UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE, HEALTH AND LIFE SCIENCES

School of Medicine

Splanchnic Injury during Coronary Surgery with and without Cardiopulmonary Bypass

by

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Thesis for the degree of Doctor of Medicine

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ABSTRACT

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SPLANCHNIC INJURY DURING CORONARY SURGERY WITH AND WITHOUT CARDIOPULMONARY BYPASS

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Coronary artery surgery is traditionally performed with the use of cardiopulmonary bypass (CPB). Coronary surgery without CPB (off-pump) is a relatively recent technique, which may confer some advantages over surgery with CPB. In this thesis several clinical studies were performed to enhance our understanding of the possible advantages and disadvantages of off-pump surgery over surgery with CPB.

In the first part of this thesis aspects of the haemodynamic performance during off-pump surgery were examined. Intraoperative haemodynamic changes were described using a continuous, real-time cardiac output monitoring technique, which is superior to the thermodilution method. The haemodynamic effects of an intraoperative pleuropericardial release manoeuvre were also investigated. A significant transient decline in cardiac output was observed during cardiac manipulation for off-pump coronary anastomoses. Significant improvement of the haemodynamic performance with a right pleuropericardial release manoeuvre was also documented.

The second part of the thesis examined the effect of surgery with and without CPB on endocrine function. This was done in a prospective randomised fashion, and the perioperative changes in thyroid and stress hormones in patients undergoing surgery with CPB vs. off-pump were measured. We observed significant transient elevations in stress hormones and thyroid hormonal changes consistent with euthyroid sick response in both groups. There were no significant differences between the groups.

In the final part of this thesis the effect of coronary surgery with and without CPB on the gastrointestinal system was examined. Significant gastric mucosal hypoxia in the early postoperative period was observed in both groups, with no significant differences between the groups. Gastric mucosal oxygenation was inversely related to global oxygen extraction fraction. There was evidence of temporary decline in intestinal absorptive and barrier function in both groups, and off-pump patients demonstrated a quicker recovery of intestinal function. There was a transient and similar reduction in hepatic function in both groups, but no significant hepatic injury.

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Declaration of Authorship

I, Theodore Velissaris, declare that the thesis entitled "Splanchnic injury during Coronary Surgery with and without Cardiopulmonary Bypass" and the work presented in it are my own.

I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University;
- Where any part of this thesis has been previously submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- Where I have consulted the published work of others, this is always clearly attributed;
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- Parts of this work have been published as:

  Original articles

  1. A prospective randomized study to evaluate splanchnic hypoxia during beating-heart and conventional coronary revascularization.
     T Velissaris, A Tang, M Murray, A El-Minshawy, D Hett, S Ohri.
     European Journal of Cardio-thoracic Surgery, 2003;23(6):917-24.

  2. A prospective randomized study to evaluate stress response during beating-heart and conventional coronary revascularization.
     T Velissaris, ATM Tang, M Murray, RL Mehta, PJ Wood, DA Hett, SK Ohri.
     Annals of Thoracic Surgery, 2004;78(2):506-12.

How to do it article

3. Right pleuropericardial release: a useful technique in off-pump coronary surgery.
   T Velissaris, RG Stuklis, DA Hett, SK Ohri.
   Asian Cardiovascular & Thoracic Annals, 2003;11(2):174-6.

Letter

4. Haemodynamic changes during off-pump surgery.
   T Velissaris, AT Tang, MM Jonas, SK Ohri.
   European Journal of Cardio-thoracic Surgery, 2002;22(5):852.

Review article

5. Gastrointestinal dysfunction following cardiac surgery.
   SK Ohri, T Velissaris.
   Perfusion, 2006, in press.

Abstracts

6. Haemodynamic advantages of right pleurotomy during cardiac verticalization in beating heart surgery.
   T Velissaris, A Al-Khaddour, D Pontefract, AT Tang, AMK El-Minshawy, RG Stuklis, DA Hett, MM Jonas, SK Ohri.
   Cardiothoracic Surgery Research Club - winter meeting, Sheffield, UK, 10/11/01.

7. A prospective randomized study to evaluate splanchnic hypoxia during beating-heart and conventional coronary revascularization.
   T Velissaris, AT Tang, AM El-Minshawy, DA Hett, SK Ohri.
   Annual meeting of the Society of Cardiothoracic Surgeons of Great Britain and Ireland, Bournemouth, UK, 18/03/02.

8. Real-time monitoring of haemodynamic changes during beating-heart coronary surgery.
   T Velissaris, A Tang, D Hett, M Jonas, S Ohri.
   Cardiothoracic Surgery Research Club - summer meeting, Southampton, UK, 18/05/02.

9. A prospective randomized study to evaluate splanchnic hypoxia during beating-heart and conventional coronary revascularization.
   T Velissaris, A Tang, M Murray, A El-Minshawy, D Hett, S Ohri.
   16th Annual meeting of the European Assosiation for Cardiothoracic Surgery, Monte-Carlo, Monaco, 23/09/02.

10. A prospective randomized study to evaluate stress response during beating-heart and conventional coronary revascularization.
    T Velissaris, A Tang, M Murray, P Wood, R Mehta, D Hett, S Ohri.
    39th Annual meeting of the Society of Thoracic Surgeons, San Diego, USA, 01/02/03.

11. A randomized prospective study to evaluate intestinal absorption and gut permeability after coronary surgery with and without cardiopulmonary bypass.
    T Velissaris, A Tang, P Wood, D Hett, S Ohri.
    Annual meeting of the Society of Cardiothoracic Surgeons of Great Britain and Ireland, Guernsey, UK, 07/03/04.

12. Thyroid hormone metabolism during coronary surgery with and without cardiopulmonary bypass: a prospective randomized study.
    T Velissaris, A Tang, P Wood, D Hett, S Ohri.
    Annual meeting of the Society of Cardiothoracic Surgeons of Great Britain and Ireland, Guernsey, UK, 09/03/04.

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I dedicate this thesis to my wife, Emmanouela, and my children, Rania and Yannis, who endured the long hours that I spent working on this project.

Abbreviations

ABP: Arterial blood pressure

ADH: Anti-diuretic hormone

AE: Acrinidium ester

AF: Atrial fibrillation

ALP: Alkaline phosphatase

ALT: Alanine aminotransferase

AST: Aspartate transaminase

ATP: Adenosine triphosphate

AXC: Aortic cross-clamp

CABG: Coronary artery bypass grafting

CaO_2: Arterial blood oxygen content

CB: Conjugated bilirubin

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

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: ethylenediaminetetraacetic acid

fT3: Free triiodothyronine

fT4: Free thyroxine

GI: Gastrointestinal

Hb: Haemoglobin

HITS: High intensity transient signals

HR: heart rate

IABP: Intra-aortic balloon pump

ICU: Intensive care unit

IL: Interleukin

IQR: Interquartile range

LAD: Left anterior descending

LFTs: Liver function tests

LIMA: Left internal mammary artery

LV: Left ventricular

LVEF: Left ventricular ejection fraction

MAP: mean arterial blood pressure

MEGX: Monoethylglycinexylidide

MI: Myocardial infarction

MIDCABG: minimally invasive direct coronary artery bypass grafting

mPAP: mean pulmonary artery pressure

NA: Noradrenaline

NAG: N-acetyl glucosaminidase

NO: Nitric oxide

NOS: Nitric oxide synthase

OFR: Oxygen-free radicals

OM: Obtuse marginal

ONCAB: On-pump coronary artery bypass

OPCAB: Off-pump coronary artery bypass

PAF: Platelet-activating factor

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

PaO_2: Partial pressure of oxygen in arterial blood

PAP: Pulmonary artery pressure

pCO_2: Partial pressure of carbon dioxide

PCV: Packed cell volume

PDA: Posterior descending artery

PE: Phenylephrine

PG: Prostaglandin

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

pHi: Intramucosal pH

PMP: Paramagnetic particles

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

RLUs: Relative light units

rT3: reverse triiodothyronine

RV: Right ventricle, right ventricular

SaO_2: Arterial blood oxygen saturation

SD: Standard deviation

SIELI: Severe ischaemic early liver injury

SIRS: Systemic inflammatory response syndrome

SVI: Stroke Volume Index

SvO_2 : Mixed venous blood oxygen saturation

SVRI: Systemic Vascular Resistance Index

T3: Triiodothyronine

T4: Thyroxine

TB: Total bilirubin

TNF-α: Tumour necrosis factor alpha

TSH: Thyroid-stimulating hormone

TxA2: Thromboxane A2

VO_2: Whole-body (global) oxygen consumption

X-clamp: Aortic cross-clamp

Chapter 1

Introduction

The History of Coronary Artery Surgery and the Development of Cardiopulmonary Bypass

Surgical revascularization of the coronary arteries has become one of the commonest major operations in the Western world. Coronary artery disease is the leading cause of death in the Western societies and angina is its most frequent manifestation. Coronary artery bypass grafting (CABG) is currently an accepted treatment for symptomatic relief and, depending on the anatomy of the disease, for improvement of the long-term prognosis and outcome. Over the last three decades there has been a dramatic increase in the number of CABG procedures, with 24,728 operations performed in the UK in the financial year 1999-2000 (Keogh and Kinsman 2004). Coronary artery surgery has also become increasingly safe over time, with the mortality of a primary, elective, isolated CABG of the order of 1.8% in the UK in 1999 and a mortality of 2.2% for all primary isolated CABG operations. This must be contrasted with mortality figures for CABG of 6-7% in the late 1970s. It should also be noted that the drop in mortality and complication rates has occurred despite a continuously higher risk profile of the patient population undergoing CABG. The explosion that we have witnessed over the past four decades in the number of CABG operations performed and the increasing safety of this operation and of cardiac surgery in general would not have been achieved without the development of cardiopulmonary bypass (CPB).

The first attempts for surgical relief of angina pectoris took the form of interruption of the sympathetic nervous pathways to the heart. Francois-Franck recommended cervical sympathetic denervation in 1899. In 1920 Jonnesco provided the first report of surgical cure of angina by left cervical sympathetic chain resection under general anaesthesia (Jonnesco 1920). This approach was pursued in the twenties by Coffee in California. Further attempts to develop procedures to denervate the heart demonstrated that the afferent pathways from the heart arose from the thoracic as well as the cervical ganglia; therefore removal of the sympathetic chain from the stellate ganglion down to the fourth thoracic ganglion bilaterally was required to

completely denervate the heart. The magnitude of these procedures plus the questionable clinical results led to their gradual abandonment.

Surgical attempts at myocardial neoangiogenesis for relief of angina were also pursued over a forty-year period in the 20th century. They initially took the form of epicardial scarification in animals by Beck and Murray in the thirties (Beck and Tichy 1934), while in 1935 Beck introduced pectoral muscle grafting to the abraded area for better results (Beck and Tichy 1934). O'Shaughnessey in 1936 introduced the use of omental pedicle grafts placed directly on the epicardium to revascularize the human heart. In 1938 Thompson introduced pericardial talc poudrage as the inflammatory stimulus for neoangiogenesis (Thompson 1939). Shortly thereafter, Beck did the same operation in humans in Cleveland, using asbestos instead of talc. Because of its simplicity, low morbidity and the lack of another approach, this procedure continued until 1960. In 1948 Vineberg introduced the implantation of an internal mammary artery into a myocardial tunnel to create new coronary collaterals (Vineberg 1949). It was later shown that small but definite collaterals did develop between the internal mammary artery and branches of the coronary vessels (Buller and Vineberg 1954). More than 5,000 such operations were performed between 1950 and 1970, with at least subjective improvement in many patients (Vineberg 1975).

The first attempts of direct surgery to the coronary arteries were made in the beginning of the 20th century by Alexis Carrel, who was honoured with the Nobel Prize in medicine. In 1896 Jaboulay, who was Carrel's teacher, introduced a technique of intima-to-intima vascular anastomosis with interrupted everted mattress sutures. Carrel refined the vascular anastomotic techniques and in 1910 he reported the first attempt at coronary artery surgery (Carrel 1910). It consisted of the construction of a graft between the descending thoracic aorta and the distal end of the left coronary artery in an anaesthetised dog, using a section of homologous cryopreserved carotid artery. The operation was not successful, as the heart fibrillated three minutes after interruption of the circulation, while the anastomosis took five minutes; the dog succumbed two hours after the operation, despite resuscitation attempts.

It was much later, in 1954, that Murray provided the first report of successful direct coronary grafting in five dogs, using axillary artery or free carotid artery anastomosed proximally to the ascending aorta (Murray et al. 1954). Murray's technique was not dissimilar to the techniques employed today for CABG without the use of CPB, as his success was due to the use of heparin and the introduction of an intraluminal shunt at the carotid-coronary artery anastomotic site. In 1956 Thal reported a technique in dogs for the direct anastomosis of the internal mammary artery to the circumflex coronary artery. Patency of up to 6 months was demonstrated using this technique.

Perhaps the most important pioneer in the early development of extracorporeal circulation was Gibbon. Gibbon described the first total bypass of the heart and lungs in experimental animals in 1937 (Gibbon 1937), but he subsequently had his work interrupted by the Second World War. In 1953 Gibbon performed the first successful total CPB on an 18-year-old woman for repair of an atrial septal defect (Gibbon 1954). Prior to that, Dogliotti and Constantini had described the first successful right heart bypass for removal of a mediastinal tumour in 1951 (Dogliotti and Costantini 1951). In the same year, Dennis described the first human application of CPB for the repair of what was preoperatively thought to be an atrial septal defect in a 6 year old (Dennis et al. 1951). However, the child died, and at autopsy the lesion was found to be a partial atrio-ventricular canal defect, which may have contributed to the child's death. In 1955 Kirklin started the first series of intracardiac operations using a modified version of Gibbon's pump-oxygenator (Kirklin et al. 1955).

However, despite progress in the oxygenation and pumping of blood, cardiac surgery was still limited by the techniques of myocardial preservation. The ability to arrest and then recommence the heart was the result of pioneering experimental work by Melrose and Baker in 1955 and 1957 (Melrose et al. 1955; Baker et al. 1957). Their work showed cardiac diastolic arrest was achieved by perfusing the heart with Locke's solution with added potassium citrate in a concentration of above 1mg/ml. Diastolic arrest occurred within 20 seconds and could be maintained as long as the coronary arteries contained the perfusate. Spontaneous beating occurred within 90

seconds of perfusing with plain Locke's solution, with recovery almost complete by 3 minutes. This work provided the foundation for the use of elective cardiac arrest in combination with hypothermia for myocardial protection during CPB. The potassium-rich perfusate became known as cardioplegia and the technique was subsequently shown to be clinically effective and safe. Effler reported the first human use of the cardioplegic technique and later reported a series of 97 patients using this method (Effler et al. 1957; Effler et al. 1957). Since then a number of cardioplegic solutions have been developed and there is ongoing research and debate about the most effective composition, mode of delivery, temperature and dose requirements. The development of CPB and cardioplegic techniques popularised coronary surgery, as it allowed the construction of coronary anastomoses on an empty, motionless and bloodless heart.

The Pathophysiology of Cardiopulmonary Bypass

While the development of CPB led to the explosion that we have witnessed in cardiac surgery over the past four decades in terms of number, complexity and safety of procedures performed, it soon became apparent that a significant degree of organ and tissue damage that occurs during cardiac surgery is related to the use of the CPB circuit (Alfieri and Kotler 1990). Ongoing research has lead to an increasing understanding of the pathophysiology of CPB, which has resulted in continuous refinement in bypass technique and technology and gradual reduction in CPB-related morbidity and mortality. Despite its complexity, CPB pathophysiology may be broadly divided into haemodynamic changes and changes related to a systemic inflammatory response. An outline of this pathophysiology follows, to provide an understanding of the different mechanisms involved in the development of splanchnic injury.

Haemodynamic changes during Cardiopulmonary Bypass

Haemodilution

Haemodilution occurs immediately on commencement of CPB, as a result of priming of the bypass circuit with crystalloid solutions. Thus on commencement of CPB the haematocrit may fall to 20-25%, depending on the preoperative haematocrit and the patient's body size. The decrease in blood oxygen content is partly offset by improvements in blood flow and free water clearance by the kidneys. Blood flow improves due to a reduction in blood viscosity; this leads to an increase in renal blood flow, urine flow, free water clearance, glomerular filtration and filtration fraction (Utley et al. 1981). Moreover, haemodilution dampens the vasoconstrictive effect of hypothermia during CPB (Utley et al. 1976).

Fluid Compartment Changes

Extracellular water and total body water increase during CPB and the increase is related to the length of CPB (Breckenridge et al. 1970). This increase is related to a rise in capillary permeability during CPB (Smith et al. 1987) and a reduced intravascular oncotic pressure, as a result of haemodilution. In the early post CPB period water overload and hyponatraemia are very common and usually persist for 24-48 hours through various mechanisms: 1) Fluid overload (CPB priming fluid, cardioplegic solution, intravenous maintenance fluids, transfusion of blood products) 2) Routine administration of diuretics (Spital 1999) 3) Increased secretion of antidiuretic hormone as part of the systemic stress response (Guy et al. 1987) and 4) CPB-related natriuretic effect via secretion of urodilatin from the kidneys and atrial natriuretic factor from the heart (Sehested et al. 1997).

The increased water content has been demonstrated in the myocardium, brain, medulla of the kidney, stomach, intestine and liver. The resultant tissue oedema has been associated with pulmonary, myocardial, brain and gastrointestinal dysfunction. One of the main advantages of blood cardioplegia as a myocardial protection technique, which has now largely replaced crystalloid cardioplegia, was the higher

oncotic pressure of blood cardioplegic fluid, compared to crystalloid solutions, with a resultant decrease in myocardial oedema (Buckberg 1990).

The effect of core temperature and pulsatility of flow

Physiological blood flow is 3.0-3.2 l/min/m^2 at rest and pulsatile in character (Tarhan and Moffitt 1971). However, many cardiac operations are still conducted using non-pulsatile flow, maintaining flow rates around 2.4 l/min/m^2 at normothermia. As the core temperature drops, tissue oxygen requirements are reduced, so that at 32°C the bypass flow may be reduced to 2.0-2.2 l/min/m^2 and at 28°C at 1.6 l/min/m^2 (Fox et al. 1982). Further reductions in blood flow are limited by the requirements of vital organs such as the brain.

The body response to the reduced flow is that of progressive peripheral vasoconstriction (Dunn et al. 1974) via release of mediators such as catecholamines, angiotensin II (Taylor et al. 1979) and vasopressin (Levine et al. 1981). Angiotensin II in particular is thought to be the most potent vasoconstrictor, and a significant correlation has been demonstrated between rises in angiotensin II and vasoconstriction during CPB (Taylor et al. 1979). The vasoconstrictive response leads to a rise in the peripheral vascular resistance and therefore an increase in the left ventricular afterload. Moreover, preferential vasoconstriction of the splanchnic beds, while the flow to more vital organs is preserved, results in an autotransfusion and increases the preload to the heart (Rothe 1983). The splanchnic capacitance vascular beds contain approximately one third of the total circulatory volume at rest.

In the last decade we have witnessed an increased use of pulsatile flow during CPB. In his pioneering theoretical work, Shepard and his colleagues described in 1966 the extra energy that may be available to the tissues during pulsatile flow, which became known as the energy equivalent pressure theory of the effects of pulsatile flow (Shepard et al. 1966). Since then, significant clinical and experimental evidence has accumulated in favour of pulsatile bypass. Chun-Hsiu in 1981 and Shepard in 1969 demonstrated improved tissue metabolism with pulsatile flow (Shepard and Kirklin 1969; Chun-Hsiu et al. 1981), while other studies have shown a dampening in the

vasoconstrictive response and a reduced release of vasopressin (Philbin et al. 1981) and angiotensin II (Taylor et al. 1979) during pulsatile bypass.

The inflammatory response to Cardiopulmonary Bypass

Cardiac surgery with the use of CPB is associated with a perioperative systemic inflammatory response syndrome (SIRS), which is secondary to the insult of a cardiac operation and perhaps to a certain extent to the use of CPB *per se* (Franke et al. 2005). The exposure of blood to nonphysiologic surfaces and conditions induces a complex inflammatory response, including activation of complement and leucocytes, and the production of various substances such as oxygen-free radicals, arachidonic acid metabolites, platelet-activating factor, nitric oxide and endothelins. Systemic inflammatory response is induced in all patients undergoing CPB, but there is a wide range in the severity of the response syndrome, with only a minority of patients demonstrating severe haemodynamic disturbance as a result of SIRS (Taylor 1996). The inflammatory response is thought to play a key role in postoperative morbidity.

Complement system

The complement system consists of around 20 plasma proteins that can be activated in a cascade sequence by the classic and the alternative pathways. The exposure of blood to the CPB circuit activates the alternative pathway, leading to the formation of C3a and C5a (Chenoweth et al. 1981), while protamine administration after discontinuation of CPB activates the classical pathway, which results in the formation of C4a and a further rise in C3a levels (Kirklin et al. 1986). Endotoxin release in the circulation may be able to activate both the classical and alternative pathways (Jansen et al. 1992). Complement activation generates a number of activated proteins, including the anaphylatoxins C3a and C5a, which cause histamine release from mast cells and basophils, a rise in vascular permeability and stimulate leucocytes to release oxygen-free radicals and lysosomal enzymes. C3a causes platelet aggregation, while C5a stimulates neutrophil aggregation and adherence to endothelial cells (Utley 1990). The clinical relevance of complement activation per

se remains uncertain. Several studies have suggested an association between the C3a levels and postoperative morbidity (Kirklin et al. 1983), however other studies have not demonstrated such correlation (Tennenberg et al. 1990; Steinberg et al. 1993). The differences possibly reflect the complex nature of the inflammatory response, with complement activation being just one of a number of factors involved. A recent randomised study evaluating the clinical efficacy of a C5 complement inhibitor (Shernan et al. 2004) did not demonstrate any significant impact on outcome.

Leucocytes

During CPB, neutrophils are activated by a number of mediators, including C3a, C5a, platelet-activating factor (PAF), and leukotriene B4. Activation of neutrophils results in the expression of specific adhesion molecules on the polymorphonuclear cell surface, such as CD11b/CD18 (also known as Mac-1, CR3, or Mo-1). Neutrophil adherence to endothelial cells is an important early step in tissue injury. Activated neutrophils are thought to be the main mediators of CPB-related pulmonary injury (Dreyer et al. 1995), as well as myocardial ischaemia-reperfusion injury (Youker et al. 1994). Experimental attempts at preventing neutrophil adhesion have been made, so as to reduce pulmonary and myocardial injury (Horgan et al. 1990; Byrne et al. 1992). This may provide practical benefit, although the potential benefit should be weighed against a possible increased infection risk. More recently, attempts at reducing the number of activated leucocytes in the circulation have been made by adding a leucocyte-depleting filter to the CPB circuit. Although there is some evidence that leucofiltration may reduce CPB-related pulmonary inflammation and renal injury (Tang et al. 2002; Alexiou et al. 2004), the impact of leucofiltration on clinical outcome remains uncertain.

Oxygen-free radicals

Leucocyte activation results in the release of oxygen-free radicals (OFR), which act on membrane lipids to increase membrane permeability, and may also decrease cardiac and pulmonary function (McCord 1985; Clermont et al. 2002). OFR may also reduce the availability of nitric oxide, and this may precipitate vasospasm and thrombosis after cardiac reperfusion (McCord 1985). Various indirect methods have

shown increased OFR activity during and after CPB. Several studies have shown a rise in the blood levels of malondialdehyde, a lipid peroxidation product, indicating free radical-mediated damage to the lipid membrane (Prasad et al. 1992). Other investigators have demonstrated a rise in other free radical reaction products and hydrogen peroxide (Davies et al. 1993; Toivonen and Ahotupa 1994). The levels of OFR activity may be higher during CPB with bubble oxygenators than membrane oxygenators (Davies et al. 1993). OFR production may also be affected by other factors, such as temperature (Haniuda et al. 1995).

Arachidonic Acid Metabolites

The release of arachidonic acid leads to the formation of prostanoids, the most important of which are thromboxane A2 (TxA2) and prostaglandins, and leukotrienes (Downing and Edmunds 1992). TxA2 is a strong vasoconstrictor and also induces platelet aggregation. The production of TxA2 in animal models has been related to myocardial dysfunction and to pulmonary hypertension following CPB (Byrne et al. 1993; Cave et al. 1993). Prostaglandins have vasodilating and platelet anti-aggregant properties and thus counterbalance the effects of TxA2. The most important prostaglandins are prostaglandin E1 (PGE1), PGE2 and prostacyclin. Prostacyclin may have more potent beneficial effects than PGE1 or PGE2 on the recovering myocardium (Downing and Edmunds 1992). PGE1 can be used in the management of pulmonary hypertension post-CPB (Vincent et al. 1992; Fortier et al. 2004). Leukotrienes are potent chemoattractants and increase vascular permeability. Their production can play an important role in acute lung injury and multiple organ failure (Gadaleta and Davis 1994).

Endotoxin

Endotoxin is a potent mediator of the inflammatory cascade. Circulating levels of endotoxin have been shown to rise during and after CPB (Jansen et al. 1992), but there is a significant variability in endotoxin levels in different studies. This is probably related to different methods for endotoxin measurement, different patient populations and different CPB protocols. There are many possible sources of endotoxin during CPB but the gut is probably the most important one (Ohri et al.

1993; Sinclair et al. 1995; Riddington et al. 1996). It is thought that gut mucosal hypoxia during and after CPB results in loss of gut barrier function, which leads to endotoxin release into the circulation. Endotoxin may be partly responsible for the activation of complement via the alternative pathway and for the increased release of cytokines including tumour necrosis factor α (TNF-α) (Jansen et al. 1992; McKinney et al. 2003). However, no association has been shown between the magnitude of endotoxin release and patient outcome.

Cytokines

CPB is associated with the release of both pro-inflammatory and anti-inflammatory cytokines (Wan et al. 1997; Halter et al. 2005). Cytokines are released via a number of mediators, such as ischaemia-reperfusion, activated complement factors, endotoxin, and via other cytokines. Increased levels of the pro-inflammatory cytokines TNF-α, interleukin 6 (IL-6) and IL-8 during and after CPB have been shown by several studies (Wan et al. 1997; Halter et al. 2005). The levels of IL-6 and IL-8 have been correlated with the duration of cardiac ischaemia during CPB (Wan et al. 1996). TNF-α and IL-6 may contribute to myocardial dysfunction and haemodynamic instability following CPB (Hennein et al. 1994; Ohkawa et al. 1995; te Velthuis et al. 1995). IL-6 has also been correlated to pulmonary dysfunction post-CPB (Halter et al. 2005). IL-8 is a potent neutrophil chemoattractant, and may contribute to lung injury via pulmonary leucocyte sequestration. Pro-inflammatory cytokines may also contribute to the development of multiple organ failure (Partrick et al. 1996). Increased levels of the anti-inflammatory cytokine IL-10 have also been observed during CPB. It is thought that IL-10 may suppress the production of pro-inflammatory cytokines (Wan et al. 1997). The balance of pro-inflammatory and anti-inflammatory cytokines may be important in determining the extent of the inflammatory response and clinical outcome.

Platelet-Activating Factor

PAF is a phospholipid that can be produced by many cells, including platelets and vascular endothelial cells (Ko et al. 1991). It is mainly known for its platelet aggregation and activation properties, but PAF receptors are also present on

neutrophils, monocytes, and endothelial cells. PAF is a potent neutrophil chemoattractant, activator, and aggregant (Kubes et al. 1990). PAF can have deleterious cardiac and haemodynamic effects, and it appears to be an important mediator of myocardial and pulmonary injury following CPB (Sawa et al. 1994; Zehr et al. 1995). PAF inhibition may represent a valuable therapeutic option to reduce morbidity after CPB (Sawa et al. 1994; Zehr et al. 1995). However, a clinical randomised study investigating the effect of a PAF antagonist on lung injury during CPB did not demonstrate any beneficial effect of PAF inhibition on pulmonary function (Taggart 2001).

Nitric Oxide

Nitric oxide (NO) is a major vasodilator and an inhibitor of platelet and neutrophil adhesion to the endothelium (Mehta 1995). NO has a very short half-life, but it is continuously synthesized and released from endothelial cells through the conversion of the amino acid L-arginine to L-citrulline by the enzyme NO synthase (NOS) (Mehta 1995). There are two isoforms of NOS: a) constitutive NOS, which is found in vascular endothelium, produces small amounts of NO, which play an important role in the maintenance of capillary blood flow and the regulation of cell function. b) Inducible NOS, which is mainly found in the macrophages, is activated by endotoxin or cytokines and is responsible for the production of much larger quantities of NO than the constitutive isoenzyme. These large amounts induce vasodilation but may also be involved in tissue damage.

Increased NO production occurs during and after CPB (Ruvolo et al. 1994), mainly through the release of pro-inflammatory cytokines, which increase NO production via the expression of inducible NOS (Tsujino et al. 1994). Heparin administration may also contribute to the NO release (Li et al. 1996). Increased levels of inducible NOS have been demonstrated in lung tissue samples from patients after CPB (Delgado et al. 1995). Airway NO rises during CPB and its levels are correlated with the duration of CPB (Hill et al. 1995). Reduced expression of NOS may contribute to pulmonary hypertension, and low dose NO inhalation is used in the management of post-CPB pulmonary hypertension (Khazin et al. 2004; Fattouch et al. 2005).

Moreover, reperfusion after aortic cross-clamping during CPB may lead to G-protein dysfunction in the coronary endothelium, which may impair NO release by constitutive NOS and lead to coronary vasospasm (Evora et al. 1994). NO donors can have protective effects against ischaemia-reperfusion injury and improve cardiac or gut function (Villarreal et al. 1995; Vinten-Johansen et al. 1995; Yeh et al. 2004).

Endothelins

Endothelin-1 is released from the endothelium and it is the most potent endogenous vasoconstrictor yet identified. Significant release of endothelin-1 after CPB has been observed in patients undergoing CABG (Hasdai et al. 1996). In post-ischaemia reperfusion conditions, endothelin-1 may induce coronary vasoconstriction, which can be reversed by nitroglycerin (McGowan et al. 1995). The vasoconstrictor effect of endothelin-1 may also be enhanced by endothelin-1-induced release of Tx A2 (Zaugg et al. 1996). Endothelin-1 is thought to be an important mediator of pulmonary hypertension, and it has been shown that blockade of endothelin-1 can reduce pulmonary vascular resistance after surgery for congenital heart disease (Schulze-Neick et al. 2002). The vasoconstrictor effects of endothelin may also contribute to gut hypoperfusion, resulting in loss of gut barrier function and endotoxaemia, which may further stimulate endothelin secretion from endothelial cells. A positive correlation has been found between endothelin-1 and endotoxin levels during CPB (te Velthuis et al. 1996). The kidney is particularly sensitive to the vasoconstrictor effects of endothelin-1. Plasma endothelin-1 levels at the end of CPB have been shown to correlate negatively with the urine volume during CPB, indicating a possible role of endothelin-1 in renal dysfunction after CPB (Zhu et al. 1994). Increased levels of endothelin-1 have also been found after cardiac or pulmonary transplantation, indicating a possible role in post-transplant complications (Berkenboom et al. 1995; Schersten et al. 1996). It has been recently shown in an animal model that endothelin blockade during cardiac allograft preservation reduces endothelial injury and enhances ventricular recovery after cardiac transplantation (Fedak et al. 2005).

The return of Off-pump Coronary Artery Bypass Surgery

As discussed earlier in this introduction, although the first attempts at surgical coronary revascularization were made using OPCAB techniques, these were quickly overshadowed in the late 1960s and early 1970s with the development of CPB and cardioplegic techniques for myocardial protection. The possibility of making an anastomosis on a motionless, empty heart without the risk of fibrillation during the anastomotic phase made this technique the gold standard and the OPCAB techniques became largely obsolete (Favaloro 1998). Perhaps the most prominent surgeon who remained working on the concepts of minimally invasive coronary surgery was Professor Vasilii I. Kolesov in St. Petersburg (then Leningrad), where he developed and performed different types of CABG (Olearchyk 1988; Olearchyk and Olearchyk 1999). Leningrad was recognised as the cultural and scientific centre of Russia and it was a very suitable place for Kolessov to develop his work. However, his ideas did not spread to the western world, as his work was published in Russia during the cold war. Gradually, his group dispersed after his retirement and OPCAB was rarely conducted anywhere. Kolesov is now recognised as one of the pioneers of off-pump coronary artery bypass surgery.

However, as surgical coronary revascularization became a well-established treatment of coronary artery disease, economic pressures in the early 1980s forced different groups, such as Benetti's and Buffolo's in South America to turn their attention back to OPCAB techniques in order to avoid the use of CPB and reduce the costs of the surgical procedure (Benetti 1985; Buffolo et al. 1985). Criticism on this clinical work arose from centres that were working with the established technique of CPB and cardioplegic arrest. Incomplete revascularization and questionable anastomotic quality were the main criticisms, despite reports of satisfactory results in large patient series.

Another factor that led to a renewed interest in OPCAB techniques was the realization that despite continuous improvements in the CPB circuits and progress in the surgical and anaesthetic techniques, there continued to be a significant morbidity

associated with CABG with CPB. The pathophysiology of CPB was studied extensively and it was thought that techniques that would avoid CPB might lead to a superior outcome.

This renewed interest led to the development of myocardial mechanical stabilisers in the mid-1990s, which significantly boosted OPCAB techniques. These stabilisers, together with the development of techniques that facilitate cardiac manipulation to adequately expose the less accessible coronary targets, allowed complete revascularization and made OPCAB accessible for most surgeons worldwide. Currently many surgeons all over the world use OPCAB for the majority of their coronary revascularization work.

On-pump or Off-pump?

Despite the growing popularity of OPCAB and the reports of excellent results in large series of patients, whether OPCAB offers clear advantages over surgery with CPB and whether it should now be considered as the gold standard technique remains debatable. Currently there is no consensus in the cardiac surgical community, with some surgeons using OPCAB as their preferred approach and some surgeons performing all their coronary revascularizations with CPB. In a recent (December 2002 – February 2003) Internet based survey performed by the Cardiothoracic surgical network, out of 543 respondent adult cardiac surgeons, 20% performed more than 80% of their coronary surgery using the OPCAB approach, while 45% would do less than 20% of their cases as OPCAB. The reasons for not performing more OPCAB surgery in the survey were unsuitability of patients for OPCAB (53%), satisfactory results with CPB (29%), lack of proof in the literature that OPCAB is superior (23%), inadequate training in OPCAB (15%), lack of obvious benefit with OPCAB (14%), and lack of anaesthetic cooperation (11%). When asked about factors that would persuade surgeons to perform more cases off-pump, the answers were more data demonstrating a benefit (45%), the arrival of further instruments to facilitate OPCAB (35%), more surgical training (26%), more anaesthetic training (21%) and anaesthetic cooperation (10%).

The above highlight that there is a big discrepancy in surgical practice and rather differing views on whether OPCAB confers any real advantages over CPB. The main reason for this debate is that OPCAB is still a relatively new technique and one would expect that as experience with it grows, the indications and contraindications for its use will become more established. The other reason is that, considering the importance of the topic, relatively few randomised studies have been done to compare OPCAB vs. CABG with CPB. Over the next few paragraphs a review of some of the evidence for and against OPCAB will be undertaken. To facilitate this, the review has been divided in three main areas: a) evidence about the potential pitfalls of off-pump, such as quality of anastomosis, b) evidence about the potential advantages of off-pump in early postoperative complications and outcome and c) evidence about medium/long-term outcome. Only evidence that arises predominantly from randomised studies and / or large retrospective series will be discussed.

A) The potential problems

Haemodynamic instability during OPCAB is perhaps the most important potential drawback of the technique. Haemodynamic instability will be discussed at length in Chapters 2 and 3 of this thesis. Essentially it is due to transient haemodynamic deterioration during cardiac manipulation for the construction of distal anastomoses (Grundeman et al. 1997; Mathison et al. 2000; Nierich et al. 2000; Watters et al. 2001; Do et al. 2002). It manifests as significant transient drops in cardiac output, despite relatively good preservation of systemic arterial pressures due to compensatory vasoconstriction. Haemodynamic disturbance during OPCAB has been well described in both clinical and experimental studies and has been shown to be primarily related to temporary right ventricular dysfunction during cardiac elevation, as the right ventricle undergoes compression between the interventricular septum and the surrounding fibrous pericardium and pleura (Grundeman et al. 1999).

Another potential disadvantage with the OPCAB approach is the quality of conduit-to-coronary artery anastomosis, which is immediately related to the short- and perhaps long-term graft patency. Obviously CPB coupled with cardioplegic myocardial arrest offers optimal conditions for the construction of coronary

anastomosis, as the heart is entirely motionless and the surgical field is bloodless. However, the use of mechanical myocardial stabilizers with OPCAB renders the immediate area around a coronary anastomosis relatively immobile and a bloodless field can also be achieved by proximal coronary occlusion or the use of intracoronary shunts during the anastomosis. Many experienced surgeons who perform regularly OPCAB think that the quality of anastomoses they perform is identical regardless whether they operate off-pump or using CPB and many OPCAB series with follow-up angiography have shown satisfactory graft patency rates up to 1 year after surgery. However, there are no long-term angiographic patency data available, and there is a relative lack of prospective randomised studies comparing angiographic patency after OPCAB vs. CPB. One of these studies showed a significantly higher patency rate (98% vs. 88%, p=0.002) after surgery with CPB vs. OPCAB at 3 months postoperatively (Khan et al. 2004). This was a prospective randomised study recruiting 104 patients and examined angiographically 130 grafts in each group. The criticisms of this study however were a) that the surgeons performing the cases were relatively inexperienced with OPCAB, as they had performed less than 100 OPCAB cases before the study and were doing under 15% of their coronary surgical cases off-pump, and b) that there was a significantly higher usage of radial artery grafts in the OPCAB group. The only other prospective randomised study where angiographic patency after on-pump CABG (ONCAB) vs. OPCAB was examined was undertaken by Puskas et al (Puskas et al. 2004), which recruited 200 patients. Coronary angiography prior to hospital discharge on 93.4% of the enrolled patients demonstrated similar graft patency with the two techniques (OPCAB 99.0% vs. ONCAB 97.7%). Coronary angiography was repeated 1 year postoperatively on 153 patients and again the angiographic patency was similar in the two groups (OPCAB 93.6% vs. ONCAB 95.8%).

Immediately relevant to the issues of ease of anastomosis and anastomotic quality is the other potential drawback of OPCAB, which is incomplete revascularization. Some surgeons argue that as it may be more challenging to perform a coronary anastomosis on a beating heart, during OPCAB one may be inclined not to graft coronary vessels that are technically more challenging, such as small,

intramyocardial, heavily atheromatous or calcified vessels, that one would perhaps be inclined to explore and possibly graft if the operation was performed with CPB. Incomplete revascularization is associated with a significant increase in 10 and 20 year mortality (Scott et al. 2000). Czerny et al randomised 80 patients undergoing elective coronary surgery into CPB and OPCAB groups (Czerny et al. 2001). The authors observed a significantly higher rate of complete revascularization in the CPB group (ONCAB 85% vs. OPCAB 65%). However, if incomplete revascularization is a significant problem with OPCAB, one would expect this to impact upon medium- and long-term clinical outcome (i.e. higher incidence of recurrent angina, reinterventions and so on). The available evidence suggests that this is not the case; several important studies that have examined clinical outcome up to 3 years after CABG with and without CPB have shown a comparable outcome with the two techniques (Angelini et al. 2002; Muneretto et al. 2003; Puskas et al. 2004). Moreover, the continuous improvement in myocardial stabilizers and surgical techniques to achieve adequate exposure of the coronary arteries further facilitate complete coronary revascularization. A more recent study by Puskas et al (Puskas et al. 2003) demonstrated complete revascularization with both CPB and OPCAB in 200 patients randomised to one of the two groups.

The final potential problem with the OPCAB approach is that occasionally one has to convert to the use of CPB. The main reasons for that are two: either difficult coronary targets that require the optimal operating conditions of CPB to graft, or haemodynamic events, such as hypotension or arrhythmias that sometimes may require prompt conversion to CPB. To the best of our knowledge there has been no study to date that has investigated the outcome in a group of patients who were intended to undergo OPCAB but were converted to CPB intraoperatively. In the hands of surgeons who routinely perform OPCAB conversions to CPB may be relatively rare, however one would be concerned that clinical outcome may be compromised in patients who require immediate conversion to CPB due to significant intraoperative haemodynamic instability.

B) Potential advantages / early postoperative outcome

- Perioperative myocardial injury

Several studies have shown reduced levels of myocardial enzymes in the early postoperative period following OPCAB compared to CPB. Khan et al measured troponin T levels and found that the area under the curve of troponin T levels in the first 72 hours was significantly higher in the CPB group than the off-pump group (Khan et al. 2004). Puskas et al found reduced levels of CKMB and troponin I in the OPCAB patients (Puskas et al. 2003). Whether the reduced release of myocardial enzymes is associated with improved myocardial function in the early postoperative period remains unclear. Ascione et al observed in a randomised study that patients undergoing OPCAB had lower levels of troponin I release and also reduced inotropic requirements, although this was not statistically significant (Ascione et al. 1999).

- Neurocognitive outcome

Neurocognitive deterioration after CPB is related to microemboli of predominantly atheromatous nature entering the cerebral circulation. The number of intraoperative microemboli can be assessed by measuring the number of high intensity transient signals (HITS) on Doppler ultrasonography of the middle cerebral artery. Several studies have demonstrated a significant reduction in the number of HITS during OPCAB compared to CPB (Diegeler et al. 2000), which would be expected, as there is less manipulation of the ascending aorta during OPCAB with a resultant decrease in the number of atheromatous microemboli. However, the results of various studies looking at early neurocognitive outcome after OPCAB vs. CPB have been conflicting and whether OPCAB confers a real advantage in neurocognitive outcome remains inconclusive. There have been 5 prospective randomised studies, 3 of which have shown no significant difference between the two techniques (Lloyd et al. 2000; Stroobant et al. 2002; Van Dijk et al. 2002), while the other 2 have shown superior neurocognitive outcome with OPCAB (Diegeler et al. 2000; Zamvar et al. 2002). To some extent these differences may be due to the lack of uniformity in the assessment of neurocognitive function. Another important factor has been patient selection; careful review of the patient characteristics in these studies would suggest that patients with a higher risk profile may gain more benefit with the OPCAB approach.

Two further studies have also investigated neurocognitive outcome 1 year after coronary surgery with and without CPB. Keizer et al (Keizer et al. 2003) investigated in a prospective randomised fashion 81 patients undergoing coronary surgery (on-pump, n=36, off-pump, n=45). They found no significant neurocognitive deterioration (compared to preoperative assessment) 1 year postoperatively in both groups and there was also no difference between the groups. Lee et al (Lee et al. 2003) randomised 60 patients into CPB (n=30) or OPCAB and observed no neurocognitive deterioration at 2 weeks and 1 year postoperatively in the on-pump patients compared to their preoperative assessment, while OPCAB patients at the same time points performed better than preoperatively and better than the on-pump group. Clearly more evidence is required before the possible neuroprotective role of OPCAB is clarified.

- Cerebrovascular accident (CVA)

To date, no prospective randomised study has shown a statistically significant reduction in perioperative CVA following OPCAB vs. surgery with CPB. Perioperative CVA is however relatively uncommon after coronary surgery, therefore large numbers of patients would be required to demonstrate a statistically significant benefit in a prospective randomised study. In a retrospective study investigating patients undergoing coronary surgery between 1994 and 2000, Stamou et al matched by propensity score 1,670 patients who underwent OPCAB with 1,670 patients who underwent ONCAB in the same period (Stamou et al. 2002). The authors observed that patients in the on-pump group were 1.8 times more likely to suffer a CVA postoperatively than OPCAB patients. In another retrospective study, Sharony et al compared 245 patients undergoing OPCAB with a propensity matched group undergoing coronary surgery with CPB (Sharony et al. 2004). All patients had severe atheromatous aortic disease identified by intraoperative transoesophageal echocardiography. The authors observed that patients undergoing on-pump were 3.6 times more likely to suffer a postoperative CVA compared to the OPCAB group. Therefore, there is some evidence that OPCAB may reduce the risk of stroke, especially in high-risk patients, but this has not yet been corroborated in a prospective randomised study.

- Lung injury

During CPB the lungs are not perfused or ventilated, as the CPB circuit takes over the gas exchange and the pulmonary side of the circulation is bypassed. One would therefore intuitively expect that the lung, which is exposed to such unphysiological conditions during CPB, would be the main organ to demonstrate a significant improvement in function with OPCAB. However, 2 prospective randomised studies that have assessed postoperative gas exchange following OPCAB vs. CPB have not demonstrated a significant difference between the two techniques. Cox et al observed similar alveolar-arterial oxygen gradients in the immediate postoperative period (up to 6 hours after extubation) in 52 patients randomised to on-pump or off-pump groups (Cox et al. 2000). Kochamba et al studied 58 patients in a randomised fashion and observed a similar postoperative deterioration in gas exchange with OPCAB vs. CPB, as assessed by the alveolar-arterial oxygen gradient and arterial partial pressure of oxygen on 100% inspired oxygen (Kochamba et al. 2000). Several studies that have not specifically looked at gas exchange as primary outcome measure have shown reduced time to tracheal extubation and reduced length of stay in the intensive care unit after off-pump surgery, however those outcomes are influenced by many factors and it would be very difficult to ascertain whether reduced time to extubation is related to superior pulmonary performance rather than reduced inotropic requirements or different anaesthetic protocols. More support for superior pulmonary function after OPCAB is found in a study by Guler et al (Guler et al. 2001); this study investigated 58 patients with severe chronic obstructive pulmonary disease undergoing CABG and randomised them into 3 groups: on-pump, off-pump, and minimally invasive direct coronary artery bypass grafting (MIDCABG), which is essentially a less invasive off-pump technique. Superior postoperative respiratory function was observed in the off-pump and MIDCABG groups compared to on-pump, evidenced by reduced time to tracheal extubation, reduced length of stay in the intensive care unit, reduced incidence of pulmonary atelectasis and superior forced expiratory volumes in 1 second at 2 months postoperatively. Patients with significant respiratory comorbidities are not uncommon in coronary surgery, as smoking is the common main risk factor for both coronary artery and lung disease. It

is important that further studies are performed to corroborate or refute the above evidence, especially in patients with pulmonary dysfunction.

- Renal injury

Only 3 prospective randomised studies have assessed renal function by measurements of subclinical renal injury markers after coronary surgery with and without CPB. Two of them (Ascione et al. 1999; Loef et al. 2002) showed an attenuation of renal injury with OPCAB compared to CPB. Ascione et al (Ascione et al. 1999) demonstrated superior postoperative renal glomerular function, assessed by creatinine clearance and the urinary albumin/creatinine ratio, and renal tubular injury, assessed by urinary excretion of N-acetyl glucosaminidase (NAG), in the OPCAB group up to 48 hours postoperatively. Loef et al studied 22 patients undergoing CABG with (n=12) and without (n=10) CPB in a prospective observational non-randomised fashion (Loef et al. 2002). Superior preservation of renal glomerular (assessed by creatinine clearance and microalbuminuria) and tubular (assessed by fractional excretion of sodium, free water clearance and urinary NAG) function was found in OPCAB patients up to 48 hours postoperatively. Interestingly, all parameters had normalised at 48 hours, while in the study by Ascione et al urinary NAG was still significantly elevated at 48 hours compared to baseline in the on-pump group. There was no obvious explanation for this discrepancy, which is indicative of the fact that perhaps subtle differences in patient profile, haemodynamic management and anaesthetic protocol may lead to conflicting outcome in prospective studies where sensitive subclinical markers are measured. In a similar study by Tang et al, 40 patients were randomised to ONCAB and OPCAB groups (Tang et al. 2002). Renal glomerular and tubular injury were assessed by measuring urinary excretion of microalbumin and retinol binding protein respectively, both indexed to urinary creatinine up to 5 days postoperatively. The authors observed a significant transient injury in both groups but no significant difference between the groups was found. In a retrospective study on patients with preoperative non-dialysis dependent renal failure (ONCAB n=202, OPCAB n=51), Ascione et al observed a trend for more postoperative dialysis in the on-pump compared to OPCAB patients (15.8 v. 5.9%, p=0.06), but this was not statistically

significant at the 0.05 level (Ascione et al. 2001). In another retrospective study Gamoso et al found no difference in perioperative creatinine clearance between OPCAB (n=55) and ONCAB (n=635) patients (Gamoso et al. 2000).

- Atrial fibrillation

Atrial fibrillation (AF) is a very common complication following CABG and although it is generally a benign arrhythmia that responds well to pharmacological therapy, it leads to prolonged hospital stay and increased cost. In a meta-analysis by Athanasiou et al (Athanasiou et al. 2004), when only high quality prospective randomised studies were considered, there was no significant difference in AF in on-pump and off-pump groups (odds ratio 0.78 for AF in the off-pump group). The same group did a meta-analysis for patients over 70 years of age and found a significantly lower incidence of AF in the off-pump patients (odds ratio for AF 0.70 in the off-pump group), however all the data was pooled from non-randomised studies (Athanasiou et al. 2004). Perhaps the study that has shown the most pronounced difference in postoperative AF after OPCAB vs. CPB is the one by Ascione et al (Ascione et al. 2000), where 200 patients were randomised into two groups (n=100 in each). Postoperative AF occurred in 39 patients in the on-pump group vs. 8 patients in the OPCAB group (p=0.001). The authors performed a multiple regression analysis that identified the use of CPB as the only independent predictor of postoperative AF. However, other studies that have also specifically looked at postoperative AF as the primary outcome measure have not demonstrated any difference between off-pump and CPB (Salamon et al. 2003; Hakala et al. 2004). The reasons for such discrepancies in the various studies are difficult to understand and they highlight that further good quality prospective randomised studies are required.

- Systemic inflammatory response

Attenuation of perioperative systemic inflammatory response with OPCAB compared to CPB is perhaps the best-established benefit of off-pump surgery. The events associated with systemic inflammatory response have been described earlier in this introductory chapter. Several studies have looked at perioperative levels of

various inflammatory markers after OPCAB vs. CPB and have almost invariably found reduced levels of these markers in the OPCAB patients. Interleukin (IL)-8 (Ascione et al. 2000; Wan et al. 2004), IL-10 (Wan et al. 2004), leukocyte elastase (Gu et al. 1998), platelet beta-thromboglobulin (Gu et al. 1998), neutrophil elastase (Ascione et al. 2000), complement factors C3a (Gu et al. 1998; Ascione et al. 2000), C5a (Wehlin et al. 2004) and the terminal complement complex (Wehlin et al. 2004) are some of the factors that have been measured in these studies. Despite discrepancies between the various studies the overall evidence for an attenuation of inflammatory response with the OPCAB technique is robust. The significance of a reduced inflammatory response with regards to clinical outcome, however, is less certain. Ascione et al in their above-mentioned study on inflammatory response also noticed reduced infective complications in the off-pump group (Ascione et al. 2000), however other authors have not confirmed these findings. However, our understanding of the clinical significance of perioperative systemic inflammatory response remains rather poor and whether it is directly associated with postoperative infections remains unknown.

- Blood loss and blood product transfusion

Reduction in perioperative blood loss and the requirement for blood product transfusion is the other rather established advantage of off-pump surgery. Several large prospective randomised studies have shown reduced perioperative blood loss and reduced transfusion of blood cell products (van Dijk et al. 2001; Angelini et al. 2002; Puskas et al. 2003). The largest retrospective series comparing on-pump and off-pump (Mack et al. 2004), where 5,774 patients undergoing OPCAB were matched by propensity score to a same number of patients undergoing ONCAB, also showed reduced transfusion requirements in the off-pump group (32.6% vs. 40.6%, $p<0.001$). These findings have not been universal: in a prospective randomised study involving 300 low-risk patients, Legare et al (Legare et al. 2004) found no difference between OPCAB and ONCAB in transfusion requirements (ONCAB 8.7% vs. OPCAB 9.3%). In the same study there were no differences between the groups in postoperative AF, time to tracheal extubation, length of intensive care stay and hospital stay. It is also noticeable that the overall transfusion requirements in this

study were far lower than in the patients reviewed by Mack et al, which would not merely be explained by the differences in patient profile between the two studies. It would rather suggest that different local perioperative management protocols may largely account for this difference, which underscores that the findings of these studies must be interpreted with caution and may not be applicable to every surgical unit.

- Cost

Off-pump surgery has been associated with cost savings of 12-30% compared to on-pump in 3 randomised studies that examined cost as the one of the outcome measures. Ascione et al found that in 200 patients randomised to on- or off-pump surgery, OPCAB was associated with 30% cost savings of the entire hospital stay (Ascione et al. 1999); this was related to cost savings in operating materials, transfusion requirements, postoperative complications and length of hospital stay. In a retrospective review of 200 off-pump cases compared with 1,000 matched contemporaneous cases, Puskas et al found a cost reduction with OPCAB of 15%, which was related to similar factors as in the previous study (Puskas et al. 2001). In a prospective randomised study involving 281 patients, Nathoe et al observed 12.3% lower cost with OPCAB compared to ONCAB at 1 year postoperatively, taking into account any health care costs additional to the original admission for surgery, such as readmissions for recurrent symptoms, reinterventions and so on (Nathoe et al. 2003). There has also been one study that found similar costs with both techniques; Bull et al, in a prospective study involving 80 patients, found that OPCAB did not reduce postoperative complications, length of hospital stay or cost compared to CPB (Bull et al. 2001).

C) Medium / long term outcome

This remains one of the main unanswered questions in off-pump surgery and is immediately related to the questions of anastomotic quality and completeness of revascularization, discussed earlier in this introduction. If off-pump surgery achieves a similar or better long-term outcome compared to surgery with CPB, this would be unequivocal evidence that revascularization of at least similar quality and

completeness can be achieved by OPCAB. Unfortunately, there is very little data on long-term outcome in patients randomised to ONCAB vs. OPCAB. The best data to date come from the series by Angelini et al, who randomised 401 patients between 1997 and 1999 into on-pump and off-pump groups (Angelini et al. 2002). The authors observed similar clinical outcome (death or cardiac-related event) at 1-3 years follow-up, although there was no angiographic follow-up in this study. Nathoe et al, in the previously mentioned randomised study involving 281 patients (OPCAB n=142, ONCAB n=139), observed similar freedom from death, stroke, myocardial infarction and coronary reintervention in the two groups at 1 year postoperatively (Nathoe et al. 2003). The authors also observed similar angiographic graft patency in a subgroup of patients that were studied (OPCAB, n=28, patency 91%; ONCAB, n=42, patency 93%, NS).

Table 1-1 summarises the advantages and disadvantages of off-pump surgery compared to surgery with CPB. From the above review it becomes apparent that there are still many debatable areas in off-pump surgery and further high quality research is required in order to fully understand the indications and contraindications for OPCAB. This thesis aims to enhance our understanding of haemodynamic events during OPCAB (Chapters 2 and 3) and then produce some evidence on the endocrine response (Chapters 4 and 5) and gastrointestinal injury (Chapters 6, 7 and 8) during OPCAB vs. ONCAB.

Table 1-1. Summary of OPCAB pros and cons vs. CPB

Early angiographic patency - probably same

Early clinical outcome (up to 1 year) - same

Long-term outcome and angiographic patency - unknown

Neurocognitive deterioration / stroke - possibly less in high risk patients

Renal injury - same/possibly less in high risk patients

Lung injury - same/possibly less in high risk patients

Atrial fibrillation - same/possibly less in the elderly

Inflammatory response - less

Transfusion requirements - probably less

Cost - probably less

Potential problems with OPCAB

- haemodynamic instability
- anastomotic quality
- completeness of revascularization
- conversion to ONCAB

Chapter 2

Real-time monitoring of haemodynamic changes during off-pump surgery

SUMMARY

Objectives: Cardiac displacement and target immobilization can significantly impair cardiac output during OPCAB. We investigated real-time haemodynamic changes during OPCAB.

Methods: Fourteen patients with normal left ventricular function undergoing primary elective multi-vessel OPCAB by a single surgeon underwent intraoperative, continuous, real-time monitoring of their cardiac index (CI), stroke volume index (SVI) and systemic vascular resistance using the PulseCO™ cardiac output monitoring system. An intracoronary shunt was used routinely during all distal anastomoses. Preload and inotropic management were standardized.

Results: There were immediate and significant reductions in CI and SVI following application of the mechanical stabilizer. Mean arterial blood pressure fell proportionally less due to compensatory tachycardia and vasoconstriction. There was a progressive partial recovery of the haemodynamic parameters, which reached a plateau 6 minutes after application of the stabilizer. At that point the cardiac index reached 90.5±9.1% of baseline values (2.65±0.45 vs. 2.94±0.50 L/min/m^2) during grafting of the left anterior descending artery, while inferior recovery was observed during grafting of the obtuse marginal (82.6±10.0%, 2.28±0.51 vs. 2.75±0.48 L/min/m^2) and posterior descending (85.9±10.5%, 2.42±0.51 vs. 2.83±0.50 L/min/m^2) arteries. Full haemodynamic recovery only occurred following removal of the stabilizing device.

Conclusions: Significant and rapid haemodynamic deterioration occurred during distal anastomoses in OPCAB. These adverse changes were amplified by greater cardiac displacement employed when grafting the less accessible coronary targets.

INTRODUCTION

Despite the development of surgical techniques that facilitate exposure of the coronary targets during OPCAB and the continuous improvement of myocardial mechanical stabilizers, there is growing awareness that the period of distal anastomoses in OPCAB represents a period of significant, albeit transient haemodynamic deterioration (Mathison et al. 2000; Watters et al. 2001; Do et al. 2002).

These studies have also highlighted that monitoring of the systemic arterial pressure alone may be misleading , as significant reduction of the cardiac output (CO) may occur despite relative preservation of the mean arterial pressure (MAP), due to compensatory vasoconstriction (Mathison et al. 2000; Watters et al. 2001). However, CO monitoring during distal anastomoses in OPCAB is not as straightforward as it may first appear. Most clinical studies to date have used a Swan-Ganz catheter to measure the CO using thermodilution, which is generally regarded as the gold standard method for CO measurement. However, there are two major limitations in the use of Swan-Ganz catheters for CO monitoring during distal anastomoses in OPCAB.

First, the technique does not provide continuous, real-time monitoring of the CO (Haller et al. 1995; Aranda et al. 1998). Instead there may be a response time delay of up to 15 minutes in acute haemodynamic changes, which is often the case during OPCAB. Second, cardiac displacement may lead to tricuspid regurgitation (Nierich et al. 2000), which will render thermodilution measurements of the CO falsely high. For these reasons, a real-time CO monitoring technique that measures forward flow without being affected by tricuspid regurgitation would be the preferred method for haemodynamic monitoring during distal OPCAB anastomoses. The LiDCO™/PulseCO™ system (Linton et al. 1993; Linton and Linton 2001) is a relatively new technique that allows real-time monitoring of the CO and has the additional benefit of being minimally invasive, as it only requires peripheral arterial and venous catheterisation. The system uses lithium injection dye dilution to measure

the CO and the measured value is used to calibrate the PulseCO™ system that calculates the CO continuously by analysing the arterial blood pressure waveform.

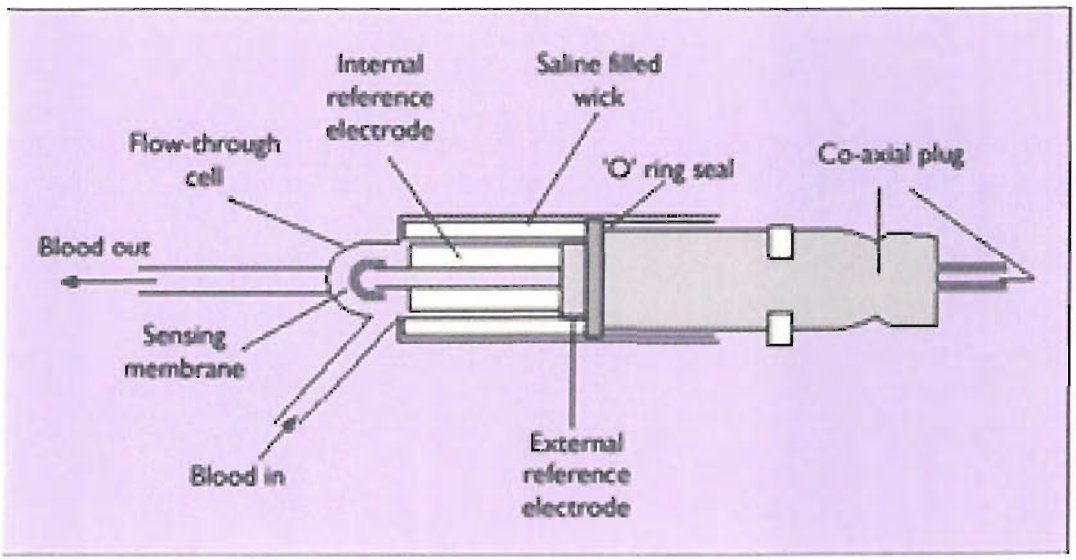
The aim of this study was to describe real-time haemodynamic changes during the distal anastomoses in OPCAB using the LiDCO™/PulseCO™ system.

BACKGROUND

Lithium dilution measurement of the cardiac output (LiDCO™)

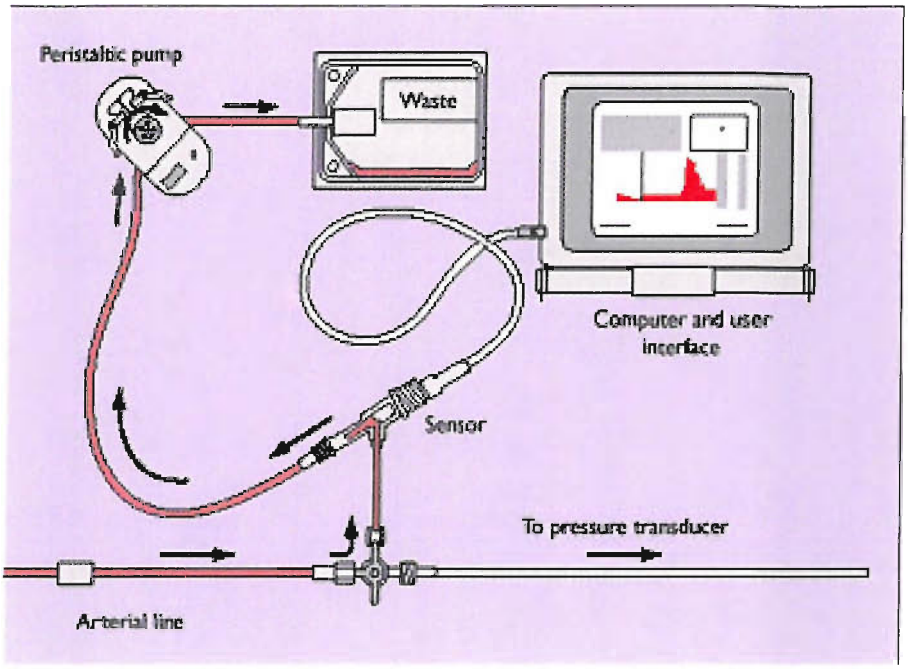
The use of lithium indicator dilution technique for the measurement of the cardiac output was first described in 1993 by Linton et al. (Linton et al. 1993) and has now been extensively validated. Isotonic lithium chloride (150mM) is injected as a bolus (0.002-0.004 mmol/kg) via a central or peripheral venous line and a concentration-time curve is generated by a lithium-selective electrode situated in a flow-through cell (figure 2-1) and attached to the arterial line manometer system.

Figure 2-1. The Lithium-selective electrode in the flow-through cell.



The electrode is connected to the arterial manometer line via a three way tap (figure 2-2), which when open allows blood to flow through the sensor assembly at 4ml/min. This is rate limited by a peristaltic, battery-powered pump.

Figure 2-2. The LiDCO™ system. Blood is sampled from the arterial line via the three-way tap in the manometer line.



The flow-through cell is made of polycarbonate and designed with an eccentric inlet so that blood swirls past the tip of the electrode. The lithium-selective electrode is made of polyurethane with a central lumen. A wick, which is soaked in heparinised saline when the cell is first primed, makes the electrical connection between the blood at the tip of the electrode and the remote reference. This arrangement ensures that the reference is far enough from the blood to avoid any significant temperature effect. The electrode contains a membrane made of polyvinyl chloride, which is selectively permeable to lithium. The voltage across the membrane is related by the Nernst equation to the plasma lithium concentration. A correction is applied for plasma sodium concentration because of the relatively low selectivity of the membrane for lithium over sodium. The voltage is measured using an isolated amplifier, digitalised and analysed on-line.

Indicator dilution curves recorded in arterial blood consist of primary and secondary curves due to the initial circulation and then recirculation of the indicator. The cardiac output is calculated from the lithium dose and the area under the concentration time curve prior to recirculation (Band et al. 1997) using the following equation:

$$\text{Cardiac output (L/min)} = \frac{\text{Lithium dose (mmol) X 60}}{\text{Area X (1-PCV)}},$$

Where area is the integral of the primary curve and PCV is the packed cell volume (the correction for PCV is needed because lithium is distributed in the plasma).

Lithium is safe, non-toxic in small doses and easy to measure using the lithium-selective electrode. The operating characteristics of lithium-selective electrode enable the use of an extremely small dose of lithium, since the voltage response is to percentage change of lithium, which is not normally present in the plasma. The pharmacokinetics of intravenous Lithium Chloride have been described. The bolus dose of lithium for CO estimation (0.15-0.3 mmol in adults) is too small to have a pharmacological effect and the manufacturers' maximum recommended total dose (3 mmol) would have to be exceeded many times before toxic levels are achieved.

For indicator dilution theory, a critical boundary condition is that there is no first pass loss of marker from the circulation, as this would lead to overestimation of cardiac output. To investigate this for lithium chloride, a study in patients comparing measurements of LiDCO™ using right or left atrial injection of lithium was undertaken, which showed that there was no significant loss of lithium during its passage through the pulmonary circulation (Band et al. 1997).

Although the technique was originally described using central venous administration of the bolus lithium dose, subsequent clinical studies (Jonas et al. 1999; Kurita et al. 1999) demonstrated that accurate CO estimation can be made using peripheral venous access for the lithium injection. Jonas et al (Jonas et al. 1999) in a study involving general intensive care patients reported excellent correlation (r=0.997)

between peripherally and centrally injected lithium dilution measurement of CO. However, as intraoperative central venous access is always available in cardiac surgical patients, central venous administration of lithium chloride was used for the patients studied in this thesis.

Lithium dilution estimation of the CO has been extensively validated and has been found to correlate very well with measurements obtained using other techniques, such as bolus thermodilution (Linton et al. 1997), which is regarded as the "gold standard" technique for CO estimation in clinical settings, and electromagnetic flowmetry (Kurita et al. 1997) using a probe placed around the ascending aorta. LiDCO™ was compared in a clinical study (Linton et al. 1997) with bolus thermodilution in forty patients on a postoperative cardiac intensive care unit and a general intensive care unit. Thirty-five patients had undergone cardiac surgery in the previous two days; two had recent myocardial infarction, two had septicaemia and one had adult respiratory distress syndrome. CO was measured five times in each patient using lithium dilution (single measurement) and bolus thermodilution (3-6 estimates averaging the closest three). The overall agreement between the two methods was very good ($r^2 = 0.94$). LiDCO™ was at least as accurate as bolus thermodilution, with significantly greater precision.

The lithium technique has also been successfully used in paediatric patients (Linton et al. 2000). Children were studied comparing lithium dilution measurements with transpulmonary thermodilution, as many of these patients were too small for pulmonary artery catheterisation. The transpulmonary technique uses cold dilution with a thermistor placed in the aorta via the femoral artery, rather than the pulmonary artery. Again agreement was very good between lithium and thermodilution.

Limitations of LiDCO

The technique cannot be used in patients receiving lithium therapy, since the increased background lithium concentration causes an overestimation of cardiac output. As for all indicator dilution methods, abnormal shunts could result in erroneous cardiac output measurements (Linton et al. 2000). A right to left shunt will

cause obvious distortion of the initial part of the dilution curve and a left to right shunt will result in the right ventricular output being higher than the flow into the aorta.

The PulseCO™ system

The PulseCO™ monitor was developed in conjunction with LiDCO™, to give a beat-to-beat real-time estimate of cardiac output. Essentially, following LiDCO™ calibration, continuous CO is derived from analysis of the arterial blood pressure waveform.

The relationship between the capacity of the arterial side of the circulation and the intravascular pressure can be expressed as the compliance: pressure change per unit volume change. This would allow a simple determination of the CO if the relationship was constant. However, arterial compliance has been shown to change as arterial pressure changes (Burton 1966). The vasculature stiffens as pressure and volume increase, thus becoming less compliant. This can be plotted as a curvilinear relationship (approximately exponential), which, though differing in its scaling, appears to be very similar in different subjects. A table can be generated, allowing the pressure waveform to be used as the basis for calculating volume changes. The arterial pressure waveform can therefore be transformed to a nominal arterial blood volume over time waveform.

In order to obtain the cardiac output, the algorithm needs to calculate the duration of the cardiac cycle and the stroke volume, or a value proportional to it (the nominal stroke volume). To calculate a nominal estimate of the stroke volume, the mean value of the derived arterial blood volume record is subtracted from the arterial volume trace. This produces a sine-like waveform, with different areas above and below zero, giving a description of how much the arterial blood volume changes around the mean arterial blood volume. By squaring the values of the sine-like curve, a double waveform is produced, with positive waves for both the positive and negative parts of the original sine wave. The square root of the mean of this double waveform, known as the root mean square, gives an estimate of nominal stroke

volume. Heart beat duration is calculated by moving one version of the volume waveform successively, step by step, relative to another until maximum reinforcement is achieved. This time period represents the duration of the cardiac cycle. The nominal stroke volume must be calibrated against a measured value, which is obtained from lithium indicator dilution estimation of the cardiac output.

How often the PulseCO™ system should be recalibrated remains under investigation. The manufacturer recommends calibration every 4-6 hours unless the patient becomes unstable. A recent (unpublished) study in Southampton compared CO measurements in 10 Intensive Care Unit patients with a variety of diagnoses over a 9-hour period using PulseCO™ (no recalibration following initial LiDCO™ calibration) versus LiDCO™ intermittent indicator dilution technique. The values from PulseCO™ and LiDCO™ measurements agreed closely over the 9-hour study period. Another study in 20 patients (Hamilton et al. 2002) undergoing cardiac surgery, showed excellent correlation between thermodilution, LiDCO™, and PulseCO™ (with no recalibration following initial LiDCO™ calibration) measurements of the cardiac output in the period between return to the intensive care immediately after surgery and 8 hours postoperatively. These studies would suggest that PulseCO™ measurements of CO are reliable for at least 8 hours in a variety of clinical settings, even when there are potential fluctuations in the arterial pressure waveform caused by temperature changes, use of vasopressors, inotropes or vasodilators, or use of the arterial line for blood sampling. Additionally, recalibration of PulseCO™ appears to be unnecessary for at least 8 hours after initial LiDCO™ calibration.

MATERIALS AND METHODS

Study design

Fourteen patients undergoing primary elective multi-vessel OPCAB who satisfied the study criteria (Table 2-1) were prospectively recruited following informed consent. Low-risk patients with normal preoperative cardiac function were included in this study. All patients required two or three vessel coronary revascularization and they had no contraindication to OPCAB on review of the preoperative coronary angiogram. All patients were operated by the same surgeon. The study was approved by the Southampton and South West Local Research Ethics Committee.

Table 2-1. Exclusion criteria

Age over 75 years
LVEF less than 50%
Recent (<3 months) MI
Diabetes Mellitus
Unstable angina
Renal insufficiency
Liver failure
Previous CVA

LVEF, left ventricular ejection fraction; MI, Myocardial infarction; CVA, cerebro-vascular accident.

Surgical technique

A median sternotomy was used for surgical access in all cases. Following harvesting of suitable conduits, the pericardium was opened and partial systemic heparinisation was employed with a target activated clotting time of 300 - 400 sec prior to cardiac manipulation. A single suture technique (Bergsland et al. 1999; Ricci et al. 2000) was used to facilitate exposure of the target coronary arteries. Trendelenburg posture was employed throughout the period of distal anastomoses, while a partial right lateral decubitus position was also used during exposure of the posterior descending (PDA) and the obtuse marginal (OM) coronary arteries. A mechanical suction-based myocardial tissue stabilizer (Octopus®3; Medtronic Ltd., Watford, UK) was used to

immobilize the operative field during coronary anastomosis. Following arteriotomy, an intraluminal coronary shunt (Flo-Thru; Biovascular Inc., Minnesota, USA) was inserted to maintain distal myocardial perfusion during the anastomosis and was removed prior to completion. A left internal mammary artery to left anterior descending coronary artery (LAD) anastomosis was performed first in all cases. The other territories were bypassed using saphenous vein, right internal mammary artery or left radial artery grafts. Following completion of the distal anastomoses, construction of the proximal anastomoses to the ascending aorta was performed in a similar fashion to on-pump techniques within a single aortic side-biting clamp period, with the systolic pressure maintained at or below 100 mm Hg to minimize the risk of aortic dissection.

Anaesthetic management

The patients' medications were continued up to the night before the operation except for anti-platelet agents, which were discontinued 7 days prior to surgery. A standardized anaesthetic protocol was followed in which fentanyl based anaesthesia was used in combination with benzodiazepine and vecuronium as a muscle relaxant. Haemodynamic stability (target mean arterial pressure of 60mmHg and cardiac index of 2.2 L/min/m^2) was achieved primarily with preload management (intravenous fluid administration and Trendelenburg posture). If preload increase did not restore target haemodynamic values, vasoactive agents were used. Intravenous infusion of dopamine (3-5 μg/kg/min) was used to raise the CO, while bolus intravenous injections of phenylephrine or noradrenaline infusion were used as vasoconstrictors. Vasoactive agents were generally started in the period immediately after cardiac manipulation and target stabilization, which was the period of most profound haemodynamic changes. If severe haemodynamic deterioration was encountered, the heart was returned to anatomical position and allowed to rest for a period of 3-5 minutes. During that period vasoactive agents were started or adjusted and attempts at coronary target exposure resumed once the haemodynamic values were restored.

Haemodynamic monitoring

Shortly after anaesthetic induction the LiDCO™ system was used to obtain a measurement of the cardiac output; this value was used to calibrate the PulseCO™ system, which was used to monitor the cardiac output for the rest of the operation. There was no subsequent recalibration of the PulseCO™ system. The methodology for obtaining a CO measurement using the lithium indicator dilution technique has already been described in the background information to this chapter. As all our patients had central venous access, we elected to use central venous administration of the lithium bolus. The PulseCO™ monitor provided continuous, real-time information on the following parameters: Cardiac Index (CI), Stroke Volume Index (SVI), Systemic Vascular Resistance Index (SVRI), mean arterial blood pressure (MAP), and heart rate (HR). Central venous pressure (CVP) measurements were also recorded. Recordings of the measured values were made at 2-minute intervals. The time of application of the mechanical stabilizer and subsequent removal was also noted. Because the duration of application of the mechanical stabilizer varied (range 10-19 min), the haemodynamic changes have been described only for the first 10 minutes following application of the stabiliser, for which period there are data for all the anastomoses. Also haemodynamic values have been described for the period prior to the application and after removal of the stabilizing device.

Statistical analysis

Values are presented as mean ± standard deviation or median and interquartile range for non-parametric variables. Repeated measures analysis of covariance, using the baseline measurement as a covariate, was used to assess the overall effect of time on the haemodynamic variables during distal anastomoses at the three different sites. Two-sided p values of less than 0.05 were considered statistically significant. The Statistical Package for Social Sciences (SPSS) version 10.1 software was used for the analysis.

RESULTS

Patient characteristics are presented in Table 2-2.

Table 2-2. Patient characteristics

Patient characteristic		Number of patients (n=14)
Age (mean±SD)		65±7
Gender	Male	10
	Female	4
CCS angina class	I	1
	II	4
	III	9
Previous MI		5
Hypertension		10
Morbid obesity		2
Parsonnet score (median, IQR)		3 (0.5-4.0)

CCS, Canadian Cardiovascular Society; MI, Myocardial Infarction.

All patients completed the study and no patient was excluded. No patient required the use of cardiopulmonary bypass and complete revascularization was achieved in all cases. The mean ± SD number of grafts performed was 2.8 ± 0.9. In total 14 LAD, 12 obtuse marginal (OM) and 11 posterior descending artery (PDA) anastomoses were studied. The use of vasoconstrictors and inotropes during the distal anastomoses is presented in Table 2-3.

Table 2-3. Administration of vasoconstrictors and inotropes during distal anastomoses.

Target vessel	PE boluses	NA infusion	Dopamine infusion
LAD (n=14)	0	1	0
OM (n=12)	2	3	1
PDA (n=11)	2	2	1

PE, phenylephrine; NA, Noradrenaline; LAD, left anterior descending artery; OM, obtuse marginal artery; PDA, posterior descending artery.

In all three anastomotic sites (LAD, OM and PDA) we observed significant and rapid changes in CI and SVI that were most pronounced during the preparatory phase just before the anastomosis, when the heart was being manipulated and the mechanical stabilizer was applied to expose the target coronary vessel. Essentially during that period there were significant beat-to-beat haemodynamic changes. Following that stormy phase there was a progressive partial recovery of haemodynamic parameters towards baseline values that mostly took place in the first 4-6 minutes after application of the stabilizer. A plateau was then reached and full haemodynamic recovery only occurred after removal of the stabilizing device and replacement of the heart in its anatomical position. Figure 2-3 shows the changes in CI at 2-minute intervals during distal anastomoses at the three settings. Changes in SVI (figure 2-4) closely matched those of CI, although they were slightly more pronounced, due to a small degree of compensatory tachycardia. There were significant compensatory temporary elevations in SVRI in all anastomotic sites (figure 2-5). As a result, MAP changes (figure 2-6) were significantly less pronounced than CI changes.

Figure 2-3. Changes in Cardiac Index during distal anastomoses.

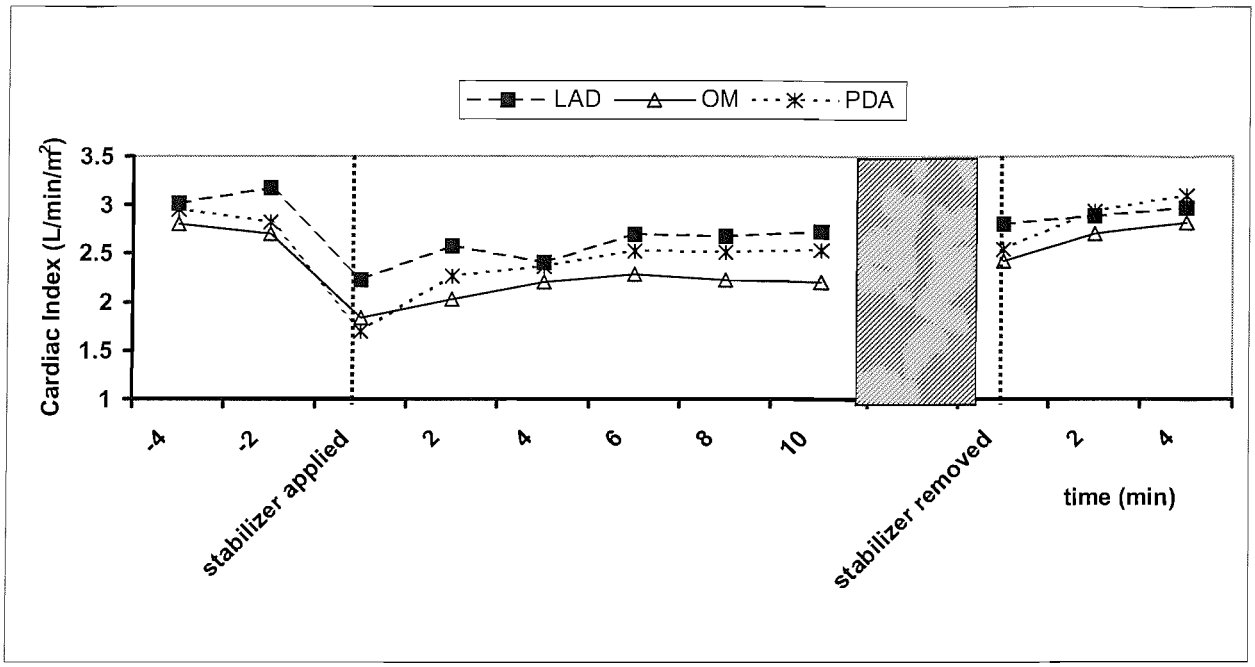


Figure 2-4. Changes in Stroke Volume Index during distal anastomoses.

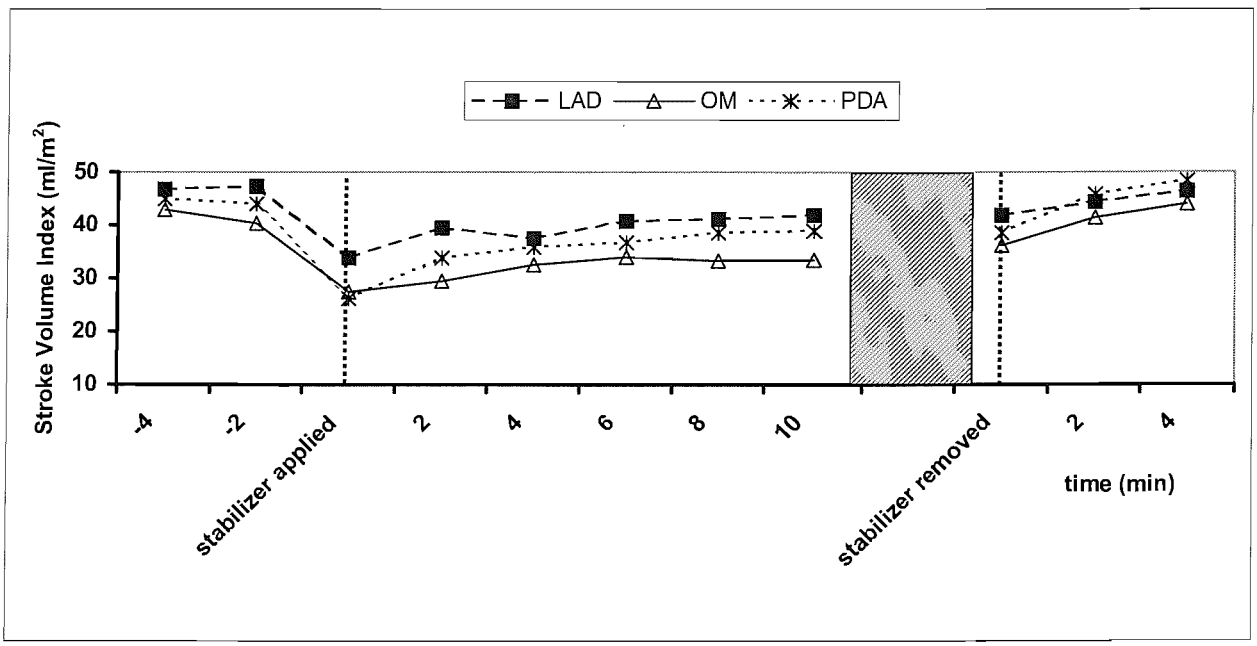


Figure 2-5. Changes in MAP during distal anastomoses.

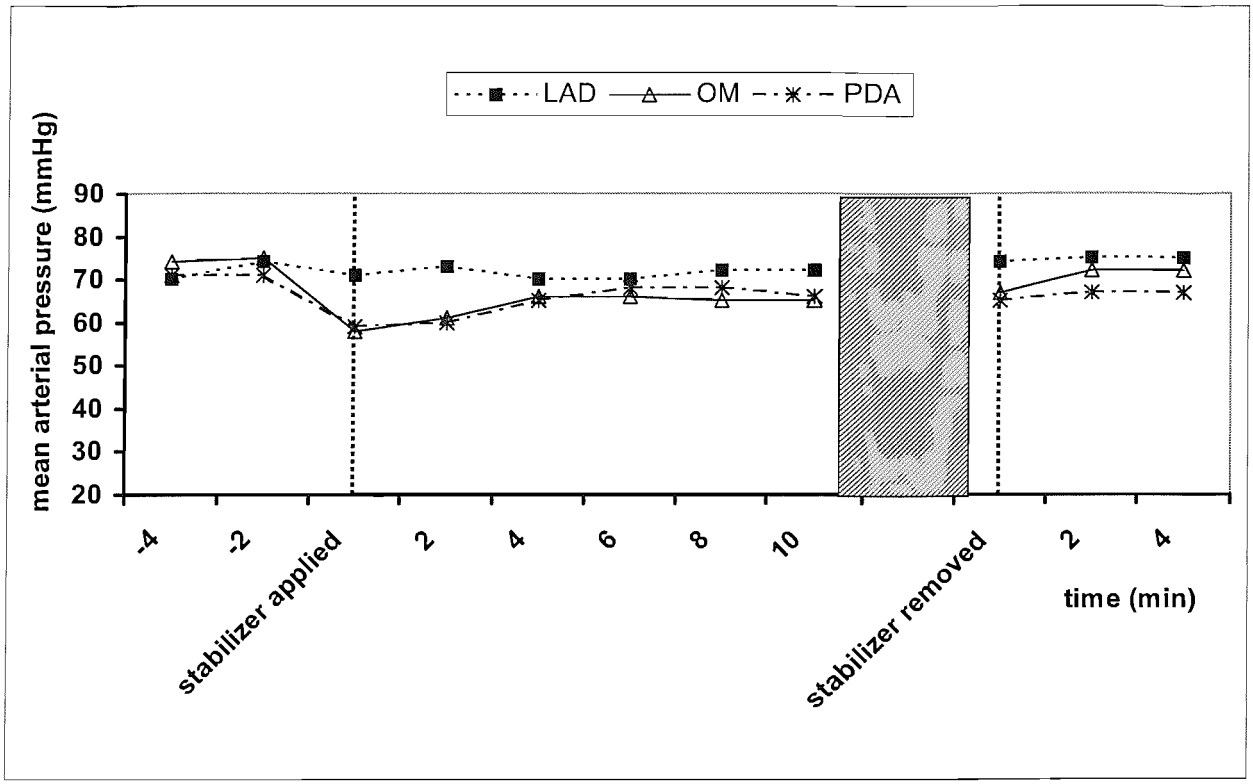
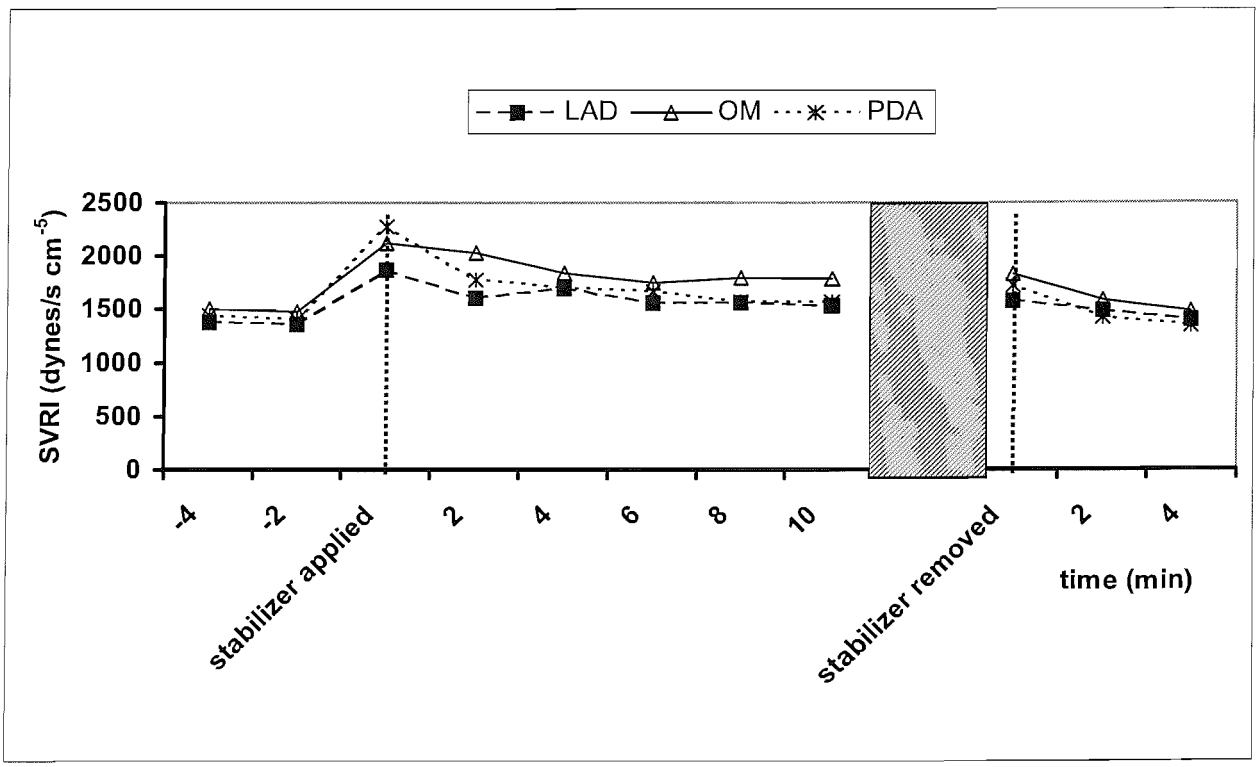


Figure 2-6. Changes in SVRI during distal anastomoses.



Repeated measures analysis of covariance showed that there were significant changes in CI, SVI and SVRI during the distal anastomoses in all anastomotic sites ($p<0.01$ for the effect of time on CI, SVI and SVRI at all three sites).

Postoperative clinical outcome is presented in Table 2-4. There were no major complications in the patient cohort.

Table 2-4. Postoperative clinical outcome

Variable	Number of patients (n=14)
Death	0
MI	0
Low cardiac output/IABP	0
End-organ failure	0
CVA	0
Atrial flutter/fibrillation	3
Chest infection	1
Wound infection	0
Time to extubation (h), median (IQR)	5.0 (3.4, 5.9)
ICU stay (d), median (IQR)	1 (1, 2)
Hospital stay (d), mean±SD	6.3±1.6

MI, myocardial infarction; IABP, intraaortic balloon pump; CVA, cerebro-vascular accident; ICU, intensive care unit.

Time to extubation and length of ICU stay are presented as median value and interquartile range.

DISCUSSION

There is growing awareness that there is significant haemodynamic instability during OPCAB. Several studies have described the haemodynamic alterations during OPCAB in experimental and clinical settings (Grundeman et al. 1997; Grundeman et al. 1999; Mathison et al. 2000; Nierich et al. 2000; Porat et al. 2000; Watters et al. 2001; Do et al. 2002). Table 2-5 summarizes some of the haemodynamic changes observed during distal anastomoses in OPCAB in clinical studies.

Table 2-5. Haemodynamic changes during grafting of coronary vessels in OPCAB.

Circumflex exposure

Study	Variable	Baseline	Exposed
Watters et al.	HR (bpm)	63.8±11.5 (mean±SD)	2.68 (mean difference)
(Watters et al. 2001)	MAP (mmHg)	78.0±12.5	-4.18
	CVP (mmHg)	10.4±3.7	5.57
	CI (L/min/m^2)	2.5±0.5	-0.63
Mathison et al.	HR (bpm)	79.0±13.8 (mean±SD)	91.3±15.7 (mean±SD)
(Mathison et al. 2000)	MAP (mmHg)	77.3±15.2	63.0±12.2
	CVP (mmHg)	5.4±2.8	10.3±3.2
	CO (L/min)	4.23±1.20	2.69±0.54
Nierich et al.	HR (bpm)	69±11 (mean±SD)	75±12 (mean±SD)
(Nierich et al. 2000)	MAP (mmHg)	65±17	63±13
	CVP (mmHg)	10±3	9±3
	CO (L/min)	4.7±1.0	4.2±1.0

Posterior Descending artery exposure

Study	Variable	Baseline	Exposed
Watters et al.	HR (bpm)	62.7±7.4 (mean±SD)	2.46 (mean difference)
(Watters et al. 2001)	MAP (mmHg)	77.4±13.0	-4.53
	CVP (mmHg)	9.1±3.4	3.86
	CI (L/min/m^2)	2.4±0.4	-0.48
Mathison et al.	HR (bpm)	78.2±6.1 (mean±SD)	83.4±21.0 (mean±SD)
(Mathison et al. 2000)	MAP (mmHg)	69.2±15.4	66.3±15.8
	CVP (mmHg)	6.6±3.9	10.0±3.5
	CO (L/min)	4.69±1.31	3.70±0.96
Nierich et al.	HR (bpm)	67±13 (mean±SD)	73±14 (mean±SD)
(Nierich et al. 2000)	MAP (mmHg)	72±11	67±11
	CVP (mmHg)	9±3	9±2
	CO (L/min)	4.9±1.1	4.7±1.0

Left Anterior Descending artery exposure

Study	Variable	Baseline	Exposed
Watters et al.	HR (bpm)	63.1±10.4 (mean±SD)	1.76 (mean difference)
(Watters et al. 2001)	MAP (mmHg)	77.8±11.6	-2.55
	CVP (mmHg)	10.3±3.8	0.86
	CI (L/min/m^2)	2.45±0.5	-0.22
Mathison et al.	HR (bpm)	72.6±16.3 (mean±SD)	78.7±14.5 (mean±SD)
(Mathison et al. 2000)	MAP (mmHg)	76.2±14.9	71.0±14.8
	CVP (mmHg)	6.7±3.2	8.1±3.2
	CO (L/min)	4.83±1.08	3.93±1.18
Nierich et al.	HR (bpm)	65±13 (mean±SD)	71±12 (mean±SD)
(Nierich et al. 2000)	MAP (mmHg)	71±11	67±11
	CVP (mmHg)	10±2	11±3
	CO (L/min)	4.6±1.0	4.4±0.8

It can be easily noticed from table 2-5 that the haemodynamic changes tend to be more severe during exposure of the posterior or lateral coronary vessels, when significant cardiac displacement is required. The haemodynamic impairment during cardiac displacement is primarily due to right ventricular dysfunction (Porat et al. 2000), as a result of compression of the right ventricle between the interventricular septum and the surrounding right fibrous pericardium and pleura (Grundeman et al. 1999). Several studies have shown the haemodynamic benefits of manoeuvres that enhance right ventricular function during OPCAB, such as Trendelenburg posture (Grundeman et al. 1997) and right lateral decubitus position (Grundeman et al. 2001), both of which improve haemodynamic performance by augmenting right ventricular preload. Moreover, several studies have shown the beneficial haemodynamic effect of right heart bypass during OPCAB, while a similar effect was not noticed during left heart assistance (Grundeman et al. 1999; Porat et al. 2000). The role of right ventricular dysfunction in haemodynamic performance in OPCAB will be discussed in more detail in Chapter 3, where we investigate the haemodynamic effects of a pleuropericardial decompressing manoeuvre. Our results are in keeping with previous studies as they show a more pronounced haemodynamic instability during grafting of the PDA and OM territories, as opposed to LAD grafting, which requires less cardiac manipulation.

Most previous studies have highlighted that monitoring of the systemic arterial pressure alone can be falsely reassuring, as significant drops of the cardiac output (CO) may occur despite relative preservation of the mean arterial pressure (MAP), due to compensatory vasoconstriction. For example Mathison et al. (Mathison et al. 2000) reported that during off-pump revascularization of the circumflex artery the mean CO dropped from 4.23 L/min to 2.69 L/min (36% reduction in CO), while the MAP only dropped from a mean baseline value of 77.3 mmHg to a mean of 63.0 mmHg during grafting (or 18% reduction). Similarly, Watters et al. (Watters et al. 2001) reported a mean baseline Cardiac index of 2.5 L/min/m^2 that dropped by 0.63 during circumflex grafting (25% drop), while the MAP had a mean baseline value of 78.0 mmHg and dropped by only 4.18 (or 5.4%). A relative preservation of MAP during distal anastomoses was confirmed by our study. These findings illustrate that

monitoring of the CO is essential in order to fully appreciate the magnitude of haemodynamic changes that occur during OPCAB.

However, CO monitoring during OPCAB using a Swan-Ganz catheter is not only rather invasive, but also presents two important methodological limitations. First, the technique does not provide continuous, real-time monitoring of the CO (Haller et al. 1995; Aranda et al. 1998). Even the so-called continuous cardiac output (CCO) Swan-Ganz catheters provide intermittent measurements that represent time-averaged information over the previous 3-5 minutes. Haller et al. (Haller et al. 1995) assessed the *in vivo* response time of CCO thermodilution catheters during acute haemodynamic changes. The measurements were made in eight patients with left heart assist devices, four of whom were subjected to an acute increase and four to an acute decrease in cardiac output by 1 L/min. The median (minimum to maximum) 50%, 75% and 90% response times were 9.3 min (7 to 11.5), 10.5 min (8 to 12) and 11.8 min (10 to 12.5) respectively. Similarly, Aranda et al. (Aranda et al. 1998) observed a 5-15 minute delay in the *in vitro* response time with CCO catheters during controlled flow changes. The response time is therefore too slow for the immediate detection of acute changes in CO, such as those encountered during cardiac manipulation and coronary grafting in OPCAB.

The second main limitation of thermodilution CCO catheters is related to the fact that during cardiac elevation in OPCAB there is considerable compression and distortion of the right cardiac chambers (Grundeman et al. 1999). This may lead to tricuspid regurgitation (Nierich et al. 2000), which will render thermodilution measurements of the CO falsely high.

For these reasons, a real-time CO monitoring technique that remains unaffected by any tricuspid regurgitation would be the preferred option for haemodynamic monitoring during OPCAB. The LiDCO™/PulseCO™ system (Linton et al. 1993; Linton and Linton 2001) is a relatively new technique that uses lithium injection dye dilution to measure the CO and arterial blood pressure waveform analysis to calculate the CO in continuous, real-time fashion. The methodology used by the

system, its validation to-date and its limitations were discussed in the background information to this Chapter. We have used this system for CO monitoring in approximately 50 OPCAB cases outside the studied patients, and we have certainly found the information displayed to be in keeping with intraoperative events and clinically very useful. In this study we were able to demonstrate how, by using a continuous, real-time CO monitoring technique, one can obtain accurate haemodynamic information throughout the course of cardiac manipulation and distal anastomoses in OPCAB, rather than a single baseline measurement, followed by another single measurement during the anastomosis, which has been used in previous studies. Our findings that the haemodynamic parameters deteriorated mostly around the time of application of the mechanical stabilizer and then gradually improved during the anastomosis indicates that there is a continuously changing haemodynamic picture that cannot be fully appreciated with non-continuous techniques.

Chapter 3

Evaluation of the haemodynamic impact of right heart decompression during off-pump surgery

SUMMARY

Objective: Cardiac manoeuvring during OPCAB can compress the right ventricle causing temporary dysfunction and haemodynamic instability. The haemodynamic impact of a decompressing technique comprising of right pleurotomy and pericardial release was investigated during cardiac verticalization in OPCAB.

Methods: Twelve consecutive patients with normal ventricular function undergoing OPCAB by a single surgeon underwent intraoperative continuous real-time monitoring of their cardiac index (CI) and stroke volume index (SVI) using the PulseCO™ system. A pulmonary artery catheter was used to monitor the pulmonary artery pressures (PAP) and systemic venous oxygen saturation (S_VO_2). Haemodynamic changes during cardiac verticalization were measured before and after performing a right pleurotomy and pericardial release.

Results: Inotropic support remained unchanged throughout the study. Following right heart decompression SVI, CI, mean arterial blood pressure (ABP) and S_VO_2 were significantly better preserved during cardiac verticalization. The influence of the decompressive manoeuvre on the central venous pressure (CVP) and the mean PAP during cardiac verticalization was not statistically significant.

Conclusion: Right heart decompression through pleurotomy and pericardial release significantly improves haemodynamic stability during cardiac manipulation. The routine use of this manoeuvre in OPCAB whenever cardiac verticalization is required may enhance haemodynamic stability and avoid inotropic support.

INTRODUCTION

Exposure of the posterior or lateral coronary vessels during OPCAB requires significant cardiac displacement, which results in transient haemodynamic impairment. Haemodynamic instability occasionally requires conversion of the surgical approach to the use of CPB (Soltoski et al. 1998). The haemodynamic changes during distal anastomoses in OPCAB have been described in Chapter 2. Previous studies have shown that the haemodynamic impairment during cardiac verticalization is primarily due to right ventricular (RV) dysfunction (Porat et al. 2000), as a result of direct mechanical compression of the RV between the interventricular septum and the surrounding right fibrous pericardium and pleura (Grundeman et al. 1999). As a result, some centres have explored the use of RV assist devices as an adjunct to haemodynamic stability during OPCAB surgery (Grundeman et al. 1999; Mathison et al. 2000). Trendelenburg position has been shown to partly restore right ventricular dimensions during cardiac verticalization by augmenting the preload and filling pressures (Grundeman et al. 1997; Grundeman et al. 1998).

As an adjunct to haemodynamic stability we have used a decompressing technique comprising of right pleurotomy and pericardial release prior to cardiac verticalization for OPCAB. This aims to decompress the right cardiac chambers and improves haemodynamic stability during cardiac manipulation. In this study we evaluated the haemodynamic impact of this manoeuvre during cardiac verticalization in OPCAB in patients with normal ventricular function.

MATERIALS AND METHODS

Study design

Twelve consecutive patients awaiting primary elective OPCAB who fulfilled the study criteria (Table 1) were recruited after obtaining informed consent. These were low-risk subjects with normal preoperative cardiac function. All patients underwent surgery by the same surgeon. The study was approved by the Southampton and South West Local Research Ethics Committee.

Table 3-1. Exclusion criteria.

Age over 75 years
LVEF less than 50%
Recent (<3 months) MI
Diabetes Mellitus
Unstable angina
Renal insufficiency
Liver failure
Previous CVA

LVEF, left ventricular ejection fraction; MI, Myocardial infarction; CVA, cerebro-vascular accident.

Surgical technique

The heart was approached through a median sternotomy and pericardiotomy. Vertical displacement of the heart was facilitated using the "single suture" technique as previously described (Bergsland et al. 1999; Ricci et al. 2000). Trendelenburg posture was employed throughout the period of performing the distal anastomoses. The Octopus®3 suction based mechanical stabilizer (Medtronic Ltd., Watford, UK) was used to immobilize the target coronary arteries prior to arteriotomy. Intraluminal coronary shunts (Flo-Thru, Biovascular Inc., Minnesota, USA) were used to maintain distal myocardial perfusion during distal anastomoses.

The right decompressing manoeuvre comprises the application of no traction to the incised right pericardial edge and right pleurotomy. The latter is performed by the surgeon's assistant using diathermy or scissors. The incision runs laterally to the incised right pericardial edge starting at the level of the superior vena cava where it joins the right atrium and continuing down to the level of the diaphragm, where it extends vertically towards the inferior vena cava in an L-shaped fashion. The incision stops just anterior to the inferior vena cava. Care is taken to avoid injury to the right phrenic nerve. During cardiac verticalization the lack of traction to the right pericardium combined with the right pleurotomy ensure that there is adequate space in the right hemithorax to accommodate the right cardiac chambers (figures 3-1 and 3-2), which would otherwise become compressed against the fibrous pericardium and pleura.

Figure 3-1. Cardiac verticalization using the single suture technique to obtain adequate exposure of an obtuse marginal artery. The in situ left internal mammary artery pedicle has already been grafted to the left anterior descending coronary artery (A) and a long saphenous vein graft has been anastomosed to a diagonal branch (B). The lack of traction on the right pericardial edge is obvious but one cannot see the right pleurotomy. The right ventricle has herniated under the right edge of the sternum into the right hemithorax.

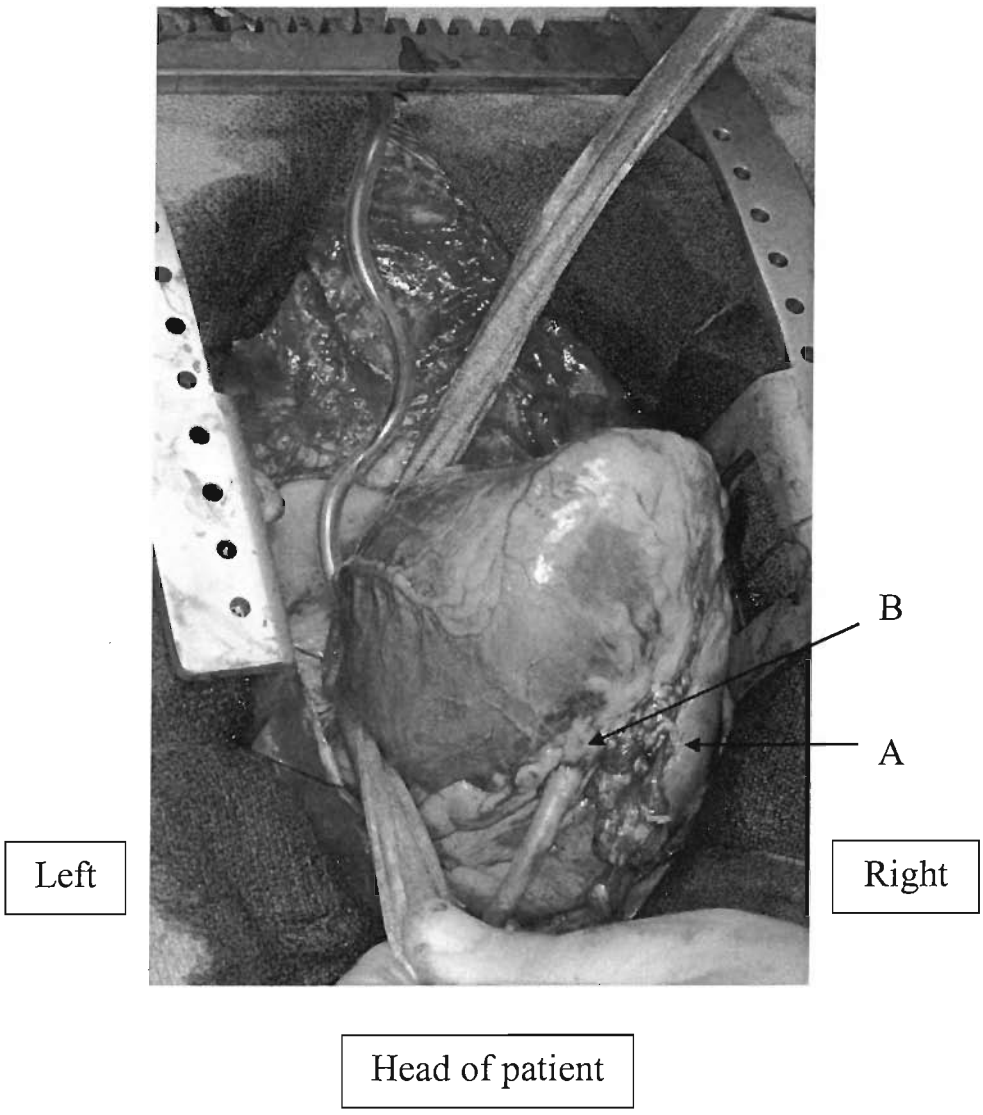
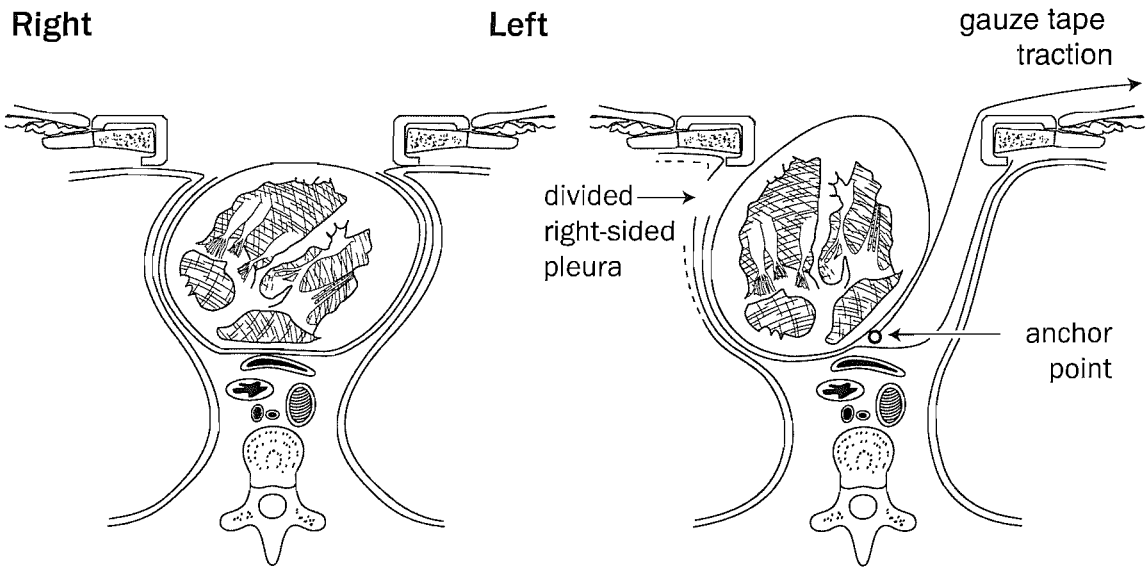


Figure 3-2. The diagram illustrates how the right cardiac chambers are allowed to herniate in the right hemithorax during cardiac verticalization following right pericardial release and right pleurotomy.



Anaesthetic management

A standard protocol was followed in which fentanyl based anaesthesia was used in combination with benzodiazepine and vecuronium as a muscle relaxant. Aspirin was discontinued 7 days prior to surgery. All other antianginal, antihypertensive or antiarrhythmic medication was continued up to the morning of the operation. Haemodynamic stability (target mean arterial pressure of above 60mmHg and cardiac index above 2 L/min/m^2) was achieved primarily with preload management (intravenous fluid administration and Trendelenburg posture) and temporary inotropic support if necessary.

Haemodynamic monitoring

The LiDCO™/PulseCO™ system (LiDCO Ltd., Cambridge, UK) was used to monitor the haemodynamic changes during cardiac verticalization. The use of the

LiDCO™/PulseCO™ system to provide continuous, real-time measurement of the Cardiac Output (CO) has been previously described (Linton et al. 1993; Linton and Linton 2001) and was explained in detail in Chapter 2. Briefly, lithium injection dye dilution is used to measure the CO and the measured value is used to calibrate the PulseCO™ system that calculates the CO continuously by analysing the arterial blood pressure waveform.

Shortly after anaesthetic induction the LiDCO™ system was used to measure the CO; isotonic lithium chloride (150mM) was injected as a bolus (0.33 mmol) via the central venous line and a concentration-time curve was generated by a lithium-selective electrode situated in a flow-through cell and attached to the arterial line manometer system. Indicator dilution curves recorded in arterial blood consist of primary and secondary curves due to the initial circulation and then recirculation of the indicator. The cardiac output is calculated from the lithium dose and the area under the concentration time curve prior to recirculation (Band et al. 1997) using the following equation:

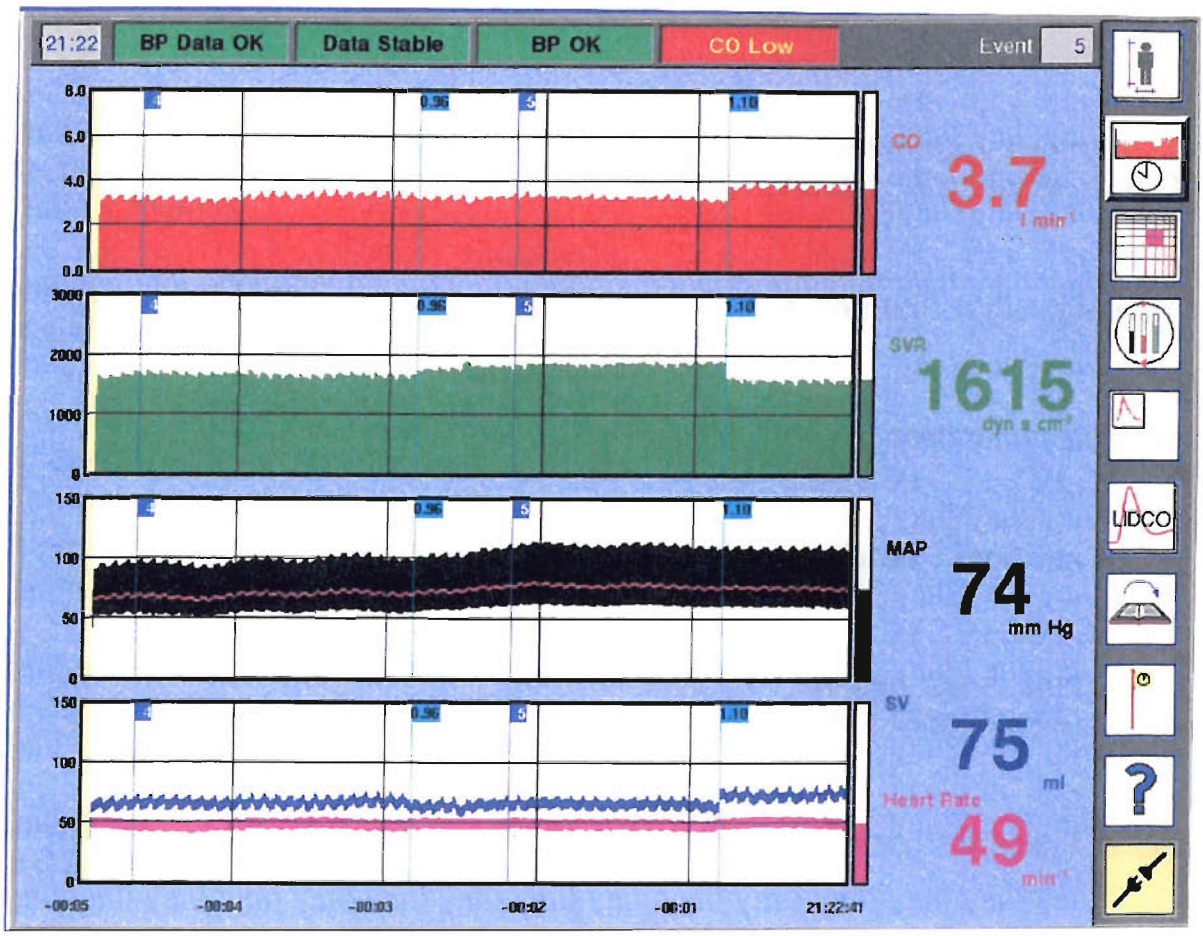
$$\text{Cardiac output (L/min)} = \frac{\text{Lithium dose (mmol) X 60}}{\text{Area X (1-PCV)}},$$

where area is the integral of the primary curve and PCV is the packed cell volume. (the correction for PCV is needed because lithium is distributed in the plasma).

The CO measurement obtained with the lithium dilution technique was used to calibrate the PulseCO™ system, which allows continuous, real-time measurement of the CO by analysis of the arterial blood pressure trace, using transformation of the arterial pressure into a volume-time waveform and the mathematical technique of autocorrelation. The following parameters were monitored: Cardiac Index (CI), Stroke Volume Index (SVI), Systemic Vascular Resistance Index (SVRI), mean arterial blood pressure (MAP), and heart rate (HR) (figure 3-3). Central venous pressure (CVP) measurements were also recorded.

A Swan-Ganz catheter (Edwards Lifesciences, Newbury, UK) was also inserted after anaesthetic induction, to monitor changes in mean pulmonary arterial pressure (mPAP) and systemic venous blood oxygen saturation (S_VO_2).

Figure 3-3. PulseCO™ system display of Cardiac Output, Systemic Vascular Resistance, Mean Arterial Presure, Heart Rate and Stroke Volume. Alternatively, values indexed to body surface area may be displayed.



Assessment of haemodynamic effect of pleuropericardial release

Revascularization of the left anterior descending coronary artery was performed first using the left internal mammary artery. Baseline haemodynamic values with the heart in anatomical position were obtained (position 1), then the heart was elevated using the single suture technique in a position that was deemed suitable for grafting the posterior descending coronary artery (position 2) and haemodynamic parameters were recorded. During this initial cardiac verticalization traction was applied to the incised right pericardial edge using two pericardial sutures. The heart was then returned to anatomical position, the right pericardial traction was released and a right pleurotomy performed and haemodynamic values recorded once more (position 3). The heart was then verticalized for a second time to expose the posterior descending artery and final haemodynamic recordings obtained (position 4). Table 3-2 summarizes the positions in which the haemodynamic parameters were measured.

Table 3-2. Cardiac positioning during haemodynamic recordings.

Position 1: Heart in anatomical position, right pleura closed
Position 2: Heart elevated, right pleura closed
Position 3: Heart in anatomical position, right pleura open, right pericardium released
Position 4: Heart elevated, right pleura open, right pericardium released

Trendelenburg posture was employed throughout the study

Percentage changes of the haemodynamic parameters during cardiac verticalization were calculated according to the formulae:

$$\% \text{ change before decompression} = \frac{\text{value in position 2} - \text{value in position 1}}{\text{value in position 1}} \times 100\%$$

$$\% \text{ change after decompression} = \frac{\text{value in position 4} - \text{value in position 3}}{\text{value in position 3}}$$

No changes were made to the fluid volume or inotropic support during the study period. Trendelenburg posture was employed throughout the manoeuvres.

Statistical analysis

Results were expressed as mean ± standard deviation. Percentage changes before and after decompression were compared using the paired-samples t-test. A paired t-test was also used to compare percentage changes in haemodynamic parameters during cardiac verticalization with the pleura either open or closed. Statistical significance was set at the $p<0.05$ level. The Statistical Package for Social Sciences (SPSS) version 10.1 software was used for the analysis.

RESULTS

All patients completed the study protocol and no patient was excluded from the study. The patient characteristics are summarized in Table 3-3. No patient required the use of cardiopulmonary bypass. The mean (SD) number of grafts performed was 2.8 (0.9). During the cardiac manipulations required by the study protocol one patient received infusion of Dopamine for cardiac function support. The infusion rate remained unchanged during the study at 4.45 μg/kg/min. No other patient required any inotropic or chronotropic support during the study.

Table 3-3. Patient characteristics.

Patient characteristic		Number of patients (n=12)
Age (mean±SD)		62±8
Gender	Male	8
	Female	4
CCS angina class	I	1
	II	5
	III	6
Previous MI		4
Hypertension		8
Morbid obesity		3
Parsonnet score (mean±SD)		4±2

CCS, Canadian Cardiovascular Society; MI, Myocardial Infarction.

The haemodynamic values recorded at the four study positions are summarized in Table 3-4. There were significant haemodynamic changes during cardiac verticalization before and after pleuropericardial release. Before pleuropericardial release (positions 1 and 2), there were significant drops in CI, SVI, MAP and S_VO_2 during cardiac verticalization. With right decompression (positions 3 and 4) there were less marked drops in the above parameters during cardiac elevation; only the SVI fall was statistically significant in that phase of the study. With the right pleura

either open or closed we observed significant elevations in CVP during cardiac verticalization. The effect of cardiac verticalization on the HR, mPAP and SVRI was not significant.

Table 3-4. Haemodynamic recordings in the four study positions.

	Before right decompression		after right decompression	
Parameter	Position 1	Position 2	Position 3	Position 4
CI ($L/min/m^2$)	2.71±0.40	2.41±0.27[a]	2.81±0.39	2.71±0.75
SVI (ml/m^2)	44.9±8.6	39.3±5.4[a]	46.1±8.3	44.1±7.2[c]
HR (min^{-1})	60.9±4.8	61.6±3.3	61.3±4.7	61.5±3.6
MAP (mmHg)	78.4±11.3	70.7±12.5[a]	80.7±10.2	77.2±7.8
CVP (mmHg)	11.4±2.6	13.3±2.6[b]	10.8±1.9	12.5±2.5[d]
SVRI (dyne s^{-1} cm^{-1})	2063±432	1936±236	2101±337	2014±286
mPAP (mmHg)	22.0±4.3	22.7±4.4	22.8±3.9	23.2±4.5
S_VO_2 (%)	73.3±5.9	70.5±6.4[b]	74.4±4.8	74.0±5.3

CI, cardiac index; SVI, stroke volume index; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure; mPAP, mean pulmonary artery pressure; S_VO_2, mixed venous oxygen saturation. Results are expressed as mean±SD.

a, $p<0.01$ compared to position 1; b, $p<0.05$ compared to position 1; c, $p<0.05$ compared to position 3; d, $p<0.01$ compared to position 3.

Table 3-5 summarizes the percentage changes in haemodynamic values during cardiac verticalization before and after a right decompression manoeuvre. Following right heart decompression the CI, SVI, mean ABP and SVO_2 were significantly better preserved during cardiac verticalization.

There were no major perioperative complications and no patient developed clinical or radiological signs of right phrenic nerve palsy.

Table 3-5. Percentage changes in haemodynamic parameters during cardiac elevation.

Parameter	Before right decompression	After right decompression
CI	-10.3±9.4%	-3.7±6.1%[a]
SVI	-11.5±8.8%	-4.0±5.2%[b]
HR	1.5±6.4%	0.6±5.6%
MAP	-9.8±9.3%	-3.8±6.7%[a]
CVP	17.9±21.0%	16.0±16.3%
SVRI	-3.8±16.1%	-3.6±9.6%
mPAP	0.9±14.5%	2.9±12.5%
S_VO_2	-3.7±4.2%	-0.6±2.5%[a]

CI, cardiac index; SVI, stroke volume index; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure; mPAP, mean pulmonary artery pressure; S_VO_2, mixed venous oxygen saturation.

a, $p<0.05$; b, $p<0.01$.

DISCUSSION

OPCAB is becoming increasingly popular as the various stabilizing devices continue to evolve and several advantages of OPCAB versus surgery with CPB have been demonstrated (Ascione et al. 1999; Diegeler et al. 2000; Matata et al. 2000). However, several studies have shown that significant transient haemodynamic impairment occurs during cardiac manipulation (Grundeman et al. 1999; Mathison et al. 2000; Porat et al. 2000; Watters et al. 2001). The haemodynamic deterioration manifests mainly as a temporary drop in the CO, despite relative preservation of the arterial blood pressure, therefore CO monitoring is essential in order to appreciate the haemodynamic changes that occur during OPCAB. Traditional CO measurements using the thermodilution technique and Swan-Ganz catheters are not useful in OPCAB, where the haemodynamic picture changes very rapidly. Continuous CO Swan-Ganz catheters are not satisfactory either, as the displayed values lag 5 to 15 minutes behind the true CO (Siegel et al. 1996; Aranda et al. 1998) and the system is too slow for the immediate detection of acute and dramatic haemodynamic changes such as those encountered in OPCAB (Haller et al. 1995).

More recently several systems that provide real-time continuous monitoring of the cardiac output have become available. The LiDCO™/PulseCO™ system (Linton et al. 1993; Linton and Linton 2001; Jonas and Tanser 2002) is a minimally invasive monitoring system that is connected to the arterial line. The system performs an initial CO measurement using lithium injection dye dilution and the measured value is used to calibrate the PulseCO™ system that calculates the CO in a continuous, real-time fashion using analysis of the arterial blood pressure waveform. The heart rate and arterial blood pressure are also displayed, as well as the calculated values of systemic vascular resistance and stroke volume. Several studies have shown that cardiac output measurements obtained using lithium dilution are at least as accurate as with thermodilution techniques (Kurita et al. 1997; Linton et al. 1997). It has also been shown that the continuous PulseCO™ measurements of CO correlate well with thermodilution measurements in cardiac surgical patients (Linton and Linton 2001; Hamilton et al. 2002). We have used the LiDCO™/PulseCO™ system routinely in our Unit during OPCAB over the last year and have found that the displayed

information is always in keeping with intraoperative events and clinically very useful.

The value of intraoperative real-time cardiac output monitoring may be questioned as the haemodynamic changes observed with cardiac manipulation largely return to baseline values after the heart is returned to anatomical position (Watters et al. 2001). However, periods of haemodynamic instability may adversely affect the perfusion and function of end organs, such as the brain, the kidney and the gut. Several studies have shown a degree of neurocognitive dysfunction after OPCAB comparable to surgery with CPB (Taggart et al. 1999; Lloyd et al. 2000) and our group has demonstrated comparable renal injury after coronary surgery with and without CPB (Tang et al. 2002). Maintaining optimal haemodynamic stability may be even more important during OPCAB in high-risk patients, especially patients with poor ventricular function. The availability to the surgical and anaesthetic team of a more accurate haemodynamic picture may improve the intraoperative circulatory management by guiding decisions such as what pharmacologic support is required, how long to allow the heart to rest or when to convert to CPB.

Haemodynamic impairment during cardiac verticalization is primarily due to a reduction in right ventricular preload and mechanical dysfunction of the right ventricle (Porat et al. 2000). A previous echocardiographic study has demonstrated that during cardiac elevation the right ventricle is compressed between the left ventricle and the surrounding tissues, to the extent that part of the right ventricular free wall is pressed against the interventricular septum during the entire cardiac cycle (Grundeman et al. 1999). Trendelenburg posture is an adjunct to haemodynamic stability during cardiac manipulation by augmenting the preload and filling pressures and restoring right ventricular dimensions (Grundeman et al. 1997). It has been shown that right ventricular assist devices significantly enhance haemodynamic stability during cardiac manipulation (Mathison et al. 2000), while left ventricular assistance does not have a beneficial effect (Grundeman et al. 1999).

The technique we describe aims to decompress the right ventricle by allowing the retracted right cardiac chambers to herniate into the right hemithorax. Our results demonstrated a beneficial haemodynamic effect of the technique during cardiac elevation. Haemodynamic changes were observed during cardiac verticalization before and after performing a right pleuropericardial release. Before the manoeuvre, there were significant falls in CI, SVI, MAP and S_VO_2 during cardiac verticalization. After opening the right pleura and releasing the right fibrous pericardium the CI, SVI, MAP and S_VO_2 were significantly better preserved during cardiac elevation. Interestingly we did not observe any significant changes in the HR and SVRI during cardiac elevation, although other studies have reported a compensatory increase in these parameters during distal anastomoses in OPCAB, which results in a relative preservation of the MAP (Mathison et al. 2000; Watters et al. 2001). This may be due to the fact that in our study we did not allow time for these compensatory changes to take place, as we recorded the haemodynamic changes immediately once the heart was elevated to a position that was deemed adequate for exposure of the posterior descending coronary artery.

To avoid several confounding factors we used every patient as his own control and studied the haemodynamic changes during cardiac verticalization on all patients before and after performing the decompressing manoeuvre. The availability of real-time haemodynamic monitoring allowed all study manipulations to be performed in a short period of time, so that no changes in inotropic support or fluid status occurred during the study. Moreover, real-time monitoring allowed us to document immediate changes after cardiac verticalization, when haemodynamic instability may be expected to be at its worst, before the heart gradually adapts to its new position. Because of the nature of the study the sequence of cardiac verticalizations was the same on all patients: the first one was the control, the second one was after a right pleuropericardial release. There is no evidence to suggest that cardiac verticalization "preconditions" the heart to tolerate better a subsequent further verticalization, therefore we do not think that this would affect the results of this study.

There are many factors that may have influenced the haemodynamic picture during the study manipulations. The most important are left ventricular (LV) function, anaesthetic management, revascularization sequence and body positioning. All our patients had normal LV function, and whether the right decompression manoeuvre may have a similar beneficial effect in patients with a poorly functioning or dilated LV remains unknown. Our patients were in Trendelenburg posture throughout the study and they all had the left anterior descending coronary artery revascularized first to improve myocardial perfusion prior to cardiac verticalization.

A limitation of this study is that we did not assess the haemodynamic impact of pleuropericardial release during a distal anastomosis, when other factors such as the application of the mechanical stabilizer, temporary coronary occlusion or administration of vasoconstrictors and inotropes may significantly affect haemodynamics. Our study was specifically designed to assess the effect of right pleuropericardial release on haemodynamic stability during cardiac elevation. However, the extent to which this manoeuvre may be haemodynamically beneficial during a distal anastomosis remains unknown.

In conclusion this study provides evidence that in patients with normal ventricular function undergoing OPCAB, right pleuropericardial release is an adjunct to haemodynamic stability whenever cardiac elevation is required to expose the less accessible coronary targets. The technique is easy to perform, it is safe and can be used in conjunction with other manoeuvres, such as Trendelenburg position, to optimize haemodynamic stability during OPCAB.

Chapter 4

Evaluation of stress hormone response during coronary surgery with and without cardiopulmonary bypass

SUMMARY

Background: Cardiopulmonary bypass is associated with a systemic stress hormonal response, that can lead to changes in haemodynamics and organ perfusion. Perioperative stress hormone release was studied in low-risk patients undergoing CABG with and without CPB.

Methods: Fifty-two patients undergoing primary CABG by the same surgeon were randomised into either on-pump (ONCAB, n=26) or off-pump (OPCAB, n=26) groups. The ONCAB group underwent mildly hypothermic (35°C) pulsatile CPB with arterial line filtration. Arterial blood samples were collected preoperatively, at the end of operation and at 1, 6 and 24 hours postoperatively. Plasma levels of vasopressin and cortisol were measured using radioimmunoassay. Anaesthetic management was standardized.

Results: Both groups had similar demographic makeup and extent of revascularization (ONCAB 2.8±1.0 grafts vs. OPCAB 2.4±0.9 grafts; $p = 0.20$). No mortality or major morbidity was observed and there were no cross-overs. The CPB and aortic cross-clamp times in the ONCAB group were 63±24 and 33±11 minutes respectively. In both groups there was a similar and significant rise in cortisol and vasopressin levels in the early postoperative phase, with a partial recovery towards baseline values observed at 24 hours postoperatively. Repeated measures analysis of covariance showed no significant difference between the groups over time for both hormones (Cortisol, $p = 0.40$; Vasopressin, $p = 0.30$).

Conclusions: Despite the avoidance of CPB, OPCAB surgery triggers a systemic stress hormone response that is comparable to conventional surgical revascularization. The neuro-hormonal environment during beating-heart surgery requires further investigation.

INTRODUCTION

Cardiopulmonary bypass is associated with well-described changes in the neuro-hormonal environment, which are characterized by the activation of the sympathetic axis and a generalized stress endocrine response (Philbin et al. 1977; Oka et al. 1981; Kono et al. 1983; Minami et al. 1990; Lehot et al. 1992). The stress response leads to the release of hormones that predominantly exert a catabolic action with resultant protein and fat mobilisation, such as cortisol and glucagon, and hormones that primarily aim to retain fluid, such as vasopressin (or anti-diuretic hormone, ADH) and aldosterone. Although not routinely measured in clinical practice, an evaluation of the magnitude of stress response is widely accepted as a valid research tool to assess the ability of different CPB or anaesthetic protocols to achieve a more physiological milieu during surgery (Taylor et al. 1978; Philbin et al. 1979; Philbin et al. 1981; NG et al. 1995). Despite a lack of data to demonstrate an association between stress response and clinical outcome, it is generally accepted that techniques that attenuate the stress response are likely to be better tolerated with preservation of perioperative organ function.

The stress hormonal response to CPB is not unique, representing a universal response to surgery, trauma and other types of injury, such as burns (Rutberg et al. 1984; Knight et al. 1986). The neuro-hormonal environment during OPCAB, which is now an established modality for the surgical treatment of coronary artery disease, has not so far been investigated. While it appears logical that avoidance of CPB should provide a more physiological milieu, the possible advantages or disadvantages of OPCAB require careful evaluation. Some of the physiologic alterations described in open-heart surgery may primarily be due to the effect of general anaesthesia and major surgery on patients with coronary artery disease, who often have significant comorbidities. Pertinent to this is the fact that several studies have shown no advantage of OPCAB vs. surgery with CPB in the perioperative function of organs such as the lung, the brain and the kidneys (Cox et al. 2000; Lloyd et al. 2000; Tang et al. 2002). The purpose of this study was to evaluate using a prospective randomised approach the stress hormonal response in low-risk patients undergoing coronary surgery with or without CPB.

MATERIALS AND METHODS

Study design

Fifty-two patients undergoing primary elective CABG who satisfied the study criteria (Table 4-1) were prospectively recruited following informed consent. We studied low-risk patients with no history of endocrine disease and normal preoperative cardiac function.

Table 4-1. Exclusion criteria.

Age over 75 years
LVEF < 50%
Recent (< 3 months) MI
Intravenous therapy for unstable angina
Diabetes mellitus
Renal insufficiency
Endocrine disease
Steroid therapy
Previous CVA

LVEF, left ventricular ejection fraction; MI, myocardial infarction; CVA, cerebro-vascular accident.

All patients were operated upon by the same surgeon and there were no contraindications to OPCAB following review of the preoperative coronary angiogram. The patients were randomised the day before the operation into either surgery with CPB (ONCAB group, n=26) or off-pump surgery (OPCAB, n=26) by simple randomisation using a table of random numbers.

Anaesthetic management

The patients' medications were continued up to the night before the operation except for anti-platelet agents, which were discontinued 7 days prior to surgery. To avoid the confounding effect of circadian rhythm on hormone levels, all operations were performed in the morning, with general anaesthesia induced between 8:30 and 9:00

am. A standardized anaesthetic protocol was followed in which premedication was administered 2 hours prior to anaesthetic induction using a combination of lorazepam 2mg, hyoscine 0.2mg and morphine 0.1 mg/kg intramuscularly. General anaesthesia was induced using a combination of midazolam 0.05mg/kg, fentanyl 10μg/kg, pancuronium 0.1mg/kg as a muscle relaxant and propofol up to 1mg/kg. Anaesthesia was maintained intraoperatively using a mixture of oxygen, air and isoflurane at an end-tidal concentration of 1% and intravenous propofol infusion 2-3 mg/kg/hr. Postoperatively the patients remained on propofol infusion until extubation. Active warming techniques were used in the recovery period, to achieve a nasopharyngeal temperature of at least 37°C before extubation. Intravenous boluses of morphine at a dose of 1-2 mg were administered for analgesia post extubation.

Target haemodynamic values were mean arterial pressure of above 60 mm Hg and cardiac index above 2.2 l/min/m^2. Invasive monitoring included continuous cardiac output monitoring using a Swan-Ganz catheter (Edwards Lifesciences LLC, Irvine, CA) inserted through the right internal jugular vein after anaesthetic induction. Dopamine was used as the first-line inotropic agent, while bolus intravenous injections of phenylephrine or noradrenaline infusion were used as vasoconstrictors.

CPB management

A standardized CPB protocol was used for the ONCAB patients. CPB was established using bicaval cannulation and an arterial cannula (Medtronic DLP®; Medtronic Ltd., Watford, UK) placed in the ascending aorta. Pulsatile CPB was conducted under mild core hypothermia (35°C), using a hollow-fiber membrane oxygenator (D903 Avant, Sorin Biomedica, Mirandola, Italy) and arterial line filtration (D734 Micro 40, Sorin Biomedica, Mirandola, Italy). The circuit was primed with 1 litre of Hartman's solution, 500 ml of gelofusine and 5000 IU of sodium heparin. Intermittent antegrade cold blood cardioplegia (4°C) delivered through a 12G aortic root cannula was used for myocardial protection. The cardioplegic mixture consisted of 20% St Thomas' Hospital No.2 solution (Martindale Pharmaceuticals, Essex, UK) and 80% autologous blood. A dose of 12 ml/kg was delivered to induce diastolic cardiac arrest and a maintenance dose of 3

ml/kg was administered after completion of each distal anastomosis. The left ventricle was vented through the aortic root during aortic cross-clamping. Flow was maintained at 2.5 l/min/m^2 during CPB with judicious use of phenylephrine and phentolamine to maintain the mean perfusion pressure between 50 and 80 mm Hg. Alpha-stat management of acid-base status was used. Proximal graft anastomoses on the ascending aorta were performed following aortic cross-clamp removal using a partially occlusive clamp.

OPCAB technique

A median sternotomy was used for surgical access in all cases. Partial systemic heparinisation was employed with a target activated clotting time of 300-400 sec prior to cardiac manipulation. Trendelenburg posture was employed throughout the period of distal anastomoses and a single suture technique (Bergsland et al. 1999) was used to facilitate exposure of the target coronary arteries. A mechanical suction-based myocardial tissue stabilizer (Octopus®3; Medtronic Ltd., Watford, UK) was used to immobilize the operative field during coronary anastomosis. Following arteriotomy, an intraluminal coronary shunt (Flo-Thru; Biovascular Inc., Minnesota) was inserted to maintain distal myocardial perfusion and was removed prior to completion of the anastomosis. Core temperature was maintained at or above 35°C throughout the procedure by minimizing heat loss and active warming techniques. Haemodynamic stability was achieved primarily with preload management (intravenous fluid administration and Trendelenburg posture) and vasoactive agents as required. Construction of the proximal anastomoses to the ascending aorta was performed within a single aortic side-biting clamp period, with the systolic arterial pressure maintained ≤100 mm Hg to minimize aortic trauma.

Vasopressin and Cortisol levels

Blood samples were collected from the radial artery into ethylenediaminetetraacetic acid (EDTA)-containing glass tubes shortly after anaesthetic induction, at the end of operation and 1, 6 and 24 hours postoperatively. The samples were immediately centrifuged in a refrigerated centrifuge at 3000g for 10 minutes to separate the plasma, which was subsequently frozen and stored at -70°C until assayed. Levels of

vasopressin were measured using a commercially available radioimmunoassay (Vasopressin 100T Kit; Nichols Institute Diagnostics, San Juan Capistrano, California). The inter-assay coefficient of variance was calculated in our laboratory at 8.4% (n=8). The observed range of plasma values is 0-8 ng/l. Cortisol levels were measured using a routinely available in-house developed radioimmunoassay (inter-assay coefficient of variance: 9.1%, n=14; reference range 8-10 AM: 150-750 nmol/l) (Moore et al. 1985).

Statistical analysis

The results are expressed as the mean ± standard deviation or median with interquartile range for non-normally distributed variables. 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 if normal distribution could not be assumed. Categorical variables were compared using the Pearson's chi-square or Fisher's exact test as appropriate. Repeated measures analysis of covariance, with the baseline measurement as a covariate, was used to assess the effect of time, group and group-time interaction on outcome. A paired *t*-test was used for intra-group comparison between individual time-points. To investigate any possible associations between the extent of cortisol or vasopressin release and clinical outcome, the area under the curve for the levels of cortisol and vasopressin as a function of time was calculated using the method described by Matthews et al (Matthews et al. 1990). Because the data contained subgroups (ONCAB vs. OPCAB), Spearman's rank correlation analysis was used to investigate the association between the extent of hormone release and continuous clinical outcome variables, while logistic regression was used for binary outcome variables. The Statistical Package for Social Sciences (SPSS) version 10.1 software was used for all descriptive statistics and inferential testing. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics, operative data and clinical outcome

All patients completed the study protocol and no patient assigned to the OPCAB group required the use of CPB. Preoperative patient characteristics are presented in Table 4-2. As explained in the methods, these were low-risk cases and no significant differences between the groups were observed.

Table 4-3 summarises the intraoperative data and clinical outcome. The groups had a similar extent of revascularization and similar operation duration. There were no significant differences in the postoperative duration of mechanical ventilation or the time required for the patients to rewarm to a systemic (nasopharyngeal) temperature of 37°C. There were no differences between the groups in dopamine or noradrenaline usage or the development of a low cardiac output (CI < 2.2 l/min/m^2) perioperatively. There were no deaths and no patient required the use of intra-aortic balloon pump. No major complications, such as myocardial infarction, major neurological complications or end-organ failure (other than transient low cardiac output) were observed.

Table 4-2. Patient characteristics.

Variable	ONCAB (n=26)	OPCAB (n=26)	*p* value
Age	63.9 ± 8.0	61.3 ± 8.5	0.27
Gender			0.73
Male	21	20	
Female	5	6	
CCS angina class			0.29
I	7	3	
II	12	10	
III	5	8	
IV	2	5	
Previous MI	9	5	0.21
Hypertension	13	13	1
Morbid obesity	1	3	0.30
Parsonnet score	3.0 (0.0 - 4.0)	3.0 (0.2 - 3.0)	0.94

CCS, Canadian Cardiovascular Society; MI, Myocardial Infarction.

Age is presented as mean ± standard deviation.

Parsonnet score is presented as median and interquartile range.

Table 4-3. Intraoperative data and clinical outcome.

Variable	ONCAB (n=26)	OPCAB (n=26)	*p* value
Distal anastomoses	2.8 ± 1.0	2.4 ± 0.9	0.20
CPB time (min)	62.6 ± 23.7		
X-clamp time (min)	32.6 ± 10.8		
Operation duration (min)	183 ± 43	181 ± 51	0.81
Time to rewarming (hr)	2.6 ± 1.0	2.7 ± 0.8	0.72
Time to extubation (hr)	5.0 (4.0 - 7.0)	4.5 (3.5 - 7.0)	0.58
ICU length of stay (days)	1.0 (1.0 - 1.5)	1.0 (1.0 - 2.0)	0.50
Perioperative low CI	2	1	0.55
Dopamine infusion	2	1	0.55
Noradrenaline infusion	6	9	0.36
Supraventricular arrhythmia	9	5	0.21
Pneumonia	3	4	0.68
Wound infection	1	0	1
Postoperative hospital stay (d)	6.8 ± 2.4	6.6 ± 2.1	0.67

CPB, cardiopulmonary bypass; X-clamp, aortic cross-clamp; ICU, intensive care unit; CI, cardiac index. Low CI is defined as below 2.2 l/min/m^2. ICU length of stay and hospital stay are presented as median with interquartile range. Other continuous variables are presented as mean ± standard deviation.

Table 4-4 summarizes the haemodynamic data in the two groups at the sampling time-points. Although in the early postoperative phase (end of operation and 1 hour postoperatively) there was a trend for the OPCAB patients to maintain superior cardiac output with less systemic vasoconstriction, there were no overall significant differences between the groups. Haemodynamic data at 24 hours postoperatively were not recorded as ethical considerations did not allow us to use Swan-Ganz catheter monitoring beyond 6 postoperative hours, unless it was clinically indicated.

Table 4-4. Perioperative haemodynamic data in the two groups.

Variable	Group	Baseline	Operation end	1 hr	6 hr
CI	ONCAB	2.47 ± 0.59	2.64 ± 0.52	2.80 ± 0.66	3.01 ± 0.68
(l/min/m^2)	OPCAB	2.49 ± 0.66	2.81 ± 0.71	2.97 ± 0.45	3.04 ± 0.63
SVRI	ONCAB	2388 ± 182	2032 ± 102	2104 ± 120	1983 ± 128
(dynes/s cm^{-5})	OPCAB	2311 ± 182	1924 ± 138	1966 ± 76	1896 ± 99
MAP	ONCAB	68 ± 6	62 ± 3	67 ± 5	70 ± 5
(mm Hg)	OPCAB	67 ± 8	63 ± 4	68 ± 3	67 ± 4

CI, cardiac index; SVRI, systemic vascular resistance index; MAP, mean arterial pressure.

Data is presented as mean ± standard deviation.

Cortisol

There was no baseline difference between the groups (ONCAB: 200.3 ± 31.2 nmol/l vs. OPCAB: 176.7 ± 27.4 nmol/l, 95% CI of the difference -16.8, 63.9, p= .25). In both groups there was a dramatic rise in cortisol levels at the end of operation that persisted in the early postoperative period with peak values reached 6 hours postoperatively (figure 4-1 and table 4-5). This was followed by a partial return towards preoperative values at 24 hours. Repeated measures analysis of covariance applied to the four measurements from end of operation to 24 hours with the baseline measurement used as a covariate did not show a significant effect of group (p = 0.40) or group-time interaction (p = 0.84) on outcome. There was also no significant effect of time on outcome (p = 0.56 and p = 0.24 on linear and quadratic analysis respectively). In other words, there was no significant overall trend with time between the end of the operation and 24 hours. All measurements from end of operation to 24 hours were significantly different to baseline values in both groups on paired t-test analysis. There was no significant association between the extent of cortisol release and any of the clinical outcome variables.

Figure 4-1. Perioperative cortisol levels in the two groups. The error bars represent 95% confidence intervals around the mean (for clarity only the plus error bars are displayed for the OPCAB group and the minus for the ONCAB).

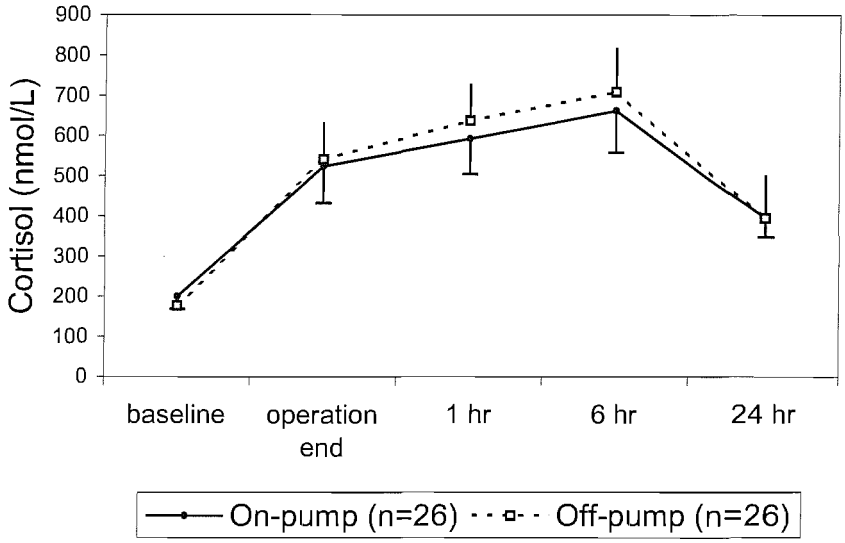


Table 4-5. Perioperative cortisol levels (nmol/L) in the two groups.

Group	Baseline	end of surgery	1hr post-op	6hr	24hr
ONCAB	200.2±31	524±91	592±88	662±104	396±48
OPCAB	177±27	541±90	636±90	709±107	394±105

ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass. The data is presented as mean ± SD.

Vasopressin

There was no baseline difference between the groups (ONCAB: 2.80 ± 0.38 pg/ml vs. OPCAB: 2.65 ± 0.43 pg/ml, 95% CI of the difference –0.43, 0.72, $p = 0.61$). In both groups there was a sharp rise in vasopressin levels at the end of operation followed by a progressive partial return towards baseline values at 24 hours (figure 4-2 and table 4-6). Analysis of covariance with repeated measures revealed a significant effect of time on outcome ($p = 0.004$), however the effect of group ($p = 0.30$) and group-time interaction ($p = 0.33$) was not significant (i.e. the groups behaved similarly across time). All post-baseline values were significantly different from baseline measurements in both groups. We found no significant association between vasopressin release and clinical outcome.

Figure 4-2. Perioperative vasopressin levels in the two groups. The error bars represent 95% confidence intervals around the mean (for clarity only the minus error bars are displayed for the OPCAB group and the plus for the ONCAB).

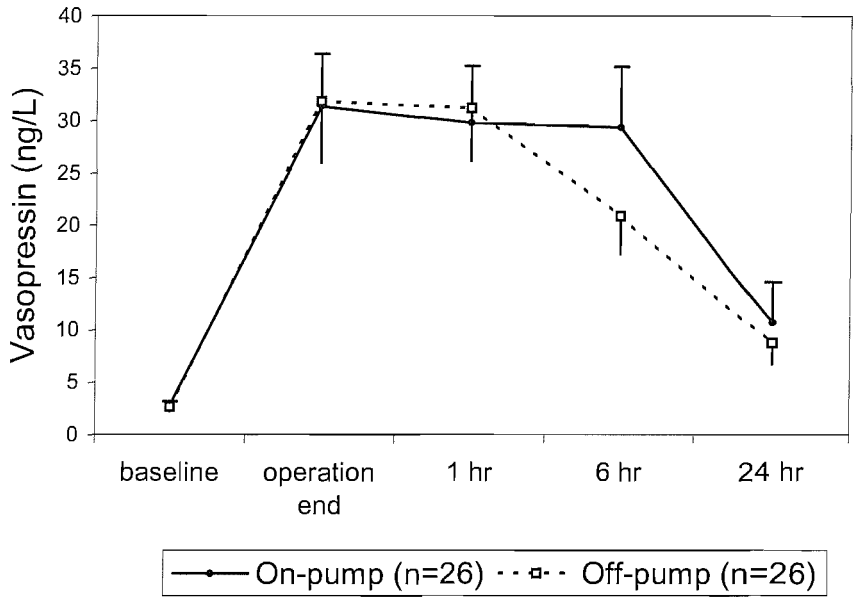


Table 4-6. Perioperative vasopressin levels (ng/L) in the two groups.

Group	Baseline	end of surgery	1hr post-op	6hr	24hr
ONCAB	2.8±0.38	31.4±5	29.8±5.4	29.3±5.8	10.7±3.8
OPCAB	2.6±0.43	31.8±5.8	31.2±5	20.9±3.6	8.7±2.0

ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass. The data is presented as mean ± SD.

DISCUSSION

This study confirms previous findings of significant stress hormonal release after CPB (Philbin et al. 1977; Oka et al. 1981; Kono et al. 1983; Minami et al. 1990; Lehot et al. 1992). The findings in the ONCAB group are consistent with previous studies showing a transient rise in vasopressin and cortisol levels, followed by a return towards baseline values in the early postoperative phase. Previous studies have also described in great detail stress hormonal changes during the period of CPB, which were not investigated in this study. This was not undertaken because there are no true corresponding intraoperative time-points between CABG performed with and without CPB. Despite numerous previous studies, the precise course of stress hormone changes during CPB is not well defined. Taylor et al, in his pioneering work in 1976 described a decline in plasma cortisol and vasopressin levels at the onset of non-pulsatile CPB due to haemodilution (Taylor et al. 1976). The plasma concentration of free cortisol was maintained at pre-bypass levels because of an increase in the percentage of plasma cortisol existing in the free form. Similar observations were made by Kono et al (Kono et al. 1983), while other authors have not confirmed these findings (Levine et al. 1981; Pollock et al. 1988; Lehot et al. 1992). In our study design it was postulated that perioperative measurements would provide a more accurate picture of the cumulative effect of the operation on the hormonal milieu, enabling a valid comparison between the groups.

Plasma hormone measurements during CPB can be difficult to interpret in the context of acute haemodilution at the onset of CPB (Taylor et al. 1976; Roth-Isigkeit et al. 2000). This issue has been debated for some time and most authors suggest that no corrections should be made for haemodilution, as the concentration of a hormone in a target organ is directly affected by its concentration in the serum rather than the total amount in the intravascular fluid. The confounding factor of haemodilution is less relevant in the postoperative period, when the body has begun to compensate by redistributing the excess volume between its fluid compartments. Although it was not intended when the study was designed, we analysed our results after correction for haemodilution as well (results not shown) and this did not alter the study findings.

Our findings of vasopressin and cortisol changes during OPCAB are not surprising if one considers that release of stress hormones is a fundamental part of the body response to surgery and major trauma (Rutberg et al. 1984; Knight et al. 1986). What is perhaps more interesting is the fact that the magnitude of hormonal changes was similar in the two groups. Given the randomised nature of the study design, the controlled anaesthetic and analgesic protocol and the absence of any significant differences in the preoperative characteristics and baseline hormone measurements of the two groups, these results may at first appear surprising. One would intuitively expect some benefit conferred by the avoidance of CPB. The only apparent difference between the groups that would explain the study findings are the inherent differences between OPCAB and CPB techniques and the limitations of each approach.

Cardiopulmonary bypass evokes a systemic inflammatory response through the exposure of blood to foreign surfaces with subsequent activation of various cellular and humoral elements. Several studies have shown an attenuation of the perioperative systemic inflammation with the OPCAB technique compared to CPB (Ascione et al. 2000; Matata et al. 2000). However, as discussed in detail in Chapter 2, there is significant transient haemodynamic deterioration during distal anastomoses in OPCAB (Grundeman et al. 1999; Mathison et al. 2000; Porat et al. 2000; Watters et al. 2001), so that the benefit of a reduced inflammatory response may have to be weighed against the potential for ischaemic injury. Compared to the controlled systemic flow conditions of CPB, cardiac manipulation during OPCAB for the exposure of target coronary arteries leads to significant haemodynamic impairment, with transient drops in the cardiac output, despite relative preservation of the mean arterial pressure. It has been shown that the haemodynamic deterioration is primarily due to right ventricular dysfunction, due to compression of the right heart chambers against the surrounding fibrous pericardium and pleura (Grundeman et al. 1999). The haemodynamic changes are more pronounced when extensive cardiac manipulation is required to expose a target vessel on the posterior aspect of the heart, and are generally reversible once the heart is replaced in its normal position. It is conceivable that in terms of stress hormone response, the benefit

conferred by avoiding CPB was negated by cumulative haemodynamic stress of OPCAB surgery.

Support for this explanation can be derived from a previous study investigating the pattern of vasopressin release during CABG with CPB and during thymectomy through median sternotomy (Knight et al. 1986). Although plasma vasopressin levels were higher in the CPB group, significant increase was also noticed during thymectomy. Interestingly, the increase in vasopressin was related to haemodynamic factors and surgical stimulation, such as median sternotomy and pericardial retraction. Further support for the central role of haemodynamic performance in stress response comes from several studies that have investigated the impact of pulsatile flow during CPB on hormone levels. The use of pulsatile flow during CPB results in a more physiological hormonal environment perioperatively with attenuation of the stress hormone response compared to non-pulsatile CPB (Philbin et al. 1979; Philbin et al. 1981; Minami et al. 1990). Philbin et al. (Philbin et al. 1981) reported their findings on 26 patients randomized to pulsatile vs. non-pulsatile perfusion during CPB. Patients undergoing non-pulsatile CPB had significantly higher perioperative levels of vasopressin, epinephrine and noradrenaline. Similarly, Minami et al. (Minami et al. 1990), randomized 30 patients into pulsatile vs. non-pulsatile CPB. The authors observed significantly lower catecholamine levels in the pulsatile group. Pulsatile flow maintains capillary patency by delivering more energy into the vasculature and ameliorates the CPB-related rise in systemic vascular resistance by reducing the release of vasoconstrictors, such as angiotensin II (Taylor et al. 1979). However, other studies have not confirmed a beneficial effect of pulsatile perfusion on perioperative stress response (Kono et al. 1983; Pollock et al. 1988); differences between various studies in the anaesthetic protocols and other aspects of the CPB protocol, such as the systemic temperature, the flow level and the pulsatile flow parameters may account for these discrepancies.

Systemic hypothermia during CPB has also been shown to attenuate perioperative stress hormone response (Taggart et al. 1989; Sun et al. 1997). Tagart et al. (Taggart et al. 1989) reported an attenuation in endocrine response, measured by urinary

excretion of adrenaline, noradrenaline and cortisol, in patients undergoing CPB at 20°C vs. 28°C. The possible effect of hypothermia on the release of stress hormones was not confirmed by Lehot et al. (Lehot et al. 1992), who reported no difference in vasopressin levels in patients undergoing CPB at 25°C and 37°C. The temperature protocol in this study was selected to eliminate the potential confounding effect of different perioperative temperatures in the two groups. Similarly, a standardized anaesthetic protocol was utilized in both groups, as several studies have shown a variable effect of different anaesthetic and analgesic regimes on the stress response (Philbin et al. 1979; Lightman and Forsling 1980; Kono et al. 1981; Morton et al. 1985; NG et al. 1995; Gruber et al. 2001). It is likely that the choice of CPB protocol and the anaesthetic management had a significant effect on the study findings, and this must be taken into account in future studies.

This study was conducted in a low-risk patient population with normal cardiac and endocrine function. This ensured homogeneity of the groups, which is essential in a prospective randomised study. However, because of the low-risk nature of the study cohort, there were very few deviations from a routine uncomplicated postoperative course, so that no associations between the magnitude of stress response and clinical outcome could be demonstrated. Further larger studies investigating the possible association between stress hormone levels and clinical outcome or subclinical organ injury markers are required to obtain a clearer picture of the clinical significance of stress response. These results are in agreement with previous findings of comparable subclinical renal injury during CPB and OPCAB in a similar patient cohort (Tang et al. 2002) and may provide an explanation for these findings.

The data demonstrate that in a low-risk patient population perioperative surgical stress is similar between OPCAB and surgery with CPB. These results cannot be extrapolated to high-risk patients. Patients with poor left ventricular function, unstable symptoms or other major co-morbidities, such as diabetes mellitus or extracardiac arteriopathy may behave differently and should be investigated separately. Moreover, a similar study in a high-risk population may reveal possible associations between the magnitude of the stress response and clinical outcome.

Chapter 5

Thyroid hormone metabolism during coronary surgery with and without cardiopulmonary bypass.

SUMMARY

Background: Cardiopulmonary bypass is associated with thyroid hormone changes consistent with euthyroid sick syndrome. Similar changes have been observed after general surgical operations. Thyroid hormone changes were studied in low-risk patients undergoing CABG with and without CPB.

Methods: Fifty-two patients undergoing primary CABG by the same surgeon were randomised into either on-pump (ONCAB, n=26) or off-pump (OPCAB, n=26) groups. Thyroid-stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) levels were measured at sequential time-points using chemiluminescence assays.

Results: In both groups TSH and fT4 remained within normal range throughout the study. There was a similar and progressive decline in fT3 levels with no significant difference between the groups over time (p=0.42). Mean fT3 levels at 24 hours were below the normal range and significantly lower than baseline values (ONCAB, 3.3±0.69 vs. 5.1±0.41 pmol/L, p<0.001; OPCAB, 3.3±0.51 vs. 5.0±0.46 pmol/L, p<0.001).

Conclusions: Off-pump surgery is associated with thyroid hormone changes similar to conventional surgical revascularization. The data suggest that further studies into T3 administration during OPCAB may be warranted.

INTRODUCTION

Cardiopulmonary bypass is associated with well-described changes in thyroid hormone levels, consistent with what is described as the euthyroid sick syndrome (Chu et al. 1991; Holland et al. 1991; Buket et al. 1994). The syndrome is characterized by depressed total (TT3) and free (fT3) triiodothyronine levels despite normal concentrations of thyroid stimulating hormone (TSH) and total (TT4) and free (fT4) thyroxine. Decreased deiodination of T4 to its active compound T3 has been implicated as the central pathophysiologic mechanism, while there is a concomitant rise in the levels of the inactive compound reverse T3 (Wartofsky and Burman). Whether these changes represent a true hypothyroid state remains debatable. It has been noticed in trauma patients that the drop in T3 occurs at a time of increased oxygen extraction (Aun et al. 1983), which would suggest that the change in thyroid hormone levels may merely represent an adaptive mechanism to stress, whereby the body tries to conserve energy by reducing catabolic expenditure. The possible association between thyroid hormone changes and VO_2 has not been investigated in cardiac surgical patients. However, the description of perioperative thyroid hormone changes led to several animal and clinical studies that investigated the impact of T3 administration during or after CPB with conflicting results (Novitzky et al. 1988; Teiger et al. 1993; Klemperer et al. 1995; Bennett-Guerrero et al. 1996; Mullis-Jansson et al. 1999).

Off-pump coronary artery bypass grafting is now an established modality for the surgical treatment of single or multiple vessel coronary artery disease. While it appears logical that avoidance of CPB should provide a more physiological milieu, the possible advantages or disadvantages of OPCAB need to be carefully evaluated. Some of the physiologic alterations described in open-heart surgery may be largely due to the simple fact that we submit patients with coronary artery disease to general anaesthesia and major surgery. Immediately relevant to this is the observation that the euthyroid sick syndrome has been described in the context of general surgical operations (Rutberg et al. 1984; Legakis et al. 1998). Previous chapters have described the significant haemodynamic deterioration with OPCAB during construction of the distal anastomoses (Chapter 2), which is primarily related to right

ventricular dysfunction (Chapter 3). Moreover, comparable stress hormonal changes were noticed between surgery with CPB and OPCAB (Chapter 4). The aim of this study was to evaluate using a prospective randomised approach thyroid hormone changes and their association with global oxygen consumption in low-risk patients undergoing coronary surgery with or without CPB.

BACKGROUND

Principles of chemiluminescence assays

Chemiluminescence assays were used in this study for thyroid hormone measurements. Chemiluminescence is a chemical reaction that emits energy in the form of light. When used in combination with immunoassay technology, the light produced by the reaction indicates the amount of analyte in a sample. The ADVIA Centaur system (Bayer Diagnostics, Newbury, UK) directly measures the amount of light that the chemiluminescent reaction emits. The system uses acridinium ester (AE) as the chemiluminescent label, which is oxidized by hydrogen peroxide, with peak light emission occurring within one second. The light emission is maximized by changing the environment from acidic to basic.

The TSH assay is a two-site sandwich immunoassay using direct chemiluminometric technology, which uses constant amounts of two antibodies. The first antibody, in the Lite Reagent, is a monoclonal mouse anti-TSH antibody labelled with AE. The second antibody, in the solid phase, is a polyclonal sheep anti-TSH antibody, which is covalently coupled to paramagnetic particles (PMP). Lite Reagent is added first to the sample, so the AE-labeled antibody binds to TSH. Solid Phase is then added, so that antibody-coated PMP bind to TSH that is bound to AE-labeled antibody. The cuvette is then exposed to a magnetic field, which draws PMP toward the magnets. While the magnets hold PMP in place, sample and reagent not bound to PMP are washed, so that the cuvette contains AE bound to TSH, which is bound to PMP by antibody.

Acid and base are then added to initiate the chemiluminescent reaction. The emission of light is measured in relative light units (RLUs). Once the light produced from the oxidation of AE is quantitated, the system calculates the concentration of antigen. In this sandwich assay, the TSH concentration and the light emission in RLUs have a direct relationship.

The fT3 chemiluminescence assay is a competitive immunoassay using AE-labeled antibody. Free T3 in the sample competes with a T3 analogue, covalently coupled to

PMP in the solid phase for a limited amount of AE-labeled monoclonal mouse anti-T3 antibodies in the Lite Reagent. The cuvette is then exposed to a magnetic field, so that only PMP-T3 analogue antigen bound to AE-labeled antibody remains, while free T3 and reagent not bound to PMP are washed away. The chemiluminescent reaction is then initiated, and obviously the concentration of fT3 and light emission in RLUs have an inverse relationship.

The fT4 chemiluminescence assay is a competitive immunoassay using AE-labeled antigen. Free T4 in the patient sample competes with AE-labeled T4 in the Lite Reagent for a limited amount of polyclonal rabbit anti-T4 antibody, which is covalently coupled to PMP in the solid phase. The cuvette is exposed to a magnetic field, so that only AE-labeled T4 bound to PMP by antibody remains, while sample and reagent not bound to PMP are washed away. Acid and base are then added to initiate the chemiluminescent reaction. Obviously the concentration of fT4 in the sample and the light emission have an inverse relationship.

MATERIALS AND METHODS

Study design

Fifty-two patients undergoing primary elective CABG who satisfied the study criteria (Table 5-1) were prospectively recruited following informed consent. Low-risk patients in euthyroid status with normal preoperative cardiac function were studied. Thyroid status was established by history and clinical examination and confirmed by preoperative thyroid function tests. All patients were operated by the same surgeon and there were no contraindications to OPCAB on review of the preoperative coronary angiogram.

Table 5-1. Exclusion criteria.

Age over 75 years
LVEF less than 50%
Recent (<3 months) MI
Diabetes Mellitus
On intravenous therapy for unstable angina
History of endocrine disease
Renal insufficiency
Liver failure
Previous CVA

LVEF, left ventricular ejection fraction; MI, Myocardial infarction; CVA, cerebro-vascular accident.

The patients were randomised into either surgery with CPB (ONCAB group, n=27) or off-pump surgery (OPCAB, n=27) by simple randomisation using a table of random numbers. Data from a previous study describing thyroid hormone changes using a CPB protocol similar to ours were used for sample size calculation (Thrush et al. 1995). Setting the significance level at 0.05 and the required study power at 0.9, a sample size of 44 patients would detect a difference in fT3 of 30 pg/dL between the groups at 24 hours postoperatively using a two-sample t-test. The time-point of 24 hours was selected because in several studies it appears to be the time that fT3

reaches a minimum postoperative value (Holland et al. 1991; Buket et al. 1994; Thrush et al. 1995).

Anaesthetic management

The patients' medications were continued up to the night before the operation except for anti-platelet agents, which were discontinued 7 days prior to surgery. A standardized anaesthetic protocol was followed in which fentanyl based anaesthesia was used in combination with benzodiazepine and pancuronium as a muscle relaxant. Target haemodynamic values were mean arterial pressure of above 60 mmHg and cardiac index above 2.2 L/min/m^2. Invasive monitoring included continuous cardiac output monitoring using a Swan-Ganz catheter (Edwards Lifesciences, Irvine, USA) inserted through the right internal jugular vein after anaesthetic induction. Dopamine was used as the first-line inotropic agent, while bolus intravenous injections of phenylephrine or noradrenaline infusion were used as vasoconstrictors. Whole-body oxygen consumption (VO_2) was measured at the start and end of operation and then at 1 and 6 hours postoperatively using the following formula:

$VO_2 = \{Hb \text{ X } (SaO_2 - SvO_2) \text{ X } 1.39 + [0.003 \text{ X } (PaO_2 - PvO_2)]\} \text{ X Cardiac Index X } 0.1$ ml/min/m^2,

where Hb is Haemoglobin concentration in g/dL,

SaO_2 is the percentage of oxygen saturation of arterial blood,

SvO2 is the percentage of oxygen saturation of mixed venous blood,

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

and PvO2 is the partial pressure of oxyen in mixed venous blood.

In the above equation the factor 0.003 X PaO_2 - PvO_2 is negligible and was not calculated for the purposes of our study. The Cardiac Index is expressed in L/min/m^2.

CPB management

A standardized CPB protocol was used for the ONCAB patients. CPB was established using bicaval cannulae or a single 2-stage venous cannula (Medtronic DLP, Medtronic UK Ltd.) inserted into the right atrium/inferior vena cava and an arterial cannula (Medtronic DLP, Medtronic UK Ltd.) placed in the ascending aorta. The circuit was primed with 1 L of Hartman's solution, 500 ml of gelofusine and

5000 IU of sodium heparin. Additional heparin, 300 IU/kg was administered intravenously prior to institution of CPB and then as required to maintain the activated clotting time (ACT) above 450 sec. CPB with pulsatile flow during aortic cross-clamping was conducted under mild core hypothermia (35°C), using a hollow-fibre membrane oxygenator (D903 Avant, Sorin Biomedica, Gloucester, UK) and arterial line filtration (D734 Micro 40, Sorin Biomedica, Gloucester, UK). Intermittent antegrade cold blood cardioplegia (4°C) delivered through a 12G aortic root cannula was used for myocardial protection. The cardioplegic mixture consisted of 20% St Thomas' Hospital No.2 solution (Martindale Pharmaceuticals, Essex, UK). A dose of 12 ml/kg was delivered to induce diastolic cardiac arrest and a maintenance dose of 3 ml/kg was administered after completion of each distal anastomosis. The left ventricle was vented through the aortic root during aortic cross-clamping. Flow was maintained at 2.5 L/min/m^2 with judicious use of phenylephrine and phentolamine to maintain the mean perfusion pressure between 50 and 80 mmHg. Alpha-stat management of acid-base status was used. Proximal graft anastomoses on the ascending aorta were performed following aortic cross-clamp removal using a partially occluding clamp.

OPCAB technique

A median sternotomy was used for surgical access in all cases. Following harvesting of suitable conduits, the pericardium was opened and partial systemic heparinisation was employed with a target ACT of 300 - 400 sec prior to cardiac manipulation. A single suture technique (Bergsland et al. 1999) was used to facilitate exposure of the target coronary arteries. Trendelenburg posture was employed throughout the period of distal anastomoses, while a partial right lateral decubitus position was also used during exposure of the PDA and OM coronary arteries. A mechanical suction-based myocardial tissue stabilizer (Octopus®3; Medtronic Ltd., Watford, UK) was used to immobilize the operative field during coronary anastomosis. Following arteriotomy, an intraluminal coronary shunt (Flo-Thru; Biovascular Inc., Minnesota, USA) was inserted to maintain distal myocardial perfusion and was removed prior to completion of the anastomosis. Core temperature was maintained at or above 35°C throughout the procedure by minimizing heat loss and active warming techniques.

Haemodynamic stability was achieved primarily with preload management (intravenous fluid administration and Trendelenburg posture). If preload increase did not restore target haemodynamic values, epicardial pacing or vasoactive agents were used as necessary. Following completion of coronary anastomoses, construction of the proximal anastomoses to the ascending aorta was performed in a similar fashion to on-pump techniques using an aortic side-biting clamp, with the systolic pressure maintained at or below 100 mm Hg to minimize the risk of aortic dissection.

Assessment of thyroid function

Blood samples were collected from the radial artery into EDTA-containing glass tubes shortly after anaesthetic induction, at the end of operation and 1, 6 and 24 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. Levels of fT3, fT4 and TSH were measured using the ADVIA Centaur automated chemiluminescence system (Bayer Diagnostics, Newbury, UK). The reference ranges are fT4: 8.0-22.0 pmol/L, fT3: 3.5-7.0 pmol/L, TSH: 0.5-5.5 mU/L. The interassay coefficients of variation were fT4: 9.8% (n=98), fT3: 2.9% (n=38) and TSH: 6.8% (n=89). The chemiluminescence assays used for thyroid hormone measurements are explained in the background information to this Chapter.

Statistical analysis

The results are expressed as the mean ± standard deviation or median with interquartile range for non-normally distributed variables. 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 if normal distribution could not be assumed. Categorical variables were compared using the Pearson's chi-square or Fisher's exact test as appropriate. Repeated measures analysis of covariance, with the baseline measurement as a covariate, was used to assess the effect of time, group and group-time interaction on outcome. A paired *t* test was used for intra-group comparison between individual time-points. Repeated measures analysis of covariance, with the baseline measurement as a covariate, was also used to assess the effect of inotropic support on thyroid hormone levels. Because the data contained subgroups (ONCAB

vs. OPCAB), Spearman's rank correlation analysis was used to investigate the association between thyroid hormone changes and whole body oxygen consumption. The Statistical Package for Social Sciences (SPSS) version 10.1 software was used for the analysis. A p value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics, operative data and clinical outcome

One patient in the OPCAB group required emergency resternotomy for mediastinal bleeding 2 hours postoperatively and was excluded from the study. That patient had an otherwise uneventful recovery and was discharged from hospital on the 6th postoperative day. The demographic variables for the two groups are presented in Table 5-2. As outlined in the methods, these were low-risk cases and there were no significant differences between the groups.

Table 5-3 summarises the intraoperative data and clinical outcome. The groups had a similar extent of revascularization and only few patients required inotropic support for a cardiac index below the target value of 2.2 L/min/m^2. Clinical outcome was similar in the two groups. No mortality or major complications, such as myocardial infarction, major neurological complications or end-organ failure were observed. No patient required the use of an intraaortic balloon pump.

Table 5-2. Patient characteristics.

Variable	ONCAB (n=26)	OPCAB (n=25)	*p* value
Age	63.9 ± 8.0	61.3 ± 8.5	.27
Gender			.94
Male	21	20	
Female	5	5	
CCS angina class			.34
I	7	3	
II	12	10	
III	5	7	
IV	2	5	
Previous MI	9	5	.24
Hypertension	13	13	.88
Morbid obesity	1	3	.28
Parsonnet score	3.0 (0.0-4.0)	3.0 (0.2-3.0)	.94

CCS, Canadian Cardiovascular Society; MI, Myocardial Infarction. Age is presented as mean ± standard deviation. Parsonnet score is presented as median and interquartile range.

Table 5-3. Intraoperative data and clinical outcome.

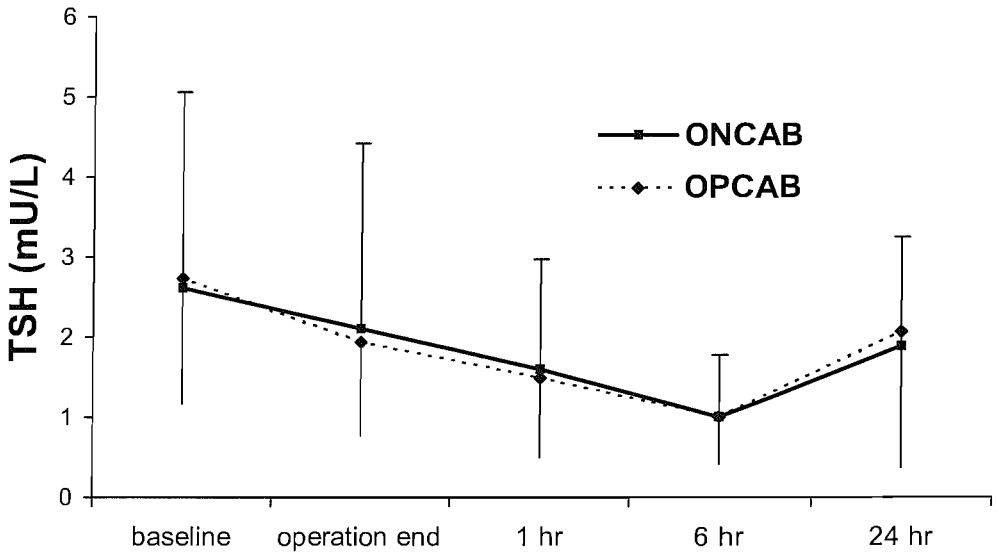
Variable	ONCAB (n=26)	OPCAB(n=25)	*p* value
Distal anastomoses	2.9 ± 1.0	2.5 ± 0.9	.17
CPB time (min)	62.6 ± 23.7		
AXC time (min)	32.6 ± 10.8		
Time to extubation (hr)	5.0 (4.0-7.0)	4.5 (3.5-7.0)	.58
ICU length of stay (d)	1.0 (1.0-1.5)	1.0 (1.0-2.0)	.50
Perioperative low CI	1	1	1
Supraventricular arrhythmia	9	5	.24
Pneumonia	3	4	.64
Wound infection	1	0	.49
Postoperative hospital stay (d)	6.8±2.4	6.6±2.1	.67

CPB, cardiopulmonary bypass; AXC, aortic cross-clamping; ICU, intensive care unit; CI, cardiac index. Low CI is defined as below 2.2 L/min/m^2. ICU length of stay and hospital stay are presented as median with interquartile range. Other continuous variables are presented as mean ± standard deviation.

Thyroid stimulating hormone

TSH levels remained within normal range in all patients at all sampling times (figure 5-1). There was no baseline difference between the groups (p=0.83). No further analysis of the data was undertaken, however in both groups there was a similar pattern of decline in TSH concentration in the early postoperative period, with minimum values reached 6 hours postoperatively. This was followed by a partial recovery towards preoperative values at 24 hours.

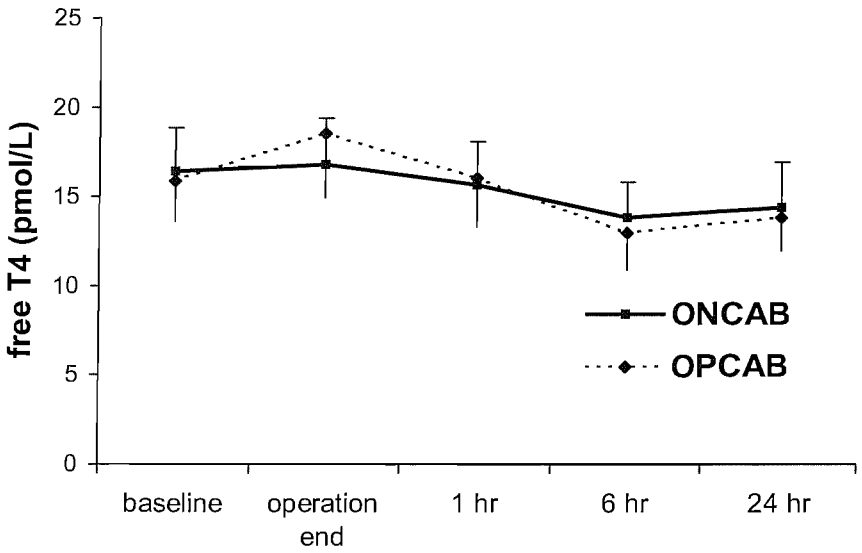
Figure 5-1. Perioperative TSH levels in the two groups. The error bars represent the standard deviation around the mean (for clarity only the negative error bars are displayed for the OPCAB group and the positive for the ONCAB). The reference range is 0.5-5.5 mU/L.



Free thyroxine

Free thyroxine remained within normal range in all patients throughout the study (figure 5-2). There was no baseline difference between the groups (p=0.44).

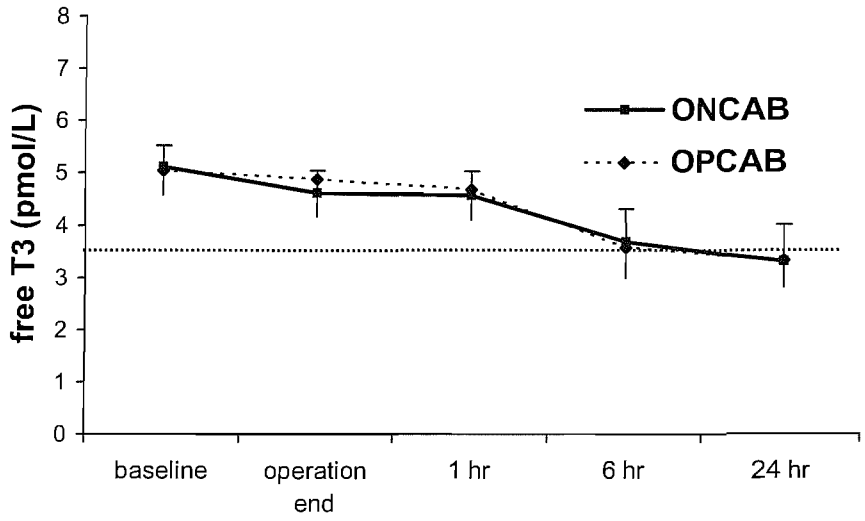
Figure 5-2. Perioperative fT4 levels in the two groups. The error bars represent the standard deviation around the mean (for clarity only the negative error bars are displayed for the OPCAB group and the positive for the ONCAB). The reference range is 8-22 pmol/L.



Free triiodothyronine

There was no baseline difference between the groups (p=0.53). In both groups there was a pattern of progressive decline in fT3 levels during the study with minimum values at 24 hours (figure 5-3). Mean fT3 levels at 24 hours were below the normal range and there was a highly significant difference to baseline values on paired t-test analysis in both groups ($p<0.001$ for both groups). Repeated measures ANCOVA confirmed a significant effect of time on outcome (p=0.01), however the effect of group (p=0.38) and group-time interaction (p=0.14) was not significant.

Figure 5-3. Perioperative fT3 levels in the two groups. The error bars represent the standard deviation around the mean (for clarity only the negative error bars are displayed for the OPCAB group and the positive for the ONCAB). The reference range is 3.5 – 7.0 pmol/L. The dotted line is at the lower end of the normal range.



The levels of thyroid hormones are also presented in table 5-4.

Table 5-4. Perioperative thyroid hormone levels in the two groups.

Variable	Preop	Operation end	1 hr	6 hr	24 hr
TSH (mU/L)					
ONCAB	2.61±2.45	2.11±2.31	1.60±1.37	1.01±0.77	1.89±1.36
OPCAB	2.74±1.57	1.94±1.17	1.49±0.98	1.01±0.59	2.07±1.70
fT4 (pmol/L)					
ONCAB	16.40±2.45	16.8±2.57	15.64±2.43	13.84±1.99	14.42±2.55
OPCAB	15.88±2.28	18.50±3.55	16.04±2.78	12.94±2.01	13.83±1.86
fT3 (pmol/L)					
ONCAB	5.12±0.41	4.62±0.43	4.56±0.47	3.68±0.63	3.31±0.69[a]
OPCAB	5.04±0.46	4.88±0.71	4.67±0.57	3.57±0.59	3.34±0.52[a]

TSH, thyroid-stimulating hormone; fT4, free thyroxine; fT3, free triiodothyronine. Data are presented as mean ± standard deviation. a = $p<0.001$ compared to preoperative value. Reference ranges, fT4: 8.0-22.0 pmol/L, fT3: 3.5-7.0 pmol/L, TSH: 0.5-5.5 mU/L.

Effect of inotropic agents

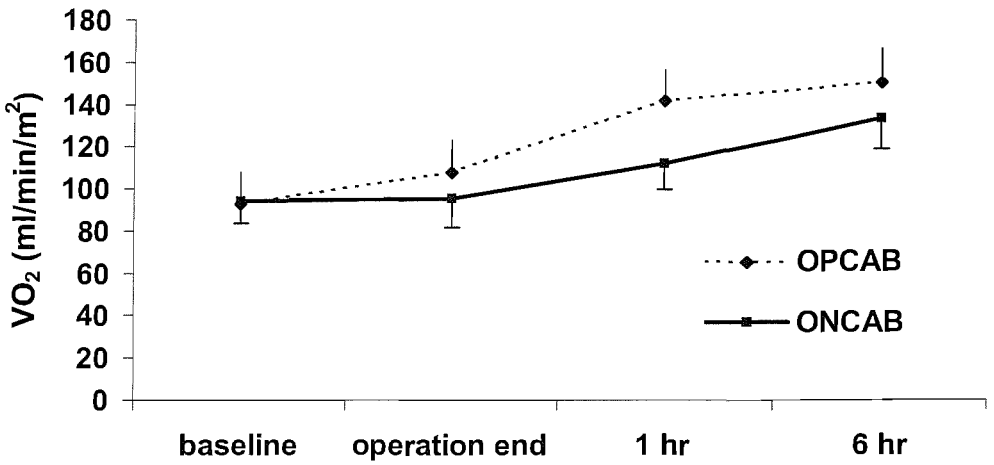
Repeated measures ANCOVA revealed no significant effect of dopamine or norepinephrine infusion on any of the measured thyroid hormones. A similar analysis was also applied separately for the ONCAB and OPCAB groups. Again, no significant effect of either dopamine or norepinephrine on thyroid hormone levels was demonstrated.

Whole body oxygen consumption and relation to free triiodothyronine

There were no baseline differences between the groups (p=0.92). There was a significant and similar trend in both groups towards increasing levels of VO_2 during the study ($p< .001$ for time and $p= .89$ for group-time interaction, figure 5-4). OPCAB patients maintained higher levels of VO_2 throughout the study ($p= .04$ for the effect of group).

Spearman's rank correlation revealed a highly significant association ($p< .001$) between VO_2 and fT3 levels ($r_s= - 0.71$).

Figure 5-4. Perioperative VO_2 levels in the two groups. The error bars represent 95% confidence intervals around the mean (for clarity only the positive error bars are displayed for the OPCAB group and the negative for the ONCAB).



DISCUSSION

The study confirms previous findings of significant thyroid hormone changes after CPB (Bremner et al. 1978; Chu et al. 1991; Holland et al. 1991; Clark 1993; Buket et al. 1994; Keceligil et al. 1996). The results in the ONCAB group are similar to previous studies showing a progressive decline in fT3 levels in the early postoperative phase, despite preserved fT4 and TSH concentrations. These thyroid hormone changes are consistent with what is known as euthyroid sick syndrome, which is also characterized by raised levels of the inactive compound reverse T3 (rT3). Previous studies have confirmed the presence of elevated rT3 during and after CPB.

The mechanism responsible for the development of euthyroid sick syndrome involves regulation of two deiodinases that control T4 metabolism (Bremner et al. 1978; Holland et al. 1991). Thyroxine is three times less potent than T3 and is entirely secreted by the thyroid gland. Approximately 40% of T4 is deiodinated to the active compound, T3, in the peripheral tissues. Two deiodinases are involved in this process: 5' deiodinase converts T4 to T3 and rT3 to 3,3'T2, and 5 deiodinase converts T4 to rT3 and T3 to 3,3'T2. It is thought that reduced activity of 5' deiodinase results in decreased formation of T3, allowing increased conversion of T4 to rT3 by 5 deiodinase. Moreover, there is concomitant reduced metabolism of rT3 to 3,3'T2, which contributes to the raised levels of rT3 (Wartofsky and Burman, 1982).

There is obvious difference between euthyroid sick state and primary hypothyroidism, in that the latter is usually characterized by decreased levels of T4 and fT4, raised concentrations of TSH and normal levels of T3 and fT3. Also primary hypothyroidism is a chronic illness, while euthyroid sick syndrome has been observed as an acute response of the thyroid axis to a variety of insults. These include general surgical operations (Burr et al. 1975; Chan et al. 1978; Prescott et al. 1979; Rutberg et al. 1984; Legakis et al. 1998), acute and chronic systemic illnesses (Carter et al. 1974; Chopra et al. 1975; Chopra and Smith 1975; Nomura et al. 1975; Burger et al. 1976; Leslie et al. 1978), fasting (Vagenakis et al. 1975) and major trauma (Aun et al. 1983; Phillips et al. 1984). The magnitude of T3 fall in the context

of chronic illnesses has been shown to correlate with the severity of the disease (Carter et al. 1974), while in the context of surgery even relatively non-major operations such as laparoscopic cholecystectomy have been found to trigger the euthyroid sick response (Legakis et al. 1998).

It is interesting to note that post-surgical euthyroid sick syndrome occurs in the early postoperative phase, at a time when the patient is in a catabolic state with increased whole body oxygen consumption and global oxygen extraction fraction (Ohri et al. 1994). Similarly, Aun et al (Aun et al. 1983) observed that in trauma patients there was a reduction in T3 levels despite increased oxygen extraction by muscular tissue. All this would suggest that the euthyroid sick syndrome represents an adaptative mechanism of the body in an attempt to reduce catabolism (Wartofsky and Burman; Holland et al. 1991), rather than a true hypothyroid state. In the case of fasting, the organism tries to reduce the basal metabolic rate, while in the context of major catabolic illness, trauma and surgery there is an attempt to control a hypermetabolic state. In keeping with this hypothesis are the observations made by Goode et al (Goode et al. 1981), in a study of 11 patients undergoing elective cholecystectomy, who were maintained on adequate caloric and carbohydrate intake perioperatively. Despite the avoidance of post-surgical starvation, the patients still developed euthyroid sick syndrome, probably as a primary response to surgery and the associated hypermetabolism, and not as a secondary response to fasting. This study has found a significant negative correlation between levels of fT3 and global oxygen consumption, which is in keeping with this hypothesis and, to the best of our knowledge, this association has not been previously demonstrated in cardiac surgical patients.

The documentation of low T3 levels after CPB led to a number of studies that investigated the possible beneficial effect of perioperative T3 administration. The well-known effects of thyroid hormones on the cardiovascular system, including a decrease in peripheral vascular resistance and positive inotropic and chronotropic effects (Morkin et al. 1983; Klein 1990; Morkin et al. 1993), provided the basis for these studies. Initial positive results on experimental settings in pigs and baboons

reported by Novitzky et al. (Novitzky et al. 1988; Novitzky et al. 1988) led to several randomized clinical studies, the results of which are summarized in Table 5-5.

Table 5-5. Summary of T3 administration studies.

Author, year	Study design	N	T3 protocol	Main findings
Mullis-Janson, 1999 (Mullis-Jansson et al. 1999)	DB, randomised placebo-controlled	170	1μg/kg bolus + 1μg/kg over 6hr	↓ inotropic use, ↓ myocardial ischaemia, ↓ pacemaker dependence, ↓ LV mechanical assistance
Bennett-Guerrero, 1996 (Bennett-Guerrero et al. 1996)	DB, randomised placebo-controlled positive control (Dopamine)	211	0.8μg/kg bolus +0.12μg/kg/hr for 6hr	No differences in haemodynamics or inotropic use
Klemperer, 1995 (Klemperer et al. 1995)	DB, randomised placebo-controlled	142	0.8μg/kg bolus +0.113μg/kg/hr for 6hr	↑CO, ↓ SVR, no difference in outcome or inotropic use
Teiger, 1993 (Teiger et al. 1993)	DB, randomised placebo-controlled	20	Total 0.55 μg/kg in 5 boluses over 20 hr	No differences
Novitzky, 1989 (Novitzky et al. 1989)	DB, randomised placebo-controlled LVEF<30%	24	Total 0.275μg/kg in 4 boluses over 8hr	↓ inotropic and diuretic requirements, no difference in outcome
	DB, randomized placebo-controlled LVEF>40%	24	Total 0.55 μg/kg in 5 boluses over 20 hr	↑ CO, ↓ SVR, ↓PVR, no difference in outcome, inotropes, diuretics

DB, double blind; LV, left ventricular; CO, cardiac output; SVR, systemic vascular resistance; LVEF, left ventricular ejection fraction; PVR, pulmonary vascular resistance

Despite methodological differences between individual studies, the majority of evidence appears to demonstrate improved haemodynamic performance with T3 administration but not to the extent that would alter clinical outcome. It may be that high-risk patients benefit the most from T3 supplementation (Novitzky et al. 1989). Of the reviewed studies in Table 5-5, the one conducted by Mullis-Janson et al included a study cohort of higher risk profile than the studies of Bennett-Guerrero and Klemperer, while in the other studies the sample sizes might have been insufficient to demonstrate a difference in clinical outcome. In any case T3 administration after CPB does not appear to have such haemodynamic impact as one perhaps would expect given the known inotropic properties of T3 and the low T3 state in the early postoperative phase. The suggestion that the euthyroid sick syndrome does not represent a true hypothyroid state may provide an explanation for these findings.

Our findings of thyroid hormone changes in the context of OPCAB are not surprising given that the euthyroid sick syndrome has been well-described in the context of abdominal surgery and major trauma, which makes it plainly obvious that stress other than the use of CPB can also elicit this hormonal response. What is more interesting is the fact that the magnitude of thyroid hormone changes was similar in the two groups. Given the randomised nature of the study design and the absence of any significant differences in the preoperative characteristics and baseline thyroid hormone measurements of the two groups, these results may at first appear surprising. One would intuitively expect some benefit conferred by the avoidance of CPB. There are certainly factors associated with the use of CPB per se that have been debated for some time as possible explanations for the development of euthyroid sick syndrome after open-heart surgery. Haemodilution during CPB, hypothermia, the use of non-pulsatile flow, hypothalamo-pituitary-thyroid axis dysfunction and changes in the concentration of thyroid binding globulin (TBG) have all been proposed as contributory factors.

Thrush et al. (Thrush et al. 1995) undertook a thorough assessment of thyroid function in a randomized study comparing normothermic (35°±1°C) vs. hypothermic (26°±5°C) non-pulsatile CPB in 13 low-risk patients undergoing primary CABG or valve replacement surgery. Both groups developed changes consistent with euthyroid sick syndrome, however there was no difference between the groups. These findings are supported by the study of Lehot et al. (Lehot et al. 1992), where no difference in thyroid function was found between hypothermic and normothermic non-pulsatile CPB in 20 patients, although the assessment of thyroid function was less comprehensive. Finally, Bremner et al (Bremner et al. 1978) reported significant decreases in total T3 and fT3 in ten patients undergoing normothermic nonpulsatile CPB.

Haemodilution by the CPB circuit priming volume presents investigators with a real methodological problem: should one correct the measured hormone levels for haemodilution? The answer to that is probably not, as it is the hormone concentration in the target organ that matters, rather than the circulating amount of hormone in the intravascular volume. In other words, the tissues "see" concentration in serum, which is the fluid compartment with which they exchange free hormones and the concentration of the hormone in blood is of no physiological significance. There may be a place for haemodilution correction in the initial period after commencement of CPB, as the intravascular volume is acutely augmented with the additional volume that is required to prime the CPB circuit, so that the intravascular hormonal concentrations will be acutely artificially lowered. However, equilibration of hormone concentration with other body fluid compartments would be expected to happen rather quickly, as the intravascular volume represents only a small amount of total body water. Therefore in the post bypass period in particular, there seems to be no reason to correct for haemodilution. This would be further supported by the observation that albumin concentrations return to normal by 2 hours after CPB, while changes in thyroid hormone levels persist for several days (Chu et al. 1991; Holland et al. 1991; Thrush et al. 1995). In any case, thyroid hormone changes move in opposite directions during and after CPB, suggesting that despite their structural similarity they are affected by haemodilution in a different way. Moreover, a

euthyroid sick syndrome has been reported even after correcting for haemodilution (Bremner et al. 1978). All this indicates that haemodilution is not a major factor affecting thyroid hormone levels (Holland et al. 1991).

The lack of pulsatile flow is perhaps the only factor that has been shown to significantly affect the magnitude of thyroid hormone changes during CPB. Buket et al. (Buket et al. 1994) examined thyroid hormone changes in 30 low-risk patients undergoing CABG with hypothermic (26°C to 30°C) CPB using pulsatile vs. nonpulsatile flow. The authors observed the development of euthyroid sick syndrome in both groups. However, total T3 and fT3 concentrations declined significantly less with pulsatile CPB. Although the authors did not attempt to explain the reasons for superior preservation of thyroid function with the use of pulsatile flow, immediately relevant to these findings is the pioneering work by Taylor and Bremner in the late 1970s.

Their group investigated the hypothalamo-pituitary-thyroid axis function during CPB (Bremner et al. 1978; Taylor et al. 1978; Taylor et al. 1978). They found a blunted TSH response to thyrotropin-releasing hormone (TRH) during both the early and late phase of CPB, in contrast to heparinised and non-heparinised patients undergoing major surgery (Bremner et al. 1978; Taylor et al. 1978). This led them to repeat the study of TRH administration in 20 patients undergoing normothermic pulsatile vs. nonpulsatile CPB for either CABG or valve replacement operations (Taylor et al. 1978). There was a marked difference between the groups, with nonpulsatile patients demonstrating the previously reported subnormal response to TRH, while pulsatile CPB resulted in a normal pituitary response to TRH in nine out of ten patients. Although Taylor's findings do not provide a direct explanation for the observations made by Buket et al (see previous paragraph), these studies provide strong evidence that pulsatile flow during CPB is a major factor contributing towards preservation of a euthyroid hormonal environment.

Displacement of thyroid hormones from binding proteins and mobilization of T4 from the liver into the circulation are triggered by the administration of heparin and

various other drugs, including several anaesthetic agents (Herschman et al. 1972; Harland et al. 1974; Bremner et al. 1978). Although the heparin effect may be relevant in the early period during CPB (Bremner et al. 1978), it is unlikely to be significant in the postoperative period, especially since heparin is neutralized with protamine sulphate at the end of surgery. In this study, differences in heparin requirements (OPCAB patients only require about half dose) was one of the reasons for not measuring intraoperative thyroid hormone levels. The lack of truly comparable intraoperative time-points in the two groups and the possible confounding factor of haemodilution in the ONCAB group were the other factors considered. The effect of various anaesthetic agents on liver mobilization of T4 is believed to be short-lived, however it is obviously important to standardize the anaesthetic management to avoid a potential confounding factor. For similar reasons it is important to ensure similarities between the groups in preoperative medication and euthyroid baseline status, as several drugs such as amiodarone (Sandhu and Davies 2001) can affect thyroid function.

Careful review of the literature therefore reveals that various factors pertinent to the use of CPB, such as hypothermia and haemodilution, have not been proven to play a major role in perioperative thyroid hormone changes. The only significant factor appears to be the use of pulsatile or non-pulsatile flow during CPB (Bremner et al. 1978; Taylor et al. 1978; Buket et al. 1994). The importance of pulsatile flow and the observation that relatively minor general surgical procedures lead to a euthyroid sick syndrome (Rutberg et al. 1984; Legakis et al. 1998) would suggest that haemodynamic factors and the stress of a surgical procedure may be the paramount factors that determine thyroid axis response. This may help us explain why OPCAB led to a thyroid response comparable to CPB.

As discussed extensively in Chapter 2 of this thesis, the presence of significant transient haemodynamic impairment during distal anastomoses in OPCAB has been well documented (Grundeman et al. 1997; Mathison et al. 2000; Nierich et al. 2000; Watters et al. 2001; Do et al. 2002). Significant drops in cardiac output may occur despite relatively well-preserved systemic arterial pressures. As described in Chapter

2, the use of continuous real-time cardiac output monitoring reveals acute dramatic haemodynamic changes, which otherwise go unnoticed using routine monitoring equipment. Haemodynamic deterioration is worse during grafting of the less accessible coronary targets that require extensive cardiac manipulation for adequate exposure. As explained in Chapter 3 of the thesis, cardiac verticalization results in compression of the right heart chambers against the surrounding fibrous pericardium and pleura and mechanical dysfunction of the right ventricle (Grundeman et al. 1999). Moreover, despite a preserved mean arterial pressure, elevation of the central venous pressure with Trendelenburg posture and cardiac manipulation results in significant drops in perfusion pressure. It is conceivable that the cumulative effect of these transient episodes of reduced cardiac output and reduced perfusion pressure in the course of distal anastomoses in OPCAB generate a thyroid axis response comparable to surgery with CPB.

Pulsatile perfusion was selected during CPB partly because it reflects current practice at the Wessex Cardiothoracic Centre but more importantly because it has been shown to result in superior preservation of thyroid function over non-pulsatile CPB (Taylor et al. 1978; Buket et al. 1994). On the contrary, body temperature during CPB has not been shown to affect perioperative thyroid hormone changes (Lehot et al. 1992; Thrush et al. 1995). Additionally, a core temperature of 35°C during CPB was utilised to avoid the confounding effect of different intraoperative core temperatures in the two groups. Therefore, a similar study using non-pulsatile flow during CPB may find significant difference in thyroid metabolism when compared to OPCAB surgery.

One limitation of this study is that it included a well-selected, low-risk patient population with normal cardiac and endocrine function. This study design ensured homogeneity of the groups, which is essential in prospective randomised studies with small numbers of patients. The data demonstrate that in a low-risk patient population thyroid hormone metabolism is similar between OPCAB and surgery with CPB using pulsatile perfusion. However, these results cannot be extrapolated on patients with a higher risk profile. Patients with poor left ventricular function, thyroid disease or

other major co-morbidities, such as diabetes mellitus or extracardiac arteriopathy may behave differently and this should be the subject of a separate investigation.

In conclusion this study has demonstrated the presence of thyroid hormone changes during OPCAB comparable to those observed after CPB and consistent with the post-surgical euthyroid sick syndrome. These results indicate that the use of mildly hypothermic pulsatile CPB for relatively brief periods of time in low-risk patients is not the prime pathophysiologic mechanism responsible for the development of euthyroid sick response. Furthermore, a significant negative correlation was found between VO_2 and fT3 levels, indicating that the thyroid hormone changes do not represent a true hypothyroid state. Whether these findings would be applicable in a high-risk patient population and whether there may be a place for T3 administration in OPCAB remains to be seen.

Chapter 6

Gut mucosal oxygenation and whole body oxygen flux during CPB vs. Off-pump

SUMMARY

Objective: Cardiopulmonary bypass is associated with gut mucosal hypoxia, which may contribute to gastrointestinal complications. Gastric mucosal oxygenation together with whole-body oxygen flux was studied in low-risk patients undergoing CABG with and without CPB.

Methods: Fifty-four patients undergoing primary CABG by the same surgeon were randomised into either on-pump (ONCAB, n=27) or off-pump (OPCAB, n=27) groups. The ONCAB group underwent mild hypothermic (35°C) pulsatile CPB with arterial line filtration. Each patient underwent perioperative monitoring with continuous tonometry and cardiac output devices. Gastric intramucosal pH (pHi), gastric-arterial carbon dioxide partial pressure difference (CO_2gap), whole-body oxygen delivery (DO_2) and consumption (VO_2) and whole-body oxygen extraction fraction were measured at sequential time-points intraoperatively and up to 6 hours postoperatively. Anaesthetic management was standardized.

Results: Both groups had similar demographic makeup and extent of revascularization (ONCAB 2.6 ± 0.9 grafts v. OPCAB 2.5 ± 0.8 grafts; p= .55). The ONCAB group had a mean (± SD) CPB time of 62 ± 25 min and aortic cross-clamp time of 32 ± 11 min. In both groups there was a similar and progressive drop in pHi intraoperatively. Postoperatively, there was a gradual separation between the groups with ONCAB patients showing no further decline in pHi, while further deterioration was observed in the OPCAB group up to 6 hours postoperatively. There was a significant difference between the groups over time (p= .03). There was a corresponding progressive rise in CO_2gap perioperatively in both groups, with ONCAB patients demonstrating superior preservation of gastric mucosal oxygenation in the early postoperative period. Global oxygen utilization measurements showed superior DO_2 and VO_2 in the OPCAB group throughout the study.

Conclusions: Despite superior global oxygen flux associated with beating-heart revascularization, gastric mucosal hypoxia occurred to similar extents in both groups with worsening trends for the OPCAB patients postoperatively.

INTRODUCTION

Several retrospective studies have shown that although gastrointestinal complications are rare after CPB (0.58 to 2.3%), they carry a very high mortality of up to 67% (Wallwork and Davidson 1980; Hanks et al. 1982; Pinson and Alberty 1983; Reath et al. 1983; Leitman et al. 1987; Krasna et al. 1988; Huddy et al. 1991; Ohri et al. 1991; Egleston et al. 1993; Christenson et al. 1994; Mercado et al. 1994; Tsiotos et al. 1994; Perugini et al. 1997; Simic et al. 1999; Zacharias et al. 2000; Mierdl et al. 2001; D'Ancona et al. 2003; McSweeney et al. 2004; Raja et al. 2004). Gut mucosal oxygenation has been shown to be an excellent predictor of patient outcome in a variety of clinical settings, including open-heart surgery and the intensive care (Fiddian_Green and Baker 1987; Friedman et al. 1995). This is probably related to the fact that the gut is one of the first organs to undergo ischaemic injury at times of haemodynamic stress (Haglund et al. 1975). Moreover, the central role of impaired gut barrier function in driving the systemic inflammatory response syndrome and multi-system organ failure (Landow and Andersen 1994) would explain why gastrointestinal (GI) integrity is a predictor of outcome.

CPB is associated with a significant reduction in gut mucosal perfusion, which may be up to 50% during hypothermic non-pulsatile bypass (Ohri et al. 1997). The use of more physiological core temperatures during CPB ameliorates splanchnic vasoconstriction and therefore enhances mucosal perfusion (Booker et al. 1996; Croughwell et al. 1997). Moreover, pulsatile flow during CPB maintains capillary patency by delivering more energy into the vascular system and ameliorates splanchnic vasoconstriction (Gaer et al. 1994; Ohri et al. 1997; Hamulu et al. 1998) by reducing the degree of activation of the renin-angiotensin axis (Taylor et al. 1979). However, measurements of mucosal perfusion are not only difficult to perform in clinical practice, but they also do not predict mucosal oxygenation status, which appears to be the paramount factor that determines mucosal integrity (Ohri 1996). Significant mucosal hypoxia has been shown to occur during times of normal or even supranormal perfusion (Ohri et al. 1997). Therefore, separate assessment of the oxygenation status of the mucosa is essential, as it reflects the adequacy of gut mucosal perfusion, in relation to the tissue metabolic demands. Oxygenation status

assessment in the gut is performed by indirect measurement of the intramucosal pH (pHi) using gastric tonometry (Kivisaari and Niinikoski 1973; Fiddian-Green et al. 1982). Another way of expressing the results of tonometric assessment of gut mucosal oxygenation is by calculating the Carbon Dioxide partial pressure difference between the gastric mucosa and the arterial blood (CO_2gap), which has become increasingly popular over the last decade (Mythen and Webb 1998; Vincent and Creteur 1998; Chapman et al. 2000).

OPCAB is currently an accepted modality of surgical coronary revascularization. The continuous improvements in myocardial stabilizers and coronary exposure techniques have made OPCAB accessible to many surgeons worldwide for the treatment of multi-vessel coronary artery disease (Ricci et al. 2000). Benefits of OPCAB over conventional coronary artery bypass grafting (CABG) with CPB have been demonstrated, such as reduced perioperative blood loss (Ascione et al. 2001) and attenuation of the inflammatory response (Matata et al. 2000). However, OPCAB does not eliminate the potential of significant perioperative organ injury, the magnitude of which may be comparable to surgery with CPB (Cox et al. 2000; Tang et al. 2002). This may be directly related to the fact that OPCAB is associated with significant transient haemodynamic instability, as discussed in Chapters 2 and 3 of this thesis. We have already seen that this leads to a stress hormone response and thyroid hormone changes that are comparable to surgery with CPB (Chapters 4 and 5).

The development of significant perioperative gastric mucosal hypoxia during CPB has been well documented (Gaer et al. 1994; Riddington et al. 1996). Understanding the pathophysiologic mechanisms that mediate this injury is a much more difficult task. Certainly mucosal hypoxia, evidenced by a reduction in pHi or an increased CO_2gap, represents an imbalance between gut mucosal oxygen delivery (DO_2) and consumption (VO_2), however measurements of intestinal DO_2 and VO_2 are very difficult in the clinical setting. In experimental settings it has been shown that changes in small bowel VO_2 are independent of DO_2 during CPB and that the pHi correlates best with intestinal VO_2 (pHi drops as VO_2 increases). It has also been

shown that changes in core body temperature during the perioperative period are associated with significant changes in intestinal VO_2 although the direct relationship between core or peripheral body temperature and pHi or CO_2gap has not been investigated. Changes in pHi do not correlate well with intestinal DO_2, because intestinal DO_2 measurements do not take into account changes in the microvasculature that result in a redistribution of blood flow between the different layers of the gut wall, with preferential perfusion of the mucosa, which is the most metabolically active part of the gut wall (Bond et al. 1979; Fan et al. 1979).

In clinical studies the relationship between gastric mucosal oxygenation and whole-body oxygen flux has been investigated during CPB. Gastric mucosal oxygenation has been shown to correlate well with whole-body VO_2 and mixed venous oxygen saturation (SvO_2). Gastric mucosal acidosis occurs at times of increasing whole-body VO_2, increasing whole-body oxygen extraction fraction and decreasing SvO_2 (Ohri et al. 1997). To date a similar evaluation of patients undergoing OPCAB surgery has not been reported. It is therefore important to specifically evaluate the role of OPCAB in gut protection before defining those who may benefit from this strategy. The aim of this study was to evaluate in a prospective randomised fashion global oxygen flux and gastric mucosal oxygenation during CABG with and without CPB.

BACKGROUND

Gastric Tonometry

The only clinical technique currently available that can provide information on gut mucosal oxygenation and is relatively non-invasive for use during routine clinical practice is gastrointestinal tonometry. Tonometry refers to the measurement of the partial pressure of a gas. Gastrointestinal tonometry uses a modified nasogastric tube to measure the partial pressure of CO_2 (pCO_2) in the gastric lumen. 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 ischaemia, 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 (Hochachka and Mommsen 1983; Gores et al. 1989). It has been shown in the human myocardium that measurements of intracellular pH correlate well with tissue levels of ATP.

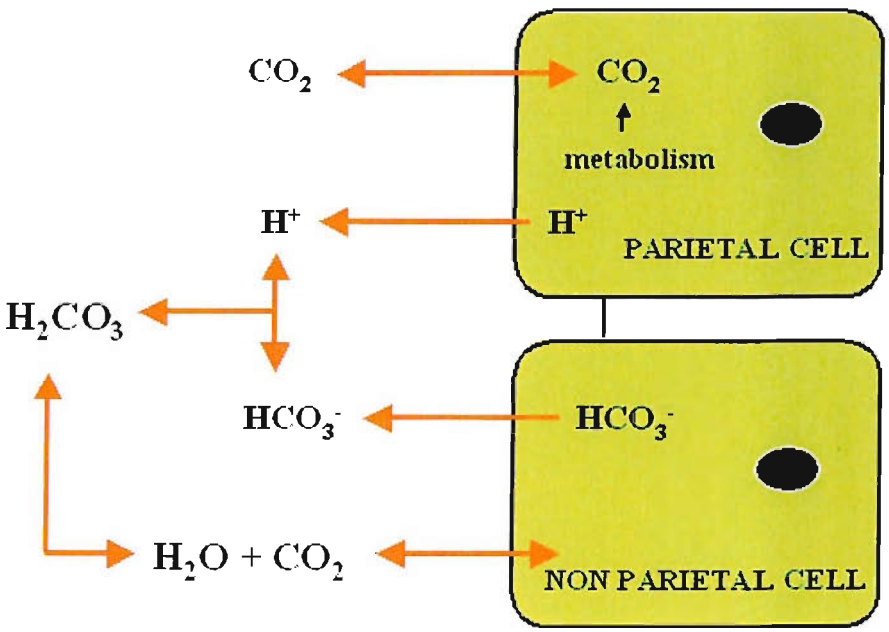
However, direct measurement of gut intramucosal pH (pHi) using tissue microelectrodes proved cumbersome and never gained clinical applicability. The indirect tonometric method of measuring pHi is based on work originally performed by Bergofsky in 1964 (Bergofsky 1964) and later by Dawson et al in 1965 (Dawson et al. 1965). They showed that the pCO_2 in the lumen of a hollow viscus can be measured by determining the pCO_2 in the intraluminal fluid. Kivisaari and Niinikoski in 1973 (Kivisaari and Niinikoski 1973) 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).

The development of tonometry was further extended by Fiddian-Green et al (Fiddian-Green et al. 1982), who suggested that pHi could be calculated tonometrically 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 tonometrically and microprobe measured pHi.

This method also depends upon the assumption 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 (Roos and Boron 1981). 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.

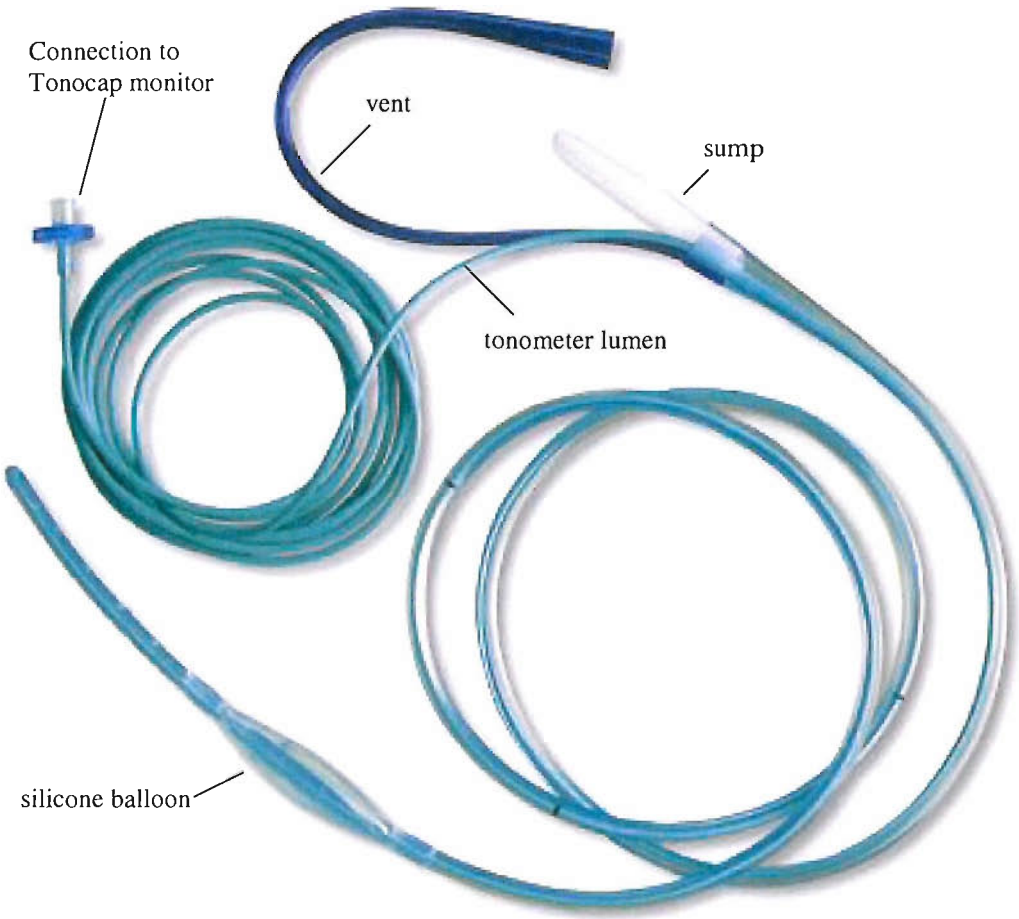
Figure 6-1. Factors determining intraluminal pCO_2.



Air tonometry

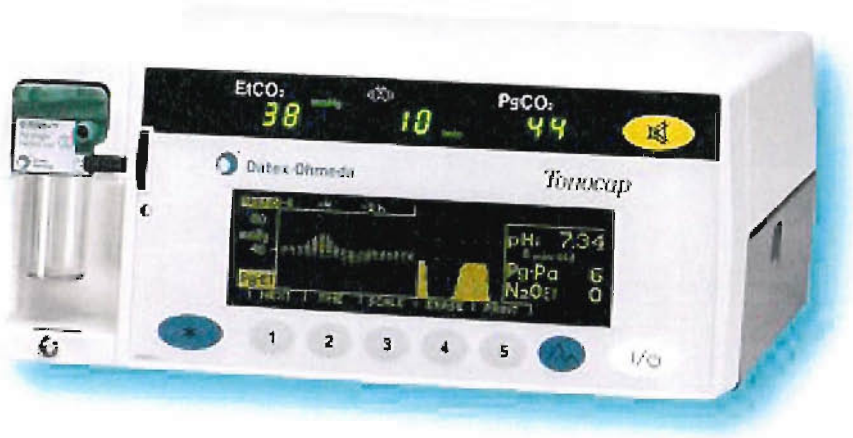
Recently saline tonometry has been largely replaced by automated air tonometry (Mythen and Webb 1998). This is done using nasogastric catheters that are very similar to saline tonometry catheters, in that they incorporate a gastric vent, a gastric sump and a silicone balloon at the end of the catheter (figure 6-2).

Figure 6-2. The air tonometry 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).

Figure 6-3. The Tonocap monitor.



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. Automated air tonometry not only makes pCO_2 measurements more readily available in clinical practice, it has also been shown to be more precise than saline tonometry in *in vitro* testing (Creteur et al. 1997; Janssens et al. 1998). 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 pCO2 levels in the clinical settings.

pHi or CO_2gap?

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 (Vincent and Creteur 1998; Chapman et al. 2000). The main reason is that the pHi calculation 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-Hasselbank equation. In other words, calculation of 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 CO2 gap should be monitored instead. Moreover, the assumption that the intramucosal and arterial bicarbonate concentrations are equal may not always be valid. Antonsson et al (Antonsson et al. 1990) studied the correlation between tonometrically and directly measured pHi in four groups of anaesthetized pigs: controls, acidotic due to endotoxaemia and acidotic due to partial or total occlusion of the superior mesenteric artery. They found that while there was an excellent correlation for controls and endotoxaemic pigs, in the presence of regional mesenteric ischaemia the tonometrically measured pHi did not correlate well with direct measurements.

In our study we have presented the results of our tonometric assessment both as pHi and as CO2 gap. The main reason is that all studies so far that have monitored gastric mucosal oxygenation in cardiac surgical patients have presented their results as pHi measurements. We are not aware of any documentation of the CO2 gap in the context of cardiac surgery. Moreover, if pHi in future studies proves in future studies to be a superior predictor than CO2 gap of patient outcome, albeit because of combining global and gut assessment, this information cannot be ignored.

Whole-body oxygen flux measurements

These are based on the following equations:

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

where Hb is Haemoglobin concentration in g/dL,

SaO_2 is the percentage of oxygen saturation of arterial blood,

and 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 X $\frac{\text{Cardiac Output}}{\text{Body surface area}}$ X 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 X SvO_2 X 1.39 + (0.003 X PvO_2) ml/dL,

SvO2 is the percentage of oxygen saturation of mixed venous blood

and PvO2 is the partial pressure of oxyen 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) X Cardiac Index X 0.1 ml/min/m^2.

Cardiac index is cardiac output / body surface area.

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

The SvO2 and cardiac output were measured using continuous cardiac output (CCO) Swan-Ganz catheters, which are specially modified pulmonary artery catheters. Plain

pulmonary artery catheters can calculate the cardiac output using the thermodilution technique, where a fixed volume of a cold solution is injected proximally to a thermistor that measures the change in temperature with time. The equation for calculating cardiac output is based on measurement of the area under the temperature over time curve; the area under the curve is an inverse measure of the cardiac output. CCO catheters work on the same thermodilution principle, using a randomly pulsed heating filament situated in the right ventricular portion of the catheter. A rapid-response thermistor analyses the thermal transients, and in conjunction with specialised hard- and soft-ware calculates and displays the cardiac output. The catheters also incorporate a fibreoptic oximetry channel to allow continuous measurement of SvO2.

MATERIALS AND METHODS

Study design

Consecutive patients undergoing primary elective CABG who fulfilled the study criteria (Table 6-1) were recruited following informed consent. Essentially we studied low-risk patients with normal preoperative cardiac function. All patients were operated upon by the same surgeon. If no contraindications were evident following review of the preoperative coronary angiogram, the patients were randomised into either surgery with CPB (ONCAB group) or off-pump (OPCAB group) by simple randomisation using a table of random numbers. The study was approved by the Southampton & South West Hants Joint Local Research Ethics Committee.

Table 6-1. Exclusion criteria.

Age over 75 years
LVEF < 50%
Recent (< 3 months) MI
Intravenous therapy for unstable angina
Diabetes Mellitus
Renal insufficiency
Liver failure
Gastrointestinal disease
Peripheral vascular disease
Previous CVA

LVEF, left ventricular ejection fraction; MI, myocardial infarction; CVA, cerebro-vascular accident.

Anaesthetic management

The patients' medications were continued up to the night before the operation except for anti-platelet agents, which were discontinued 7 days prior to surgery. A standardized balanced anaesthetic protocol was utilized in which fentanyl-based anaesthesia was used in combination with benzodiazepine and pancuronium as a muscle relaxant. Anaesthesia was maintained intraoperatively with a mixture of isoflurane and intravenous propofol infusion. Postoperatively the patients remained

on propofol infusion until extubation. Active warming techniques were used in the recovery period, to achieve a nasopharyngeal temperature of at least 37°C before extubation. Target haemodynamic values were mean arterial pressure above 60 mmHg and cardiac index over 2.2 L/min/m^2. Dopamine was used as the first-line inotrope to support a low cardiac output, whilst bolus intravenous injections of phenylephrine or infusion of noradrenaline were used as vasoconstrictors.

CPB management

A standardized CPB protocol was used for the ONCAB patients. CPB was established using bicaval cannulation and an arterial cannula (Medtronic DLP®; Medtronic Ltd., Watford, UK) placed in the ascending aorta. Pulsatile CPB was conducted under mild core hypothermia (35°C), using a hollow-fibre membrane oxygenator (D903 Avant, Sorin Biomedica, Mirandola, Italy) and arterial line filtration (D734 Micro 40, Sorin Biomedica, Mirandola, Italy). The circuit was primed with 1 L of Hartman's solution, 500 ml of gelofusine and 5000 IU of sodium heparin. Intermittent antegrade cold blood cardioplegia (4°C) delivered through a 12G aortic root cannula was used for myocardial protection. The cardioplegic mixture consisted of 20% St Thomas' Hospital No.2 solution (Martindale Pharmaceuticals, Essex, UK) and 80% autologous blood. A dose of 12 ml/kg was delivered to induce diastolic cardiac arrest and a maintenance dose of 3 ml/kg was administered after completion of each distal anastomosis. The left ventricle was vented through the aortic root during aortic cross-clamping. Flow was maintained at 2.5 L/min/m^2 during CPB with judicious use of phenylephrine and phentolamine to maintain the mean perfusion pressure between 50 and 80 mmHg. Alpha-stat management of acid-base status was used. Proximal graft anastomoses on the ascending aorta were performed following aortic cross-clamp removal using a partially occlusive clamp.

OPCAB technique

A median sternotomy was used for surgical access in all cases. Partial systemic heparinisation was employed with a target activated clotting time of 300-400 sec prior to cardiac manipulation. Trendelenburg posture was employed throughout the

period of distal anastomoses and a single suture technique (Bergsland et al. 1999) was used to facilitate exposure of the target coronary arteries. A mechanical suction-based myocardial tissue stabilizer (Octopus®3; Medtronic Ltd., Watford, UK) was used to immobilize the operative field during coronary anastomosis. Following arteriotomy, an intraluminal coronary shunt (Flo-Thru; Biovascular Inc., Minnesota, USA) was inserted to maintain distal myocardial perfusion and was removed prior to completion of the anastomosis. Core temperature was maintained at or above 35°C throughout the procedure by minimizing heat loss and active warming techniques. Haemodynamic stability was achieved primarily with preload management (intravenous fluid administration and Trendelenburg posture) and vasoactive agents as required. Construction of the proximal anastomoses to the ascending aorta was performed within a single aortic side-biting clamp period, with the systolic arterial pressure maintained around 100 mm Hg to minimize aortic trauma.

Assessment of gastric mucosal oxygenation

An automated air tonometry technique was used to measure the partial pressure of carbon dioxide in the gastric lumen ($PgCO_2$), using a 14F nasogastric catheter connected to a Tonocap monitor (Datex-Ohmeda Ltd., Hatfield, Herts, UK). The catheter was inserted during anaesthetic induction. Correct placement was confirmed by auscultating the epigastrium while 20 ml of air was insufflated through the nasogastric tube. Measurements were obtained at the start and end of operation and 2, 4 and 6 hours postoperatively. Two additional intraoperative measurements were made; in the ONCAB group at the onset of CPB and 10 minutes after discontinuation of CPB. The corresponding measurements in the OPCAB group were made immediately prior to the onset of the distal anastomotic phase and 10 minutes after completion of the proximal anastomoses. The following formulae were used:

$$pHi = 6.1 + \log_{10} (HCO_3^-/PgCO_2 \text{ X } 0.03)$$

$$CO_2gap = PgCO_2 - PaCO_2,$$

where pHi is the gastric intramucosal pH and CO_2gap is the difference between gastric and arterial carbon dioxide tension. HCO_3^- and $PaCO_2$ are the simultaneously

measured arterial bicarbonate concentration and arterial carbon dioxide partial pressure respectively. All arterial blood gas measurements were obtained using the same blood gas analyser (ABL 700, Radiometer, Crawley, UK).

Whole body oxygen utilization

The cardiac index (CI) was measured using a continuous cardiac output Swan-Ganz catheter (Edwards Lifesciences, Newbury, UK) inserted through the right internal jugular vein shortly after anaesthetic induction. Whole-body oxygen utilization was measured at the same time-points as gastric mucosal oxygenation. Blood was simultaneously drawn from the arterial line and the pulmonary artery port of the Swan-Ganz catheter (mixed venous blood). The formulae already described at the background information of this chapter were used to measure the DO_2, VO_2 and whole-body oxygen extraction fraction.

Statistical analysis

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 if normal distribution could not be assumed. Categorical variables were compared using the Pearson's chi-square or Fisher's exact test as appropriate. Repeated measures analysis of variance was used to assess the effect of time, group and group-time interaction on pHi, CO_2gap, DO_2, VO_2 and Oxygen extraction fraction. Because the data contained subgroups (ONCAB vs. OPCAB), the association between different variables was investigated using Spearman's rank correlation analysis. The Statistical Package for Social Sciences (SPSS) version 10.1 software was used for all descriptive statistics and inferential testing. A p value of less than 0.05 was considered statistically significant.

RESULTS

Patient demographics and clinical outcome

54 patients were recruited into the study and randomized to two equal groups (ONCAB, n=27 and OPCAB, n=27). All patients completed the study protocol and no patient was excluded. No patient allocated to the OPCAB group required the use of CPB.

The demographic variables for the two groups are presented in Table 6-2. As outlined in the methods, these were low-risk cases and there were no significant differences between the groups.

Table 6-3 summarizes the intraoperative data and clinical outcome. The groups received similar extent of revascularization using comparable mixture of conduits. There were no differences in operation duration and mechanical ventilation time. Rewarming to a core (nasopharyngeal) temperature of 37°C required a similar period of time in both groups. There was a significant difference between the groups in the use of vasoconstrictors, this was mainly due to the use of phenylephrine during CPB in all but one patients in the ONCAB group. No mortality or major complications, such as myocardial infarction, major neurological deficit or end-organ failure were observed. No patient required the use of an intraaortic balloon pump.

Table 6-2. Patient characteristics.

Variable	ONCAB (n=27)	OPCAB (n=27)	*p* value
Age	63.1 ± 8.5	61.8 ± 8.7	.59
Gender			.74
Male	22	21	
Female	5	6	
CCS angina class			.48
I	6	3	
II	12	10	
III	6	8	
IV	3	6	
Previous MI	9	5	.21
Hypertension	11	13	.58
Morbid obesity	4	7	.31
Parsonnet score	3.0 (0.0-3.5)	3.0 (0.5-4.0)	.65

CCS, Canadian Cardiovascular Society; MI, myocardial infarction.

Age is presented as mean ± standard deviation. Parsonnet score is presented as median with interquartile range.

Table 6-3. Intraoperative data and clinical outcome.

Variable	ONCAB (n=27)	OPCAB (n=27)	*p* value
Distal anastomoses	2.6 ± 0.9	2.5 ± 0.8	.55
Type of conduit			
LIMA	26	24	.61
RIMA	3	1	.61
Radial artery	3	2	.68
Saphenous vein	22	22	1
CPB time (min)	62 ± 25		
AXC time (min)	32 ± 11		
Operation duration (min)	186 ± 47	177 ± 45	.47
Time to rewarming (hr)	2.4 ± 1.1	2.8 ± 0.9	.28
Time to extubation (hr)	5.0 (4.2-5.8)	5.0 (3.5-5.8)	.62
ICU length of stay (d)	1.0 (1.0-1.8)	1.0 (1.0-2.0)	.44
Perioperative low CI	3	2	.68
Perioperative vasoconstrictors	26	14	<.01
Inotropic support	3	2	.68
Supraventricular arrhythmia	6	6	1
Pneumonia	3	4	.71
Wound infection	1	0	1
Postoperative hospital stay (d)	6.9 ± 2.6	6.6 ± 2.0	.71

LIMA, left internal mammary artery; RIMA, right internal mammary artery; CPB, cardiopulmonary bypass; AXC, aortic cross-clamping; ICU, intensive care unit; CI, cardiac index; low CI is defined as below 2.2 L/min/m^2; norepinephrine or phenylephrine were used as vasoconstrictors; dopamine was used for inotropic support.

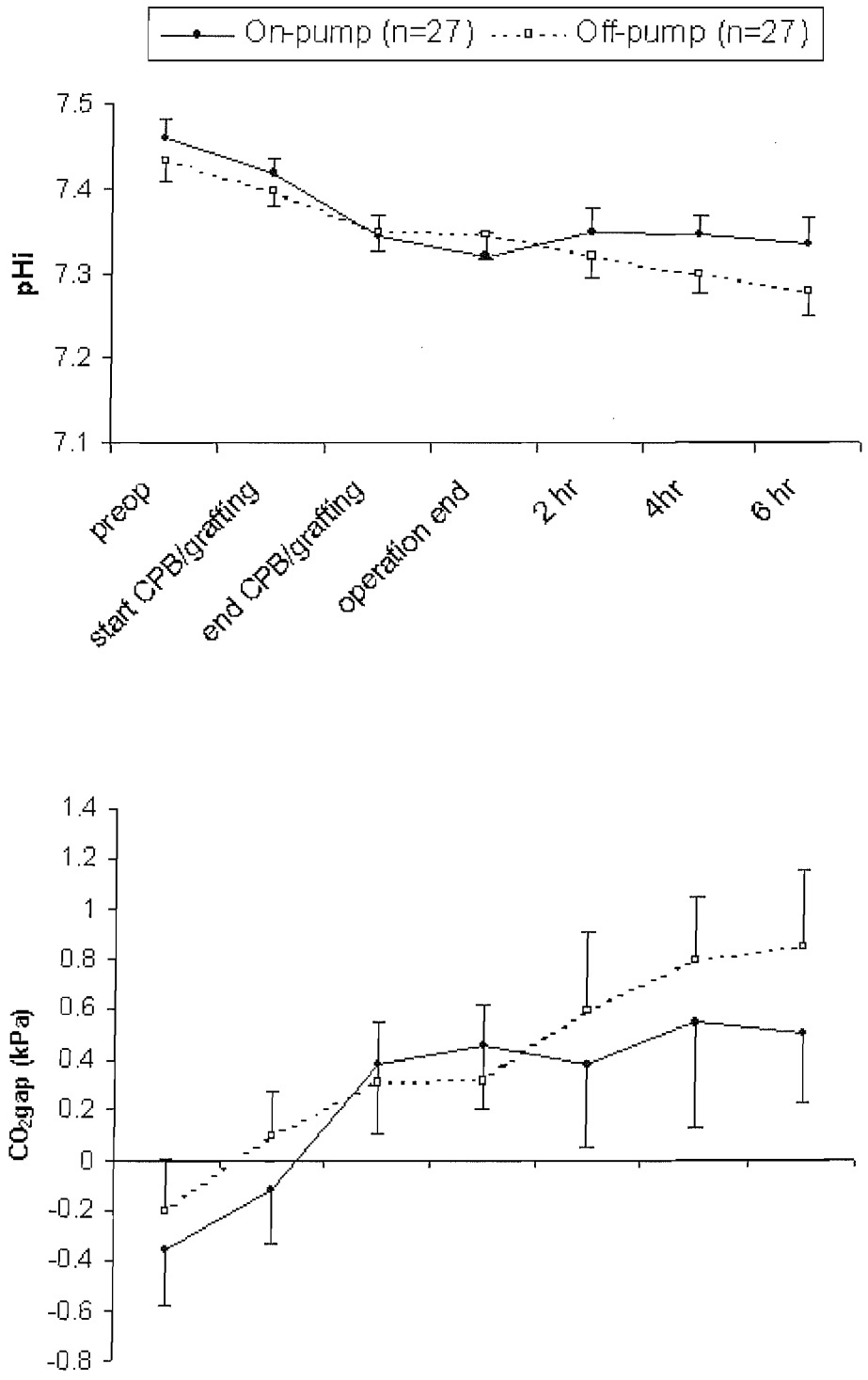
Time to extubation and ICU length of stay are presented as median with interquartile range. Other continuous variables are presented as mean ± standard deviation.

Gastric mucosal oxygenation

The perioperative pHi and CO_2gap in the two groups are displayed in figure 6-4. There were no baseline differences between the groups. A progressive and similar decline in the pHi was observed in both groups intraoperatively. Postoperatively there was a gradual separation between the groups with the ONCAB patients essentially stabilizing, while further deterioration in pHi was observed in the OPCAB group for up to 6 hours postoperatively. Repeated-measures ANOVA showed a significant effect of group (ONCAB vs. OPCAB) on outcome (p= .03). There was also a significant effect of time (p< .001) and group-time interaction (p= .02) on outcome, indicating that the groups demonstrated different trends across time. The changes in CO_2gap generally mirrored pHi changes (mucosal acidosis results in a lower pHi and a higher gastric-arterial CO_2gap). Repeated-measures ANOVA revealed a significant effect of group (p= .046) and time (p< .001) on outcome, although the effect of group-time interaction (p= .07) was not quite significant at the 5% level.

There was a highly significant correlation (p< .001) between pHi and CO_2gap on Spearman's rank correlation analysis (r_s= -0.82).

Figure 6-4. Perioperative pHi and CO_2 gap in the two groups. The error bars represent 95% confidence intervals around the mean (for clarity either the plus or minus error bar for each group is displayed; the sampling time-points are explained in methods).



Whole body oxygen utilization

Perioperative DO_2, VO_2 and whole-body oxygen extraction fraction are displayed in figure 6-5. There were no preoperative differences between the groups. DO_2 was higher in the OPCAB group throughout the study period, this was largely due to the effect of haemodilution during CPB in the ONCAB group (Table 6-4). There was a significant effect of time (p= .01) and group (p= .004) on outcome, however the effect of group-time interaction was not significant (p= .30), i.e. the difference between the groups did not depend on the sampling time.

There was a significant and similar trend in both groups towards increasing levels of VO_2 during the study (p< .001 for time and p= .96 for group-time interaction). OPCAB patients maintained higher levels of VO_2 throughout the study (p= .03 for the effect of group).

There was also a significant trend towards increasing levels of oxygen extraction fraction with time (p< .001), however there were no differences between the groups (p= .11 for the effect of group and p = .59 for group-time interaction).

Spearman's rank correlation revealed a highly significant association (p< .001) between pHi and VO_2 (r= -0.22) and pHi and global oxygen extraction fraction (r= -0.20).

Figure 6-5. Perioperative whole-body oxygen delivery (DO_2) and consumption (VO_2) and global oxygen extraction fraction in the two groups. The data are presented as mean with 95% confidence interval error bars (time-points are explained in methods).

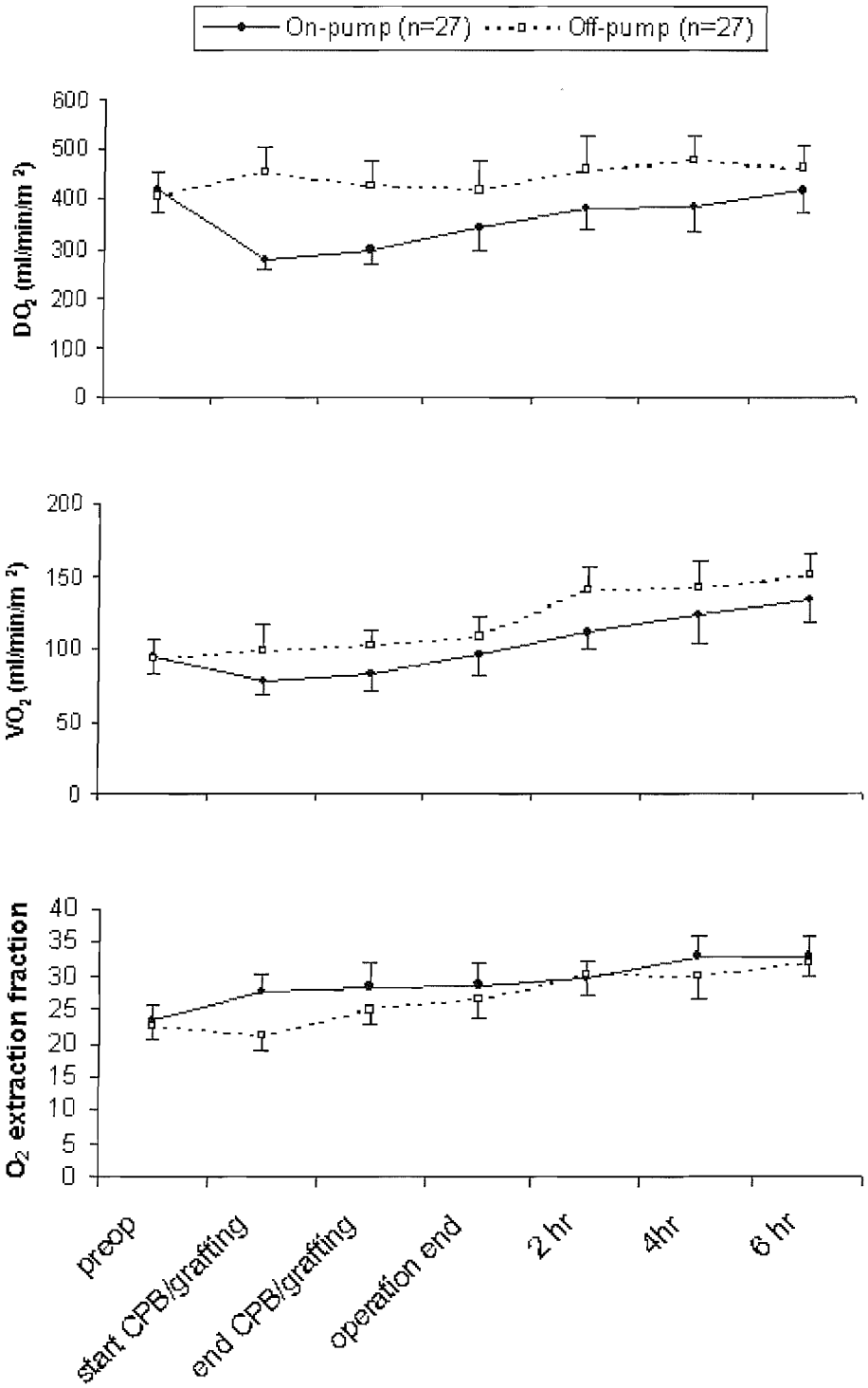


Table 6-4. Perioperative haemoglobin and cardiac index in the two groups.

Variable	Group	Baseline	Operation end	2 hours	6 hours
Hb (g/dL)	ONCAB	11.9 ± 1.2	9.2 ± 1.4	9.6 ± 0.9	10.0 ± 1.0
	OPCAB	11.8 ± 0.9	10.6 ± 1.1	11.0 ± 1.2	10.8 ± 1.0
CI ($L/min/m^2$)	ONCAB	2.51 ± 0.61	2.67 ± 0.51	2.84 ± 0.75	2.99 ± 0.71
	OPCAB	2.48 ± 0.71	2.83 ± 0.80	3.01 ± 0.42	3.08 ± 0.63

Hb, haemoglobin; CI, cardiac index.

Data is presented as mean ± standard deviation.

DISCUSSION

The absence of GI complications or any major morbidity in our study is not surprising, given the low-risk profile of the patient population. Previous retrospective studies have demonstrated a relatively low incidence of GI complications in cardiac surgical populations, which is under 1% in most studies (Wallwork and Davidson 1980; Hanks et al. 1982; Pinson and Alberty 1983; Reath et al. 1983; Leitman et al. 1987; Krasna et al. 1988; Huddy et al. 1991; Ohri et al. 1991; Egleston et al. 1993; Christenson et al. 1994; Mercado et al. 1994; Tsiotos et al. 1994; Perugini et al. 1997; Simic et al. 1999; Zacharias et al. 2000; Mierdl et al. 2001; D'Ancona et al. 2003; McSweeney et al. 2004; Raja et al. 2004). Ohri et al (Ohri et al. 1991) observed GI complications in 27 out of 4602 patients undergoing cardiac surgery (0.58%) between 1973 and 1989. Interestingly, in a subgroup of patients who underwent CPB using pulsatile perfusion with arterial line filtration, which is the protocol we used in our study, there was only one gastrointestinal complication out of 562 cases.

However, in both groups studied there was evidence of significant gastric mucosal hypoxia, as demonstrated by a reduction in pHi and a corresponding rise in CO_2gap. As explained in more detail in the methodological background information to this chapter, the optimal way of expressing gastrointestinal tonometry findings has been recently debated. Currently most experts agree that the gastric-arterial CO_2gap should be regarded as the gold standard measurement (Vincent and Creteur 1998; Chapman et al. 2000), while the pHi concept should probably be abandoned. The reason is that the pHi calculation is not solely dependent on adequacy of GI perfusion but is also affected by the systemic acid-base status, as the arterial bicarbonate value enters the Henderson-Hasselbach equation. In other words, calculation of the pHi is thought to combine global and gut specific markers. This may explain why the pHi has been found to be a very sensitive early predictor of patient outcome in a variety of clinical settings, including cardiac surgery (Fiddian-Green and Baker 1987; Friedman et al. 1995). In this study we elected to document both pHi and CO_2gap results. All studies so far that have monitored gastric mucosal oxygenation in cardiac surgical patients have documented pHi changes and this

important clinical and research record cannot be ignored. Equally, it is imperative that the CO_2gap is documented in the context of cardiac surgery. Interestingly, we found that changes in CO_2gap closely mirrored those of pHi so that a progressive perioperative decline in pHi was reflected by a progressive increase in CO_2gap. Correlation analysis confirmed a highly significant inverse relationship between the two variables, which explained 67% of the variation of each other ($r= -0.82$). Statistical analysis revealed a similar effect of group, time and group-time interaction on outcome using either pHi or CO_2gap as a dependent variable. Despite the similarity of the results, gut mucosal oxygenation should be reported using both parameters until more information on CO_2gap changes during cardiac surgery becomes available.

This study confirms previous findings of significant perioperative gastric intramucosal acidosis after CPB (Gaer et al. 1994; Riddington et al. 1996; Ohri et al. 1997). Ohri et al (Ohri et al. 1997) observed the development of intramucosal acidosis in the early post-CPB period in cardiac surgical patients undergoing surgery using four different bypass protocols. Mucosal hypoxia is at it's nadir 4 to 5 hours after the end of CPB. Gaer et al (Gaer et al. 1994) obtained similar results and reported that the reduction in pHi was less in patients undergoing CPB with pulsatile flow.

Interestingly, a similar degree of intraoperative injury to the gastric mucosa was found during OPCAB, with a worsening trend for OPCAB patients in the early postoperative period. Given the single-surgeon and randomized nature of the study design, the standardized anaesthetic protocol and the absence of any significant differences in the preoperative characteristics of the two groups, these results may at first appear surprising. One would intuitively expect some benefit conferred by the avoidance of CPB. There are certainly factors associated with the use of CPB *per se* that would partly explain the development of gastric mucosal hypoxia. These factors include the use of subphysiological flow levels during CPB and the release of various endogenous vasoconstrictors, including angiotensin II, with a concomitant rise in systemic vascular resistance (Taylor et al. 1979). Indeed CPB duration has been

shown to be a predictor of gastrointestinal complications (Ohri et al. 1991; Zacharias et al. 2000).

However, considering that perioperative gastric mucosal hypoxia has been well described in the context of major abdominal and vascular surgery (Bjorck and Hedberg 1994; Theodoropoulos et al. 2001), it is likely that factors other than the use of CPB play an important role in its development. The paramount factor that determines gut mucosal oxygenation status is global haemodynamic stability, since the gut is perhaps the first tissue in the body to become compromised at times of haemodynamic stress (Haglund et al. 1975). The GI tract is known to receive a disproportionately small portion of the cardiac output at times of haemodynamic deterioration (Hamilton_Davies et al. 1997), and the gut mucosa is especially susceptible to hypoperfusion due to the counter-current flow of its microcirculation (Shepherd and Kiel 1992). Therefore, it is not surprising that the main predictors of GI complications after cardiac surgery are factors such as older age, perioperative hypoperfusion episodes, peripheral vascular disease and congestive cardiac failure, which indicate the importance of haemodynamic performance and implicate an ischaemic nature of injury (Ohri et al. 1991; Zacharias et al. 2000). This also explains why the use of acid-neutralizing or acid-reducing therapy does not affect the incidence of GI haemorrhage after CPB (Lehot et al. 1990; Rosen et al. 1992).

As discussed in detail in chapters 2 and 3 of this thesis, several studies have documented the presence of significant transient haemodynamic impairment during distal anastomoses in OPCAB (Grundeman et al. 1997; Mathison et al. 2000; Nierich et al. 2000; Watters et al. 2001). Significant drops in cardiac output may occur despite relatively well-preserved systemic arterial pressures. Haemodynamic deterioration is worse during grafting of the less accessible coronary targets that require extensive cardiac manipulation for adequate exposure. Cardiac verticalization results in compression of the right heart chambers against the surrounding fibrous pericardium and pleura and mechanical dysfunction of the right ventricle (Grundeman et al. 1999). Moreover, despite a preserved mean arterial pressure, elevation of the central venous pressure due to a combination of Trendelenburg

posture and cardiac elevation results in significant drops in perfusion pressure. It is conceivable that the cumulative effect of these transient episodes of reduced cardiac output and reduced perfusion pressure in the course of distal anastomoses during OPCAB resulted in a degree of ischaemic injury to the gastric mucosa at least comparable to CPB. It is important to note that these transient haemodynamic alterations are not reflected in global oxygen utilization measurements. These measurements were made at time-points of relative haemodynamic stability, as one of the limitations of continuous cardiac output thermodilution catheters is that they have a long response time when there is an acute change in cardiac output (Siegel et al. 1996). The acute and often dramatic haemodynamic changes that occur during cardiac manipulation and distal anastomoses in OPCAB would require a continuous real-time cardiac output monitoring technique.

Of immediate relevance to the above is the fact that two recent retrospective studies demonstrated a similar incidence of GI complications after cardiac surgery with and without CPB (Musleh et al. 2003; Sanisoglu et al. 2004). Musleh et al (Musleh et al. 2003) reported their findings on 2327 patients undergoing surgery with CPB (1210 cases) or off-pump (1117 cases) over a 4-year period. They observed GI complications in 14 patients (1.2%) in the on-pump group, vs. 18 patients (1.6%) in the off-pump group, with a resultant mortality of 28.6% vs. 22.2% respectively. Their analysis demonstrated that renal dysfunction, older age and previous GI surgery were the only factors associated with a higher risk of GI complication. Similar results were obtained by Sanisoglu et al (Sanisoglu et al. 2004), who concluded that older age and extracardiac atherosclerosis were the main predictors of adverse GI outcome. They also observed that prolonged CPB (over 98 minutes) was associated with a higher incidence of GI complication. Our results are in keeping with the results of these retrospective studies and provide a possible explanation for these findings.

The results of this study confirm previous findings of a progressive rise in DO_2, VO_2 and oxygen extraction fraction after cardiac surgery (Riddington et al. 1996; Ohri et al. 1997). Superior DO_2 was observed in the OPCAB group, which was largely

related to lower haemoglobin levels in the ONCAB patients from CPB-related haemodilution. Despite the disparity in DO_2, there was a progressive and similar rise in global oxygen extraction fraction in the two groups, resulting in higher VO_2 in the OPCAB group. There were no differences in mechanical ventilation time or speed of systemic rewarming postoperatively that would easily account for this difference in VO_2.

A significant inverse relationship between VO_2 and pHi has been previously reported (Ohri et al. 1997) and was confirmed in this study. This may partly explain the difference in gut mucosal oxygenation between the groups postoperatively. However, the latter observation may primarily reflect a difference in the accumulated intraoperative ischaemic injury, as there were no clinical differences in the early postoperative period that would provide an alternative explanation. A significant association was also found between pHi and global oxygen extraction fraction, with worsening gastric mucosal oxygenation during increased global oxygen extraction. This finding is similar to the previously reported association between pHi and SvO_2 (Ohri et al. 1997) and indicates that the gut becomes particularly susceptible to injury at times of increased global oxygen demand. As discussed in the introduction of this chapter significant mucosal hypoxia has beeen observed despite normal or supranormal intestinal perfusion in the rewarming phase of CPB and the early post-bypass period (Ohri et al. 1997). This also indicates that gut injury can occur at times of "relative ischaemia", when the balance between gastrointestinal blood supply and oxygen demand (VO_2) becomes unfavourable.

The use of pulsatile flow during CPB reflects current practice at the Wessex Cardiothoracic Centre but more importantly has been associated with superior perioperative pHi and enhanced gastric mucosal perfusion compared to non-pulsatile CPB (Gaer et al. 1994; Hamulu et al. 1998). As previously mentioned, a lower incidence of GI complications in patients undergoing pulsatile CPB was also observed by Ohri et al, although the difference was not statistically significant. Pulsatile flow maintains capillary patency by delivering more energy into the vasculature and ameliorates the increase in systemic vascular resistance by reducing

the release of vasoconstrictors, such as angiotensin II (Taylor et al. 1979). Although core temperature during CPB has not been shown to influence gastric pHi (Croughwell et al. 1997), a systemic temperature of 35°C during CPB was used in this study to avoid the confounding effect of different intraoperative core temperatures in the two groups. Moreover, any possible effect of the temperature would be less important, as the temperature was only allowed to drift to 35°C rather than the more commonly used mild hypothermia of 28-32°C. However, it is likely that the choice of CPB protocol, particularly the use of pulsatile flow, had a significant effect on the study findings, and this must be taken into account in future studies.

One limitation of this study is that only low-risk patients with normal cardiac function were studied. This strategy was adopted to ensure homogeneity of the groups, which is essential in prospective randomised studies with small numbers of patients. However, patients with poor left ventricular function or other co-morbidities, such as diabetes mellitus or extracardiac arteriopathy may behave in a rather different manner and the results of this study cannot be extrapolated to such populations. With hindsight, it would be valuable in future studies to observe postoperative gut mucosal oxygenation beyond 6 hours, possibly up to 24 hours, to reveal potential differences between ONCAB and OPCAB in the pattern of recovery of pHi or CO_2gap towards baseline values.

In conclusion this study has demonstrated the presence of significant perioperative gastric mucosal hypoxia during CABG either with or without CPB. How these findings may relate to the incidence of GI complications after OPCAB vs. surgery with CPB remains to be seen. Whether these findings may be applicable to a high-risk patient population also requires further investigation. However, these results suggest that haemodynamic impairment during OPCAB, though transient, causes significant subclinical end-organ injury.

Chapter 7

Intestinal absorption and permeability during CPB vs. Off-pump

SUMMARY

Objective: Cardiopulmonary bypass is associated with a decrease in intestinal absorption and a rise in gut permeability. We examined intestinal absorption and permeability in low-risk patients undergoing CABG with and without CPB.

Methods: Fifty-eight patients undergoing CABG were randomised into on-pump (ONCAB, n=30) or off-pump (OPCAB, n=28) groups. Urinary excretion of 3-O-methyl-D-glucose, D-xylose, L-rhamnose, and lactulose were used to assess active carrier-mediated, passive carrier-mediated, transcellular, and paracellular transport respectively. Gut permeability was assessed using the lactulose/L-rhamnose ratio. Patients were studied before, immediately after, and 5 days after surgery.

Results: Immediately after surgery there was a similar and significant drop in the urinary excretion of 3-O-methyl-D-glucose, D-xylose and L-rhamnose in both groups. The permeation of these saccharides returned to normal levels in the OPCAB group 5 days postoperatively, while in the ONCAB group there was only a partial recovery towards normality with all values significantly lower than baseline values and significantly lower compared to the OPCAB group. No changes were observed in the permeation of lactulose. There was a similar and significant rise in the gut permeability ratio immediately postoperatively in both groups. Gut permeability returned to baseline values in the OPCAB patients 5 days after surgery, while in the ONCAB group it remained significantly higher than baseline values and significantly higher compared to the OPCAB group.

Conclusions: There is significant temporary decrease in intestinal absorption and rise in gut permeability following CABG with or without CPB. OPCAB patients show a quicker recovery of intestinal absorption and gut barrier function.

INTRODUCTION

In the previous Chapter we demonstrated that off-pump surgery results in perioperative gastric mucosal hypoxia, which is comparable to coronary surgery with CPB. We also discussed that this is likely to be due to haemodynamic deterioration during OPCAB, which was studied in more detail in Chapters 2 and 3. Previous studies have shown that CPB results not only in gut mucosal hypoxia, but also in a transient decline in intestinal function, evidenced by reduced intestinal absorption and decline in gut barrier function, which leads to a rise in gut permeability. So far the effect of off-pump surgery on perioperative intestinal absorption and permeability has not been examined. The purpose of this study was to investigate, in a prospective randomised fashion, the effect of coronary surgery with and without CPB on intestinal absorption and gut permeability.

BACKGROUND

The function of the gut is not only the absorption of water, electrolytes and nutrients, but also to maintain a barrier for potentially deleterious agents like bacteria and toxins and prevent them from entering the portal circulation. It is now well recognised that increased intestinal permeability with translocation of bacterial flora into the circulation plays a key role in the development of multiple organ failure in critically ill patients (Deitch 1990; Doig et al. 1998; Moore 1999). Fine's group was the first to suggest the presence and importance of a "leaky gut" following his studies on animal models of experimental shock (Schweinburg and Fine 1955). Fine noticed that a) the administration of enteral non-absorbable antibiotics improved survival in experimental shock, b) circulating concentration of lipopolysaccharides was higher in haemorrhagic shock and c) the lethality of exogenously administered endotoxins was markedly increased by haemorrhage. Fine suggested translocation of bacterial endotoxins through the intestinal mucosal barrier could take place in the presence of impaired host resistance.

The assessment of intestinal absorption and permeability

Physiological principles

The development of methods for assessing the gut barrier function became possible following the introduction of nonmetabolized oligosaccharides as test substances in the 1970s (Menzies 1974). The techniques involving oligosaccharides are now established as an accurate non-invasive way to assess intestinal barrier function and have been used in screening for small intestinal disease, assessing the response to treatment and predicting the prognosis. Gut barrier function is immediately related to permeability, which refers to the property of a membrane that enables passage of a solute by unmediated diffusion. Diffusion of a solute across a simple membrane involves random bi-directional movement of molecules from an area of higher concentration to one of lower concentration, as described in Fick's law (Fick 1855). The diffusion of a solute is dependent upon the concentration gradient, the properties of the membrane (composition, charge, thickness etc.), the properties of the solute (size, shape, charge, solubility), temperature and viscosity of the solvent (Bjarnason et al. 1995).

It is important to distinguish between the terms of absorption and permeation, which describe carrier-mediated and unmediated transport across the small intestine. The transfer of a solute across the human intestine can therefore occur: a) by simple diffusion, which is referred to as permeation. The permeation of a solute across a membrane is an indicator of the permeability of the membrane. b) by carrier-mediated transport, which is referred to as absorption. This may be active (energy-consuming) or passive. The absorption of a solute across a membrane is an indicator of the absorptive function of the membrane.

Non-invasive techniques

Fordtran and his colleagues (Fordtran et al. 1965) were instrumental in the development of ideas for assessing intestinal permeability. They described a method for assessing gut permeability by perfusing intestinal segments with hyperosmolar solutions of solutes with graded molecular weights. The principle of the technique was that a non-permeating solute would draw a fixed amount of water into the lumen while a solute of smaller size capable of permeating would exert less osmotic effect and therefore draw less water. In 1974, Menzies (Menzies 1974) introduced oligosaccharides for the non-invasive assessment of intestinal permeability by measuring urinary excretion of orally administered test substances. Initially, single test substances were used, such as lactulose and other oligosaccharides, various polymers of polyethylene glycol, ^{51}chromium-labeled ethylenediaminetetraacetic acid (^{51}Cr EDTA) and ^{99m}technetium-diethylenetriaminopentaacetate (^{99m}Tc-DTPA). However, it soon became apparent that test results could be affected by changes in pre-mucosal and post-mucosal factors, as well as changes in permeability per se. This led to the principle of differential urinary excretion of test substances, which provides a specific index of intestinal permeability (Menzies et al. 1979; Menzies 1984).

Urinary excretion of a test substance and differential excretion of saccharides

The amount of a test substance that is excreted in the urine following its oral administration depends on several factors, which can be broadly divided into pre-mucosal, mucosal and post-mucosal. These are presented in table 7-1.

Table 7-1. Factors affecting urinary excretion of orally administered test substance.

Pre-mucosal factors

- Content of test substance
- Ingestion / regurgitation
- Gastric dilution
- Gastric emptying
- Bacterial degradation
- Hydrolytic degradation

Mucosal factors

- Dilution by secretions
- Rate of transit
- Mucosal area
- Mucosal permeability

Post-mucosal factors

- Metabolism and hepatic clearance
- Endogenous production
- Tissue distribution
- Glomerular filtration rate
- Renal clearance
- Timing and completeness of urinary collection

From the above table it is clear that when only one marker is used, any changes in the amount excreted in the urine may be due to a variety of factors. This was the pitfall of employing ^{51}Cr EDTA as a sole marker of intestinal permeability in previous studies.

Differential urine excretion of saccharides is based upon the principle that if all the above factors affect equally two substances such as lactulose and L-rhamnose

between their enteral administration and urine detection, then the ratio of urinary excretion of lactulose / L-rhamnose will be a meaningful indicator of permeation of the mucosa to macromolecules such as lactulose, therefore it can be treated as an index of intestinal permeability. Administration of saccharides also has the advantage of avoiding radioactive tracers.

Properties of probe molecules used for assessment of intestinal permeability

The "ideal" probe (Chadwick et al. 1977; Chadwick et al. 1977) should be water-soluble, follow first-order kinetics of permeation, non-toxic, non-degradable, and not metabolised before, during or after permeating the intestine. The probe should be completely excreted in urine following intravenous injection, it should not be naturally present in urine, and measurement of the probe should be accurate and easy. Lactulose (4-O-β-D-galactopyranosyl-D-fructose, molecular weight 342 Da) approaches the criteria of the ideal probe with urinary excretion approaching 100% following intravenous administration (Menzies 1974; Maxton et al. 1986). It is normally excreted in very small amounts following oral ingestion and it is therefore necessary to administer 5.0g of this disaccharide. Other suitable oligosaccharides include melibiose, raffinose, stachyose and dextrans, while cellobiose is unsuitable because there is some small intestinal cellobiase activity (Dahlqvist 1962).

Previous studies have shown that the permeation of lactulose and other oligosaccharides is influenced by the osmolarity of the test solution (Maxton et al. 1986). The urinary excretion of lactulose increases when the test dose osmolarity is increased beyond 1500 mOsm/L. This is known as hyperosmolar stress and is due to structural intestinal epithelial damage (Kameda et al. 1968). Hyperosmolar solutions have been shown to cause subepithelial blebs with loss of cellular regularity and loss of contour of epithelial cells with eventual loss of cells. Hyperosmolar stress does not affect the permeation of L-rhamnose even at 3600 mOsm/L. It is therefore important to administer isosmolar solution to the gut lumen to avoid a spurious increase in gut permeability index induced by the test solution itself.

It is generally accepted that large molecules, such as lactulose and ^{51}Cr EDTA cannot pass through the cell membrane and their permeation takes place through a paracellular route, more specifically through the intercellular tight junctions, which is a low capacity pathway (Maxton et al. 1986). Although a smaller molecule such as the monosaccharide L-rhamnose may partly share this low capacity intercellular route, the experiments by Maxton et al demonstrated that its permeation was 40 times greater than lactulose and was not affected by hyperosmolar stress, unlike lactulose. The data suggested that another small pore or high capacity pathway existed for the permeation of L-rhamnose. It is thought that this high capacity pathway consists of small aqueous membranous pores and is therefore part of the transcellular pathway (Lieb and Stein 1969) (figure 7-1). This model would explain why villus atrophy that occurs in patients with untreated celiac disease is associated with increased permeation of lactulose and decreased permeation of L-rhamnose (Bjarnason et al. 1986). The former would be explained by impaired function of the intercellular tight junctions, while L-rhamnose permeation is decreased due to loss of absorptive surface area, with a resultant decrease in the number of available aqueous membranous pores. Dawson et al demonstrated that in celiac disease, while the total permeation of mannitol, another monosaccharide, is reduced by up to 35%, its permeation when corrected for mucosal surface area is increased by at least twofold (Dawson et al. 1988).

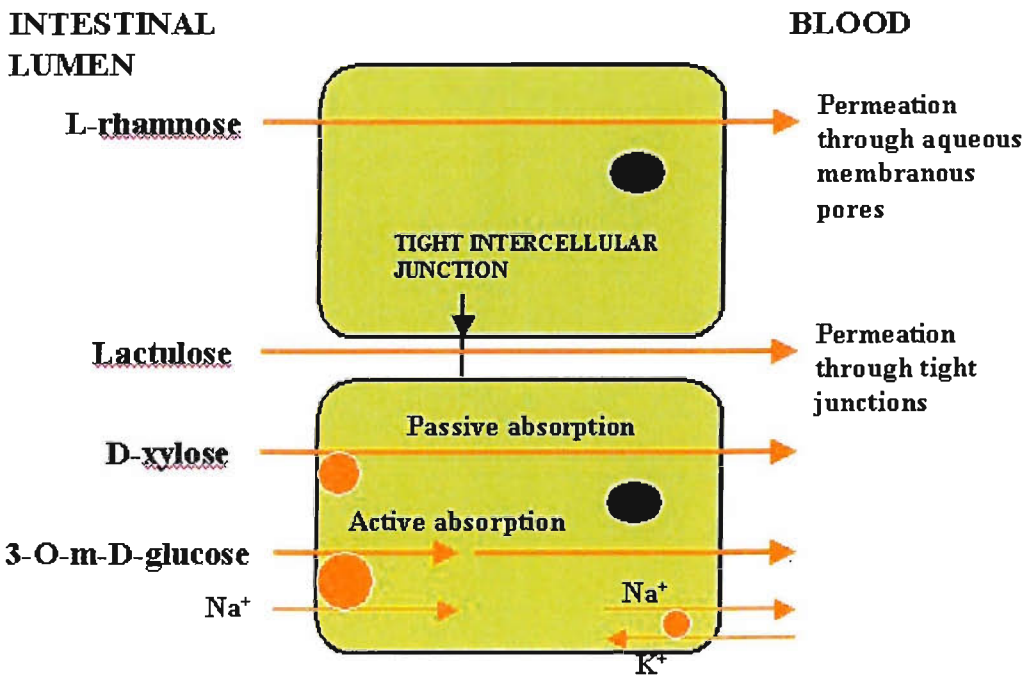
Urinary excretion of monosaccharides for assessment of intestinal absorption

Intestinal absorption is a carrier-mediated process that may be active (energy-requiring) or passive. Assessment of intestinal absorption follows the principle of urinary excretion of orally administered test substances (monosaccharides). The properties of the ideal probe have been already discussed. 3-O-m-D-glucose and D-xylose are the test substances used to assess active and passive absorption respectively.

3-O-m-D-glucose is a synthetic sugar that is non-toxic, it is readily absorbed by the small bowel, it is not metabolised and there is 90% recovery of an enteral dose within 48 hours. Small intestinal absorption of 3-O-m-D-glucose is preserved even in

the presence of intestinal disease, hence it is not a useful marker for malabsorption (Fordtran et al. 1962). 3-O-m-D glucose shares the same carrier as glucose, and the presence of both sugars inhibits each other's absorption. The absorption of glucose from the intestinal lumen is linked to the transport of sodium (Na^+), through the Na^+-glucose cotransporter (Hediger et al. 1987). This carrier protein actively transports glucose from the intestinal lumen into the cell against its concentration gradient by coupling glucose transport with that of Na^+, which is transported down its concentration gradient (Fig 7-1). The Na^+ gradient is maintained by active transport of Na^+ by membrane bound Na^+-K^+-ATPase (Bell et al. 1990).

Figure 7-1. The mechanisms of permeation and absorption for lactulose, L-rhamnose, D-xylose and 3-O-m-D-glucose.



D-xylose is predominantly absorbed in the jejunum and proximal ileum, with 90% of the test dose absorbed in the first 100cm of small bowel and little absorption in the distal ileum, unlike glucose (Fordtran et al. 1962). D-xylose does not fulfil the requirements of the ideal probe because it undergoes metabolism and can be influenced by metabolic or endocrine disorders such as myxoedema (Broitman et al. 1964). Approximately 50% of an administered dose is excreted unchanged in the urine in healthy subjects (Craig et al. 1983), while in patients with renal failure the absorption half-life of D-xylose approximately doubles, by mechanisms which are not understood (Worwag et al. 1987). Approximately 15% of the administered D-xylose is metabolised to CO2, another 15% converted to D-threitol and 5% is eliminated unchanged in the bile (Segal and Foley 1959; Pitkanen 1977; Huguenin et al. 1978).

Similar to glucose, the absorption of D-xylose from the intestinal lumen stimulates Na^+ transport and is dependent upon the presence of Na^+ (Csaky and Lassen 1964). However, although transport of D-xylose is competitively inhibited by glucose *in vitro*, it is unaffected by the inhibition of glucose transport. This suggests a different absorption mechanism and it is thought that D-xylose is absorbed through a passive carrier mediated process (Heyman et al. 1981). Fine and colleagues (Fine et al. 1994) observed that active absorption of glucose enhances xylose passive absorption, due to glucose-induced water absorption, which leads to increased passive solute absorption a) through solvent drag, and b) through passive diffusion, as the luminal concentration of xylose rises as water is removed from the lumen.

Intestinal absorption and permeability after CPB

Cardiac surgery with CPB is associated with a transient drop in intestinal absorption and rise in gut permeability. Ohri et al (Ohri et al. 1993) observed a marked impairment of intestinal absorptive and barrier function in the immediate postoperative period, with no differences between patients undergoing CABG and those undergoing valve surgery. The rise in gut permeability was more pronounced in patients with long duration (>100 min) of CPB. Intestinal absorption of 3-O-m-D glucose and D-xylose returned to baseline values on the 5^{th} postoperative day, while

gut permeability was still raised 5 days after surgery compared to preoperative values. Similar observations of an immediate postoperative rise in gut permeability and reduced intestinal absorption after CPB were made by Sinclair et al (Sinclair et al. 1995), who also demonstrated that the rise in gut permeability was significantly more pronounced in patients who had demonstrated intraoperative intramucosal acidosis, evidenced by a drop in pHi. Riddington et al (Riddington et al. 1996) confirmed a rise in gut permeability after CPB, but they found no significant correlation between gut permeability and pHi. In another study by Sinclair et al (Sinclair et al. 1997), the authors observed that the postoperative rise in gut permeability was more pronounced in patients who were randomly assigned to receive dopamine infusion intraoperatively, compared to a group who received dopexamine, which highlights the importance of following strictly standardized protocols for the design of such studies. The possible role of pulsatile flow and temperature during CPB on intestinal function has not been investigated, although in unpublished data Ohri et al observed superior preservation of gut permeability during pulsatile CPB compared to non-pulsatile flow.

Intestinal permeability after general surgery and stress

Reduced gut barrier function with raised intestinal permeability has been well described in the context of intestinal, abdominal and vascular surgery (Corson et al. 1992; Kanwar et al. 2000; Lau et al. 2000; Lau et al. 2001; McGinley et al. 2001; Jiang et al. 2003; Quan et al. 2004). Similar observations have been made in the context of other conditions of stress in both experimental models and clinical settings, such as haemorrhagic shock (Russell et al. 1995), chemotherapy (Johansson et al. 2001), burns (Ziegler et al. 1988), malnutrition (Johansson and Ekman 1997; Welsh et al. 1998), multiple injury (Kompan et al. 1999; Kompan and Kompan 2001), cholestatic jaundice (Welsh et al. 1998), and following bone marrow transplantation (Blijlevens et al. 2005). Increased intestinal permeability is also observed in critically ill patients in the intensive care unit (Oudemans-van Straaten et al. 1996), and it is thought that in some patients, loss of gut barrier function is a key event that leads to translocation of bacteria and toxins, with subsequent systemic inflammation, sepsis and multiple organ failure (Doig et al. 1998). Possible ways to

influence the reduction of gut barrier function in response to trauma have also been investigated: Lau et al (Lau et al. 2001) observed superior preservation of gut barrier function in patients undergoing abdominal aortic aneurysm (AAA) repair by using an extraperitoneal surgical approach compared to the transperitoneal one. McGinley et al (McGinley et al. 2001) observed no difference in postoperative lactulose/L-rhamnose permeability ratio in patients undergoing AAA repair with and without intraoperative infusion of Dopexamine. Jiang et al (Jiang et al. 2003) demonstrated in a prospective randomized study that enteral nutrition after abdominal surgery results in quicker recovery of gut barrier function compared to parenteral feeding.

MATERIALS AND METHODS

Study design

Consecutive patients undergoing primary elective CABG who fulfilled the study criteria (Table 7-2) were recruited following informed consent. Essentially we studied low-risk patients with normal preoperative cardiac function. All patients were operated upon by the same surgeon. If no contraindications were evident following review of the preoperative coronary angiogram, the patients were randomised into either surgery with CPB (ONCAB group) or off-pump (OPCAB group) by simple randomisation using a table of random numbers. The study was approved by the Southampton & South West Hants Joint Local Research Ethics Committee.

Table 7-2. Exclusion criteria.

Age over 75 years
LVEF < 50%
Recent (< 3 months) MI
Intravenous therapy for unstable angina
Diabetes Mellitus
Renal insufficiency
Liver failure
Gastrointestinal disease
Abdominal surgery
Connective tissue disease
Peripheral vascular disease
Previous CVA

LVEF, left ventricular ejection fraction; MI, myocardial infarction; CVA, cerebro-vascular accident.

Anaesthetic management

The patients' medications were continued up to the night before the operation except for anti-platelet agents, which were discontinued 7 days prior to surgery. A standardized balanced anaesthetic protocol was utilized in which fentanyl-based

anaesthesia was used in combination with benzodiazepine and pancuronium as a muscle relaxant. Anaesthesia was maintained intraoperatively with a mixture of isoflurane and intravenous propofol infusion. Postoperatively the patients remained on propofol infusion until extubation. Active warming techniques were used in the recovery period, to achieve a nasopharyngeal temperature of at least 37°C before extubation. Target haemodynamic values were mean arterial pressure above 60 mmHg and cardiac index over 2.2 L/min/m^2. Dopamine was used as the first-line inotrope to support a low cardiac output, whilst bolus intravenous injections of phenylephrine or infusion of noradrenaline were used as vasoconstrictors.

CPB management

A standardized CPB protocol was used for the ONCAB patients. CPB was established using bicaval cannulation and an arterial cannula (Medtronic DLP®; Medtronic Ltd., Watford, UK) placed in the ascending aorta. Pulsatile CPB was conducted under mild core hypothermia (35°C), using a hollow-fibre membrane oxygenator (D903 Avant, Sorin Biomedica, Mirandola, Italy) and arterial line filtration (D734 Micro 40, Sorin Biomedica, Mirandola, Italy). The circuit was primed with 1 L of Hartman's solution, 500 ml of gelofusine and 5000 IU of sodium heparin. Intermittent antegrade cold blood cardioplegia (4°C) delivered through a 12G aortic root cannula was used for myocardial protection. The cardioplegic mixture consisted of 20% St Thomas' Hospital No.2 solution (Martindale Pharmaceuticals, Essex, UK) and 80% autologous blood. A dose of 12 ml/kg was delivered to induce diastolic cardiac arrest and a maintenance dose of 3 ml/kg was administered after completion of each distal anastomosis. The left ventricle was vented through the aortic root during aortic cross-clamping. Flow was maintained at 2.5 L/min/m^2 during CPB with judicious use of phenylephrine and phentolamine to maintain the mean perfusion pressure between 50 and 80 mmHg. Alpha-stat management of acid-base status was used. Proximal graft anastomoses on the ascending aorta were performed following aortic cross-clamp removal using a partially occlusive clamp.

OPCAB technique

A median sternotomy was used for surgical access in all cases. Partial systemic heparinisation was employed with a target activated clotting time of 300-400 sec prior to cardiac manipulation. Trendelenburg posture was employed throughout the period of distal anastomoses and a single suture technique (Bergsland et al. 1999) was used to facilitate exposure of the target coronary arteries. A mechanical suction-based myocardial tissue stabilizer (Octopus®3; Medtronic Ltd., Watford, UK) was used to immobilize the operative field during coronary anastomosis. Following arteriotomy, an intraluminal coronary shunt (Flo-Thru; Biovascular Inc., Minnesota, USA) was inserted to maintain distal myocardial perfusion and was removed prior to completion of the anastomosis. Core temperature was maintained at or above 35°C throughout the procedure by minimizing heat loss and active warming techniques. Haemodynamic stability was achieved primarily with preload management (intravenous fluid administration and Trendelenburg posture) and vasoactive agents as required. Construction of the proximal anastomoses to the ascending aorta was performed within a single aortic side-biting clamp period, with the systolic arterial pressure maintained around 100 mm Hg to minimize aortic trauma.

Assessment of intestinal absorption

Intestinal absorption was assessed by measuring the urinary excretion of enterally administered saccharides, as discussed in detail in the background section of this chapter. Four saccharides, 3-O-methyl-D-glucose, D-xylose, L-rhamnose and lactulose were used to assess active carrier-mediated, passive carrier-mediated, transcellular and paracellular transport respectively. Three studies were conducted for each patient, the first was the day prior to surgery, the second started one hour postoperatively and the third was on the fifth postoperative day. For each study 100 ml of a solution (240 mOsm/L) containing the four saccharide markers (0.2g 3-O-methyl-D-glucose, 0.5g D-xylose, 1.0g L-rhamnose and 5.0g lactulose) was administered orally or enterally followed by a 5-hour urine collection. For the immediate postoperative study the test solution was administered via a nasogastric tube, which then remained clamped for the duration of the study period. Patients were allowed only water for 5 hours prior to sugar administration and during urine

collection. The volume of the 5-hour urine collection was recorded and a 20-ml sample was stored with methiolate at 10°C to 15°C until analysed. Methiolate was used to prevent bacterial degradation in the sample. High performance liquid chromatography with pulsed electrochemical detection (Dionex UK Ltd, Camberley, UK) was used to analyse the saccharide markers; results were expressed as a percentage of enterally administered saccharide. The analysis of the samples was performed by Dr I Phillips, Department of Chemical Pathology, Southampton General Hospital, Southampton.

Assessment of intestinal permeability

Intestinal permeability was assessed by measuring the urinary excreted lactulose/L-rhamnose ratio, as explained in detail in the background information of this chapter. Three studies were conducted, the day before operation, immediately postoperatively and 5 days postoperatively, exactly as outlined in the previous paragraph.

Statistical analysis

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 if normal distribution could not be assumed. Categorical variables were compared using the Pearson's chi-square or Fisher's exact test as appropriate. A one-sample Student *t*-test was used to compare outcome within a group to baseline values, while a two-sample *t*-test was used to compare outcome between the groups. The Statistical Package for Social Sciences (SPSS) version 10.1 software was used for all descriptive statistics and inferential testing. A p value of less than 0.05 was considered statistically significant.

RESULTS

Patient demographics and clinical outcome

58 patients were recruited into the study and randomized to two groups (ONCAB, n=30 and OPCAB, n=28). All patients completed the study protocol and no patient was excluded. No patient allocated to the OPCAB group required the use of CPB.

The demographic variables for the two groups are presented in Table 7-3. As outlined in the methods, these were low-risk cases and there were no significant differences between the groups.

Table 7-4 summarizes the intraoperative data and clinical outcome. The groups received similar extent of revascularization using comparable mixture of conduits. There were no differences in operation duration and mechanical ventilation time. Rewarming to a core (nasopharyngeal) temperature of 37°C occurred within similar length of time in both groups. There was a significant difference between the groups in the use of vasoconstrictors, this was mainly due to the use of phenylephrine during CPB in all but one patients in the ONCAB group. No mortality or major complications, such as myocardial infarction, major neurological deficit or end-organ failure were observed. No patient required the use of intraaortic balloon pump.

Table 7-3. Patient characteristics.

Variable	ONCAB (n=30)	OPCAB (n=28)	*p* value
Age	63.2 ± 8.0	61.3 ± 8.4	.39
Gender			.55
Male	26	21	
Female	5	6	
CCS angina class			.39
I	7	3	
II	16	12	
III	5	6	
IV	3	6	
Previous MI	9	5	.35
Hypertension	15	14	.79
Morbid obesity	5	7	.36
Parsonnet score	3.0 (0.0-3.5)	3.0 (0.5-3.5)	.86

CCS, Canadian Cardiovascular Society; MI, myocardial infarction.

Age is presented as mean ± standard deviation. Parsonnet score is presented as median with interquartile range.

Table 7-4. Intraoperative data and clinical outcome.

Variable	ONCAB (n=30)	OPCAB (n=28)	*p* value
Distal anastomoses	2.6 ± 0.9	2.5 ± 0.8	.55
Type of conduit			
LIMA	29	26	.61
RIMA	2	1	.61
Radial artery	3	2	.68
Saphenous vein	25	23	1
CPB time (min)	62 ± 25		
AXC time (min)	32 ± 11		
Operation duration (min)	186 ± 47	177 ± 45	.47
Time to rewarming (hr)	2.4 ± 1.1	2.8 ± 0.9	.28
Time to extubation (hr)	5.0 (4.2-5.8)	5.0 (3.5-5.8)	.62
ICU length of stay (d)	1.0 (1.0-1.8)	1.0 (1.0-2.0)	.44
Perioperative low CI	3	2	.68
Perioperative vasoconstrictors	26	14	<.01
Inotropic support	3	2	.68
Supraventricular arrhythmia	6	6	1
Pneumonia	3	4	.71
Wound infection	1	0	1
Postoperative hospital stay (d)	6.9 ± 2.6	6.6 ± 2.0	.71

LIMA, left internal mammary artery; RIMA, right internal mammary artery; CPB, cardiopulmonary bypass; AXC, aortic cross-clamping; ICU, intensive care unit; CI, cardiac index; low CI is defined as below 2.2 L/min/m^2; norepinephrine or phenylephrine were used as vasoconstrictors; dopamine was used for inotropic support.

Time to extubation and ICU length of stay are presented as median with interquartile range. Other continuous variables are presented as mean ± standard deviation.

Intestinal absorption and permeability

Immediately after surgery there was a similar and significant drop in the urinary excretion of 3-O-methyl-D-glucose, D-xylose and L-rhamnose in both groups. The permeation of these saccharides returned to normal levels in the OPCAB group 5 days postoperatively, while in the ONCAB group there was only a partial recovery towards normality with all values significantly lower than baseline values and significantly lower compared to the OPCAB group. No changes were observed in the permeation of lactulose. There was a similar and significant rise in the gut permeability ratio immediately postoperatively in both groups. Gut permeability returned to baseline values in the OPCAB patients 5 days after surgery, while in the ONCAB group it remained significantly higher than baseline values and significantly higher compared to the OPCAB group. Table 7-5 summarizes all the results, which are depicted graphically in figures 7-2 to 7-6.

Table 7-5. Urinary recovery of saccharides and gut permeability index (lactulose/L-rhamnose ratio) in the two groups.

		Pre-op	Immediately post-op	5 days post-op
3-O-methyl-D-glucose	ONCAB	40.3 ± 3.1	7.5 ± 1.5 [b]	28.8 ± 2.6 [a,b]
	OPCAB	39.4 ± 4.7	6.8 ± 1.4 [b]	40.4 ± 3.8
D-xylose	ONCAB	20.1 ± 1.6	4.2 ± 1.3 [b]	15.8 ± 2.2 [a,b]
	OPCAB	18.6 ± 2.3	2.2 ± 0.6 [b]	22.3 ± 1.8
L-rhamnose	ONCAB	8.7 ± 0.8	2.5 ± 0.7 [b]	5.4 ± 0.7 [a,b]
	OPCAB	8.8 ± 1.2	1.8 ± 0.4 [b]	8.0 ± 0.7
Lactulose	ONCAB	0.20 ± 0.02	0.16 ± 0.02	0.20 ± 0.03
	OPCAB	0.18 ± 0.03	0.15 ± 0.02	0.16 ± 0.03
Lactulose/L-rhamnose ratio	ONCAB	0.025 ± 0.004	0.112 ± 0.014 [b]	0.056 ± 0.013 [a,b]
	OPCAB	0.025 ± 0.004	0.108 ± 0.013 [b]	0.022 ± 0.005

a=$p<0.05$ between groups; b=$p<0.05$ within group compared to pre-op value.

Figure 7-2. 3-O-m-D-glucose absorption

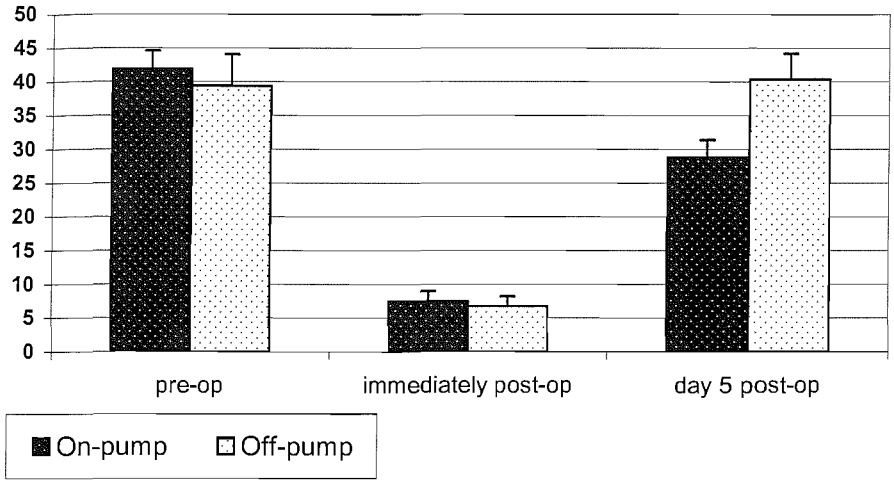


Figure 7-3. D-xylose absorption

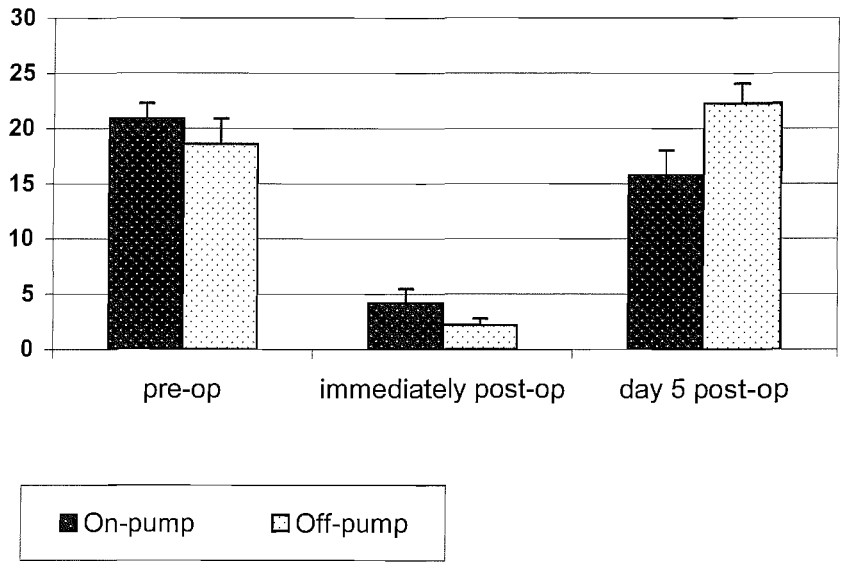


Figure 7-4. L-rhamnose transcellular permeation

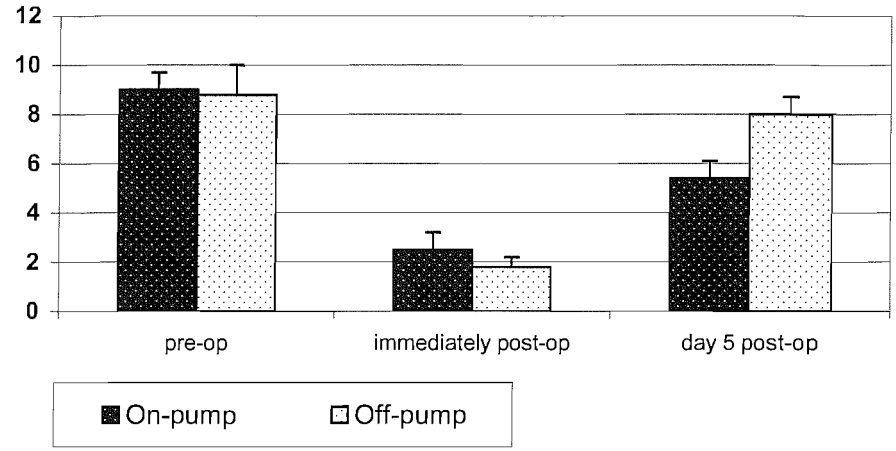


Figure 7-5. Lactulose paracellular permeation

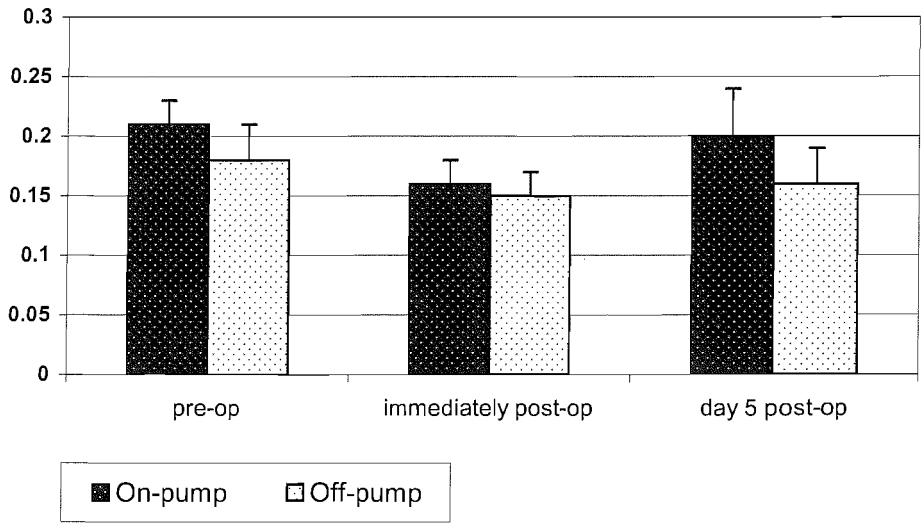
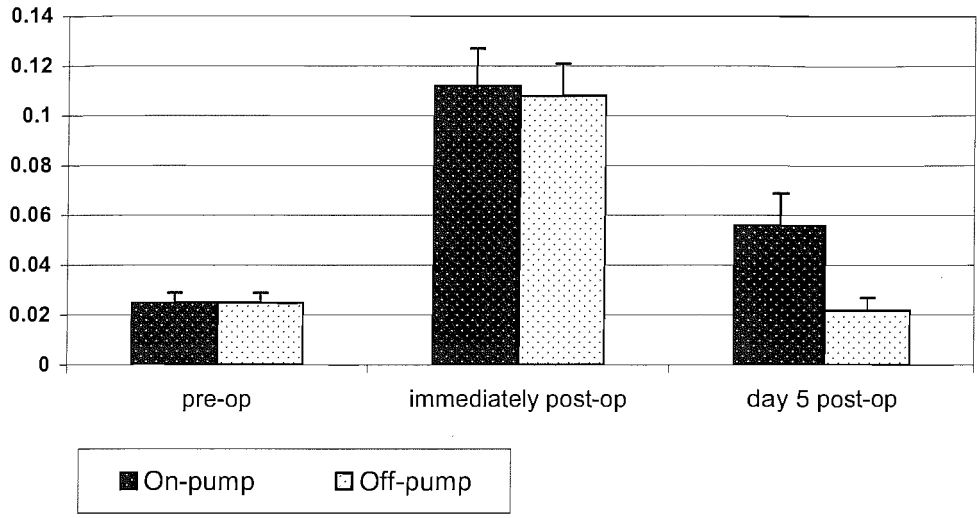


Figure 7-6. Gut permeability ratio



DISCUSSION

The absence of GI complications or any major morbidity in our study is not surprising, given the low-risk profile of the patient population. Previous retrospective studies have demonstrated a relatively low incidence of GI complications in cardiac surgical populations, which is under 1% in most studies (Wallwork and Davidson 1980; Hanks et al. 1982; Pinson and Alberty 1983; Reath et al. 1983; Leitman et al. 1987; Krasna et al. 1988; Huddy et al. 1991; Ohri et al. 1991; Egleston et al. 1993; Christenson et al. 1994; Mercado et al. 1994; Tsiotos et al. 1994; Perugini et al. 1997; Simic et al. 1999; Zacharias et al. 2000; Mierdl et al. 2001; D'Ancona et al. 2003; McSweeney et al. 2004; Raja et al. 2004). Ohri et al (Ohri et al. 1991) observed GI complications in 27 out of 4602 patients undergoing cardiac surgery (0.58%) between 1973 and 1989. Interestingly, in a subgroup of patients who underwent CPB using pulsatile perfusion with arterial line filtration, which is the protocol we used in our study, there was only one gastrointestinal complication out of 562 cases.

The results in the on-pump group are in keeping with previous studies and they confirm transient deterioration in intestinal absorption and gut barrier function in the early postoperative period subsequently returning towards baseline values by the 5th postoperative day. Several studies have demonstrated a similar pattern of transient perioperative decline in intestinal function after CPB (Ohri et al. 1993; Sinclair et al. 1995; Oudemans-van Straaten et al. 1996; Riddington et al. 1996; Braun et al. 2004) and have attributed this mainly to the systemic inflammatory response to cardiopulmonary bypass and the perioperative gut mucosal hypoxia. What is more interesting is that we observed a similar temporary decline in intestinal function between CPB and OPCAB groups in the immediate postoperative period.

Given the single-surgeon and randomized nature of the study design, the standardized anaesthetic protocol and the absence of any significant differences in the preoperative characteristics of the two groups, these results may at first appear surprising. One would intuitively expect some benefit conferred by the avoidance of CPB. There are certainly factors associated with the use of CPB *per se* that would

partly explain the transient loss of intestinal function. These factors include the systemic inflammatory response to CPB, the use of subphysiological flow levels during CPB and the release of various endogenous vasoconstrictors, including angiotensin II, with a concomitant rise in systemic vascular resistance (Taylor et al. 1979).

However, as discussed in the background information to this chapter, a transient decline in gut barrier function has been described in the context of intestinal, abdominal and vascular surgery (Corson et al. 1992; Kanwar et al. 2000; Lau et al. 2000; Lau et al. 2001; McGinley et al. 2001; Jiang et al. 2003; Quan et al. 2004). Moreover, 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 (Ziegler et al. 1988; Russell et al. 1995; Kompan et al. 1999; Johansson et al. 2001). It therefore becomes obvious that factors other than the use of CPB can affect intestinal function. It would appear logical to assume that in both groups, the stress of undergoing general anaesthesia and surgery was a major factor contributing to transient reduction in intestinal function. Moreover, it would appear that in the OPCAB patients the added stress of haemodynamic deterioration during distal anastomoses, which was discussed in detail in Chapters 2 and 3, may explain why the magnitude of intestinal function changes in the immediate perioperative period was comparable to surgery with CPB. Our findings of comparable intestinal absorption and permeability changes between the two groups are also in keeping with our findings in Chapter 6, where we demonstrated a comparable transient drop in the adequacy of mucosal perfusion in both groups in the early postoperative period. Changes in the oxygenation status of the intestinal mucosa are likely to contribute to changes in intestinal function and a positive correlation between perioperative gut mucosal oxygenation and preservation of intestinal function has been previously reported (Sinclair et al. 1995).

Our findings of comparable decline in intestinal function in the immediate postoperative period between OPCAB and CPB are immediately relevant to the findings of two recent retrospective studies that demonstrated a similar incidence of

GI complications after cardiac surgery with and without CPB (Musleh et al. 2003; Sanisoglu et al. 2004). Musleh et al (Musleh et al. 2003) reported their findings on 2327 patients undergoing surgery with CPB (1210 cases) or off-pump (1117 cases) over a 4-year period. They observed GI complications in 14 patients (1.2%) in the on-pump group, vs. 18 patients (1.6%) in the off-pump group, with a resultant mortality of 28.6% vs. 22.2% respectively. Their analysis demonstrated that renal dysfunction, older age and previous GI surgery were the only factors associated with a higher risk of GI complications. Similar results were obtained by Sanisoglu et al (Sanisoglu et al. 2004), who concluded that older age and extracardiac atherosclerosis were the main predictors of adverse GI outcome. They also observed that prolonged CPB (over 98 minutes) was associated with a higher incidence of GI complications. Our results are in keeping with the results of these retrospective studies and provide a possible explanation for these findings.

We do not fully understand the reasons why superior return of gut barrier and intestinal absorptive function was observed at 5 days postoperatively in the OPCAB group compared to the patients who underwent CPB. As explained above, it would be logical to assume that the haemodynamic stress during OPCAB led to a comparable initial decline in intestinal function compared to the CPB-related factors in the on-pump group. The predominant CPB-related factor is thought to be the systemic inflammatory response, and several studies have shown an attenuation in the systemic inflammatory response with OPCAB compared to CPB (Ascione et al. 2000; Matata et al. 2000; Chello et al. 2002). Although these studies have only compared changes in humoral markers of the inflammatory response, such as cytokines, one would expect an attenuation in the cellular inflammatory response as well. Based on that hypothesis, one would assume that our findings at 5 days indicate that recovery of intestinal function from haemodynamic stress (OPCAB group) occurs quicker than recovery of intestinal function from systemic inflammation (CPB group). It is interesting to note that in Chapter 6 we only observed perioperative gut mucosal oxygenation for up to 6 hours postoperatively and the pattern of recovery of mucosal oxygenation in later postoperative stages remains unknown.

The use of pulsatile flow during CPB reflects our current practice but more importantly has been associated with superior preservation of gut mucosal oxygenation (Gaer et al. 1994; Hamulu et al. 1998). Adequacy of mucosal perfusion has been shown to be associated with preservation of intestinal function (Sinclair et al. 1995), although another study did not confirm this (Riddington et al. 1996). Moreover, Ohri et al observed superior preservation of gut barrier function during pulsatile compared to non-pulsatile CPB (unpublished data). Pulsatile flow maintains capillary patency by delivering more energy into the vasculature and ameliorates the increase in systemic vascular resistance by reducing the release of vasoconstrictors, such as angiotensin II (Taylor et al. 1979). Although the effect of core temperature during CPB on intestinal function has not been investigated, a systemic temperature of 35°C during CPB was used in this study to avoid the confounding effect of different intraoperative core temperatures in the two groups. It is likely that the choice of CPB protocol, particularly the use of pulsatile flow, had a significant effect on the study findings, and this must be taken into account in future studies.

One limitation of this study is that only low-risk patients with normal cardiac and intestinal function were studied. This strategy was adopted to ensure homogeneity of the groups, which is essential in prospective randomised studies with small numbers of patients. However, patients with poor left ventricular function or other co-morbidities, such as diabetes mellitus, extracardiac arteriopathy or intestinal disease may behave differently and the results of this study cannot be extrapolated to such populations.

In conclusion this study has demonstrated the presence of significant perioperative decline in intestinal absorption with a concomitant rise in gut permeability during CABG either with or without CPB. It also showed a quicker recovery of intestinal function in the off-pump population. The clinical significance of these findings is unclear. Whether these findings may be applicable to a high-risk patient population also requires further investigation. However, our results are in agreement with our previous findings and provide further evidence of significant transient subclinical end-organ injury during OPCAB.

Chapter 8

Liver function during coronary surgery with CPB vs. Off-pump

SUMMARY

Objective: Cardiopulmonary bypass is associated with temporary liver dysfunction and occasionally severe hepatic injury and failure. Perioperative liver function was examined in low-risk patients undergoing CABG with and without CPB.

Methods: Fifty-eight patients undergoing primary CABG by the same surgeon were randomised into either on-pump (ONCAB, n=30) or off-pump (OPCAB, n=28) groups. The ONCAB group underwent mild hypothermic (35°C) pulsatile CPB with arterial line filtration. Conventional liver function tests were measured in all patients at sequential perioperative time-points up to 5 days postoperatively. A subgroup of 16 patients (ONCAB, n=8; OPCAB, n=8) also underwent assessment of liver function using the monoethylglycinexylidide (MEGX) test. Anaesthetic management was standardized.

Results: Both groups had similar demographic makeup and extent of revascularization (ONCAB 2.8 ± 1.0 grafts v. OPCAB 2.4 ± 0.9 grafts; p= .32). The ONCAB group had a mean (± SD) CPB time of 59 ± 24 min and aortic cross-clamp time of 31 ± 10 min. Mean values of total and conjugated bilirubin and alkaline phosphatase remained within normal range in both groups throughout the study. Mean values of hepatic enzymes were mildly above normal range at 5 days postoperatively, but there were no differences between the groups. The MEGX test demonstrated no significant deterioration in hepatic function at 6 hours postoperatively in both groups and there were no differences between the groups.

Conclusions: Both OPCAB and CABG with mildly hypothermic pulsatile CPB in low-risk patients result in only mild transient hepatic dysfunction. In these patients, OPCAB does not confer any advantage in preservation of liver function over surgery with CPB.

INTRODUCTION

In previous chapters the effect of coronary surgery on gastric mucosal oxygenation and intestinal function was examined, and significant perioperative gastric mucosal hypoxia and transient impairment in intestinal absorptive and barrier function were observed using either CPB or the OPCAB approach (chapters 6 and 7). In this chapter the impact of coronary surgery with and without CPB on liver function will be studied.

Although clinically significant hepatic failure after cardiac surgery is rare, liver dysfunction at subclinical level, evidenced by a rise in conventional liver function tests, is well described after cardiac surgery with CPB (Robinson et al. 1967; Gautam 1969; Collins et al. 1983; Chu et al. 1984; Wang et al. 1994). Although the precise pathophysiologic mechanisms remain unknown, liver injury is thought to be related to the same pathophysiologic mechanisms that cause mucosal hypoxia of the gut: episodes of haemodynamic instability with inadequate perfusion of the gastrointestinal bed, increased levels of circulating vasoconstrictors and the inflammatory response to surgery and CPB. Additionally, it is thought that haemolysis related to surgery and the use of CPB may contribute to elevated bilirubin levels. Perioperative liver function in the context of OPCAB has not been documented.

Conventional liver function tests (LFTs) 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 and there is vast experience with their use. However, conventional LFTs do not quantitate liver function but assess qualitatively the presence of hepatic injury (McIntyre 1983). Moreover, their sensitivity and specificity for hepatic injury is relatively low. More recently, more sensitive and specific tests that attempt to monitor liver function more accurately in a quantitative fashion have become available. One 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 monoethylglycinexylidide (MEGX) (Oellerich et al.

1987). This test is usually reserved for research purposes or for complicated clinical scenarios, such as assessing the suitability of a human liver for transplantation (Oellerich et al. 1989).

The aim of this study was to compare perioperative liver function in low-risk patients undergoing coronary artery surgery with CPB vs. OPCAB. In a subgroup of patients MEGX measurements were used for further evaluation of the liver function after cardiac surgery.

Background

Evidence for liver dysfunction after CPB

Severe ischaemic hepatic injury resulting in clinically significant hepatic failure is uncommon after cardiac surgery. Raman et al (Raman et al. 2002) reported 20 cases of severe early ischaemic liver injury (SIELI) in 1800 consecutive cardiac surgical patients. In that study, SIELI was defined as ALT levels above 500 IU/L in the early postoperative period. All patients who developed SIELI had normal LFTs preoperatively. Postoperative hepatic injury was associated with a low cardiac output state and high filling pressures, indicating that a combination of liver ischaemia, caused by reduced forward flow, and liver congestion, secondary to elevated central venous pressure, was responsible for its pathogenesis.

Subclinical hepatic dysfunction, evidenced mainly by elevated bilirubin levels and / or mild elevations of hepatic enzymes, is not uncommon after CPB. Chu et al (Chu et al. 1984) reported a 23.4% incidence of jaundice in 154 cardiac surgical patients, and the most important preoperative risk factor was severity of heart failure. Other perioperative risk factors for hyperbilirubinaemia were episodes of hypotension or hypoxia and blood transfusion. Similarly, Collins et al (Collins et al. 1983) observed a 20% incidence of jaundice in 248 cardiac surgical patients, although jaundice occurred in only 8% of 96 patients who underwent isolated CABG. Multiple valve replacements, higher transfusion requirements and longer CPB time were factors associated with postoperative jaundice. Preoperative bilirubin and ALP levels were not predictive of jaundice, and it was also noticed that preoperative right atrial pressure was significantly higher in the group of patients that developed jaundice postoperatively, suggesting a role of right heart dysfunction in the occurrence of this complication. Similar observations were also made by Wang et al (Wang et al. 1994), who documented an incidence of postoperative jaundice of 35.1% in 302 patients undergoing cardiac surgery. Higher preoperative right atrial pressure and total bilirubin levels and multiple valve replacement procedures were the risk factors associated with the development of hyperbilirubinaemia postoperatively.

Cardiac surgery in the presence of hepatic disease

Cardiac surgery with CPB in the presence of preoperative liver cirrhosis represents a significant challenge irrespective of the aetiology (cardiac or non-cardiac) of the cirrhosis. In a retrospective review of 13 patients with cirrhosis undergoing CPB, Klemperer et al (Klemperer et al. 1998) observed major complications in 2 out of 8 patients (25%) with class A cirrhosis and all 5 patients (100%) with class B cirrhosis. Hospital mortality was observed in 4 out of 5 (80%) class B patients and was related to gastrointestinal and septic complications, rather than cardiovascular failure. The authors concluded that advanced cirrhosis (Child class B or C) was associated with unacceptable operative risk and could be considered a contraindication to CPB. Bizouarn et al (Bizouarn et al. 1999) described their experience with CPB on 12 patients with cirrhosis, 10 of whom had class A and 2 had class B cirrhosis. There was one early death (day 10 postoperatively) in a class B patient from multiple organ failure and 2 late deaths (1 month and 4 months) in class A patients from further deterioration of hepatic failure. Similar experiences have been described in few smaller series of adult (Ninomiya et al. 2001) and paediatric (Bacha et al. 2004; Odim et al. 2006) cardiac surgical patients with concomitant advanced liver disease. More encouraging results have been published by Lin et al (Lin et al. 2005). In 18 cirrhotic patients (13 class A, 4 class B, 1 class C) undergoing cardiac surgery, they observed only 1 death in a class A patient.

There is limited experience with OPCAB in the presence of cirrhosis, however it appears to be a more promising approach than CPB for these high-risk patients. In a retrospective review by Hayashida et al (Hayashida et al. 2004), the authors described their cardiac surgical results in 18 patients with cirrhosis. In that study 3 patients, who were all in class B cirrhosis, underwent OPCAB and no mortality occurred. In the remaining 15 patients who underwent CPB, the mortality was 0/10 (0%) in patients with class A cirrhosis, 2/4 (50%) in patients with class B cirrhosis and 1/1 (100%) with class C cirrhosis. In the above-mentioned study by Lin et al (Lin et al. 2005), 2 patients underwent OPCAB with satisfactory outcome. A few more cases of good outcome with OPCAB in the presence of cirrhosis have been

reported (Sakakibara et al. 1998; Kaplan et al. 2002; Yamamoto et al. 2002; Carr and Desai 2004; Lin et al. 2005).

Lignocaine metabolite formation for the assessment of liver function

The use of the rate of lignocaine metabolism as a quantitative liver function test was first described by Oellerich in 1987 (Oellerich et al. 1987). Lignocaine is an aminoethylamide and after intravenous injection it undergoes a rapid oxidative N-deethylation reaction in the liver, catalysed by the hepatic cytochrome P450 system. This results in the formation of MEGX (Oellerich et al. 1987). Since lignocaine is totally and rapidly metabolised by the liver, the rate of MEGX formation correlates with the rate of lignocaine clearance. In healthy subjects, lignocaine has a high hepatic extraction ratio, and its clearance is predominantly affected by hepatic blood flow (Gremse et al. 1990). In the presence of hepatic dysfunction, lignocaine clearance is affected more by hepatic metabolic capacity or intrinsic clearance rather than changes in hepatic blood flow (Huet and Villeneuve 1983). Although the concentration-time curve for MEGX following a bolus lignocaine injection has been described, the test only requires two blood tests for MEGX measurement: one prior to and one 15 minutes after the injection of a 1mg/kg lignocaine bolus.

Several studies have investigated the use of the MEGX test to assess the liver function of potential organ donors. Oellerich et al. (Oellerich et al. 1989) demonstrated that a MEGX test value of above 90μg/L was associated with a significantly higher probability of graft survival over 120 days than for grafts from donors with MEGX values below 90μg/L. Moreover, the MEGX test had a high prognostic sensitivity and specificity, unlike conventional LFTs. Schroeder et al. (Schroeder et al. 1989) assessed 10 liver transplant recipients with the MEGX test, conventional LFTs and liver biopsies. The authors observed higher MEGX values in patients with histologically demonstrated stable liver function (MEGX: 97±10.6 ng/ml) than in patients with ischaemic injury (61±10.1) or rejection (63±12.4). They also found that a decline in serum MEGX concentration preceded a rise in standard LFTs and histological changes in some patients undergoing rejection, indicating that this may be an early and sensitive index of hepatic dysfunction. The use of the

MEGX test has also been described in other clinical settings, such as for quantitative assessment of liver function in children with hepatic disease (Gremse et al. 1990). On the basis of the studies in the context of liver transplantation, it has been proposed that 15 minute MEGX values of above 90 ng/ml represent normal hepatic function (Kumle et al. 2003).

Few previous studies have described the use of the MEGX test for assessment of liver function during cardiac surgery (Autschbach et al. 1996; Braun et al. 2004). Autschbach et al assessed 14 patients undergoing CPB and found reduced formation of MEGX during CPB compared to pre-CPB values, despite increased hepatic blood flow during bypass, which would indicate decreased hepatic metabolic activity. In another prospective observational study Braun et al observed a reduction in MEGX formation the 1st postoperative day in 31 patients undergoing valve replacement surgery with CPB (Braun et al. 2004). Kumle et al (Kumle et al. 2003) performed perioperative measurements of MEGX in 30 patients undergoing CABG with CPB. The authors observed that patients who underwent prolonged (more than 80 minutes) CPB had significantly lower MEGX concentrations postoperatively than patients with shorter CPB duration. We are not aware of any other studies where the MEGX test has been used in the context of cardiac surgery and we are not aware of any study that has evaluated liver function during off-pump surgery.

MATERIALS AND METHODS

Study design

Consecutive patients undergoing primary elective CABG who fulfilled the study criteria (Table 7-1) were recruited following informed consent. Patients with no significant comorbidities and normal cardiac function were studied. All patients were operated upon by the same surgeon. If no contraindications were evident following review of the preoperative coronary angiogram, The patients were randomised into either surgery with CPB (ONCAB group, n=30) or off-pump surgery (OPCAB, n=28) by simple randomisation using a table of random numbers. The study was approved by the Southampton & South West Hants Joint Local Research Ethics Committee.

Table 8-1. Exclusion criteria.

Age over 75 years
LVEF < 50%
Recent (< 3 months) MI
Intravenous therapy for unstable angina
Diabetes Mellitus
Renal insufficiency
Liver failure
Gastrointestinal disease
Peripheral vascular disease
Previous CVA

LVEF, left ventricular ejection fraction; MI, myocardial infarction; CVA, cerebro-vascular accident.

Anaesthetic management

The patients' medications were continued up to the night before the operation except for anti-platelet agents, which were discontinued 7 days prior to surgery. A standardized balanced anaesthetic protocol was utilized in which fentanyl-based anaesthesia was used in combination with benzodiazepine and pancuronium as a

muscle relaxant. Anaesthesia was maintained intraoperatively with a mixture of isoflurane and intravenous propofol infusion. Postoperatively the patients remained on propofol infusion until extubation. Active warming techniques were used in the recovery period, to achieve a nasopharyngeal temperature of at least 37°C before extubation. Target haemodynamic values were mean arterial pressure above 60 mmHg and cardiac index over 2.2 L/min/m^2. Dopamine was used as the first-line inotrope to support a low cardiac output, whilst bolus intravenous injections of phenylephrine or infusion of noradrenaline were used as vasoconstrictors.

CPB management

A standardized CPB protocol was used for the ONCAB patients. CPB was established using bicaval cannulation and an arterial cannula (Medtronic DLP®; Medtronic Ltd., Watford, UK) placed in the ascending aorta. Pulsatile CPB was conducted under mild core hypothermia (35°C), using a hollow-fibre membrane oxygenator (D903 Avant, Sorin Biomedica, Mirandola, Italy) and arterial line filtration (D734 Micro 40, Sorin Biomedica, Mirandola, Italy). The circuit was primed with 1 L of Hartman's solution, 500 ml of gelofusine and 5000 IU of sodium heparin. Intermittent antegrade cold blood cardioplegia (4°C) delivered through a 12G aortic root cannula was used for myocardial protection. The cardioplegic mixture consisted of 20% St Thomas' Hospital No.2 solution (Martindale Pharmaceuticals, Essex, UK) and 80% autologous blood. A dose of 12 ml/kg was delivered to induce diastolic cardiac arrest and a maintenance dose of 3 ml/kg was administered after completion of each distal anastomosis. The left ventricle was vented through the aortic root during aortic cross-clamping. Flow was maintained at 2.5 L/min/m^2 during CPB with judicious use of phenylephrine and phentolamine to maintain the mean perfusion pressure between 50 and 80 mmHg. Alpha-stat management of acid-base status was used. Proximal graft anastomoses on the ascending aorta were performed following aortic cross-clamp removal using a partially occlusive clamp.

OPCAB technique

A median sternotomy was used for surgical access in all cases. Partial systemic heparinisation was employed with a target activated clotting time of 300-400 sec prior to cardiac manipulation. Trendelenburg posture was employed throughout the period of distal anastomoses and a single suture technique (Bergsland et al. 1999) was used to facilitate exposure of the target coronary arteries. A mechanical suction-based myocardial tissue stabilizer (Octopus®3; Medtronic Ltd., Watford, UK) was used to immobilize the operative field during coronary anastomosis. Following arteriotomy, an intraluminal coronary shunt (Flo-Thru; Biovascular Inc., Minnesota, USA) was inserted to maintain distal myocardial perfusion and was removed prior to completion of the anastomosis. Core temperature was maintained at or above 35°C throughout the procedure by minimizing heat loss and active warming techniques. Haemodynamic stability was achieved primarily with preload management (intravenous fluid administration and Trendelenburg posture) and vasoactive agents as required. Construction of the proximal anastomoses to the ascending aorta was performed within a single aortic side-biting clamp period, with the systolic arterial pressure maintained around 100 mm Hg to minimize aortic trauma.

Assessment of liver function

a. Conventional liver tests

Venous blood was collected from the radial artery into lithium-heparin tubes the day before surgery and then at 1, 6, 24 hours and 2 and 5 days postoperatively. The blood was centrifuged for 10 minutes at 2700 rounds per minute and conventional liver function tests (ALT, AST, ALP, CB, TB) were performed using the ADVIA system (Bayer Diagnostics, Newbury, UK).

b. MEGX test

This was performed in a subgroup of patients, as the test was not available in our laboratory at the beginning of this study. Hepatic function was assessed with the MEGX test twice, after anaesthetic induction and then 6 hours postoperatively. For each test the serum concentration of monoethylglycinexylidide was measured 0 and 15 minutes after central venous administration of 1mg/kg Lignocaine. Blood samples

were collected from the radial artery into EDTA-containing glass tubes. The samples were immediately centrifuged in a refrigerated centrifuge to separate the plasma, which was subsequently frozen and stored at -70°C until assayed.

Statistical analysis

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 if normal distribution could not be assumed. Categorical variables were compared using the Pearson's chi-square or Fisher's exact test as appropriate. For the conventional liver function tests, repeated measures analysis of covariance using the baseline measurement as a covariate was used to assess the effect of time, group and group-time interaction on outcome. For the MEGX test, a one-sample Student *t*-test was used to compare outcome within a group to baseline values, while a two-sample *t*-test was used to compare outcome between the groups. The Statistical Package for Social Sciences (SPSS) version 10.1 software was used for all descriptive statistics and inferential testing. A p value of less than 0.05 was considered statistically significant.

RESULTS

Demographics, operative data and clinical outcome

The demographic variables for the two groups are presented in Table 8-2. As outlined in the methods, these were low-risk cases and there were no significant differences between the groups.

Table 8-3 summarizes the intraoperative data and clinical outcome. The groups had a similar extent of revascularization and only few patients required inotropic support for a cardiac index below the target value of 2.2 L/min/m^2. Clinical outcome was similar in the two groups. No mortality or major complications, such as myocardial infarction, major neurological complications or end-organ failure were observed. No patient required the use of an intraaortic balloon pump.

Table 8-2. Patient characteristics.

Variable	ONCAB (n=30)	OPCAB (n=28)	*p* value
Age	64.3 ± 8.2	60.8 ± 7.7	0.21
Gender			0.89
Male	22	21	
Female	8	7	
CCS angina class			0.45
I	8	5	
II	12	11	
III	9	9	
IV	1	3	
Previous MI	7	6	0.76
Hypertension	14	11	0.82
Morbid obesity	2	1	0.59
Parsonnet score	3.0 (0.0 - 4.0)	3.0 (0.0 - 3.0)	0.97

CCS, Canadian Cardiovascular Society; MI, Myocardial Infarction.

Age is presented as mean ± standard deviation.

Parsonnet score is presented as median and interquartile range.

Table 8-3. Intraoperative data and clinical outcome.

Variable	ONCAB (n=30)	OPCAB(n=28)	*p* value
Distal anastomoses	2.8 ± 1.0	2.4 ± 0.9	.32
CPB time (min)	59.1 ± 24.2		
AXC time (min)	31.0 ± 10.5		
Time to extubation (hr)	4.5 (3.5-7.0)	4.5 (3.5-7.0)	.87
ICU length of stay (d)	1.0 (1.0-1.5)	1.0 (1.0-2.0)	.50
Perioperative low CI	1	1	1
Supraventricular arrhythmia	8	5	.34
Pneumonia	2	3	.81
Wound infection	1	1	1
Postoperative hospital stay (d)	6.8±2.4	6.5±2.2	.72

CPB, cardiopulmonary bypass; AXC, aortic cross-clamping; ICU, intensive care unit; CI, cardiac index. Low CI is defined as below 2.2 L/min/m^2. ICU length of stay and hospital stay are presented as median with interquartile range. Other continuous variables are presented as mean ± standard deviation.

Total and Conjugated Bilirubin

The total (TB) and conjugated (CB) bilirubin measurements for the two groups are presented in Table 8-4 and are displayed graphically over time in Figures 8-1 and 8-2. No patient had biochemical evidence of jaundice (TB >50 μmol/L) at any time point. There were no baseline differences between the groups (TB: ONCAB, 12.8 ± 5.1, vs. OPCAB 13.2 ± 5.6, p= 0.92; CB: ONCAB 3.0 ± 1.5, vs. OPCAB 2.5 ± 1.4, p= 0.49). Repeated measures analysis of covariance showed a significant effect of time (p<0.001) on both total bilirubin and conjugated bilirubin measurements, however the interaction of group with time did not have a significant effect on outcome (TB p= 0.15, CB p= 0.53).

Table 8-4. Total and conjugated bilirubin in the two groups.

	ONCAB		**OPCAB**	
	TB	**CB**	**TB**	**CB**
Baseline	12.8 ± 5.1	3.0 ± 1.5	13.2 ± 5.6	2.5 ± 1.4
1 hr	11.1 ± 3.6	4.6 ± 2.2	11.1 ± 4.8	4.4 ± 2.9
6 hr	12.4 ± 6.1	5.9 ± 2.9	10.8 ± 3.9	5.9 ± 3.7
24 hr	15.9 ± 6.6	6.7 ± 4.7	13.6 ± 5.4	5.4 ± 3.9
2 days	14.8 ± 4.2	4.6 ± 2.3	13.7 ± 4.1	4.3 ± 2.2
5 days	16.2 ± 4.1	4.0 ± 1.8	13.7 ± 4.2	3.9 ± 1.5

TB = total bilirubin, CB = conjugated bilirubin.

All results are in μmol/L. The results are expressed as mean ± SD.

Figure 8-1. Perioperative TB levels in the two groups. The error bars represent the standard deviation around the mean (for clarity only the negative error bars are displayed for the OPCAB group and the positive for the ONCAB). The reference range is 7-17 μmol/L.

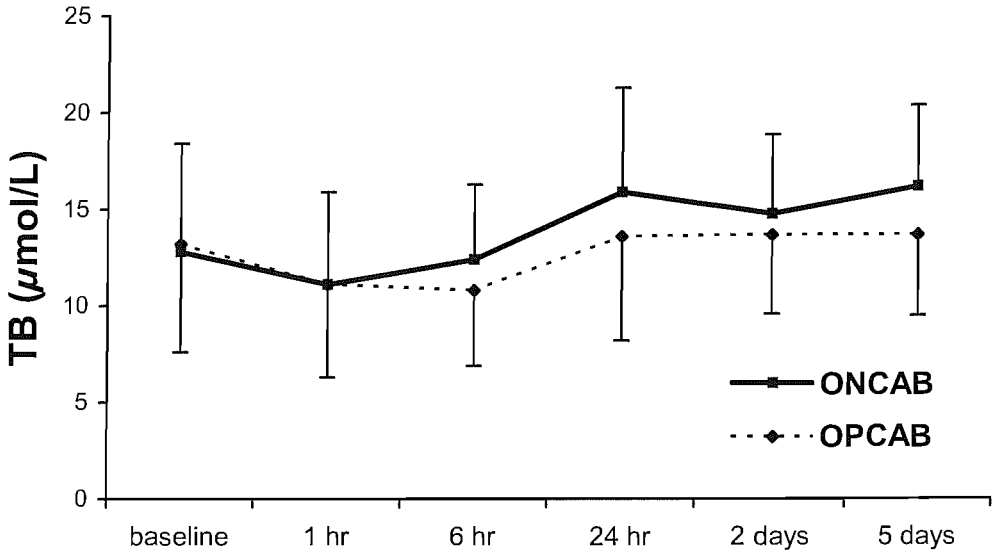
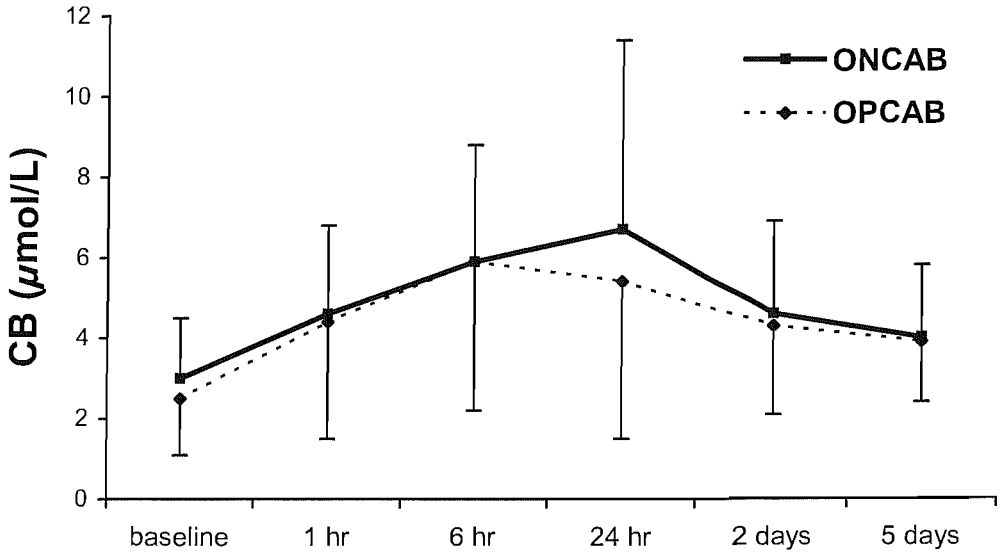


Figure 8-2. Perioperative CB levels in the two groups. The error bars represent the standard deviation around the mean (for clarity only the negative error bars are displayed for the OPCAB group and the positive for the ONCAB).



Alkaline Phosphatase

The ALP measurements for the two groups are presented in Table 8-5 and displayed graphically over time in figure 8-3.

Table 8-5. Perioperative ALP levels in the two groups.

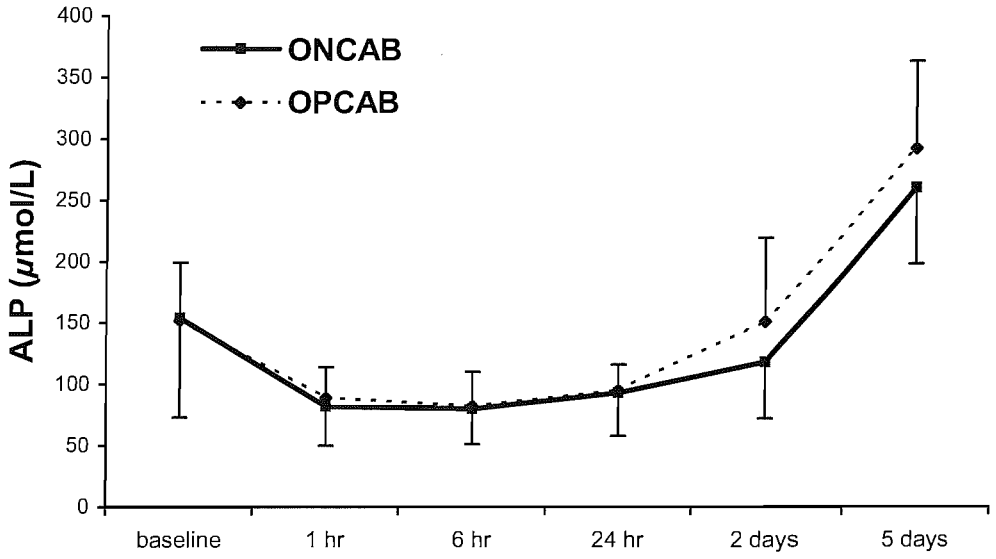
	ONCAB	**OPCAB**
Baseline	154 ± 81	152 ± 47
1 hr	82 ± 32	89 ± 25
6 hr	80 ± 29	82 ± 28
24 hr	93 ± 35	95 ± 21
2 day	118 ± 46	151 ± 68
5 day	260 ± 62	292 ± 71

ALP = Alkaline phosphatase.

Results are in IU/L. Results are expressed as mean ± SD.

There was an initial fall in the ALP values in the first 24 hours after surgery, followed by a progressive rise, with ALP values 5 days postoperatively significantly higher than baseline values. Although mean ALP values remained below the upper normal range (460 IU/L), 4 patients had ALP>460 at 5 days postoperatively. Three of these patients were in the on-pump and one in the off-pump group (p= 0.60). This was not associated with an adverse effect on outcome. There was no baseline difference between the groups (p= 0.93). Repeated measures analysis of covariance showed a significant effect of time (p<0.001) on ALP measurements, however the interaction of group with time did not have a significant effect on outcome (p= 0.34).

Figure 8-3. Perioperative ALP levels in the two groups. The error bars represent the standard deviation around the mean (for clarity only the negative error bars are displayed for the ONCAB group and the positive for the OPCAB).



Alanine Aminotransferase & Aspartate Transaminase

The ALT and AST measurements for the two groups are presented in Table 8-6 and are displayed graphically over time in figures 8-4 and 8-5 respectively.

Table 8-6. ALT and AST levels in the two groups.

	ONCAB		**OPCAB**	
	ALT	**AST**	**ALT**	**AST**
Baseline	27.6 ± 12.4	24.6 ± 9.0	37.4 ± 20.6	26.8 ± 14.1
1 hr	18.6 ± 6.7	31.5 ± 9.6	27.5 ± 9.3	26.9 ± 10.4
6 hr	19.9 ± 7.8	35.9 ± 11.5	26.6 ± 13.8	30.2 ± 18.4
24 hr	23.0 ± 9.6	41.4 ± 21.2	30.5 ± 12.2	40.3 ± 18.4
2 day	28.4 ± 12.4	38.2 ± 18.9	35.2 ± 11.0	41.7 ± 22.0
5 day	53.6 ± 31.5	47.4 ± 30.8	53.9 ± 36.0	52.7 ± 39.5

ALT= Alanine Aminotransferase, AST= Aspartate Transaminase

The results are presented as IU/L. The reference ranges are: ALT, 5-42 IU/L and AST, 5-42 IU/L.

ALT and AST showed a progressive in the postoperative period, and the mean ALT and AST on the 5th postoperative day was higher than the upper Normal range (42 IU/L for both enzymes). Repeated measures analysis of covariance showed a significant effect of time ($p<0.001$) on ALT and AST measurements, however there was no difference between the groups over time (ALT; $p=0.68$, AST; $p=0.57$).

Figure 8-4. Perioperative ALT levels in the two groups. The error bars represent the standard deviation around the mean (for clarity only the negative error bars are displayed for the ONCAB group and the positive for the OPCAB).

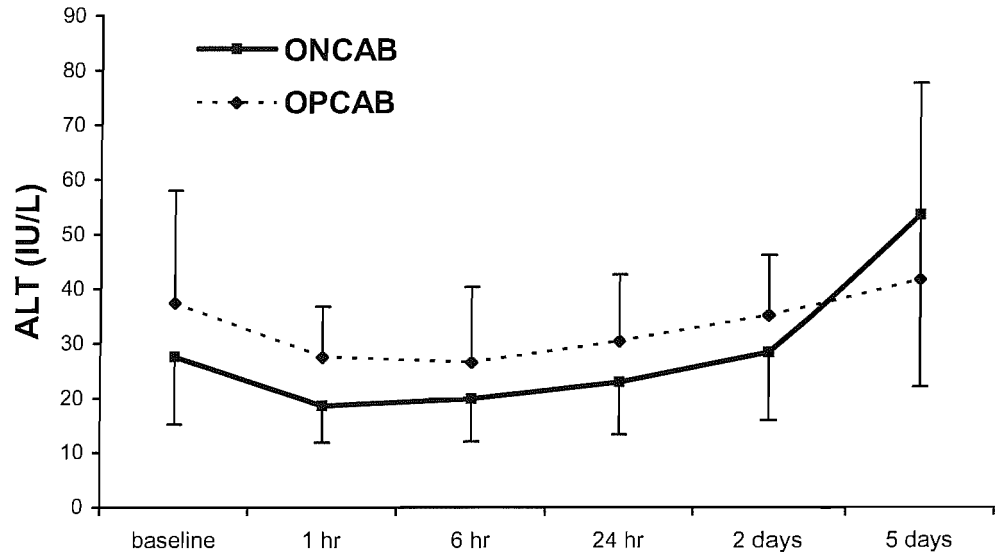
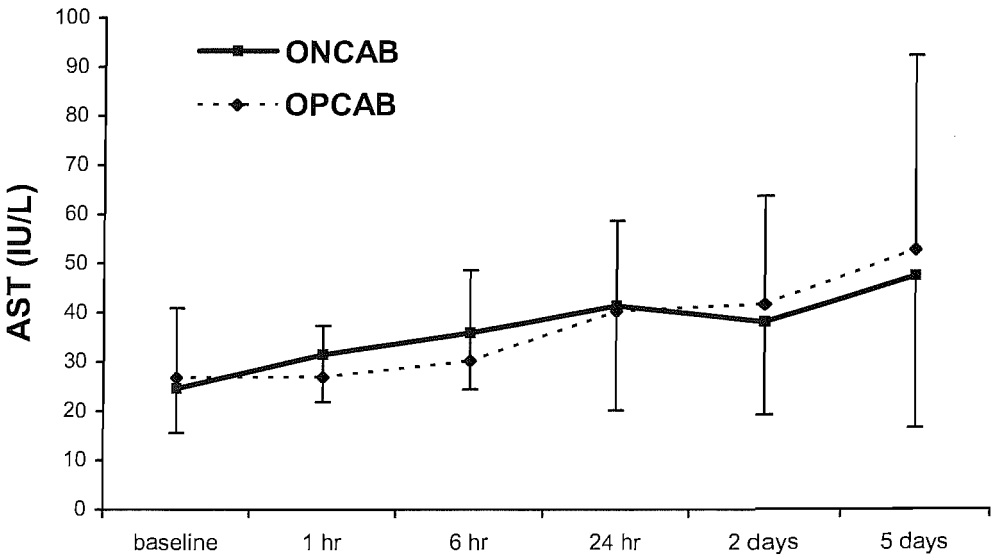


Figure 8-5. Perioperative AST levels in the two groups. The error bars represent the standard deviation around the mean (for clarity only the negative error bars are displayed for the ONCAB group and the positive for the OPCAB).



Monoethylglycinexylidide formation (MEGX test)

The test was performed in 16 patients, 8 in each group. No adverse events to the injection of lignocaine were noted. In the ONCAB group, MEGX levels 15 minutes after lignocaine injection were 132 ± 29 ng/ml during anaesthetic induction, and they decreased to 115 ± 20 ng/ml at the postoperative test. This difference was not statistically significant (p= 0.13).

In the OPCAB group, MEGX levels 15 minutes post-lignocaine injection decreased from 126 ± 21 ng/ml at baseline, to 112 ± 24 ng/ml 6 hours postoperatively. This difference was not significant (p= 0.28).

There were no significant differences between the groups either at baseline (p= 0.85) or at the postoperative test (p= 0.91).

DISCUSSION

The absence of GI complications or any major morbidity in this study is not surprising, given the low-risk profile of the patient population. As discussed in chapter 6, the incidence of GI complications in cardiac surgery is under 1% in most studies (Ohri et al. 1991). The absence of clinically apparent hyperbilirubinaemia (TB >50 μmol/L) in the CPB group may initially appear surprising, given the relatively high incidence of transient jaundice after cardiac surgery reported previously (Collins et al. 1983; Chu et al. 1984; Wang et al. 1994). As discussed in the background section of this chapter these studies have reported an incidence of postoperative jaundice ranging between 20 and 35% of the cases. However, the above-mentioned studies included significantly more heterogeneous patient populations than the one examined in this study. The incidence of jaundice in the CABG subgroups in these studies was significantly lower, ranging between 8 and 11%. These studies revealed preoperative right heart function (Chu et al. 1984; Wang et al. 1994) as the most important predicting factor for postoperative hyperbilirubinaemia. Other prognostic factors were valvular surgery, prolonged CPB time, perioperative episodes of hypoxia or hypotension and preoperative bilirubin levels. The patients recruited in this study had normal biventricular function, relatively short CPB times, relatively uneventful perioperative course and normal preoperative LFTs, therefore the absence of postoperative jaundice is not unexpected. The modest rises in ALP, AST and ALT observed in this study in the CPB group are in keeping with previous observations (Collins et al. 1983; Wang et al. 1994). As previously discussed SIELI is very uncommon after cardiac surgery and occurred in 20 out of 1800 cases in a previous study (Raman et al. 2002).

The crucial role of right ventricular dysfunction and elevated central venous pressure in the development of hepatic congestion and dysfunction is also supported from studies in patients with congestive cardiac failure (CCF) and the Fontan population. Mild elevation of TB, ALP, ALT and AST with no clinical signs of hepatic failure are often seen in patients with CCF causing passive hepatic congestion, reduced hepatic perfusion or both (Naschitz et al. 2000). Kubo et al (Kubo et al. 1987)

examined the association between severity of CCF, determined by the severity of reduction in CI and elevation of right-sided filling pressures, and hepatic dysfunction, measured by LFTs. They found significant correlation between right atrial pressure and LFTs, pulmonary capillary wedge pressure and LFTs and a negative correlation between CI and LFTs. In other words, higher filling pressures and a lower cardiac index were both significant in the development of hepatic dysfunction. Interestingly, all the correlation coefficients were small, suggesting large interpatient variability. However, the data demonstrated that passive congestion and reduced systemic perfusion were both important in the development of liver function abnormalities. Abnormal LFTs, mainly reflecting cholestasis, but also with coagulation abnormalities are also very common in patients who have undergone the Fontan procedure or one of its modifications (van Nieuwenhuizen et al. 1999; Narkewicz et al. 2003). In one study there were liver function test abnormalities in 21 out of 28 patients (van Nieuwenhuizen et al. 1999), with bilirubin levels showing a correlation with time since surgery. In another study, Narkewicz et al (Narkewicz et al. 2003) demonstrated abnormal galactose elimination half-life in 10 out of 10 patients who had undergone the Fontan procedure. Interestingly, galactose elimination half-life was greater in patients with a dilated inferior vena cava, which would suggest further that in the univentricular circulation of Fontan patients, elevated systemic venous pressures play a pivotal role in the development of hepatic congestion and liver dysfunction.

The important role of the right-sided circulation in the development of liver function abnormalities would possibly explain why mild abnormalities in LFTs, of comparable magnitude to the CPB group, were also observed in the OPCAB group in this study. Several studies have documented the presence of significant transient haemodynamic impairment during distal anastomoses in OPCAB (Grundeman et al. 1997; Mathison et al. 2000; Nierich et al. 2000; Watters et al. 2001) and this was confirmed in chapter 2 of this thesis. Significant drops in cardiac output occur despite relatively well-preserved systemic arterial pressures, especially during grafting of the less accessible coronary targets that require cardiac verticalization. Right ventricular dysfunction is the predominant factor causing haemodynamic

instability during OPCAB (Porat et al. 2000), as the right heart chambers undergo compression during cardiac elevation against the surrounding fibrous pericardium and pleura (Grundeman et al. 1999). One would assume that the repeated episodes of transient RV dysfunction that occurred in the OPCAB group were sufficient to cause mild elevations in the LFTs comparable to the CPB group.

However, in this study only low-risk patients with normal cardiac and liver function were studied. This strategy was adopted to ensure homogeneity of the groups, which is essential in prospective randomised studies with small numbers of patients. However, patients with poor left ventricular function or preoperative liver dysfunction may behave differently and the results of this study cannot be extrapolated to such populations. As discussed in the background section of this chapter, although there is very few data on patients with hepatic disease undergoing OPCAB, it would appear that OPCAB may lead to a better outcome compared to surgery with CPB in these patients (Hayashida et al. 2004; Lin et al. 2005). However, the available data is only on very few successfully performed cases, and further studies into high-risk patients investigating liver function using the OPCAB approach vs. CPB are required. Such studies will generate useful evidence as to whether OPCAB confers a liver protection advantage in patients who are at risk of developing perioperative hepatic dysfunction, such as patients with right ventricular dysfunction.

The use of mildly hypothermic CPB with pulsatile flow reflects current practice at the Wessex Cardiothoracic Centre but more importantly it may have had a significant effect on study findings, as the CPB protocol has been shown to affect hepatic blood flow. In an experimental protocol in dogs undergoing CPB and deep hypothermic circulatory arrest, Mori et al (Mori et al. 1988) demonstrated superior hepatic blood flow with pulsatile vs. nonpulsatile CPB. However, the effect of temperature on hepatic blood flow during CPB is probably more important than pulsatility. Using the galactose clearance technique, Hampton et al observed a mean reduction in hepatic blood flow of 19% during hypothermic nonpulsatile CPB (Hampton et al. 1989). Mathie et al studied the effect of both pulsatility and temperature during CPB on

hepatic blood flow by using the indocyanine green clearance technique (Mathie et al. 1997). The authors observed that normothermic (37°C) CPB was associated with superior preservation of hepatic blood flow compared to hypothermic (28°C) CPB and there was no significant difference between pulsatile and nonpulsatile groups at normothermia. Chetty et al (Chetty et al. 2004) also observed a significant reduction in hepatic blood flow, assessed by indocyanine green clearance, during hypothermic (30°C) CPB. The effect of temperature on hepatic blood flow may be another reason why the results in the presented study in the CPB group compare very favourably to previous studies on post-CPB hepatic dysfunction (Chu et al. 1984; Wang et al. 1994), where a hypothermic CPB protocol was used.

A standardized and similar anaesthetic and haemodynamic management protocol was followed in both groups, so that the study findings would not be confounded by the effect of various anaesthetic agents and inotropes on hepatic blood flow and metabolism. In an experimental protocol during CPB in beagles, Koizumi et al (Koizumi et al. 1998) observed a reduction in hepatic blood flow with increased doses of fentanyl anaesthesia. Mitchell et al (Mitchell et al. 1995) investigated the effect of dopamine infusion on liver blood flow in children with congenital heart disease undergoing CPB. They observed that in the early postoperative period, the addition of Dopamine infusion resulted in increased hepatic perfusion, evidenced by a 31% increased clearance of indocyanine green. Sharpe et al (Sharpe et al. 1999) also documented a rise in hepatic blood flow in the early post-CPB period with a dopamine or dopexamine infusion, and the effect of the two drugs on hepatic perfusion was similar.

The results of the MEGX test in this study suggest satisfactory hepatic perfusion and metabolism in both OPCAB and CPB patients at 6 hours postoperatively. Although there is a relative lack of experience with this test, values above 90 ng/ml 15 minutes after injecting 1mg/kg lignocaine are thought to represent normal hepatic function (Kumle et al. 2003). Although there was a non-significant drop compared to baseline values, the results in both groups at 6 hours postoperatively were above that level and there was no difference between the groups. Further experience with the MEGX test

needs to be acquired in cardiac surgical patients so that the value of the test for research and possibly clinical purposes can be fully understood.

In conclusion this study has demonstrated a similar transient decline in liver function during CABG either with or without CPB. We found no evidence however of any significant or clinically important liver injury with either approach. Whether these findings may be applicable to a high-risk patient population also requires further investigation. Our results suggest that off-pump surgery does not confer an advantage over surgery with CPB in preservation of liver function in low risk patients.

Chapter 9

Discussion

Summary and overall discussion of thesis findings

In the introductory chapter to this thesis the problems associated with the use of cardiopulmonary bypass were outlined and some of the relevant pathophysiology was explained, such as the systemic inflammatory response that is triggered by CPB. It was discussed how the costs associated with CPB and the desire to reduce cardiac surgical complications led increasing numbers of surgeons to start performing coronary surgery without CPB (off-pump or OPCAB) in the early 80's. However, despite the fact that coronary surgery remains the most commonly performed cardiac surgical operation, extremely variable practice is observed, with some surgeons currently performing the majority of their coronary surgical workload as OPCAB procedures, while others almost exclusively use CPB. The main reasons for this discrepancy are three: one, the fact that the OPCAB technique does not confer any immediately obvious advantages over CPB, two that long-term outcome with OPCAB remains largely unknown, and three that there is a relative lack of good quality prospective randomised studies in the literature. A review of the literature comparing OPCAB vs. CPB was performed and this identified attenuation of the inflammatory response to surgery and reduced blood loss as the most established advantages of OPCAB over CPB.

One of the main concerns about OPCAB is haemodynamic instability during cardiac manipulation and fashioning of graft to coronary artery anastomosis. Haemodynamic instability during OPCAB has been described in a variety of clinical and experimental settings and, despite its transient occurrence, may lead to clinical or subclinical organ injury in the perioperative period. In Chapter 2 the haemodynamic changes during OPCAB were described using a continuous, real-time cardiac output monitoring technique with the LiDCO^{TM}/PulseCo^{TM} system. The technique offers the distinct advantage of real-time cardiac output monitoring, unlike the thermodilution technique with a pulmonary artery catheter, where only intermittent measurements are obtained, which lack real-time accuracy, as there is a significant response time between acute haemodynamic changes, such as those encountered during OPCAB, and their detection with thermodilution (Haller et al. 1995; Aranda et al. 1998). We observed significant transient decline in cardiac index around the time of cardiac

manipulation and application of the mechanical stabilizer, which then reached a plateau during grafting and fully recovered following completion of anastomosis and removal of the stabilizing device. In agreement with previous studies, mean arterial pressure fell proportionally less due to compensatory tachycardia and vasoconstriction. This demonstrates that routine haemodynamic monitoring in surgical practice that does not involve cardiac output monitoring, may not detect significant intraoperative haemodynamic changes. The study confirmed that there is a significant, albeit transient, haemodynamic deterioration intraoperatively during OPCAB and this is pertinent to our findings in subsequent studies in chapters 4 to 8. Transient haemodynamic deterioration during OPCAB appears to be the main limitation of the technique, which although it may not cause immediate complications, it contributes to end-organ damage at sub-clinical level. Our study also showed that haemodynamic deterioration was more pronounced during grafting of the less accessible coronary targets, that require cardiac verticalization (obtuse marginal and posterior descending arteries).

Previous studies have demonstrated that haemodynamic deterioration during OPCAB is predominantly related to transient right ventricular dysfunction, as the right ventricle undergoes compression between the interventricular septum and fibrous pericardium and pleura during cardiac elevation (Grundeman et al. 1999; Porat et al. 2000). In Chapter 3 we examined the haemodynamic effects of right pleuropericardial release manoeuvre during cardiac verticalization in OPCAB. Following right heart decompression, there was significantly superior preservation of stroke volume, cardiac output and arterial blood pressure during cardiac verticalization. The results provide further evidence for the key role of right heart function on haemodynamic stability during OPCAB and lend strong support for the routine use of a pleuropericardial release manoeuvre during cardiac verticalization in OPCAB.

Having established temporary haemodynamic disturbance as one of the drawbacks of OPCAB, one needs to examine the possible effect of haemodynamic deterioration on perioperative organ function, and, more importantly, how it compares to the

previously described organ injury that occurs during CPB. Several sensitive markers of systemic stress and organ injury were compared, in a prospective randomised fashion, between OPCAB and CPB groups, in chapters 4 to 8 of this thesis.

In chapters 4 and 5 aspects of the endocrine response to surgery were examined, and similar patterns of stress hormonal response and thyroid hormone changes were observed during surgery with and without CPB. In chapter 4 similar transient elevations in stress hormones vasopressin and cortisol were documented after OPCAB vs. CPB. Although elevation in the levels of stress hormones has been described in the context of abdominal surgery (Rutberg et al. 1984), one would intuitively expect more pronounced hormonal changes with the use of CPB. However, stress hormone changes during surgery have been shown to occur mainly as a result of haemodynamic stress (Knight et al. 1986). It would therefore appear that the cumulative effect of transient haemodynamic deterioration during OPCAB results in a systemic stress hormone response of similar magnitude to the one elicited by the use of CPB. Our study on thyroid hormone changes elicited similar findings. The previously described euthyroid sick syndrome response to surgery and CPB was confirmed (Burr et al. 1975; Holland et al. 1991), with both groups demonstrating temporary reduction in free triiodothyronine levels and no compensatory rise in thyroid-stimulating hormone. There was no significant difference between the two groups in the pattern of hormonal changes. Our study also showed that the reduction in free triiodothyronine levels occurred at a time when global oxygen consumption was increased, an observation that lends support to the theory that the perioperative euthyroid sick response represents an adaptive mechanism of the body to stress in an attempt to reduce catabolism and they do not represent a true hypothyroid state. This may explain why attempts to improve cardiac surgical outcome by administering triiodothyronine in the perioperative period have not always been successful in various studies (Klemperer et al. 1995; Bennett-Guerrero et al. 1996; Mullis-Jansson et al. 1999). Our findings of a similar perioperative endocrine milieu between OPCAB and CPB patients may also partly explain the comparable gastrointestinal organ injury that was observed between the two groups in subsequent studies.

In Chapters 6,7 and 8 we turned out attention to the gastrointestinal system. In Chapter 6 the effect of coronary surgery with and without CPB on gut mucosal oxygenation was examined, by measuring the gastric intramucosal pH and the gastric-arterial CO_2gap. Gastric mucosal hypoxia is a very sensitive marker of body response to stress, it has been shown to have an excellent predictive value of outcome in patients in the intensive care and is also thought to be the main underlying pathophysiologic driver of gastrointestinal complications. Our results showed that there was a similar perioperative gastric mucosal hypoxia in both groups in the early postoperative period. This would suggest that although the use of CPB may contribute to the development of gut mucosal hypoxia, perioperative haemodynamic stability is of at least equal significance. We hypothesize that the transient haemodynamic impairment that OPCAB patients sustain intraoperatively, as described in detail in chapter 2, results in gut mucosal hypoxia, which is comparable to the injury sustained by patients undergoing CPB. The results were somewhat limited by the fact that our observations only extended to 6 hours postoperatively, by which point no recovery towards baseline values had commenced. We therefore do not know at which point mucosal hypoxia reaches its lowest values and whether the pattern of decline and recovery are similar in OPCAB and CPB patients. We recommend that future studies investigating gut mucosal hypoxia in cardiac surgical patients monitor the CO_2gap for at least 24 hours if possible. We also demonstrated that mucosal hypoxia occurred at a time when global oxygen extraction fraction was raised, indicating that the gut is most susceptible to injury at times of increased global oxygen demand. This finding is similar to the previously reported association between pHi and SvO_2 (Ohri et al. 1997) and indicates that the gut becomes particularly susceptible to injury at times of haemodynamic stress. The release of endogenous catecholamines and other stress hormones in the perioperative period may play a pivotal role in the increase in global VO_2 and the disturbance in gut oxygen supply and demand ratio. The findings in chapters 4 and 5 of similar hormonal changes in the two groups may provide a further explanation why the avoidance of CPB does not appear to confer a significant advantage in gut mucosal oxygenation.

In chapter 7 the effect of surgery on intestinal absorptive and barrier function was examined. Intestinal absorption and gut permeability were assessed by measuring the urinary extraction of enterally administered saccharides, which is an established method for the assessment of intestinal function (Menzies 1974). We observed a similar decline in both absorptive and gut barrier function in both groups in the immediate postoperative period. This is not surprising, given the findings in previous Chapters, especially the findings of significant and comparable mucosal hypoxia. At 5 days postoperatively we observed that while the intestinal function of OPCAB patients had returned to preoperative values, in the ONCAB group there had been an incomplete recovery of intestinal function, with measurements still significantly different (worse) than preoperative values and those of the OPCAB group. It is difficult to explain why these differences occurred but the most likely explanations are two: a) the two groups may demonstrate a different temporal pattern of recovery from gut mucosal hypoxia, which is the main contributory factor to loss of intestinal function. As mentioned previously, in the study in Chapter 6 any possible differences in the pattern of recovery from mucosal hypoxia in the two groups were not documented, as the CO_2gap was only monitored for up to 6 hours postoperatively. b) there are well-documented differences between OPCAB and CPB in perioperative inflammatory response, with OPCAB patients showing a significant attenuation in systemic postopetative inflammation in most studies. Although the interaction between gut function and inflammatory mediators remains poorly understood, it is likely that differences in the inflammatory response may account for the different pattern of recovery of gut function between the two groups.

Finally, in chapter 8 we examined liver function during coronary surgery with and without CPB. When conventional tests were used, there were transient elevations of bilirubin, ALP, AST and ALT. However, the mean values remained within normal range throughout the perioperative period and more importantly, there were no significant differences between the groups. These findings were confirmed by the MEGX test, which provides a more accurate assessment of the metabolic activity of the liver; this demonstrated a transient reduction in hepatic function in the immediate postoperative period with no significant differences between the groups. It is

important to note that in a prospective study of 248 patients undergoing CPB, Collins et al (Collins et al. 1983) identified right atrial pressure and multiple valve replacements as the only significant prognostic factors for postoperative liver dysfunction, while preoperative alcohol intake, hepatic enzymes and bilirubin were not associated with postoperative liver injury. In another study Chu et al (Chu et al. 1984) documented a 21.7% incidence of hyperbilirubinaemia in patients undergoing congenital cardiac procedures, who often have right-sided cardiac dysfunction. These findings suggest that perioperative liver dysfunction is mainly due to elevated right-sided cardiac pressures, which would cause liver congestion or valve lesions causing tricuspid incompetence. The above are immediately relevant to OPCAB, where transient haemodynamic instability during cardiac positioning is predominantly related to right ventricular compression, resulting in right ventricular dysfunction and elevated right atrial pressures. This may explain why, in the patient population of this study, OPCAB did not confer any additional advantage over surgery with CPB on preservation of liver function.

The future

This thesis has provided strong evidence that, under the conditions of these studies, there is significant subclinical endocrine response and end-organ injury during off-pump surgery, to an extent comparable to surgery with CPB. These findings are likely to be largely related to the transient haemodynamic instability that occurs during OPCAB. Regardless of the precise mechanisms that lead to our findings, what becomes clear from this thesis is that more work is required before the possible advantages and disadvantages of OPCAB over surgery with CPB are fully understood.

Overall, this thesis has demonstrated similar outcome in the areas studied between surgery with CPB and off-pump in patients with good cardiac function and low co-morbidities. However, there may be other patient groups who benefit from one of the two approaches and this must be investigated in further studies. Data from several retrospective studies would suggest that it may be the high-risk patients who get more benefit from the OPCAB approach. This needs to be corroborated by prospective randomised studies, which have the advantage of well-defined patient populations and sensitive outcome measures. Patient groups need to be carefully defined, as for example patients with cardiac dysfunction and no other co-morbidities may respond to OPCAB differently than patients with normal heart function but other problems, such as diabetes, arteriopathy or hepatic dysfunction. Such prospective studies would be the best way to identify what is the best approach for each individual patient.

The effect of cardiac manipulations during OPCAB on gastrointestinal perfusion will need to be studied in more detail in experimental settings. This thesis has provided clinical evidence of acute global haemodynamic disturbance, which manifested with drops in cardiac output and mixed venous oxygen saturation, and subclinical end-organ damage. Experimental animal models will be able to monitor liver and gut perfusion during OPCAB and examine the effect of various surgical manoeuvres or anaesthetic manipulations on organ perfusion. This will enhance our understanding

of organ injury during surgery and may refine our surgical techniques and anaesthetic management during OPCAB.

Immediately related to the above is the fact that the possible beneficial or deleterious effect of various anaesthetic agents or inotropic medication on gastrointestinal perfusion remains largely unknown and often controversial. Some agents that are splanchnic vasodilators, such as dopexamine, may enhance gastrointestinal perfusion and lead to a superior outcome, while the influence of anaesthetic agents on mesenteric blood flow is poorly understood. In this thesis we did not intend to study different anaesthetic strategies and instead we adopted a standardized anaesthetic protocol in both patient groups (on-pump vs. off-pump) so that this would not be a confounding factor to the study findings. However, refinement and optimisation of anaesthetic and haemodynamic management during OPCAB is likely to lead to a real improvement in outcome, especially since haemodynamic instability would appear to be the most important factor causing organ injury. Further research with clinical and experimental models is therefore required on the effects of various anaesthetic agents on gastrointestinal perfusion so that a more appropriate selection of drugs can be made perioperatively.

The time-course of perioperative gastric mucosal hypoxia needs to be further defined. Although we observed gastric mucosal hypoxia in the early postoperative period in both OPCAB and CPB groups, our observation period of up to 6 hours postoperatively was not long enough to observe the recovery of gut mucosal oxygenation state. Any differences in the pattern of recovery of mucosal oxygenation between OPCAB and CPB may be clinically relevant, especially in high-risk patients. The pattern of recovery of gut mucosal oxygenation may be found to be a useful guide for clinical interventions, such as extubation time or a reduction in inotropic support. Similarly, future studies are required to answer whether monitoring gastric mucosal oxygenation can be clinically useful by directing therapeutic interventions, which would aim to maintain the gastric-arterial CO_2gap within a certain range. Clearly a lot of research work is required before the

prognostic and clinical usefulness of gastric tonometry in cardiac surgical patients is fully understood.

Another area that requires further investigation is the relationship between endocrine response to surgery and clinical outcome. In this thesis we were unable to demonstrate a relationship between the magnitude of stress hormonal response and clinical outcome. However, this may be due to the fact that our patient population was a low-risk group that developed very few complications. Further studies in high-risk patients may provide us with a better understanding of how endocrine response relates to clinical outcome and whether we can intervene and manipulate this response in a beneficial way for the patient. The administration for example of thyroxine in patients undergoing CPB has been investigated by several authors and some positive findings have been reported, although the results have been variable. Similar studies have not been performed yet in the context of off-pump surgery.

We are convinced that both off-pump surgery and surgery with CPB have a definite role in modern cardiac surgery. What we do not fully understand yet is which technique is best suited to each individual patient's needs. With this thesis, we hope that we have made a small but useful contribution to that effect.

List of references

Alexiou C, Tang A A, Sheppard S V, Smith D C, Gibbs R, Livesey S A, Monro J L, Haw M P (2004). The effect of leucodepletion on leucocyte activation, pulmonary inflammation and respiratory index in surgery for coronary revascularisation: a prospective randomised study. Eur J Cardiothorac Surg 26: 294-300.

Alfieri A, Kotler M N (1990). Noncardiac complications of open-heart surgery. Am Heart J 119: 149-158.

Angelini G D, Taylor F C, Reeves B C, Ascione R (2002). Early and midterm outcome after off-pump and on-pump surgery in Beating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2): a pooled analysis of two randomised controlled trials. Lancet 359: 1194-1199.

Antonsson J B, Boyle C C, 3rd, Kruithoff K L, Wang H L, Sacristan E, Rothschild H R, Fink M P (1990). Validation of tonometric measurement of gut intramural pH during endotoxemia and mesenteric occlusion in pigs. Am J Physiol 259: G519-523.

Aranda M, Mihm F G, Garrett S, Mihm M N, Pearl R G (1998). Continuous cardiac output catheters: delay in in vitro response time after controlled flow changes. Anesthesiology 89: 1592-1595.

Ascione R, Caputo M, Calori G, Lloyd C T, Underwood M J, Angelini G D (2000). Predictors of atrial fibrillation after conventional and beating heart coronary surgery: A prospective, randomized study. Circulation 102: 1530-1535.

Ascione R, Lloyd C T, Gomes W J, Caputo M, Bryan A J, Angelini G D (1999). Beating versus arrested heart revascularization: evaluation of myocardial function in a prospective randomized study. Eur J Cardiothorac Surg 15: 685-690.

Ascione R, Lloyd C T, Underwood M J, Gomes W J, Angelini G D (1999). On-pump versus off-pump coronary revascularization: evaluation of renal function. Ann Thorac Surg 68: 493-498.

Ascione R, Lloyd C T, Underwood M J, Lotto A A, Pitsis A A, Angelini G D (1999). Economic outcome of off-pump coronary artery bypass surgery: a prospective randomized study. Ann Thorac Surg 68: 2237-2242.

Ascione R, Lloyd C T, Underwood M J, Lotto A A, Pitsis A A, Angelini G D (2000). Inflammatory response after coronary revascularization with or without cardiopulmonary bypass. Ann Thorac Surg 69: 1198-1204.

Ascione R, Nason G, Al-Ruzzeh S, Ko C, Ciulli F, Angelini G D (2001). Coronary revascularization with or without cardiopulmonary bypass in patients with preoperative nondialysis-dependent renal insufficiency. Ann Thorac Surg 72: 2020-2025.

Ascione R, Williams S, Lloyd C T, Sundaramoorthi T, Pitsis A A, Angelini G D (2001). Reduced postoperative blood loss and transfusion requirement after beating-heart coronary operations: a prospective randomized study. J Thorac Cardiovasc Surg 121: 689-696.

Athanasiou T, Aziz O, Mangoush O, Al-Ruzzeh S, Nair S, Malinovski V, Casula R, Glenville B (2004). Does off-pump coronary artery bypass reduce the incidence of post-operative atrial fibrillation? A question revisited. Eur J Cardiothorac Surg 26: 701-710.

Athanasiou T, Aziz O, Mangoush O, Weerasinghe A, Al-Ruzzeh S, Purkayastha S, Pepper J, Amrani M, Glenville B, Casula R (2004). Do off-pump techniques reduce the incidence of postoperative atrial fibrillation in elderly patients undergoing coronary artery bypass grafting? Ann Thorac Surg 77: 1567-1574.

Aun F, Medeiros-Neto G A, Younes R N, Birolini D, de Oliveira M R (1983). The effect of major trauma on the pathways of thyroid hormone metabolism. J Trauma 23: 1048-1051.

Autschbach R, Falk V, Lange H, Oellerich M, Walther T, Mohr F W, Dalichau H (1996). Assessment of metabolic liver function and hepatic blood flow during cardiopulmonary bypass. Thorac Cardiovasc Surg 44: 76-80.

Bacha E A, Hardin J, Cronin D C, Brady L, Millis M J, Starr J P, Koenig P, Daves S, Kahana M (2004). Open-heart surgery in pediatric patients with end-stage liver disease. Ann Thorac Surg 78: e30-33.

Baker J B, Bentall H H, Dreyer B, Melrose D G (1957). Arrest of isolated heart with potassium citrate. Lancet 273: 555-559.

Band D M, Linton R A, O_Brien T K, Jonas M M, Linton N W (1997). The shape of indicator dilution curves used for cardiac output measurement in man. 498 (Pt 1): 225-229.

Beck C S, Tichy V L (1934). The production of a collateral circulation to the heart; an experimental study. Am Heart J 1: 17.

Bell G I, Kayano T, Buse J B, Burant C F, Takeda J, Lin D, Fukumoto H, Seino S (1990). Molecular biology of mammalian glucose transporters. Diabetes Care 13: 198-208.

Benetti F J (1985). Direct coronary surgery with saphenous vein bypass without either cardiopulmonary bypass or cardiac arrest. J Cardiovasc Surg (Torino) 26: 217-222.

Bennett-Guerrero E, Jimenez J L, White W D, D_Amico E B, Baldwin B I, Schwinn D A (1996). Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery. A randomized, double-blind, placebo- controlled trial. Duke T3 study group. JAMA 275: 687-692.

Bergofsky E H (1964). Determination of Tissue O2 Tensions by Hollow Visceral Tonometers: Effect of Breathing Enriched O2 Mixtures. J Clin Invest 43: 193-200.

Bergsland J, Karamanoukian H L, Soltoski P R, Salerno T A (1999). "Single suture" for circumflex exposure in off-pump coronary artery bypass grafting. Ann Thorac Surg 68: 1428-1430.

Berkenboom G, Giot C, Unger P, Vachiery J L, Antoine M, LeClerc J L (1995). Plasma endothelin and early coronary endothelial dysfunction in recipients of a

cardiac transplant. Am Heart J 129: 1178-1184.

Bizouarn P, Ausseur A, Desseigne P, Le Teurnier Y, Nougarede B, Train M, Michaud J L (1999). Early and late outcome after elective cardiac surgery in patients with cirrhosis. Ann Thorac Surg 67: 1334-1338.

Bjarnason I, MacPherson A, Hollander D (1995). Intestinal permeability: an overview. Gastroenterology 108: 1566-1581.

Bjarnason I, Peters T J, Levi A J (1986). Intestinal permeability: clinical correlates. Dig Dis 4: 83-92.

Bjorck M, Hedberg B (1994). Early detection of major complications after abdominal aortic surgery: predictive value of sigmoid colon and gastric intramucosal pH monitoring. Br J Surg 81: 25-30.

Blijlevens N M, Donnelly J P, DePauw B E (2005). Inflammatory response to mucosal barrier injury after myeloablative therapy in allogeneic stem cell transplant recipients. Bone Marrow Transplant 36: 703-707.

Bond J H, Prentiss R A, Levitt M D (1979). The effects of feeding on blood flow to the stomach, small bowel, and colon of the conscious dog. J Lab Clin Med 93: 594-599.

Booker P D, Prosser D P, Franks R (1996). Effect of hypothermia on rectal mucosal perfusion in infants undergoing cardiopulmonary bypass. Br J Anaesth 77: 591-596.

Braun J P, Schroeder T, Buehner S, Dohmen P, Moshirzadeh M, Grosse J, Streit F, Schlaefke A, Armstrong V W, Oellerich M, Lochs H, Konertz W, Kox W J, Spies C (2004). Splanchnic oxygen transport, hepatic function and gastrointestinal barrier after normothermic cardiopulmonary bypass. Acta Anaesthesiol Scand 48: 697-703.

Breckenridge I M, Digerness S B, Kirklin J W (1970). Increased extracellular fluid after open intracardiac operation. Surg Gynecol Obstet 131: 53-56.

Bremner W F, Taylor K M, Baird S, Thomson J E, Thomson J A, Ratcliffe J G, Lawrie T D, Bain W H (1978). Hypothalamo-pituitary-thyroid axis function during cardiopulmonary bypass. J Thorac Cardiovasc Surg 75: 392-399.

Broitman S A, Bondy D C, Yachnin I, Hoskins L C, Ingbar S, Zamcheck N (1964). Absorption And Disposition Of D-Xylose In Thyrotoxicosis And Myxedema. N Engl J Med 270: 333-337.

Buckberg G D (1990). Oxygenated cardioplegia: blood is a many splendored thing. Ann Thorac Surg 50: 175-177.

Buffolo E, Andrade J C, Succi J, Leao L E, Gallucci C (1985). Direct myocardial revascularization without cardiopulmonary bypass. Thorac Cardiovasc Surg 33: 26-29.

Buket S, Alayunt A, Ozbaran M, Hamulu A, Discigil B, Cetindag B, Ozkilic H, Balkan Z, Bilkay O, Durmaz I (1994). Effect of pulsatile flow during cardiopulmonary bypass on thyroid hormone metabolism. Ann Thorac Surg 58: 93-96.

Bull D A, Neumayer L A, Stringham J C, Meldrum P, Affleck D G, Karwande S V (2001). Coronary artery bypass grafting with cardiopulmonary bypass versus off-pump cardiopulmonary bypass grafting: does eliminating the pump reduce morbidity and cost? Ann Thorac Surg 71: 170-173.

Buller W K, Vineberg A M (1954). A study of the amount of blood and oxygen delivered to the myocardium through the implanted mammary artery. Surg Forum 5: 78-84.

Burger A, Nicod P, Suter P, Vallotton M B, Vagenakis P, Braverman L (1976). Reduced active thyroid hormone levels in acute illness. Lancet 1: 653-655.

Burr W A, Black E G, Griffiths R S, Hoffenberg R (1975). Serum triiodothyronine and reverse triiodothyronine concentrations after surgical operation. Lancet 2: 1277-1279.

Burton A C (1966). Role of geometry, of size and shape, in the microcirculation. Fed Proc 25: 1753-1760.

Byrne J G, Appleyard R F, Sun S C, Couper G S, Sloane J A, Laurence R G, Cohn L H (1993). Cardiac-derived thromboxane A2. An initiating mediator of reperfusion injury? J Thorac Cardiovasc Surg 105: 689-693.

Byrne J G, Smith W J, Murphy M P, Couper G S, Appleyard R F, Cohn L H (1992). Complete prevention of myocardial stunning, contracture, low-reflow, and edema after heart transplantation by blocking neutrophil adhesion molecules during reperfusion. J Thorac Cardiovasc Surg 104: 1589-1596.

Carr C, Desai J (2004). OPCAB surgery in a cirrhotic hepatocellular carcinoma patient awaiting liver transplant. Ann Thorac Surg 78: 1460-1462.

Carrel A (1910). On the experimental surgery of the thoracic aorta and the heart. Ann Thorac Surg 52: 83.

Carter J N, Eastman C J, Corcoran J M, Lazarus L (1974). Effect of severe, chronic illness on thyroid function. Lancet 2: 971-974.

Cave A C, Manche A, Derias N W, Hearse D J (1993). Thromboxane A2 mediates pulmonary hypertension after cardiopulmonary bypass in the rabbit. J Thorac Cardiovasc Surg 106: 959-967.

Chadwick V S, Phillips S F, Hofmann A F (1977). Measurements of intestinal permeability using low molecular weight polyethylene glycols (PEG 400). I. Chemical analysis and biological properties of PEG 400. Gastroenterology 73: 241-246.

Chadwick V S, Phillips S F, Hofmann A F (1977). Measurements of intestinal permeability using low molecular weight polyethylene glycols (PEG 400). II. Application to normal and abnormal permeability states in man and animals. Gastroenterology 73: 247-251.

Chan V, Wang C, Yeung R T (1978). Pituitary-thyroid responses to surgical stress.

Acta Endocrinol (Copenh) 88: 490-498.

Chapman M V, Mythen M G, Webb A R, Vincent J L (2000). Report from the meeting: Gastrointestinal Tonometry: State of the Art. 22nd-23rd May 1998, London, UK. Intensive Care Med 26: 613-622.

Chello M, Mastroroberto P, Quirino A, Cuda G, Perticone F, Cirillo F, Covino E (2002). Inhibition of neutrophil apoptosis after coronary bypass operation with cardiopulmonary bypass. Ann Thorac Surg 73: 123-129.

Chenoweth D E, Cooper S W, Hugli T E, Stewart R W, Blackstone E H, Kirklin J W (1981). Complement activation during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxins. N Engl J Med 304: 497-503.

Chetty G, Sharpe D A, Nandi J, Butler S J, Mitchell I M (2004). Liver blood flow during cardiac surgery. Perfusion 19: 153-156.

Chopra I J, Chopra U, Smith S R, Reza M, Solomon D H (1975). Reciprocal changes in serum concentrations of 3,3',5-triiodothyronine (T3) in systemic illnesses. J Clin Endocrinol Metab 41: 1043-1049.

Chopra I J, Smith S R (1975). Circulating thyroid hormones and thyrotropin in adult patients with protein-calorie malnutrition. J Clin Endocrinol Metab 40: 221-227.

Christenson J T, Schmuziger M, Maurice J, Simonet F, Velebit V (1994). Gastrointestinal complications after coronary artery bypass grafting. J Thorac Cardiovasc Surg 108: 899-906.

Chu C M, Chang C H, Liaw Y F, Hsieh M J (1984). Jaundice after open heart surgery: a prospective study. Thorax 39: 52-56.

Chu S H, Huang T S, Hsu R B, Wang S S, Wang C J (1991). Thyroid hormone changes after cardiovascular surgery and clinical implications. Ann Thorac Surg 52: 791-796.

Chun-Hsiu Y, Bang-Yu C, W I S (1981). Preliminary observations on physiological

effects of pulsatile cardiopulmonary bypass in animals. Trans Am Soc Artif Intern Organs 27: 480-484.

Clark R E (1993). Cardiopulmonary bypass and thyroid hormone metabolism. Ann Thorac Surg 56: S35-41.

Clermont G, Vergely C, Jazayeri S, Lahet J J, Goudeau J J, Lecour S, David M, Rochette L, Girard C (2002). Systemic free radical activation is a major event involved in myocardial oxidative stress related to cardiopulmonary bypass. Anesthesiology 96: 80-87.

Collins J D, Bassendine M F, Ferner R, Blesovsky A, Murray A, Pearson D T, James O F (1983). Incidence and prognostic importance of jaundice after cardiopulmonary bypass surgery. Lancet 1: 1119-1123.

Corson R J, Paterson I S, O'Dwyer S T, Rowland P, Kirkman E, Little R A, McCollum C N (1992). Lower limb ischaemia and reperfusion alters gut permeability. Eur J Vasc Surg 6: 158-163.

Cox C M, Ascione R, Cohen A M, Davies I M, Ryder I G, Angelini G D (2000). Effect of cardiopulmonary bypass on pulmonary gas exchange: a prospective randomized study. Ann Thorac Surg 69: 140-145.

Cox C M, Ascione R, Cohen A M, Davies I M, Ryder I G, Angelini G D (2000). Effect of cardiopulmonary bypass on pulmonary gas exchange: a prospective randomized study. Ann Thorac Surg 69: 140-145.

Craig R M, Murphy P, Gibson T P, Quintanilla A, Chao G C, Cochrane C, Patterson A, Atkinson A J, Jr. (1983). Kinetic analysis of D-xylose absorption in normal subjects and in patients with chronic renal failure. J Lab Clin Med 101: 496-506.

Creteur J, De Backer D, Vincent J L (1997). Monitoring gastric mucosal carbon dioxide pressure using gas tonometry: in vitro and in vivo validation studies. Anesthesiology 87: 504-510.

Croughwell N D, Newman M F, Lowry E, Davis R D, Landolfo K P, White W D, Kirchner J L, Mythen M G (1997). Effect of temperature during cardiopulmonary bypass on gastric mucosal perfusion. Br J Anaesth 78: 34-38.

Csaky T Z, Lassen U V (1964). Active intestinal transport of D-xylose. Biochim Biophys Acta 82: 215-217.

Czerny M, Baumer H, Kilo J, Zuckermann A, Grubhofer G, Chevtchik O, Wolner E, Grimm M (2001). Complete revascularization in coronary artery bypass grafting with and without cardiopulmonary bypass. Ann Thorac Surg 71: 165-169.

D'Ancona G, Baillot R, Poirier B, Dagenais F, de Ibarra J I, Bauset R, Mathieu P, Doyle D (2003). Determinants of gastrointestinal complications in cardiac surgery. Tex Heart Inst J 30: 280-285.

Dahlqvist A (1962). Specificity of the human intestinal disaccharidases and implications for hereditary disaccharide intolerance. J Clin Invest 41: 463-470.

Davies S W, Duffy J P, Wickens D G, Underwood S M, Hill A, Alladine M F, Feneck R O, Dormandy T L, Walesby R K (1993). Time-course of free radical activity during coronary artery operations with cardiopulmonary bypass. J Thorac Cardiovasc Surg 105: 979-987.

Dawson A M, Trenchard D, Guz A (1965). Small bowel tonometry: assessment of small gut mucosal oxygen tension in dog and man. Nature 206: 943-944.

Dawson D J, Lobley R W, Burrows P C, Notman J A, Mahon M, Holmes R (1988). Changes in jejunal permeability and passive permeation of sugars in intestinal biopsies in coeliac disease and Crohn's disease. Clin Sci (Lond) 74: 427-431.

Deitch E A (1990). The role of intestinal barrier failure and bacterial translocation in the development of systemic infection and multiple organ failure. Arch Surg 125: 403-404.

Delgado R, Rojas A, Glaria L A, Torres M, Duarte F, Shill R, Nafeh M, Santin E, Gonzalez N, Palacios M (1995). Ca(2+)-independent nitric oxide synthase activity in

human lung after cardiopulmonary bypass. Thorax 50: 403-404.

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

Diegeler A, Hirsch R, Schneider F, Schilling L O, Falk V, Rauch T, Mohr F W (2000). Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. Ann Thorac Surg 69: 1162-1166.

Do Q B, Goyer C, Chavanon O, Couture P, Denault A, Cartier R (2002). Hemodynamic changes during off-pump CABG surgery. Eur J Cardiothorac Surg 21: 385-390.

Dogliotti A M, Costantini A (1951). [First case of the human use of an apparatus for extracorporeal blood circulation.]. Minerva Chir 6: 657-659.

Doig C J, Sutherland L R, Sandham J D, Fick G H, Verhoef M, Meddings J B (1998). Increased intestinal permeability is associated with the development of multiple organ dysfunction syndrome in critically ill ICU patients. Am J Respir Crit Care Med 158: 444-451.

Downing S W, Edmunds L H, Jr. (1992). Release of vasoactive substances during cardiopulmonary bypass. Ann Thorac Surg 54: 1236-1243.

Dreyer W J, Michael L H, Millman E E, Berens K L (1995). Neutrophil activation and adhesion molecule expression in a canine model of open heart surgery with cardiopulmonary bypass. Cardiovasc Res 29: 775-781.

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

Effler D B, Groves L K, Sones F M, Jr., Knight H F, Jr., Kolff W J (1957). Elective cardiac arrest; an adjunct to open-heart surgery. J Thorac Surg 34: 500-508.

Effler D B, Knight H F, Jr., Groves L K, Kolff W J (1957). Elective cardiac arrest for open-heart surgery. Surg Gynecol Obstet 105: 407-416.

Egleston C V, Wood A E, Gorey T F, McGovern E M (1993). Gastrointestinal complications after cardiac surgery. Ann R Coll Surg Engl 75: 52-56.

Evora P R, Pearson P J, Schaff H V (1994). Impaired endothelium-dependent relaxation after coronary reperfusion injury: evidence for G-protein dysfunction. Ann Thorac Surg 57: 1550-1556.

Fan F C, Schuessler G B, Chen R Y, Chien S (1979). Determinations of blood flow and shunting of 9- and 15-micrometer spheres in regional beds. Am J Physiol 237: H25-33.

Fattouch K, Sbraga F, Bianco G, Speziale G, Gucciardo M, Sampognaro R, Ruvolo G (2005). Inhaled prostacyclin, nitric oxide, and nitroprusside in pulmonary hypertension after mitral valve replacement. J Card Surg 20: 171-176.

Favaloro R G (1998). Landmarks in the development of coronary artery bypass surgery. Circulation 98: 466-478.

Fedak P W, Rao V, Verma S, Ramzy D, Tumiati L, Miriuka S, Boylen P, Weisel R D, Feindel C M (2005). Combined endothelial and myocardial protection by endothelin antagonism enhances transplant allograft preservation. J Thorac Cardiovasc Surg 129: 407-415.

Fick A (1855). Uber diffusion. Ann Physik U Chem 94: 59-86.

Fiddian-Green R G, Pittenger G, Whitehouse W M, Jr. (1982). Back-diffusion of CO2 and its influence on the intramural pH in gastric mucosa. J Surg Res 33: 39-48.

Fiddian-Green R G, Baker S (1987). Predictive value of the stomach wall pH for complications after cardiac operations: comparison with other monitoring. Crit Care Med 15: 153-156.

Fine K D, Santa Ana C A, Porter J L, Fordtran J S (1994). Mechanism by which

glucose stimulates the passive absorption of small solutes by the human jejunum in vivo. Gastroenterology 107: 389-395.

Fordtran J S, Clodi P H, Soergel K H, Ingelfinger F J (1962). Sugar absorption tests, with special reference to 3-0-methyl-d-glucose and d-xylose. Ann Intern Med 57: 883-891.

Fordtran J S, Rector F C, Jr., Ewton M F, Soter N, Kinney J (1965). Permeability characteristics of the human small intestine. J Clin Invest 44: 1935-1944.

Fordtran J S, Soergel K H, Ingelfinger F J (1962). Intestinal absorption of D-xylose in man. N Engl J Med 267: 274-279.

Fortier S, DeMaria R G, Lamarche Y, Malo O, Denault A, Desjardins F, Carrier M, Perrault L P (2004). Inhaled prostacyclin reduces cardiopulmonary bypass-induced pulmonary endothelial dysfunction via increased cyclic adenosine monophosphate levels. J Thorac Cardiovasc Surg 128: 109-116.

Fox L S, Blackstone E H, Kirklin J W, Stewart R W, Samuelson P N (1982). Relationship of whole body oxygen consumption to perfusion flow rate during hypothermic cardiopulmonary bypass. J Thorac Cardiovasc Surg 83: 239-248.

Franke A, Lante W, Fackeldey V, Becker H P, Kurig E, Zoller L G, Weinhold C, Markewitz A (2005). Pro-inflammatory cytokines after different kinds of cardio-thoracic surgical procedures: is what we see what we know? Eur J Cardiothorac Surg 28: 569-575.

Friedman G, Berlot G, Kahn R J, Vincent J L (1995). Combined measurements of blood lactate concentrations and gastric intramucosal pH in patients with severe sepsis. Crit Care Med 23: 1184-1193.

Gadaleta D, Davis J M (1994). Pulmonary failure and the production of leukotrienes. J Am Coll Surg 178: 309-319.

Gaer J A, Shaw A D, Wild R, Swift R I, Munsch C M, Smith P L, Taylor K M (1994). Effect of cardiopulmonary bypass on gastrointestinal perfusion and function.

Ann Thorac Surg 57: 371-375.

Gamoso M G, Phillips-Bute B, Landolfo K P, Newman M F, Stafford-Smith M (2000). Off-pump versus on-pump coronary artery bypass surgery and postoperative renal dysfunction. Anesth Analg 91: 1080-1084.

Gautam H P (1969). Jaundice following cardiopulmonary bypass. J Cardiovasc Surg (Torino) 10: 404-406.

Gibbon J H, Jr. (1937). Artificial maintenance of circulation during expermental occlusion of pulmonary artery. Arch Surg 34: 1105-1131.

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

Goode A W, Herring A N, Orr J S, Ratcliffe W A, Dudley H A (1981). The effect of surgery with carbohydrate infusion on circulating triiodothyronine and reverse triiodothyronine. Ann R Coll Surg Engl 63: 168-172.

Gores G J, Nieminen A L, Wray B E, Herman B, Lemasters J J (1989). Intracellular pH during "chemical hypoxia" in cultured rat hepatocytes. Protection by intracellular acidosis against the onset of cell death. J Clin Invest 83: 386-396.

Gremse D A, HH A K, Schroeder T J, Balistreri W F (1990). Assessment of lidocaine metabolite formation as a quantitative liver function test in children. Hepatology 12: 565-569.

Gruber E M, Laussen P C, Casta A, Zimmerman A A, Zurakowski D, Reid R, Odegard K C, Chakravorti S, Davis P J, McGowan F X, Hickey P R, Hansen D D (2001). Stress response in infants undergoing cardiac surgery: a randomized study of fentanyl bolus, fentanyl infusion, and fentanyl-midazolam infusion. Anesth Analg 92: 882-890.

Grundeman P F, Borst C, van Herwaarden J A, Verlaan C W, Jansen E W (1998). Vertical displacement of the beating heart by the octopus tissue stabilizer: influence on coronary flow. Ann Thorac Surg 65: 1348-1352.

Grundeman P F, Borst C, van-Herwaarden J A, Mansvelt_Beck H J, Jansen E W (1997). Hemodynamic changes during displacement of the beating heart by the Utrecht Octopus method. Ann Thorac Surg 63: S88-92.

Grundeman P F, Borst C, Verlaan C W, Damen S, Mertens S (2001). Hemodynamic changes with right lateral decubitus body positioning in the tilted porcine heart. The Ann Thorac Surg 72: 1991-1996.

Grundeman P F, Borst C, Verlaan C W, Meijburg H, Moues C M, Jansen E W (1999). Exposure of circumflex branches in the tilted, beating porcine heart: echocardiographic evidence of right ventricular deformation and the effect of right or left heart bypass. J Thorac Cardiovasc Surg 118: 316-323.

Gu Y J, Mariani M A, van Oeveren W, Grandjean J G, Boonstra P W (1998). Reduction of the inflammatory response in patients undergoing minimally invasive coronary artery bypass grafting. Ann Thorac Surg 65: 420-424.

Guler M, Kirali K, Toker M E, Bozbuga N, Omeroglu S N, Akinci E, Yakut C (2001). Different CABG methods in patients with chronic obstructive pulmonary disease. Ann Thorac Surg 71: 152-157.

Guy A J, Michaels J A, Flear C T (1987). Changes in the plasma sodium concentration after minor, moderate and major surgery. Br J Surg 74: 1027-1030.

Haglund U, Hulten L, Ahren C, Lundgren O (1975). Mucosal lesions in the human small intestine in shock. Gut 16: 979-984.

Hakala T, Pitkanen O, Hartikainen J (2004). Cardioplegic arrest does not increase the risk of atrial fibrillation after coronary artery bypass surgery. Eur J Cardiothorac Surg 25: 415-418.

Haller M, Zollner C, Briegel J, Forst H (1995). Evaluation of a new continuous thermodilution cardiac output monitor in critically ill patients: a prospective criterion standard study. Crit Care Med 23: 860-866.

Halter J, Steinberg J, Fink G, Lutz C, Picone A, Maybury R, Fedors N, DiRocco J, Lee H M, Nieman G (2005). Evidence of systemic cytokine release in patients undergoing cardiopulmonary bypass. J Extra Corpor Technol 37: 272-277.

Hamilton T T, Huber L M, Jessen M E (2002). PulseCO: a less-invasive method to monitor cardiac output from arterial pressure after cardiac surgery. Ann Thorac Surg 74: S1408-1412.

Hamilton_Davies C, Mythen M G, Salmon J B, Jacobson D, Shukla A, Webb A R (1997). Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. Intensive Care Med 23: 276-281.

Hampton W W, Townsend M C, Schirmer W J, Haybron D M, Fry D E (1989). Effective hepatic blood flow during cardiopulmonary bypass. Arch Surg 124: 458-459.

Hamulu A, Atay Y, YaŸdi T, DiŸcigil B, Bakalim T, Buket S, Bilkay O (1998). Effects of flow types in cardiopulmonary bypass on gastric intramucosal pH. Perfusion 13: 129-135.

Haniuda M, Dresler C M, Mizuta T, Cooper J D, Patterson G A (1995). Free radical-mediated vascular injury in lungs preserved at moderate hypothermia. Ann Thorac Surg 60: 1376-1381.

Hanks J B, Curtis S E, Hanks B B, Andersen D K, Cox J L, Jones R S (1982). Gastrointestinal complications after cardiopulmonary bypass. Surgery 92: 394-400.

Harland W A, Horton P W, Strang R, Fitzgerald B, Richards J R, Holloway K B (1974). Release of thyroxine from the liver during anaesthesia and surgery. Br J Anaesth 46: 818-820.

Hasdai D, Erez E, Gil-Ad I, Raanani E, Sclarovsky S, Barak Y, Sulkes J, Vidne B A (1996). Is the heart a source for elevated circulating endothelin levels during aorta-coronary artery bypass grafting surgery in human beings? J Thorac Cardiovasc Surg 112: 531-536.

Hayashida N, Shoujima T, Teshima H, Yokokura Y, Takagi K, Tomoeda H, Aoyagi S (2004). Clinical outcome after cardiac operations in patients with cirrhosis. Ann Thorac Surg 77: 500-505.

Hediger M A, Coady M J, Ikeda T S, Wright E M (1987). Expression cloning and cDNA sequencing of the Na+/glucose co-transporter. Nature 330: 379-381.

Hennein H A, Ebba H, Rodriguez J L, Merrick S H, Keith F M, Bronstein M H, Leung J M, Mangano D T, Greenfield L J, Rankin J S (1994). Relationship of the proinflammatory cytokines to myocardial ischemia and dysfunction after uncomplicated coronary revascularization. J Thorac Cardiovasc Surg 108: 626-635.

Herschman J M, Jones C M, Bailey A L (1972). Reciprocal changes in serum thyrotropin and free thyroxine produced by heparin. J Clin Endocrinol Metab 34: 574-579.

Heyman M, Desjeux J F, Grasset E, Dumontier A M, Lestradet H (1981). Relationship between transport of D-xylose and other monosaccharides in jejunal mucosa of children. Gastroenterology 80: 758-762.

Hill G E, Snider S, Galbraith T A, Forst S, Robbins R A (1995). Glucocorticoid reduction of bronchial epithelial inflammation during cardiopulmonary bypass. Am J Respir Crit Care Med 152: 1791-1795.

Hochachka P W, Mommsen T P (1983). Protons and anaerobiosis. Science 219: 1391-1397.

Holland F W, Brown P S, Weintraub B D, Clark R E (1991). Cardiopulmonary bypass and thyroid function: a "euthyroid sick syndrome". Ann Thorac Surg 52: 46-50.

Horgan M J, Wright S D, Malik A B (1990). Antibody against leukocyte integrin (CD18) prevents reperfusion-induced lung vascular injury. Am J Physiol 259: L315-319.

Huddy S P, Joyce W P, Pepper J R (1991). Gastrointestinal complications in 4473

patients who underwent cardiopulmonary bypass surgery. Br J Surg 78: 293-296.

Huet P M, Villeneuve J P (1983). Determinants of drug disposition in patients with cirrhosis. Hepatology 3: 913-918.

Huguenin P, Cochet B, Balant L, Loizeau E (1978). [D-xylose absorption test. A pharmacokinetic and statistical study]. Schweiz Med Wochenschr 108: 206-214.

Jansen N J, van Oeveren W, Gu Y J, van Vliet M H, Eijsman L, Wildevuur C R (1992). Endotoxin release and tumor necrosis factor formation during cardiopulmonary bypass. Ann Thorac Surg 54: 744-747.

Janssens U, Graf J, Koch K C, Hanrath P (1998). Gastric tonometry: in vivo comparison of saline and air tonometry in patients with cardiogenic shock. Br J Anaesth 81: 676-680.

Jiang X H, Li N, Li J S (2003). Intestinal permeability in patients after surgical trauma and effect of enteral nutrition versus parenteral nutrition. World J Gastroenterol 9: 1878-1880.

Johansson J E, Ekman T (1997). Gastro-intestinal toxicity related to bone marrow transplantation: disruption of the intestinal barrier precedes clinical findings. Bone Marrow Transplant 19: 921-925.

Johansson J E, Soussi B, Bagge U, Ekman T (2001). Disturbance of purine nucleotide metabolism: a possible early key event in development of intestinal damage induced by chemotherapy. Dig Dis Sci 46: 257-261.

Jonas M M, Kelly F E, Linton R A, Band D M, O'Brien T K, Linton N W (1999). A comparison of lithium dilution cardiac output measurements made using central and antecubital venous injection of lithium chloride. J Clin Monit Comput 15: 525-528.

Jonas M M, Tanser S J (2002). Lithium dilution measurement of cardiac output and arterial pulse waveform analysis: an indicator dilution calibrated beat-by-beat system for continuous estimation of cardiac output. Curr Opin Crit Care 8: 257-261.

Jonnesco T (1920). Traitment chirurgical de l'angine de poitrine par la resection du sympathique cervicothoracique. Bull Acad Med: 93.

Kameda H, Abei T, Nasrallah S, Iber F L (1968). Functional and histological injury to intestinal mucosa produced by hypertonicity. Am J Physiol 214: 1090-1095.

Kanwar S, Windsor A C, Welsh F, Barclay G R, Guillou P J, Reynolds J V (2000). Lack of correlation between failure of gut barrier function and septic complications after major upper gastrointestinal surgery. Ann Surg 231: 88-95.

Kaplan M, Cimen S, Kut M S, Demirtas M M (2002). Cardiac operations for patients with chronic liver disease. Heart Surg Forum 5: 60-65.

Keceligil H T, Kolbakir F, Adam B, Arikan A, Erk M K (1996). Thyroid hormone alterations during and after cardiopulmonary bypass. Cardiovasc Surg 4: 617-622.

Keizer A M, Hijman R, van Dijk D, Kalkman C J, Kahn R S (2003). Cognitive self-assessment one year after on-pump and off-pump coronary artery bypass grafting. Ann Thorac Surg 75: 835-838.

Keogh B E, Kinsman R (2004). Fifth National Adult Cardiac Surgical Database Report 2003. The Society of Cardiothoracic Surgeons of Great Britain and Ireland.

Khan N E, De Souza A, Mister R, Flather M, Clague J, Davies S, Collins P, Wang D, Sigwart U, Pepper J (2004). A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. N Engl J Med 350: 21-28.

Khazin V, Kaufman Y, Zabeeda D, Medalion B, Sasson L, Schachner A, Ezri T (2004). Milrinone and nitric oxide: combined effect on pulmonary artery pressures after cardiopulmonary bypass in children. J Cardiothorac Vasc Anesth 18: 156-159.

Kirklin J K, Chenoweth D E, Naftel D C, Blackstone E H, Kirklin J W, Bitran D D, Curd J G, Reves J G, Samuelson P N (1986). Effects of protamine administration after cardiopulmonary bypass on complement, blood elements, and the hemodynamic state. Ann Thorac Surg 41: 193-199.

Kirklin J K, Westaby S, Blackstone E H, Kirklin J W, Chenoweth D E, Pacifico A D (1983). Complement and the damaging effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg 86: 845-857.

Kirklin J W, Dushane J W, Patrick R T, Donald D E, Hetzel P S, Harshbarger H G, Wood E H (1955). Intracardiac surgery with the aid of a mechanical pump-oxygenator system (gibbon type): report of eight cases. Mayo Clin Proc 30: 201-206.

Kivisaari J, Niinikoski J (1973). Use of silastic tube and capillary sampling technic in the measurement of tissue PO 2 and PCO 2. Am J Surg 125: 623-627.

Klein I (1990). Thyroid hormone and the cardiovascular system. Am J Med 88: 631-637.

Klemperer J D, Klein I, Gomez M, Helm R E, Ojamaa K, Thomas S J, Isom O W, Krieger K (1995). Thyroid hormone treatment after coronary-artery bypass surgery. N Engl JMed 333: 1522-1527.

Klemperer J D, Ko W, Krieger K H, Connolly M, Rosengart T K, Altorki N K, Lang S, Isom O W (1998). Cardiac operations in patients with cirrhosis. Ann Thorac Surg 65: 85-87.

Klemperer J D, Zelano J, Helm R E, Berman K, Ojamaa K, Klein I, Isom O W, Krieger K (1995). Triiodothyronine improves left ventricular function without oxygen wasting effects after global hypothermic ischemia. J Thorac Cardiovasc Surg 109: 457-465.

Knight A, Forsling M, Treasure T, Aveling W, Loh L, Sturridge M F (1986). Changes in plasma vasopressin concentration in association with coronary artery surgery or thymectomy. Br J Anaesth 58: 1273-1277.

Ko W, Hawes A S, Lazenby W D, Calvano S E, Shin Y T, Zelano J A, Antonacci A C, Isom O W, Krieger K H (1991). Myocardial reperfusion injury. Platelet-activating factor stimulates polymorphonuclear leukocyte hydrogen peroxide production during myocardial reperfusion. J Thorac Cardiovasc Surg 102: 297-308.

Kochamba G S, Yun K L, Pfeffer T A, Sintek C F, Khonsari S (2000). Pulmonary abnormalities after coronary arterial bypass grafting operation: cardiopulmonary bypass versus mechanical stabilization. Ann Thorac Surg 69: 1466-1470.

Koizumi M, Matsumoto N, Ueda K (1998). Influences of cardiopulmonary bypass and fentanyl anesthesia on hepatic circulation and oxygen metabolism in beagles. Anesth Analg 86: 1177-1182.

Kompan L, Kompan D (2001). Importance of increased intestinal permeability after multiple injuries. Eur J Surg 167: 570-574.

Kompan L, Kremzar B, Gadzijev E, Prosek M (1999). Effects of early enteral nutrition on intestinal permeability and the development of multiple organ failure after multiple injury. Intensive Care Med 25: 157-161.

Kono K, Philbin D M, Coggins C H, Moss J, Rosow C E, Schneider R C, Slater E E (1981). Renal function and stress response during halothane or fentanyl anesthesia. Anesth Analg 60: 552-556.

Kono K, Philbin D M, Coggins C H, Slater E E, Triantafillou A, Levine F H, Buckley M J (1983). Adrenocortical hormone levels during cardiopulmonary bypass with and without pulsatile flow. J Thorac Cardiovasc Surg 85: 129-133.

Krasna M J, Flancbaum L, Trooskin S Z, Fitzpatrick J C, Scholz P M, Scott G E, Spotnitz A J, Mackenzie J W (1988). Gastrointestinal complications after cardiac surgery. Surgery 104: 773-780.

Kubes P, Ibbotson G, Russell J, Wallace J L, Granger D N (1990). Role of platelet-activating factor in ischemia/reperfusion-induced leukocyte adherence. Am J Physiol 259: G300-305.

Kubo S H, Walter B A, John D H, Clark M, Cody R J (1987). Liver function abnormalities in chronic heart failure. Influence of systemic hemodynamics. Arch Intern Med 147: 1227-1230.

Kumle B, Boldt J, Suttner S W, Piper S N, Lehmann A, Blome M (2003). Influence of prolonged cardiopulmonary bypass times on splanchnic perfusion and markers of splanchnic organ function. Ann Thorac Surg 75: 1558-1564.

Kurita T, Morita K, Kato S, Kawasaki H, Kikura M, Kazama T, Ikeda K (1999).

Lithium dilution cardiac output measurements using a peripheral injection site comparison with central injection technique and thermodilution. J Clin Monit Comput 15: 279-285.

Kurita T, Morita K, Kato S, Kikura M, Horie M, Ikeda K (1997). Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output. Br J Anaesth 79: 770-775.

Landow L, Andersen L W (1994). Splanchnic ischaemia and its role in multiple organ failure. Acta Anaesthesiol Scand 38: 626-639.

Lau L L, Halliday M I, Lee B, Hannon R J, Gardiner K R, Soong C V (2000). Intestinal manipulation during elective aortic aneurysm surgery leads to portal endotoxaemia and mucosal barrier dysfunction. Eur J Vasc Endovasc Surg 19: 619-624.

Lau L L, Halliday M I, Smye M G, Lee B, Hannon R J, Gardiner K R, Soong C V (2001). Extraperitoneal approach reduces intestinal and renal dysfunction in elective abdominal aortic aneurysm repair. Int Angiol 20: 282-287.

Lee J D, Lee S J, Tsushima W T, Yamauchi H, Lau W T, Popper J, Stein A, Johnson D, Lee D, Petrovitch H, Dang C R (2003). Benefits of off-pump bypass on neurologic and clinical morbidity: a prospective randomized trial. Ann Thorac Surg 76: 18-25.

Legakis I N, Golematis B C, Dourakis N, Lymberopoulou I, Mountokalakis T, Leandros E A (1998). Low T3 syndrome with asynchronous changes of TT3 and rT3 values in laparoscopic cholecystectomy. Endocr Res 24: 205-213.

Legare J F, Buth K J, King S, Wood J, Sullivan J A, Friesen C H, Lee J, Stewart K, Hirsch G M (2004). Coronary bypass surgery performed off pump does not result in lower in-hospital morbidity than coronary artery bypass grafting performed on pump. Circulation 109: 887-892.

Lehot J J, Deleat-Besson R, Bastien O, Brun Y, Adeleine P, Robin J, Estanove S (1990). Should we inhibit gastric acid secretion before cardiac surgery? Anesth

Analg 70: 185-190.

Lehot J J, Villard J, Piriz H, Philbin D M, Carry P Y, Gauquelin G, Claustrat B, Sassolas G, Galliot J, Estanove S (1992). Hemodynamic and hormonal responses to hypothermic and normothermic cardiopulmonary bypass. J Cardiothorac Vasc Anesth 6: 132-139.

Leitman I M, Paull D E, Barie P S, Isom O W, Shires G T (1987). Intra-abdominal complications of cardiopulmonary bypass operations. Surg Gynecol Obstet 165: 251-254.

Leslie R D, Isaacs A J, Gomez J, Raggatt P R, Bayliss R (1978). Hypothalamo-pituitary-thyroid function in anorexia nervosa: influence of weight gain. Br Med J 2: 526-528.

Levine F H, Philbin D M, Kono K, Coggins C H, Emerson C W, Austen W G, Buckley M J (1981). Plasma vasopressin levels and urinary sodium excretion during cardiopulmonary bypass with and without pulsatile flow. Ann Thorac Surg 32: 63-67.

Levine F H, Philbin D M, Kono K, Coggins C H, Emerson C W, Austen W G, Buckley M J (1981). Plasma vasopressin levels and urinary sodium excretion during cardiopulmonary bypass with and without pulsatile flow. Ann Thorac Surg 32: 63-67.

Li J M, Hajarizadeh H, La Rosa C A, Rohrer M J, Vander Salm T J, Cutler B S (1996). Heparin and protamine stimulate the production of nitric oxide. J Cardiovasc Surg (Torino) 37: 445-452.

Lieb W R, Stein W D (1969). Biological membranes behave as non-porous polymeric sheets with respect to the diffusion of non-electrolytes. Nature 224: 240-243.

Lightman S L, Forsling M L (1980). Evidence for endogenous opioid control of vasopressin release in man. J Clin Endocrinol Metab 50: 569-571.

Lin C H, Lin F Y, Wang S S, Yu H Y, Hsu R B (2005). Cardiac surgery in patients with liver cirrhosis. Ann Thorac Surg 79: 1551-1554.

Linton N W F, Linton R A F (2001). Estimation of changes in cardiac output from the arterial blood pressure waveform in the upper limb. Br J Anaesth 86: 486-496.

Linton R, Band D, O_Brien T, Jonas M, Leach R (1997). Lithium dilution cardiac output measurement: a comparison with thermodilution. Crit Care Med 25: 1796-1800.

Linton R A, Band D M, Haire K M (1993). A new method of measuring cardiac output in man using lithium dilution. Br J Anaesth 71: 262-266.

Linton R A, Jonas M M, Tibby S M, Murdoch I A, O_Brien T K, Linton N W, Band D M (2000). Cardiac output measured by lithium dilution and transpulmonary thermodilution in patients in a paediatric intensive care unit. Intensive Care Med 26: 1507-1511.

Lloyd C T, Ascione R, Underwood M J, Gardner F, Black A, Angelini G D (2000). Serum S-100 protein release and neuropsychologic outcome during coronary revascularization on the beating heart: a prospective randomized study. J Thorac Cardiovasc Surg 119: 148-154.

Loef B G, Epema A H, Navis G, Ebels T, van Oeveren W, Henning R H (2002). Off-pump coronary revascularization attenuates transient renal damage compared with on-pump coronary revascularization. Chest 121: 1190-1194.

Mack M J, Pfister A, Bachand D, Emery R, Magee M J, Connolly M, Subramanian V (2004). Comparison of coronary bypass surgery with and without cardiopulmonary bypass in patients with multivessel disease. J Thorac Cardiovasc Surg 127: 167-173.

Matata B M, Sosnowski A W, Galinanes M (2000). Off-pump bypass graft operation significantly reduces oxidative stress and inflammation. Ann Thorac Surg 69: 785-791.

Matata B M, Sosnowski A W, Galinanes M (2000). Off-pump bypass graft operation

significantly reduces oxidative stress and inflammation. Ann Thorac Surg 69: 785-791.

Mathie R T, Ohri S K, Batten J J, Peters A M, Keogh B E (1997). Hepatic blood flow during cardiopulmonary bypass operations: the effect of temperature and pulsatility. J Thorac Cardiovasc Surg 114: 292-293.

Mathison M, Buffolo E, Jatene A D, Jatene F B, Reichenspurner H, Matheny R G, Shennib H, Akin J J, Mack M J (2000). Right heart circulatory support facilitates coronary artery bypass without cardiopulmonary bypass. Ann Thorac Surg 70: 1083-1085.

Mathison M, Edgerton J R, Horswell J L, Akin J J, Mack M J (2000). Analysis of hemodynamic changes during beating heart surgical procedures. Ann Thorac Surg 70: 1355-1361.

Matthews J N, Altman D G, Campbell M J, Royston P (1990). Analysis of serial measurements in medical research. Br Med J 300: 230-235.

Maxton D G, Bjarnason I, Reynolds A P, Catt S D, Peters T J, Menzies I S (1986). Lactulose, 51Cr-labelled ethylenediaminetetra-acetate, L-rhamnose and polyethyleneglycol 400 [corrected] as probe markers for assessment in vivo of human intestinal permeability. Clin Sci (Lond) 71: 71-80.

McCord J M (1985). Oxygen-derived free radicals in postischemic tissue injury. N Engl J Med 312: 159-163.

McGinley J, Lynch L, Hubbard K, McCoy D, Cunningham A J (2001). Dopexamine hydrochloride does not modify hemodynamic response or tissue oxygenation or gut permeability during abdominal aortic surgery. Can J Anaesth 48: 238-244.

McGowan F X, Jr., Davis P J, Siewers R D, del Nido P J (1995). Coronary vasoconstriction mediated by endothelin-1 in neonates. Reversal by nitroglycerin. J Thorac Cardiovasc Surg 109: 88-97.

McIntyre N (1983). The limitations of conventional liver function tests. Semin Liver

Dis 3: 265-274.

McKinney W, Newman W H, Webb J G, Castresana M R (2003). Bacterial lipopolysaccharide-stimulated release of tumor necrosis factor-alpha from the isolated rat heart: the effect of aprotinin and forskolin. Am Surg 69: 131-134.

McSweeney M E, Garwood S, Levin J, Marino M R, Wang S X, Kardatzke D, Mangano D T, Wolman R L (2004). Adverse gastrointestinal complications after cardiopulmonary bypass: can outcome be predicted from preoperative risk factors? Anesth Analg 98: 1610-1617.

Mehta J L (1995). Endothelium, coronary vasodilation, and organic nitrates. Am Heart J 129: 382-391.

Melrose D G, Dreyer B, Bentall H H, Baker J B (1955). Elective cardiac arrest. Lancet 269: 21-22.

Menzies I (1974). Absorption of intact oligosaccharide in health and disease. Biochem Soc Trans 2: 1040-1046.

Menzies I (1984). Transmucosal passage of inert molecules in health and disease. Intestinal absorption and secretion. Falk Symposium 36. S. E. and H. K. Lancaster: MTP: 527-543.

Menzies I, Pounder R, Heyer S, Laker M, Bull J, Wheeler P, Creamer B (1979). Abnormal intestinal permeability to sugars in villus atrophy. Lancet 2: 1107-1109.

Mercado P D, Farid H, O'Connell T X, Sintek C F, Pfeffer T, Khonsari S (1994). Gastrointestinal complications associated with cardiopulmonary bypass procedures. Am Surg 60: 789-792.

Mierdl S, Meininger D, Dogan S, Aybek T, Wimmer-Greinecker G, Lischke V, Kessler P (2001). Abdominal complications after cardiac surgery. Ann Acad Med Singapore 30: 245-249.

Minami K, Korner M M, Vyska K, Kleesiek K, Knobl H, Korfer R (1990). Effects of

pulsatile perfusion on plasma catecholamine levels and hemodynamics during and after cardiac operations with cardiopulmonary bypass. J Thorac Cardiovasc Surg 99: 82-91.

Mitchell I M, Pollock J C, Jamieson M P (1995). Effects of dopamine on liver blood flow in children with congenital heart disease. Ann Thorac Surg 60: 1741-1744.

Moore A, Aitken R, Burke C, Gaskell S, Groom G, Holder G, Selby C, Wood P (1985). Cortisol assays: guidelines for the provision of a clinical biochemistry service. Ann Clin Biochem 22 (Pt 5): 435-454.

Moore F A (1999). The role of the gastrointestinal tract in postinjury multiple organ failure. Am J Surg 178: 449-453.

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

Morkin E, Flink I L, Goldman S (1983). Biochemical and physiologic effects of thyroid hormone on cardiac performance. Prog Cardiovasc Dis 25: 435-464.

Morkin E, Pennock G D, Raya T E, Bahl J J, Goldman S (1993). Studies on the use of thyroid hormone and a thyroid hormone analogue in the treatment of congestive heart failure. Ann Thorac Surg 56: S54-60.

Morton J J, Connell J M, Hughes M J, Inglis G C, Wallace E C (1985). The role of plasma osmolality, angiotensin II and dopamine in vasopressin release in man. Clin Endocrin (Oxf)g 23: 129-138.

Mullis-Jansson S L, Argenziano M, Corwin S, Homma S, Weinberg A D, Williams M, Rose E A, Smith C R (1999). A randomized double-blind study of the effect of triiodothyronine on cardiac function and morbidity after coronary bypass surgery. J Thorac Cardiovasc Surg 117: 1128-1134.

Muneretto C, Bisleri G, Negri A, Manfredi J, Metra M, Nodari S, Dei Cas L (2003).

Off-pump coronary artery bypass surgery technique for total arterial myocardial revascularization: a prospective randomized study. Ann Thorac Surg 76: 778-782.

Murray G, Porcheron R, Hilario J, Roschlau W (1954). Anastomosis of systemic artery to the coronary. Can Med Assoc J 71: 594-597.

Musleh G S, Patel N C, Grayson A D, Pullan D M, Keenan D J, Fabri B M, Hasan R (2003). Off-pump coronary artery bypass surgery does not reduce gastrointestinal complications. Eur J Cardiothorac Surg 23: 170-174.

Mythen M G, Webb A R (1998). Gastrointestinal tonometry comes of age? Br J Anaesth 81: 667-668.

Narkewicz M R, Sondheimer H M, Ziegler J W, Otanni Y, Lorts A, Shaffer E M, Horgan J G, Sokol R J (2003). Hepatic dysfunction following the Fontan procedure. J Pediatr Gastroenterol Nutr 36: 352-357.

Naschitz J E, Slobodin G, Lewis R J, Zuckerman E, Yeshurun D (2000). Heart diseases affecting the liver and liver diseases affecting the heart. Am Heart J 140: 111-120.

Nathoe H M, van Dijk D, Jansen E W, Suyker W J, Diephuis J C, van Boven W J, de la Riviere A B, Borst C, Kalkman C J, Grobbee D E, Buskens E, de Jaegere P P (2003). A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. N Engl J Med 348: 394-402.

NG A, Tan S S, Lee H S, Chew S L (1995). Effect of propofol infusion on the endocrine response to cardiac surgery. Anaesth Intensive Care 23: 543-547.

Nierich A P, Diephuis J, Jansen E W, Borst C, Knape J T (2000). Heart displacement during off-pump CABG: how well is it tolerated? Ann Thorac Surg 70: 466-472.

Ninomiya M, Takamoto S, Kotsuka Y, Ohtsuka T (2001). Indication and perioperative management for cardiac surgery in patients with liver cirrhosis. Our experience with 3 patients. Jpn J Thorac Cardiovasc Surg 49: 391-394.

Nomura S, Pittman C S, Chambers J B, Jr., Buck M W, Shimizu T (1975). Reduced peripheral conversion of thyroxine to triiodothyronine in patients with hepatic cirrhosis. J Clin Invest 56: 643-652.

Novitzky D, Cooper D K, Barton C I, Greer A, Chaffin J, Grim J, Zuhdi N (1989). Triiodothyronine as an inotropic agent after open heart surgery. J Thorac Cardiovasc Surg 98: 972-977.

Novitzky D, Human P A, Cooper D K (1988). Effect of triiodothyronine (T3) on myocardial high energy phosphates and lactate after ischemia and cardiopulmonary bypass. An experimental study in baboons. J Thorac Cardiovasc Surg 96: 600-607.

Novitzky D, Human P A, Cooper D K (1988). Inotropic effect of triiodothyronine following myocardial ischemia and cardiopulmonary bypass: an experimental study in pigs. Ann Thorac Surg 45: 50-55.

Odim J N, Wu J, Laks H, Banerji A, Drant S (2006). Cardiac surgery in children with end-stage liver disease awaiting liver transplantation. Ann Thorac Surg 81: 697-700.

Oellerich M, Burdelski M, Ringe B, Lamesch P, Gubernatis G, Bunzendahl H, Pichlmayr R, Herrmann H (1989). Lignocaine metabolite formation as a measure of pre-transplant liver function. Lancet 1: 640-642.

Oellerich M, Raude E, Burdelski M, Schulz M, Schmidt F W, Ringe B, Lamesch P, Pichlmayr R, Raith H, Scheruhn M, et al. (1987). Monoethylglycinexylidide formation kinetics: a novel approach to assessment of liver function. J Clin Chem Clin Biochem 25: 845-853.

Ohkawa F, Ikeda U, Kanbe T, Kawasaki K, Shimada K (1995). Effects of inflammatory cytokines on vascular tone. Cardiovasc Res 30: 711-715.

Ohri S K (1996). Systemic inflammatory response and the splanchnic bed in cardiopulmonary bypass. Perfusion 11: 200-212.

Ohri S K, Becket J, Brannan J, Keogh B E, Taylor K M (1994). Effects of cardiopulmonary bypass on gut blood flow, oxygen utilization, and intramucosal pH.

Ann Thorac Surg 57: 1193-1199.

Ohri S K, Bjarnason I, Pathi V, Somasundaram S, Bowles C T, Keogh B E, Khaghani A, Menzies I, Yacoub M H, Taylor K M (1993). Cardiopulmonary bypass impairs small intestinal transport and increases gut permeability. Ann Thorac Surg 55: 1080-1086.

Ohri S K, Bowles C W, Mathie R T, Lawrence D R, Keogh B E, Taylor K M (1997). Effect of Cardiopulmonary Bypass Perfusion Protocols on Gut Tissue Oxygenation and Blood Flow. Ann Thorac Surg 64: 163-170.

Ohri S K, Desai J B, Gaer J A, Roussak J B, Hashemi M, Smith P L, Taylor K M (1991). Intraabdominal complications after cardiopulmonary bypass. Ann Thorac Surg 52: 826-831.

Oka Y, Wakayama S, Oyama T, Orkin L R, Becker R M, Blaufox M D, Frater R W (1981). Cortisol and antidiuretic hormone responses to stress in cardiac surgical patients. Can Anaesth Soc J 28: 334-338.

Olearchyk A S (1988). Vasilii I. Kolesov. A pioneer of coronary revascularization by internal mammary-coronary artery grafting. J Thorac Cardiovasc Surg 96: 13-18.

Olearchyk A S, Olearchyk R M (1999). Reminiscences of Vasilii I. Kolesov. Ann Thorac Surg 67: 273-276.

Oudemans-van Straaten H M, Jansen P G, Hoek F J, van Deventer S J, Sturk A, Stoutenbeek C P, Tytgat G N, Wildevuur C R, Eysman L (1996). Intestinal permeability, circulating endotoxin, and postoperative systemic responses in cardiac surgery patients. J Cardiothorac Vasc Anesth 10: 187-194.

Partrick D A, Moore F A, Moore E E, Biffl W L, Sauaia A, Barnett C C, Jr. (1996). The inflammatory profile of interleukin-6, interleukin-8, and soluble intercellular adhesion molecule-1 in postinjury multiple organ failure. Am J Surg 172: 425-429; discussed 429-431.

Perugini R A, Orr R K, Porter D, Dumas E M, Maini B S (1997). Gastrointestinal

complications following cardiac surgery. An analysis of 1477 cardiac surgery patients. Arch Surg 132: 352-357.

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

Philbin D M, Coggins C H, Wilson N, Sokoloski J (1977). Antidiuretic hormone levels during cardiopulmonary bypass. J Thorac Cardiovasc Surg 73: 145-148.

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

Philbin D M, Levine F H, Kono K, Coggins C H, Moss J, Slater E E, Buckley M J (1981). Attenuation of the stress response to cardiopulmonary bypass by the addition of pulsatile flow. Circulation 64: 808-812.

Phillips R H, Valente W A, Caplan E S, Connor T B, Wiswell J G (1984). Circulating thyroid hormone changes in acute trauma: prognostic implications for clinical outcome. J Trauma 24: 116-119.

Pinson C W, Alberty R E (1983). General surgical complications after cardiopulmonary bypass surgery. Am J Surg 146: 133-137.

Pitkanen E (1977). The conversion of D-xylose into D-threitol in patients without liver disease and in patients with portal liver cirrhosis. Clin Chim Acta 80: 49-54.

Pollock E M, Pollock J C, Jamieson M P, Beastall G S, Wright C, Torsney B, McNicol L R (1988). Adrenocortical hormone concentrations in children during cardiopulmonary bypass with and without pulsatile flow. Br J Anaesth 60: 536-541.

Porat E, Sharony R, Ivry S, Ozaki S, Meyns B P, Flameng W J, Uretzky G (2000). Hemodynamic changes and right heart support during vertical displacement of the

beating heart. Ann Thorac Surg 69: 1188-1191.

Prasad K, Kalra J, Bharadwaj B, Chaudhary A K (1992). Increased oxygen free radical activity in patients on cardiopulmonary bypass undergoing aortocoronary bypass surgery. Am Heart J 123: 37-45.

Prescott R W, Yeo P P, Watson M J, Johnston I D, Ratcliffe J G, Evered D C (1979). Total and free thyroid hormone concentrations after elective surgery. J Clin Pathol 32: 321-324.

Puskas J D, Thourani V H, Marshall J J, Dempsey S J, Steiner M A, Sammons B H, Brown W M, 3rd, Gott J P, Weintraub W S, Guyton R A (2001). Clinical outcomes, angiographic patency, and resource utilization in 200 consecutive off-pump coronary bypass patients. Ann Thorac Surg 71: 1477-1483.

Puskas J D, Williams W H, Duke P G, Staples J R, Glas K E, Marshall J J, Leimbach M, Huber P, Garas S, Sammons B H, McCall S A, Petersen R J, Bailey D E, Chu H, Mahoney E M, Weintraub W S, Guyton R A (2003). Off-pump coronary artery bypass grafting provides complete revascularization with reduced myocardial injury, transfusion requirements, and length of stay: a prospective randomized comparison of two hundred unselected patients undergoing off-pump versus conventional coronary artery bypass grafting. J Thorac Cardiovasc Surg 125: 797-808.

Puskas J D, Williams W H, Mahoney E M, Huber P R, Block P C, Duke P G, Staples J R, Glas K E, Marshall J J, Leimbach M E, McCall S A, Petersen R J, Bailey D E, Weintraub W S, Guyton R A (2004). Off-pump vs conventional coronary artery bypass grafting: early and 1-year graft patency, cost, and quality-of-life outcomes: a randomized trial. JAMA 291: 1841-1849.

Quan Z F, Yang C, Li N, Li J S (2004). Effect of glutamine on change in early postoperative intestinal permeability and its relation to systemic inflammatory response. World J Gastroenterol 10: 1992-1994.

Raja S G, Haider Z, Ahmad M (2004). Cardiopulmonary bypass is the main predictor of gastrointestinal complications after cardiac surgery. Tex Heart Inst J 31: 108.

Raman J S, Kochi K, Morimatsu H, Buxton B, Bellomo R (2002). Severe ischemic early liver injury after cardiac surgery. Ann Thorac Surg 74: 1601-1606.

Reath D B, Maull K I, Wolfgang T C (1983). General surgical complications following cardiac surgery. Am Surg 49: 11-14.

Ricci M, Karamanoukian H L, D'Ancona G, Bergsland J, Salerno T A (2000). Exposure and mechanical stabilization in off-pump coronary artery bypass grafting via sternotomy. Ann Thorac Surg 70: 1736-1740.

Riddington D W, Venkatesh B, Boivin C M, Bonser R S, Elliott T S, Marshall T, Mountford P J, Bion J F (1996). Intestinal permeability, gastric intramucosal pH, and systemic endotoxemia in patients undergoing cardiopulmonary bypass. JAMA 275: 1007-1012.

Robinson J S, Cole F R, Gibson P, Simpson J A (1967). Jaundice following cardiopulmonary bypass. Thorax 22: 232-237.

Roos A, Boron W F (1981). Intracellular pH. Physiol Rev 61: 296-434.

Rosen H R, Vlahakes G J, Rattner D W (1992). Fulminant peptic ulcer disease in cardiac surgical patients: pathogenesis, prevention, and management. Crit Care Med 20: 354-359.

Roth-Isigkeit A K, Dibbelt L, Schmucker P (2000). Blood levels of corticosteroid-binding globulin, total cortisol and unbound cortisol in patients undergoing coronary artery bypass grafting surgery with cardiopulmonary bypass. Steroids 65: 513-520.

Rothe C F (1983). Reflex control of veins and vascular capacitance. Physiol Rev 63: 1281-1342.

Russell D H, Barreto J C, Klemm K, Miller T A (1995). Hemorrhagic shock increases gut macromolecular permeability in the rat. Shock 4: 50-55.

Rutberg H, Hakanson E, Anderberg B, Jorfeldt L, Schildt B, Tegler L (1984). Thyroid hormones, catecholamine and cortisol concentrations after upper abdominal

surgery. Acta Chir Scand 150: 273-278.

Ruvolo G, Greco E, Speziale G, Tritapepe L, Marino B, Mollace V, Nistico G (1994). Nitric oxide formation during cardiopulmonary bypass. Ann Thorac Surg 57: 1055-1057.

Sakakibara Y, Imazuru T, Watanabe K, Matsuzaki K, Mitsui T, Unno H, Doi T (1998). Repeat coronary artery bypass in a patient with liver cirrhosis. Thorac Cardiovasc Surg 46: 99-100.

Salamon T, Michler R E, Knott K M, Brown D A (2003). Off-pump coronary artery bypass grafting does not decrease the incidence of atrial fibrillation. Ann Thorac Surg 75: 505-507.

Sandhu R S, Davies P H (2001). Amiodarone induced thyroid dysfunction: pathophysiology, diagnosis and management. Adverse Drug React Toxicol Rev 20: 105-116.

Sanisoglu I, Guden M, Bayramoglu Z, Sagbas E, Dibekoglu C, Sanisoglu S Y, Akpinar B (2004). Does off-pump CABG reduce gastrointestinal complications? Ann Thorac Surg 77: 619-625.

Sawa Y, Schaper J, Roth M, Nagasawa K, Ballagi G, Bleese N, Schaper W (1994). Platelet-activating factor plays an important role in reperfusion injury in myocardium. Efficacy of platelet-activating factor receptor antagonist (CV-3988) as compared with leukocyte-depleted reperfusion. J Thorac Cardiovasc Surg 108: 953-959.

Schersten H, Hedner T, McGregor C G, Miller V M, Martensson G, Riise G C, Nilsson F N (1996). Increased levels of endothelin-1 in bronchoalveolar lavage fluid of patients with lung allografts. J Thorac Cardiovasc Surg 111: 253-258.

Schroeder T J, Gremse D A, Mansour M E, Theuerling A W, Brunson M E, Ryckman F C, Suchy F J, Penn I, Alexander J W, Pesce A J, et al. (1989). Lidocaine metabolism as an index of liver function in hepatic transplant donors and recipients. Transplant Proc 21: 2299-2301.

Schulze-Neick I, Li J, Reader J A, Shekerdemian L, Redington A N, Penny D J (2002). The endothelin antagonist BQ123 reduces pulmonary vascular resistance after surgical intervention for congenital heart disease. J Thorac Cardiovasc Surg 124: 435-441.

Schweinburg F B, Fine J (1955). Resistance to bacteria in hemorrhagic shock. II. Effect of transient vascular collapse on sensitivity to endotoxin. Proc Soc Exp Biol Med 88: 589-591.

Scott R, Blackstone E H, McCarthy P M, Lytle B W, Loop F D, White J A, Cosgrove D M (2000). Isolated bypass grafting of the left internal thoracic artery to the left anterior descending coronary artery: late consequences of incomplete revascularization. J Thorac Cardiovasc Surg 120: 173-184.

Segal S, Foley J B (1959). The metabolic fate of C14 labeled pentoses in man. J Clin Invest 38: 407-413.

Sehested J, Wacker B, Forssmann W G, Schmitzer E (1997). Natriuresis after cardiopulmonary bypass: relationship to urodilatin, atrial natriuretic factor, antidiuretic hormone, and aldosterone. J Thorac Cardiovasc Surg 114: 666-671.

Sharony R, Grossi E A, Saunders P C, Galloway A C, Applebaum R, Ribakove G H, Culliford A T, Kanchuger M, Kronzon I, Colvin S B (2004). Propensity case-matched analysis of off-pump coronary artery bypass grafting in patients with atheromatous aortic disease. J Thorac Cardiovasc Surg 127: 406-413.

Sharpe D A, Mitchel I M, Kay E A, McGoldrick J P, Munsch C M, Kay P H (1999). Enhancing liver blood flow after cardiopulmonary bypass: the effects of dopamine and dopexamine. Perfusion 14: 29-36.

Shepard R B, Kirklin J W (1969). Relation of pulsatile flow to oxygen consumption and other variables during cardiopulmonary bypass. J Thorac Cardiovasc Surg 58: 694-702 passim.

Shepard R B, Simpson D C, Sharp J F (1966). Energy equivalent pressure. Arch Surg 93: 730-740.

Shepherd A P, Kiel J W (1992). A model of countercurrent shunting of oxygen in the intestinal villus. Am J Physiol 262: H1136-1142.

Shernan S K, Fitch J C, Nussmeier N A, Chen J C, Rollins S A, Mojcik C F, Malloy K J, Todaro T G, Filloon T, Boyce S W, Gangahar D M, Goldberg M, Saidman L J, Mangano D T (2004). Impact of pexelizumab, an anti-C5 complement antibody, on total mortality and adverse cardiovascular outcomes in cardiac surgical patients undergoing cardiopulmonary bypass. Ann Thorac Surg 77: 942-949.

Siegel L C, Hennessy M M, Pearl R G (1996). Delayed time response of the continuous cardiac output pulmonary artery catheter. Anesth Analg 83: 1173-1177.

Simic O, Strathausen S, Hess W, Ostermeyer J (1999). Incidence and prognosis of abdominal complications after cardiopulmonary bypass. Cardiovasc Surg 7: 419-424.

Sinclair D G, Haslam P L, Quinlan G J, Pepper J R, Evans T W (1995). The effect of cardiopulmonary bypass on intestinal and pulmonary endothelial permeability. Chest 108: 718-724.

Sinclair D G, Houldsworth P E, Keogh B, Pepper J, Evans T W (1997). Gastrointestinal permeability following cardiopulmonary bypass: a randomised study comparing the effects of dopamine and dopexamine. Intensive Care Med 23: 510-516.

Smith E E, Naftel D C, Blackstone E H, Kirklin J W (1987). Microvascular permeability after cardiopulmonary bypass. An experimental study. J Thorac Cardiovasc Surg 94: 225-233.

Soltoski P, Salerno T, Levinsky L, Schmid S, Hasnain S, Diesfeld T, Huang C, Akhter M, Alnoweiser O, Bergsland J (1998). Conversion to cardiopulmonary bypass in off-pump coronary artery bypass grafting: its effect on outcome. J Card Surg 13: 328-334.

Spital A (1999). Diuretic-induced hyponatremia. Am J Nephrol 19: 447-452.

Stamou S C, Jablonski K A, Pfister A J, Hill P C, Dullum M K, Bafi A S, Boyce S

W, Petro K R, Corso P J (2002). Stroke after conventional versus minimally invasive coronary artery bypass. Ann Thorac Surg 74: 394-399.

Steinberg J B, Kapelanski D P, Olson J D, Weiler J M (1993). Cytokine and complement levels in patients undergoing cardiopulmonary bypass. J Thorac Cardiovasc Surg 106: 1008-1016.

Stroobant N, Van Nooten G, Belleghem Y, Vingerhoets G (2002). Short-term and long-term neurocognitive outcome in on-pump versus off-pump CABG. Eur J Cardiothorac Surg 22: 559-564.

Sun L S, Adams D C, Delphin E, Graham J, Meltzer E, Rose E A, Heyer E J (1997). Sympathetic response during cardiopulmonary bypass: mild versus moderate hypothermia. Crit Care Med 25: 1990-1993.

Taggart D P (2001). Effects of a platelet-activating factor antagonist on lung injury and ventilation after cardiac operation. Ann Thorac Surg 71: 238-242.

Taggart D P, Browne S M, Halligan P W, Wade D T (1999). Is cardiopulmonary bypass still the cause of cognitive dysfunction after cardiac operations? J Thorac Cardiovasc Surg 118: 414-420.

Taggart D P, Fraser W D, Borland W W, Shenkin A, Wheatley D J (1989). Hypothermia and the stress response to cardiopulmonary bypass. Eur J Cardiothorac Surg 3: 359-363.

Tang A T, Alexiou C, Hsu J, Sheppard S V, Haw M P, Ohri S K (2002). Leukodepletion reduces renal injury in coronary revascularization: a prospective randomized study. Ann Thorac Surg 74: 372-377.

Tang A T, Knott J, Nanson J, Hsu J, Haw M P, Ohri S K (2002). A prospective randomized study to evaluate the renoprotective action of beating heart coronary surgery in low risk patients. Eur J Cardiothorac Surg 22: 118-123.

Tarhan S, Moffitt E A (1971). Anesthesia and supportive care during and after cardiac surgery. Ann Thorac Surg 11: 64-89.

Taylor K M (1996). SIRS--the systemic inflammatory response syndrome after cardiac operations. Ann Thorac Surg 61: 1607-1608.

Taylor K M, Bain W H, Jones J V, Walker M S (1976). The effect of hemodilution on plasma levels of cortisol and free cortisol. J Thorac Cardiovasc Surg 72: 57-61.

Taylor K M, Bain W H, Russell M, Brannan J J, Morton I J (1979). Peripheral vascular resistance and angiotensin II levels during pulsatile and no-pulsatile cardiopulmonary bypass. Thorax 34: 594-598.

Taylor K M, Brannan J J, Bain W H, Caves P K, Morton I J (1979). Role of angiotensin II in the development of peripheral vasoconstriction during cardiopulmonary bypass. Cardiovasc Res 13: 269-273.

Taylor K M, Wright G S, Bain W H, Caves P K, Beastall G S (1978). Comparative studies of pulsatile and nonpulsatile flow during cardiopulmonary bypass. III. Response of anterior pituitary gland to thyrotropin-releasing hormone. J Thorac Cardiovasc Surg 75: 579-584.

Taylor K M, Wright G S, Bremner W F, Bain W H, Caves P K, Beastall G H (1978). Anterior pituitary response to thyrotrophin-releasing hormone during open-heart surgery. Cardiovasc Res 12: 114-119.

Taylor K M, Wright G S, Reid J M, Bain W H, Caves P K, Walker M S, Grant J K (1978). Comparative studies of pulsatile and nonpulsatile flow during cardiopulmonary bypass. II. The effects on adrenal secretion of cortisol. J Thorac Cardiovasc Surg 75: 574-578.

te Velthuis H, Jansen P G, Oudemans-van Straaten H M, Sturk A, Eijsman L, Wildevuur C R (1995). Myocardial performance in elderly patients after cardiopulmonary bypass is suppressed by tumor necrosis factor. J Thorac Cardiovasc Surg 110: 1663-1669.

te Velthuis H, Jansen P G, Oudemans-van Straaten H M, van Kamp G J, Sturk A, Eijsman L, Wildevuur C R (1996). Circulating endothelin in cardiac operations: influence of blood pressure and endotoxin. Ann Thorac Surg 61: 904-908.

Teiger E, Menasche P, Mansier P, Chevalier B, Lajeunie E, Bloch G, Piwnica A (1993). Triiodothyronine therapy in open-heart surgery: from hope to disappointment. Eur Heart J 14: 629-633.

Tennenberg S D, Clardy C W, Bailey W W, Solomkin J S (1990). Complement activation and lung permeability during cardiopulmonary bypass. Ann Thorac Surg 50: 597-601.

Theodoropoulos G, Lloyd L R, Cousins G, Pieper D (2001). Intraoperative and early postoperative gastric intramucosal pH predicts morbidity and mortality after major abdominal surgery. Am Surg 67: 303-308.

Thompson S A (1939). Development of cardiopericardial adhesions following use of talc. Proc Soc Exp Biol Med: 260.

Thrush D N, Austin D, Burdash N (1995). Cardiopulmonary bypass temperature does not affect postoperative euthyroid sick syndrome? Chest 108: 1541-1545.

Toivonen H J, Ahotupa M (1994). Free radical reaction products and antioxidant capacity in arterial plasma during coronary artery bypass grafting. J Thorac Cardiovasc Surg 108: 140-147.

Tsiotos G G, Mullany C J, Zietlow S, van Heerden J A (1994). Abdominal complications following cardiac surgery. Am J Surg 167: 553-557.

Tsujino M, Hirata Y, Imai T, Kanno K, Eguchi S, Ito H, Marumo F (1994). Induction of nitric oxide synthase gene by interleukin-1 beta in cultured rat cardiocytes. Circulation 90: 375-383.

Utley J R (1990). Pathophysiology of cardiopulmonary bypass: current issues. J Card Surg 5: 177-189.

Utley J R, Todd E P, Wachtel C C, Cain R B, Collins J C (1976). Effect of hypothermia, hemodilution, and pump oxygenation on organ water content and blood flow. Surg Forum 27: 217-219.

Utley J R, Wachtel C, Cain R B, Spaw E A, Collins J C, Stephens D B (1981). Effects of hypothermia, hemodilution, and pump oxygenation on organ water content, blood flow and oxygen delivery, and renal function. Ann Thorac Surg 31: 121-133.

Vagenakis A G, Burger A, Portnary G I, Rudolph M, O'Brian J R, Azizi F, Arky R A, Nicod P, Ingbar S H, Braverman L E (1975). Diversion of peripheral thyroxine metabolism from activating to inactivating pathways during complete fasting. J Clin Endocrinol Metab 41: 191-194.

Van Dijk D, Jansen E W, Hijman R, Nierich A P, Diephuis J C, Moons K G, Lahpor J R, Borst C, Keizer A M, Nathoe H M, Grobbee D E, De Jaegere P P, Kalkman C J, Group. T O S (2002). Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. JAMA 287: 1405-1412.

van Dijk D, Nierich A P, Jansen E W, Nathoe H M, Suyker W J, Diephuis J C, van Boven W J, Borst C, Buskens E, Grobbee D E, Robles De Medina E O, de Jaegere P P (2001). Early outcome after off-pump versus on-pump coronary bypass surgery: results from a randomized study. Circulation 104: 1761-1766.

van Nieuwenhuizen R C, Peters M, Lubbers L J, Trip M D, Tijssen J G, Mulder B J (1999). Abnormalities in liver function and coagulation profile following the Fontan procedure. Heart 82: 40-46.

Villarreal D, Grisham M B, Granger D N (1995). Nitric oxide donors improve gut function after prolonged hypothermic ischemia. Transplantation 59: 685-689.

Vincent J L, Carlier E, Pinsky M R, Goldstein J, Naeije R, Lejeune P, Brimioulle S, Leclerc J L, Kahn R J, Primo G (1992). Prostaglandin E1 infusion for right ventricular failure after cardiac transplantation. J Thorac Cardiovasc Surg 103: 33-39.

Vincent J L, Creteur J (1998). Gastric mucosal pH is definitely obsolete--please tell us more about gastric mucosal PCO2. Crit Care Med 26: 1479-1481.

Vineberg A (1975). Evidence that revascularization by ventricular-internal mammary

artery implants increases longevity. Twenty-four year, nine month follow-up. J Thorac Cardiovasc Surg 70: 381-397.

Vineberg A M (1949). Development of anastomosis between the coronary vessels and a transplanted internal mammary artery. J Thorac Surg 18: 839-850.

Vinten-Johansen J, Zhao Z Q, Sato H (1995). Reduction in surgical ischemic-reperfusion injury with adenosine and nitric oxide therapy. Ann Thorac Surg 60: 852-857.

Wallwork J, Davidson K G (1980). The acute abdomen following cardiopulmonary bypass surgery. Br J Surg 67: 410-412.

Wan I Y, Arifi A A, Wan S, Yip J H, Sihoe A D, Thung K H, Wong E M, Yim A P (2004). Beating heart revascularization with or without cardiopulmonary bypass: evaluation of inflammatory response in a prospective randomized study. J Thorac Cardiovasc Surg 127: 1624-1631.

Wan S, LeClerc J L, Vincent J L (1997). Cytokine responses to cardiopulmonary bypass: lessons learned from cardiac transplantation. Ann Thorac Surg 63: 269-276.

Wan S, Marchant A, DeSmet J M, Antoine M, Zhang H, Vachiery J L, Goldman M, Vincent J L, LeClerc J L (1996). Human cytokine responses to cardiac transplantation and coronary artery bypass grafting. J Thorac Cardiovasc Surg 111: 469-477.

Wang M J, Chao A, Huang C H, Tsai C H, Lin F Y, Wang S S, Liu C C, Chu S H (1994). Hyperbilirubinemia after cardiac operation. Incidence, risk factors, and clinical significance. J Thorac Cardiovasc Surg 108: 429-436.

Wartofsky L, Burman K D (1982). Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome". Endocr Rev 3: 164-217.

Watters M P, Ascione R, Ryder I G, Ciulli F, Pitsis A A, Angelini G D (2001). Haemodynamic changes during beating heart coronary surgery with the 'Bristol Technique'. Eur J Cardiothorac Surg 19: 34-40.

Watters M P R, Ascione R, Ryder I G, Ciulli F, Pitsis A A, Angelini G D (2001). Haemodynamic changes during beating heart coronary surgery with the Bristol Technique. Eur J Cardiothorac Surg 19: 34-40.

Wehlin L, Vedin J, Vaage J, Lundahl J (2004). Activation of complement and leukocyte receptors during on- and off pump coronary artery bypass surgery. Eur J Cardiothorac Surg 25: 35-42.

Welsh F K, Farmery S M, MacLennan K, Sheridan M B, Barclay G R, Guillou P J, Reynolds J V (1998). Gut barrier function in malnourished patients. Gut 42: 396-401.

Welsh F K, Ramsden C W, MacLennan K, Sheridan M B, Barclay G R, Guillou P J, Reynolds J V (1998). Increased intestinal permeability and altered mucosal immunity in cholestatic jaundice. Ann Surg 227: 205-212.

Worwag E M, Craig R M, Jansyn E M, Kirby D, Hubler G L, Atkinson A J, Jr. (1987). D-xylose absorption and disposition in patients with moderately impaired renal function. Clin Pharmacol Ther 41: 351-357.

Yamamoto T, Takazawa K, Hariya A, Ishikawa N, Dohi S, Matsushita S (2002). Off-pump coronary artery bypass grafting in a patient with liver cirrhosis. Jpn J Thorac Cardiovasc Surg 50: 526-529.

Yeh C H, Lin Y M, Wu Y C, Wang Y C, Lin P J (2004). Nitric oxide attenuates cardiomyocytic apoptosis via diminished mitochondrial complex I up-regulation from cardiac ischemia-reperfusion injury under cardiopulmonary bypass. J Thorac Cardiovasc Surg 128: 180-188.

Youker K A, Hawkins H K, Kukielka G L, Perrard J L, Michael L H, Ballantyne C M, Smith C W, Entman M L (1994). Molecular evidence for induction of intracellular adhesion molecule-1 in the viable border zone associated with ischemia-reperfusion injury of the dog heart. Circulation 89: 2736-2746.

Zacharias A, Schwann T A, Parenteau G L, Riordan C J, Durham S J, Engoren M, Fenn-Buderer N, Habib R H (2000). Predictors of gastrointestinal complications in cardiac surgery. Tex Heart Inst J 27: 93-99.

Zamvar V, Williams D, Hall J, Payne N, Cann C, Young K, Karthikeyan S, Dunne J (2002). Assessment of neurocognitive impairment after off-pump and on-pump techniques for coronary artery bypass graft surgery: prospective randomised controlled trial. Br Med J 325: 1268.

Zaugg C E, Hornstein P S, Zhu P, Simper D, Luscher T F, Allegrini P R, Buser P T (1996). Endothelin-1-induced release of thromboxane A2 increases the vasoconstrictor effect of endothelin-1 in postischemic reperfused rat hearts. Circulation 94: 742-747.

Zehr K J, Poston R S, Lee P C, Uthoff K, Kumar P, Cho P W, Gillinov A M, Redmond J M, Winkelstein J A, Herskowitz A, et al. (1995). Platelet activating factor inhibition reduces lung injury after cardiopulmonary bypass. Ann Thorac Surg 59: 328-335.

Zhu Z G, Wang M S, Jiang Z B, Jiang Z, Xu S X, Ren C Y, Shi M X (1994). The dynamic change of plasma endothelin-1 during the perioperative period in patients with rheumatic valvular disease and secondary pulmonary hypertension. J Thorac Cardiovasc Surg 108: 960-968.

Ziegler T R, Smith R J, O'Dwyer S T, Demling R H, Wilmore D W (1988). Increased intestinal permeability associated with infection in burn patients. Arch Surg 123: 1313-1319.