthetase (NOS). Much of the research in this area has focused on understanding the effects of applying NO donors such as glyceryl trinitrate or NOS inhibitors. In several models, NO donors significantly reduced the severity of mucosal injury induced by toxic chemicals (e.g. ethanol) or associated with ischemia and reperfusion. Similarly, healing of gastric ulcers in rats has been accelerated by application of NO donors. Another intriguing observation is that co-administration of NO donors and NSAIDs results in anti-inflammatory properties comparable to NSAIDs alone, but with less damage to the gastrointestinal mucosa. NOS inhibitors are under investigation for treatment of situations in which NO is overproduced and contributes to mucosal injury.

An important part of barrier function is to prevent transit of bacteria from the lumen through the epithelium. Paneth cells are epithelial granulocytes located in small intestinal crypts of many mammals. They synthesize and secrete several antimicrobial peptides, chief among them isoforms of alpha-defensins known also as cryptins (crypt defensins). These peptides have antimicrobial activity against of number of potential pathogens, including several genera of bacteria, some yeasts and Giardia trophozoites. Their mechanism of action is likely similar to neutrophilic alpha-defensins, which permeate target cell membranes.

In addition to non-specific antimicrobial molecules, barrier function is supported by the gastrointestinal immune system. One facet of this defence system is that much of the epithelium is bathed in secretory immunoglobulin A. This class of antibody is secreted from sub-epithelial plasma cells and transported across the epithelium into the lumen. Luminal IgA provides an antigenic barrier by binding bacteria and other antigens. This barrier function is specific for particular antigens and requires previous exposure for development of the response.

Despite its robust and multi-faceted nature, the gastrointestinal barrier can be breached. Local infections by bacteria and virus, exposure to toxins or physical insults, and a variety of systemic diseases lead to its disruption. Such problems can be mild and readily repaired, or massive and fatal.

Damage To The Gastrointestinal Barrier

Damage to the gastrointestinal barrier due to ischemia and reperfusion injury (IRI) is a common and serious condition. Gut mucosal injury observed during IRI is believed to trigger systemic inflammatory response leading to multiple organ failure[63]. Furthermore, gut IRI markedly reduces gut associated lymphoid tissue cell numbers, with changes in lymphocyte phenotypes. These alterations may be associated with increased morbidity due to infectious complications after severe surgical insults[64]. Ischemia occurs when blood flow is insufficient to deliver an amount of oxygen and nutrients necessary for maintenance of cell integrity. Reperfusion injury occurs when blood flow is restored to ischaemic tissue.

Gastrointestinal ischemia results from two fundamental types of disorders, both of which can compromise the epithelial barrier:

Non-occlusive ischemia results from systemic conditions such as circulatory shock, sepsis or cardiac insufficiency.

Occlusive ischemia refers to conditions that directly disrupt gastrointestinal blood flow, such as strangulation, volvulus or thromboembolism.

Reperfusion injury to the gastrointestinal wall, especially the mucosa, is thought to be due primarily to generation of reactive oxygen species, including superoxide, hydrogen peroxide and hydroxyl radicals. These oxidants are generated within the mucosa and also in the numerous local leukocytes activated during the course of ischemia.

Oxygen-derived free radicals generated during reperfusion initiate a series of events that causes mucosal damage and disruption of the barrier. They directly damage cell membranes by forming lipid peroxides, which also leads to production of a number of inflammatory mediators derived from phospholipids (e.g. platelet-activating factor and leukotrienes). These pro-inflammatory agents function as chemo-attractants for neutrophils, which migrate into the mucosa, release their own reactive oxygen metabolites and cause further damage to the intrinsic epithelial barrier. An initially minor effect from ischemia is thus amplified into very significant damage to barrier function. Additionally, the inflammatory mediators generated in the gastrointestinal tract can harm distant tissues, leading to the systemic inflammatory response syndrome (SIRS). SIRS may be defined as a condition including two or more of the following abnormalities: a) fever or hypothermia; b) tachycardia; c) tachypnea; or d) leucocytosis or leucopoenia[65]. It occurs as result of non-specific activation of white cells and platelets as well as increases in complement and various

cytokines, associated with profound changes in micro-vascular permeability and mediated by a variety of humoral amplification systems[66]. The clinical importance of SIRS is its role in the development of multiple organ failure, a term introduced by Eisman et al (MOF)[67]. Less severe forms of SIRS add to postoperative morbidity, prolonged hospital stay and increased patient costs. Of the many theories on the origin of SIRS one that continues to perplex is the role of the splanchnic region or gastrointestinal tract (GIT). Expressions such as "The GI tract is the un-drained abscess of MOF," or "The gut is the motor of MOF"[68],[69] are clichés to cardiac surgeons. Hypo-perfusion of the splanchnic bed is thought to be the cause of these complications[70]. This allows the breech of the gastrointestinal barrier and subsequent clinical sequelae.

The observed effects of ischemia-reperfusion injury range from increased vascular permeability and consequent sub-epithelial oedema, to massive loss of epithelial cells and villi. Even relatively mild damage to the epithelium disrupts barrier function and can lead to translocation and permeation of bacteria and toxins respectively from the lumen to the systemic circulation.

Diverse insults to the intestinal mucosa, including infectious processes, ischemia and damaging chemicals, promote infiltration of neutrophils. This common endpoint results because many types of injuries lead to the local production of neutrophil chemo-attractants such as leukotrienes, interleukins and activated complement components. In response to chemo-attractants, neutrophils migrate out of capillaries, infiltrate the sub-epithelial mucosa and often transmigrate through the gastric or intestinal epithelium. In crossing the epithelium, neutrophils must break junctional complexes between epithelial cells. This 'impalement' through tight junctions causes transient increases in permeability[71]. When the insult is minor, the junctions reseal quickly, but transmigration of large numbers of neutrophils induces significant damage to barrier function.

Stress comes in a myriad of forms and is an integral part of all illness and trauma. The stress response involves modulation of numerous hormones and cytokines, as well as significant effects on neurotransmission. However, the foremost effect of stress on the gastrointestinal tract is to decrease mucosal blood flow and thereby compromise the integrity of the mucosal barrier. Glucocorticoids play a role in the control of vascular smooth muscle tone through the alteration of vasoconstrictor and vasodilator factor production[72]. Open heart surgery causes a rise in the level of stress hormones such as cortisol and that this is

solely due to CPB is a commonly held view[73]. Reduction of this hormonal response is beneficial in the recovery period[74] .

Reduced mucosal blood flow suppresses production of mucus and limits the ability to remove back diffusing protons. As a consequence, significant stress is almost always associated with mucosal erosions, particularly in the stomach. A majority of these lesions are subclinical, but gastrointestinal haemorrhage and sepsis are not infrequent consequences.

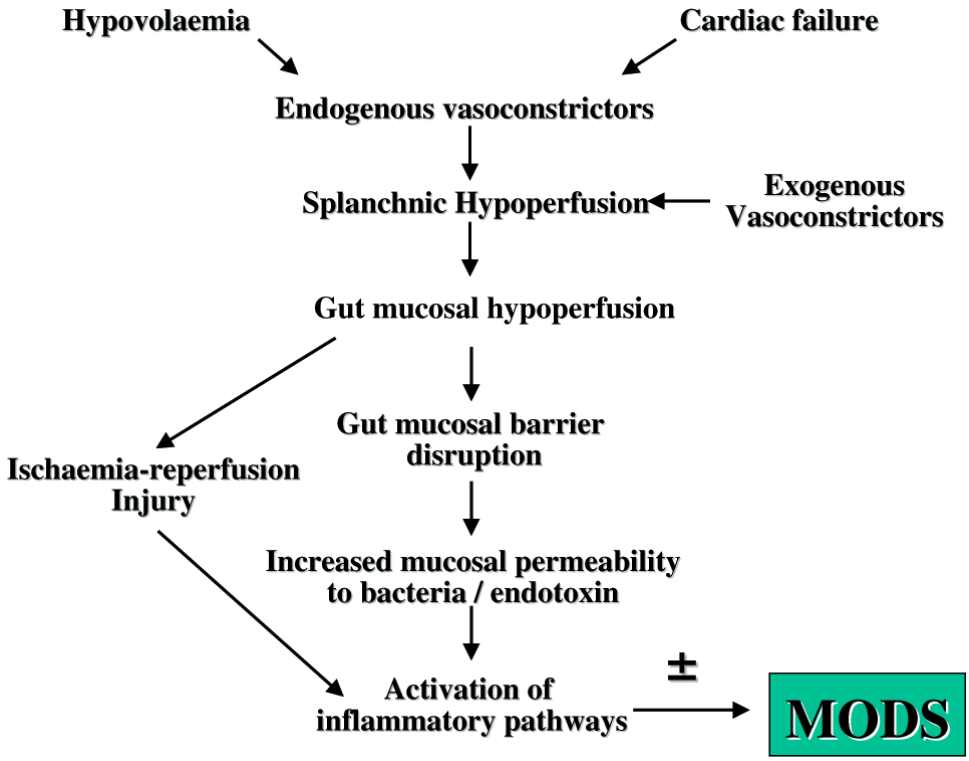
The critical first task following disruption of the gastrointestinal epithelium is to cover the denuded area and re-establish the intrinsic barrier. Following injury epithelial cells adjacent to the defect flatten and migrate over the exposed basement membrane. In the small intestine, this process is aided by a rapid contraction and shortening of the affected villi, which reduces the area of basement membrane that must be covered. Restitution provides a rapid mechanism for covering a defect in the barrier and does not involve proliferation of epithelial cells. It results in an area that, while protected, is not physiologically functional. Healing requires that the epithelial cells on the margins of the defect proliferate, differentiate and migrate into the damaged area to restore the normal cellular architecture and function. This repair is regulated by a number of paracrine regulators. Local prostaglandins and trefoil proteins[75] are clearly involved in this process, and suppression of their production significantly delays restitution. Another group of molecules involved in restitution is the polyamines such as spermine, spermidine and putrescine. These molecules are present in many diets and also synthesized by the gastrointestinal mucosa. Enteral administration of polyamines has been shown in experimental models to accelerate restitution and healing of mucosal lesions[76, 77].

Splanchnic Circulatory Control

The primary regulatory mechanism of blood flow in the splanchnic circulation is the sympathetic nervous system. Intense sympathetic adrenergic stimulation can cause a profound decrease in the blood supply to the spleen and gut. Because a large fraction of the blood volume is contained in the splanchnic bed, vasoconstriction can ‘mobilize’ blood and the splanchnic vasculature serves as a blood ‘reservoir’. Thus in hypovolaemic and low cardiac output states splanchnic vasoconstriction accounts for 25% of the increase in total systemic vascular resistance and results in auto-transfusion of about 15% of the blood volume. Mesenteric veins are more sensitive than arteries to the constrictor effects of

sympathetic nerve stimulation and alpha-adrenergic receptor agonists[78]. This splanchnic hypo-perfusion is a normal defence mechanism and is usually well tolerated[79]. Mesenteric vasoconstriction is mediated by alpha adrenergic postganglionic sympathetic fibres and by the effects of circulating hormones and peptides like catecholamines, vasopressin[80], angiotensin[81], myocardial depressant factor, leukotriene's, thromboxane A_2 and serotonin[82]. However when severe or prolonged, splanchnic perfusion is compromised resulting in splanchnic ischemia[83, 84] and abdominal organ injury. The counter current nature of the exchange system within the intestinal mucosa makes the innermost layers of the gut particularly sensitive to the effects of these vasoconstrictors as even modest decreases in perfusion shunt oxygen away from the mucosa[85]. Hypoxia renders the mucosa susceptible to the cytolytic effects of the acid, bile, proteolytic enzymes and or bacteria present in the lumen of the gut[86]. Mucosal disruption is further aided and abetted by oxygen derived free radicals released during reperfusion[87, 88].

Figure 2-6. The GUT Hypothesis For MODS[89]



Splanchnic Circulation

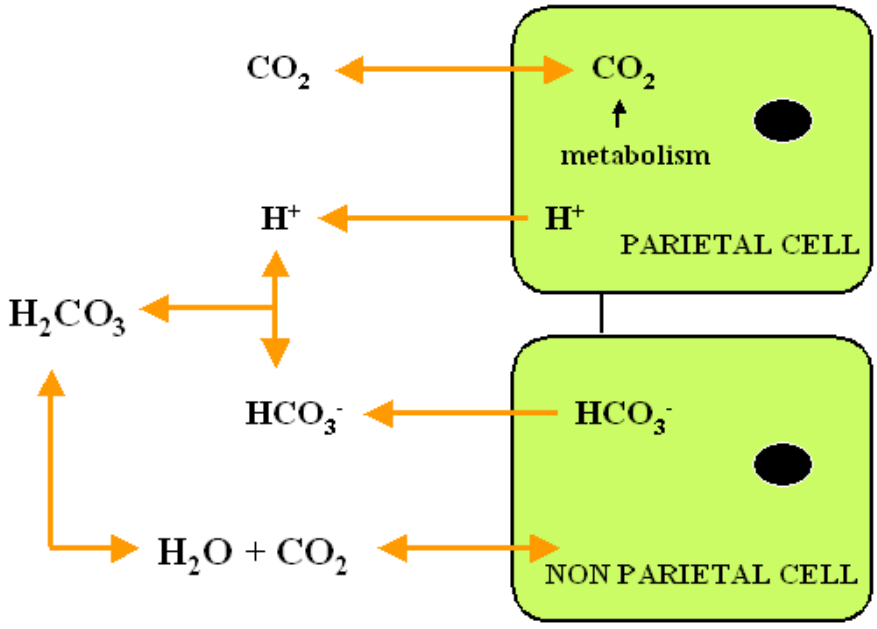
CPB induced splanchnic hypo-perfusion has long been seen as the sole culprit the SIRS. The gut has been variously referred to as "the un-drained abscess of multi-organ failure," or "as the motor of multi organ failure." Hypoxia renders the mucosa susceptible to the cytolytic effects of the acid, bile, proteolytic enzymes and or bacteria present in the lumen of the gut. Mucosal disruption is further aided and abetted by oxygen-derived free radicals released during reperfusion. Although up to 50% of patients undergoing cardiac surgery show objective evidence of mucosal ischemia the incidence of overt gastrointestinal complications after cardiac surgery is 1.2% with an average mortality of 33%. One model proposed to explain the involvement of the gut in this process is a two-step mechanism: First, gastrointestinal perfusion and therefore tissue oxygenation is compromised. Then, as a result of tissue damage, disruption of the mucosal barrier and access to the systemic circulation of toxic entities occurs[89].

Indirect Measurement Of Gastrointestinal Function: Gastric Tonometry

Gastric tonometry has long been proposed as a way to indirectly measure splanchnic perfusion and provides a relatively non-invasive and indirect way to detect splanchnic hypo-perfusion[90]. Tonometry refers to the measurement of the partial pressure of a gas. Gastric tonometry uses a modified nasogastric tube to measure the partial pressure of CO_2 (pCO_2) in the gastric lumen ($PgCO_2$). This allows indirect calculation of the pH of the gastric mucosa. Intracellular measurement of hydrogen ion concentration or pH ($pH= -\log [H^+]$) is the best way of assessing oxygenation status of the tissues. During tissue ischemia, protons are produced primarily by excessive hydrolysis of adenosine triphosphate (ATP) and adenosine 5'-diphosphate (ADP) and secondarily by hydrolysis of organic esters and lactic acid production [91, 92]. It has been shown in the human myocardium that measurements of intracellular pH correlate well with tissue levels of ATP. However, direct measurement of gut intra-mucosal pH (pHi) using tissue is not clinically feasible. The indirect tonometric method of measuring pHi is based on work originally performed by Bergofsky in 1964 [93] and later by Dawson et al in 1965 [94]. They showed that the pCO_2 in the lumen of a hollow viscus could be measured by determining the pCO_2 in the intraluminal fluid. Kivisaari and Niinikoski in 1973 [95] showed that pCO_2 and pO_2 could be indirectly measured by measuring the pCO_2 and pO_2 in saline contained within a balloon highly permeable to these gases (saline

tonometry). Fiddian-Green et al [96] suggested that pHi could be calculated by tonometry if it was assumed that the tissue bicarbonate and arterial blood bicarbonate were similar, permitting the substitution of this value into the Henderson-Hasselbach equation. Fiddian-Green et al studied nine animals using a gastric tonometer (hollow viscus tonometry) and a glass tissue microprobe. They observed a correlation of r=0.79 between tonometer measured and microprobe measured pHi. This method also assumes that the pCO_2 in the lumen of the bowel equilibrates with the bowel wall and in part on the knowledge that the pCO_2 within the cellular cytosol is linearly related to the pCO_2 in the extracellular environment [97].

Figure 2-7. Factors Determining Intraluminal Carbon Dioxide



The intraluminal pCO2 is determined both by the diffusion of CO_2 from the mucosal cells as a result of metabolism and secondly as a result of the production of CO_2 from the secretion of acid and bicarbonate (figure 6-1). The equilibration of intraluminal CO_2 with intracellular and blood CO_2 does not occur instantly. This is mainly due to the fact that back diffusion of CO_2 from the gastric lumen into the cells occurs relatively slowly, so that gastric intraluminal CO_2 may be higher than intracellular and blood CO_2. In the canine stomach it has been shown that the half-life for the equilibration of CO_2 is 18 to 22 minutes. Recently saline tonometry has been largely replaced by automated air tonometry [98]. This is done using nasogastric catheters that are very similar to saline tonometry catheters, in that they

incorporate a gastric vent, a gastric sump and a silicone balloon at the end of the catheter. However, rather than injecting saline into the silicone balloon (saline tonometry), the balloon is instead inflated with a small volume of air and the sampling line is connected to a special monitoring device (Tonocap, Datex-Ohmeda, Instrumentarium Corp., Helsinki, Finland), (figure 6-3). The device inflates the balloon with a small volume of air, allows for equilibration with the gastric lumen, then automatically withdraws a sample from the balloon and calculates the pCO_2 using infrared measurement. The sample is then replaced into the balloon to decrease the equilibration time for the next measurement. Measurements are automatically done and the pCO_2 displayed at 10-minute intervals in a semi-continuous way. The data generated was directly downloaded into a computer. Automated air tonometry thus makes pCO_2 measurements more readily available in clinical practice; it has also been shown to be more precise than saline tonometry in *vitro* testing [99, 100]. Studies of *in vitro* testing have also shown that many of the systematic errors involved in saline tonometry and concerns about equilibration times have been eliminated. Consequently automated air tonometry is currently considered to be the most reliable method of measuring gastric pCO_2 levels in the clinical settings.

Over the last decade there has been an increasing trend towards reporting tonometric findings as the difference in partial pressure of CO_2 between the gastric lumen and the arterial blood (CO_2gap = $PgCO_2$ – $PaCO_2$). Currently most of the experts on gastrointestinal tonometry agree that the CO_2gap is the gold standard measurement, while the pHi concept should gradually be abandoned[101), (102-104)]. The main reason is that the pHi calculation (pHi = 6.1 + Log 10 (arterial HCO_3/PgCO2)*K = time dependant equilibration constant) is not solely dependent on gastrointestinal perfusion and oxygenation but is also affected by systemic acid base status, as the arterial bicarbonate value is entered into the Henderson-Hasselbach equation. The pHi is thought to combine global and gut specific markers. This may explain why the pHi has been found to be an extremely sensitive early predictor of patient outcome in various clinical settings, including cardiac surgery. However, when looking specifically at the effect of various interventions on gut mucosal oxygenation is thought that the CO_2 gap should be monitored instead. Moreover, the assumption that the intra-mucosal and arterial bicarbonate concentrations are equal may not always be valid. Antonsson et al [105] studied the correlation between tonometer measured and directly measured pHi and noted that in the presence of regional mesenteric ischemia the tonometer

measured pHi did not correlate well with direct measurements. The normal limit for the CO_2 gap is 9.5 mmHg or 1.27 KPa[106]. Pestel et al[107] in a study of multiple injured patients noted that those with a CO_2 gap > 10 mmHg or 1.33 KPa had a higher injury severity score, were ventilated longer, had a longer intensive care stay and a higher incidence of complications in comparison to patients with a CO_2 gap < 10 mmHg or <1.33KPa. To our knowledge no study to date has performed such detailed monitoring of $PgCO_2$. Normal values for $PgCO_2$ should be <50 mmHg or 6.5 KPa. Values between 51 to 60 mmHg or 6.5 to 8.0 KPa require careful observation to see if the trend is improving or deteriorating. Values >60 mmHg or 8.0 KPa require urgent therapy[108].

Figure 2-8. The Air Tonometer Catheter

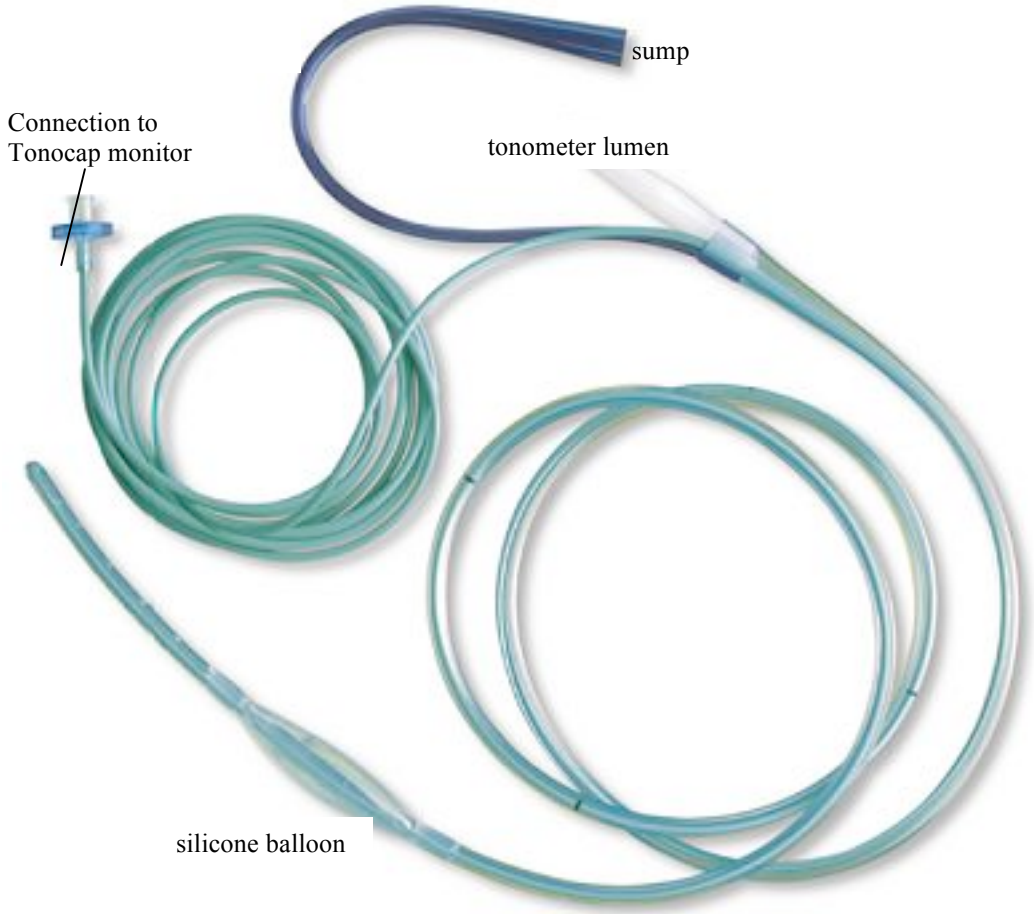


Figure 2-9. The Tonocap Monitor

Biomarkers Of Gastrointestinal Injury

Host immune defence mechanisms to infectious agents are classified as either innate or adaptive. Innate responses are antigen independent whereas adaptive responses are antigen specific. Innate mechanisms may provide a trigger for the initiation of systemic inflammatory response syndrome (SIRS)[109]. The innate immune system is a phylogenetically ancient component responsible for immediate non-antigenic responses. Key components include mannan-binding lectin (MBL), defensins and bactericidal/permeability increasing protein (BPI).

Bactericidal Permeability Increasing Protein

Bactericidal permeability increasing protein (BPI) is a 456 residue (~50kDa) protein, which is part of the innate immune system. BPI was discovered by Jerrold Weiss and Peter Elsbach at New York University Medical School. BPI was initially identified in neutrophils, but is found in other tissues including the epithelial lining of mucus membranes. It is an endogenous antibiotic protein with potent killing activity against some bacteria (gram-negative bacteria). It binds to compounds called lipopolysaccharides produced by gram-negative bacteria. Lipo-polysaccharides are potent activators of the immune system, however BPI at certain concentrations can prevent this activation[110].

Mannan-Binding Lectin

The MBL pathway of complement activation has been established as the third pathway of complement activation. MBL is a carbohydrate-binding serum protein, which circulates in complex with serine proteases known as mannan-binding lectin associated serine proteases (MASPs). Mannose Binding Lectin (MBL), also called mannose- or mannan-binding protein (MBP), is a member of the collectins and an important element in innate immunity. MBL is an oligomeric lectin that recognizes carbohydrates as mannose and N-acetyl-glucosamine on pathogens. MBL contains a cysteine rich, a collagen-like and a carbohydrate recognition domain. It forms a complex with C1r/C1s like serine proteases, designated MASP, that proteo-lytically cleaves C4, C2 and C3. MBL is able to activate the complement pathway independent of the classical and alternative complement activation pathways. The MBL-MASP pathway (better known as the lectin pathway) is antibody and C1q-independent. MBL exhibits complement-dependent anti-bacterial activity and acts directly as an opsonic. Therefore, it plays an important role in innate immunity. MBL is synthesized by hepatocytes and has been isolated from the liver or serum of several vertebrate species. In this assay, any influence of the classical pathway of complement activation has been eliminated by using a special MBL-binding buffer, which inhibits the binding of C1q to immuno-complexes and disrupt the C1 complex, while leaving the function of the MBL complex intact. Normal human plasma contains a MBL concentration range from 10 - 5,000 ng/mL, while up to 12% of healthy Caucasian blood donors can be below 100 ng/mL. Low plasma concentrations have been associated with an inherited defect in opsonisation. The MBL concentration is enhanced in infectious diseases. Measurement of MBL is indicated in recurrent infections (especially in children), primary/secondary immunodeficiency's, atherosclerosis/coronary heart disease, cystic fibrosis, autoimmune diseases (SLE/Rheumatoid arthritis) and habitual abortion. The measurement of MBL is not affected by the presence of antibodies against mannan. When bound to microorganisms, the MBL complex activates the complement components C4 and C2, thereby generating the C3 convertase and leading to opsonisation by the deposition of C4b and C3b fragments. This C4/C2 cleaving activity is shared with the C1 complex of the classical pathway of complement activation[(111)]. The HBT human MBL (Lectin assay) ELISA kit was used for the quantitative measurement of natural human MBL in serum. The kit has a minimum detection

level of 0.41 ng/mL and a measurable concentration range of 0.41 to 100 ng/mL.

Defensins

First identified in 1985 by Ganz et al, defensins are a family of microbicidal and cytotoxic peptides thought to be involved in host defence. They consist of three small (molecular weight less than 3,500Kda) antibiotic peptides that were named human neutrophil peptide (HNP)-1, HNP-2, and HNP-3[112]. They are abundant in the granules of neutrophils and also found in the epithelium of mucosal surfaces such as those of the intestine, respiratory tract, urinary tract, and vagina. They are small 29-35 amino acid residues with a molecular mass of less than 3500 KDa[113] In normal plasma low levels of HNP are present ranging from undetectable levels to 50-100 ng/mL, whilst in septicaemia the levels of HNP may become elevated to 900 ng/ml to 170,000 ng/mL[114]. HNP have a broad spectrum of properties including antibacterial activity, mediating lung inflammation, promoting cytokine production, leukocyte recruitment, inducing mast cell degranulation, decreasing antioxidant levels, altering the permeability and potential of the cell membrane[115]. HNP levels have been shown to be raised in patients with sepsis16 and in the post CPB period[116]. HNPs are one of the effector mechanisms of the innate immune pathway[117] which has been shown to be activated by CPB[118]. CPB also causes the release of antimicrobial peptides as shown in a small study by Tasiemski et al[119], which may be a defence response to the bacteraemia of CPB[120]. Human neutrophil defensins (α-defensins) belong to the family of cationic trisulphide microbicidal peptides. Besides microbicidal, the peptides exert chemotactic, immunomodulating and cytotoxic activity and participate in host defence and inflammation. Azurophilic granules of neutrophils contain Human Neutrophil Peptide (HNP)-1-4, which are highly homologous. The three principal human defensins, HNP 1-3, are unique to neutrophils and account for about 99 of the total defensin content of these cells. Measured amount of defensins is 3-5 ug per million human neutrophils. Activation of neutrophils leads to rapid release of defensins. Thus, only one cell type, neutrophils, may be the source of HNP 1-3 measured in plasma and other body fluids during infection and inflammation.

Intestinal Fatty Acid-Binding Protein

Fatty acid-binding proteins (FABP) are a group of relatively small (15 KDa) cytoplasmic proteins that are abundantly expressed in tissues with active fatty acid metabolism. Presently, nine distinct types have been identified, with each type showing a characteristic pattern of tissue distribution and a stable intracellular half-life of 2–3 days[33]. These FABP types are named after the tissue in which they were first identified and belong to a multi-gene family of intracellular lipid-binding proteins. Intestinal fatty acid binding protein (I-FABP) is specifically localised to the epithelial cells of the small bowel. Normally levels of FABP are generally low to undetectable in serum of healthy individuals[121]. However following cellular damage FABP readily leaks due to its small size and becomes detectable in blood and urine. Ischemia damaged cells are characterized histologically by the absence or low presence of FABP[38].

Endotoxin

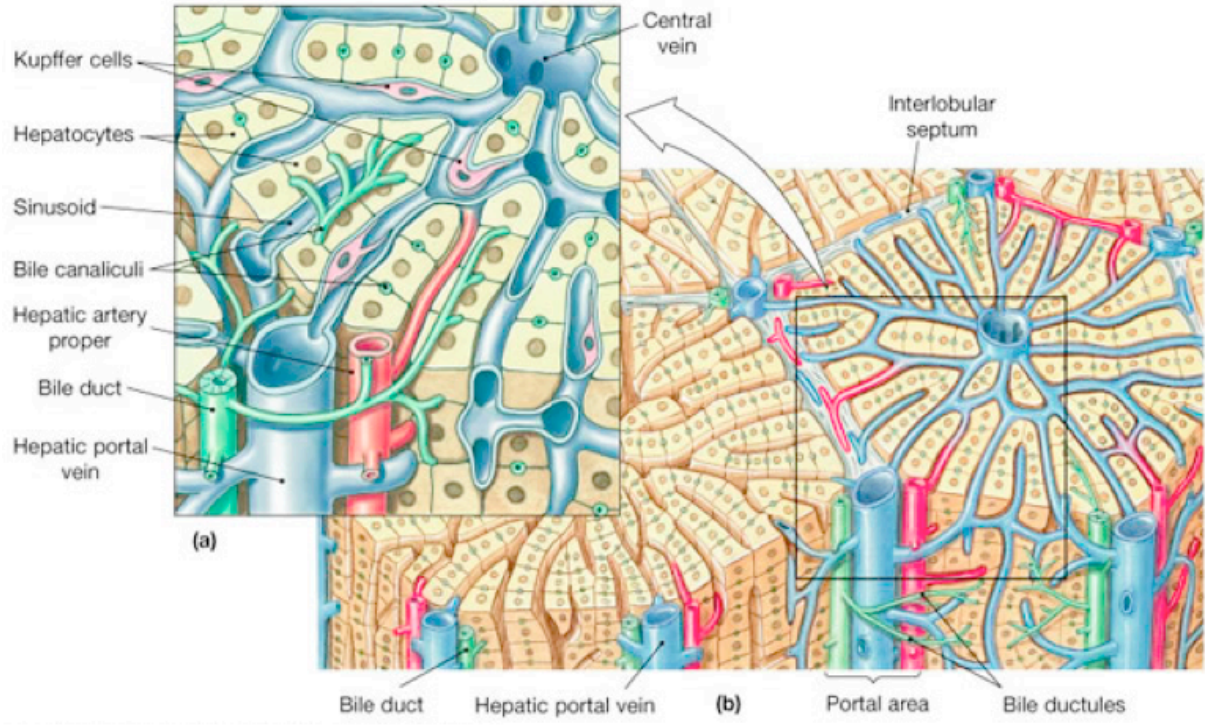
Endotoxin has long been suspected to be a key factor in the generation of the SIRS[122] and has been previously measured in OPCAB[123]. In this study we sought to determine levels of endogenous endotoxin-core antibody (EndoCAB) as a marker of endotoxin exposure. This test was developed by Barclay et al at the Scottish national blood service in Edinburgh[124]. There is marked preoperative variability in humoral immunity against endotoxin core, which is not accounted for by differences in known preoperative risk factors. In this latter study, low levels of IgM EndoCAb were an important independent predictor of adverse postoperative outcome, which supports the theory that endotoxaemia, is a cause of postoperative morbidity[125]. Adverse outcome after routine non-cardiac surgery is common and is predicted in part by low concentrations of EndoCAb. The authors' findings suggest that endotoxaemia may be a cause of postoperative morbidity after routine non-cardiac surgery[126]. Both IgM and IgG EndoCAB have equivalent potency[127].

Liver injury

Hepatic Structure and Function

The liver is the second largest organ in the body and weighs about 1-1.5 kg. The liver derives 70 – 80% of its blood supply from the portal vein and the remainder from the hepatic artery. Waldhausen et al[9] showed in an animal model that hepatic oxygen consumption is preserved at pump flow rates down to 2.2 L/m^2 which corresponds to a hepatic blood flow of about 110ml per 100g of liver per minute. Yamada et al[128] have shown that portal venous blood flow is maintained during non-pulsatile CPB at a flow rate of 2.4 L/min/m^2 and dependent upon systemic blood flow. A thin connective tissue capsule known as Glisson's capsule covers the liver. The basic structural component of the liver is the hepatocyte. These epithelial cells are grouped in interconnected plates and constitute two-thirds of the mass of the liver. Hepatocytes are further organized into structural units called liver lobules. These polygonal masses of tissue about 0.7- 2.0 mm in size has a portal space at the periphery and a central vein in the centre. Between the lobules are branches of the hepatic artery, hepatic portal vein and bile duct. The hepatic vein is connected to the hepatic artery and hepatic portal vein by sinusoids. These are blood spaces rather than blood vessels but serve the same function. They radiate like the spokes of a wheel from the centre to the edges of the lobule. Blood flows slowly from the hepatic artery and hepatic portal vein to the hepatic vein past the hepatocytes, which also form rows across the lobule. As blood flows along the sinusoids, exchange of materials takes place between the blood and the hepatocytes, across the microvilli of the hepatocytes lining the sinusoids. The sinusoids have a lining of thin endothelial cells containing pores with a diameter of up to 10 nm. A sub-endothelial space known as the space of Disse separates the endothelial cells from the hepatocytes. The sinusoids alternate with bile canaliculi carrying bile made by the hepatocytes to the branches of the bile duct. The bile flows in the opposite direction to the blood and does not mix with the blood. The function of the liver include the following: (a) the production of glucose and clearance of lactate in the Cori cycle; (b) synthesis of plasma proteins such as albumin, coagulation factors and plasma cholinesterase; (c) maintenance of immune function via Kupffer cell, which mediate the clearance of intravascular debris and micro organisms; and (d) metabolism of many drugs, including cytochrome P450 oxidation[9].

Figure 2-10. Hepatic Structural Arrangement[129]



Liver Dysfunction

The incidence of acute ischaemic liver injury after isolated CABG is low. Yilmaz et al described 1 case out of 3158 patients who developed liver failure[130]. In 2002 Raman et al reported the incidence of severe ischaemic early liver injury after CABG to be 13 patients in a series of 1800 patients (0.7%)[131]. However the incidence of hyper-bilirubinaemia in patients undergoing CABG with CPB henceforth referred to as ONCAB has been reported to be of the order 8% with an associated 25% mortality [132] in historical controls. Hyper-lactatemia after cardiac surgery has also been reported[133]. Aspects of CPB considered deleterious to liver function include duration of CPB[134], non-pulsatile CPB[135, 136] and hypothermia[137]. There are also increasing numbers of case reports of successful CABG without CPB (OPCAB) in patients with liver cirrhosis[138]. The advent of OPCAB allows the study of the relative magnitude of the physiologic insult caused by CPB.

Biomarkers Of Liver Injury

Conventional liver function tests (LFT) are performed by measuring plasma concentrations of conjugated and total bilirubin (CB and TB), alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT). These tests are easy to perform; they are readily available with a vast experience in their clinical use. However, conventional LFT do not quantitate liver function but assess qualitatively the presence of hepatic injury. Moreover, their sensitivity and specificity for hepatic injury is relatively low. Recently, more sensitive and specific tests that aim to monitor liver function more accurately in a quantitative fashion have become available. The HBT human liver FABP kit has been developed for the quantitative measurement of human liver FABP in cell culture medium, serum, plasma and urine of both natural and recombinant origin. Liver FABP is a sensitive marker for cell damage of liver cells in vitro and vivo. Fatty acid-binding proteins (FABPs) are a class of cytoplasmic proteins that bind long chain fatty acids. They are abundantly present in various cell types and seem to play an important role in the intracellular utilization of fatty acids. There are at least six distinct types of FABP, each showing a specific pattern of tissue expression. FABP leaks due to its small size rapidly out of ischemically damaged dying cells leading to a rise in serum levels. Ischemically damaged tissues are characterized histologically by absence (or low presence) of FABP facilitating recognition of such areas. Serum/plasma and urine of healthy individuals contains approximately 12 ng/mL and 16 ng/mL respectively.

Another marker is alpha glutathione-s-transferase (α-GST), which has a molecular mass of 26KDa. α-GST is distributed equally in both the centri-lobular and peri-portal regions[139]. Plasma α-GST has been shown to be a more sensitive and specific marker of hepatocellular damage than aminotransferase activity and correlate better with hepatic histology[140].

Renal Injury

Renal Anatomy

The kidneys are paired retroperitoneal organs; each weighing about 150 grams and are located between T12 and L3[(141)]. There are two major portions. The outer cortex just under the fibrous capsule receives 90% of renal blood flow and is the most highly perfused tissue per gram of any organ. All glomeruli are located in the cortex (about 1 million per kidney). The inner medulla extends all the way to the renal pelvis and receives only 10% of renal blood flow, so perfusion is similar to other tissues. The urine formed leaves the ends of the collecting ducts at tips of the renal papillae and enters the minor calices. Minor calices join to form about three major calices, which come together to form the renal pelvis. This continues as the ureter to enter the urinary trigone of the bladder. An obstruction at any point causes an increase of tubular pressure with resultant loss of GFR due to disturbed Starling forces. Each kidney is perfused by a single main renal artery, which branches at the hilum into 3 to 4 segmental branches. These segmental branches give off inter-lobar arteries which course between lobes up to the cortico-medullary junction. At the cortico-medullary junction, the inter-lobar vessels give off perpendicular branches called arcuate arteries, which run along cortico-medullary junction and are perpendicular to the inter-lobar artery. Arcuate arteries are end arteries; if one is occluded, the part of the kidney it perfuses will undergo infarction. Ascending perpendicular branches of the arcuate arteries are called interlobular arteries. Afferent arterioles branch off the interlobular arteries. Afferent arterioles branch into glomerular capillaries. Glomerular capillaries re-form into efferent arterioles—a unique situation where capillaries have arterioles on either side (pre- and post-capillary).

Figure 2-11. Renal Anatomy[141]

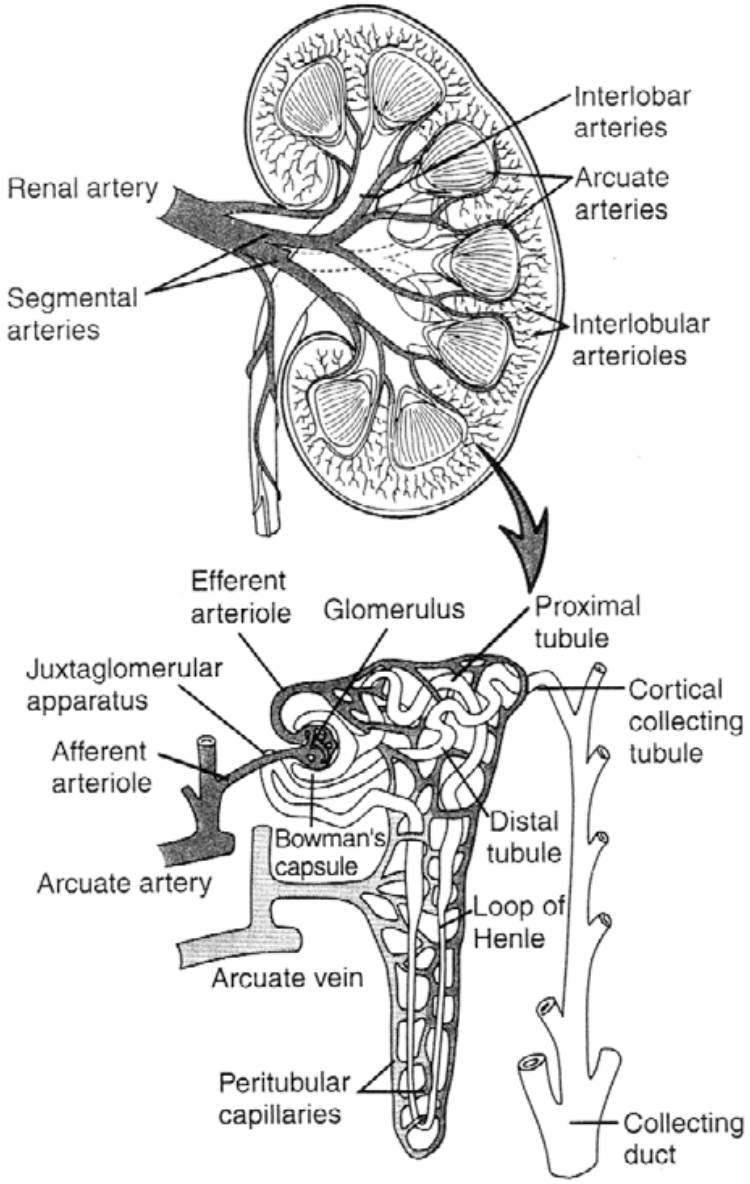
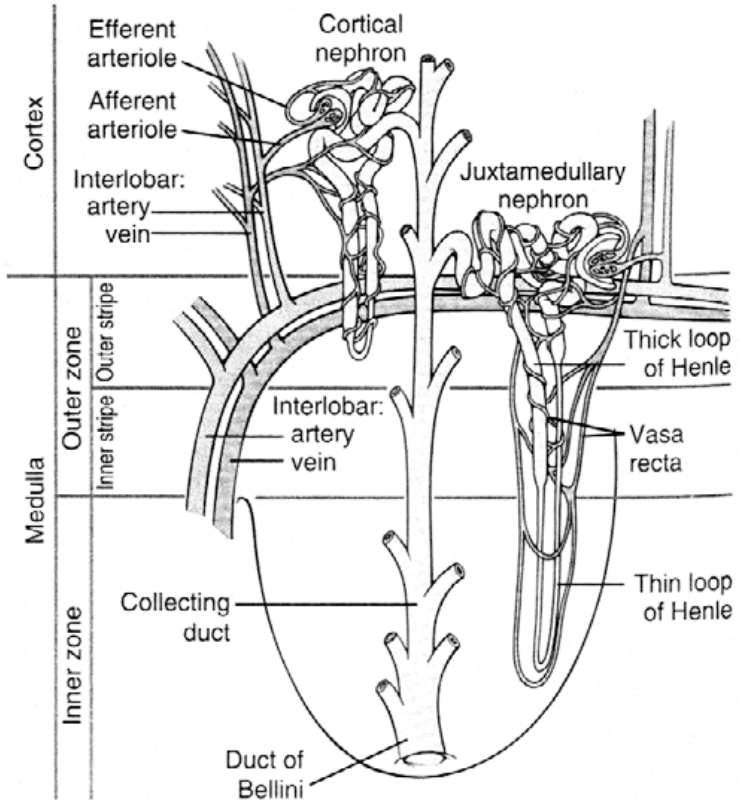


Figure 2-12. Renal Ultrastructure[141]



There are two types of nephrons in the kidney cortical and medullary. Cortical nephrons account for 85% of all nephrons. The afferent arteriole comes off the interlobular vessel closer to the capsule (farther from main artery) and therefore perfusion pressure is less and filtration rate is less. The afferent arteriole becomes the glomerulus; the glomerulus then reforms an efferent arteriole. The efferent arteriole then breaks down into the peri-tubular capillary network. Peri-tubular capillaries reabsorb 98-99% of glomerular filtrate they have a shorter loop of Henle (does not descend deep into inner medulla) and shorter thick ascending limb, and therefore are not nearly as important in concentrating the urine or reabsorbing sodium or avidly conserving sodium. These never operate at full capacity, but always have some reserve left so that they can further increase GFR when needed (such as after a high protein meal)

Juxta-medullary (long-looped) nephrons—lie close to cortico-medullary junction. They constitute 15% of all nephrons. The afferent arteriole comes off the interlobular vessel close to the cortico-medullary junction and therefore perfusion pressure is higher and filtration rate is higher. The afferent arteriole forms the glomerulus, which then converges to

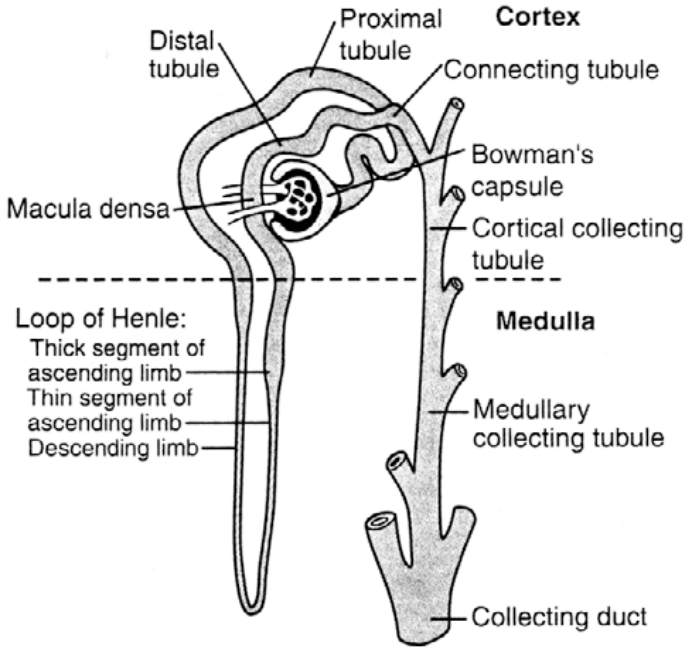
form efferent arteriole. The efferent arteriole becomes the descending vasa recta. The vasa recti are the sole blood supply to the medulla. The vasa recti function as a counter current exchange system: solute material can move from descending to ascending vasa recta and vice versa: there is also counter current exchange of oxygen; such that the oxygen tension decreases with increasing depth into the medulla. Therefore, the medulla is at increased risk for hypoxic injury when there is prolonged shock or hypoxemia. Because these nephrons have a long loop of Henle (descends deep into medulla) and a long thick ascending limb (major site of salt transport), they play a very important role in conserving sodium and concentrating urine.

Renal Function

Production of Glomerular Filtrate

The glomerulus is a ball of capillaries invaginated into the beginning of the proximal tubule. This ball of glomerular capillaries is surrounded by a fibrous capsule called Bowman's capsule that is lined by epithelial cells called parietal epithelial cells.

Figure 2-13. Production of GFR[(141)]



Glomerular filtrate is made from capillary loops into Bowman's space; the most important factor in filtration is the glomerular capillary pressure. This space is contiguous with the tubule system, where materials are selectively absorbed and secreted. The mesangium is the

skeletal support system that holds all of the capillary loops in place. It is composed of resident mesangial cells, which produce a matrix composed primarily of proteoglycans and type IV collagen. The mesangial cells contain actin and myosin, so they contract to control the number of capillary loops that are open and thus the surface area available for filtration. A part of each capillary loop is adjacent to the mesangium. This part of the loop is not covered by basement membrane. Therefore, the mesangium is exposed to inflammatory mediators or immune complexes in the plasma. Mesangial cells function as phagocytic cells, and thus frequently ingest immune complexes. This can promote the inflammatory cascade, so that mesangial inflammation is often a component of glomerulonephritis. The filtrate has to pass through the glomerular capillary wall to enter the urinary space. Glomerular capillaries are perfused by a higher pressure than systemic capillaries. Endothelial cells line the glomerular capillary wall. Glomerular capillary endothelial cells have larger fenestrations than other fenestrated capillaries. The Endothelial cells are surrounded by a basement membrane, which prevents the passage of protein and cells. Unique to the glomerular capillaries is a third layer composed of visceral epithelial cells, or podocytes, that produce foot processes that attach at the external part of the glomerular basement membrane. Between the foot processes are small slit diaphragms. The three-layered capillary wall very efficiently prevents the loss of cells and large molecules like protein into urine, but allows small molecular weight molecules like water and electrolytes to pass through. All three layers are also rich in negative charges from sialic acid residues and heparan sulphate. In addition to acting as a simple size barrier that prevents the passage of larger molecules, the capillary wall is also a charge barrier. Positively charged substances move most readily across the capillary wall; neutral substances move less readily than positive substances and negatively charged substances move least readily. The major plasma protein is albumin—a polyvalent anion. The negative charge barrier is an important mechanism to maintain plasma albumin concentration. There are three places in the glomerulus that immune complexes can deposit, which are the sub-epithelial, the sub-endothelial (?) and within the mesangium.

The juxtaglomerular apparatus (JGA) is a microscopic structure in the kidney, which regulates the function of each nephron. The juxtaglomerular apparatus is named for its proximity to the glomerulus: it is found between the vascular pole of the renal corpuscle and the returning distal convoluted tubule of the same nephron. This location is critical to its function in regulating renal blood flow and glomerular filtration rate. The three microscopic

components of the apparatus are the macula densa, the extra-glomerular mesangial cells, and the juxtaglomerular cells.

The macula densa is at the end of the cortical thick ascending limb. It is adjacent to the afferent and efferent arterioles of the same nephron. Everything before the macula densa is considered the proximal nephron; everything after the macula densa is considered the distal nephron. The macula densa cells function as sensors to determine how much filtrate is being delivered from the glomerulus.

The proximal tubule is where 90% of the filtrate is reabsorbed. The distal tubule is only responsible for reabsorption of about 10% of filtrate; the distal tubule is more for fine-tuning. The macula densa is important for regulating the amount of filtrate reaching the distal tubule so that it is not overwhelmed with more than it can reabsorb. If the macula densa senses too much filtrate being delivered to the distal nephron, it feeds back to the afferent arteriole via autocrine mechanisms to cause vasoconstriction, which will reduce capillary pressure and filtration rate. This mechanism is called tubulo-glomerular feedback. Through tubulo-glomerular feedback, each nephron can influence the rate of filtration at its glomerulus

The afferent arteriole functions as a baroreceptor. It responds to stretch and pressure by myogenic mechanism. If pressure is increased, the afferent arteriole vasoconstricts to prevent injury to the kidney and keep GFR constant. If pressure is decreased, afferent arteriole will vasodilate to keep GFR constant. It also functions as an endocrine structure and produces renin. Renin is released in response to reduced pressure or adrenergic stimulation. Renin release is inhibited in response to increased pressure

Fluid movement across the glomerular capillary is a passive process governed by Starling's law, which states that movement is determined by capillary surface area and permeability and hydrostatic and oncotic pressure gradients. $GFR=LpS(\Delta P - \Delta \Pi)$

1. Lp = capillary wall permeability
2. S = surface area available for filtration
3. ΔP = hydrostatic pressure gradient between capillary and Bowman's space
4. $\Delta \Pi$= oncotic pressure gradient between capillary and Bowman's space

Hydrostatic pressure is high in the capillary and low in Bowman's space because of continuous reabsorption in the proximal tubule; this drives filtration into Bowman's space. There is virtually no oncotic pressure in Bowman's space due to the lack of protein, while oncotic pressure is high in the capillary. This would tend to favour fluid movement into the

capillary. Filtration rate is determined by the pressure gradients between the two spaces. In the proximal part of the capillary, the hydrostatic pressure gradient favouring filtration is much greater than the oncotic pressure gradient opposing filtration, resulting in the huge amount of filtrate. In the distal capillary, where much of the fluid has crossed into Bowman's space and all of the protein remains, the oncotic pressure gradient becomes equal to the hydrostatic pressure gradient. At this point, net filtration stops. The kidneys can auto-regulate GFR via afferent and efferent arterioles. The glomerular capillaries have resistance vessels on either side—an afferent arteriole carrying blood to the capillary and an efferent arteriole carrying blood away. Changes in resistance of either vessel can cause changes in capillary pressure and thus in GFR. Vasodilation of the afferent arteriole results in increased renal blood flow and increases GFR. Vasoconstriction of the afferent arteriole decreases renal blood flow and decreases GFR. Vasodilation of the efferent arteriole will raise renal blood flow, but decrease capillary pressure and thus GFR. Vasoconstriction of the efferent arteriole reduces renal blood flow, but increases capillary pressure and GFR. The above mechanisms operate together to maintain GFR. In response to a dramatic drop in cardiac output, kidney would vasodilate afferent arteriole and vasoconstrict efferent arteriole to maintain GFR. Through auto-regulation, renal blood flow and GFR can be kept constant over a very wide range of arterial pressures. Urine flow rate is not auto regulated and therefore, urine flow is not a good index of GFR or overall kidney function (more urine does not necessarily equate with better kidney function). Increased arterial pressure results in increased urine flow rate; this is known as pressure natriuresis (as pressure increases, sodium excretion increases, which obligates water excretion). Thus it can be seen that the kidney produces an enormous amount of ultra-filtrate across the glomerulus approximately 180 L/day (60x total plasma volume). This enormous amount of filtrate is produced passively at the glomerulus due to Starling forces, and therefore requires an enormous amount of blood flow to the kidneys. The kidneys receive about 20% of total cardiac output (10% to each kidney). 98-99% of this filtrate must be reabsorbed. The kidney uses processes of selective reabsorption and secretion at tubular level to determine final contents of the urine and maintain homeostasis

Filtration is the first step, resulting in a protein-free ultra-filtrate of plasma coming from the glomerular capillaries into Bowman's space; a passive process driven by Starling forces. Subsequently, once in the tubule it is either reabsorbed or excreted. Constituents that are reabsorbed are required to maintain homeostasis such as salt and water. These are

reabsorbed from tubular fluid, renal epithelial cells, interstitium and peri-tubular capillaries. Substances that are secreted not only can enter the tubular fluid by glomerular filtration, but also by active secretion from the peri-tubular capillaries directly into the renal tubules to enhance elimination from the body (e.g. potassium and drugs). The glomerulus and the tubule must operate jointly; if one becomes dysfunctional, the other will become equally affected. Glomerular filtration rate (GFR) is the best overall index of kidney function and renal mass. Normal GFR is 120 mL/min. All renal functions, including endocrine, are related to the GFR.

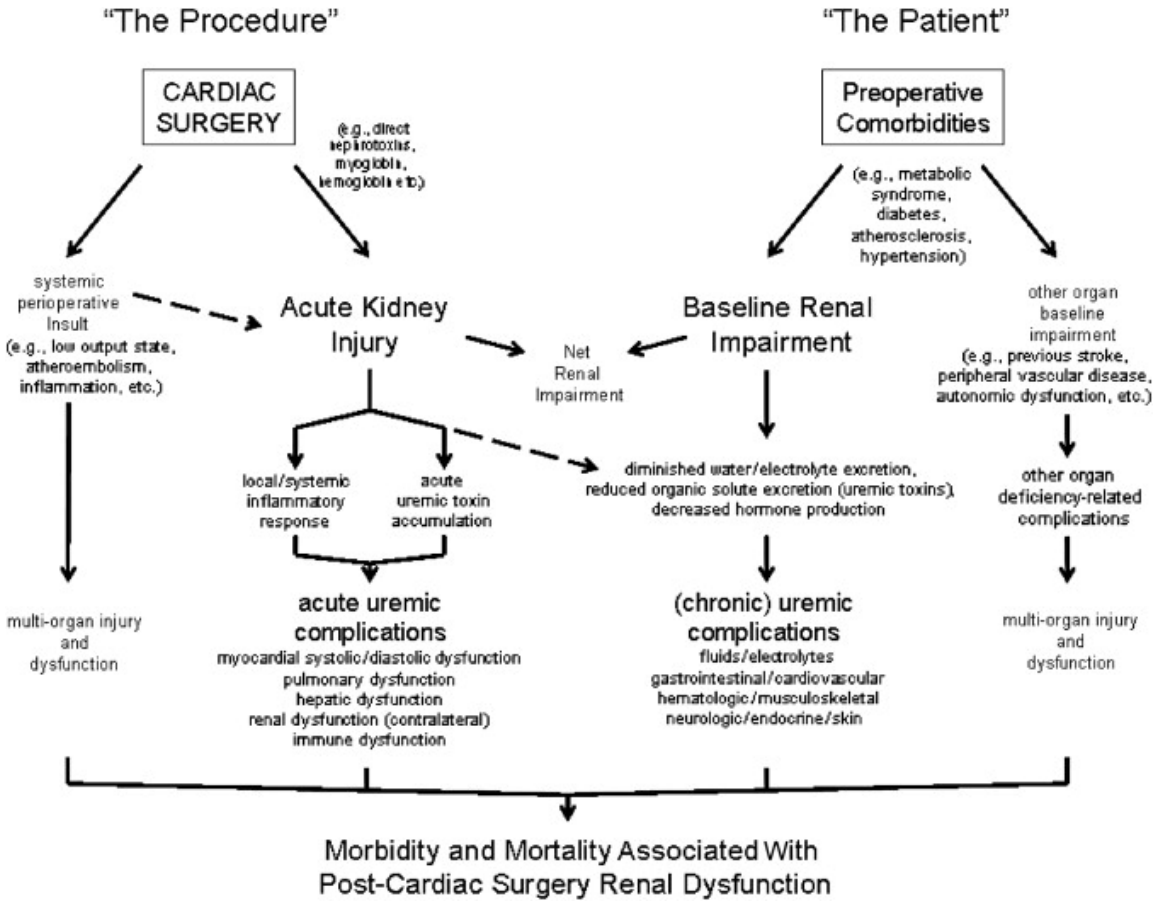
The kidney is thus the main organ of homeostasis for a large number of solutes and water. The kidney also produces erythropoietin, 1-alpha-hydroxylase and renin. There are also a number of paracrine substances in the kidney that regulate homeostasis within the kidney. These include bradykinin, prostaglandins (PGE_2 and PGI_2, which are natriuretic and vasodilatory). The endothelial cells produce nitric oxide, which causes vasodilation and natriuresis and endothelin. Endothelin is usually only produced in response to injury and is one of the most potent vasoconstrictors known.

Renal Dysfunction

Acute renal failure (ARF) may be defined as a 50% or greater rise in serum creatinine from baseline. The incidence of ARF after CABG is approximately 2.5%. Mortality associated with the development of ARF is as high as 60% in some studies but averages at 15 to 30%, depending on the definition of ARF and the postoperative period studied (hospital discharge or 30-day mortality)[142]. In patients who require dialysis, the mortality is uniformly high in all studies and averages 60 to 70%. It is interesting that even small rises in serum creatinine are associated with significant mortality. Lassnigg *et al*[143] demonstrated that the 30-day mortality of patients who developed a 0 to 44μmol/L and > 44μmol/L rise in serum creatinine were 2.77- and 18.64-fold higher, respectively, than patients without a change in serum creatinine. The development of post-CPB ARF also influences long-term mortality as identified by Loef *et al*[144] who found that the hazard ratio for death at 100 months after hospital discharge was 1.63 in patients who developed a 25% or greater rise in serum creatinine after surgery. This increase in long-term mortality was independent of whether renal function had recovered at discharge from the hospital. Lok *et al* also found that patients who experienced ARF after CPB had a relative risk for death at 1 year of 4.6 as compared with patients who did not sustain renal injury. Lloyd and colleagues[145] showed that creatinine

clearance (p<0.0004), urinary micro-albumin/creatinine ratio were significantly worse in their on pump group (p<0.0083) and increased N-acetyl glucosaminidase activity *(p*<0.0272) leading them to conclude that off pump coronary revascularization offered superior renal protection when compared with conventional coronary revascularization with CPB and cardioplegic arrest in first time CABG patients. Furthermore even small rises in serum creatinine (Cr) are associated with significant mortality as shown by Lassnigg et al [(143)]; that CPB is the main culprit is not questioned. The proponents of OPCAB point to studies such as by Ascione and colleagues showing reduced release of markers of renal injury to support this view[(145)]. However, others including Asimakopoulos and colleagues have found no significant change in creatinine clearance, as determined by the Cockcroft-Gault formula, for patients undergoing CABG with either OPCAB or ONCAB [(146)]. Similarly Tang et al[(147)] investigated low risk patients undergoing CABG with pulsatile CPB or OPCAB. They found no differences in morbidity or mortality or renal injury. Serum Cr and blood urea remained normal in both groups throughout the study.

Figure 2-14. Aetiology of Acute Kidney Injury[(148)]



A significant and similar rise in urinary retinol binding protein: Cr occurred in both groups peaking on day 1 before returning to baseline levels. These trends were also observed with urinary micro-albumin: Cr.

Biomarkers Of Renal Injury

Traditional tests of renal function such as serum creatinine and creatinine clearance focus on glomerular filtration and are relatively insensitive indicators of early damage because of the large renal functional reserve. More than more than 50% of renal function must be lost before an elevation in serum creatinine is detected[149].

Recently, sensitive markers that differentiate between renal tubular and glomerular injury have become available.

Glutathione S-transferases (GSTs) are found in high concentrations (2-3%) in the cells of the proximal and distal renal tubules. GSTs are readily released into the urine in the event of renal tubular injury. Urinary GSTs are highly sensitive and specific biomarkers of acute renal injury. In addition different isoforms have different locations in the kidney; alpha GST is localised in the proximal tubule and pi-GST localised in the distal tubule.

Human neutrophil gelatinase-associated lipocalin NGAL, a member of the lipocalin superfamily is a 25-kDa protein that is covalently bound to gelatinase in neutrophils and expressed at low concentrations in normal kidney, trachea, lungs, stomach, and colon. NGAL expression is induced in injured epithelia, including lung, colon, and especially the kidney. In the early phases of acute renal injury, NGAL accumulates within two distinct pools, namely a systemic and a renal pool. Acute renal injury results in increased NGAL mRNA expression in distant organs, especially the liver and spleen, and the over-expressed NGAL protein is most likely released into the circulation and constitutes the systemic pool. Additional contributions to the systemic pool in AKI may derive from the fact that NGAL is a known acute phase reactant and may be released from neutrophils, macrophages, and other immune cells. Furthermore, any decrease in glomerular filtration rate resulting from acute renal injury would be expected to decrease the clearance of NGAL, with further accumulation in the systemic pool. Gene expression studies in acute renal injury have also shown rapid up regulation of NGAL mRNA in the thick ascending limb of Henle's loop and the collecting

ducts, with resultant synthesis of NGAL protein in the distal nephron (the renal pool) and secretion into the urine where it comprises the major fraction of urinary NGAL[149].

Neurological Injury

Anatomy Of The Brain

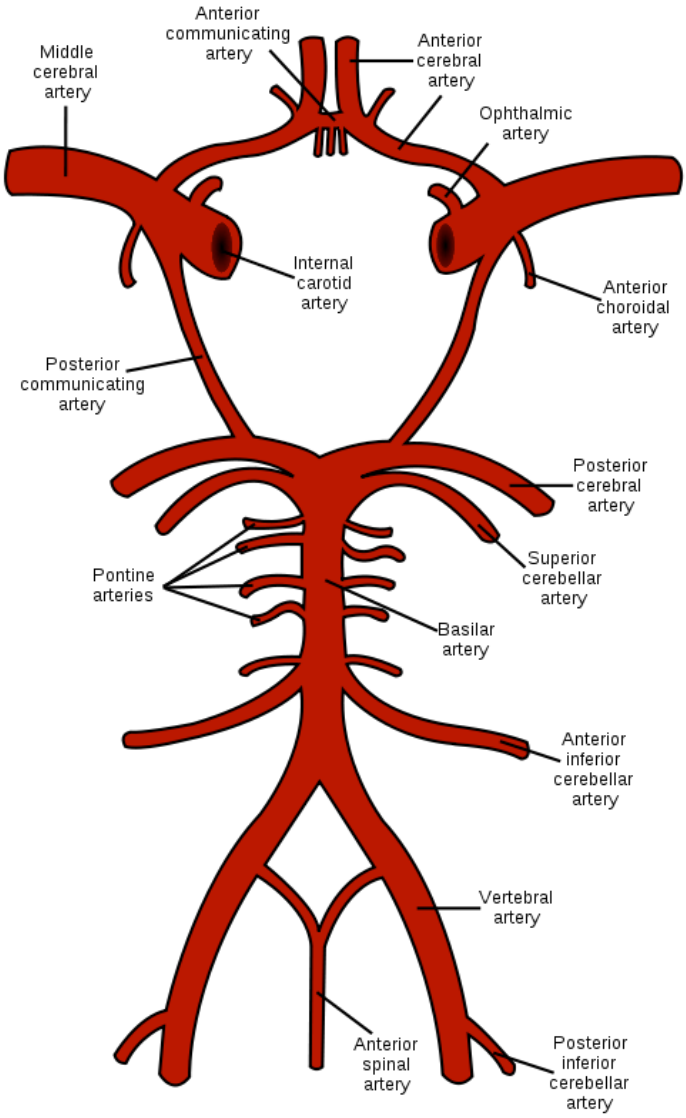
The major regions of the brain are the cerebral hemispheres, diencephalon, brain stem and cerebellum. The cerebral hemispheres, located on the most superior part of the brain, are separated by the longitudinal fissure. They make up approximately 83% of total brain mass, and are collectively referred to as the cerebrum. The cerebral cortex constitutes a 2-4 mm thick grey matter surface layer and, because of its many convolutions, accounts for about 40% of total brain mass. It is responsible for conscious behaviour and contains three different functional areas: the motor areas, sensory areas and association areas. Located internally is the white matter, responsible for communication between cerebral areas and between the cerebral cortex and lower regions of the CNS, as well as the basal nuclei (or basal ganglia), involved in controlling muscular movement. The diencephalon is located centrally within the forebrain. It consists of the thalamus, hypothalamus and epithalamus, which together enclose the third ventricle. The thalamus acts as a grouping and relay station for sensory inputs ascending to the sensory cortex and association areas. It also mediates motor activities, cortical arousal and memories. The hypothalamus, by controlling the autonomic (involuntary) nervous system, is responsible for maintaining the body's homeostatic balance. Moreover it forms a part of the limbic system, the 'emotional' brain. The epithalamus consists of the pineal gland and the CSF producing choroid plexus. The brain stem is similarly structured as the spinal cord: it consists of grey matter surrounded by white matter fibre tracts. Its major regions are the midbrain, pons and medulla oblongata. The midbrain, which surrounds the cerebral aqueduct, provides fibre pathways between higher and lower brain centres, contains visual and auditory reflex and subcortical motor centres. The pons is mainly a conduction region, but its nuclei also contribute to the regulation of respiration and cranial nerves. The medulla oblongata takes an important role as an autonomic reflex centre involved in maintaining body homeostasis. In particular, nuclei in the medulla regulate respiratory rhythm, heart rate, blood pressure and several cranial nerves. Moreover, it provides conduction pathways between the inferior spinal cord and higher brain centres. The cerebellum, which is located dorsal to the pons and medulla, accounts for about 11% of total

brain mass. Like the cerebrum, it has a thin outer cortex of grey matter, internal white matter, and small, deeply situated, paired masses (nuclei) of grey matter. The cerebellum processes impulses received from the cerebral motor cortex, various brain stem nuclei and sensory receptors in order to appropriately control skeletal muscle contraction, thus giving smooth, coordinated movements.

The Cerebral Circulation

The cerebral circulation consists of the vertebral and internal carotid arteries. The two posterior and single anterior communicating arteries form the circle of Willis, which equalises blood pressures in the brain's anterior and posterior regions,

Figure 2-15. The Cerebral Circulation[150]



and protects the brain from damage should one of the arteries become occluded. However, there is little communication between smaller arteries on the brain's surface. Hence occlusion of these arteries usually results in localised tissue damage.

The cardiac output is about 5 L/min of blood for a resting adult. Blood flow to the brain is about 14% of this, or 700 mL/min. Resistance arises from friction, and is proportional to the following expression

Cerebral Physiology

In standard fluid dynamics notation:

$$\Delta P = \frac{8\mu LQ}{\pi r^4}$$

Where:

ΔP is the pressure drop
L is the length of pipe
μ is the dynamic viscosity
Q is the volumetric flow rate
r is the radius
d is the diameter
π is the mathematical constant (approximately 3.1416).

Hence blood flow is slowest in the small vessels of the capillary bed, allowing time for the exchange of nutrients and oxygen to surrounding tissue by diffusion through the capillary walls.

The auto-regulation of blood flow in the cerebral vascular bed is the mechanism by which cerebral blood flow (CBF) tends to remain relatively constant despite changes in cerebral perfusion pressure (CPP). With a constant metabolic demand, changes in CPP or arterial blood pressure that would increase or reduce CBF, are compensated by adjusting the vascular resistance. This maintains a constant O_2 supply and constant CBF. Therefore cerebral auto-regulation allows the blood supply to the brain to match its metabolic demand and also to protect cerebral vessels against excessive flow due to arterial hypertension. Cerebral blood flow is auto-regulated much better than in almost any other organ. Even for arterial pressure variations between 50 and 150 mm Hg, CBF only changes by a few percent. This can be accomplished because the arterial vessels are typically able to change their

diameter about 4-fold, corresponding to a 256-fold change in blood flow. Only when the brain is very active is there an exception to the close matching of blood flow to metabolism, which can rise by up to 30-50% in the affected areas[151].

Blood Brain Barrier

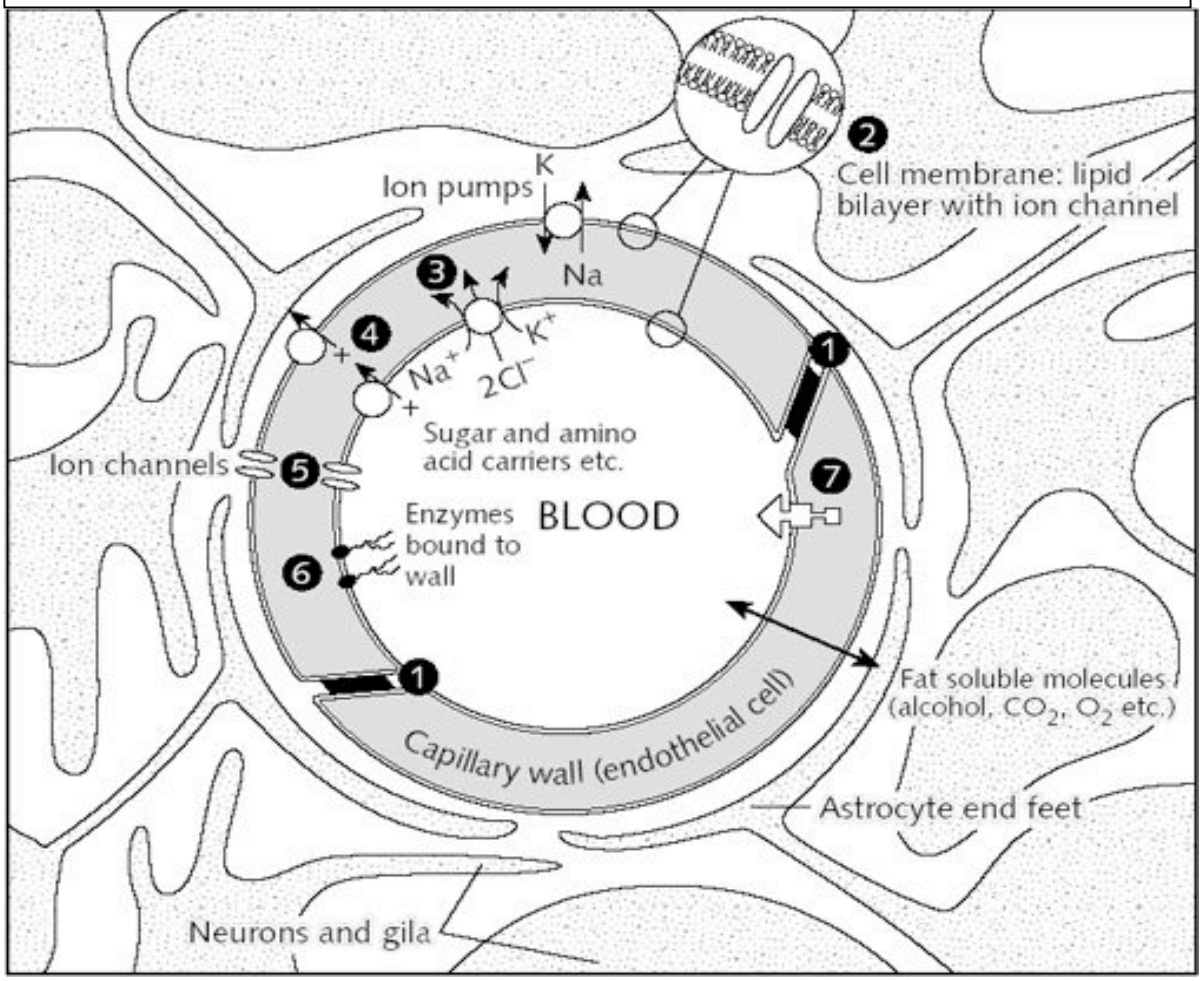
The blood brain barrier is a physiological mechanism that alters the permeability of brain capillaries, so that some substances, such as certain drugs, are prevented from entering brain tissue, while other substances are allowed to enter freely. The main function of the blood-brain barrier (BBB) is to protect the brain from changes in the levels in the blood of ions, amino acids, peptides, and other substances. Throughout the body, the walls of the capillaries (the smallest of the blood vessels) are made up of fenestrated endothelial cells, separated by small gaps (fenestrations). Soluble chemicals within the various tissues pass through these gaps into the blood stream, to be carried throughout the body and into different tissues. In the brain, however, these endothelial cells are packed more tightly together, due to the existence of zonulae occludens (tight junctions) between them. This blocks the passage of most molecules. The blood-brain barrier blocks all molecules except those that cross cell membranes by means of lipid solubility (such as oxygen, carbon dioxide, ethanol, and steroid hormones) and those that are allowed in by specific transport systems (such as sugars and some amino acids). Substances with a molecular weight higher than 500 Daltons (500 u) generally cannot cross the blood-brain barrier, while smaller molecules often can. In addition, the endothelial cells metabolize certain molecules to prevent their entry into the central nervous system. For example, L-DOPA, the precursor to dopamine, can cross the BBB, whereas dopamine itself cannot. In addition to tight junctions acting to prevent transport in between epithelial cells, there are two mechanisms to prevent passive diffusion through the cell membranes. Glial cells surrounding capillaries in the brain pose a secondary hindrance to hydrophilic molecules, and the low concentration of interstitial proteins in the brain prevent access by hydrophilic molecules. The blood-brain barrier protects the brain from the many chemicals flowing within the blood. However, many bodily functions are controlled by hormones in the blood, and while the secretion of many hormones is controlled by the brain, these hormones generally do not penetrate the brain from the blood. This would prevent the brain from directly monitoring hormone levels. In order to control the rate of hormone secretion effectively, there exist specialised sites where neurons can "sample" the

composition of the circulating blood. At these sites, the blood-brain barrier is 'leaky'; these sites include three important 'circumventricular organs', the subfornical organ, the area postrema and the organum vasculosum of the lamina terminalis (OVLT). The barrier is located at the brain blood capillaries, which are unusual in two ways.

Apart from these passive elements of the BBB there are also enzymes on the lining of the cerebral capillaries that destroy unwanted peptides and other small molecules in the blood as it flows through the brain.

Finally, there is another barrier process that acts against lipid-soluble molecules, which may be toxic and can diffuse straight through capillary walls into the brain. In the capillary wall there are three classes of specialized ‘efflux pumps’ which bind to three broad classes of molecules and transport them back into the blood out of the brain. However, in order for nutrients to reach the brain, water-soluble compounds must cross the BBB, including the vital glucose for energy production and amino acids for protein synthesis. To achieve this transfer, brain vessels have evolved special carriers on both sides of the cells forming the capillary walls, which transport these substances from blood to brain, and also move waste products and other unwanted molecules in the opposite direction. Since the brain is contained in a rigid, bony skull, its volume has to be kept constant. The BBB plays a key role in this process, by limiting the freedom of movement of water and salts from the blood into the extracellular fluid of the brain. Whereas in other body tissues extracellular fluid is formed by leakage from capillaries, the BBB in fact secretes brain extracellular fluid at a controlled rate and is thus critical in the maintenance of normal brain volume. If the barrier is made leaky by trauma or infection, water and salts cross into the brain, causing it to swell (cerebral oedema), which leads to raised intracranial pressure; this can be fatal. The blood-brain barrier is thus a key element in the normal functioning of the brain, and isolates it from disturbances in the composition of the fluids in the rest of the body[152].

Figure 2-16. The Blood Brain Barrier[2]



Characteristics of the blood-brain barrier are indicated: (1) tight junctions that seal the pathway between the capillary (endothelial) cells; (2) the lipid nature of the cell membranes of the capillary wall which makes it a barrier to water-soluble molecules; (3), (4), and (5) represent some of the carriers and ion channels; (6) the 'enzymatic barrier that removes molecules from the blood; (7) the efflux pumps which extrude fat-soluble molecules that have crossed into the cells.

Neurological Dysfunction

Central nervous system (CNS) injury after cardiac surgery is classified into two categories. Type 1 inury is defined as stroke or hypoxic encephalopathy, nonfatal stroke, transient ischaemic attack, or stupor or coma at time of discharge. Type 2 injury is defined as a new deterioration, memory deficit, or seizure without evidence of focal injury[153]. The incidence of clinically obvious stroke was 5 to 9% in the 1960s[154], but this had reduced to between 0.8% to 5.2%[155] by the mid 90s. This under scores the ever-improving quality and

safety of CPB despite an aging population. Nevertheless, CABG remains the largest cause of iatrogenic stroke in the USA[156]. The incidence of type 2 injury such as postoperative delirium vary from (10 - 30%), short-term (33 - 83%) as well as long-term cognitive changes (20 - 60%)[157]. The estimated financial cost is of the order 4 billion US dollars[158]. The personal tragedy for the affected patients and relatives is simply not quantifiable.

Table 2-4. Predictors Of Adverse Neurological Outcome CABG[158]

Risk factor	Type 1 outcomes	Type 2 outcomes
Proximal aortic atherosclerosis	4.52 (2.52 – 8.09)	
History of neurological disease	3.19 (1.65 – 6.15)	
Use of intra aortic balloon pump	2.60 (1.21 – 5.58)	
Diabetes mellitus	2.59 (1.46 – 4.60)	
History of hypertension	2.31 (1.20 – 4.47)	
History of pulmonary disease	2.09 (1.14 – 3.85)	2.37 (1.34 – 4.18)
History of unstable angina	1.83 (1.03 – 3.27)	
Age (per decade)	1.75 (1.27 – 2.43)	2.20 (1.60 – 3.02)
Admission systolic BP>180 mm Hg		3.47(1.41 – 8.55)
History of excessive alcohol intake		2.64 (1.27 – 5.47)
History of prior CABG surgery		2.18 (1.14 – 4.17)
Arrhythmia on day of surgery		1.97 (1.12 – 3.46)
Antihypertensive therapy		1.78 (1.02 – 3.10)

The etiology of stroke after CABG is complex and multifactorial. Proposed mechanisms include surgery-related trauma, genetic susceptibility, micro embolization of gaseous or particulate matter, other vascular or ischemic changes, temperature during surgery, hypo-perfusion during CPB, or the result of inflammatory changes that cause an increase in permeability across the blood-brain barrier with resultant cerebral oedema[159].

Biomarkers Of Neurological Injury

Brain-type fatty acid binding protein (B-FABP) is a 15-kDa cytoplasmic, non-enzymatic protein involved in the intracellular buffering and transport of long-chain fatty acids[160]. FABPs are released rapidly from damaged cells into the circulation and are cleared from the circulation by the kidney with a plasma half-life of 20 min. S-100 beta protein (S100β) is expressed constitutively by brain astrocytes. Elevated S100β levels in cerebrospinal fluid and serum have been found after head trauma, subarachnoid hemorrhage, and stroke, which correlated with the extent of brain damage[161]. S100β has also been studied

in patients undergoing cardiac surgery as a marker of brain injury[162]. B-FABP concentrations ranged from 0.8 μg/g wet weight in striatum tissue to 3.1 μg/g in frontal lobe[163]. B-FABP is not detected in the serum of healthy donors. In the minor traumatic brain injury study, serum B-FABP increased in 68% of patients compared with S100β (increased in 45%) and neuron specific enolase (increased in 51% of patients). In electro-convulsive therapy serum B-FABP was increased in 6% of all samples (2 of 14 patients), and S100β was above its upper reference limit (0.3 μg/L) in 0.4% of all samples[163].

Chapter 3 Materials and Methods

Study Participants

Eligibility Criteria For Participants

All patients undergoing isolated first time CABG at Southampton General Hospital who satisfied one or more of the major criteria or two or more of the minor criteria were entered into the study: Major Criteria: Preoperative serum Creatinine > 130 mmol/L (upper range of normal in our laboratory); pre-existing renal disease: Minor Criteria: Age >75 years; left ventricular ejection fraction <40%; chronic hypertension; diabetes mellitus; peripheral vascular disease; unstable angina requiring intravenous therapy for class IV symptoms at the time of surgery were candidates for inclusion in the study. They were not admitted to the study if any of the following criteria were present: (1) Preoperative dialysis dependency for renal failure; (2) Pre-existing gastrointestinal and liver disease; (3) calcified coronaries, (4) intra-myocardial vessels, (5) small targets or (6) ventricular aneurysm; (7) emergency cases; (8) redo cases; (9) requiring combined procedures (including left ventricular aneurysmectomy); (10) unwilling to consent. The aim of these criteria was to try and exclude low risk patients from the study. In hindsight a more reasoned approach would have been to recruit according to the patients EuroSCORE[164]. The EuroSCORE is a prognostic scoring system developed in Europe for patients undergoing cardiac surgery. Patients' are risk stratified according to the variables shown below. The additive EuroSCORE can then be used to further classify patients as either low risk (additive EuroSCORE 1–2), medium risk (EuroSCORE 3–5) or high-risk groups (EuroSCORE 6 plus).

Table 3-1 EuroSCORE[165]

Patient related factors		Score
Age	Per 5 years or part thereof over 60 years	1
Gender	Female	1
Chronic pulmonary disease	Long term use of bronchodilators or steroids for lung disease	1
Extra-cardiac arteriopathy	Any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids	2
Neurological dysfunction disease	Severely affecting ambulation or day to day functioning	2
Previous cardiac surgery	Requiring opening of the pericardium	3
Serum creatinine	Serum creatinine >200 micro moles/Litre	2
Active endocarditis	Patient still under antibiotic treatment for endocarditis at the time of surgery	3
Critical preoperative state	Any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intra-aortic balloon counter pulsation or preoperative acute renal failure (anuria or oliguria <10ml/hour)	3
Cardiac related factors		
Unstable angina	Rest angina requiring intravenous nitrates until arrival in the anaesthetic room	2
LV dysfunction	Moderate or LVEF 30-50% Poor or LVEF <30%	1 3
Recent myocardial infarct	Recent myocardial infarct within last 90 days	2
Pulmonary hypertension	Systolic PA pressure >60 mmHg	2
Operation related factors		
Emergency	Operation carried out on referral before the beginning of the next working day	2
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta	For disorder of ascending, arch or descending aorta	3
Post-infarct septal rupture		4

Study Intervention

Patients who met the eligibility criteria were randomised to undergo ether OPCAB or ONCAB. A standard anaesthetic protocol was followed in which fentanyl based anaesthesia was used in combination with benzodiazepine and vecuronium as a muscle relaxant. Each patient had a pulmonary artery balloon catheter inserted for perioperative continuous cardiac output measurement and monitoring of haemodynamic status until 12 hours postoperatively.

OPCAB Technique

The pericardium was opened and positioning sutures placed to optimise exposure of target coronary arteries. Stable haemodynamic during manoeuvring of the heart was maintained by preload management (fluids and Trendelenburg posture), heart rate control (chronotropic agents and pacing) and if necessary, temporary inotropic support. Where haemodynamic stability could not be achieved despite these measures, CPB was instituted and these patients were excluded from further analysis. Partial systemic heparinisation was achieved with a target ACT > 200 sec prior to manipulation of the coronary vessels. Core temperature was maintained at or above 35°C throughout the procedure. A mechanical stabiliser was used to immobilise the operative field on the beating heart during coronary anastomosis. Following arteriotomy, an intracoronary shunt was inserted to maintain distal myocardial perfusion during the anastomosis and removed prior to completion. Construction of the proximal anastomosis to the ascending aorta was performed in a similar fashion to on-pump techniques using a side-biting clamp. Heparinisation was reversed towards the end of the procedure using protamine before removal of pericardial stay sutures.

ONCAB Technique

CABG was performed in one group with the institution of CPB. Pulsatile CPB with a mean amplitude of 25mmHg was conducted under mild core hypothermia (32°C), using a hollow-fibre membrane oxygenator (D903 Avant, Sorin Biomedica, Gloucester, UK) and arterial line filtration (D734 Micro 40, Sorin Biomedica, Gloucester, UK). The CPB circuit was primed with 1L of Hartman's and 500 mL of Gelofusine fluid. Intermittent antegrade cold blood cardioplegia delivered through a 12G aortic root cannula was used for myocardial protection. Flow was maintained at 2.5 L/min/m^2 during CPB with judicious use of vasoconstrictors to maintain the perfusion pressure above 50 mmHg. Alpha-stat management of acid-base status during CPB was used. No vasoactive agent was administered other than for maintenance of

perfusion pressure during CPB. Haematocrit was maintained >20% during CPB.

Study Objectives

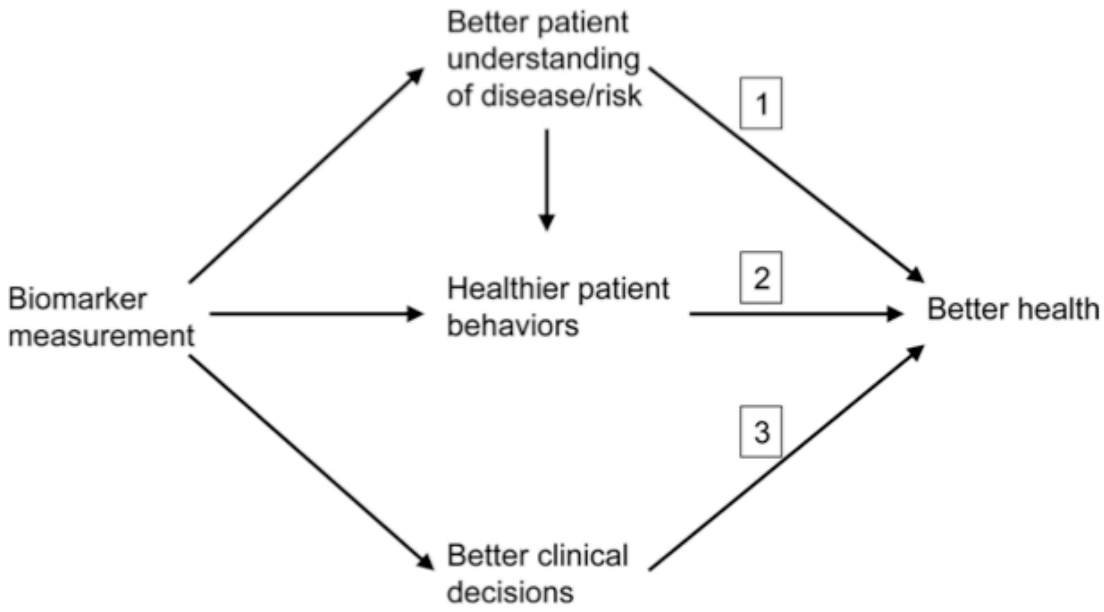
In the current study we tested the hypothesis that there is no difference in organ function in patients undergoing OPCAB or ONCAB. This was done by evaluating the release of a range of novel biomarkers as surrogate measurement of organ dysfunction. Blood samples were collected from the radial artery into ethylene-diamine-tetra-acetic acid (EDTA)-containing glass tubes after anaesthetic induction, at the end of operation and 4,8,12 hours postoperatively. The samples were immediately centrifuged in a refrigerated centrifuge to separate the plasma, which was subsequently frozen and stored at -70°C until assayed. Details of the specific assays are shown in the relevant chapters to avoid unnecessary repetition. The assays were carried out at Southampton General Hospital by a team of specialised technicians. The following demographic data was recorded: age; sex; body mass index; Canadian Cardiology Society classification of angina; New York Heart Association of heart failure; previous MI; hypertension; COPD; smoking status; EuroSCORE and Parsonnet score; >50% left main stem stenosis. The following data was also recorded: number of distal anastomoses; number and type of arterial grafts; aortic cross-clamp time; CPB time; cardiac index at sequential time points pre and postoperatively until 12 hours postoperatively; length and maximum doses of inotropic requirements; use of intra-aortic balloon pump; re-exploration for bleeding; length of stay on the ventilator; length of stay on ICU; respiratory failure; oliguria; anuria; renal replacement therapy; multiple organ failure; neurological complications; dysrhythmias; chest infection; infective wound complications; length of hospital stay. All patients were treated according to routine protocols employed in our unit. Upon arrival in the intensive care after surgery an infusion of 1 mL/kg/hour of crystalloid fluid was commenced, while the colloid fluids and inotropic medication were used according to clinical need. The use of any potential nephrotoxic agents such as non-steroidal anti-inflammatory drugs was not allowed during the study.

Study Outcomes

Early-phase studies must prove that a biomarker is associated statistically with the clinical state of interest and adds information about presence or risk of disease above and beyond established markers. The aim of this pilot study was to assess if there were any changes in biomarker profile between the two groups. Thus whilst the null

hypothesis was that there should be no differences between the two groups any change from baseline may be of benefit in the future to help detect organ dysfunction at an earlier stage when therapeutic intervention would be more efficacious. In many units it is quite normal to do a full blood analysis once the patient has been returned from the operating room. Thus it may that in the future should these markers prove useful they could be routinely tested for also postoperatively.

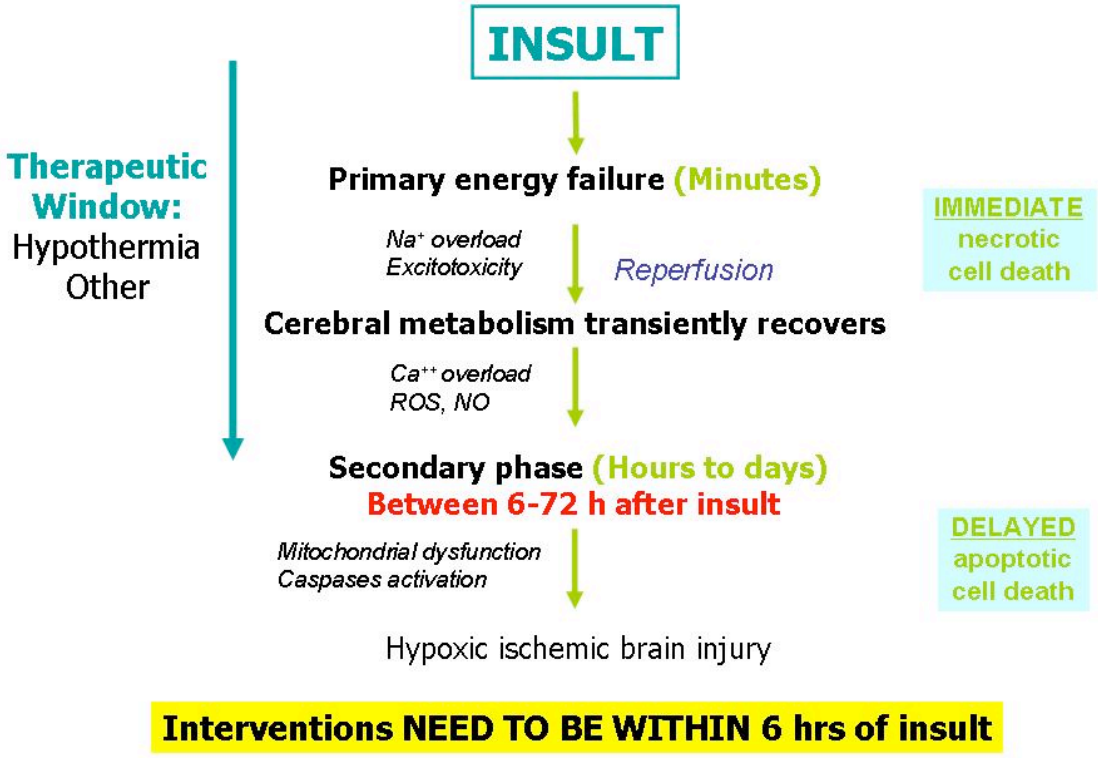
Figure 3-1. Potential Benefit of Biomarkers[166]



Neurological Outcomes

S100 beta was assayed using a readily available commercial kit BioVendor GmbH, Germany. B-FABP was assayed using a specialist assay by Mr M Pelsers. At present there are no markers of early damage that would facilitate the earlier detection and treatment of brain injury

Figure 3-2. The Importance of Early Intervention In Cerebral Injury[167]



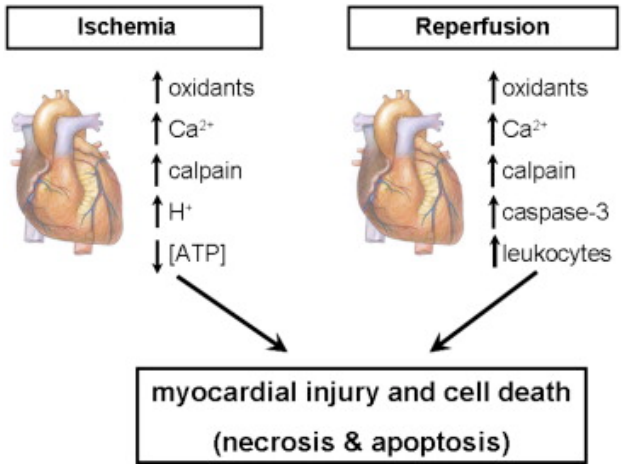
Myocardial Outcomes

There is an old adage that "time is myocardium". Hence the earlier that injury can be detected the greater the amount of myocardium that can be salvaged.

Numerous factors contribute to cardiac injury during both ischemia and reperfusion. During ischemia, cellular levels of oxygen and ATP decrease. These declines are associated with increases in cellular oxidant production, calcium overload (Ca2+), increased levels of

hydrogen ions (H+), and activation of the calcium activated protease calpain. Early in reperfusion, there is an acute exacerbation of both cellular calcium overload and oxidant production in cardiac myocytes. Collectively, the increased levels of calcium and oxidants promote activation of calpain and caspase-3; both calpain and caspase-3 contribute to cellular injury, which can lead to cell death. Ischemia-reperfusion induced cellular injury results in neutrophil activation and the production of reactive oxygen species that can further contribute to cellular injury. Collectively, these ischemia-reperfusion induced disturbances in cellular homeostasis contribute to cellular injury and cell death due to both necrosis and apoptosis.

Figure 3-3. Ischemia-Repefusion Injury of the Myocardium[168]



Whilst to date cardiac troponin I has been considered the gold standard for the detection of myocardial injury, there has been considerable interest in H-FABP for even earlier detection of myocardial damage.

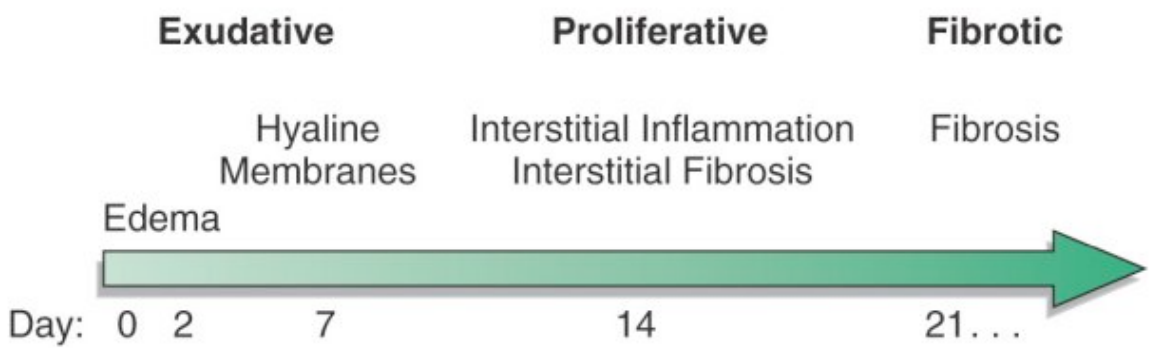
The human H-FABP ELISA kit is intended for the quantitative measurement of natural human H-FABP in plasma or serum (Hycult Biotechnology, Uden, the Netherlands). The kit shows no cross reactivity with human intestinal-type or human liver-type FABP. The kit has a minimum detection level of 250 pico grams/mL and a measurable concentration range of 102 pico grams/mL to 25,000 pico grams/mL. Cardiac troponin I was assayed by using a commercially available assay used for routine measurement of at Southampton General Hospital.

Pulmonary Outcomes

The lungs are particularly vulnerable to damage during cardiac surgery, particularly with the use of CPB. Whilst the respiratory index is certainly helpful in the latter stages of lung injury it would be very useful to have an earlier marker of pulmonary dysfunction. Early markers of the exudative phase of lung injury have been quite sparse and not readily available.

The diagram below illustrates the time course for the development and resolution of ARDS. The exudative phase is notable for early alveolar edema and neutrophil-rich leukocytic infiltration of the lungs with subsequent formation of hyaline membranes from diffuse alveolar damage. Within 7 days, a proliferative phase ensues with prominent interstitial inflammation and early fibrotic changes. Approximately 3 weeks after the initial pulmonary injury, some patients enter the fibrotic phase, with substantial fibrosis and bullae formation.

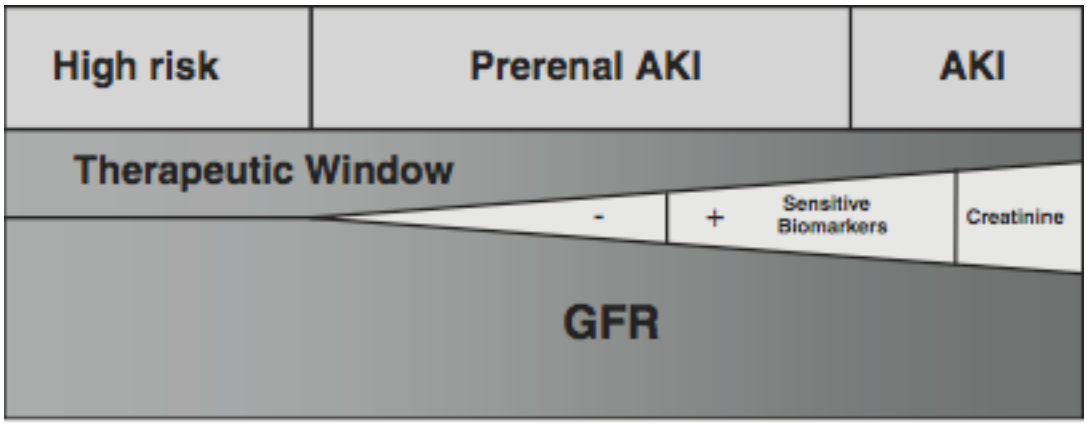
Figure 3-4. Time course of ARDS[169]



A commercially available assay from www.bovendor.com was used to measure SP-D. CC-16 was measured by Professor Bernard's' team in Belgium using a specialist assay

Renal Outcomes

Figure 3-5. The importance of early detection of Acute Kidney Injury[170]



The clinical phases of acute kidney injury (AKI) occur across a continuum beginning with high-risk patients and progressing to pre-renal azotemia and then to frank AKI. The therapeutic window is likely to be in the earliest stages of this ischemia before injury is manifest. Serum creatinine rises late in this process, and thus sensitive biomarkers of kidney injury are needed to identify patients for timely therapeutic intervention. Hence the excitement regarding these novel markers.

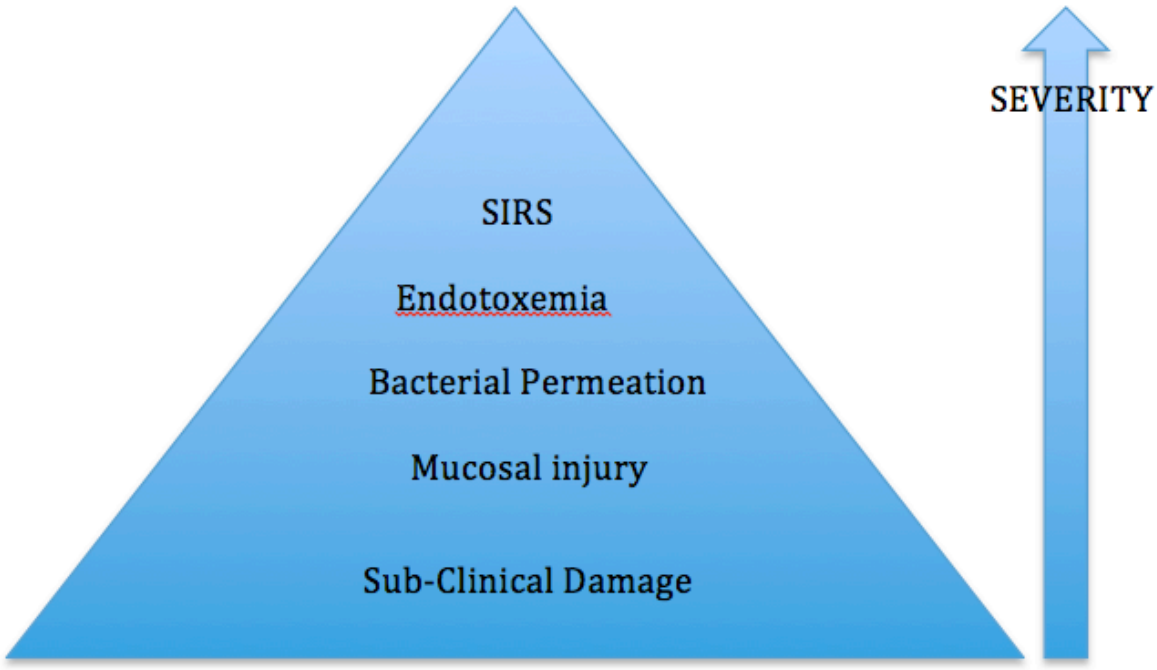
The blood samples were assayed for neutrophil gelatinase associated lipocalin (NGAL) using an assay supplied by Antibodyshop, Grusbakken 8, DK-2820 Gentofte, Denmark. Urine was collected at the same time points and stored according to the manufacturers instructions. Briefly 200 μL of Nephkit urine stabilising buffer was added to 800 micro litres of urine and the samples frozen at -70 degrees centigrade until assayed. GST-pi urine concentrations were measured by enzyme immunoassay (Nephkit™-Pi, Biotrin International, Sinsheim-Reihen, Germany) (normal values in healthy volunteers: 12–15 μg/L), and Alpha-GST urine concentrations were analysed by enzyme immunoassay (Nephkit™-Alpha, Biotrin International) (normal values in healthy volunteers: 3.5 - 11.1 μg/L). In the setting of polyuria it is more relevant to express GST release rate per unit time rather than the absolute concentration. This was calculated as follows:

$$\underline{\mu g\ GST/\ min = GST\ \mu g/L \times Volume\ of\ urine\ in\ 240\ minutes/\ time\ (240\ minutes)}$$

Gastrointestinal Outcomes

The importance of assessing gastrointestinal dysfunction has been discussed previously. The early detection of such damage would go a long way to ameliorate some of the morbidity associated with CPB

Figure 3-6. Progression of Gastrointestinal Damage



The advent of automated gastric air tonometer together with some readily available assays of biologic markers of gut injury if realised would provide considerable early warning of impending doom.

Whole body oxygen flux requirements

This is the amount of oxygen delivered to the peripheral tissues per minute. These were based on the following equations:

Arterial blood oxygen content (CaO_2) = Hb * SaO_2 * 1.39 + (0.003 * PaO_2) mL/dL,

Hb is Haemoglobin concentration in g/dL,

SaO_2 is the percentage of oxygen saturation of arterial blood,

PaO_2 is the partial pressure of oxygen in the arterial blood.

In the above equation the factor 0.003 X PaO_2 is negligible and was not calculated for the purposes of our study.

Whole body oxygen delivery (DO_2) = CaO_2 * $\frac{\text{Cardiac Output}}{\text{Body surface area}}$ * 0.1 mL/min/m^2,

Where cardiac output is expressed as L/min and body surface area in m^2.

(Body surface area is calculated from a nomogram, using the patient's height and weight.)

Mixed venous oxygen content (CvO_2) = Hb * SvO_2 * 1.39 + (0.003 * PvO_2) ml/dL,

SvO2 is the percentage of oxygen saturation of mixed venous blood

PvO2 is the partial pressure of oxygen in mixed venous blood.

The factor 0.003 X PvO_2 is negligible and was not calculated in this study.

Whole body oxygen consumption (VO_2) = (CaO_2 – CvO_2) * Cardiac Index * 0.1 mL/min/m^2.

Cardiac index is cardiac output / body surface area.

Extraction Fraction = $\frac{VO_2}{DO_2}$ * 100 %

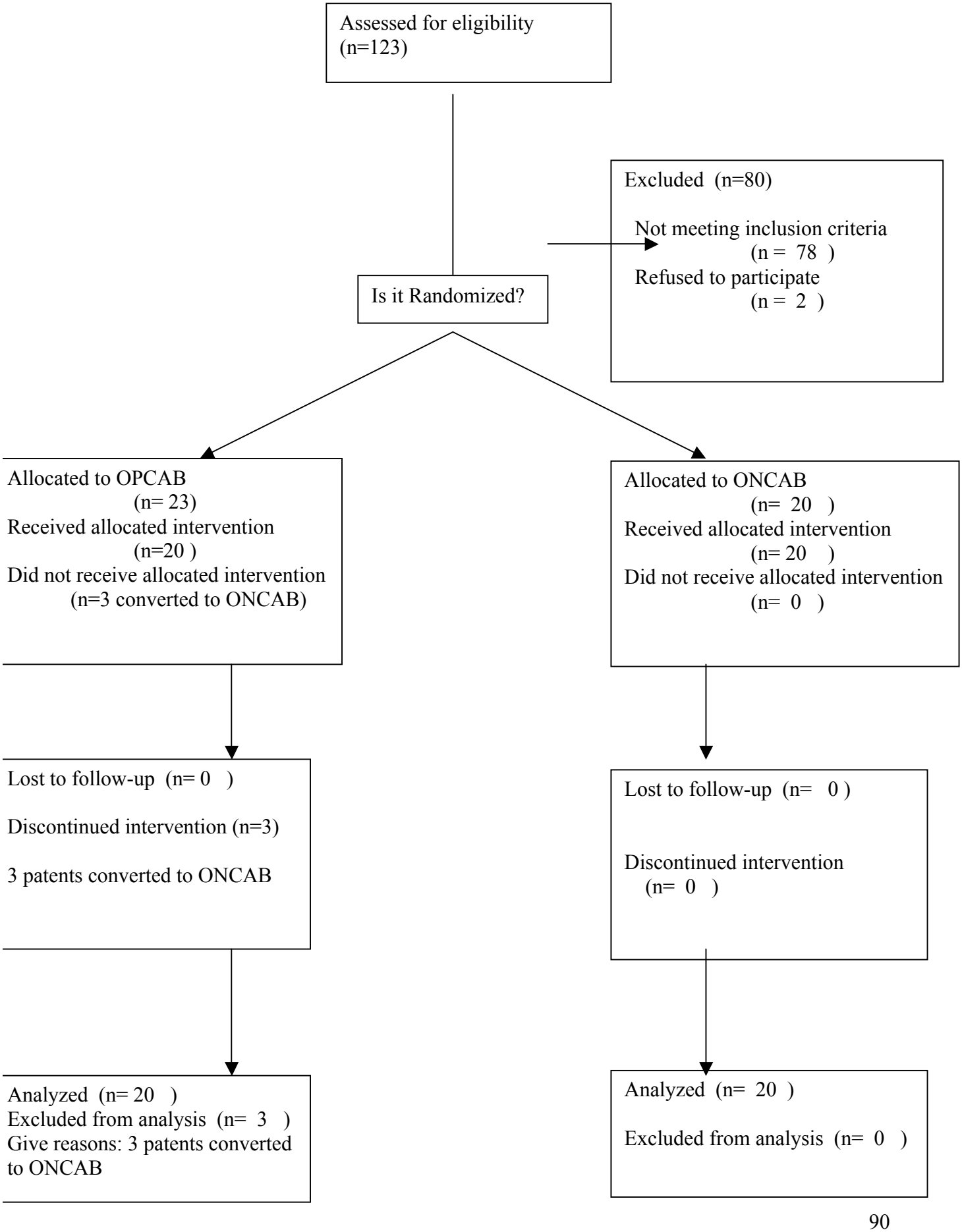
Sample Size

This was a pilot study using a variety of novel markers that had not largely been investigated in patients undergoing CABG. The aim of the study was to study what changes if any were demonstrated between the two techniques. The study population size was determined according to level of funding available for assays, time scale, and availability of single surgeon who performs OPCAB. This would yield valuable data that could be used in the future to design a study of adequate power and size to detect organ injury at an earlier stage and thus help attenuate the morbidity associated with CABG.

Randomization

All patients meeting the criteria for the study were randomized to either OPCAB or ONCAB according to a random-number table. Mr D.Varghese reviewed all angiograms to evaluate the suitability for the trial. Mr SK Ohri carried out both ONCAB and all OPCAB operations. When a patient was randomised to OPCAB and no OPCAB surgeon was available the patient was excluded from the trial. However this meant that the ONCAB group was recruited more quickly than the OPCAB group. This is another limitation of this study.

Figure 3-7. Randomisation Process



Statistical Analysis

Whilst the gold standard for assessing clinical outcomes is based on the intention to treat principle the aim of this study was to discover if there were any changes in biomarker profile elicited by the procedure of CABG either done with OPCAB or ONCAB. This study was not designed to detect clinical outcomes and thus we have used the "per-protocol" or "on-treatment" analysis[171] to evaluate changes in biomarker profile. Only participants who fulfilled the protocol in the terms of the eligibility and intervention underwent outcome assessment. Hence patients that were converted from OPCAB to ONCAB were excluded from the study. A per-protocol analysis is a recognized method for determining the biological effects of a new treatment. However, by restricting the analysis to a selected patient population, it does not show the practical value of the new treatment, which was never the aim of the study. This we fully accept is a drawback of the study.

Numerical results are presented as means (standard deviations) or medians (inter-quartile ranges) for non-normally distributed variables unless otherwise indicated. Categorical variables are presented as frequency counts and percentages. Patient characteristics and perioperative clinical data in the two groups were compared using a two-sample Student *t*-test or a Mann-Whitney *U* test or Sign test if normal distribution could not be assumed. Categorical variables were compared using the Pearson's chi-square or Fisher's exact test as appropriate. The difference between treatments over time in respect of numeric outcomes was investigated using repeated measures analysis of variance with baseline scores used as a covariate. To investigate any possible associations between the extent of organ injury and clinical outcome, the area under the curve as a function of time was calculated using the method described by Matthews et al[172]. Data analysis was performed using SPSS version 16.0. A p value of less than 0.05 was considered statistically significant.

Chapter 4 Results

Table 4-1 Patient Characteristics

Preoperative characteristics	**OPCAB**	**ONCAB**	**p value**
Age	70.5 (SD = 8.2)	71.4 (SD = 8.8)	0.57
Male gender	14 (70%)	14 (70%)	0.63
Good LV function	7 (35%)	13 (65%)	0.08
NIDDM/IDDM	6 (30%)	10 (50%)	0.37
Hypertension	20 (100%)	20 (100%)	1.00
Unstable angina	3 (15%)	3 (15%)	0.67
EuroSCORE	4.3 +/- 2.2	4.5 +/- 2.4	0.66
Operative features			
Average number of grafts	2.7 (0.8)	3.3 (0.9)	0.13
Index of completeness	1.05 (0.12)	1.15 (0.37)	0.97
Cross clamp time		44.8 (14.1)	
CPB time		76.4 (20.7)	
Postoperative Course			
Inotropic support			
Dopamine	10	12	0.38
Nor adrenaline	10	12	0.38
Milrinone	1	0	0.50
Adrenaline	2	0	0.49
IABP	1	0	1.00
Atrial fibrillation	6	13	0.06
Renal failure	0	0	1.00
Blood used	0.65 +/- 1.46	0.55 +/- 1.05	0.88
FFP	0.45 +/- 1.23	0.85 +/- 1.50	0.43
Platelets	0.55 +/- 1.19	0.55 +/- 0.78	0.48
LOS	8.2 +/- 4.7	9.8 +/- 5.4	0.32

Table 4-2. Vessels Grafted And Conduits Used In OPCAB

OPCAB				
	LIMA	RA	LSV	TOTAL
LAD	18			18
D1			9	9
RCA		1	2	3
PDA			11	11
INT			5	5
OM1			5	5
OM2			2	2
OM3			1	1
TOTAL	18	1	35	54

Table 4-3. Vessels Grafted And Conduits Used In ONCAB

ONCAB				
	LIMA	RA	LSV	TOTAL
LAD	19		1	20
D1			4	4
D2			1	1
RCA			4	4
PDA		1	12	13
LV BRANCH		1	1	2
CX			2	2
INT			1	1
OM1		1	11	12
OM2			6	6
TOTAL	19	3	43	65

LIMA= Left internal mammary artery

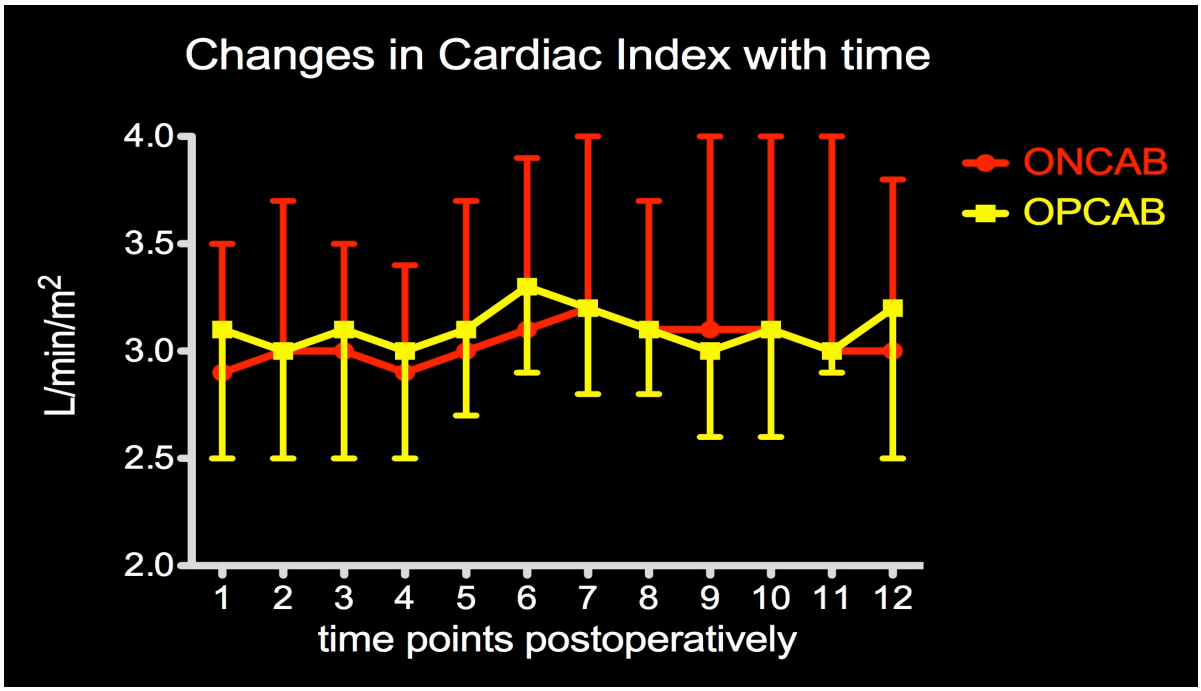
RA= Radial artery

LSV= Long saphenous vein

Myocardial Function

Cardiac Index

Figure 4-1. Change in Cardiac Index Over Time



1=Postop, 2= 2nd Hour, 3=3rd Hour, 4=4th Hour, 5=5th Hour, 6=6th Hour, 7=7th Hour, H=8th Hour, 9=9th Hour, 10=10th Hour, 11=11th Hour, 12=12th Hour

Table 4-4. Cardiac Index Over Time

Time	ONCAB		OPCAB	
	Mean	Standard deviation	Mean	Standard Deviation
Post op	2.9	0.6	3.1	0.6
2nd hour	3	0.7	3	0.5
3rd hour	3	0.5	3.1	0.6
4th hour	2.9	0.5	3	0.5
5th hour	3	0.7	3.1	0.4
6th hour	3.1	0.8	3.3	0.4
7th hour	3.2	0.8	3.2	0.4
8th hour	3.1	0.6	3.1	0.3
9th hour	3.1	0.9	3	0.4
10th hour	3.1	0.9	3.1	0.5
11th hour	3	1	3	0
12th hour	3	0.8	3.2	0.7

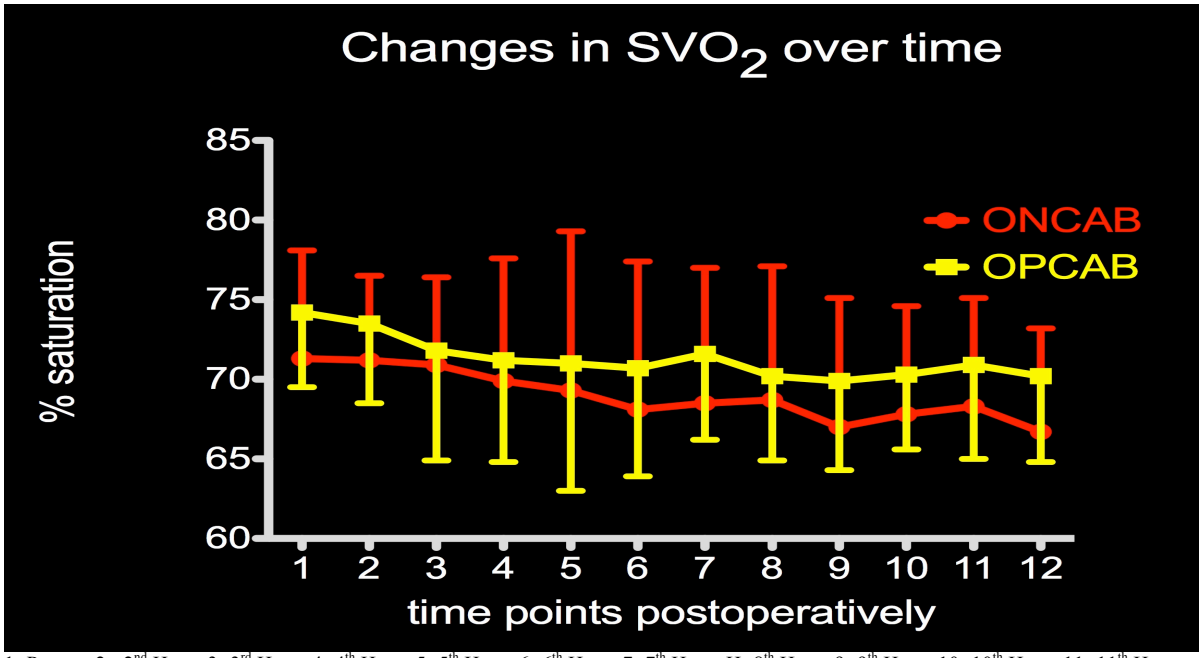
There was no significant change in cardiac index post operatively between the two groups, group*procedure interaction (p=0.81)

Mixed Venous Saturation

Table 4-5. Mixed Venous Saturation

Time	Procedure			
	ONCAB		OPCAB	
	Mean	Standard Deviation	Mean	Standard Deviation
Postop	71.3	6.8	74.2	4.7
2nd hour	71.2	5.3	73.5	5
3rd hour	70.9	5.5	71.8	6.9
4th hour	69.9	7.7	71.2	6.4
5th hour	69.3	10	71	8
6th hour	68.1	9.3	70.7	6.8
7th hour	68.5	8.5	71.6	5.4
8th hour	68.7	8.4	70.2	5.3
9th hour	67	8.1	69.9	5.6
10th hour	67.8	6.8	70.3	4.7
11th hour	68.3	6.8	70.9	5.9
12th hour	66.7	6.5	70.2	5.4

Figure 4-2. Change in Mixed Venous Saturation Over time

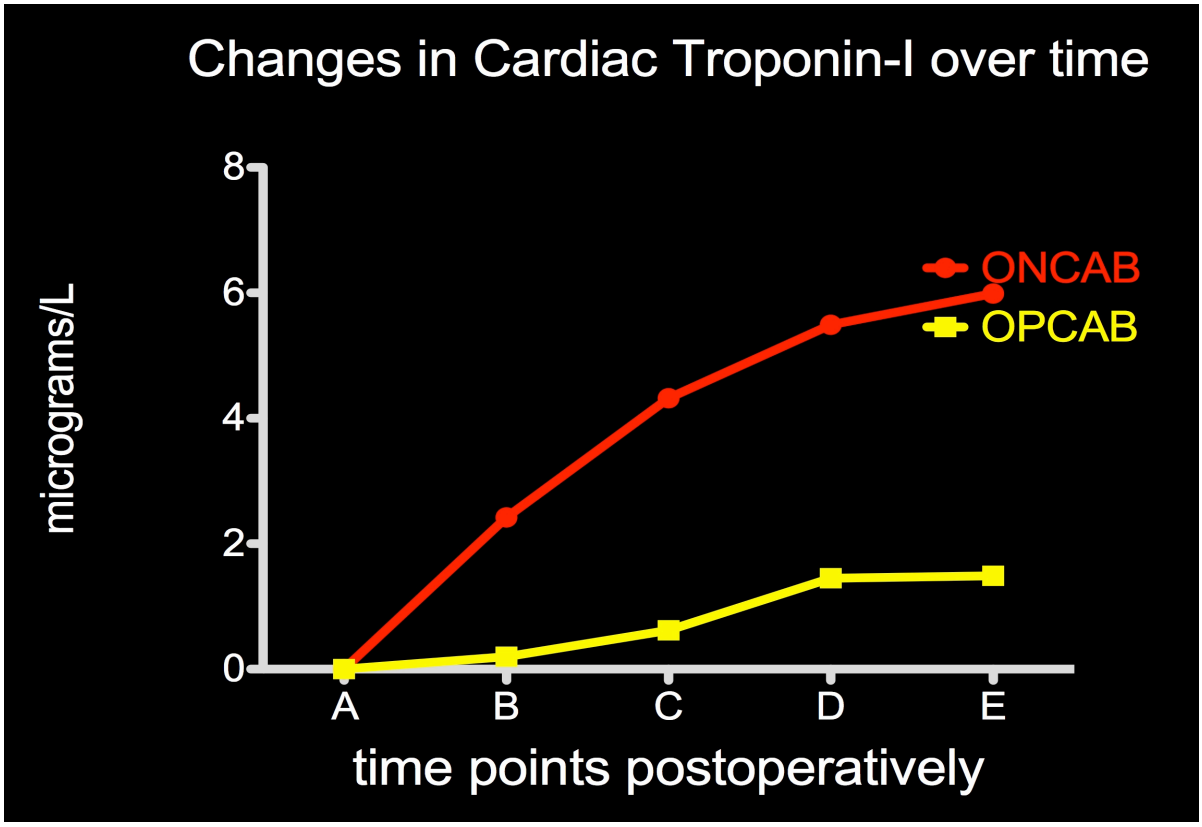


1=Postop, 2= 2nd Hour, 3=3rd Hour, 4=4th Hour, 5=5th Hour, 6=6th Hour, 7=7th Hour, H=8th Hour, 9=9th Hour, 10=10th Hour, 11=11th Hour, 12=12th Hour

The mixed venous oxygen saturation *(SvO2)* is the percentage of oxygen bound to hemoglobin in blood returning to the right side of the heart. This reflects the amount of oxygen "left over" after the tissues remove what they need. There was a significant change in SvO2 postoperatively (p=0.004) in both groups. However there was no significant difference between the two procedures (p=0.86).

Myocardial Damage – Release of Troponin I

Figure 4-3. Changes in Cardiac Troponin I over time



A = Pre-op, B = Postop, C = 4 hours, D = 8 hours, E = 12 hours

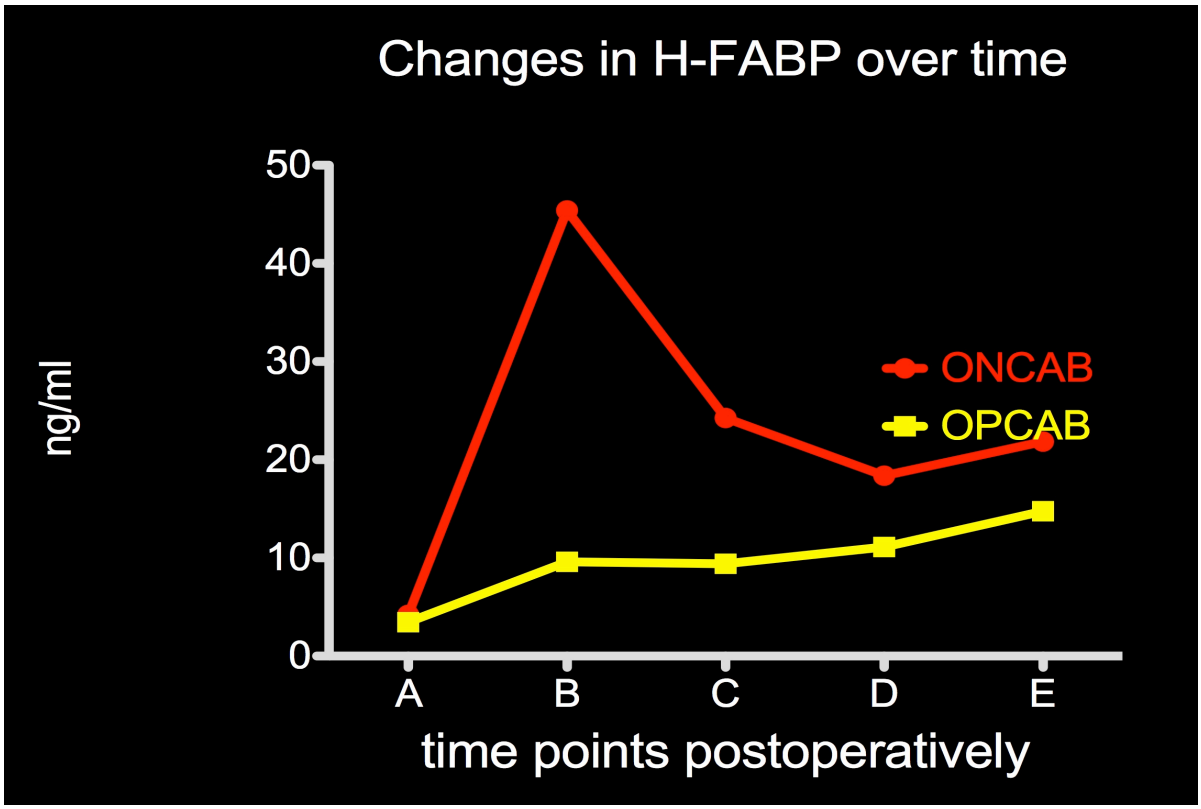
Table 4-6. Troponin I release

Troponin I		Pre-op	Postop	4 HRS	8 HRS	12 HRS
ONCAB	Median	0.00	2.42	4.32	5.49	5.99
	IQR	0.00	3.60	6.53	5.63	6.92
OPCAB	Median	0.00	0.20	0.62	1.45	1.49
	IQR	0.00	0.61	0.82	3.23	6.66

Human troponin I is found in cardiac muscle tissue as a single isoform with molecular weight 23876 Da and it consists of 209 amino acid residues. It is the most widely recognized marker of cardiac muscle tissue injury. The total amount of troponin-I released postoperatively was 107 +/- 22 μg/L in the ONCAB group vs. 53.4 +/- 23.6 μg/L in the OPCAB group (p=0.001). Troponin-I levels were significantly higher in the ONCAB group postoperatively (p<0.001) and at 4 hours (p=0.003)

Myocardial Damage – Release of H-FABP

Figure 4-4. Changes in H-FABP over time



A = Pre-op, B = Postop, C = 4 hours, D = 8 hours, E = 12 hours

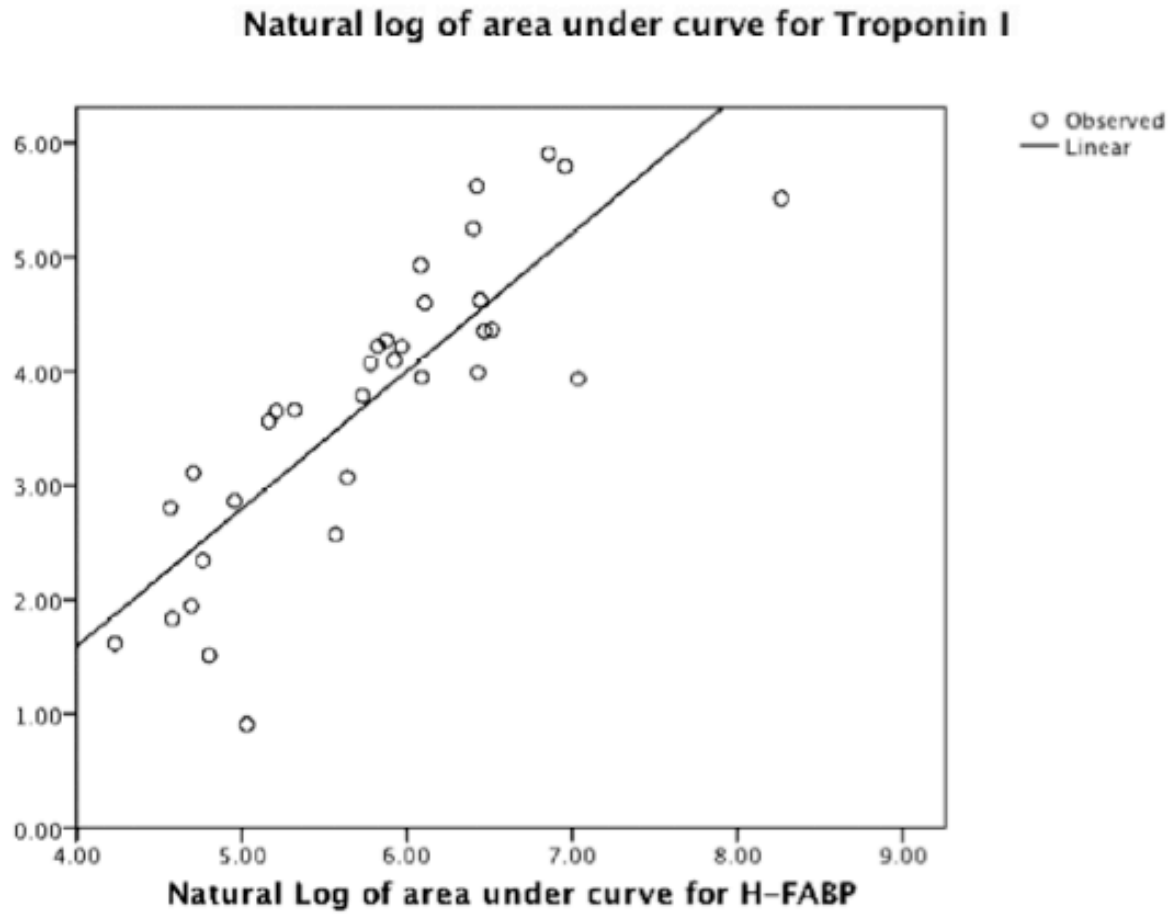
Table 4-7. H-FABP release

H-FABP		Pre-op	Postop	4 HRS	8 HRS	12 HRS
ONCAB	Median	4.21	45.40	24.26	18.39	21.86
	IQR	2.78	57.61	23.42	18.92	25.53
OPCAB	Median	3.46	9.60	9.41	11.13	14.76
	IQR	2.66	7.90	13.86	26.94	15.42

Heart-type Fatty Acid-Binding Protein (H-FABP) is a small cytoplasmic protein (15 KDa) released from cardiac myocytes following an ischemic episode. H-FABP levels were significantly higher in the ONCAB group immediately postoperatively ($p<0.001$). There was greater cumulative release of H-FABP as measured by the AUC in the ONCAB group ($p=0.007$). H-FABP levels also changed with time in each group. The time*procedure interaction was highly significant ($p=0.001$).

Coefficient of Determination cTnI & H-FABP

Figure 4-5. Coefficient of determination cTnI & H-FABP



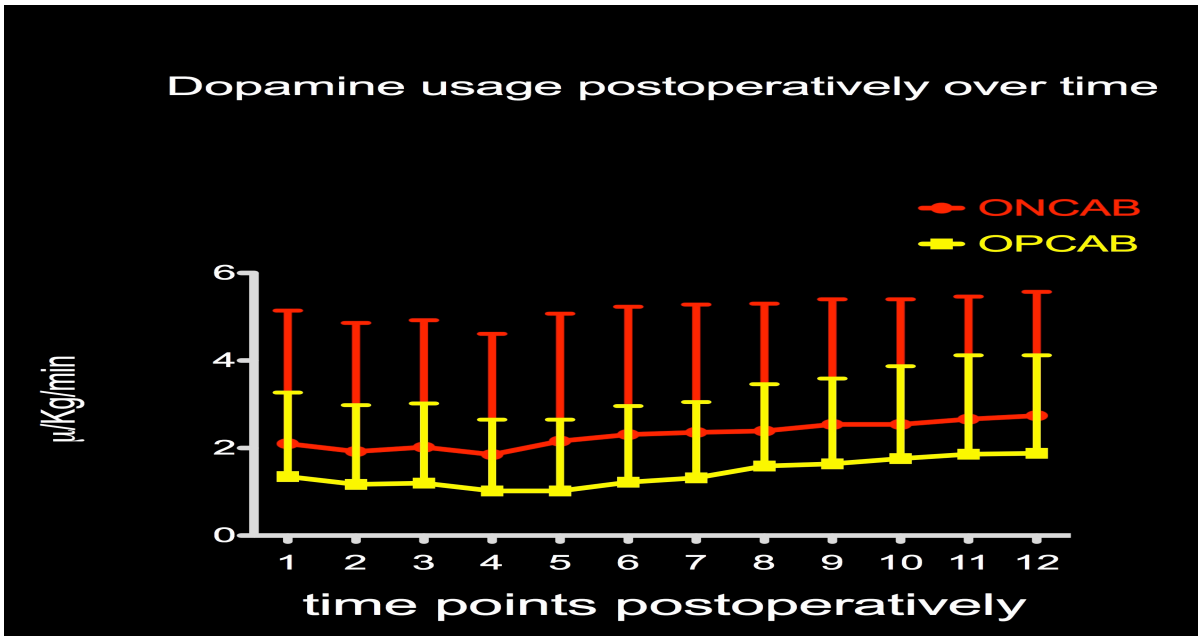
The coefficient of determination R^2 was 0.69. This strongly suggests that changes in cardiac troponin I was also mirrored in changes in H-FABP.

Inotropic Use

Table 4-8. Dopamine use

Dopamine Usage				
Time	ONCAB Mean	ONCAB Std. Deviation	OPCAB Mean	OPCAB Std. Deviation
Post op	2.10	3.04	1.35	1.92
Second Hour	1.92	2.94	1.17	1.81
Third Hour	2.02	2.90	1.20	1.82
Fourth Hour	1.85	2.76	1.02	1.63
Fifth Hour	2.16	2.91	1.02	1.63
Sixth Hour	2.31	2.92	1.22	1.74
Seventh Hour	2.36	2.92	1.32	1.73
Eighth Hour	2.39	2.91	1.59	1.87
Ninth Hour	2.54	2.86	1.64	1.95
Tenth Hour	2.54	2.86	1.76	2.11
Eleventh Hour	2.66	2.80	1.86	2.26
Twelfth Hour	2.74	2.83	1.88	2.24

Figure 4-6. Dopamine use



1=Postop, 2= 2nd Hour, 3=3rd Hour, 4=4th Hour, 5=5th Hour, 6=6th Hour, 7=7th Hour, H=8th Hour, 9=9th Hour, 10=10th Hour, 11=11th Hour, 12=12th Hour.

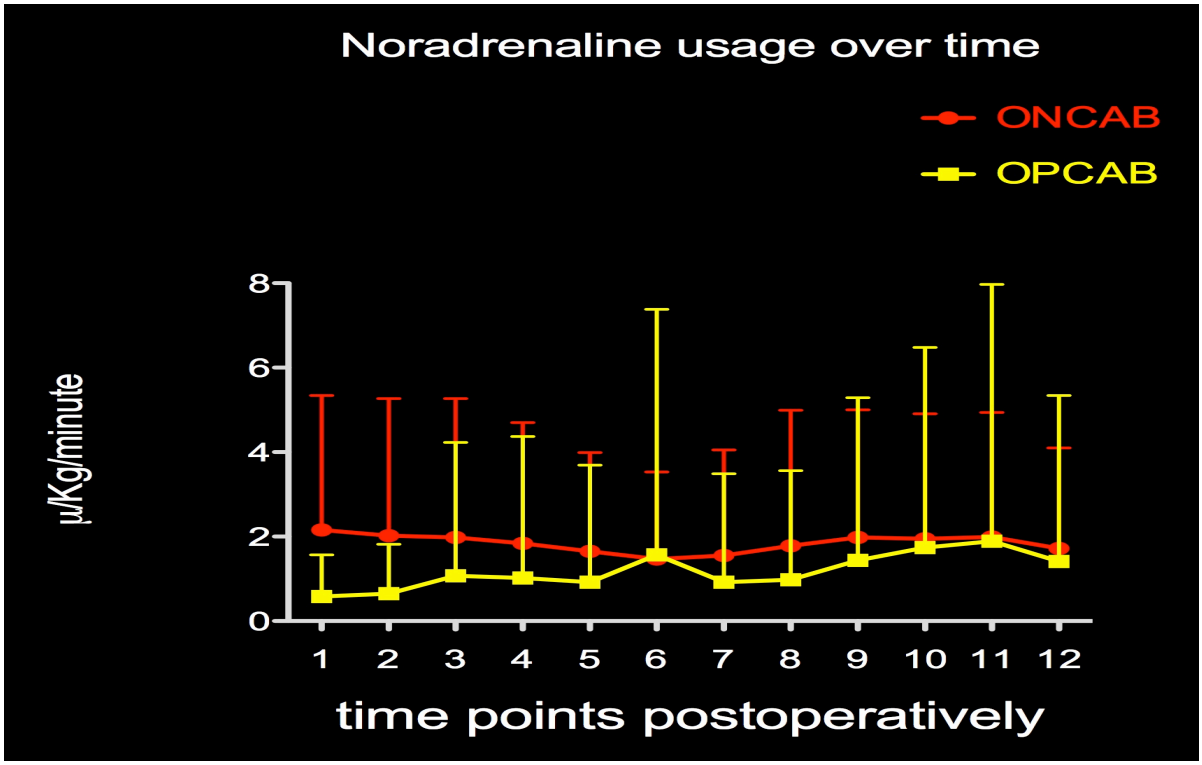
Dopamine is a member of the catecholamine family. It is a commonly used agent postoperatively in cardiac surgery for its inotropic, chronotropic and natriuretic properties. The ONCAB group needed more dopamine postoperatively than the OPCAB group

(Sign test, (p<0.001)

Table 4-9. Noradrenaline Use

Noradrenaline Usage				
Time	ONCAB MEAN	ONCAB Std. Deviation	OPCAB Mean	OPCAB Std. Deviation
Post op	2.16	3.18	0.58	0.99
Second Hour	2.02	3.25	0.65	1.17
Third Hour	1.98	3.29	1.07	3.16
Fourth Hour	1.84	2.86	1.02	3.35
Fifth Hour	1.65	2.34	0.92	2.77
Sixth Hour	1.47	2.06	1.57	5.81
Seventh Hour	1.55	2.50	0.92	2.57
Eighth Hour	1.78	3.21	0.98	2.58
Ninth Hour	1.98	3.02	1.44	3.85
Tenth Hour	1.95	2.96	1.74	4.74
Eleventh hour	1.99	2.95	1.89	6.08
Twelfth Hour	1.72	2.38	1.41	3.93

Figure 4-7. Noradrenaline use



1=Postop, 2= 2nd Hour, 3=3rd Hour, 4=4th Hour, 5=5th Hour, 6=6th Hour, 7=7th Hour, H=8th Hour, 9=9th Hour, 10=10th Hour, 11=11th Hour, 12=12th Hour

Noradrenaline is a catecholamine. It has a strong alpha-receptor stimulating function as well as a weak beta-receptor stimulating activity. When administered to patients, norepinephrine has a net effect of increasing blood pressure through peripheral vasoconstriction (a result of alpha stimulation) in addition to a slight positive inotropic effect (a result of weak beta stimulation). It is commonly used in patients post cardiac surgery. There was greater use of it in the ONCAB group (Sign test p=0.006).

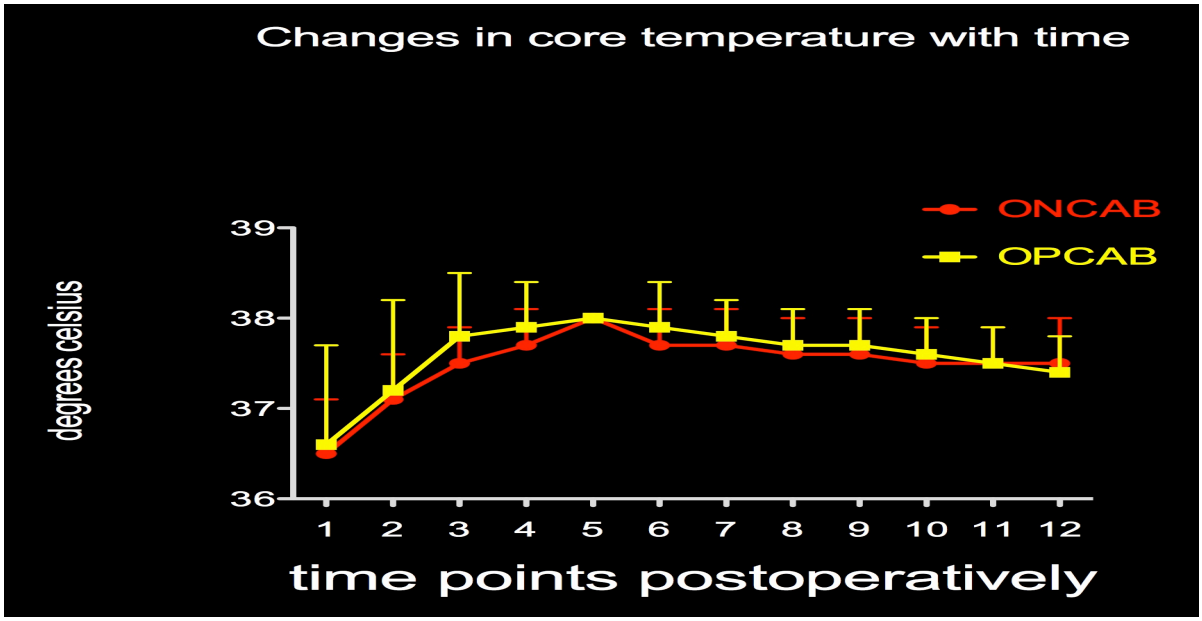
Core Temperature

Table 4-10. Core temperature

Time	Procedure			
	ONCAB		OPCAB	
	Mean	Standard Deviation	Mean	Standard Deviation
Post Op Temp	36.5	.6	36.6	1.1
Second Hour Temp	37.1	.5	37.2	1.0
Third Hour Temp	37.5	.4	37.8	.7
Fourth Hour Temp	37.7	.4	37.9	.5
Fifth Hour Temp	38.0	0	38.0	0
Sixth Hour Temp	37.7	.4	37.9	.5
Seventh Hour Temp	37.7	.4	37.8	.4
Eighth Hour Temp	37.6	.4	37.7	.4
Ninth Hour Temp	37.6	.4	37.7	.4
Tenth Hour Temp	37.5	.4	37.6	.4
Eleventh Hour Temp	37.5	.4	37.5	.4
Twelfth Hour Temp	37.5	.5	37.4	.4

1=Postop, 2= 2nd Hour, 3=3rd Hour, 4=4th Hour, 5=5th Hour, 6=6th Hour, 7=7th Hour, H=8th Hour, 9=9th Hour, 10=10th Hour, 11=11th Hour, 12=12th Hour

Figure 4-8. Core temperature



Core body temperature (Tc) is 36.8°C. Tc is essentially the temperature of the blood in the circulation, and the gold standard for Tc is taken to be the temperature of the blood from the pulmonary artery. The strong association between Tc and physiological homeostasis and disturbances makes Tc an important clinical and laboratory indicator of thermal strain in the body. Our results show that there was a significant change in temperature over time ($p<0.001$) in both groups. There was no difference between the groups ($p=0.49$).

ECG changes

Figure 4-9. Average ECG ST Segment Changes During Study Period

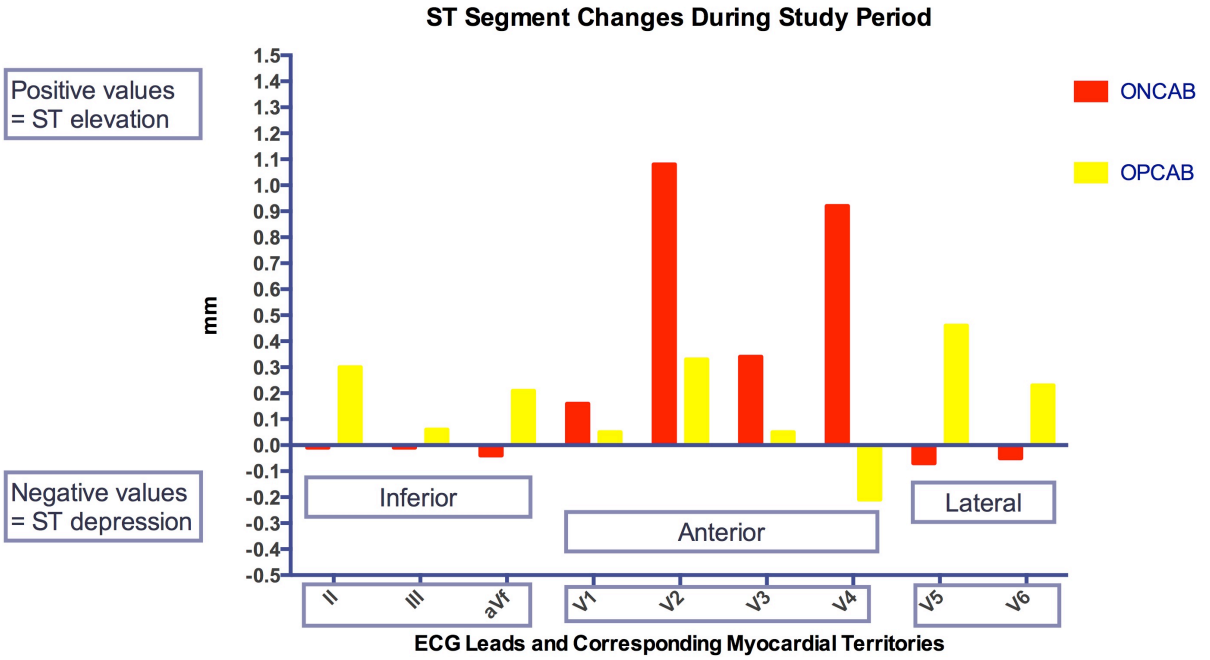


Table 4-11. ST Segment ECG Changes During Study Period

Myocardial Territory	Lead	Procedure	Mean	Std. Deviation	P VALUE
Inferior	AVF	ONCAB	-0.04	1.12	0.38
		OPCAB	0.21	0.41	
	Lead II	ONCAB	-0.01	1.06	0.25
		OPCAB	0.30	0.54	
	Lead III	ONCAB	-0.01	1.00	0.70
		OPCAB	0.06	0.29	
Anterior	V1	ONCAB	0.16	1.53	0.81
		OPCAB	0.05	0.48	
	V2	ONCAB	1.08	1.93	0.28
		OPCAB	0.33	1.07	
	V3	ONCAB	0.34	0.89	0.41
		OPCAB	0.05	0.44	
	V4	ONCAB	0.92	2.76	0.18
		OPCAB	-0.21	0.95	
Lateral	V5	ONCAB	-0.07	0.52	0.01
		OPCAB	0.46	0.41	
	V6	ONCAB	-0.05	0.56	0.22
		OPCAB	0.23	0.54	

A computer logged the ST segment ECG changes in each lead over the postoperative period for each patient. The average change from baseline was calculated for each patient. From this was derived the group average for each lead. The means of the two groups were compared by means of t-test. The data is presented in a similar manner to the way one would assess an ECG with positive values implying ST segment elevation and negative values implying ST segment depression. The data has been tabulated and graphically represented by grouping the ECG leads according to the corresponding myocardial territory

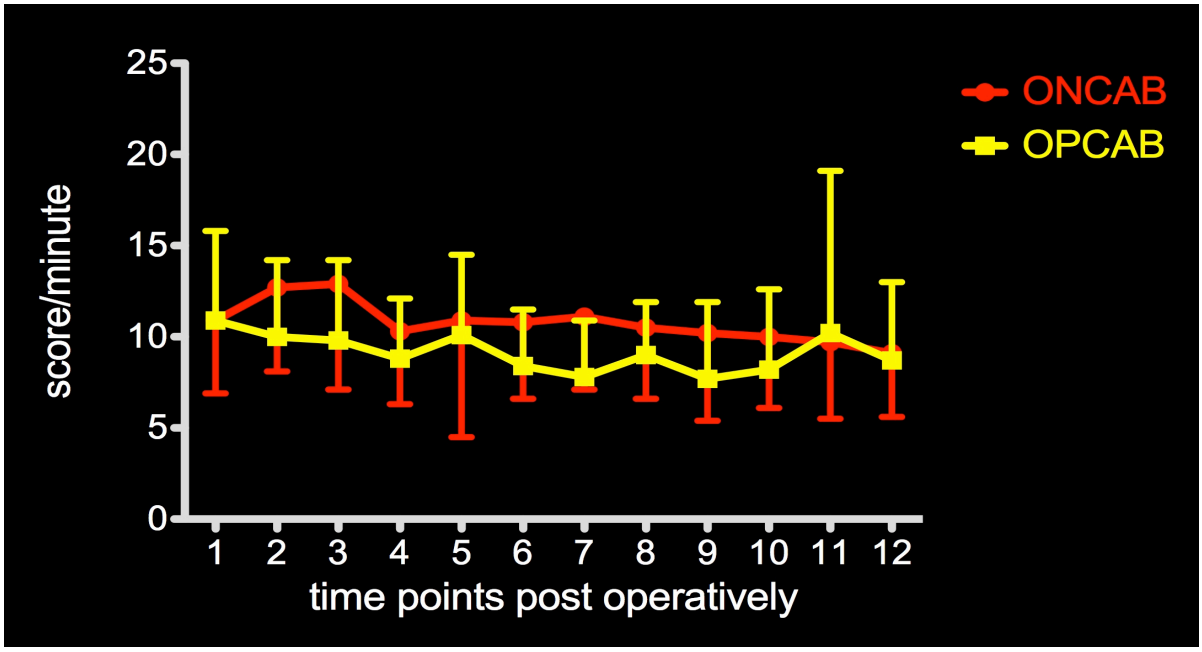
Pressure Adjusted Rate (PAR)

Table 4-12. Pressure Adjusted Rate

	Procedure			
	ONCAB		OPCAB	
Time	Mean	Standard Deviation	Mean	Standard Deviation
Post op	10.9	4	10.9	4.9
2nd hour	12.7	4.6	10	4.2
3rd hour	12.9	5.8	9.8	4.4
4th hour	10.3	4	8.8	3.3
5th hour	10.9	6.4	10.1	4.4
6th hour	10.8	4.2	8.4	3.1
7th hour	11.1	4	7.8	3.1
8th hour	10.5	3.9	9	2.9
9th hour	10.2	4.8	7.7	4.2
10th hour	10	3.9	8.2	4.4
11th hour	9.7	4.2	10.2	8.9
12th hour	9.1	3.5	8.7	4.3

1=Postop, 2= 2nd Hour, 3=3rd Hour, 4=4th Hour, 5=5th Hour, 6=6th Hour, 7=7th Hour, H=8th Hour, 9=9th Hour, 10=10th Hour, 11=11th Hour, 12=12th Hour

Figure 4-10 Changes in Pressure Adjusted Rate over time



The pressure-adjusted heart rate (PAR) is calculated as the product of heart rate (HR) multiplied by the ratio of the central venous pressure (CVP) to the mean arterial pressure (MAP). The score is then graded on a scale from 0 to 4 score points. Zero representing normal or minimally deranged function; four correlating with a markedly deranged function. There was no difference in graded scores between the two groups (p=0.07)

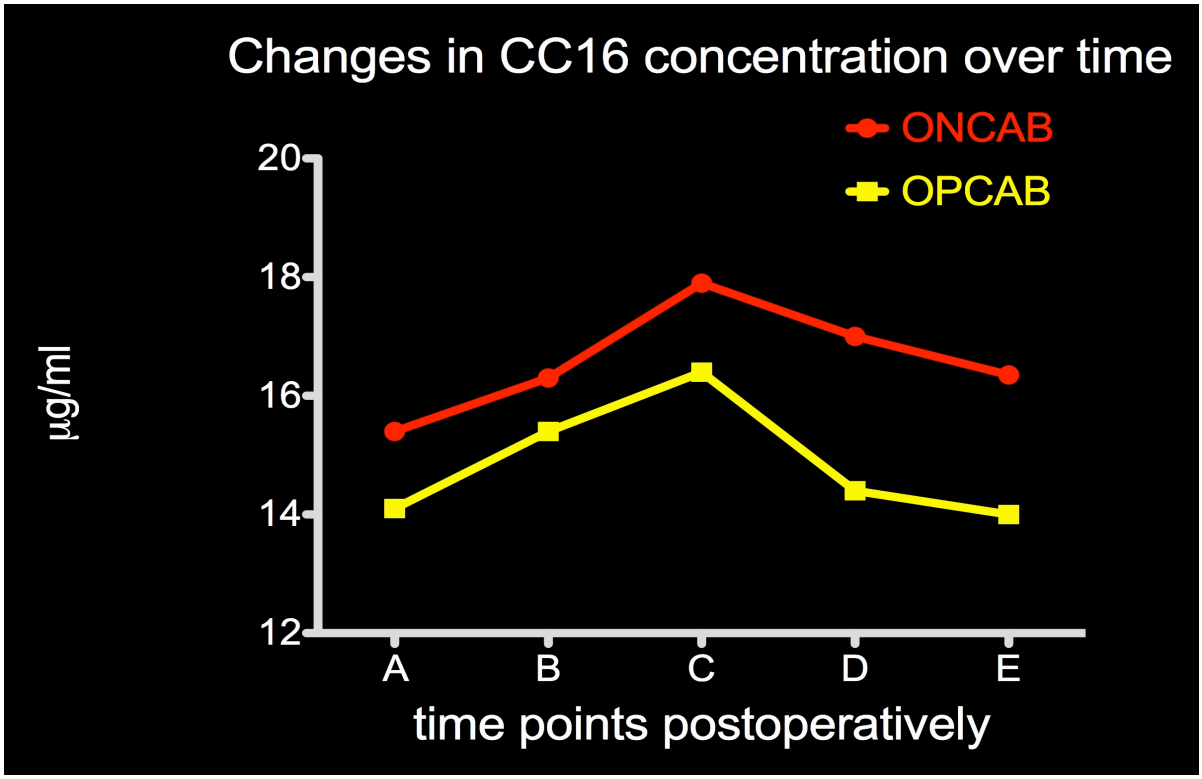
Pulmonary Injury

CC16 Release

Table 4-13. CC16 Release

CC16	Pre-op	Postop	4 hours	8 hours	12 hours
ONCAB	15.4	16.3	17.9	17.0	16.35
IQR	8.0	14.8	9.8	10.8	12.4
OPCAB	14.1	15.4	16.4	14.4	14.00
IQR	12.7	15.0	11.5	16.9	7.8

Figure 4-11. Changes In CC16 Concentration Over Time



A = Pre-op, B = Postop, C = 4 hours, D = 8 hours, E = 12 hours

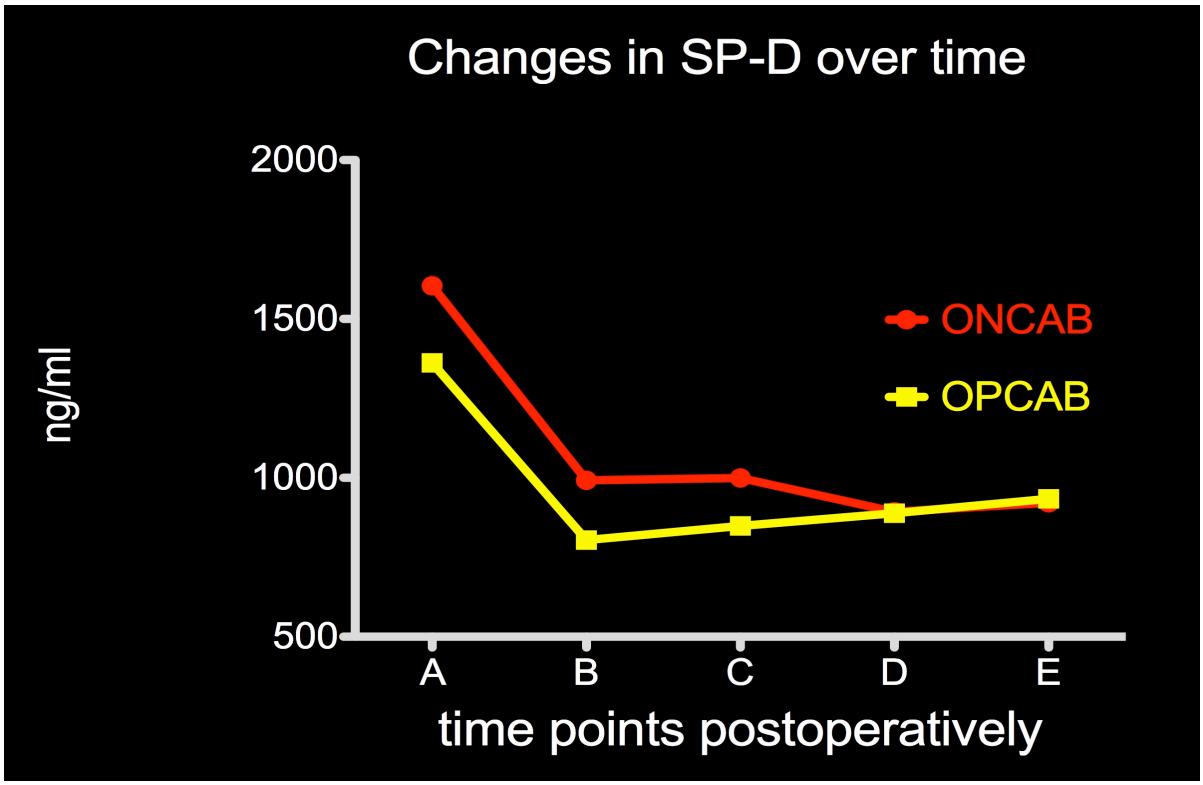
Clara cell protein is a low-molecular-weight protein (LMWP) of 16 KDa (CC16), mainly secreted by bronchiolar Clara cells Statistical analysis showed there was no statistically significant change in CC16 levels over time (p=0.08). There was no significant time procedure interaction (p=0.35). There was no significant procedure interaction (p=0.97). There was no significant difference in the AUC between groups p=0.874.

Surfactant Protein – D Release

Table 4-14. Surfactant Protein-D release

SP-D	Pre-op	Postop	4 hours	8 hours	12 hours
ONCAB	1604.5	992.00	999.50	893.00	921.50
IQR	1330.5	992.75	1417.25	575.00	1375.25
OPCAB	1362.00	804.00	849.00	889.00	934.00
IQR	755.00	506.5	707.5	575.00	613.50

Figure 4-12. Changes In SP-D Over Time



A = Pre-op, B = Postop, C = 4 hours, D = 8 hours, E = 12 hours

SP-D is a member of the collectin family of innate defense proteins that binds inflammatory molecules. SP-D concentrations changed with time (p=0.001) but not in a linear fashion. The change was dependent on the preoperative value (p=0.001). There was no time procedure interaction (p=0.11) or procedure interaction (p=0.91). Cumulative release as assessed by the AUC was similar between the two groups p=0.30.

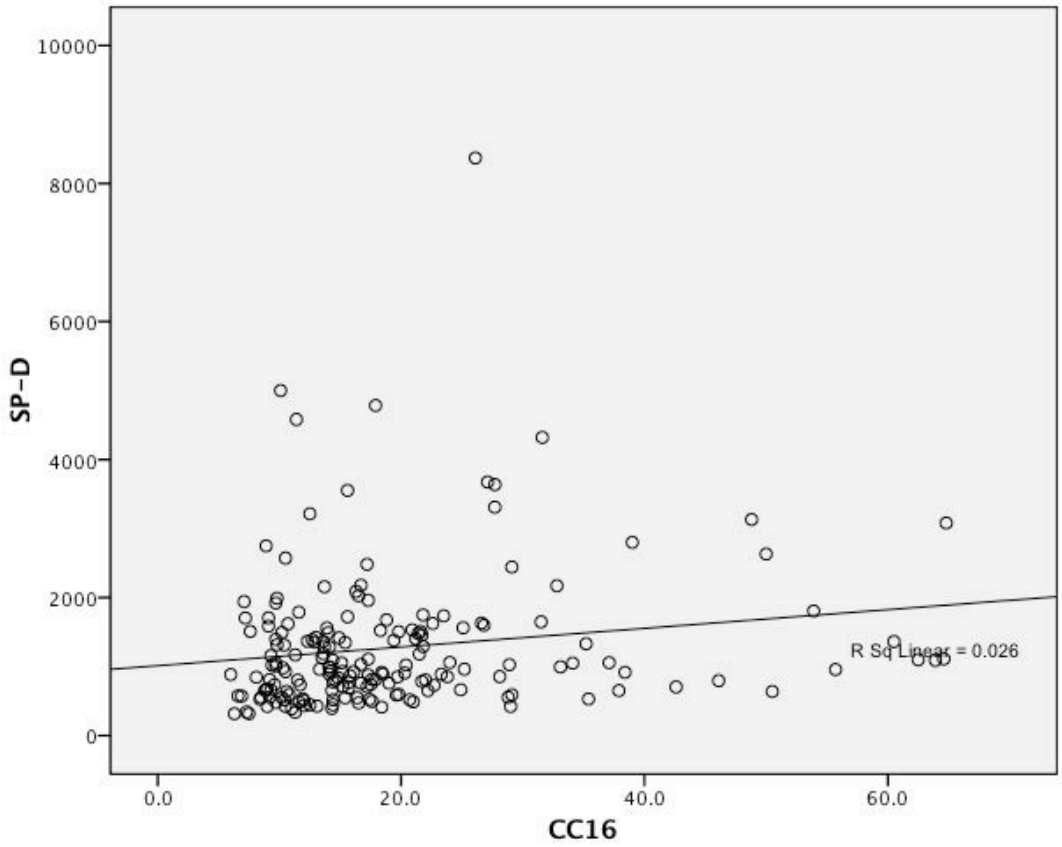
Correlation between SP-D and CC16

Table 4-15. Correlation between SP-D and CC16

Spearman's rho			SP-D
	CC16	Correlation Coefficient	.211
		Sig. (2-tailed)	.004

Coefficient of Determination CC16 & SP-D

Figure 4-13. Coefficient of determination CC16 & SP-D



r-squared linear:	0.002636
P-value:	0.4692

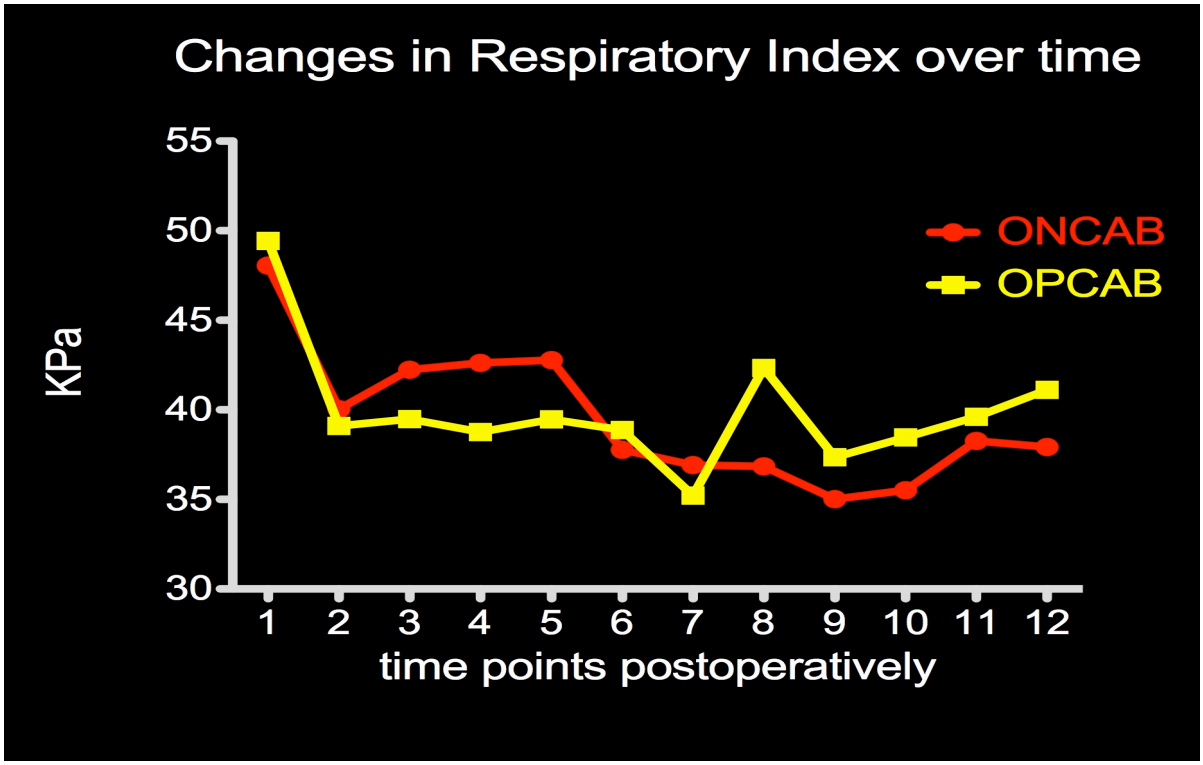
There was no statistically significant correlation between changes in SP-D and CC-16.

Respiratory Index (RI) PaO_2/FiO_2 Ratio

Table 4-16. Respiratory Index

Time	ONCAB	OPCAB
Postop	48.06	49.43
1st hour	40.72	41.38
2nd hour	40.04	39.1
3rd hour	42.24	39.48
4th hour	42.62	38.76
5th hour	42.77	39.47
6th hour	37.77	38.88
7th hour	36.92	35.22
8th hour	36.84	42.33
9th hour	35.02	37.36
10th hour	35.51	38.46
11th hour	38.27	39.61
12th hour	37.92	41.11

Figure 4-14. Change in Respiratory Index over time



The respiratory index is defined as the ratio of the partial pressure of arterial O2 to the fraction of inspired O2. There were no significant differences between the two groups (p=0.58).

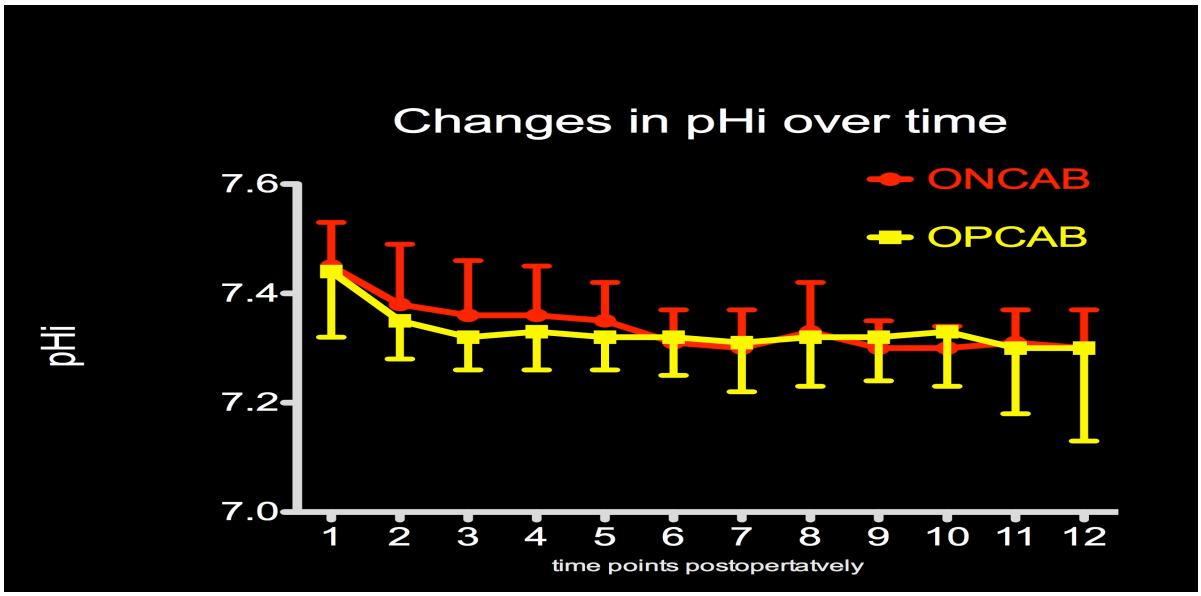
Table 4-17. Extubation times

Extubation times	ONCAB	OPCAB
Median time to extubation in hours	16.75	13.00
IQR	15	13.75

There were no significant differences in extubation times between the two groups (p=0.97).

Gastric tonometry

Figure 4-15. Changes in pHi over time



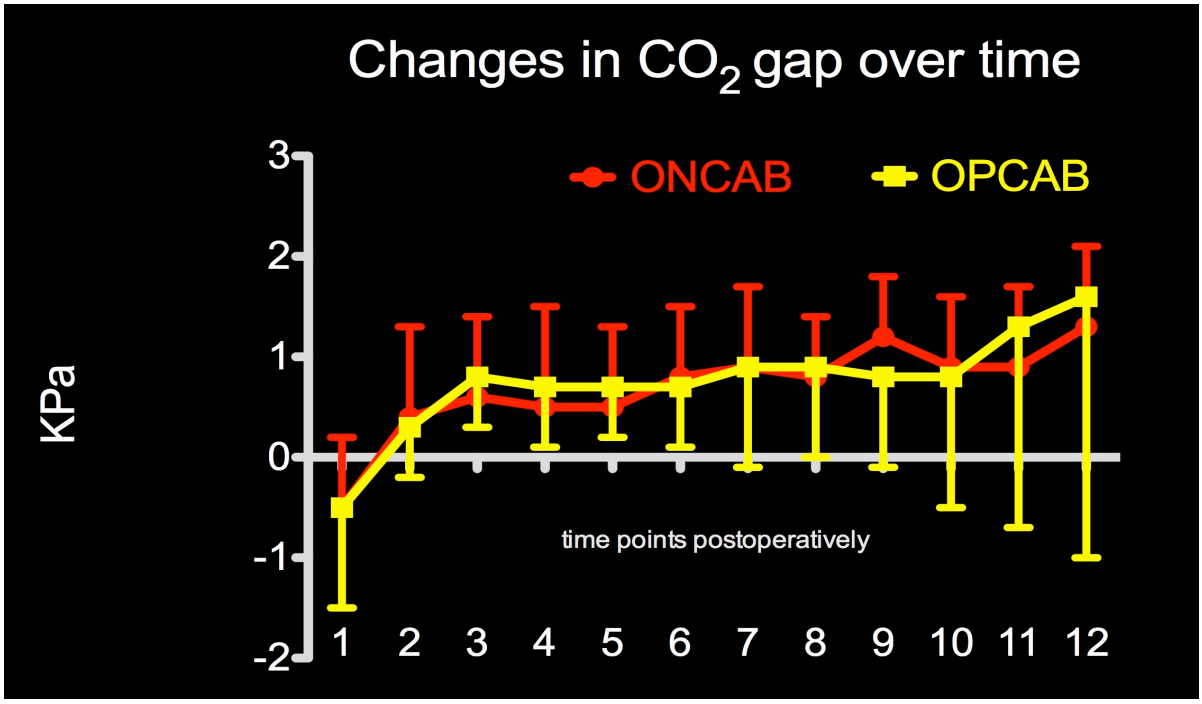
1=Postop, 2= 2nd Hour, 3=3rd Hour, 4=4th Hour, 5=5th Hour, 6=6th Hour, 7=7th Hour, H=8th Hour, 9=9th Hour, 10=10th Hour, 11=11th Hour, 12=12th Hour

Table 4-18. pHi

	Procedure			
	ONCAB		OPCAB	
Time	Mean	Standard Deviation	Mean	Standard Deviation
Postop	7.45	0.08	7.44	0.12
2nd hour	7.38	0.11	7.35	0.07
3rd hour	7.36	0.10	7.32	0.06
4th hour	7.36	0.09	7.33	0.07
5th hour	7.35	0.07	7.32	0.06
6th hour	7.31	0.06	7.32	0.07
7th hour	7.30	0.07	7.31	0.09
8th hour	7.33	0.09	7.32	0.09
9th hour	7.30	0.05	7.32	0.08
10th hour	7.30	0.04	7.33	0.10
11th hour	7.31	0.06	7.30	0.12
12th hour	7.30	0.07	7.30	0.17

There was a tendency towards increasing gastric mucosal acidosis in both groups over the study period. However there were no statistically significant differences between the two groups (ANOVA p=0.69)

Figure 4-16. Changes In Carbon Dioxide Gap Over Time



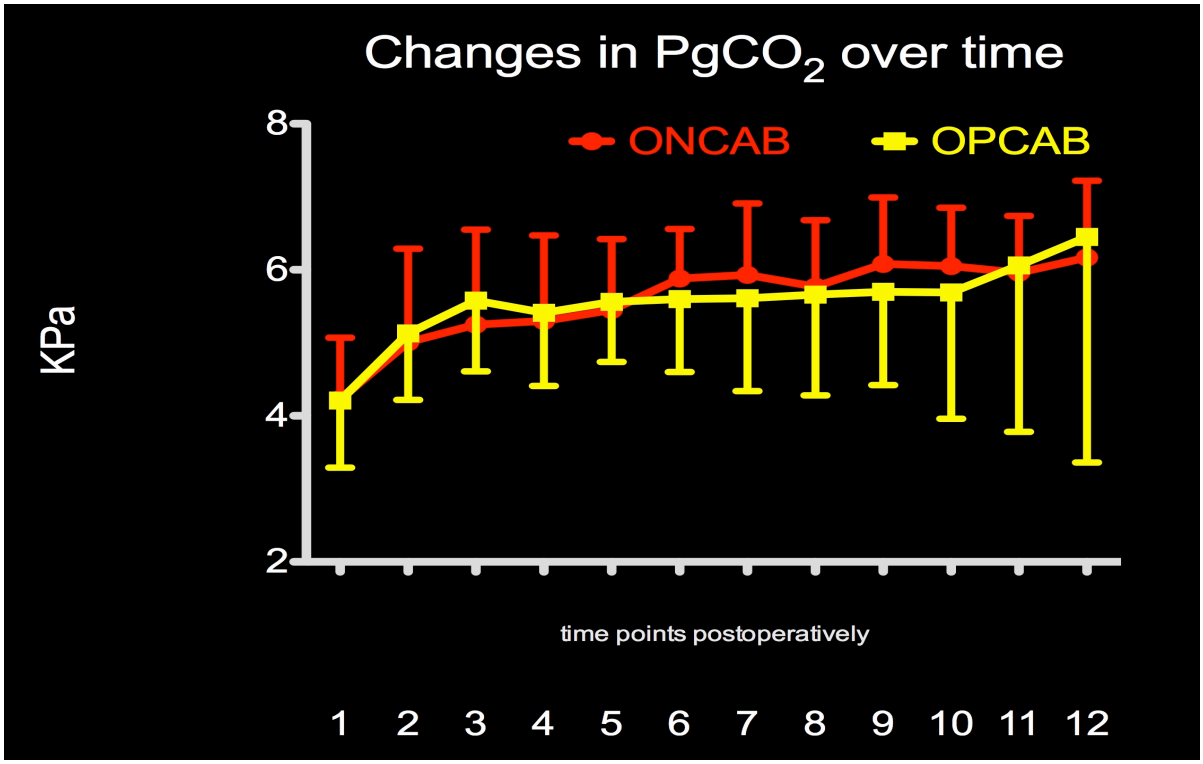
1=POSTOP, 2= 2ND HOUR, 3=3RD HOUR, 4=4TH HOUR, 5=5TH HOUR, 6=6TH HOUR, 7=7TH HOUR, H=8TH HOUR, 9=9TH HOUR, 10=10TH HOUR, 11=11TH HOUR, 12=12TH HOUR

Table 4-19. Carbon Dioxide Gap

	Procedure			
	ONCAB		OPCAB	
Time	Mean (KPa)	Standard Deviation	Mean (KPa)	Standard Deviation
Postop	-0.50	0.70	-0.50	1.00
2nd hour	0.40	0.90	0.30	0.50
3rd hour	0.60	0.80	0.80	0.50
4th hour	0.50	1.00	0.70	0.60
5th hour	0.50	0.80	0.70	0.50
6th hour	0.80	0.70	0.70	0.60
7th hour	0.90	0.80	0.90	1.00
8th hour	0.80	0.60	0.90	0.90
9th hour	1.20	0.60	0.80	0.90
10th hour	0.90	0.70	0.80	1.30
11th hour	0.90	0.80	1.30	2.00
12th hour	1.30	0.80	1.60	2.60

The CO_2 gap showed a significant increase over time (p=<0.001). This was similar in both groups over the study period. There was no significant time procedure interaction (p=0.80).

Figure 4-17. Changes in $PgCO_2$ over time



1=POSTOP, 2= 2ND HOUR, 3=3RD HOUR, 4=4TH HOUR, 5=5TH HOUR, 6=6TH HOUR, 7=7TH HOUR, H=8TH HOUR, 9=9TH HOUR, 10=10TH HOUR, 11=11TH HOUR, 12=12TH HOUR

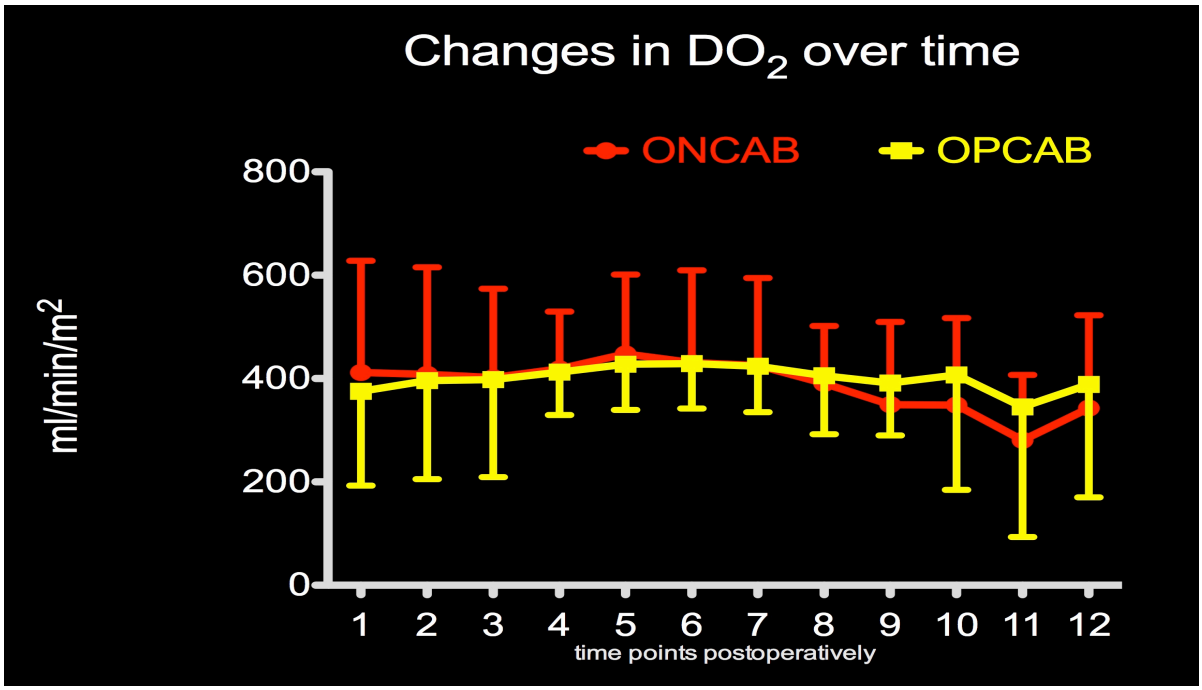
Table 4-20. $PgCO_2$

Time		Procedure			
		ONCAB		OPCAB	
		Mean	Standard Deviation	Mean	Standard Deviation
Postop	$PgCO_2$	4.23	0.84	4.21	0.92
2nd hour	PgCO2	5.01	1.28	5.13	0.91
3rd hour	PgCO2	5.25	1.3	5.58	0.97
4th hour	PgCO2	5.3	1.17	5.41	1
5th hour	PgCO2	5.45	0.97	5.56	0.82
6th hour	PgCO2	5.88	0.68	5.6	1
7th hour	PgCO2	5.93	0.98	5.61	1.27
8th hour	PgCO2	5.77	0.91	5.66	1.38
9th hour	PgCO2	6.08	0.91	5.7	1.28
10th hour	PgCO2	6.05	0.8	5.69	1.73
11th hour	PgCO2	5.96	0.78	6.06	2.28
12th hour	PgCO2	6.17	1.05	6.45	3.09

Our results showed that there was a rise in gastric intraluminal carbon dioxide in both groups over the study period. However there were no significant differences between the two groups (ANOVA p=0.58)

Oxygen Utilization

Figure 4-18. Changes In DO_2 Over Time



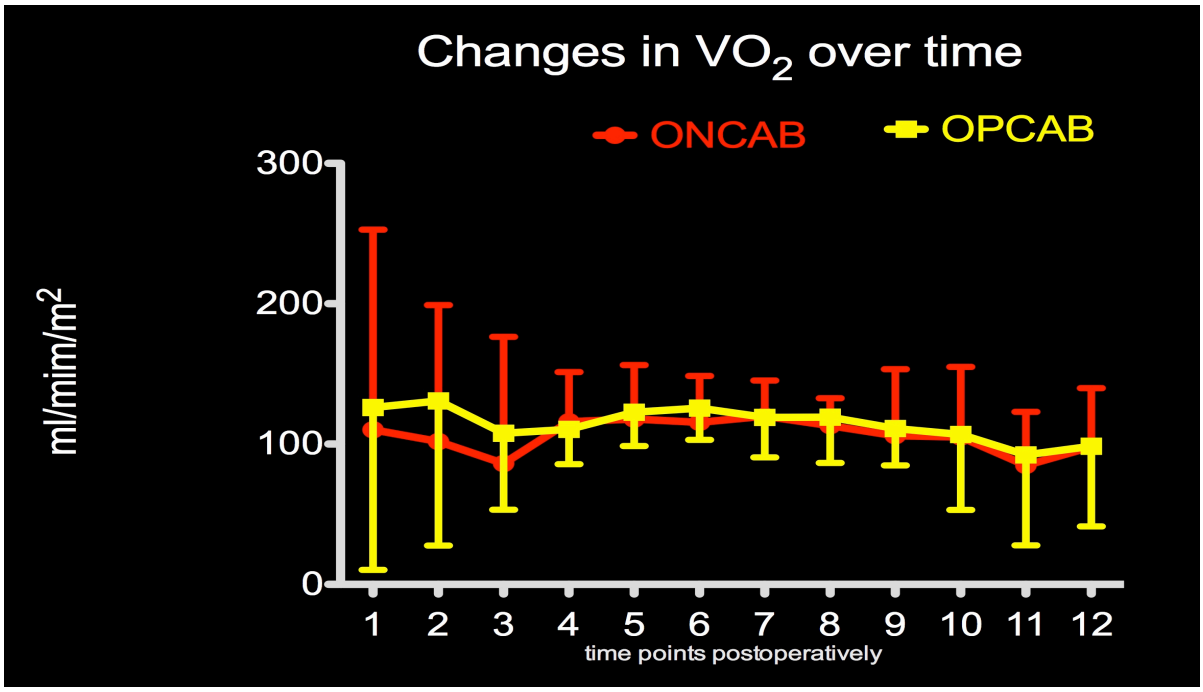
1=Postop, 2= 2nd Hour, 3=3rd Hour, 4=4th Hour, 5=5th Hour, 6=6th Hour, 7=7th Hour, H=8th Hour, 9=9th Hour, 10=10th Hour, 11=11th Hour, 12=12th Hour

Table 4-21. DO_2

	Procedure			
	ONCAB		OPCAB	
Time	Mean	Standard Deviation	Mean	Standard Deviation
Postop	411.70	216.33	375.39	182.53
2nd hour	408.10	207.44	396.24	190.83
3rd hour	401.91	171.97	397.95	188.72
4th hour	418.78	110.86	412.48	83.11
5th hour	447.73	153.57	427.88	88.60
6th hour	431.11	178.33	428.83	86.97
7th hour	425.42	169.18	423.88	88.70
8th hour	390.62	111.02	405.59	113.29
9th hour	349.53	160.09	391.57	101.80
10th hour	348.72	168.23	407.22	222.43
11th hour	280.73	126.46	345.04	251.53
12th hour	342.71	179.92	388.55	218.41

The delivery of oxygen to the tissues is the key to cellular metabolism. Our results show that both techniques provided adequate oxygenation, ANOVA P=0.683

Figure 4-19. Changes In Whole Body Oxygen Consumption, VO_2 Over Time



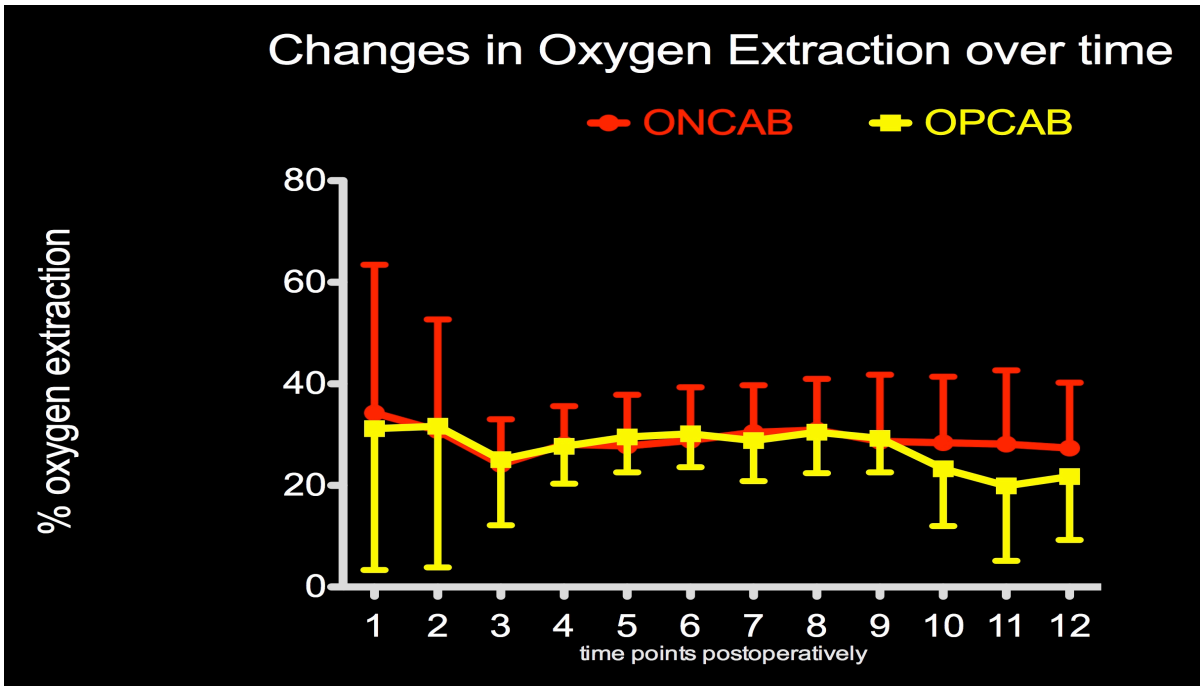
1=Postop, 2= 2nd Hour, 3=3rd Hour, 4=4th Hour, 5=5th Hour, 6=6th Hour, 7=7th Hour, H=8th Hour, 9=9th Hour, 10=10th Hour, 11=11th Hour, 12=12th Hour

Table 4-22. VO_2

	Procedure			
	ONCAB		OPCAB	
Time	Mean	Standard Deviation	Mean	Standard Deviation
Postop	110.20	142.55	126.09	115.69
2nd hour	101.90	97.18	130.71	102.97
3rd hour	86.12	90.26	107.67	54.41
4th hour	115.98	35.32	110.51	24.82
5th hour	117.80	38.53	122.69	24.12
6th hour	115.49	33.06	125.66	22.59
7th hour	119.92	25.38	119.00	28.53
8th hour	113.08	19.65	119.11	32.50
9th hour	106.02	47.39	111.05	26.22
10th hour	105.11	49.85	106.89	53.87
11th hour	84.73	38.28	92.23	64.36
12th hour	97.96	41.84	98.43	57.11

There was a general increase in whole body oxygen consumption postoperatively with a gradual decline to base line over the study period. There were no statistically significant differences in whole body oxygen consumption between the two groups, ANOVA P=0.304

Figure 4-20. Oxygen Extraction Over Time



1=Postop, 2= 2nd Hour, 3=3rd Hour, 4=4th Hour, 5=5th Hour, 6=6th Hour, 7=7th Hour, H=8th Hour, 9=9th Hour, 10=10th Hour, 11=11th Hour, 12=12th Hour

Table 4-23. Oxygen Extraction

	Procedure			
	ONCAB		OPCAB	
Time	Mean	Standard Deviation	Mean	Standard Deviation
Postop	34.30	29.17	31.20	27.84
2nd hour	30.79	21.91	31.67	27.83
3rd hour	24.14	8.90	25.08	12.91
4th hour	28.08	7.54	27.72	7.38
5th hour	27.79	10.04	29.54	6.96
6th hour	28.87	10.45	30.16	6.56
7th hour	30.46	9.25	28.83	7.96
8th hour	30.93	10.05	30.48	8.08
9th hour	28.70	13.10	29.27	6.68
10th hour	28.41	13.01	23.27	11.27
11th hour	28.15	14.51	19.90	14.76
12th hour	27.34	12.91	21.74	12.49

The oxygen extraction ratio of a tissue describes the interplay between oxygen delivery and consumption and, as such, directly reflects the viability and activity of any organ. In order to compare in a meaningful manner the organ dysfunction between two procedures one needs to ensure that there is no undue disparity in oxygen delivery between the two techniques that may account for the release of biomarkers of injury. In this study there were no statistically significant differences in oxygen extraction ratio between the two groups, ANOVA P=0.491

Table 4-24 Correlations for VO2

Correlations for VO_2				
	pHi	$PgCO_2$	Cardiac index	CO_2 gap
Spearman's rho Correlation coefficient	0.117	-0.137	0.450	-0.130
Sig. (2-tailed)	0.069	0.032	<0.001	0.042

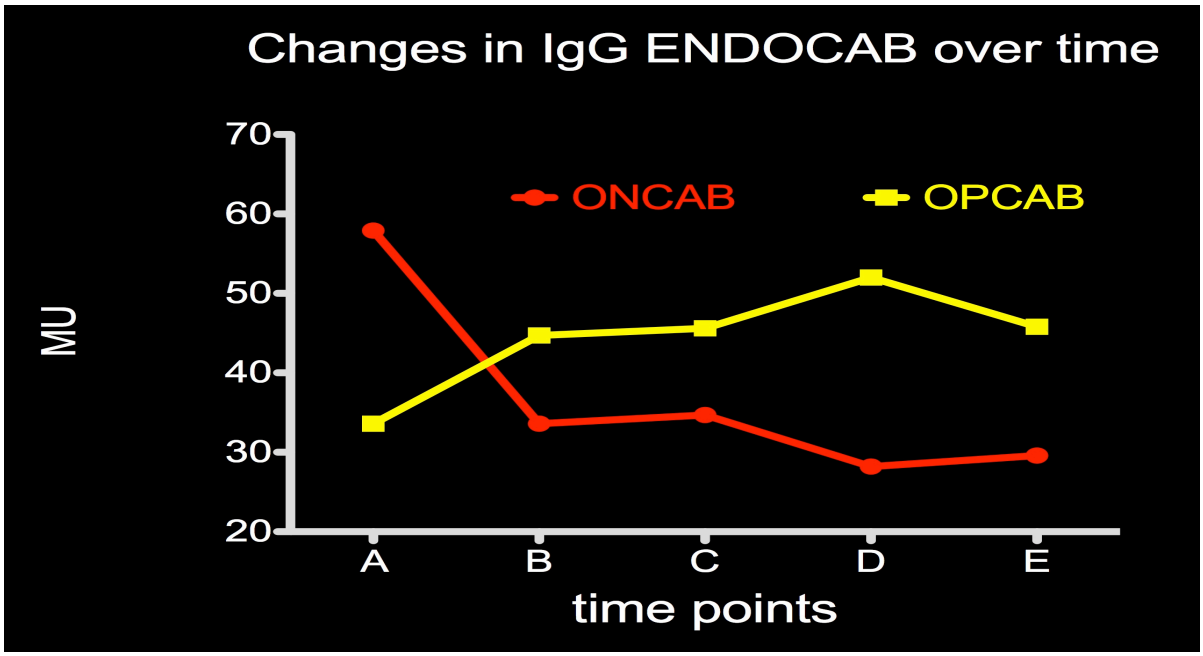
Table 4-25. Correlations for Cardiac Index

Correlations for Cardiac Index			
	CO_2gap	pHi	$PgCO_2$
Spearman's rho Correlation coefficient cardiac index	-0.169	0.102	-0.039
Sig. (2-tailed)	0.01	0.122	0.549

Biomarkers of Gastrointestinal Injury

Release of ENDOCAB

Figure 4-21. Changes In IgG ENDOCAB Over Time



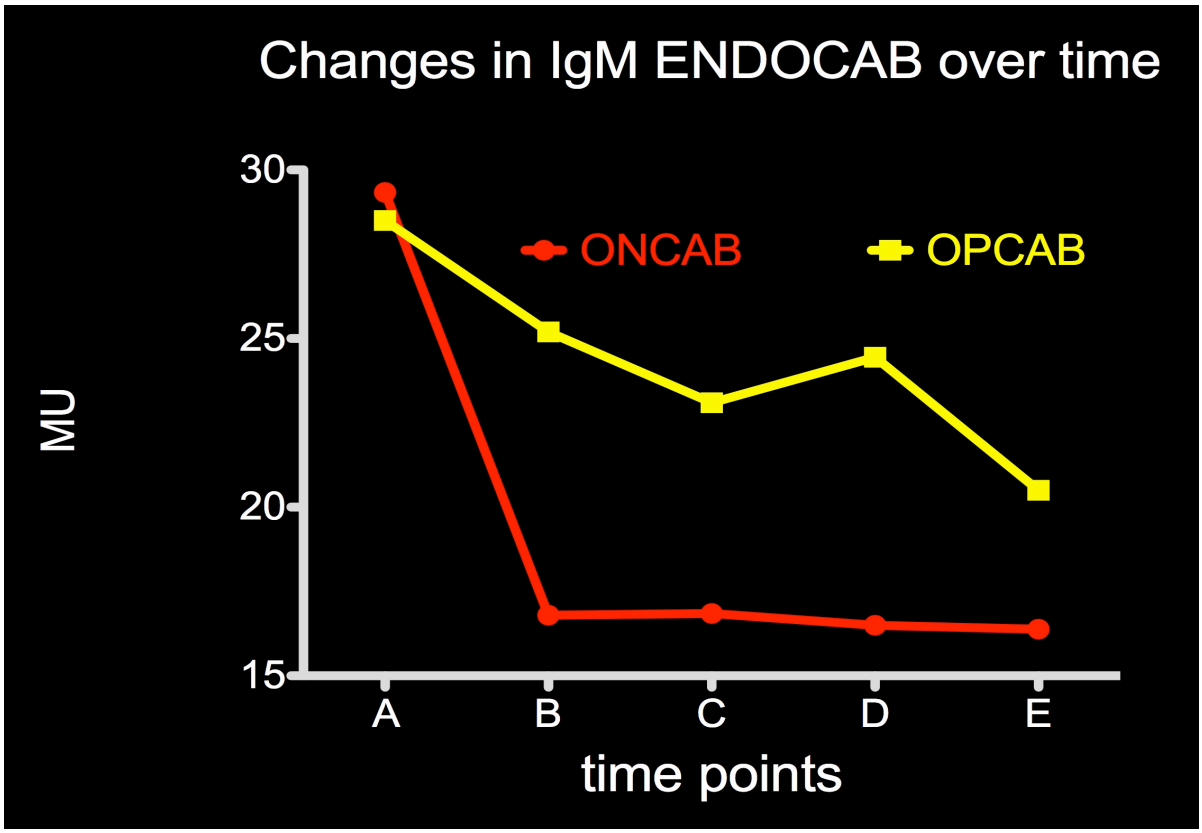
A=Pre-op, B=Postop, C=4 Hours, D=8 Hours, E=12 Hours

Several studies show a consistent drop in postoperative levels of circulating anti-endotoxin core antibodies from the preoperative value. This drop has been interpreted as consumption of antibodies to endotoxin by systemic release of endotoxin. Furthermore it has ben theorized that if the patients pre-operative EndoCab level is low, even moderately low, patients may not be able to cope with the efflux of endotoxin, which may have mild to severe clinical consequences. These results are difficult to interpret. In the ONCAB group there is a decline from baseline values. However the OPCAB group show no decline. In fact there seems to be a rise in postoperative levels compared to the baseline. However detailed statistical analysis revealed that these changes were not statistically significant in this small pilot study. For IgG EndoCAB there was no time (p=0.84) or time procedure interaction (p=0.59).

Table 4-26. IgG ENDOCAB Release

IgG EndoCAB (Median Units)	Pre-op	Postop	4 hours	8 hours	12 hours
ONCAB	57.90	33.60	34.70	28.20	29.60
Inter Quartile Range	81.00	56.00	66.60	65.00	50.40
OPCAB	33.60	44.70	45.60	52.00	45.80
Inter Quartile Range	68.00	46.00	35.80	36.30	48.80

Figure 4-22. Changes In IgM ENDOCAB Over Time



A=Pre-op, B=Postop, C=4 Hours, D=8 Hours, E=12 Hours

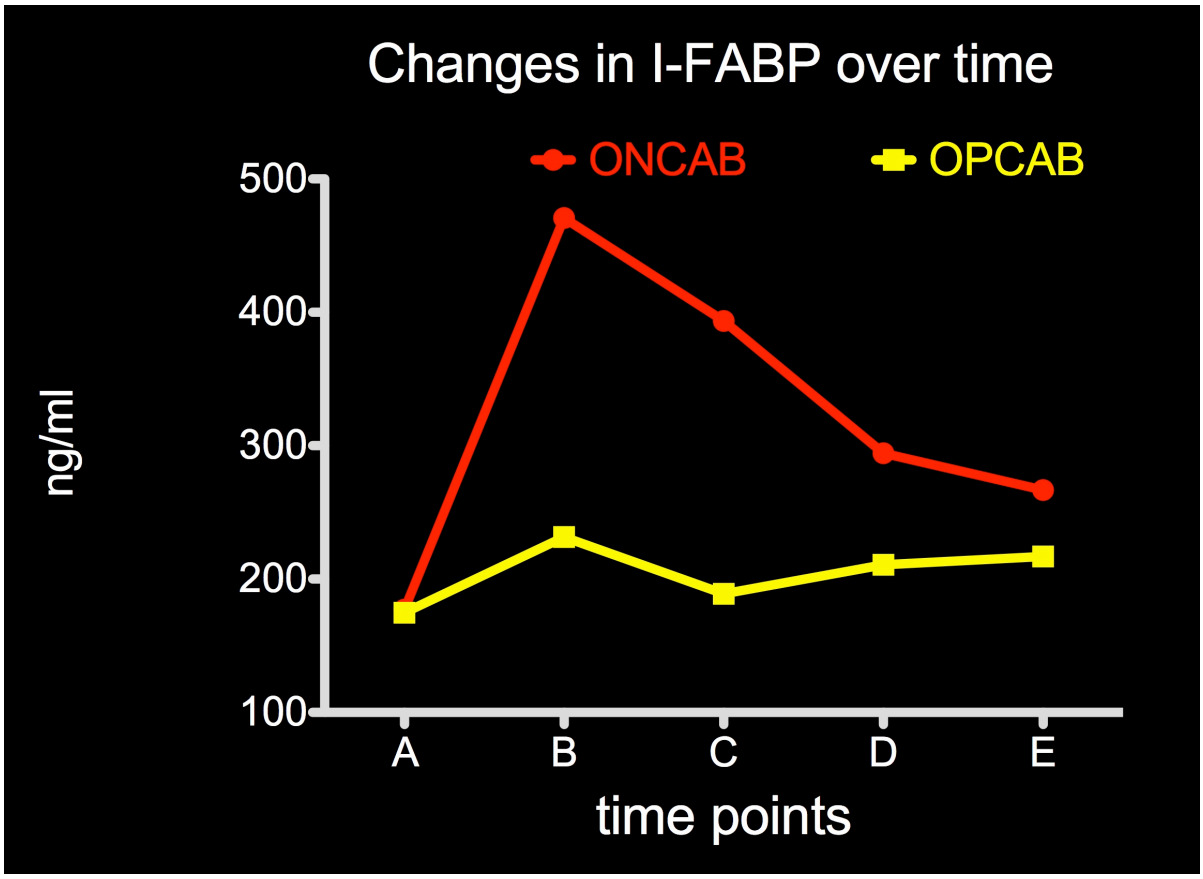
Antibodies of the IgM class are the first to appear in the blood stream following the initial exposure to antigen. In both groups there was a general decline from baseline over the study period. This decline was particularly prominent immediately postoperatively in the ONCAB group and then quickly plateaued. There were no statistically significant differences in this small pilot study between the two groups, time procedure interaction (p=0.81). There was also no statistically significant cumulative release as assessed by the area under the curve AUC p=0.19.

Table 4-27. IgM ENDOCAB Release

IgM EndoCAB (Median Units)	Pre-op	Postop	4 hours	8 hours	12 hours
ONCAB	29.33	16.80	16.85	16.50	16.38
Inter Quartile Range	24.70	9.30	14.00	16.60	8.30
OPCAB	28.50	25.20	23.10	24.45	20.50
Inter Quartile Range	42.70	25.80	20.30	21.20	12.70

Release of I-FABP

Figure 4-23. Changes In I-FABP Over Time



A=Pre-op, B=Postop, C=4 Hours, D=8 Hours, E=12 Hours

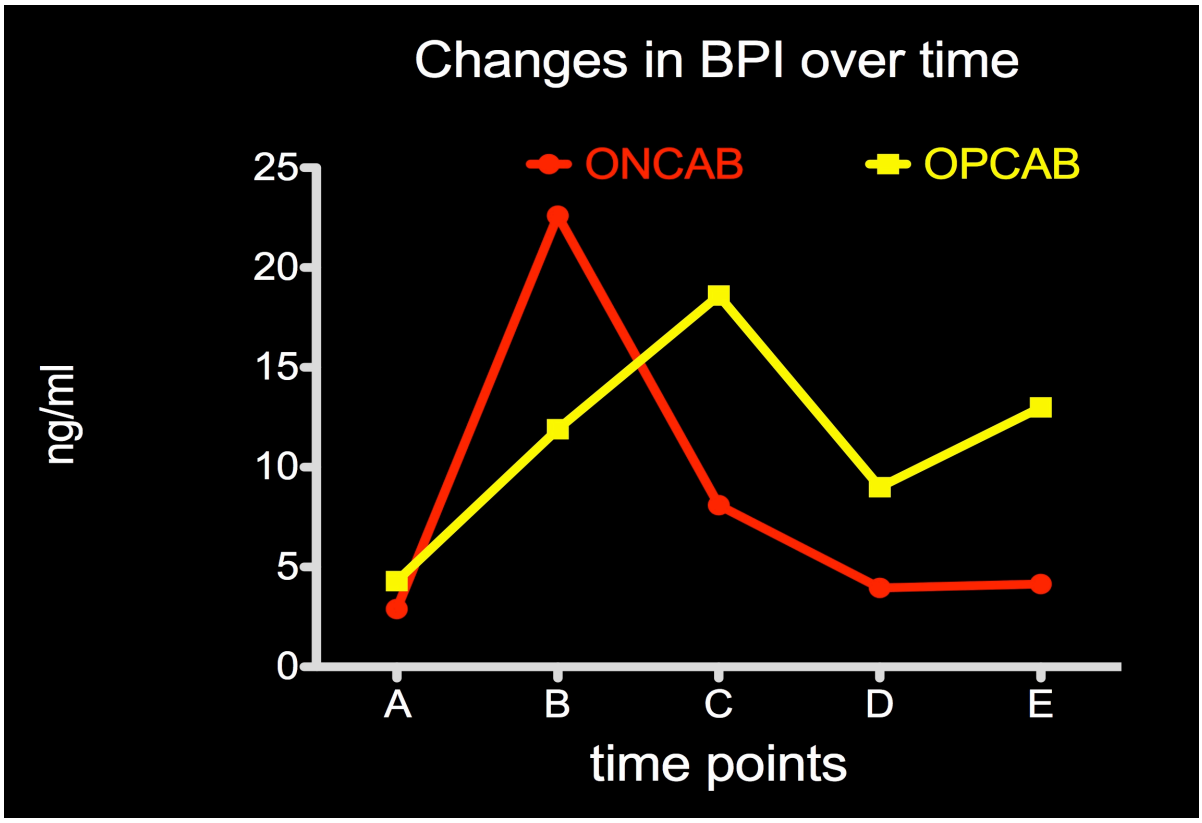
Table 4-28. I-FABP Release

I-FABP	Pre-op	Postop	4 hours	8 hours	12 hours
ONCAB	177.1	470.8	393.6	294.3	266.8
IQR	262.5	1060.3	1198.8	616.2	274.2
OPCAB	174.8	231.6	188.9	210.8	217.0
IQR	196.8	292.8	631.9	369.7	306.3

Release of I-FABP showed no significant time (p=0.61) or time procedure interaction (p=0.55) between the two groups. However there was a greater release of I-FABP as measured by the AUC in the ONCAB group (p=0.001) and this was highly significant

Release of BPI

Figure 4-24. Changes In BPI Over Time



A=Pre-op, B=Postop, C=4 Hours, D=8 Hours, E=12 Hours

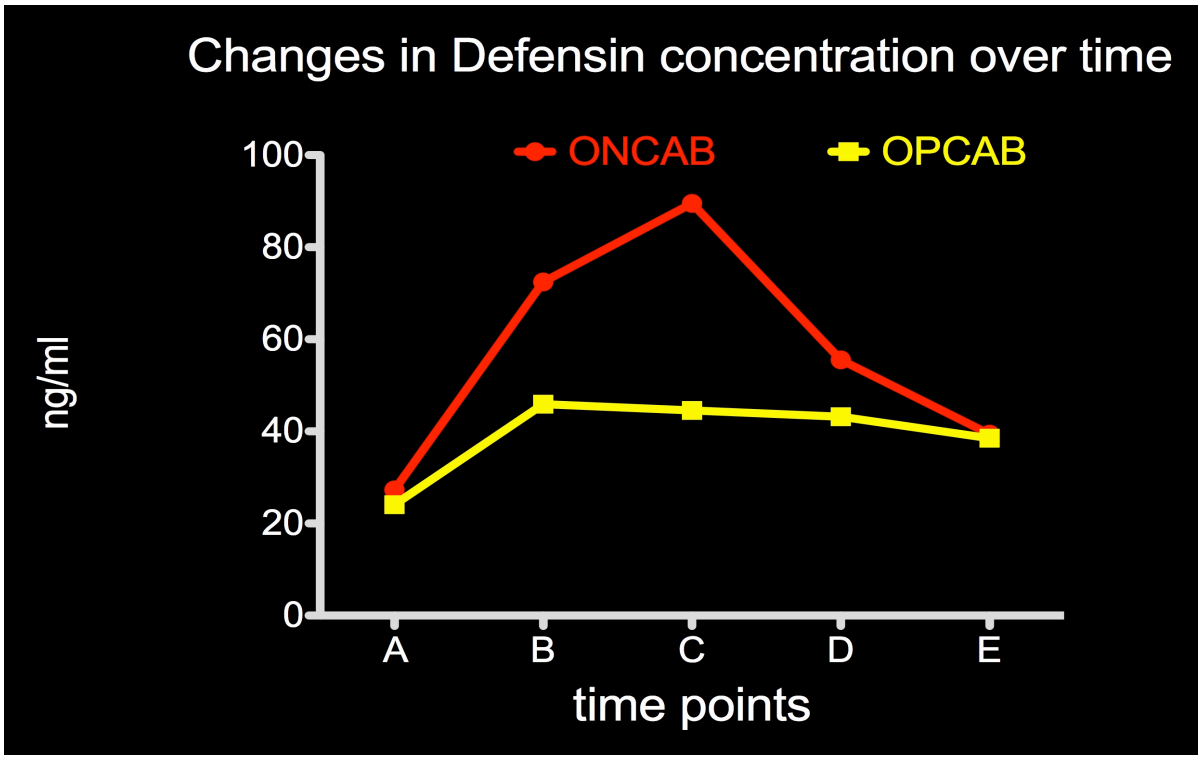
Table 4-29. BPI release

BPI (ng/ml)	Pre-op	Postop	4 hours	8 hours	12 hours
ONCAB	2.90	22.60	8.10	3.95	4.15
IQR	4.62	29.45	8.02	3.03	8.38
OPCAB	4.30	11.90	18.60	9.00	13.00
IQR	3.15	13.55	21.55	29.30	14.50

Post-operative values of BPI were dependent on the preoperative levels ($p=0.016$). There was a statistically significant time procedure interaction ($p<0.001$). There was greater release of BPI in the ONCAB group postoperatively ($p=0.001$) and at 4 hours ($p=0.031$). There was no difference in the AUC ($p=0.22$) between the two groups

Release of Defensins

Figure 4-25. Changes In Defensin Concentration Over Time



A=Pre-op, B=Postop, C=4 Hours, D=8 Hours, E=12 Hours

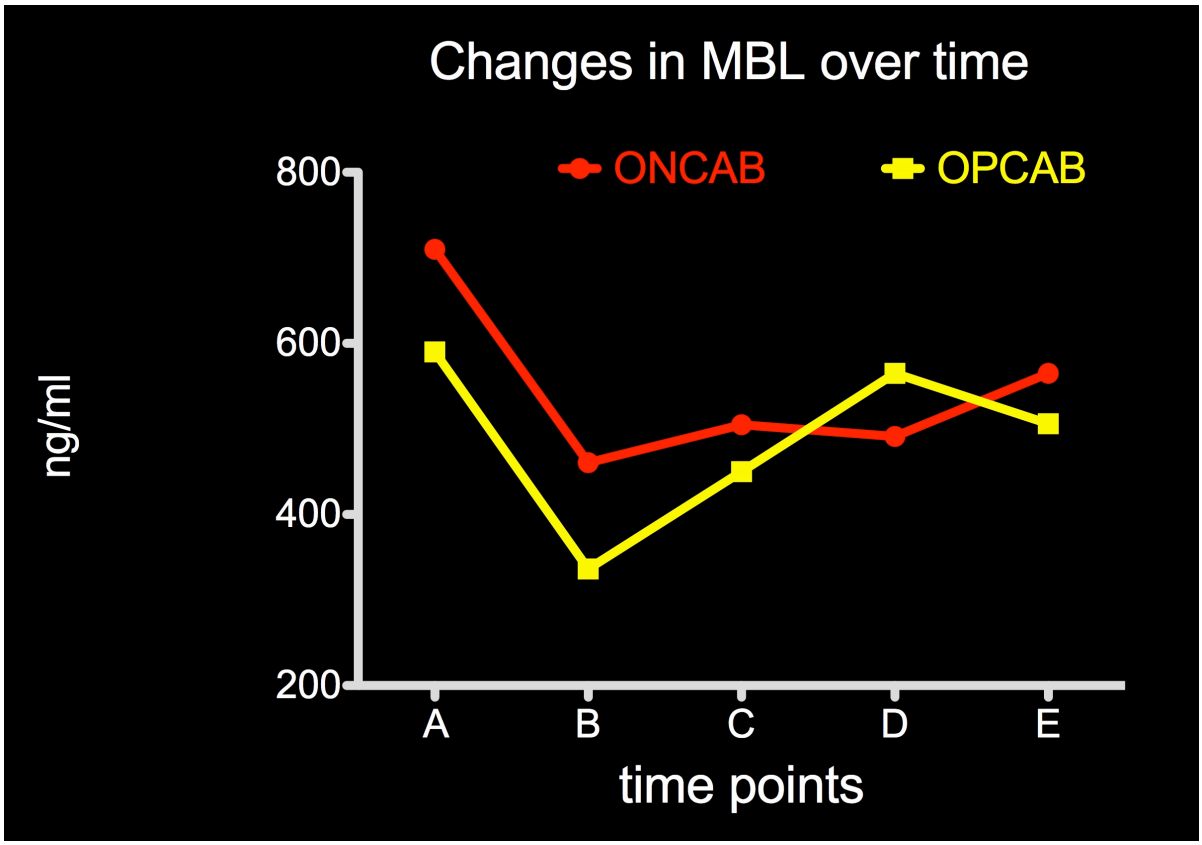
Table 4-30. Defensin Release

Defensin (ng/ml)	Pre-op	Postop	4 hours	8 hours	12 hours
ONCAB	27.29	72.47	89.50	55.53	39.38
IQR	33.00	106.60	61.40	64.00	28.00
OPCAB	24.10	45.90	44.55	43.20	38.55
IQR	28.00	62.70	98.70	24.00	70.00

Defensin release showed a statistically significant time procedure interaction. There was greater release of defensins in the ONCAB group (p=0.05). There was greater release of defensins in the ONCAB group postoperatively (p=0.001) and at 4 hours (p=0.031). There was no statistically significant difference in the AUC (P=0.31) between the two groups.

Release of MBL

Figure 4-26. Changes In MBL Over Time



A=Pre-op, B=Postop, C=4 Hours, D=8 Hours, E=12 Hours

Table 4-31. MBL release

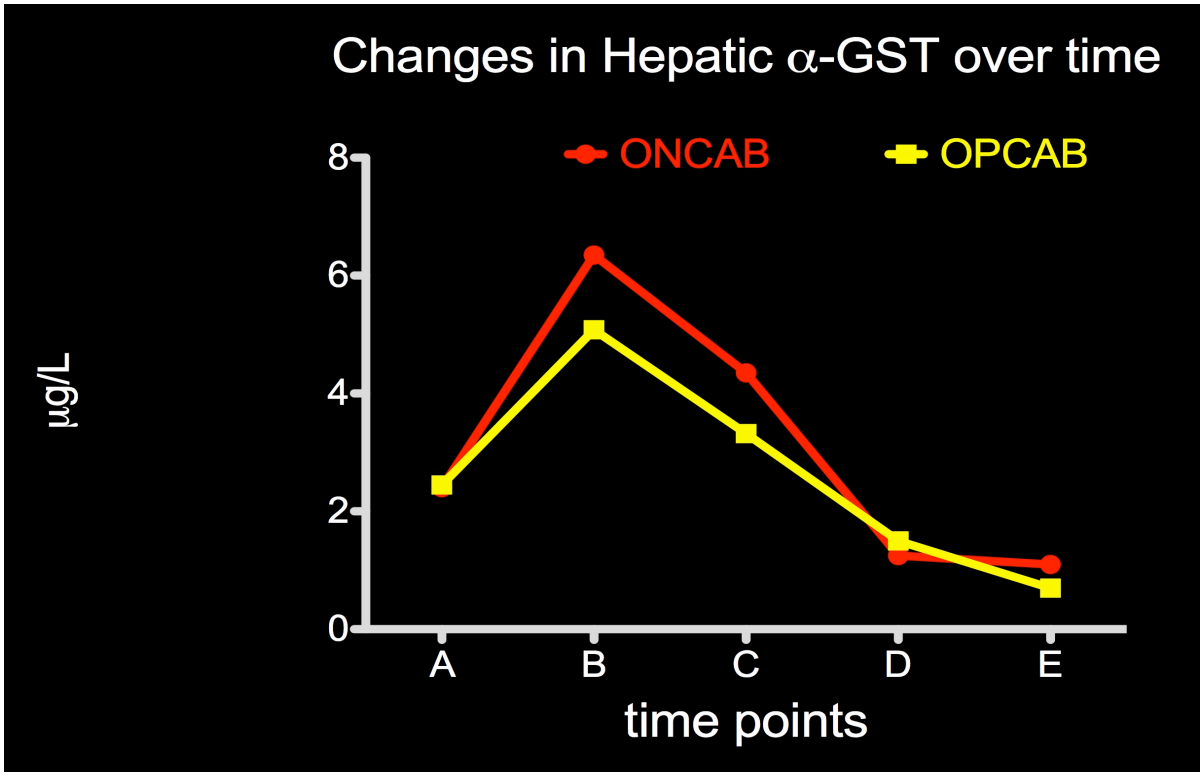
MBL (ng/ml)	Pre-op	Postop	4 hours	8 hours	12 hours
ONCAB	710.00	460.50	505.00	491.25	565.00
IQR	974.00	588.00	829.00	1090.80	734.00
OPCAB	590.00	336.50	450.00	565.00	506.25
IQR	1311	870	825.00	734.00	1021.00

Release of MBL showed a significant time (p=0.002) interaction. The post-operative levels were dependent on preoperative levels (p=0.023). There was no time procedure interaction (p=0.66). There was no difference in the AUC (P=0.47) between the two groups.

Liver Injury

Release of Hepatic GST

Figure 4-27. Changes In Hepatic GST Over Time



A=PREOP, B=POSTOP, C=4 HOURS, D=8 HOURS, E=12 HOURS

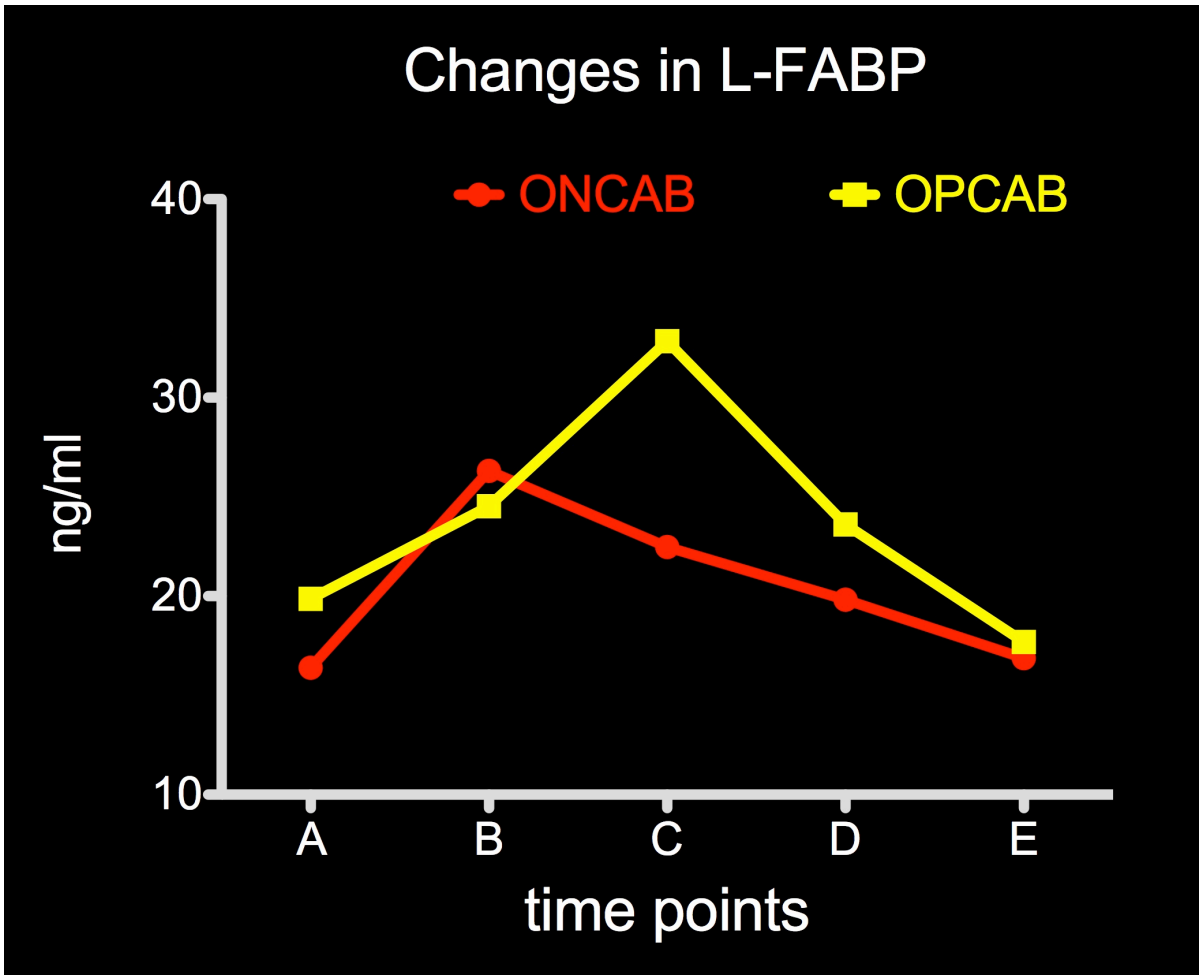
Table 4-32. Hepatic GST Release

αGST (µg/l)	Pre-op	Postop	4 hours	8 hours	12 hours
ONCAB	2.40	6.35	4.35	1.25	1.10
IQR	2.30	8.58	6.00	3.92	1.30
OPCAB	2.45	5.08	3.32	1.50	0.70
IQR	2.70	6.71	8.00	2.78	1.10

Release of hepatic α GST showed a significant time ($p<0.001$) interaction and that this relationship was linear ($p<0.001$). There was no time procedure interaction ($p=0.74$). There was no difference in the AUC ($p=0.51$) between the two groups

Release of L-FABP

Figure 4-28. Changes In L-FABP Over Time



A=PREOP, B=POSTOP, C=4 HOURS, D=8 HOURS, E=12 HOURS

Table 4-33. L-FABP Release

L-FABP (ng/ml)	Pre-op	Postop	4 hours	8 hours	12 hours
ONCAB	16.39	26.31	22.47	19.82	16.88
IQR	8.71	27.78	33.79	18.60	11.46
OPCAB	19.86	24.54	32.85	23.61	17.70
IQR	16.31	16.74	30.54	19.34	16.76

Release of L-FABP showed no significant time ($p=0.70$) interaction or time procedure interaction ($p=0.26$). There was also no difference in the AUC ($p=0.90$) between the two groups.

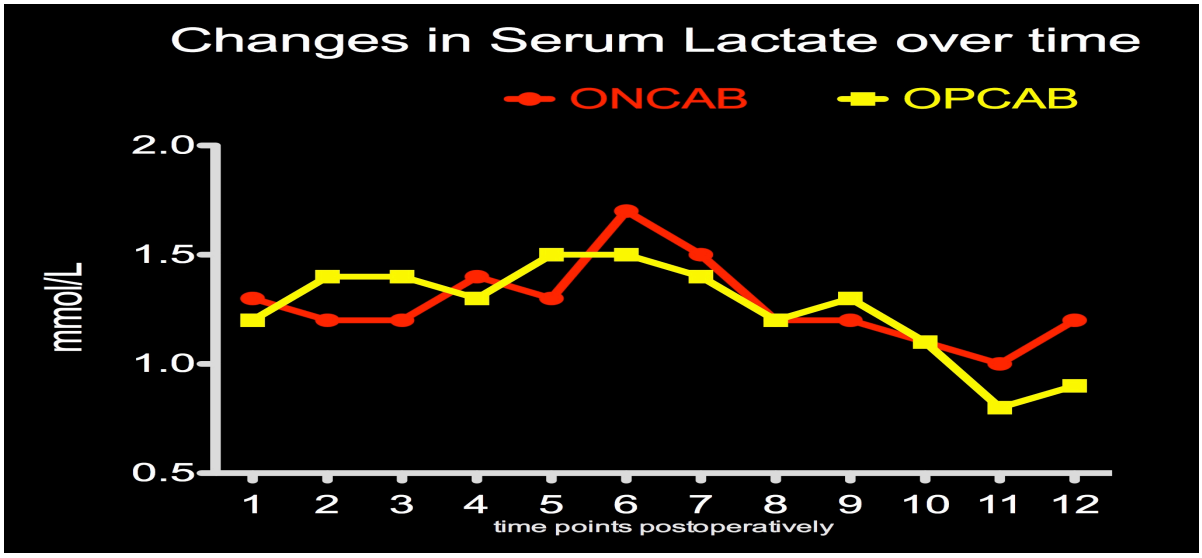
Serum Lactate

Table 4-34. Serum Lactate

Time	Procedure			
	ONCAB		OPCAB	
	Median	Range	Median	Range
Post op	1.3	1.5	1.2	3.1
2nd hour	1.2	1.7	1.4	4.5
3rd hour	1.2	1.3	1.4	19.7
4th hour	1.4	1.8	1.3	5.3
5th hour	1.3	1.7	1.5	5.3
6th hour	1.7	23.3	1.5	5.5
7th hour	1.5	2.6	1.4	5.2
8th hour	1.2	2.7	1.2	5.2
9th hour	1.2	2.7	1.3	3.6
10th hour	1.1	23.4	1.1	2.9
11th hour	1.0	3.6	0.8	0.8
12th hour	1.2	3.3	0.9	0.7

1=Postop, 2= 2nd Hour, 3=3rd Hour, 4=4th Hour, 5=5th Hour, 6=6th Hour, 7=7th Hour, H=8th Hour, 9=9th Hour, 10=10th Hour, 11=11th Hour, 12=12th Hour

Figure 4-29. Change In Serum Lactate Over Time



There were no statistically significant changes in serum lactate concentration between the two groups over the study period as judged by ANOVA (p=0.96)

Stress Hormones

Release of Cortisol

Figure 4-30. Cortisol Release

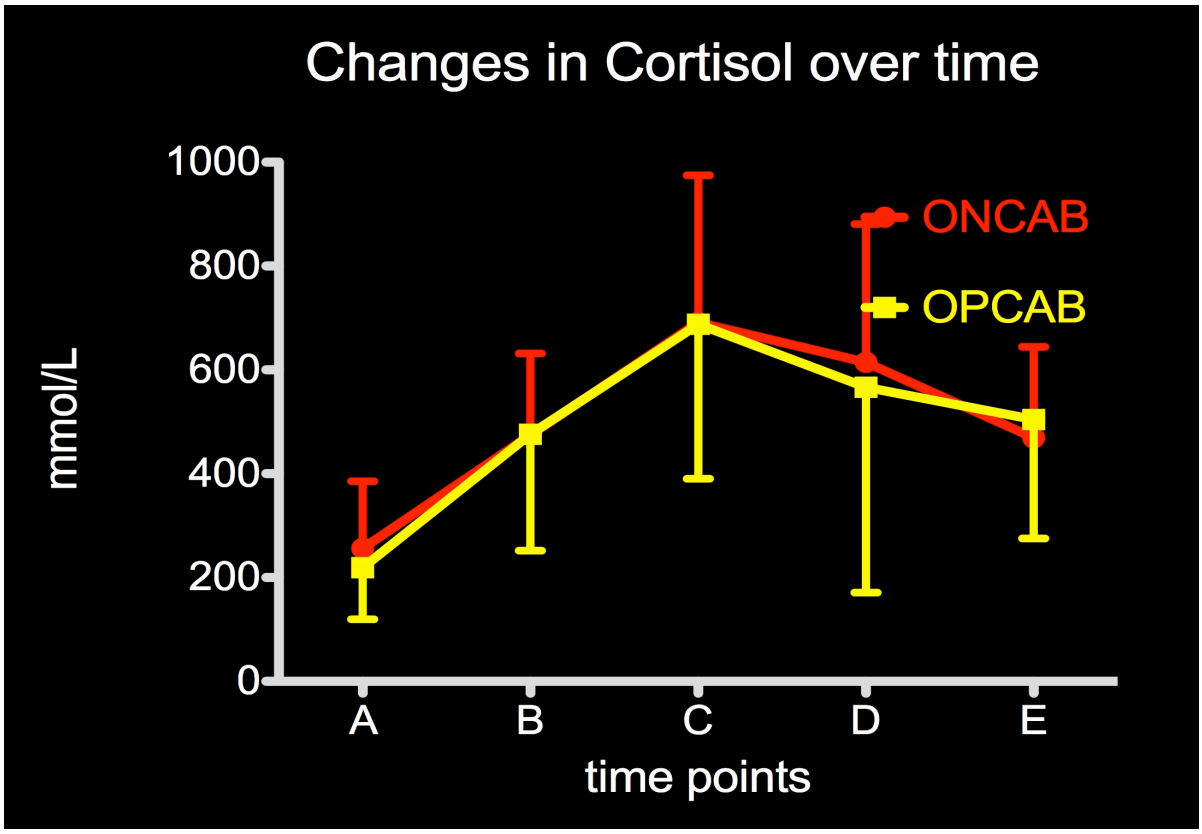


Table 4-35. Cortisol Release

Cortisol	Pre-op (A)	Postop (B)	4 hours (C)	8 hours (D)	12 hours (E)
ONCAB mean	256.24	474.59	691.59	614.59	469.12
SD	129.36	156.92	283.24	266.14	175.13
OPCAB mean	219.24	475.88	687.94	566.65	504.18
SD	99.54	224.06	297.56	395.72	228.73

Release of Cortisol showed was no time procedure interaction (p=0.89). There was a similar rise in both groups from baseline and then a decline

Renal System

The Cleveland clinic score is a well-recognised risk stratifying scoring system for renal injury. The minimum score is 0 and the maximum 17. The average score of the ONCAB patients in this study was 2.25 vs. 2.15 for the OPCAB group (p=0.84).

Cleveland Clinic Foundation Acute Renal Failure Scoring System

Table 4-36. Cleveland Clinic Foundation Acute Renal Failure Scoring System

Risk factor	Score
Female gender	1
Congestive heart failure	2
Left ventricular function <35%	1
Preoperative use of IABP	2
Chronic obstructive airways disease	1
Insulin dependent diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only (reference to CABG)	1
CABG + valve (reference to CABG)	2
Other cardiac surgeries	2
Preoperative creatinine 1.2 to <2.1mg/dl (106mmol/L to 186 mmol/L)	2
Preoperative creatinine > 186 mmol/L	5

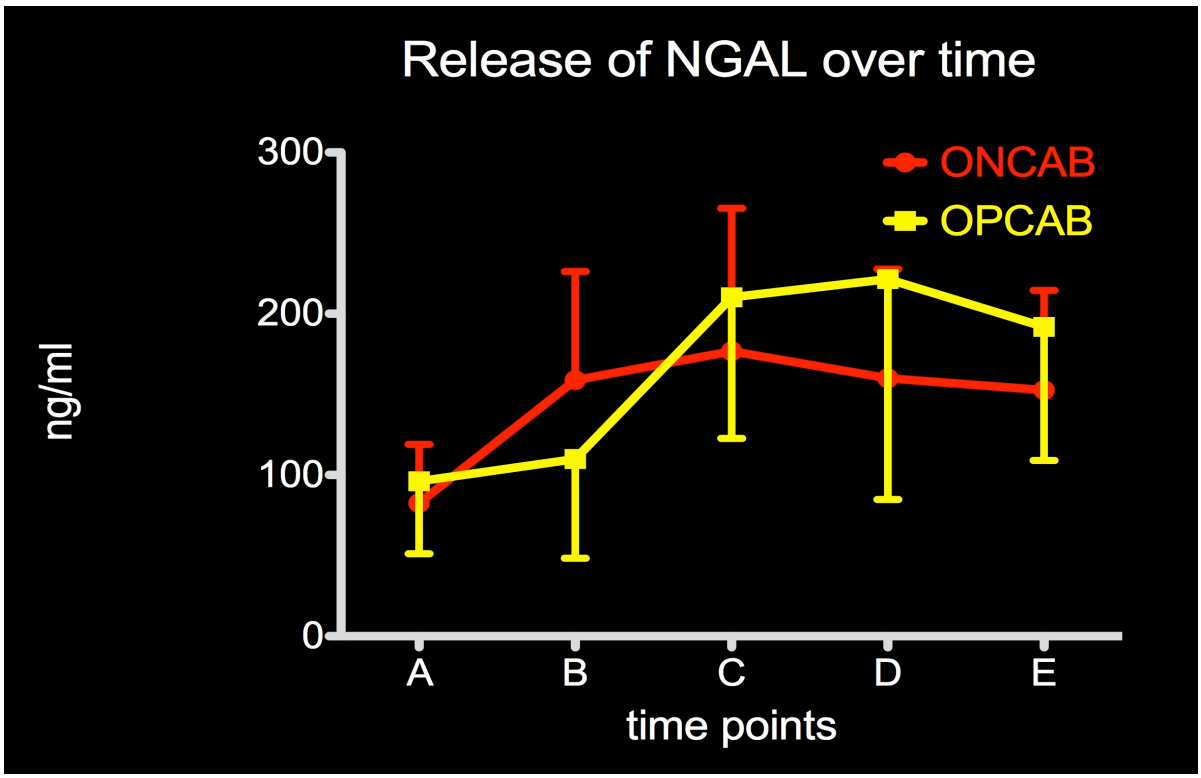
Cleveland Score

Table 4-37. Cleveland Score

	Procedure			
	ONCAB		OPCAB	
	Mean	Standard deviation	Mean	Standard deviation
Cleveland Score	2.25	1.21	2.15	1.84

Release of NGAL

Figure 4-31. Release Of NGAL Over Time



A=PREOP, B=POSTOP, C=4 HOURS, D=8 HOURS, E=12 HOURS

Table 4-38. NGAL Release

Time	PROCEDURE			
	ONCAB		OPCAB	
	Mean	Standard Deviation	Mean	Standard Deviation
A	82.62	36.39	96.08	44.96
B	158.85	67.29	109.84	61.47
C	176.69	88.69	210.25	87.52
D	160.05	67.60	221.48	136.70
E	152.68	61.83	191.84	82.81
Area Under Curve	2342.82	975.19	2644.29	1085.53

NGAL release showed a significant time*procedure interaction (p=<0.001). There was greater release of NGAL post operatively in the ONCAB group than the OPCAB group (p=<0.001). There was no significant difference in the AUC between the two groups (p=0.32).

Release rate of α-GST

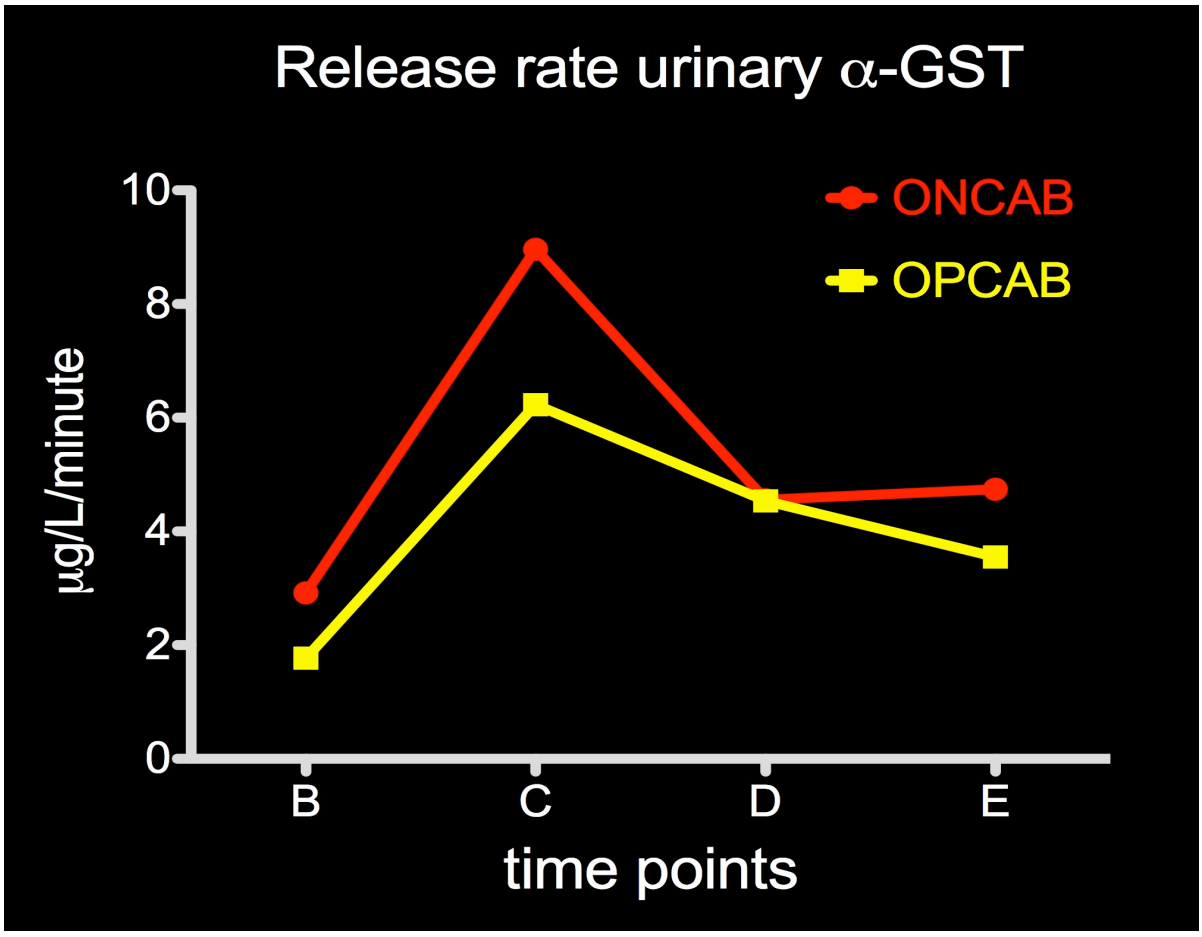
Alpha GST

Table 4-39. Release Rate Of Alpha GST

		Release of Alpha GST			
PROCEDURE		POSTOP	4 HOURS	8 HOURS	12 HOURS
ONCAB	Median	2.92	8.96	4.56	4.74
	IQR	3.09	19.11	7.55	17.24
OPCAB	Median	1.77	6.23	4.54	3.55
	IQR	1.72	9.03	5.35	7.83

Analysis by repeated measures with parameter estimates showed that the changes were related to time. Release rates changed in a linear fashion (p=0.01). There was also a time procedure interaction (p=0.05). The release rate of alpha of GST was statistically significantly higher at 4 hours in the ONCAB group (p=0.05)

Figure 4-32. Release Rate Of Alpha GST Over Time



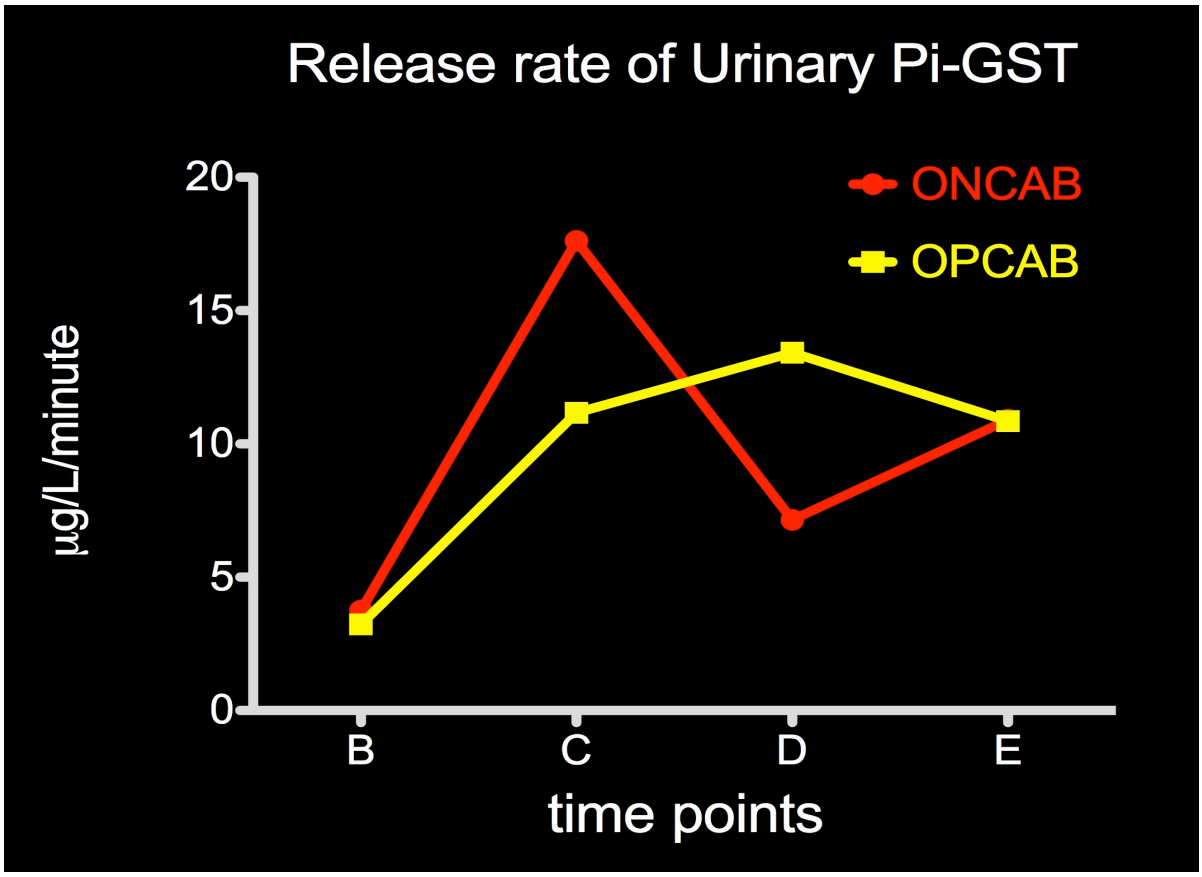
B=postop, C=4hours, D=8hours, E=12hours

Pi-GST

Table 4-40. Release Rate Of Pi GST

		Release rate of Pi GST			
PROCEDURE		POST OP	4 HOURS	8 HOURS	12 HOURS
CPB	Median	3.75	17.61	7.15	10.90
	IQR	9.54	26.21	10.19	20.80
OPCAB	Median	3.23	11.17	13.42	10.86
	IQR	6.27	29.31	21.26	25.54

Figure 4-33. Release Rate Of Pi GST Over Time



B=postop, C=4hours, D=8hours, E=12hours

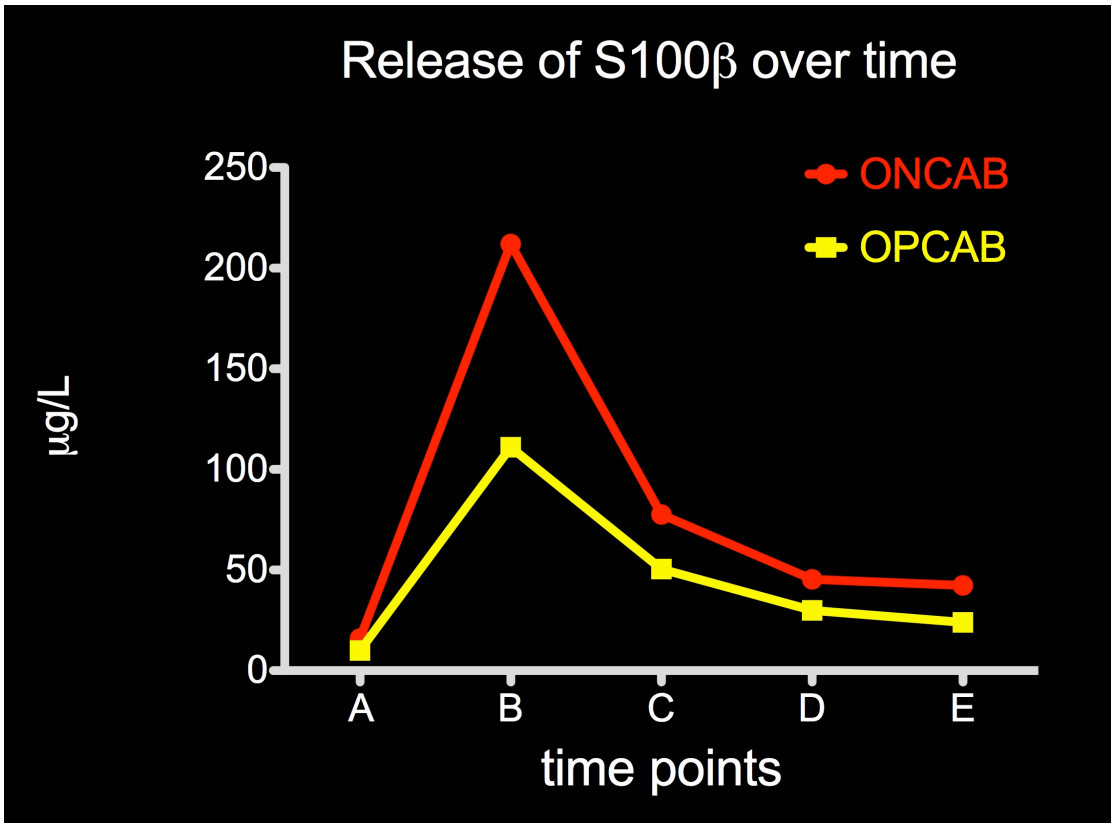
There was a significant change over time (p=0.001). There was no significant time*procedure interaction (p=0.29). There were no significant differences between procedures (p=0.69). There was a linear change in release of Pi-GST over time (p=0.01).

S100β

Table 4-41. S100 Beta Release

Time	Procedure			
	ONCAB		OPCAB	
	Median	IQR	Median	IQR
PREOP	16.00	34.70	10.00	5
POSTOP	212.00	251.85	111.00	69.00
4 HRS	77.60	82.40	50.55	43.95
8 HRS	45.45	22.05	30.00	25.10
12HRS	42.40	52.60	24.00	29.95
AUC	1316.40	951.20	670.00	428.60

Figure 4-34. Release of S100 beta over time



A = Pre-op, B = Postop, C = 4 hours, D = 8 hours, E = 12 hours

There was a significant time interaction ($p<0.001$). There was no significant group*time interaction ($p=0.45$). There was a significant difference between procedures ($p=0.003$). This was significant post operatively ($p=0.001$), 4 hours ($p=0.004$), 8 hours ($p=0.05$) and at 12 hours ($p=0.008$). AUC $p=0.002$

The Newman stroke risk score risk stratifies neurological dysfunction postoperatively. The two groups in this study are once again well matched in their patient characteristics. There is also a good correlation with the EUROSCORE.

Table 4-42. Newman Stroke Risk Scoring System

Risk Factors	Score
Age	((Age-25)10)/7
Unstable angina	14
Diabetes mellitus	17
History of neurological disease	18
Prior CABG	15
History of vascular disease	18
History of Pulmonary disease	15

Table 4-43. Newman Stroke Risk Score

	Procedure			
	ONCAB		OPCAB	
	Median	Range	Median	Range
Newman stroke risk score[158]	92.54	109.61	76.22	70.03

P=0.06

Table 4-44. Correlation of Newman score & EUROSCORE & PARSONNET Scores

Spearman's rho		EUROSCORE	PARSONNET
Newman stroke risk score	Correlation Coefficient	0.652	0.202
	Sig. (2-tailed)	<0.001	0.210

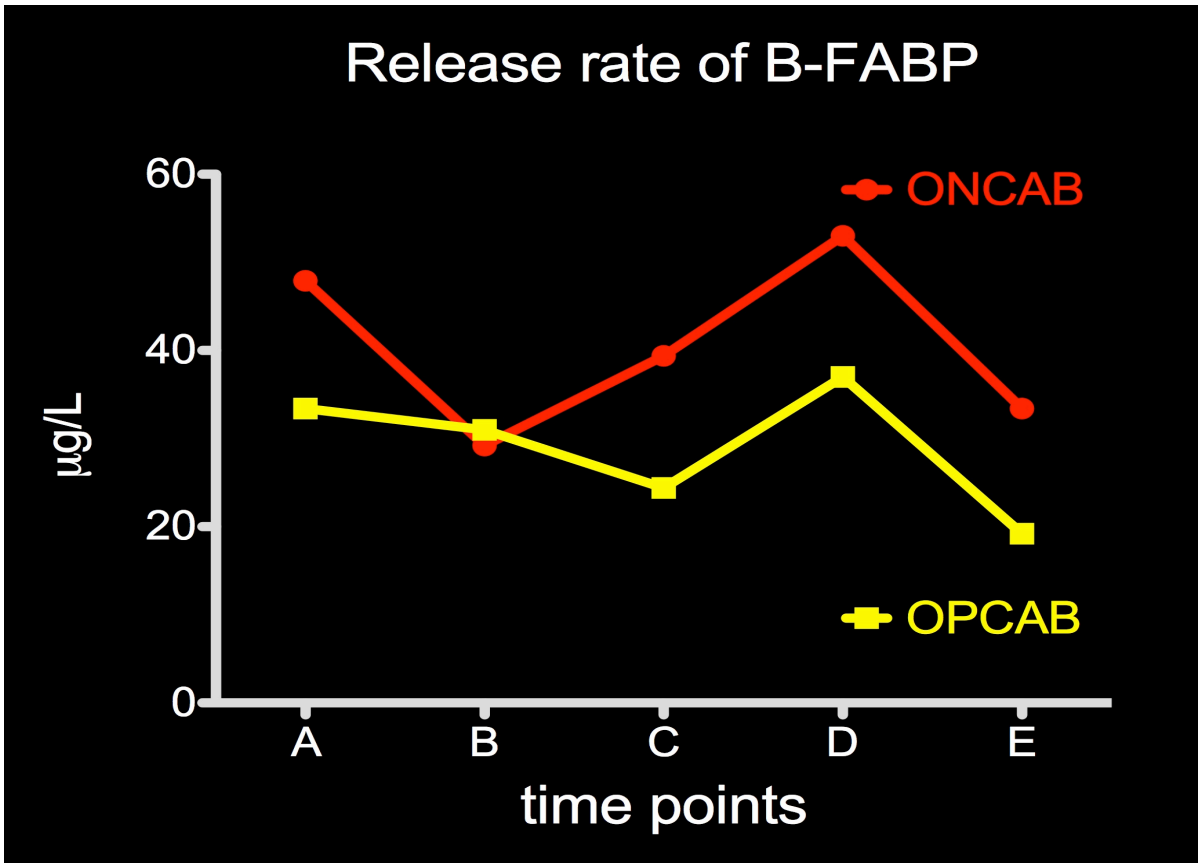
B-FABP

Table 4-45. B-FABP Release

Time	PROCEDURE			
	ONCAB		OPCAB	
	Median	Range	Median	Range
A	47.9	75.4	33.4	129.0
B	29.2	31.7	31.0	95.6
C	39.4	91.7	24.4	59.1
D	53.0	85.7	37.0	89.0
E	33.4	94.2	19.2	132.0

A=Pre-op; B=Post op; C= 4 hours; D= 8 hours; E= 12 hours

Figure 4-35. Release Of B-FABP Over Time

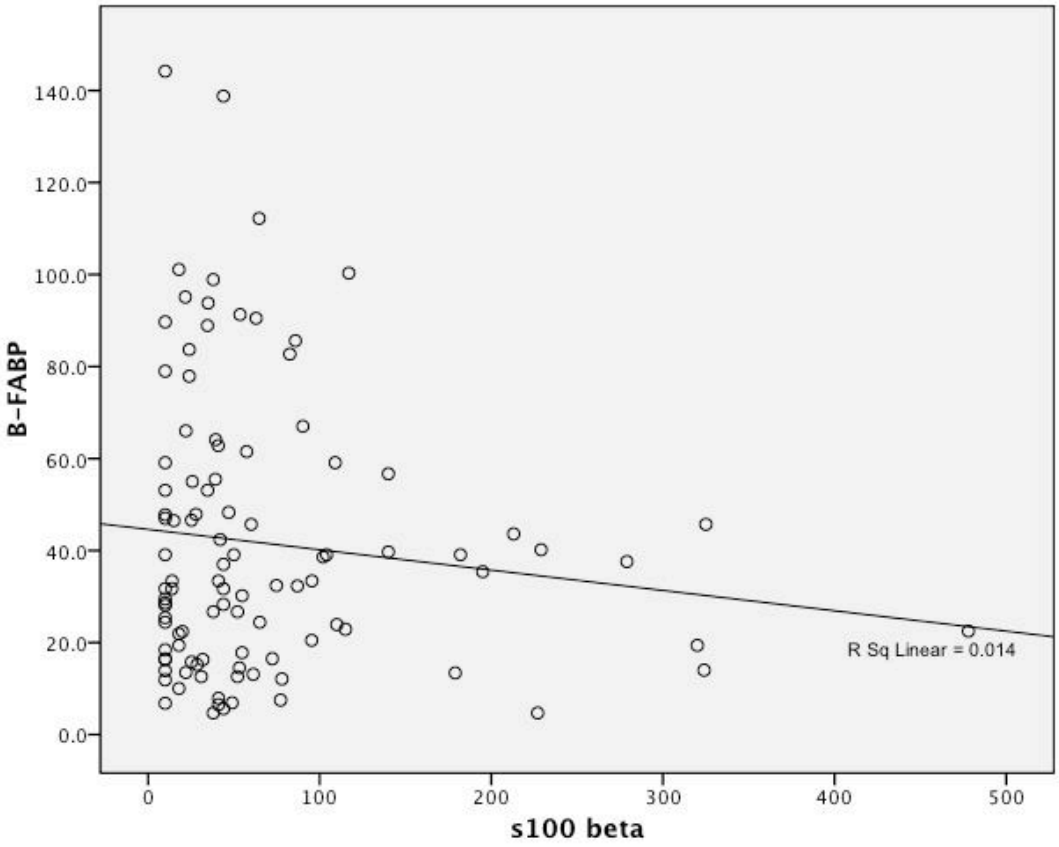


A = Pre-op, B = Postop, C = 4 hours, D = 8 hours, E = 12 hours
There was no significant time interaction (p=0.46). There was no significant time*procedure interaction (p=0.67). There was no significant difference between procedures (p=0.73). There was no difference in AUC between the two groups (p=0.49)

Table 4-46. Correlation Between S100 Beta & B-FABP

Spearman's correlation		B-FABP
S100 Beta	Correlation Coefficient	-.016
	Sig. (2-tailed)	.875

Figure 4-36. Coefficient Of Determination S100 Beta & B-FABP



r-squared: 0.0136
P-value: 0.1936

This graph shows that there is very little correlation between B-FABP and s100 beta levels. The coefficient of determination is very low and statistically insignificant.

Chapter 5 Discussion

Introduction

Table 4-1 summarizes the salient patient characteristics. The two groups are quite similar in demographics and this is reflected in the EuroSCORE, which shows no statistically difference between the two groups. Furthermore the groups are also very similar in Cleveland score (table 4-37) and Newman stroke risk score (table 4-43). This suggests that the randomisation was quite robust despite the fact there was only one OPCAB surgeon and the analysis of results by the "on-treatment" protocol. The Cleveland score for renal injury and the Newman score for neurological injury are dealt with in more detail later.

Intra-operatively the average number of grafts in the OPCAB group was 2.7 +/- 0.8 vs. 3.3 +/- 0.9 in the ONCAB group, p=not significant. The index of completeness, that is the number of grafts planned from the angiogram to that actually performed at surgery was also similar in both ONCAB and OPCAB. Thus post-operative sequelae were not a reflection of inadequate myocardial revascularisation. Tables 4-2 and 4-3 provide detailed information on the vessels grafted and conduits used. The most commonly used conduits were the left internal mammary artery (LIMA) and the long saphenous vein (LSV).

The number of patients requiring inotropic support post-operatively was similar with both ONCAB and OPCAB. Though there was a tendency towards lower rates of atrial fibrillation in the OPCAB group this did not reach statistical significance (p=0.06). No differences were noted in the use of blood products between the two groups.

Myocardial function

Cardiac operations can lead to myocardial cell damage including myocardial cell death secondary to both necrosis and apoptosis. The earlier that this is detected the earlier that therapeutic intervention can be instituted.

The total amount of troponin-I released postoperatively was 107 +/- 22 μg/L in the ONCAB group vs. 53.4 +/- 23.6 μg/L in the OPCAB group (p=0.001). Troponin-I levels were significantly higher in the ONCAB group postoperatively (p<0.001) and at 4 hours (p=0.003). The total amount of H-FABP released postoperatively was 498.9 +/- 262.7 ng/mL in the ONCAB group vs. 478.3 +/- 914.7 ng/ml in the OPCAB group (p=NS). H-FABP levels were significantly higher in the ONCAB group immediately postoperatively (p<0.001). The coefficient of determination R^2 was 0.69 for H-FABP and cTnI. The average amount of dopamine used per hour was 2.3 μg/Kg/minute in the ONCAB group vs. 1.4 μg/Kg/minute in

the OPCAB group ($p<0.001$). The average amount of noradrenaline used per hour was 1.8 μg/Kg/minute in the ONCAB group and 1.18 μg/Kg/minute in the OPCAB group. There was no significant change in cardiac index post operatively ($p=0.81$). There was no group procedure interaction ($p=0.81$). There was a significant and similar decline in SvO_2 post operatively ($p=0.004$) in both groups. There was no significant difference between OPCAB and ONCAB ($p=0.86$). The average pressure adjusted rate score per minute was 10.8 (ONCAB) vs. 9.1 (OPCAB); $p=0.07$. Changes in cardiac enzymes postoperatively need to be interpreted with great care. Though as noted previously OPCAB did result in less myocardial damage as shown by the reduced release of both H-FABP and cTnI with a concomitant reduction in use of postoperative inotropic support levels of inotropic support were quite reasonable in the ONCAB group and not particularly excessive. However elevated levels of cardiac troponin I (cTnI) are frequently observed in patients with patients with systemic inflammatory response syndrome (SIRS) without evidence of an acute coronary syndrome These findings suggest that pathophysiological mechanisms other than thrombus-associated myocardial damage might play a major role, including reversible myocardial membrane leakage and/or cytokine mediated apoptosis in these patients[173]. Vazquez-Jimenez[174] suggested that the release of cTnI is not related to the amount of cell death but rather due to increased cardiac myocyte membrane permeability, which is responsible for intraoperative and postoperative cTnI release. It is of note that Epema et al[175] noted lower cTnI levels in their dexamethasone treatment group, 6 hours postoperatively, corroborating the plausibility of a role for inflammatory mediated alteration of cell membrane permeability. Nevertheless this has been seized on by OPCAB proponents to recommend OPCAB as a strategy for acute coronary syndrome, acute myocardial infarction[176, 177] and those with left ventricular dysfunction[178]. This may be a particularly risky strategy as it is the sickest patients that have the least physiological reserve to tolerate the haemodynamic instabilities associated with OPCAB. The temptation to "get out quick" inevitably leads to reduced revascularization with attendant long-term problems[179]. A more reasoned approach would be to have a lower threshold for the use of an intra-aortic balloon pump. The timing, delivery and routes of cardioplegia have also been discussed at great length in the literature. In this study there was no use of retrograde cardioplegia or hot shot. It has been shown that a hot shot may provide a significant benefit in myocardial preservation during CABG especially in patients with unstable angina[180]. The CABG Patch trial[181] showed that patients who received combined

antegrade and retrograde cardioplegia had significantly less inotropic use (71% versus 84%, p=0.002), right ventricular dysfunction (23% versus 41%, p=0.001), and postoperative balloon pump use (12% versus 19%, p=0.02) than did those who received antegrade cardioplegia. Further research is also needed to develop more effective cardioplegia.

Our results (table 4-7, figure 4-4) are similar to that of Malik et al[182] who noted that the total amount H-FABP released was higher in their ONCAB group and for each time point examined post operatively. It has also been suggested that raised cardiac markers have been shown to be independent risk factors for predicting the long-term mortality and morbidity rate[183],[184] even after non cardiac surgery[185]. Although, an exception to this rule is in acute myocarditis where there is late recovery of left ventricular ejection fraction, which is independent of the initial myocardial damage measured by cardiac enzyme release[186]. In this study the total area under the curve for cTnI was greater with ONCAB than OPCAB. The cardiac index (table 4-4, figure 4-1) was maintained at similar levels in both groups. There was a similar and progressive decline in SvO2 in both groups (table 4-5, figure 4-2). The OPCAB group needed less dopamine (table 4-8, figure 4-6) and noradrenaline (table 4-9, figure 4-7) postoperatively as documented by previous studies commensurate with the lower release of markers of myocardial injury. Analysis of ECG changes (table 4-11, figure 4-9) suggested that there was greater ischemia in the lateral territories in the OPCAB group postoperatively. There were no significant differences in the PAR between two groups, which suggest equivalent overall haemodynamic cardiac status between the two groups. Chang et al studied postoperative changes in ventricular function (EF) in patients undergoing ONCAB and OPCAB. They noted that EF was reduced in both groups. However the pattern of decline was quite different. The ONCAB group had a significant decline in ejection fraction (EF) from pre to postoperative day 1 ($p<0.05$) whereas the OPCAB had a decline from pre to postoperative day 3 ($p<0.07$). Interestingly, the postoperative changes in EF had resolved in both groups 1 month postoperatively. A meta-analysis by Cheng[187] concluded that mortality; stroke, myocardial infarction, and renal failure were not reduced in off-pump coronary artery bypass surgery. The number of grafts performed has always tended to be lower with OPCAB than ONCAB[188, 189] procedures. That some of these procedures have been performed on patients with at least moderately impaired left ventricular function must be a cause for concern. Concerns also persist about the completeness of revascularisation and about the quality of the anastomoses constructed during OPCAB, particularly in the right and

circumflex territories which are less accessible than the anterior descending artery[190]. Rauch and colleagues noted significant differences in the mean flow rate through saphenous vein grafts (SVG) to the obtuse marginal artery (OM; p = .014), to the diagonal artery (Diag; p = .003), to the right coronary artery (RCA; p = .001), and to the posterior descending artery (PDA; p = .001) in patients undergoing OPCAB[191]. Angiographic graft patency is another contentious issue. Whilst Khan[192] and Kobayashi[193] noted lower rates of angiographic patency with OPCAB, Puskas[194] has not found any difference; this may reflect greater dependence on operator ability and experience for OPCAB. Lattouf and colleagues[195] demonstrated that surgeons tend to perform OPCAB for patients requiring 1 to 3 grafts and ONCAB for those requiring 4 to 7 grafts. Another important issue is that of emergency conversion from OPCAB to ONCAB. Even in expert hands the conversion rate is about 3.71%[196] to 13.3%[197]. Operative Mortality of patients converted to ONCAB range from 10%[197] to 18%[196]. Converted patients also had an increased hazard of death for 3 years after surgery compared to unconverted OPCAB (hazard ratio 3.21, 95% CI 1.20-8.59)[198]. Urgently converted patients had a higher incidence of postoperative cardiac arrest (25% versus 1.1%, $p < 0.001$), multisystem organ failure (10.7% versus 0.6%, $p < 0.001$), vascular complications (7.1% versus 1.1%, p = 0.03), and perioperative myocardial infarction (10.7% versus 1.1%, p = 0.02).

Pulmonary dysfunction

There was no statistically significant change in CC16 levels over time (p=0.08). There was no significant time procedure interaction (p=0.35). There was no significant procedure interaction (p=0.97) either. There was no significant difference in the AUC between groups for release of CC16, p=0.874. Surfactant protein-D concentrations changed with time (p=0.001) but not in a linear fashion. The change was dependent on the preoperative value (p=0.001). There was no time procedure interaction (p=0.11) or procedure interaction (p=0.91). There was no difference in the AUC between groups p=0.30. There were no significant differences in extubation times (p=0.97). There was no difference in respiratory index (p=0.58).

Surgical technique is another confounder. The role of pleurotomy in CABG is controversial. Lim et al concluded that a left pleurotomy was found to increase the rate of atelectasis. However, this was not associated with an adverse clinical outcome[199]. Further

more Guizilini et al[200] noted that OPCAB independent of pleurotomy induced a significant reduction of early postoperative pulmonary function though the patients undergoing pleurotomy demonstrated more pronounced pulmonary dysfunction. In this study pleurotomy was performed routinely as per the preference of the surgeon. It has been suggested that in such circumstances if positive end expiratory pressure (PEEP) is initiated immediately after pleurotomy during the harvest of the internal mammary artery graft then this may further attenuate postoperative oxygen impairment and pulmonary atelectasis[201].

Our findings corroborate those of Van Boven in that there is an increased release of CC16 following CABG[54]. The integrity of the broncho-alveolar/ capillary membranes is an important determinant of this equilibrium as indicated by situations in which this barrier is compromised as in acute lung injury[202]. The alveolar macrophage (AM) is considered to be the primary phagocyte in the lung. However, compared with other professional phagocytes, unstimulated alveolar macrophages (AMs) clear apoptotic cells poorly both in vivo and in vitro. During acute inflammation, this defect is overcome, enabling AMs to have a phagocytic capacity similar to that of other professional phagocytes. The intriguing hypothesis therefore arises that the normal environment of the lung suppresses phagocytosis, whereas the environment of an inflamed lung promotes apoptotic cell clearance. The alveolar macrophage is also bathed in fluid that contains high levels of surfactant proteins. Surfactant protein (SP)-A and SP-D in particular play an important role in immune modulation. In the native lung, binding of SP-A and SP-D to a trans-membrane receptor called signal inhibitory receptor protein alpha (SIRPα) on the AM may tonically inhibit apoptotic cell engulfment, resulting in the inefficient uptake observed for these cells. During inflammation, this inhibitory effect may be lifted to facilitate apoptotic cell removal. As inflammation progresses, the production of SP-A and SP-D may be reduced due to alveolar epithelial cell dysfunction. In addition, high numbers of cells rapidly undergoing apoptosis (and subsequent phagocytic cell clearance) may bind free collectins and serve as a sink for their removal. Indeed, SP-A levels are reduced in the lavage fluid of patients suffering from ARDS, acute lung injury after trauma, sepsis, and pneumonia [203, 204]. SP-D has been less well studied in lung injury but may be reduced in some patients with ARDS[204].

The reasons for earlier extubation for OPCAB patients remain unanswered [205]. There is a relative paucity of randomised controlled trials (RCT) specifically looking at pulmonary dysfunction after CABG. Raja et al[206] could identify only six relevant RCTs. In a well

conducted RCT, Staton et al[207] found that OPCAB was associated with a greater reduction in postoperative respiratory compliance associated with increased fluid administration and rotation of the heart into the right chest to perform postero-lateral grafts. However OPCAB yielded better gas exchange and earlier extubation, but no difference in chest radiographs, spirometry, or rates of death, pneumonia, pleural effusion, or pulmonary oedema. In a small study by Covino et al[208], OPCAB patients had a better postoperative course and shorter duration of ventilation. However in this latter study matching of patients was poor, with CPB patients having significantly longer operating times and higher post-operative bleeding rates. Cox et al[209] concluded that both techniques resulted in similar degrees of pulmonary dysfunction, as assessed by alveolar-arterial oxygen gradient. Findings corroborated by Syed et al[210] in a RCT that OPCAB did not result in superior alveolar-arterial oxygen difference, PaO_2/FiO_2 ratio or respiratory index. However, Cheng et al[187] in their meta-analysis showed that OPCAB reduced the incidence of respiratory infections (odds ratio [OR], 0.41; 95% confidence interval [95%], 0.23-0.74; number needed to treat [NNT] = 19). This may be due to the increased inflammatory response caused by CPB and the ability to keep the lungs fully inflated during OPCAB.

In this pilot study the elimination of CPB did not attenuate the inflammatory response in the lungs. Levels of CC16 and SP-D, which are effectors of the inflammatory response, changed appropriately in a similar fashion within the two groups. There were no significant changes in the respiratory index or the extubation times.

Gastrointestinal dysfunction

There was significant gastric mucosal hypoxia in both groups as shown by the reduction in pHi (table 4-15, figure 4-18), increased CO_2 gap (table 4-19, figure 4-16) and rise in $PgCO_2$ (table 4-20, figure 4-17) but no significant differences between the two groups. We agree that the CO_2 gap should remain the gold standard in gastrointestinal tonometry[101] as it had the highest Spearman correlation coefficient with the cardiac index (Spearman rho=-0.169, p=0.01). We were able to confirm that there was a significant positive Spearman correlation between the PgCO2 and CO_2 gap, Spearman's rho =0.844; $p<0.001$. There was a significant negative Spearman correlation between the $PgCO_2$ and the pHi, Spearman's rho = -0.928; $p<0.001$ as previously noted by Masai et al[211]. Thus future work should investigate if routine $PgCO_2$, monitoring which would be far easier to semi-continuously measure, could

be used as a guide to gut perfusion.

The results of this study confirm previous findings of increased DO_2 (table 4-21, figure 4-18), VO_2 (table 4-22, figure 4-19) or O_2 extraction fraction[212] (table 4-23, figure 4-20). However, in contrast to the findings of Velissaris et al[212] there were no significant differences in DO_2, VO_2 or O_2 extraction fraction between the two groups. This is not as surprising as it may appear. Velissaris et al[212] studied a low risk group of patients. One would expect low risk patients to have greater physiologic reserve and thus be able to tolerate greater haemodynamic instability than those in our study. Whilst numerous gut perfusion studies performed on patients undergoing cardiac surgery with CPB have demonstrated that there is a significant drop in splanchnic blood flow on CPB and during the post operative period[212] it is also known that OPCAB results in considerable haemodynamic changes during positioning of the heart and construction of distal anastomoses[213]. Thus despite the added advantage of pulsatile flow with OPCAB, compensatory vaso-motion results in vasoconstriction of the splanchnic bed to restore the blood pressure but also exacerbates splanchnic ischemia. Furthermore, it has also been shown that non-pulsatile CPB is associated with even more significant decrease in splanchnic flow[214]. Pulsatile CPB also attenuates the detrimental whole body inflammatory response to CPB[215]. In addition, non pulsatile CPB and by extension pulsatile CPB causes transient impairment of mesenteric endothelium-dependent relaxation[216, 217] not related to complement mediated processes[217] which renders the intestinal mucosa more susceptible to the action of vasoconstrictors.

Both groups experienced similar levels of stress as suggested by similar changes in the level of cortisol (table 4-35, figure 4-30). Our data confirms the findings by Velissaris et al[218] that OPCAB does not ameliorate this response.

Overall the integrity of the small intestinal mucosa was better preserved with OPCAB as suggested by analysis of the total area under the curve for release of I-FABP ($p=0.001$) (table 4-28, figure 4-23). Tofukji et al[217] found increased ileal myeloperoxidase activity in an animal model of non-pulsatile CPB induced mesenteric injury. This would explain why levels of BPI (table 4-29, figure 4-24) and defensins (table 4-30, figure 4-25) were higher in the ONCAB group immediately postoperatively and at 4 hours postoperatively. Why intestinal mucosal ischemia should occur despite adequate global perfusion in the setting of pulsatile CPB remains a mystery. The effect of CPB on endothelial cells appears variable and depends on the vascular territories studied[216]. Kirshborn and associates[219] reported the

effects of CPB on endothelium-dependent vasodilatation in the lung and demonstrated that CPB did not alter the responses to acetylcholine. Cooper and associates[220] obtained similar results with pulmonary veins and renal arteries. This suggests that splanchnic endothelium might be more sensitive to CPB than that in other territories. Doguet et al further emphasise the maintenance of normal arterial pressure[216]. Thus visceral organ hypo-perfusion be it triggered by inflammatory mediators as in ONCAB or haemodynamic instability with OPCAB is exacerbated when vasoconstrictors are used to increase mean arterial pressure by virtue of inflammatory priming of the splanchnic endothelium. Furthermore it has been postulated that pulsatile flow provides enhanced energy which is responsible for maintaining the patency of the microcirculation[9]. Shepard et al[15] concluded that at the same mean blood pressure and flow rate, a pulsatile regimen delivered up to 3.4 times as much energy to the circulation, and that this improved energy delivery might be responsible for maintaining normal peripheral blood flow distribution under pulsatile blood flow conditions. In chapter 3 it was noted postoperatively that there was greater use of noradrenaline in the ONCAB group, which is similar to the findings of Velissaris et al[221]. Previous work by Epema et al[175] has shown that urinary excretion of I-FABP is increased significantly during CPB and that this response is not attenuated by dexamethasone. Thus it would seem that that an ischaemic aetiology is more likely especially given the precarious counter current blood supply[60] of the intestinal villi rather than an inflammatory aetiology and fits with the hypothesis of overall reduced energy transfer during CPB. However, the gut cannot be viewed in isolation. Reilly and Bulkey[9] have proposed that the vasoactive gut response to circulatory shock is mediated by activation of the renin-angiotensin system which increases gut permeability. Transient changes in gut function have been described in the context of intestinal, abdominal and vascular surgery. Raised intestinal permeability has also been described in various clinical stress conditions such as burns, trauma, chemotherapy, haemorrhagic shock and patients in the intensive care unit[221]. Studies of intestinal permeability by Ohri et al[222] showed that non-pulsatile hypothermic CPB does increase small intestinal permeability and reduces absorption. However using similar methodology but with the addition of an arterial line filter Velissaris et al[70] were able to demonstrate that similar changes in gut permeability occurred when ONCAB was compared with OPCAB. It is theorized that during these transient disruptions of gut function endo-toxaemia occurs. Thus there was a significant decrease in EndoCAB levels after surgery in both groups strongly suggestive of a occult dysfunction of

the gut. These findings are similar to those of Braun et al and suggest that endotoxins released after surgery elicit an immune response reaction in all patients[223]. However levels of EndoCAB were unchanged between the two groups suggesting that both groups experienced similar levels of endo-toxaemia. It has been shown that lower preoperative serum EndoCAB level is a significant predictor of long-term mortality independent of other known risk factors[224]. Therapeutic passive immunisation with EndoCAB hyper-immune fresh frozen plasma has been advocated to counter this problem[225]. The levels of MBL were also similar between the two groups suggesting that the distinctive 3rd pathway of complement activation occurred to a similar degree in both groups. This study confirms findings by Marcheix et al[10] that MBL levels decreased postoperatively with a gradual increase there after but not returning to basal levels in patients undergoing ONCAB only. Marcheix et al conclude that the use of a cell saver as in this study reduces activation of the alternate pathway and further serves to attenuate the inflammatory response to CPB.

Despite being somewhat counter intuitive this study suggests that modern CPB is well tolerated and OPCAB surgery does not confer significantly superior subclinical gut protection.

Liver dysfunction

The traditional explanation for CPB induced liver dysfunction proposed by Hampton and colleagues was that effective hepatic blood flow is reduced during hypothermic non-pulsatile CPB[226] which leads to redistribution of intrahepatic flow[227] thus paving the way for the development of hepatocellular injury. However OPCAB also results in numerous repeated, prolonged and transient haemodynamic changes that may be just as deleterious. Therefore, this hypothesis may apply equally to OPCAB.

α-GST levels changed in a similar fashion in both groups (table 4-32, figure 4-27). There was a strong time interaction and this relationship was linear. This explains why Yamada et al[228] in their study mistakenly concluded that OPCAB was superior. That prolonged CPB times are associated with greater release of α-GST has been demonstrated previously[134]. The results of L-FABP are interesting in that the OPCAB group seem to release more L-FABP in the early postoperative period than the ONCAB group although this did not reach statistical significance (table 4-33, figure 4-28). Serum lactate levels were similar in both groups (table 4-34, figure 4-29). Another test that is currently considered to be

the most accurate method of assessing liver function is based on the rate of lignocaine metabolism to form mono-ethyl-glycine-xylidide (MEGX)[229] and has been used to study liver function in CABG. Velissaris et al[221] noted no differences in either the total bilirubin (TB) or conjugated bilirubin (CB) alanine aminotransferase (ALT) or aspartate transaminase (AST) or MEGX in patients undergoing ONCAB or OPCAB. Similar results with MEGX have been noted by Ascione et al[230] although pulsatile CPB was not used in this study. Thus it would seem that in the absence of liver cirrhosis OPCAB is not superior to ONCAB in terms of hepatocellular injury.

However there may be a role for OPCAB in the presence of preoperative liver cirrhosis. Mustafa et al in an observational study suggested that OPCAB was associated with better lactate clearance than ONCAB[133]. The biggest advantage of OPCAB over ONCAB would be the reduced dose of heparin made possible by OPCAB. In a retrospective review by Klemperer et al[231] of 13 patients with cirrhosis undergoing CPB, there were 6 patients undergoing ONCAB. Three were elective, 2 urgent and 1 emergency. The emergent patient had Childs class B cirrhosis. The remaining patients were Childs class A. The emergent patient died giving an overall mortality of 17%. Bizouarn et al[232] described their experience with CPB on 12 patients with cirrhosis. One patient with Childs cirrhosis underwent CABG and survived. In their series of 18 cirrhotic patients Lin et al [233] describe 3 patients undergoing CABG. All had Childs cirrhosis. One had ONCAB and 2 had OPCAB. All 3 survived. Ben Ari et al[138] have reported a case of OPCAB in a patient with Child C cirrhosis with successful outcome. Thus the headline mortality often quoted in these studies is not applicable to patients undergoing isolated CABG. Clearly where multiple procedures are performed the mortality may be higher and the only way currently to perform these procedures is to use CPB.

In conclusion, this study has not found any advantages for OPCAB surgery over conventional surgery using CPB for hepatocellular injury in patients who have no pre-existing evidence of liver dysfunction.

Renal dysfunction

The kidney is uniquely vulnerable organ to injury as a result of its anatomy and physiology, and cardiac surgery provides a plethora of potential renal insults[234].

The majority of renal blood flow goes to the cortex, where glomerular filtration

occurs. The renal medulla receives only 5-10% of renal blood flow, but plays an important role in the regulation of salt and water homeostasis. The renal medulla exists in a relatively low oxygen environment under normal conditions because oxygen diffuses from the descending to the ascending limbs of the vasa recta capillaries.

Haemodilution increases blood flow and oxygen delivery to tissues and has its most profound effect on the microcirculation. It also attenuates the effects of aggregation of red cells in post capillary venules. This facilitates the transfer of interstitial fluid into the vascular space thereby increasing venous return to the heart, increasing cardiac output and renal blood flow[9]. The use of colloid priming solution has also been shown to reduce interstitial oedema when compared to using crystalloid prime[235] and improve end organ function[236]. Furthermore pulsatile CPB has been shown to improve microcirculatory flow, improve cerebral perfusion and enhance renal perfusion[237] and is associated with reduced levels of endothelin-1 and IL-8[238]. IL-8 has been shown to be another early marker of acute renal injury in cardiac surgery[239]. These modifications reduce the haemodynamic compromise that occurs during CPB and changes in renal vascular resistance that cause redistribution of renal blood flow during CPB to maintain glomerular perfusion at the expense of worsening medullary oxygenation. The renal tubular cells have a high metabolic demand resulting in an oxygen extraction ratio of 80% in contrast to the myocardium, which extracts 65% of the available oxygen. Renal tubular cells, particularly the thick ascending limb of the loop of Henle, are therefore particularly susceptible to hypoxia. The renal response to reperfusion following a hypoxic insult is vasoconstriction, rather than hyperaemic vasodilation, which is mediated by local adenosine pathways – the tubulo-glomerular feedback mechanism[240]. This mechanism modulates afferent glomerular arteriolar [241] resistance to reduce glomerular filtration when the feedback mechanism is activated. Under these circumstances the medullary counter-current exchange of oxygen increases, further reduces medullary oxygenation, while the tubular cells increase their oxygen consumption by reabsorbing electrolytes, particularly sodium, more avidly.

Renal ischemia results in cellular oedema secondary to the arrest of the active trans-membrane sodium-potassium pump. Sodium accumulates within the cells and water is then drawn in down the osmotic gradient. Glomerular capillary endothelial cell swelling further impedes the microcirculation within the kidney, so reperfusion may not restore normal blood flow. Ischemia generates free radicals, which continue to cause renal damage during

reperfusion. This damage affects the glomerulus, tubules, and the renal microvasculature. The kidney does have an adenosine-mediated ischaemic preconditioning capacity[241] that has been demonstrated to be clinically beneficial in vascular surgery[242].

Hypoxia causes weakening of tubule cell attachment to the basement membrane, resulting in sloughing of these cells and their aggregation within the tubular lumen, sometimes termed acute tubular necrosis. This tubular obstruction causes diffusion of glomerular filtrate into the interstitium of the kidney, a phenomenon known as tubular "back leak". Although the GFR is diminished by a decrease in renal blood flow outside the auto-regulatory range, tubular "back leak" results in a larger deterioration in renal function than the decrease in renal blood flow and GFR would predict. The combination of obstruction and compression of the kidney tubules by oedema increases the intra-tubular hydrostatic pressure, which opposes glomerular filtration pressure.

Haemolysis, which sometimes occurs during CPB due to cardiotomy suction resulting in mechanical trauma of red blood cells, causes the release of haemoglobin, which is nephrotoxic and directly related to the development of ARF. The mechanism is a mixture of direct cytotoxicity, renal vasoconstriction, and tubular obstruction. If CPB-associated acute renal injury is a pigment nephropathy, alkalinisation of urine with sodium bicarbonate may provide protection protect from: (1) tubular cast formation from met-haemoglobin; (2) proximal tubular cell necrosis by reduced endo-cytotic haemoglobin uptake, and (3) free iron-mediated radical oxygen species production and related injury. Sodium bicarbonate is safe, simple to administer and inexpensive. If part of acute renal injury after CPB is truly secondary to haemoglobin-induced pigment nephropathy, prophylactic sodium bicarbonate infusion might help attenuate it. A trial of such treatment might be a reasonable future investigation in higher risk patients receiving CPB[243].

The autonomic nervous system has an important role in the control of renal blood flow. The stress response to CABG and the administration of exogenous catecholamines both provide α -1 adreno-receptor-mediated vasoconstriction. However previous work by Velssaris[218] et al has shown that despite the avoidance of CPB, OPCAB surgery triggers a systemic stress hormone response that is comparable to conventional surgical revascularization.

CPB causes abnormalities of the renin-angiotensin-aldosterone system, resulting in decreased urine output and an accumulation of water in the third space[238] that can aggravate

interstitial oedema and renal ischemia. Again the discrimination between pulsatile and non-pulsatile CPB is not made. Pulsatile CPB has been shown to eliminate the intraoperative and postoperative increases in plasma renin activity and postoperative increases in both angiotensin 2 and aldosterone[244, 245].

The kidney has little collateral blood flow potential so renal arterial embolization produces wedge-shaped infarcts in affected areas. Both gaseous and particulate micro emboli, which occur during CPB, may have a role in renal damage, although the former are less of a problem since membrane oxygenators have replaced bubble oxygenators. However further attempts to remove micro emboli gaseous emboli should further attenuate end organ damage[246, 247]. Manipulation of the ascending aorta can produce atheromatous emboli, and the risk of postoperative ARF increases with increasing severity of ascending aortic atheroma. However, very few OPCAB surgeons use a non-touch aortic technique[248, 249]. In one study the use of an intra-aortic filter trapped atheromatous debris, released on removal of the aortic cross clamp, in 40% of patients. Thrombus, platelet-fibrin aggregates, lipid droplets from mediastinal suction, fragments of vessel wall and endocarditic vegetations are other sources of micro-emboli, which may impair renal function. Similarly few ONCAB surgeons routinely use an intra-aortic filter but it may be worth bearing in mind for high-risk patients[250, 251]. A simple epi-aortic ultrasound may delineate areas of aortic atheroma and thus aid placement of the aortic cannula and placement of grafts thereby attenuating embolic end organ damage [252]. We routinely use a cell saver thus further reducing the lipid embolic load[253].

The systemic inflammatory response (SIRS) provoked by the stress of CABG releases a cocktail of mediators that can impact on all the mechanisms detailed above resulting in acute renal injury. Whilst numerous studies have shown that the inflammatory response is lower with OPCAB than ONCAB[73, 254] only recently has it being appreciated that for example the incidence of low systemic vascular resistance (SVR), and patterns of SVR changes, cardiac outputs were similar in ONCAB and OPCAB, resulting in equivalent clinical outcomes in both groups[255]. Clinicians should strive towards attenuating the untoward effects of CPB where possible and only then begin to compare it with OPCAB.

The patients in this study were well matched for general characteristics as shown in chapter 2 but also in terms of the Cleveland clinic score that has been extensively validated[256]. There was a significantly greater release of NGAL in the ONCAB group

postoperatively compared to the OPCAB group ($p<0.001$). Also of note was the pattern of release. The OPCAB group had a greater and more pronged release of NGAL than the ONCAB group. Dent et al[149] have shown in a paediatric population that the 2 hour postoperative plasma NGAL levels strongly correlated with change in creatinine ($r = 0.46$, $p< 0.001$), duration of AKI ($r = 0.57$, $p < 0.001$), and length of hospital stay ($r = 0.44$, $p < 0.001$) where as the 12-hour plasma NGAL strongly correlated with mortality ($r = 0.48$, $p = 0.004$) and all measures of morbidity mentioned above. Further research is required in appropriate adult populations to determine the clinical significance of these changes in NGAL. According to the forest fire theory of Mori[257] the forest (kidney) is composed of trees (nephrons). Serum creatinine level or glomerular filtration rate is a marker for functional nephron numbers (trees), whereas serum, urinary, or renal NGAL level indicates the extent of active lesions in the kidney (fire in the forest). Thus it would seem that the fire burns ferociously and quickly in the ONCAB group but slower and longer in the OPCAB group.

The release rate of alpha of GST was statistically significantly higher at 4 hours in the ONCAB group ($p=0.05$). For Pi-GST there were no significant differences between procedures ($p=0.69$). Our findings corroborate that of Boldt et al in that the release rates of both proteins are time dependent[258]. Further work is required to determine what levels of release rate correlate with kidney injury. That the benefit of OPCAB seems to be confined to the proximal tubular system is a novel finding and needs further investigation.

In conclusion factors that favour OPCAB include reduced SIRS, lack of haemolysis and reduced embolic phenomenon. ONCAB offers greater haemodynamic stability. Modern CPB further attenuates vasoconstriction and SIRS. The repeated transient episodes of hypotension during construction of distal anastomoses with OPCAB cause repeated activation of the tubulo-glomerular feedback mechanism. This overwhelms any native ischaemic preconditioning capacity resulting in worsening cellular oedema. Hence the OPCAB group suffer a greater and more prolonged deterioration of renal function whereas the ONCAB group experiences a short sharp shock.

Neurological dysfunction

The major cause of neurologic impairment following CABG is embolic. The International Council of Emboli Management (ICEM) study group was formed to investigate the impact of particulate capture and removal during surgery. ICEM reported that particulate

material, most often fibrous atheroma, is generated in most CPB procedures. The ICEM study group also reported that particulate material is captured in 98% of all cardiac surgery cases using CPB, and that 73% of filters contain fibrous atheromatous material[259]. The mechanism by which aortic atherosclerosis leads to adverse neurological outcome after cardiac surgery is cerebral embolization of atheromatous debris. This embolization occurs primarily as a result of aortic manipulation during palpation, cannulation, cross-clamping, proximal coronary anastomosis and decannulation, and possibly as a result of a 'sandblasting' effect from the high-velocity jet exiting the aortic cannula[260].

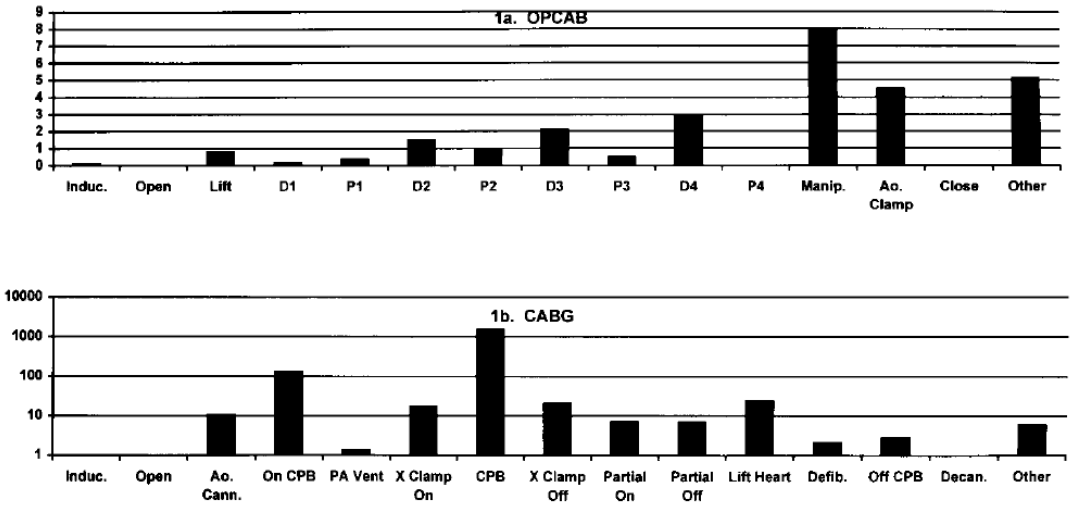
The patients in this study were well matched in terms of general characteristics as shown in chapter 2, but they were also well matched in terms of their Newman stroke risk. Kanner et al[161] have shown that S100β is a marker of blood brain barrier dysfunction (BBBD). Our results confirm previous studies showing raised levels of S100β postoperatively in the ONCAB group compared with OPCAB[261]. There was a similar but greater change of BBBD in the ONCAB group for all time points studied postoperatively. There was a greater area under the curve for S100β in the ONCAB group indicative of greater BBBD. Analysis of B-FABP found an initial decline in both groups. The maximal decline occurred about 4 hours postoperatively. Subsequently there was a dramatic rise in the ONCAB group at 4 hours and at 8 hours in the OPCAB group. Thereafter there was a decline to baseline. This is commensurate with the greater embolic load associated with establishment of CPB. There after embolic load is mainly due to aortic manipulation during construction of proximal anastomoses. A recent comparison of single clamp (SC) vs. multi-clamp (MC) technique[262] concluded that there was no reduction in terms of stroke with MC. However MC was associated with lower levels of release of S100 beta.

B-FABP and S100β are cytosolic proteins and, therefore, are released simultaneously from injured cells. In addition, the release of cerebrovascular proteins into blood plasma is dependent on disruption of the blood–brain barrier. Because these proteins are of similar size (B-FABP, 15 KDa; S100β, 22 KDa), they will not differentially pass through the blood–brain barrier. The similarity in the sizes of these molecules also implies that the elimination of these proteins from plasma occurs by renal clearance and at equal rates. B-FABP and S100β have a plasma half-life of 20–25 min, indicating that the so-called diagnostic time window is limited but is similar for B-FABP and S100β. The use of B-FABP as biomarkers for early

identification and treatment stratification of may improve patient care and outcome. It is known that in patients with acute ischaemic injury, rapid initiation of treatment will decrease the amount of neuronal cell death[163].

The bar chart below shows that OPCAB results in significantly fewer cerebral micro emboli[263]. However the advent of new intra-aortic filter devices such as the EMBOL-X device has the potential to considerably attenuate embolic complications[264, 265] in ONCAB.

Figure 5-1. Occurrence of Micro emboli in OPCAB (top) and ONCAB (bottom)



Occurrence of micro emboli (average number per patient event) in OPCAB (*top*) and CABG (*bottom*).
Induc = induction; Lift = lift heart; D = distal anastomosis; P = proximal anastomosis; Manip = manipulation; Ao Clamp = aortic partial occlusion clamp (*top*); Ao Cann = aortic cannulation; On CPB = initiation of CPB; PA Vent = pulmonary artery vent; X Clamp On/Off = cross-clamp aorta; Partial On/Off = aortic partial occlusion clamp (*bottom*); Defib = defibrillation; Decan = remove cannulas.

Another strategy to reduce arterial emboli is the dynamic bubble trap. Gaseous micro emboli can be removed with a dynamic bubble trap. Subclinical cerebral injury detectable by increases of S100β disappears earlier after surgical intervention[266]. Elimination of gaseous micro emboli is dependent on the design of the CPB circuit. A membrane oxygenator, although not specifically designed for this purpose, can remove gaseous micro emboli. However arterial line filtration is not the best solution for removal of gaseous micro emboli, because larger emboli may be fractionated before reaching the arterial filter. Venous line filtration is a more efficient way for clearing gaseous micro emboli[267]. Leucocyte depleting filters during CABG have also reduced the number of cerebral micro emboli recorded by trans-cranial doppler and showed a strong trend towards improving neurologic performance

post-operatively[268]. Epi-aortic scanning may also significantly reduce neurocognitive impairment following CABG [252]. This technique has been shown to be far superior to both digital palpation and trans-oesophageal echo for the detection of aortic atheroma[269].

Non-embolic phenomena known to attenuate postoperative neurocognitive impairment include the use of pulsatile CPB. This has been shown to associated with the release of lower levels of S100β than non pulsatile CPB[270]. Moderate hypothermia during CPB as in this study has also been shown to be beneficial. However as shown in chapter 3 there was a significant and similar rise in temperature in both groups postoperatively in contrast to the findings of Clark et al[271]. Postoperative hyperthermia leads to adverse cognitive outcome[272]. Clark et al suggested that OPCAB resulted in a reduced inflammatory response. Our findings suggest that both groups experienced similar levels of inflammation. We suggest that giving routine intravenous paracetamol in the post-operative period may help reduce the incidence of postoperative hyperthermia. A recent meta-analysis of neurocognitive outcomes after OPCAB vs. ONCAB involving five neurocognitive tests (Rey Auditory Verbal Learning, Grooved Pegboard, Trail A and B, and Digit Symbol) concluded that overall there were no convincing differences in outcomes in neurocognitive testing between off-pump and on-pump CABG groups. The majority of patients reported improved health after CABG surgery compared with their preoperative status irrespective of surgical technique[273].

Shroyer and colleagues[274] conducted a prospective randomized controlled study to assess the relative clinical efficacy of on-pump and off-pump CABG, entitled the Randomized On/Off Bypass (ROOBY) trial. They randomly assigned 2203 patients scheduled for urgent or elective CABG to either on-pump or off-pump procedures. The primary short-term end point was a composite of death or complications (reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure) before discharge or within 30 days after surgery. The primary long-term end point was a composite of death from any cause, a repeat revascularization procedure, or a nonfatal myocardial infarction within 1 year after surgery. Secondary end points included the completeness of revascularization, graft patency at 1 year, neuropsychological outcomes, and the use of major resources.

There was no significant difference between off-pump and on-pump CABG in the rate of the 30-day composite outcome (7.0% and 5.6%, respectively; P=0.19). The rate of the 1-year composite outcome was higher for off-pump than for on-pump CABG (9.9% vs. 7.4%,

P=0.04). The proportion of patients with fewer grafts completed than originally planned was higher with off-pump CABG than with on-pump CABG (17.8% vs. 11.1%, P<0.001). Follow-up angiograms in 1371 patients who underwent 4093 grafts revealed that the overall rate of graft patency was lower in the off-pump group than in the on-pump group (82.6% vs. 87.8%, P<0.01). There were no treatment-based differences in neuropsychological outcomes or short-term use of major resources.

At 1 year of follow-up, patients in the off-pump group had worse composite outcomes and poorer graft patency than did patients in the on-pump group. No significant differences between the techniques were found in neuropsychological outcomes or use of major resources

Chapter 6 Conclusions and Summary of Findings

This was a pilot study designed to evaluate the changes in a novel range of biomarkers to assess organ dysfunction. Hence results were analysed on a per protocol basis. Also there was only one surgeon who performed OPCAB. The number of patients in the study is small. These are all accepted as limitations of the study. Clinical outcomes are described but no claims of superiority or inferiority for either technique can be drawn from this study.

Chapter 1 outlined some of the developments and ideas that led to the development of the "heart-lung" machine. It also highlighted the pioneers of what is now considered to be one of the most successful treatments for coronary artery disease, coronary artery bypass grafting (CABG). Though the first CABG operations were carried out without the use of CPB the supremacy of CPB was quickly established such that by the 1970s virtually all CABG was routinely performed with CPB. Nevertheless there were numerous problems associated with the use of CPB.

Chapter 2 gave an overview of the range of organ damage that is known to occur in patients undergoing CPB. This is in part due to the inflammatory response triggered by CPB (SIRAB). Thus was reborn the concept that the avoidance of CPB should eliminate SIRAB. However what has become apparent over the years is the relative magnitude of the generalized systemic inflammatory response (SIRS) related to the stress of surgery and general anaesthesia. By definition OPCAB eliminates SIRAB and allows us to study in detail the relative magnitude of SIRAB induced organ damage.

Chapter 3 detailed the study methodology. This was a randomised pilot study that investigated patients undergoing CABG with CPB with cardioplegic arrest and without. We assessed end organ injury with a range of novel biomarkers. In addition we also studied some currently used markers and sought to determine any relationships between them. We also sought to assess physiological end organ function of the myocardium and gut. The primary endpoints were change in biomarker levels. Thus the trial was not carried out on an intention to treat principle.

Chapter 4 showed the results obtained. The patients were well matched and would be considered as moderate risk. Of particular note was that the index of completeness of vascularization was similar between the two groups. This has been another issue where OPCAB has been used. Reduced rates of vascularization are associated with excess long-term

mortality and morbidity. There were also 3 patients that had to be converted as an intra-operative emergency to ONCAB. Here in is another even more significant drawback of OPCAB. Rates of conversion from OPCAB to ONCAB are about 13% in randomized controlled trials[197]. The mortality rate for converted patients is 10%[197, 275]. Thus if all the 800,000 patients who undergo isolated CABG world wide had been performed using OPCAB there would have been about 10,000 deaths due to conversion alone. That this does not happen is due to careful patient selection. Thus at a time when mortality has continued to decline decade after decade despite increasing comorbidity of patients presenting for surgery OPCAB itself could become the biggest iatrogenic cause of mortality if practiced in an unselected manner.

As regards postoperative myocardial function this pilot study confirms previous findings of lower release of biochemical markers of myocardial injury. The OPCAB group also had reduced inotropic requirements compared to the ONCAB group. Earlier diagnosis of myocardial injury with H-FABP may better guide postoperative care.

As regards postoperative lung dysfunction there is a general rise in CC16 and a trend towards return to baseline. Analysis of the AUC showed no significant differences between the two groups (table 4-13, figure 4-11). As regards SP-D there was a sharp fall in SP-D levels postoperatively in both groups as the lungs become inflamed with no return to baseline after 12 hours. There was no difference in the AUC between the two groups (table 4-14, figure 4-12). Analysis of the respiratory index or PaO_2/FiO_2 ratio (table 4-16, figure 4-14) shows a concordant fall postoperatively in both groups. There were no statistically significant differences between the two groups over the study period ($p=0.58$). Both groups had similar extubation times (table 4-17) in our study. That there was a change in biomarker profile may provide further avenues of earlier detection of lung injury.

As regards gastrointestinal function there was a similar and significant decline in pHi in both groups over time but no difference between groups ($p=0.69$). The CO_2 gap showed significant interaction with time ($p<0.001$). There was no difference between groups ($p=0.80$). There was a significant ($p<0.001$) negative Spearman's correlation Rs -0.84 between pHi and CO_2 gap. There was a similar and significant rise in $PgCO_2$ in both groups but no difference between groups ($p=0.58$) There was a significant positive Spearman correlation between the $PgCO_2$ and CO_2 gap, Spearman's rho =0.844; $p<0.001$. There was a significant negative Spearman correlation between the $PgCO_2$ and the pHi, Spearman's rho =

0.928; p<0.001. There was a similar rise in cortisol in both groups but no difference between groups (p=0.89). There was a similar decline in levels of endotoxin antibody in both groups for both classes of immunoglobulin. There was no difference between groups For IgG EndoCAB (p=0.59) or IgM EndoCAB (p=0.81). I-FABP release was similar between both groups (p=0.55). However the area under the curve (AUC) was greater in the ONCAB group (p=0.001). Release of BPI was dependent on the preoperative levels (p=0.016). There was a greater release of BPI in the ONCAB group postoperatively (p=0.001) and at 4 hours (p=0.031). Release of defensins was greater in the ONCAB group post operatively (p=0.001) and at 4 hours (p=0.031). Release of MBL showed a significant time (p=0.002) interaction. The post-operative levels were affected by preoperative levels (p=0.023). There was no difference between the groups (p=0.66). There were no significant differences in oxygen extraction (p=0.49) between the two groups. So is the gut the originator of the SIRAB? Probably not as suggested by the apparently similar changes in a plethora of markers of splanchnic perfusion. Can the gut perpetuate SIRAB? Probably yes due to the three fold reduced overall energy transfer to the gut associated with non pulsatile CPB[15] which facilitates transient deterioration in mucosal barrier function and endotoxemia. That this response was attenuated in this study may be a reflection of the use of modern CPB. Future work needs to be undertaken using technology that delivers "true" pulsatile CPB. From a clinical point of view the routine use of tonometry may be another useful aid in the monitoring of gut perfusion.

As regards liver injury: hepatic α-GST showed a significant time (p<0.001) interaction and this relationship was linear (p<0.001). There were no differences between groups (p=0.74). For L-FABP there was no significant time (p=0.70) interaction. There was no difference between groups (p=0.26). There was no significant difference in serum lactate between groups (p=0.96). Ischaemic liver injury is a very rare complication after CABG. This study finds no evidence in favour of OPCAB in the absence of any pre-existing liver dysfunction.

As regards renal function levels of NGAL showed no significant change over time (p=0.33). There was a significant time procedure interaction (p=<0.001). There was greater release of NGAL post operatively in the ONCAB group than the OPCAB group (p=<0.001). There was no significant difference in the AUC between the two groups (p=0.32). Release rate of α-GST showed that the changes were related to time. Release rates changed in a linear

fashion (p=0.01). There was also a time procedure interaction (p=0.05). The release rate of α-GST was statistically significantly higher at 4 hours in the ONCAB group (p=0.05). Release rate of π-GST showed a significant change over time (p=0.001). There was no significant time procedure interaction (p=0.29). There were no significant differences between procedures (p=0.69). This is one area where there has been considerable interest in OPCAB. It would be interesting to see if others can corroborate our results.

As regards cerebral injury: release of S100 beta showed a significant time interaction (p<0.001). There was no significant group time interaction (p=0.45). There was a significant difference between procedures (p=0.003). There was greater release of S100 beta in the ONCAB group for all time points: post operatively (p=0.001), 4 hours (p=0.004), 8 hours (p=0.05) and at 12 hours (p=0.008). Release of B-FABP showed no significant time interaction (p=0.46), no significant time procedure interaction (p=0.67) and no significant difference between procedures (p=0.73). B-FABP showed an initial decline in both groups. The maximal decline occurred about 4 hours postoperatively. Subsequently there was a dramatic rise in the ONCAB group at 4 hours and at 8 hours in the OPCAB group. Thereafter there was a decline to baseline. Changes in B-FABP suggested greater damage occurred with ONCAB than OPCAB. One of the usefulness of such markers is to see if their release can be attenuated by potential therapies. This will become more important with an ever-increasing aging population presenting for cardiac surgery.

In conclusion though somewhat counter intuitive, modern CPB is well tolerated. Modern CPB considerably attenuates SIRAB. However the repeated and persistent haemodynamic changes during cardiac placement and graft construction in OPCAB are a considerable source of post-operative morbidity. Future developments in CPB should concentrate on providing truly pulsatile flow as this may deliver the energy the body needs to ameliorate the morbidity associated with CPB. The haemodynamic instabilities inherent in OPCAB would seem to make this technique potentially unsuitable for high-risk patents, as these are the ones with the least physiologic reserve.

The ROOBY trial[274] concluded that there was no overall advantage to the use of the OPCAB as compared with the ONCAB cardiac surgical approach for coronary bypass. Instead, there was a consistent trend toward better outcomes in patients undergoing the conventional on-pump CABG technique, including better 1-year composite outcomes and 1-year patency rates. Moreover, no significant differences between the off-pump and the on-

pump techniques were identified in neuropsychological outcomes or the use of major resources.

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