70

EPIDURAL ANALGESIA FOR CORONARY ARTERY BYPASS GRAFT SURGERY

DISSERTATION
for

MASTER OF MEDICINE IN ANAESTHESIA

BERNHARD J.C.J. RIEDEL, MB.ChB, FCA (SA).

DEPARTMENT OF ANAESTHESIA
FACULTY OF MEDICINE
UNIVERSITY OF CAPE TOWN
SOUTH AFRICA

1999

CONTENTS

TABLE OF ABBREVIATIONS

ACE:	angiotensin-converting enzyme
ACT:	activated coagulation time
CABG:	coronary artery bypass graft surgery
CAD:	coronary artery disease
CI:	cardiac index
CK:	creatine kinase
CK-MB:	creatine kinase - MB isoenzyme
CO:	cardiac output
CPB:	cardiopulmonary bypass
cTn-I:	cardiac troponin-I isoform
CVP:	central venous pressure
ECG:	electrocardiograph
GA:	general anaesthesia
IHD:	ischaemic heart disease
ITU:	intensive therapy (care) unit
LMWH:	low molecular weight heparin
LVSWI:	left ventricular stroke work index
MAP:	mean arterial pressure

MPAP:	mean pulmonary artery pressure
MI:	myocardial infarction
MIDCAB:	minimally invasive direct vision coronary artery bypass surgery
NSAID:	non steroidal anti-inflammatory drug
NYHA:	New York Heart Association functional class
PAI-1:	plasminogen activator inhibitor-1
PAOP:	pulmonary artery occlusion (wedge) pressure
P-MI:	perioperative myocardial infarction
PTCA:	percutaneous transluminal coronary angioplasty
PVRI:	pulmonary vascular resistance index
SPECT:	technetium-pyrophosphate scanning
SVRI:	systemic vascular resistance index
TEA:	thoracic epidural analgesia
TEG:	thromboelastography

I.PREFACE AND ACKNOWLEDGEMENT

It has been suggested that, in addition to superlative analgesia, regional anaesthetic and analgesic techniques may reduce surgical stress-induced alterations of organ function thereby contributing to accelerated recovery following surgery. For example, the specific blockade of nociceptive reflex arches by using thoracic epidural analgesic (TEA) techniques may improve the following stress-induced alterations of organ function;

i) improved pulmonary function (the superior pain relief - allows patients to breathe and cough sufficiently),
ii) improved recovery of gastrointestinal function after upper abdominal surgery - thereby reducing the risk of bacterial translocation, and
iii) a decrease in graft occlusion rate following vascular surgery.

It is therefore unsurprising that regional techniques, which can be performed safely in most patients when contraindications are carefully observed, are widely used either alone or as an adjuvant anaesthetic and postoperative analgesic technique in most surgical disciplines.

The perception of many anaesthetists, that there is less risk of traumatising the spinal cord in the lumbar region has led to this being the preferred site of neuraxial instrumentation. However, it is important to note that many of the positive effects of regional analgesia (especially epidural analgesia) are forgone at this level. In fact, if there is insufficient rostral spread of a lumbar epidural block above the fifth thoracic level, it is suggested that cardiac complications can occur due to reflex activation and sympathetic outflow in the unblocked thoracic region. This has led to renewed interest in thoracic epidural techniques, especially in patients suffering from ischaemic heart disease (IHD) or other forms of cardiac disease, as they may possibly benefit the most from the advantages of this technique *viz.*,

- stress response attenuation
- sympatholysis,
- superlative analgesia.

In fact, the benefits of TEA in IHD were subsequently supported when Blomberg *et. al* [1992] showed that TEA provided selective vasodilation of atherosclerotic coronary arteries without inducing coronary steal.

The paradox of cardiac anaesthesia lies in the fact that patients with ischaemic heart disease scheduled for coronary artery bypass graft (CABG) surgery would most likely benefit the most from TEA, however, cardiac surgery has traditionally been regarded as an absolute contra-indication to this technique. This contraindication relates to the potential risk of epidural haematoma formation in these patients who are on aspirin therapy, as well as needing full systemic heparinisation to facilitate cardiopulmonary bypass (CPB).

On reviewing the medical literature, there is a clear resurgence of interest in the use of TEA in cardiac anaesthesia. This resurgence was brought about by laboratory-based evidence that TEA-induced sympatholysis may be cardioprotective through the promotion of myocardial blood flow to areas at-risk and subsequent early, small clinical studies suggesting that TEA was feasible, and possibly also beneficial in CABG surgery [Joachimsson *et. al*, 1989; Liem (1-3) *et. al*, 1992; Stenseth *et. al*, 1994].

Despite the positive results of these early studies and suggestions that TEA may be the preferred anaesthetic/analgesic technique in select groups of patients (promoting early extubation and fast-tracking) undergoing cardiac surgery, many anaesthetists are still reluctant, however, to use this technique because of the theoretical increased risk of the patient suffering a spinal haematoma and subsequent paraplegia.

In order to outweigh this theoretical risk it is important that we show that **added benefit**, in addition to the provision of analgesia and expedited postoperative convalescence, can be obtained by using TEA.
It is therefore our duty as anaesthetists and perioperative physicians to determine whether TEA may also affect the pathophysiology of the disease process, especially in the perioperative period - and thereby influencing the subsequent long term outcome and quality of life of the patient. An example of this latter point would be the potential role of TEA in ;

- reducing the incidence of perioperative myocardial infarction (P-MI), through the suggested cardioprotective effects of TEA,
- reducing the incidence of early postoperative graft failure, through either;

* reduction of native coronary artery and/or graft (conduit) spasm, or
* reduction of postoperative hypercoagulability.

Furthermore, we as anaesthetists should firmly establish the risk-benefit ratio of this technique and gain proficiency in the management of the patient with a TEA before cardiac units are lured into routine use of TEA in an attempt to facilitate early extubation and 'fast-tracking' through their intensive therapy units in this era where 'fast-tracking' is encouraged by a cost-saving driven economic climate, rather than on pure clinical grounds.

During my postgraduate training years in anaesthesia, under the privileged supervision of Professor M. F. M. James (Head, Department of Anaesthetics, Groote Schuur Hospital & University of Cape Town, South Africa) I developed a special interest in the fields of regional and cardiac anaesthesia. These formative years spent in postgraduate anaesthetic training coincided with numerous medical and political events that helped promote this interest, these included;

- a resurgence of interest in regional anaesthesia for cardiac surgery,
- an ongoing search for anaesthetic techniques that allow for cardioprotection and facilitation of fast-tracking in cardiac surgery,
- a changing health policy in the new South Africa, with diminishing funding for academic-based tertiary medicine, bought on by a shift of emphasis towards a much needed primary health care.

It was therefore a natural process to want to investigate the role of TEA in the setting of cardiac surgery, attempting to find where this technique fits into both the medical and economical realms of everyday clinical practice.

Under the guidance of Dr David Royston (Consultant Anaesthetist, Royal Brompton & Harefield NHS Trust and Senior Lecturer, Department of Anaesthetics, St George's Medical School, University of London, UK) we set out to design a pilot study, of which the **primary aim** was to confirm or refute the role of TEA in cardiac surgery.
This pilot study was designed to;

- investigate whether a **favourable risk-benefit ratio** exists or not - i.e. whether the theoretical increase in risk of epidural haematoma is

outweighed by provision of a potentially more favourable perioperative physiological milieu *viz.*, stress response attenuation, sympatholysis and superlative analgesia.

- investigate whether an opioid-free technique could **improve postoperative recovery**, with improved haemodynamic stability, earlier extubation and facilitated patient fast-tracking.
- subsequently identify the subgroup of patients that would benefit the most from this technique, thereby allowing us to design a larger prospective, randomised trial which would allow us to investigate the more important issue of whether the promotion of a more favourable perioperative physiological milieu could translate into **myocardial protection** and/or **graft protection**, with an improved outcome for the population as a whole (evidence-based medicine).

Undoubtedly any study of this magnitude requires assistance from various clinical and laboratory persons and I am therefore grateful to : Professor George Hall (Head, Department of Anaesthesia, St George's Medical School, University of London, UK), a world authority on the reduction of the perioperative stress response, for his guidance in designing this pilot study, as well as for allowing us access to his laboratory; Mr Marcus Haw (Senior Lecturer & Honorary Consultant Cardiac Surgeon, Royal Brompton & Harefield NHS Trust, UK) for his enthusiasm and willingness to adapt to and subsequently prefer this technique during cardiac surgery; and to members of the following departments for their ongoing help in processing specimens ;

- Department of Anaesthesia (especially Dr Fionnuala Lyons), Royal Brompton & Harefield NHS Trust, UK.
- Department of Anaesthesia (especially Annette Bryant)
- St George's Medical School, University of London, UK.
- Department of Biochemistry (especially Dr Frank Murphy), Royal Brompton & Harefield NHS Trust, UK.
- Department of Cardiology, (especially Yvonne Stern) Northwick Park Hospital, UK.
- School of Biomedical Sciences (especially David Forster), Queens Medical Centre, University of Nottingham, UK.

II. BACKGROUND

A.Introduction

Effective analgesia together with hormonal stress-response suppression is suggested to have favourable associations with postoperative outcome in noncardiac surgery [Yeager et. al, 1987; Tuman et. al, 1991; Lui et. al, 1995]. This possible reduction in morbidity and mortality rates relates to the reduction in adverse hemodynamic, metabolic, immunologic, and hemostatic alterations [Roizen, 1988; Kehlet, 1989; Weissman, 1990].

Aggressive postoperative pain management and stress-response attenuation may also be of benefit in cardiac surgery, with a decrease in morbidity and mortality rates [Mangano et. al, 1992; Anand et. al, 1992].
With the possible exception of remifentanil, however, high-dose opioids alone or in combination with other pharmacological agents (e.g. ganglion blockers [Desborough et. al, 1990]) have proved insufficient in preventing the hormonal changes related to cardiopulmonary bypass (CPB). Procedures directed at the sympathetic nervous system may have benefits extending beyond superlative analgesia, with a reduction in surgical stress-induced alterations of organ function thereby contributing to accelerated recovery in the postoperative period. These and other factors have lead to an increasing interest in the use of TEA for patients undergoing coronary artery bypass graft (CABG) surgery [Liem et. al, 1992; Stenseth et. al, 1994; Moore et. al, 1995].

Catecholamine responses to CPB were abolished in patients who received TEA in addition to intravenous sufentanil [Moore et. al, 1995]. The epidural technique (as high as C7-T1 or T1-T2) in combination with full intraoperative heparinisation, however, lends itself to potentially serious adverse effects, the most devastating of which is the formation of an epidural haematoma resulting in an irreversible neurologic deficit, such as paraplegia or worse still, ventilator dependency. Other adverse effects could potentially include epidural abscess formation, dural puncture, respiratory depression and poor epidural positioning with a detrimental increase in sympathetic outflow.

It is therefore crucial that TEA be used with great caution in selected patients, that the risks and benefits be firmly established, and that further clinical trials be conducted before it becomes routine clinical practice.

B.Potential benefits

To establish whether the haemodynamic, metabolic, immunologic, and haemostatic effects of TEA, brought about by improved stress response attenuation, sympatholysis and superlative analgesia, offers any benefits above current general anaesthetic techniques in cardiac surgery we need to explore whether TEA; provides protection to the myocardium (figure 1.) and other end-organs, and / or promotes numerous additional benefits, including; early mobilisation and facilitation of fast-tracking.

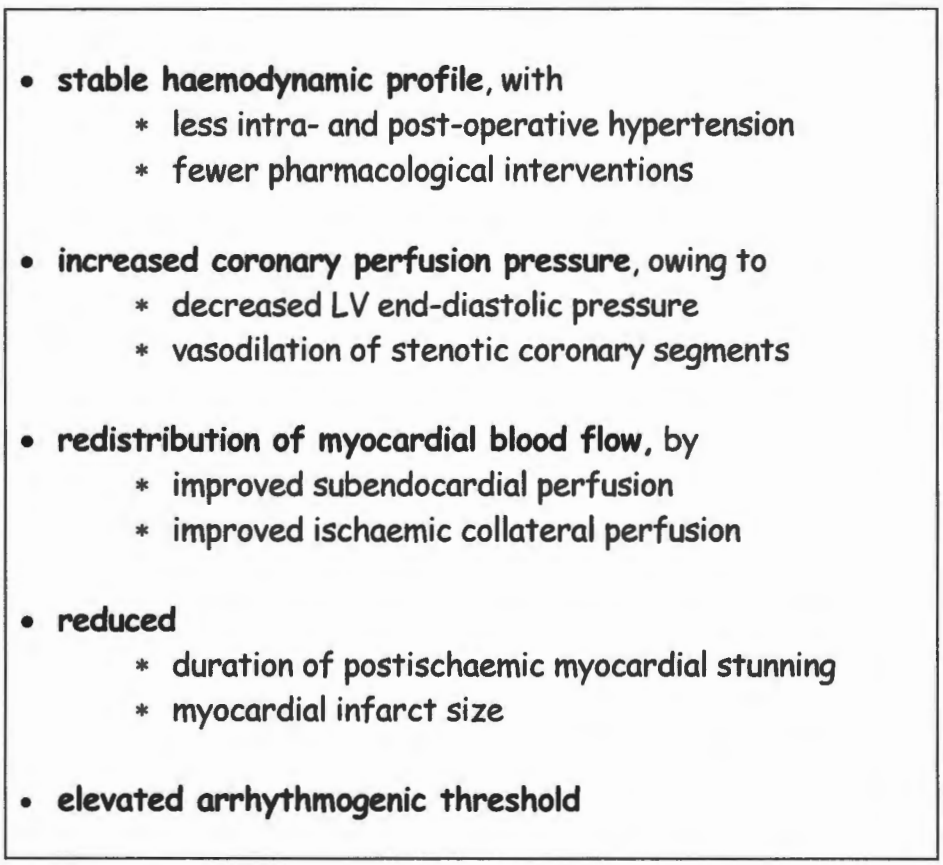


Figure 1. Potential cardiovascular benefits conferred by thoracic epidural analgesia (TEA).

- **Myocardial protection :**

Perioperative ischaemic events occur in up to 37% of patients, with a threefold increase in the incidence of P-MI in those who develop ischaemia [Slogoff & Keats, 1985]. The overall frequency of P-MI following cardiac surgery varies from 2.8% to 13.7% [Miller et. al, 1982; Gray et. al, 1982] and accounts for 40% of CABG-related deaths [Chaitman et. al, 1983].

Sympathetic stimulation promotes constriction of stenosed arteriosclerotic coronary arteries [Gould 1980; Brown et. al, 1985], a redistribution of blood flow from the endocardium to the epicardium and an increase in infarct size. These factors contribute to perioperative myocardial ischaemia and infarction (P-MI) that may complicate CABG surgery.

Both coronary arteries and arterioles have innervated vasoconstrictor α-receptors, and there is considerable evidence for α-adrenergic regulation of large coronary arteries and coronary resistance vessels [Feigl, 1982; Young et. al, 1986]. Blomberg *et al.* (1990) showed with arteriography that TEA **increased the diameter of stenotic segments** significantly without any change in non-stenotic segments or small vessel coronaries, thereby alleviating the theoretical fear that TEA could promote a coronary "steal syndrome". This withdrawal of the cardiac vasoconstrictor tone (T1 - T5) by TEA revealed a paradoxical resting vasoconstrictor tone, that may relate to the damaged endothelium in diseased epicardial arteries. It is interesting to note that Fujita *et al.* [1996] showed that TEA reduced the regional ischaemia induced by intracoronary injection of endothelin, in a dog model. Endothelin is a potent endothelium-dependent vasoconstrictor whose concentrations are known to rise during CPB.

TEA has been shown to provide a stable haemodynamic profile and decreased left-ventricular end-diastolic pressure in animal models [Blomberg et. al, 1990] and bradycardia without increasing LVEDP in humans [Blomberg et. al, 1989]. Most clinical studies are in agreement that TEA provides greater haemodynamic stability (in particular a reduction in the incidence of perioperative hypertension) thereby requiring fewer pharmacological interventions to maintain coronary perfusion pressure in CABG surgery [Blomberg et. al, 1990; Liem et. al, 1992; Stenseth et. al, 1994]. TEA, furthermore, mediates a profound **redistribution of myocardial blood flow in favour of the vulnerable subendocardial layers** and decreases coronary

vascular resistance for collateral flow into ischaemic myocardium, as shown in dog models [Klassen et. al, 1980; Davis et. al, 1986].

All these factors improve the myocardial oxygen supply/demand balance (figure 2.) and experimental data exist showing a reduction in myocardial infarction size by TEA [Flatley et. al, 1985; Tsuchida et. al, 1984]. Supporting this, Rolf *et al.* [1996] demonstrated a beneficial effect of TEA on recovery of myocardial stunning in awake chronically instrumented dogs. The TEA was effective during the induction of brief regional myocardial ischaemia and resulted in a reduction of postischaemic myocardial dysfunction (stunning) as assessed by loss of wall-thickening fraction with pulsed Doppler epicardial probes. However, in the presence of propofol anaesthesia [Rolf et. al, 1996] TEA subsequently failed to reduce this duration of postischaemic myocardial dysfunction, with an unaltered blood-flow ratio between the subepicardial and subendocardial layers, which possibly relates to the vasodilatory properties of propofol. In a similar follow up study [Meissner et. al, 1998] sevoflurane-anaesthetised dogs showed similar recovery from myocardial stunning to that evidenced previously in awake dogs with TEA. This cardioprotective effect by sevoflurane was seen in the presence of, as well as in the absence of TEA and they therefore suggested that there was no synergistic protective effect (on the recovery of WTF) by TEA and sevoflurane anaesthesia, despite their known single protective effects. This may be due to both agents influencing sympathetic activity and influencing coronary vascular tone. Nevertheless, the non-additive effect of sevoflurane and TEA is in accordance with non-cardiac clinical studies in which TEA failed to improve cardiac outcome when used intra-operatively only [Baron et. al, 1991; Bode et. al, 1996], but improved outcome when used in the postoperative period [Yeager et. al, 1987; Brodner et. al, 1998]. The main effect of TEA may therefore result from postoperative effects.

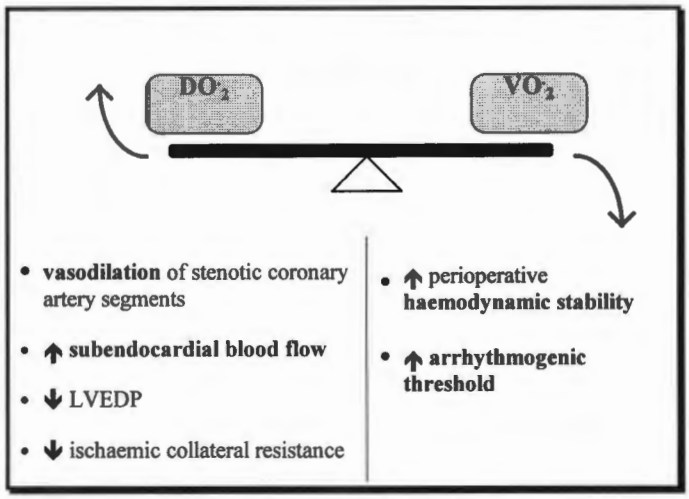


Figure 2. Cardiac sympatholysis (T_{1-4}) promotes an improved myocardial oxygen supply/demand relationship.

The autonomic nervous system plays a critical role in the central modulation of cardiac rhythm and may predispose the ischaemic myocardium to dysrhythmias [Euler et. al, 1985; Podrid et. al, 1990]. TEA has been shown to **elevate the arrhythmogenic threshold** to exogenously administered adrenaline in myocardium sensitised with halothane, an effect that may be mediated by unopposed parasympathetic activity [Kamibayashi et. al, 1995]. Similarly, Blomberg *et al.* [1988] showed a lower incidence of malignant ventricular arrhythmias during acute myocardial ischaemia in rats under TEA. In contrast, however, TEA instituted after the ischaemic episode did not reduce postinfarction ventricular dysrhythmia suggesting the epidural should be effective at the time of the ischaemic insult [Hogan et. al, 1997].

• **Acute coronary syndromes :**

The role of high-TEA in the management of the patient presenting with an acute coronary syndrome (unstable angina, non-Q wave infarction) is under investigation.

These patients stand to benefit from the following effects of TEA: good analgesia with cessation of myocardial ischaemia-induced cardiac sympathetic reflexes, and the beneficial effects on the major determinants of myocardial oxygen supply and demand. The sympathetic reflexes increase circulatory catecholamines, thereby triggering platelet accumulation in focal areas of diseased coronary arteries (Folt's phenomenon). Subsequent activation of these platelets releases serotonin which further precipitates coronary vasoconstriction [Staats et. al, 1997].

Patients with unstable angina can benefit from the haemodynamic stability and epicardial vasodilation brought on by TEA sympatholysis, however, these patients have a reduction in myocardial oxygen supply rather than an increase in demand. This is attributed to the development of a sudden destabilising coronary event [Fuster et. al, 1992] due to either or a combination of clot formation, rupture of a fatty plaque, and intense coronary vasoconstriction. These processes are the endpoints of several activated pathophysiological cascades such as the clotting and inflammatory cascades, disturbed cardiac noradrenaline metabolism and the involvement of smooth muscle cells and fibroblast growth factors [Fuster et. al, 1992; Kleinman, 1997]. It is important to note that some of these cascades are not addressed by TEA and thus stand to benefit more from conventional therapies such as aspirin and heparin [Theroux et. al, 1988] or newer therapeutic modalities such as platelet glycoprotein IIb/IIIa receptor antagonists [Kereiakes, 1998].

The role and safety of what could be an optimal management strategy for patients with unstable angina on the medical care unit, that is, the combination of TEA (instituted prior to heparin administration) followed by chronic heparin infusion, or newer therapeutic modalities such as platelet glycoprotein IIb/IIIa receptor antagonists needs careful study by prospective randomised trials.

- **Thromboembolism :**

The risk of fatal pulmonary embolism is estimated at 5% following major surgery for individuals at high thrombotic risk [Clagett et. al, 1995; NCEPOD, 1996]. Meta-analysis has shown a reduced incidence in deep venous thrombosis when regional anaesthesia is used instead of general anaesthesia for emergency hip surgery, elective hip replacement, and other forms of non-cardiac surgery [Sorensen et. al, 1991].

Although the risk-profile of patients undergoing CABG surgery is high for deep venous thrombosis and fatal pulmonary embolism, this is offset by the use of preoperative aspirin therapy and perioperative anticoagulation. It thus remains to be shown that thromboembolism is pertinent in CABG surgery, whether TEA can reduce the incidence of deep vein thrombosis and

pulmonary embolism in this setting, and whether TEA blockade into the postoperative period is necessary.

- **Graft Patency :**

Current experience in peripheral vascular surgery suggests that patients requiring re-operation for graft thrombosis have higher circulating concentrations of noradrenaline [Parker et. al, 1995] and plasminogen activator inhibitor-1 (marker of impaired fibrinolytic activity) [Rosenfeld et. al (PIRAT Study Group), 1993] in the perioperative period.
It has been reported that regional anaesthesia results in a reduction in the incidence of graft thrombosis after peripheral vascular surgery [Tuman et. al, 1991; Christopherson et. al (PIRAT Study Group), 1993]. These studies have, however, been criticised for methodological limitations. Unlike the study by Yeager [1987], Tuman [1991] studied a homogeneous group of patients undergoing vascular surgery, however, the limitation of this study was that these patients were exposed to an inhomogeneous surgical stress (approximately half underwent aortic surgery and half underwent lower extremity arterial grafting). Additionally, non-equivalent modalities for postoperative pain control were used. Patients who were randomised to the epidural group received continuous postoperative epidural analgesia in contrast to the those randomised to the unsupplemented general anaesthesia group who received intramuscular or oral narcotics as needed from the surgical ward nurses with no special monitoring of the efficacy of this modality. The differences reported by this group may therefore, be related to the fact that the patients randomised to unsupplemented general anaesthesia received systematically inferior postoperative analgesia. In contrast, Christopherson studied a homogeneous group of patients undergoing a similar homogeneous surgical stress, namely, lower extremity vascular surgery. It may be argued that the limitations of this study was that the surgical procedure was not stressful enough and that they were unable to separate the differences due to intraoperative techniques and postoperative techniques because all patients who received epidural anaesthesia received epidural analgesia, and all who received general anaesthesia received intravenous patient controlled analgesia. It may be that the type of postoperative analgesia used may influence the frequency of thrombotic complications and graft occlusion.

In contrast other groups [Cook et. al, 1986; Pierce et. al, 1997] have failed to show any benefit of regional anaesthesia (spinal, and spinal or epidural, respectively) during or after surgery. Clearly, further prospective randomised studies are required to provide an answer to this issue.

With respect to cardiac surgery, the Society of Thoracic Surgeons National Database reveals that 15% of patients underwent reoperative surgery related to progression of disease in native vessels or atherosclerotic occlusion in previously placed vein grafts in the year 1995/96. Graft occlusion within the first month and 10 years postoperatively is estimated at 10% and 50% of vein grafts, respectively.
Factors promoting early phase graft occlusion include; surgical technique exposure of the sub-endothelial tissues, surgical stress-response promoting a hypercoagulable postoperative state, and increased levels of catecholamines which may promote vasoconstriction with poor distal run off.

The use of the internal mammary artery to the left anterior descending coronary artery is associated with patency rates greater than 90%. However, the use of multiple arterial grafts may be associated with an increase in perioperative morbidity that is related to the increased reactivity of these arterial conduits, which in the presence of increased circulating catecholamines may result in graft spasm and secondary myocardial ischaemia. If arterial revascularisation is superior to vein grafts, then the role of TEA in the prevention of graft spasm during complete arterial coronary revascularisation needs to be studied. Furthermore, the suggestion that regional anaesthesia may reduce the incidence of graft thrombosis after peripheral vascular surgery [Tuman et. al, 1991; Christopherson et. al (PIRAT Study Group), 1993] it is therefore not too inconceivable that TEA may reduce this early phase of coronary bypass graft occlusion, thereby reducing the need for reoperative CABG surgery. These possible benefits by TEA, however, still need to be explored.

- **Pulmonary effects :**

Whether the frequency and severity of postoperative pulmonary complications can be favourably influenced with TEA is controversial [Yeager et. al, 1987; Pierce et. al, 1997]. It is suggested that TEA may diminish ventilation through peripheral neural blockade or the systemic effect of local anaesthetics. The provision of superb analgesia, however, more

importantly allows earlier mobilisation and more effective physiotherapy. Recently, Sakura et al. [1996] investigating the effects of lumbar and thoracic epidural anaesthesia on the ventilatory response to hypercapnia and hypoxia in elderly patients, found that lumbar epidural anaesthesia had no significant effect on resting ventilation, whereas thoracic epidural block caused a significant decrease in minute ventilation (13%) and tidal volume (14%). The ventilatory response to hypercapnia was significantly increased after lumbar epidural anesthesia, but no change was observed after thoracic epidural anaesthesia. The slope of the hypoxic response curve did not show any change in either group, but minute ventilation at a SpO_2 of 90% significantly increased after lumbar epidural anaesthesia.
It can therefore be assumed that neither lumbar nor thoracic epidural anesthesia per se impairs the ventilatory response to hypercapnia and hypoxia, despite slight impairment in resting ventilation by thoracic epidural anesthesia, in elderly patients.

Stenseth et al. [1996] [53], comparing a low-dose opioid TEA group to a high-dose opioid general anaesthesia group, showed similar reductions in forced vital capacity and forced expiratory volume in 1 second ($FEV_{1.0}$) and increased pulmonary shunt and alveolar-arterial oxygen gradients between the groups in the early postoperative period. However, higher FEV_1 and PEFR on days 2 and 3 were seen in the TEA group than in the control group. Pulmonary shunt and alveolar-arterial oxygen difference increased similarly in both groups, whereas oxygen delivery and mixed venous oxygen saturation were higher in the epidural group. This suggests that TEA yields a slight, but significant, improvement in pulmonary function, most likely due to a more profound postoperative analgesia.

- **Fast tracking:**

Financial and clinical considerations have prompted many anaesthetists to advocate early extubation after uncomplicated revascularisation instead of traditional prolonged respiratory support. Studies by Joachimsson et al. [1989] and Liem et al. [1992], comparing the influence of a general anaesthetic technique using intravenous opioids with a combined regional and general anaesthetic technique, showed that TEA provides superlative analgesia, obviating the need for opioids and reducing the duration of mechanical ventilation, facilitating early extubation with improved respiratory function and enhanced control of blood pressure in the postoperative period. Improvement of these factors could therefore

potentially facilitate fast-tracking, with earlier discharge from intensive therapy and surgical wards.

Newer pharmacological agents, including the ultrashort-acting opioids like remifentanil, also facilitate stress-response attenuation and allow almost immediate awakening, extubation and facilitation of fast-tracking. The draw back of these agents, however, is the lack of postoperative analgesia, requiring the administration of other opioids such as morphine.

A randomised prospective trial comparing either TEA or remifentanil or in combination intraoperatively, followed by postoperative TEA, would be meaningful, as this may be the most effective way of providing perioperative analgesia, stress-response attenuation, and the ability to fast-track a patient through the intensive therapy unit, with early mobilisation and discharge from hospital.

C. Potential adverse effects

Neurologic sequelae:

The incidence of neurologic complications following TEA remains controversial. A major concern of TEA is the possibility of blood vessel damage during insertion of the epidural needle or during the insertion or removal of the epidural catheter resulting in the development of an epidural haematoma, with compression of the spinal cord. Paradoxically, safe catheterisation has been performed on patients with known coagulopathies [Dahlgren N et. al, 1995], however, it is argued that there is increased risk in patients with coagulation disorders and those treated with anti-coagulants [Kane, 1981; Dickman et. al, 1990; Schmidt et. al, 1992].

In the setting of cardiac surgery the patient, often on aspirin, is fully heparinised to facilitate CPB, and this should theoretically increase the incidence of this adverse event. Although rare, it should be remembered that epidural haematoma, most commonly found in the thoracic spine, can also occur spontaneously, without trauma.

In a prospective trial, Giebler et. al [1997] studied the incidence of neurologic sequelae in 2,059 prospective and 2,126 retrospective patients undergoing TEA for abdominothoracic surgery. The following complications occurred; failed block (1.1%), dural puncture (0.7% - with an interesting observation that incidence increased proportional to the usage of more caudal sites), and postoperative radicular type pain (0.2% - all were responsive to catheter removal), and peripheral nerve lesions (0.6% - most of which were attributed to patient positioning). No evidence of permanent sensory or motor defects were attributable to epidural catheterisation, and no evidence of epidural haematoma was seen. In this article Giebler et. al [1997] calculated a 0.07% maximum risk at 95% confidence for permanent neural lesions after TEA.

Reviewing case reports of spinal haematomas associated with both epidural and spinal regional anaesthetic techniques from 1906 to 1994 Vandermuelen et. al [1994] identified a total of only 61 cases. It was noted that 68% (n = 42) of these were associated with impaired coagulation. In most instances (n = 30) some form of heparin therapy was in use. The remaining 12 patients had a variety of conditions including thrombocytopenia, chronic alcohol abuse, chronic renal failure, or were receiving aspirin or other antiplatelet

medication at the time of bleeding. Overall, in 87% of these cases, there were either puncture difficulties or a coagulation disorder. Vandermuelen et. al [1994], estimated the incidence of haematoma formation at 1: 150,000 after epidural catheterisation.

Similarly, Wulf [1996] in a comprehensive search (from 1966 to 1995) found only 51 case reports of spinal haematomas associated with epidural anaesthesia. Most cases were associated with catheter insertion and 42% of these were graded as difficult or traumatic. Coagulopathies or anticoagulant therapy were the predominant risk factors identified. In comparison, low-dose heparin thromboprophylaxis or non-steroidal anti-inflammatory (NSAID) treatment was rarely associated with spinal bleeding complications.

Tryba *et. al* [1997] in a similar review of case reports describing spontaneous epidural haematomas over a 30-year period found 199 cases, of which 20% were associated with anticoagulation therapy.

Bleeding can follow epidural catheter insertion, manipulation [Usubiaga, 1975], migration or removal [Tekkok et. al, 1991, Onishchuk et. al, 1992, Skilton et. al, 1998]. It is important to note that Vandermuelen et. al [1994] found that spinal bleeding occurred immediately after removal of the epidural catheter in 15 out of 32 cases that were reviewed. 11 of these catheters were removed when heparin levels were therapeutic or within 2-hours of stopping heparinisation.

Unfractionated heparin is rapidly cleared from plasma with an average half-life of 1-2 hours. This half-life, however, is dose dependent and may be significantly prolonged at higher doses (56 min at 100 iu/kg cf. 152 min at 400 iu/kg) [McEnvoy, 1997]. Compared to the immediate anticoagulant effects with an intravenous bolus of heparin, peak plasma level is only reached at 2 to 4- hours following subcutaneous administration. Wildsmith and McClure et. al [1991] suggest that a 4- to 6- hour interval is safe following the administration of subcutaneous heparin before instituting a block, and that intravenous heparin should be stopped for 1 to 2- hours to allow safe catheter removal. However, note that this latter time interval represents only one half-life and it would seem more appropriate to recommend that a minimum of two half-lives, or 4-hours pass before epidural catheter removal [Skilton et. al, 1998].

Enoxaparin, a low-molecular-weight heparin (LMWH), was approved for general use in May 1993. It is interesting to note that since the approval the United States Food and Drug Administration (FDA) have received reports of nearly 40 patients in the United States who had spinal / epidural haematoma, following the concurrent use of enoxaparin and neuraxial anaesthesia between May 1993 and April 1998 [Wysowski et. al, 1998, Horlocker et. al, 1998]. In 6 of these patients, bleeding or haematoma developed after removal of the catheter.
In comparison, only 11 cases have been reported since 1987 in the European literature, where the recommended dosage regimen is lower (20 to 40 mg, once daily in Europe vs. 60 mg daily [30 mg twice daily] in the USA), and where published guidelines for the timing of LMWH dosing in relationship to neuraxial instrumentation are in place i.e. 8-12 h prior to neuraxial instrumentation, 8-12 h delay from instrumentation to the next dose, and 8-12 h following the last dose before the epidural catheter is removed [Tryba et. al, 1997]. This represents two half-lives and the equivalent for standard heparin, as mentioned above, would therefore be a time interval of 2-4 h, allowing for a true trough in anticoagulant activity. The plasma half-life of LMWH is 2-4 times that of standard heparin and increases in patients with renal failure. Peak anti-Xa activity occurs 3-4 h after a subcutaneous injection of LMWH, and 12- h anti-Xa levels are approximately 50% of peak levels [Hirsh et. al, 1994]. It is, furthermore, important to remember that the residual anticoagulant effect of LMWH is only partially reversed by protamine.

Recent calculations based on the knowledge of the number of doses of LMWH distributed, estimated the frequency of spinal haematoma between 1: 1,000 and 1: 10,000 neuraxial blocks when used concurrently with LMWH [Horlocker et. al, 1997]. This incidence for spinal haematoma is more frequent than that of previous assessments, which have estimated the probability of significant spinal bleeding after regional anaesthesia to be approximately 1: 200,000. (1: 190,000 - Wulf; 1: 150,000 - Giebler). However, because this represents the upper 95% confidence interval, the actual incidence of spinal haematoma should be much lower, approximately 1: 1,000,000 [Tryba, 1993].

Aspirin therapy is common in patients with IHD, and the evidence for safety of epidurals in patients on aspirin is increasing [Horlocker et. al, 1990; De Swiet et. al (CLASP), 1992; Orlikowski et. al, 1992; Beilin et. al, 1997].

In a prospective study, to determine the risk of haemorrhagic complications associated with regional anaesthesia, Horlocker et. al reviewed 924 patients given spinal or epidural anaesthesia for orthopaedic procedures. Preoperative antiplatelet medications were taken by 39% of patients (21% on aspirin) and it was found that this did not increase the incidence of minor haemorrhagic complications (defined as blood noted during needle or catheter placement) - which was noted to occur in 22% of patients. There were no documented major haemorrhagic complications (spinal haematoma) in this study.
Olikowski et. al [1992] used thromboelastography (TEG) to assess all phases of coagulation in a group of healthy volunteers and in a group of pregnant patients after aspirin therapy, showed that TEG measured indices were unaltered after aspirin therapy, suggesting a functioning coagulation system despite prolonged bleeding time in both groups. The criticism of this study, however, is that the TEG does not evaluate interaction at platelet-endothelial level.

The development of a spinal haematoma is a catastrophic complication. Using an extensive Medline search, the author was unable to find any case reports of spinal haematoma associated with TEA for cardiac surgery. Undoubtedly there are cases and the author is aware of at least 3 unpublished cases of paraplegia (UK and USA, 1997) related to neuraxial techniques for cardiac surgery. A number of important issues that need addressing arise here;
Firstly, the importance of reporting all cases of epidural haematoma in the medical literature, thereby allowing a true assessment of the associated risks, rather than by hear-say.
Secondly, these cases of haematoma are believed to have had their epidural catheter inserted using a more liberal technique, that is, immediately prior to surgery, ensuring at least 60 minutes lapse from the time of instrumentation to the time of full heparinisation. These findings are of extreme concern and we would recommend a more conservative approach be used, that is, epidural catheter insertion at least 2 heparin half-lives (4-hours) [Skilton et. al, 1998] or preferably 12- hours (evening prior to) prior to surgery. Thirdly, guidelines should be in place and strictly adhered to during neuraxial instrumentation. The guidelines suggested for the use of TEA in cardiac surgery (figure 3.) [Vandermeulen et. al, 1994; Rolf et. al, 1997] are sound, if conservative [Liem et. al, 1992; Stenseth et. al, 1994] as several groups [Moore et. al, 1995; Tuffrey et. al, 1997] place the epidural catheter immediately prior to surgery, ensuring at least 60 minutes lapse from the time of instrumentation to the time of full heparinisation

[Vandermeulen et. al, 1994], with postponement of surgery if a bloody tap occurs. Fourthly, all patients undergoing neuraxial block require repeated neurological evaluation to facilitate early diagnosis of spinal haematoma.

Recommended Peri-operative Guidelines

Pre-operative Guidelines

1. Discontinue oral anticoagulants
    - 3 days before epidural catheter insertion
    - check coagulation parameters immediately prior to instrumentation
2. Discontinue aspirin therapy
    - preferably up to 10 days before instrumentation

Intra-operative Guidelines

1. Allow time between epidural catheter placement and heparinisation
    - 12 hours is currently recommended as safe.
    - the epidural catheter is best placed the evening before surgery
2. Intraoperative activated clotting time
    - should not exceed 600 - 700 s.
3. Ensure unobstructed venous drainage during CPB to prevent epidural venous bleeding

Post-operative Guidelines

1. Restore prebypass coagulation parameters following CPB
    - by protamine administration
    - appropriate treatment of other clotting disorders (e.g. thrombocytopenia)
2. Before epidural catheter removal
    - ensure coagulation parameters are within normal ranges

Figure 3. Guidelines recommended for the safe practice of thoracic epidural anesthesia in cardiac surgery [Rolf et. al, 1996].

It is important to emphasise that failed or abandoned neuraxial instrumentation should also be followed up by repeated neurological evaluation in the postoperative period. This is highlighted by a recent case of paraplegia in a patient scheduled for thoracotomy at the authors institution. Neuraxial instrumentation failed, was abandoned, and the elected surgical procedure was successfully completed under general anaesthesia. However, the failure to implement postoperative neurological evaluation resulted in a missed diagnosis of spinal haematoma and the subsequent dire consequence of irreversible paraplegia developing in the postoperative period.

Although certain groups of patients undergoing cardiac surgery may benefit more from the use of TEA e.g. left ventricular hypertrophy (secondary to aortic valve disease etc.), the use of TEA in patients not suitable for fast tracking is more controversial. This relates to the immediate need to investigate patients with computerised tomography or magnetic resonance imaging if a motor deficit out of proportion to the expected block is detected, with emergent neurosurgical decompression within 6 to 12- hours, in an attempt to preserve neurologic function [Stephanov et. al, 1982; Vandermeulen et. al, 1994;]. This also highlights the importance of having a neurosurgical referral system in place.
In an attempt to monitor for spinal haematoma formation in patients with TEA catheters *in situ,* who require prolonged ventilation and sedation in the intensive therapy unit following unexpected complicated surgery, it may be warranted to explore the role of evoked potential monitoring or pressure monitoring of the epidural space.

Other potential complications
Other potential complications of neuraxial blockade include severe cardiovascular events, respiratory depression / apnoea, incomplete block, malpositioned catheters, dural puncture, dural abscess, and site infection.

Well documented series include the American Society of Anaesthesiologists Closed Claim Study [1988] report of 14 cases of sudden cardiac arrest during spinal anaesthesia in healthy patients undergoing minor surgical procedures [Caplan et. al, 1988], and several cases of sudden cardiac arrest during lumbar epidural anaesthesia [Fredericks et. al, 1988; Gild et. al, 1990]. Case reports of severe bradycardia and asystole during TEA catheter insertion [Sprung et. al, 1998] and similarly asystole after segmental TEA in

a healthy patient following breast surgery [Chan et. al, 1997] have been reported.

More commonly, the risk of a more extensive epidural blockade causing marked systemic hypotension with a subsequent reduction in coronary perfusion pressure, and onset of myocardial ischaemia exists. The maintenance of coronary perfusion pressure often requires early prebypass administration of pharmacological vasoconstrictors.

Sympathetic blockade during TEA, may exceed the sensory block in the caudal direction, however, with lumbar epidural sympathetic blockade does not exceed the sensory block in the cephalad direction [Hopf et. al, 1990]. Leaving the parasympathetic tone unopposed, may result in a marked reduction in cardioacceleration (sympathetic activity) in response to a decrease in blood pressure while preserving the cardiac slowing (parasympathetic activity) in response to increased blood pressure [Goertz et. al, 1992]. Chan et al. [1997] warn that in the presence cardiac sympathetic fibre inhibition and enhanced vagal tone, a decrease in central venous return can be an important factor in triggering cardiac arrest during epidural anaesthesia. Postoperative bleeding is often severe following cardiac surgery, and the responsiveness of heart rate to hypovolaemia in patients with TEA is reduced, the hypovolemia may therefore go unnoticed, and risk triggering cardiac arrest.

Measuring sympathetic nerve activity directly in cardiac and renal nerves, it is suggested that sympathetic nerve activity is enhanced in the unanaesthetised segments of cats undergoing thoracic or lumbar epidural anaesthesia [Taniguchi et. al, 1997]. This was, however, associated with a significant decrease in mean arterial pressure and heart rate. On further study it was shown that with the disruption of the carotid sinus and vagoaortic nerves, enhanced sympathetic nerve activity in the unanaesthetised segments was not seen, concluding that the enhanced sympathetic nerve activity in the unanaesthetised segments was produced by the baroreceptor reflex response to anaesthesia-induced hypotension. The effect of the baroreceptor reflex on sympathetic nerve activity has been shown to be quantitatively non-uniform for different organs; for example, the baroreceptor-dependent component of sympathetic nerve activity to the heart or kidney exceeds 95%, where as that to the skin is only 5%.

This suggests that patients with TEA who become hypovolaemic will have compensatory excitation of the renal sympathetic nerves and renal vasoconstriction. Similar reductions in splanchnic bed perfusion are also possible, and studies using gastric tonometry are awaited. These data emphasise the importance of maintaining an adequate perfusion pressure in the presence of TEA, in an attempt to avoid the compensatory baroreceptor reflex-induced sympathetic nerve hyperactivity in the unanaesthetised segments.

It thus follows that catheter position is an important variable if this technique is to be successful. For example if the catheter is malpositioned and the cardiac nerves (T1-4) are left unblocked then compensatory baroreceptor reflex-induced sympathetic nerve hyperactivity will have detrimental effects, promoting constriction of stenosed arteriosclerotic coronary arteries [Gould 1980; Brown et. al, 1985], redistribution of blood flow from the endocardium to the epicardium and an increase in infarct size. These factors may all contribute to perioperative myocardial ischaemia and result in perioperative myocardial infarction (P-MI) and complicate CABG surgery.
Catheters are positioned by various authors in a wide range of positions ranging from vertebral interspace C7 to T6. Radiographs of radio-opaque epidural catheters inserted for patients undergoing thoracic surgery showed that despite the positioning of the epidural needle orifice in the cephalad direction and advancement of the catheter 3 to 4 cm in the same direction, only 39 % of the catheters were positioned cephalad compared with the insertion level. To study the migration of these catheters, chest radiography was performed daily for 3 days after operation. The catheter tip position remained unchanged in all patients operated upon in the supine position. In those operated on in the lateral position, the catheter tip retracted from day 1 to day 2 by an average of 0.69 cm (SD, 1.08; $p < 0.05$), and from day 2 to day 3 by an average of 0.35 cm (SD, 0.67; $p < 0.05$) [Hendriks et. al, 1997]. Clearly, every attempt should be made for optimal catheter positioning, thereby ensuring blockade of cardiac sympathetic innervation.

D. Summary

It has been suggested that thoracic epidural anaesthesia and analgesia (TEA) should be considered as a therapeutic option for patients with symptomatic end-stage multivessel disease, not amenable to revascularisation [Blomberg, 1994].

Patients with unstable angina may stand to benefit more from anticoagulation with heparin and aspirin or glycoprotein IIb / IIIa receptor antagonists than from TEA, in an attempt to arrest various pathophysiological cascades. The optimal benefit may, however, be gained by combining TEA and anticoagulation and randomised clinical trials are awaited.

Experimental data suggests that TEA may have anti-ischaemic effects, and clinical data suggests that the supplemental use of TEA with general anaesthesia results in improved hemodynamic stability, perioperative stress-response attenuation, improved postoperative analgesia and facilitates 'fast-tracking' in the setting of cardiac surgery.

The risk-benefit ratio of TEA in the setting of cardiac surgery, however, needs to be firmly established before it is routinely used - especially in view of the potential risk of epidural haematoma formation associated with full intraoperative heparinisation. TEA is still uncommon during CABG surgery and well designed trials with adequate numbers of patients to investigate the ability of TEA to reduce the morbidity and mortality of patients undergoing cardiac surgery are still needed [Chaney et. al, 1997].

The true benefit of TEA may lie in ;

1) the **reduction of adverse perioperative cardiac outcome.** This is supported by experimental data, showing that TEA may have anti-ischaemic effects with a resultant reduction in myocardial ischaemia, stunning and infarction size.
2) the **reduction in early graft occlusion** with a subsequent reduction in the need for re-operation. This is supported by clinical data suggesting that TEA facilitates coronary vasodilation, as well as clinical data suggesting that regional anaesthetic techniques reduce the peripheral vascular surgery graft occlusion incidence.

If this can be proved, then these data will provide for a favourable risk-benefit ratio, justifying the use of this analgesic technique in cardiac

surgery. Recent trials include a retrospective trial by Tuffrey et. al, [1997] and a prospective trial by Sanchez et. al [1998], however, to the authors knowledge no clinical studies have addressed these endpoints.

E. Hypothesis

Based on this background we designed a pilot study using primary and secondary endpoints (see below) to test the hypothesis that thoracic epidural analgesia (TEA) (through stress response attenuation, cardiac sympatholysis and peri-operative analgesia) provides a more favourable perioperative physiological milieu than conventional opioid-based general anaesthesia for coronary artery bypass grafting (CABG) surgery.
Furthermore, the provision of a favourable perioperative physiological milieu may result in a reduction in the incidence of perioperative ischaemia and a reduction in the incidence of early graft occlusion, with improved immediate perioperative as well as long-term outcome (including a reduction in the incidence of re-operative procedures) of patients undergoing CABG surgery. Thereby, despite the theoretical increased risk of spinal haematoma, the use of TEA in cardiac surgery would be associated with a favourable risk / benefit profile.

We tested our hypothesis by comparing 2 anaesthetic techniques: namely, the use of TEA as an adjunct to an opioid-free, general anaesthetic technique, *vs.* an opioid-based, balanced, general anaesthetic technique. This was studied in patients scheduled for elective CABG surgery at Harefield Hospital, Harefield & Royal Brompton NHS Trust, an independent cardiothoracic institution in the United Kingdom.

The following endpoints were used in this study to evaluate this hypothesis;

1. **sympatholysis:**
    - haemodynamic stability
    - thermodilution derived haemodynamic indices
    - preservation of cardiac performance
    - myocardial ischaemia:
        * Holter monitoring (ST-segment monitoring, arrhythmias)
        * ischaemic injury markers - creatine kinase (CK), cardiac troponin-I (cTn-I)

2. **stress-response attenuation**
    - catecholamines
    - cortisol
    - hypercoagulability indices - plasminogen activator inhibitor-1
    - endothelin-1,2

3. **analgesia**
    - visual analog pain scoring (VAS)
    - facilitation of fast-track recovery
        * respiratory function (PaO_2/FiO_2),
        * mini-mental test
        * time to extubation
        * time to discharge from ITU and discharge from hospital

III. GENERAL METHODOLOGY

A. Patients

Regional ethical committee (Hillingdon Health Authority, Middlesex, UK: Ethics Committee Submission 693) approval was obtained for this prospective study. Twenty consenting patients in the New York Heart Association (NYHA) functional class II or III, with preoperative ejection fractions greater than 45 % (as determined by ventriculography) scheduled for routine myocardial revascularisation were studied. They were randomised to receive either;

- a cervico-thoracic epidural (C7 - T1), as an adjunct to an opioid-free general anaesthetic technique (TEA group; n = 10)

or

- a balanced, opioid-based general anaesthetic technique (propofol-fentanyl-isoflurane), as routinely used in our institution (GA group; n = 10).

Patients were randomised by envelope. Once randomisation had occurred, however, there was no further blinding and each patient was managed in an in such a manner as to maintain haemodynamic stability in the perioperative setting. Maintained blinding of the investigators would be ideal, and this could be done by placement of an epidural catheter in all patients. However, with the current controversy and relative risk of a spinal haematoma - we regarded it as unethical to position an epidural catheter and not use it appropriately in the general anaesthetic (control) group.

Patients on anticoagulation therapy (e.g. warfarin) were excluded from this study. Aspirin was discontinued preoperatively (range: 2 days to 1 week) by all patients. A preoperative coagulation screen (partial thromboplastin time & prothrombin time) was done and found to be normal in all patients.

B. Conduct of anaesthesia and surgery.

In all patients pre-operative anti-anginal therapy was continued until the morning of surgery. Temazepam (10 - 20 mg) and ranitidine (150 mg) was administered orally as premedication 90 minutes prior to surgery. All

patients underwent anaesthesia and surgery by the same medical practitioners, in accordance with the same anaesthetic and operative protocols.

1. Thoracic epidural analgesic technique:

Patients in the TEA group had an epidural catheter sited in theatre the evening prior to surgery. Venous access was obtained prior to the procedure and the patient monitored throughout the procedure with pulse-oximetry and non-invasive blood pressure measurements.

Using the sitting position, a 16-G Touhey needle, with the bevel directed cephalad, was sited into the epidural space at the C7/T1 or T1/2 interspace using a mid line approach. On localisation of the epidural space, with the 'hanging-drop' technique, the epidural catheter was then advanced 4 - 5 cm through the needle. Correct placement was then tested with a 3-ml 1% lignocaine test dose. Once the epidural was sited the patients were returned to the ward and allowed to mobilise fully. Ward nursing staff were instructed to do 4 hourly epidural observations.

This procedure was abandoned in one patient only, following three unsuccessful attempts to localise the epidural space.

In theatre, the following morning, the epidural catheter was aspirated for cerebrospinal fluid or blood to check for catheter migration and correct placement was tested again with a 3-ml 1% lignocaine test dose.

Prior to the induction of general anaesthesia, the regional blockade was established using 0.125 $ml.kg^{-1}$ bolus of 0.5% bupivicaine (with 2 $\mu g.ml^{-1}$ fentanyl). The spread of blockade was evaluated 10-15 minutes later using onset of paraesthesia in the finger tips (C7 - T1 dermatomes) or reduced ability to discriminate temperature differences in upper thoracic dermatomes as signs of blockade onset. Adequate blockade was maintained with an infusion of 0.1% bupivicaine (with 2 $\mu g.ml^{-1}$ fentanyl) at a rate of 5 - 8 $ml.h^{-1}$ (0.1 $ml.kg^{-1}.h^{-1}$).

Radial artery and peripheral venous catheters were inserted under local anaesthesia. General anaesthesia was then induced with propofol (1 - 2 $mg.kg^{-1}$) and neuromuscular blockade obtained by pancuronium (0.15 $mg.kg^{-1}$). Following the induction of general anaesthesia and oral intubation, central venous and pulmonary artery catheters were inserted using the right internal jugular vein.

The lungs were ventilated with a nitrous oxide / oxygen mixture prior to aortic cannulation, followed by a air / oxygen mixture after cannulation for CPB. Propofol (3 $mg.kg^{-1}.h^{-1}$) was infused throughout the entire procedure and into the ITU period until the patient was considered ready for extubation. Isoflurane was added to supplement the propofol infusion and was allowed as escape therapy (0.5 - 1.5%) to control hypertensive episodes, otherwise both groups were ventilated with 0.5 MAC isoflurane. No data was collected on the mean isoflurane partial pressures. Midazolam (0.1 $mg.kg^{-1}$) was administered at the commencement of CPB in both groups of patients.

Postoperative analgesic management for all TEA patients consisted of a single dose of diclofenac (100 mg rectally) and an epidural infusion of 0.1% bupivicaine (with 2 $\mu g.ml^{-1}$ fentanyl) at a rate of 0.1 $ml.kg^{-1}.h^{-1}$, which was maintained until 72-hours postoperatively. Once the patient was extubated and tolerating oral fluids, analgesia was supplemented as required on request by the patient, using oral analgesic formulations containing paracetamol and either dihydrocodeine tartrate (Co-dydramol®) or dextro-propoxyphene hydrochloride (Co-proxamol®).

2. General anaesthetic technique:

Radial artery and peripheral venous catheters were inserted under local anaesthesia. General anaesthesia was then induced with propofol (1 - 2 $mg.kg^{-1}$). Fentanyl (low - intermediate dose; 10 - 15 $\mu g.kg^{-1}$) was titrated from induction to sternotomy. Neuromuscular blockade was obtained by pancuronium (0.15 $mg.kg^{-1}$). Following the induction of general anaesthesia and oral intubation, central venous and pulmonary artery catheters were inserted using the right internal jugular vein.

The lungs were ventilated with a nitrous oxide / oxygen mixture prior to aortic cannulation, followed by a air / oxygen mixture after cannulation for CPB. Propofol (3 $mg.kg^{-1}.h^{-1}$) was infused throughout the entire procedure and into the ITU period until the patient was considered ready for extubation. Isoflurane was added to supplement the propofol infusion and was allowed as escape therapy (0.5 - 1.5%) to control hypertensive episodes, otherwise both groups were ventilated with 0.5 MAC isoflurane. No data was collected on the mean isoflurane partial pressures. Midazolam (0.1 $mg.kg^{-1}$) was administered at the commencement of CPB in both groups of patients.

Postoperative analgesic management for all GA patients consisted of a single dose of diclofenac (100 mg rectally) and a continuous intravenous morphine infusion (1-3 $ml.h^{-1}$) that was commenced during CPB. Once the patient was extubated and tolerating oral fluids, analgesia was supplemented as required on request by the patient, using oral analgesic formulations containing paracetamol and either dihydrocodeine tartrate (Co-dydramol®) or dextro-propoxyphene hydrochloride (Co-proxamol®).

C. Cardiopulmonary bypass and myocardial preservation:

During surgery, all patients received porcine heparin (300 $IU.kg^{-1}$) for systemic anticoagulation to facilitate cardiopulmonary bypass (CPB). Additional heparin boluses were given to maintain an activated coagulation time (ACT) > 480 seconds. CPB was established with drainage via atrial cannulation and with return via an aortic cannula. The extracorporeal circuit, consisting of a cardiotomy reservoir, a rollerpump (Cobe Stöckert; Stöckert Instrument, Rungis, France) and a membrane oxygenator (Sorin Laboratories, Mirandola, Italy) providing nonpulsatile bypass (bypass flow: 2.4 $L.min^{-1}.m^{-2}$). The circuit was primed with 1,500 ml of lactated Hartmans solution, and mannitol (20 % : 1 $ml.kg^{-1}$).

Myocardial preservation strategy utilised moderate systemic hypothermia (32-34 °C, nasopharyngeal temperature), cold (4 °C) crystalloid cardioplegia (St Thomas I), delivered anterogradely via the aortic root and topical cooling (ice-slush) of the heart during the period of aortic cross-clamping. Cardioplegia was repeated every 30 minutes or earlier if electrical activity was observed on the ECG.

Once revascularisation was completed, the patient was weaned from bypass, heparin neutralised by protamine sulphate, bleeding controlled, the sternum closed, and the patient taken to ITU for recovery.

D. Experimental protocol

The study-design aimed to investigate whether TEA provided a more favourable perioperative physiological milieu than the GA technique, through sympatholysis, stress response attenuation and improved analgesia.

Measurements, included a full haemodynamic profile (pressures, and thermodilution technique), Holter ECG analysis, and collection of plasma / serum samples for analysis of catecholamines (noradrenaline & adrenaline), creatine kinase (CK), creatine kinase-MB isoenzyme (CK-MB), cortisol, cardiac troponin-I (cTn-I), endothelin and plasminogen activator-inhibitor-1 (PAI-1).

A full haemodynamic profile was obtained at the following time points:

- baseline - after induction of anaesthesia
- intraoperative - following pericardiotomy, prior to cannulation
- postoperative - 1-, 3-, 6-, 12, 18-hours following CPB cessation

Holter ECG monitoring was commenced at least 6- to 12-hours prior to CPB for baseline (pre-operative) analysis, and continued for 72-hours following the cessation of CPB for post-operative analysis.

Plasma / serum samples were collected at the following time points:

- baseline - prior to induction of anaesthesia
- intraoperative - 10- minutes after initiation of CPB
  - 10- minutes after aortic cross-clamp removal (plasma catecholamines only)
- postoperative - 1-, 3-, 6-, 12-, 18-, 24-, 72-hours following cessation of CPB, and Day 5.

Samples were collected into lithium-heparin tubes (noradrenaline, adrenaline, CK, CK-MB isoenzyme), clotting tubes (cortisol, cTn-I), and strong acidic citrate tubes (PAI-1), centrifuged (3 500 rpm for 15 minutes; 4°C) immediately, and the supernatant aliquoted into vials and stored frozen at -20^{0}C until assayed.
Arterial blood samples were collected before, during CPB and for the first 24- hours following CPB. Venous blood was collected after 24-hours following CPB due to removal of arterial lines.

1. <u>Parameters of sympatholysis</u>

a) Haemodynamic data:

A full haemodynamic profile was obtained at the time points mentioned above. All pressure measurements (central venous pressure (CVP), pulmonary artery occlusion / wedge pressure (PAOP), mean systemic arterial pressure

(MAP), mean pulmonary artery pressure (MPAP)) were made with reference to the midaxillary line. Cardiac output (CO) was measured in triplicate using the thermodilution technique (10-ml; 4 °C; 5 % dextrose in water), and indexed to body mass (e.g. cardiac index (CI), $L.min^{-1}.m^{-2}$). Derived parameters (systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI) - $dyne.sec.cm^{-5}$; left ventricular stroke work index (LVSWI) - $g.g.m^{2}$) were calculated using standard formulae.

b) Holter ECG analysis:

Monitoring was commenced at the time-points described above. All patients were continuously monitored with a two-channel (CM5 & CM1), Holter ECG recorder (Tracker 2, Reynolds Medical, Hertford, UK) with the following characteristics; frequency response : 0.04Hz to 250 Hz -3dB and input sensitivity : 7 mV (pp), dynamic range.

For general analysis, ECG recordings on Holter tapes were scanned visually using an ECG analysis system (series 1500; Marquette Electronics Ltd, Milwaukee, WI, USA). Continuous ST-segment trends and reports for arrhythmia counts were generated. For analysis of significant ST-segment changes, calibration with 2 Hz, 60 milliseconds pulses of 1 mV amplitude was done on all ECG channels.

The incidence of myocardial ischaemia and the number of ischaemic episodes were determined after hard copy 12-lead ECG recordings were studied to exclude left bundle branch block or postoperative pericarditis. An ischaemic episode was defined as ST-segment shift from the baseline of ≥0.1 mV depression at the J-point + 60 ms, or ≥0.2 mV increase at the J-point, lasting for more than 60 seconds. The ST measurement point was not adjusted for heart rate.

c) Myocardial infarction:

- **Creatine kinase & MB-isoenzyme measurement.**

Blood samples were collected in Lithium heparin tubes, stored at 4 °C and analysed within 24- hours by immunoinhibition and immunoprecipitation methods at 340 nm (KONE Diagnostics CK-NAC 981372 kit and KONE Optima analyser). The normal reference range in our institution is 24-195 IU/L & 24-170 IU/L for males and females, respectively. CK-MB reference range is < 24 IU/L.

- **Troponin-I measurement.**

Blood samples were collected in clotted tubes (no additive), centrifuged (3,500 rpm for 15 minutes; 4°C) immediately, and the supernatant aliquoted into vials and stored at -20°C until assayed. Assay was done by a two site immunoassay using goat polyclonal antibodies to cardiac isoform of troponin I (Opus kit, Cat No. 703-050, and Opus Plus analyser, Behring Diagnostics UK Ltd). The normal reference range is < 0.05 μg/L for both adults and females.

In this study the following criteria were used to define **P-MI**:

- **Q-wave P-MI:**

(i) CK-MB activity >50 IU/L occurring 21- h after CABG surgery [Farah et. al, 1984], or lasting more than 12 to 18- h [Delva et. al, 1978; Lee et. al, 1986; Graeber et. al, 1986], or cTn-I levels >15 μg/L [Alyanakian et. al, 1998]; and

(ii) the appearance of new persistent Q-waves >0.04 s or equivalents (R-wave increment leading to an R/S ratio >1 in leads V1 and V2) in at least 2 contiguous leads of the same vascular territory of the postoperative standard 12-lead ECG, using the Minnesota Code criteria [Blackburn et. al, 1960].

- **Non-Q-wave P-MI:**

(i) CK-MB activity >50 IU/L occurring 21- h after CABG surgery [Farah et. al, 1984], or lasting more than 12 to 18- h [Delva et. al, 1978; Lee et. al, 1986; Graeber et. al, 1986], or cTn-I levels >15 μg/L [Alyanakian et. al, 1998]; and

(ii) development of new persistent (> 24 hours) conduction abnormalities or ST-T alterations (ST segment depression or elevation >0.1 mV at 0.08s after the J point; T wave inversion) in at least 2 contiguous leads of the same vascular territory of the postoperative standard 12-lead ECG, using the Minnesota Code criteria [Blackburn et. al, 1960].

2. Parameters of stress response attenuation

a) Plasma catecholamine (noradrenaline, adrenaline) measurements:

Blood samples were collected in Lithium heparin tubes, centrifuged (3,500 rpm for 15 minutes; 4°C) immediately, and the supernatant aliquoted into vials containing reduced glutathione and EGTA and stored at -20°C until analysis by high-pressure liquid chromatography with electrochemical detection

[MacDonald et. al, 1985]. The reference range for noradrenaline and adrenaline is 0.5 - 3.5 nmol/L and 0.05 - 0.5 nmol/L, respectively.

b) Serum cortisol measurement:

Blood samples were collected in plain tubes, centrifuged (3,500 rpm for 15 minutes; 4°C) immediately, and the supernatant aliquoted into vials and stored at -20°C until assayed. Serum concentrations were analysed in duplicate with commercially available enzyme linked immunoassay (ELISA) kits (Milenia Cortisol EIA, USA) [Seth et. al, 1988].

c) Plasma plasminogen activator inhibitor-1 measurement:

Blood samples were collected in strong acidic citrate tubes (Biopool Stabilyte™), centrifuged (3 500 rpm for 15 minutes; 4°C) immediately, and the supernatant aliquoted into vials and stored at -20°C until assayed. Serum concentrations were analysed in duplicate with commercially available enzyme linked immunoassay (ELISA) kits (TintElize®, Biopool International, USA).

d) endothelin measurement:

Blood samples were collected in EDTA-coated polystyrene tubes and centrifuged (3 500 rpm for 15 minutes; 4°C) immediately, and the supernatant aliquoted into vials and stored at -20°C until assayed. Endothelin was quantitatively determined using a Endothelin-1,2 (high sensitivity) [^{125}I] assay system (Amersham International Ltd, United Kingdom).

3. Parameters of analgesia and fast-tracking

a) Visual analog pain score:

Postoperative analgesia was scored by a Visual Analog Pain Score (VAS - 10cm scale) at the following time points; 1, 3, 6, 12, 18, 24, 48, 72-hours, day 4 and day 5.

b) Fast-track parameters:

(i) **A ventilation weaning score** was used to assess the ability to wean the patient from ventilation in the intensive therapy unit. This was based on a scoring system where one point was given for each of 4 criteria, if they were met. The suitability to stop sedation and wean a patient from ventilation was done at 4- h following CPB. This did not preclude a patient from weaning and extubation prior to this if considered suitable by an independent ITU physician. Criteria used included the following parameters;

- haemodynamic stability - with minimal inotropic support,
- warm peripheral temperature (axillary temperature > 35 °C),
- minimal postoperative blood loss from the surgical site (< 100 $ml.hr^{-1}$),
- adequate gas exchange (PaO_2/FiO_2 > 25).

(ii) **A mini mental test** consisting of 30 points was compiled to assess recovery of mental status following surgery, with different anaesthetic techniques. This was a test of short (object recollection) and long term (orientation in time, place and person) memory recall, the ability to perform simple mathematical mental tasks and simple hand-eye co-ordination tasks. The test was given to the patient preoperatively (evening prior to surgery) and repeated at 6- hours following CPB cessation. This postoperative score was compared to, and expressed as a percentage of the preoperative score.

(iii) **The timing of discharge from ITU and hospital** was decided by an independent ITU physician, and by the postoperative surgical team, in conjunction with a physiotherapist, respectively. The decision to discharge from ITU were based on maintained or improved parameters of weaning, as discussed above. The decision to discharge from hospital was based on meeting the following criteria; haemodynamic stability, apyrexia, no other complications, and ability to mobilise adequately.

E. Data and Statistical Analyses:

Data are expressed throughout as mean ± standard error of the mean (sem) or median + range, where appropriate.
For variables with multiple assessment times, area under curve (AUC) were calculated from the baseline measure using the trapezoid rule. For individual missing values in AUC measures, these values were interpolated if they were not consecutive (except for missing baseline values, where group means were used). This AUC analysis is sensitive to large, transient effects which may be masked by variability in individual t-tests at each time point.
Statistical comparisons of continuous variables used parametric (two-tailed unpaired t-test for samples at a given time point between the two groups) or non-parametric repeated-measures analysis of variance (ANOVA) as appropriate, unless otherwise stated.
Time to an event (e.g. time in ICU, time in hospital) and visual analog pain score was analysed with Wilcoxon tests.

Two sided p-values are reported and statistical significance is defined as $p < 0.05$. (UNISTAT®, Version 4 for windows, UNISTAT Ltd, London, UK).

IV.RESULTS

A. Patient demographics

Patients received an average of 2.4 and 2.8 grafts in the TEA and GA groups, respectively. Conduits included saphenous vein grafts in all patients, and an internal mammary artery graft to the left anterior descending (LAD) coronary artery in all except 2 patients (both were in the GA group).
CPB duration ranged between 45 - 83 minutes (61.8 ± 4.3) in the TEA group. CPB duration was longer in the GA group, ranging from 51 - 125 minutes (84.7 ± 7.2). The longer CPB duration seen in the GA group, probably relates to the small number of patients studied in each group of this pilot study, and would probably even-out in a larger study. Of importance, however, is that the duration of aortic cross-clamp was similar between groups, ranging between 19 - 57 minutes (36.8 ± 3.9 minutes) and 25 - 78 minutes (49.7 ± 6.2 minutes) in the TEA and GA groups, respectively. The aortic cross-clamp time is equivalent to the duration of the ischaemia and thus the period that dictates the severity of the myocardial ischaemia-reperfusion injury that occurs following CABG surgery. This similarity between cross clamp times of the two groups, therefore makes the groups comparable. With regards to other demographic indices (summarised in table 1.) the groups were comparable and all patients survived to hospital discharge.

The age of the patients studied in the TEA and general anaesthetic groups ranged from 53 - 68 years (average 61.7 ± 1.9 years) and 46 - 75 years (average 60.6 ± 2.7 years), respectively. Of the twenty patients whose data are reported, two patients required re-operation for bleeding and one patient required prolonged mechanical ventilation for a confusional-state (post-pump delirium) following CPB (both patients were in the TEA group).

Epidural catheters were left in situ for the planned 72-hours post-CPB in 7 out of 10 patients, in the TEA group. Of the 3 patients whose epidural catheters did not remain in-situ for the full duration;

- one was accidentally dislodged at 21- hours post-CPB
- two were intentionally removed at 48-hours (one to allow commencement of warfarin therapy for a coronary artery endartrectomy done during surgery, and the other because the patient's epidural catheter had reached the allowed maximum in-situ stay of 5 days - due to surgery being

cancelled, due to the lack of an intensive care bed for postoperative recovery.

There were no documented spinal haematomas causing neurological symptoms, no complaints of new severe radiating back pain or unexplained or progressive neurologic deficits.

	No. Patients	
	TEA (N=10)	GA (N=10)
Sex (male/female)	09 / 01.	09 / 01.
Age, years (mean ± sem)	61 .7 (53 - 68)	60.6 (46 - 75)
Medical Treatment		
beta-blockers	6	9
calcium antagonists	5	7
ACE inhibitors	2	1
nitrates	7	7
aspirin	10	7
NYHA functional class		
I-II / III	7 / 3	10 / 0
Previous medical history		
Diabetes Mellitus	3	3
MI	5	7
CABG	0	0
PTCA	0	0
LV ejection fraction >45%	10	10
No. of obstructed vessels		
1	0	1
2	3	4
3	7	5
left main stem	0	3
No. of bypass grafts done	2.4	2.8
Duration of aortic cross clamp	36.8	49.7
Postoperative atrial fibrillation	2	3

Table 1. Patient demographic data.

Abbr.: ACE, angiotensin-converting enzyme; NYHA, New York Heart Association; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; LV, left ventricle.

B. Parameters of sympatholysis

1. Haemodynamic parameters:

There were no differences in heart rate, MAP, MPAP, filling pressures (CVP, PAOP), and derived indices (SVRI, PVRI, LVSWI) at the designated measuring times between the groups as a whole (table 2.).

	Baseline	Pre-CPB	1 h.	3 h.	6 h.	12 h.	18 h.
Heart rate (bpm)	70.6 ± 4.0	67.9 ± 3.6	71.2 ± 4.7	76.0 ± 2.0	79.4 ± 4.4	79.9 ± 2.8	77.5 ± 2.0
	64.0 ± 2.6	67.5 ± 4.0	77.8 ± 2.9	**82.9 ± 3.4***	**90.3 ± 4.5***	**89.4 ± 4.5***	84.6 ± 5.8
MAP (mmHg)	81.4 ± 5.8	74.3 ± 3.7	77.8 ± 4.3	82.7 ± 2.9	80.0 ± 3.9	81.3 ± 2.8	83.0 ± 2.9
	74.2 ± 3.6	75.2 ± 2.2	79.7 ± 1.4	77.6 ± 2.4	78.5 ± 2.2	71.9 ± 1.5	79.1 ± 3.4
PAOP (mmHg)	7.9 ± 0.8	7.9 ± 0.9	8.8 ± 0.8	8.2 ± 0.9	9.7 ± 1.2	9.3 ± 1.3	9.3 ± 1.2
	7.6 ± 1.0	6.8 ± 0.7	7.4 ± 0.6	7.3 ± 1.1	7.3 ± 0.6	8.5 ± 0.6	11.3 ± 1.3
Cardiac index ($L.min^{-1}.m^{-2}$)	2.9 ± 0.2	2.3 ± 0.1	2.5 ± 0.1	2.4 ± 0.2	2.8 ± 0.3	2.8 ± 0.3	2.6 ± 0.2
	2.0 ± 0.1	2.1 ± 0.2	2.4 ± 0.1	2.4 ± 0.3	2.8 ± 0.2	2.8 ± 0.2	2.4 ± 0.1
SVRI ($dyne.sec.cm^{-5}$)	2837.7 ± 226.7	2460.6 ± 205.7	2291.2 ± 234.7	2691.1 ± 258.5	2186.4 ± 184.9	2250.6 ± 219.7	2443.3 ± 214.4
	2701.3 ± 114.3	2879.8 ± 269.2	2529.0 ± 161.5	2545.5 ± 239.8	2120.4 ± 126.8	1900.7 ± 124.2	2325.5 ± 153.0
LVSWI ($g.m.m^2$)	31.9 ± 4.3	31.5 ±3.3	31.1 ± 2.6	32.1 ± 3.1	33.8 ± 4.0	33.7 ± 3.3	33.4 ± 3.3
	29.0 ± 2.5	29.0 ± 2.8	29.7 ± 1.7	27.8 ± 3.1	30.3 ± 2.1	27.7 ± 2.0	26.6 ± 1.87

Table 2. Haemodynamic parameters. Swan Ganz derived parameters, presented as mean ± sem. TEA- and GA-group values are represented by the shaded and unshaded lines, respectively. No statistical significance was shown between groups, however, the GA group showed a significant ($p < 0.05$) increase in heart rate, when compared to baseline value at 3- through to 12- hours following CPB.

Abbr.: MAP, mean arterial pressure (systemic); PAOP, pulmonary artery occlusion (wedge) pressure; SVRI, systemic vascular resistance, indexed; LVSWI, left ventricular stroke work, indexed; Pre-CPB, pre cardiopulmonary bypass; 1 h. - 18h, hours following cessation of CPB.

The TEA group, however, showed consistently greater haemodynamic stability to perioperative stimuli, e.g. intubation, sternotomy, aortic cannulation, extubation (see figure 4, as an example). This is evidenced by a lesser change in heart rate when compared to baseline in the TEA group. In comparison, the GA group showed a statistically significant increase in heart rate when compared to baseline between 3-h and 12-h following the cessation of CPB. Furthermore, there was a clear trend towards requiring

less perioperative pharmacologic intervention; vasodilators (TEA *vs.* GA = 4 : 10 patients) and inotropes (TEA *vs.* GA = 1 : 5 patients) in the TEA group.

It is interesting to note that a similar number of patients required vasoconstriction with α-adrenergic agonists in both groups (TEA *vs.* GA = 6 : 8 patients). No vasoconstriction was required by either group in the postoperative period.

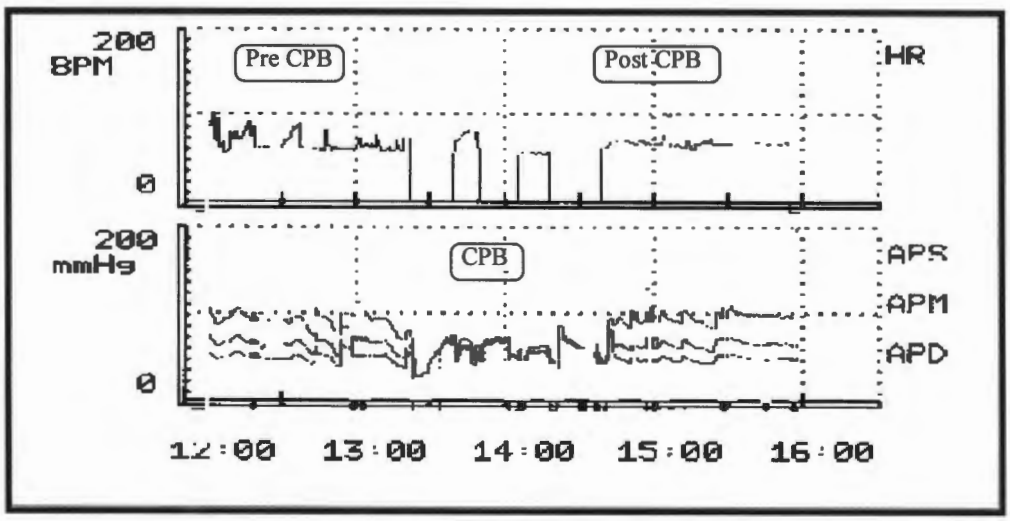


Figure 4. Intra-operative trend of haemodynamics monitored in a patient during CABG surgery using the TEA technique. This figure is only used as a representative example to illustrate the haemodynamic stability obtained with the TEA technique.
Abbr.: HR = heart rate, APS, APM, APD = systolic, mean, diastolic arterial pressure, respectively.

Previous studies [Krukenkamp et. al, 1987] suggest that the relationship between end-diastolic volume and stroke work (calculated as the area of the pressure-volume loop) is linear, afterload independent, and sensitive to the inotropic state.
For the want of a better method of assessing ventricular function in the clinical setting, we constructed a left ventricular function curve (figure 6.), using LV-stroke work [y-axis] plotted against preload (using PAOP as a substitute for end-diastolic volume) on the x-axis. Mean haemodynamic values were used for each group.

Movement along the same plot of the left ventricular function curve (see figure 5; line A-B) reflects preservation of the inotropic state [Frank-Starling mechanism], as opposed to a downward movement (see figure 5; line B-C) to another ventricular function plot, which would represent a deterioration in the state of inotropy [Suga et. al, 1991].

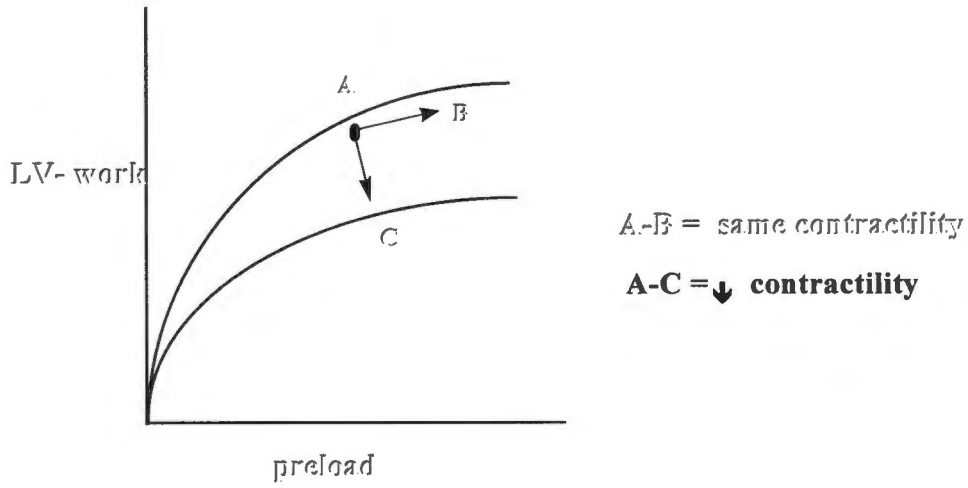


Figure 5. Left ventricular function curve. Movement along the line from point A to B reflects preservation of the inotropic state [Frank-Starling mechanism]. Downward movement from point B to C represents a deterioration in the state of inotropy.
Abbr.: LV = left ventricle.

By constructing ventricular function curves, our data suggests that the inotropic state is maintained at baseline level in the early postoperative period in the TEA group. Thus suggesting early postoperative recovery or maintained LV function in this group. This is in contrast to a persistent state of lower inotropy, suggestive of myocardial stunning in the GA group.

Using a similar method, Mangano et. al, [1985] reported that transient RV function depression occurs in the immediate post-CPB period as evidenced by a deterioration in RV stroke work index / CVP relationships, with normalisation or gradual recovery of function over the succeeding 24 hours.

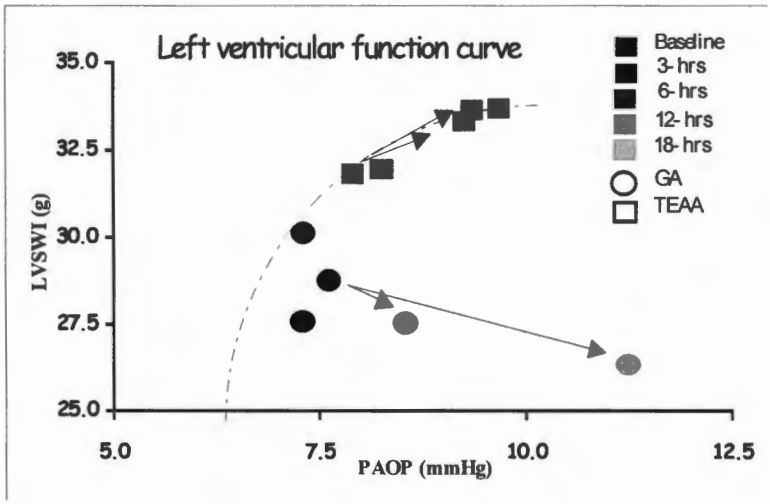


Figure 6. Left ventricular function curve.
When compared to the pre-operative position on the Frank-Starling curve (broken line), we see that early postoperative ventricular function is preserved in the TEA group (= □). The GA group (= ○), however, moves downward from this Frank-Starling curve, suggesting deterioration in the state of inotropy.

2. Holter ECG analysis:

No differences were observed between TEA and GA groups with regards to pre-operative ST-segment changes (elevation and depression) and postoperative ST-segment depression.

Postoperatively, however, there were significantly more ST-segment elevations in the GA group. The maximum ST-segment elevation (mm; $p<0.05$) and duration of ST-segment elevation greater than 2 mm (hours; $p < 0.005$, Mann-Whitney-U test; see figure 7.) were significantly elevated in the GA group, within the first 24- h following CPB. Significantly more patients in the GA group than in the TEA group (6/9 *vs.* 1/9 patients, respectively; $p = 0.025$, Fisher's Exact test) presented with episodes of ST-segment elevation >2 mm within the first 24- hours following CPB.
The duration of, and number of patients with ST-segment elevation showed a reduction at 48- hours (3/9 *vs.* 2/9 patients) and 72- hours (2/6 vs. 0/5 patients) following CPB in the GA and TEA groups, respectively. No statistical significant difference was observed between groups at 48- hours and 72- hours. These data, are suggestive of coronary artery vasoconstriction occurring in the early postoperative period following CPB in the GA group, and this is despite the use of intravenous glyceryl-trinitrate infusions for 24 - 48 hours postoperatively, in all patients within the GA group (GA *vs.* TEA; 10/4 patients, respectively).

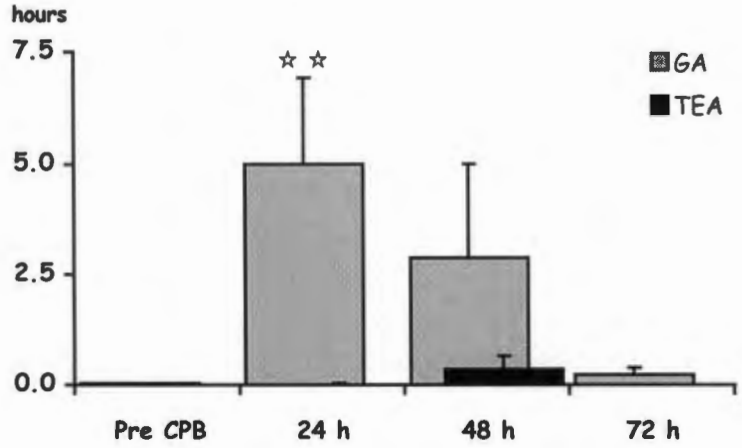


Figure 7. Holter monitoring.
Duration (hours; mean ⇧ sem) of ST-segment elevation >2 mm during 72- h of postoperative Holter monitoring.
Abbr. 24- h, 48- h, 72- h, hours following cessation of cardiopulmonary bypass. ☆ ☆= $p < 0.005$; Mann-Whitney-U test.

3. Perioperative myocardial infarction:

• **CK-MB isoenzyme and cTn-I levels** (figure 8.) were similar between TEA and GA-groups preoperatively.
Postoperatively, CK-MB levels trended towards lower values in the TEA group, however these did not reach statistical significance.
cTn-I levels were significantly lower at 6- h post-CPB (3.5 ± 0.6 vs. 12.4 ± 4.2 µg/L; $p = 0.05$) and for $AUC_{0\text{-}6h}$ (18.1 ± 2.8 *vs.* 58.1 ± 19.1; $p < 0.05$) in the TEA group when compared to the GA group, respectively.

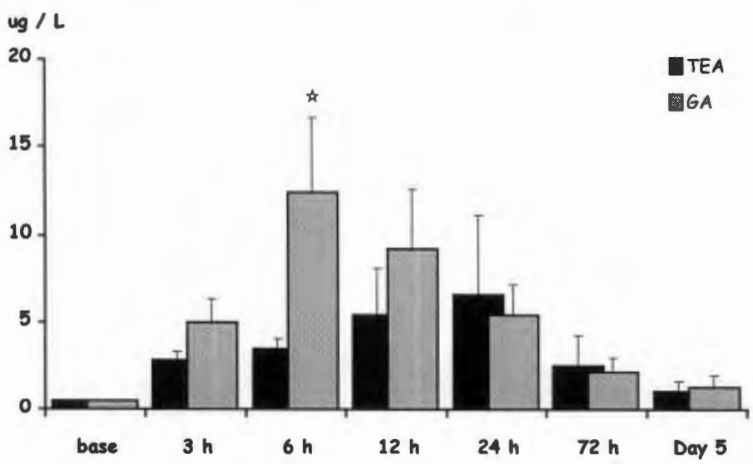


Figure 8. Cardiac Troponin-I. Significantly lower cTn-I levels were seen in the TEA group at 6- hours following CPB, and for the area under curve (AUC 0-6 hours).

- **Total CK levels**

Total CK values (figure 9.) were significantly lower in the TEA group at 1- h (300.0 ± 32.5 *vs.* 486.3 ± 50.5 IU/L; $p < 0.01$), 3- h (405.0 ± 41.5 *vs.* 624.1 ± 62.6 IU/L; $p < 0.01$), 6- h (460.8 ± 37.9 *vs.* 758.8 ± 126.2 IU/L; $p < 0.05$) and 72- h (352.0 ± 54.2 *vs.* 985.3 ± 321.4 IU/L; $p < 0.05$).

Furthermore, a significant reduction was seen for $AUC_{0\text{-}12h}$ in the TEA group (5773.0 ± 443.3 *vs.* 8539.1 ± 1119.1 IU/L; $p < 0.05$), with a similar trend in $AUC_{0\text{-}72h}$ and $AUC_{0\text{-}Day\ 5}$.

Total CK values peaked earlier in the TEA group at 24- h post CPB, in contrast to peak values being reached later (72- h) in the GA group.

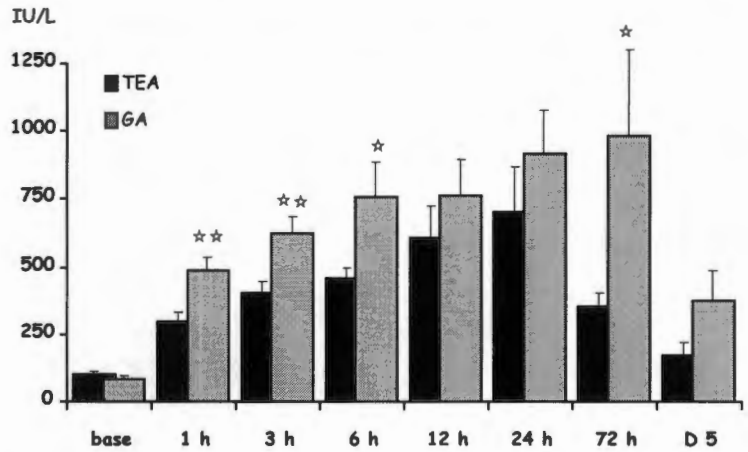


Figure 9. Total creatine kinase plasma levels.

Abbr. Base, pre-cardiopulmonary bypass; h, hours & D, day following cessation of cardiopulmonary bypass. ☆☆ = $p < 0.01$; ☆ = $p < 0.05$.

- **P-MI**

Using the predefined criteria to diagnose non-Q and Q-wave myocardial infarctions;

* 3 patients in the GA group suffered non-Q wave myocardial infarctions as opposed to 1 patient in the TEA group.
* Neither group suffered any new Q-wave myocardial infarction.

C. Parameters of stress response attenuation

1. Plasma catecholamine (noradrenaline, adrenaline) measurements:
Throughout the perioperative period the catecholamine levels were consistently lower in the TEA group than in the GA group.

- **Noradrenaline levels** (figure 10.) were significantly lower during CPB (1.10 ± 0.32 *vs.* 2.57 ± 0.39 nmol/L; $p < 0.01$), at 1- h (1.07 ± 0.25 *vs.* 1.93 ± 0.24 nmol/L; $p < 0.05$), 12- h (3.25 ± 0.56 *vs.* 4.81 ± 0.37 nmol/L; $p < 0.05$), and 24- h (3.61 ± 0.69 *vs.* 6.11 ± 0.81 nmol/L; $p < 0.05$) following CPB in the TEA group when compared to the GA group.
Statistical significant reductions for $AUC_{0\text{-}6,\ 0\text{-}12,\ 0\text{-}24,\ 0\text{-}72\ hours}$ (0-72-h; 250.8 ± 41.3 *vs.* 416.7 ± 50.9; $p < 0.05$) were also observed in the TEA group.

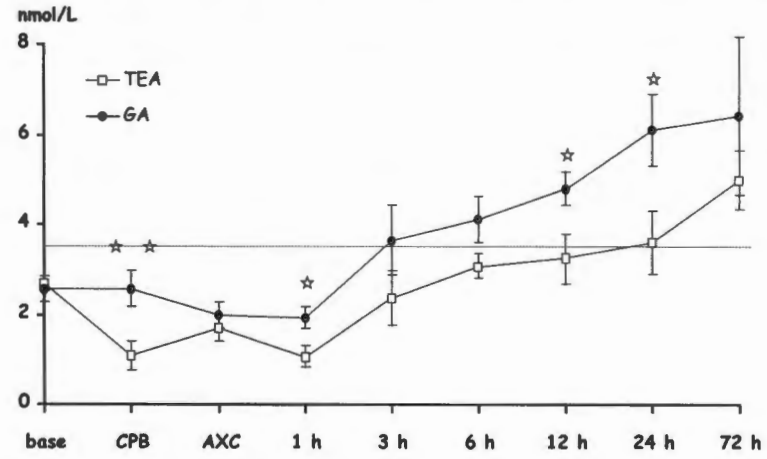


Figure 10. Noradrenaline plasma levels.
The broken line represents the upper range of physiologic levels of serum noradrenaline (3.5 nmol/L).
Abbr. Base, pre-cardiopulmonary bypass; AXC, aortic cross clamp release; h, hours following cessation of cardiopulmonary bypass.
☆☆ = $p < 0.01$; ☆ = $p < 0.05$.

It is of interest to note that noradrenaline levels were maintained below the upper reference range intraoperatively by both anaesthetic techniques. However, when compared to the TEA group, the GA group showed earlier elevation of levels above the reference range in the post operative period (3- h vs. 24- h post CPB, respectively).

• **Adrenaline levels** (figure 11.) remained unchanged in the perioperative period in the TEA group and were, similarly, significantly lower when compared to the GA group during CPB (0.49 ± 0.11 *vs.* 1.36 ± 0.21 nmol/L; $p < 0.01$). Statistical significant differences were shown between the groups for the $AUC_{0\text{-}6,\ 0\text{-}12,\ 0\text{-}24\ hours}$ (0-24- hours; 66.7 ± 18.1 *vs.* 21.0 ± 3.6; $p < 0.05$).

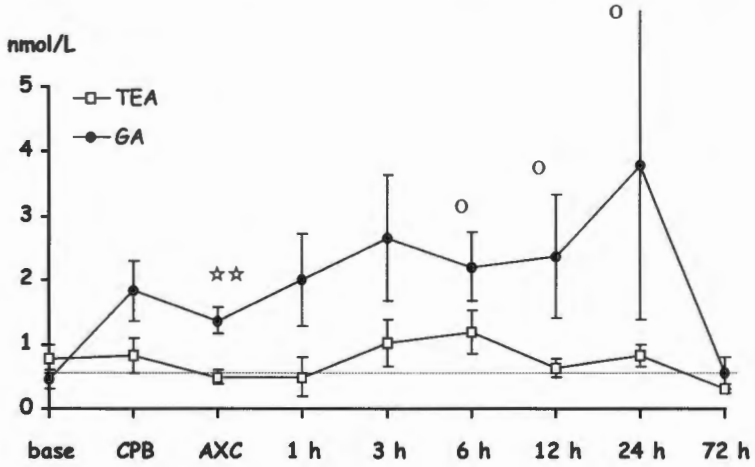


Figure 11. Adrenaline plasma levels.
The broken line represents the upper range of physiologic levels of serum adrenaline (0.5 nmol/L). ☆ ☆ = $p < 0.01$; o = $p < 0.05$ for $AUC_{0\text{-}6,\ 0\text{-}12,\ 0\text{-}24\ hours}$.
Abbr. Base, pre-cardiopulmonary bypass; AXC, aortic cross clamp release; h, hours following cessation of cardiopulmonary bypass.

2. Serum cortisol measurement:

Cortisol levels (figure 12.) peaked at 6- hours following cessation of CPB, however no differences were observed between the TEA and GA groups.

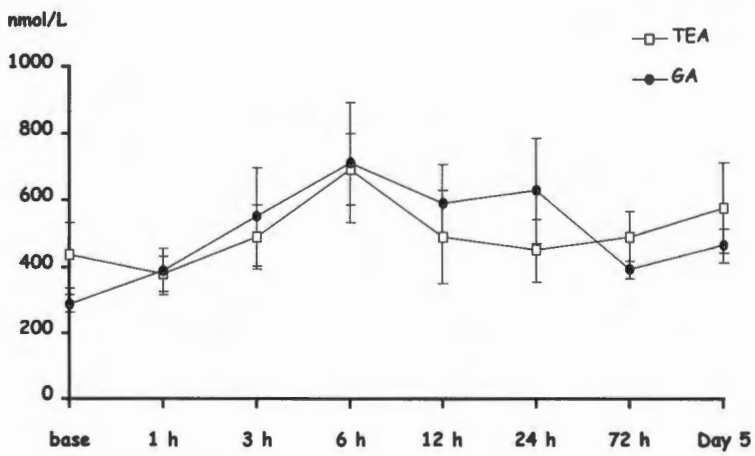


Figure 12. Cortisol serum levels.
Abbr. Base, pre-cardiopulmonary bypass; h, hours following cessation of cardiopulmonary bypass.

3. Plasma plasminogen activator inhibitor-1 (PAI-1) measurement:
Plasminogen activator inhibitor-1 levels (figure 13.) were significantly lower in the TEA group at 72- hours (24.3 ± 2.9 *vs.* 34.1 ± 3.5 μg/L, $p < 0.05$) following the cessation of CPB, with a trend ($p = 0.06$) to reduction in AUC $_{0\text{-}5 \text{ postoperative days}}$ in the TEA group .
On termination of the epidural infusion, PAI-1 levels return to correspond with the levels in the GA group.

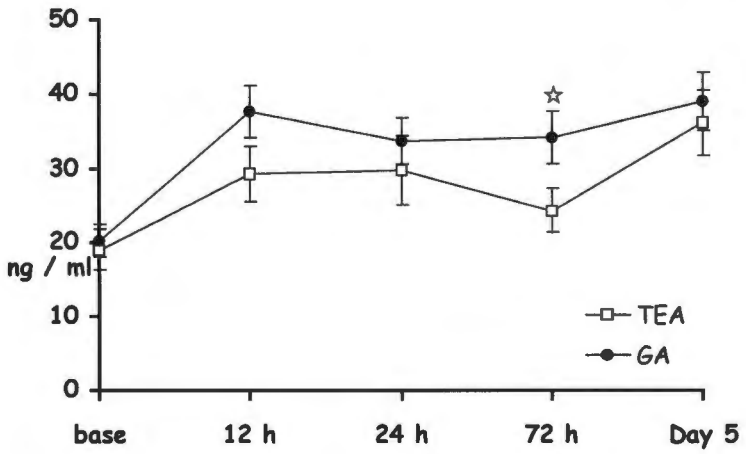


Figure 13. Plasminogen activator inhibitor-1 levels.
Abbr. Base, pre-cardiopulmonary bypass; h, hours following cessation of cardiopulmonary bypass.
☆ = $p < 0.05$.

4. endothelin measurement:
Endothelin-1,2 levels were significantly lower in the TEA group during CPB (23.4 ± 2.5 *vs.* 40.3 ± 7.4 ng/L, $p < 0.05$). No differences, however, were observed between groups in the early postoperative period.

D. Parameters of analgesia and fast-tracking

1. Visual analog pain score:

Visual analog pain scoring (figure 14.) showed significant reductions at all postoperative time points ($p < 0.01$ at 24- hours, $p < 0.02$ at 6-, 12-, day 2, day 3 and day 4 and $p < 0.05$ at 18- hours and day 5 following CPB). A marked leftward shift was seen in the TEA group, which correlates with earlier awakening and extubation of patients in this group.

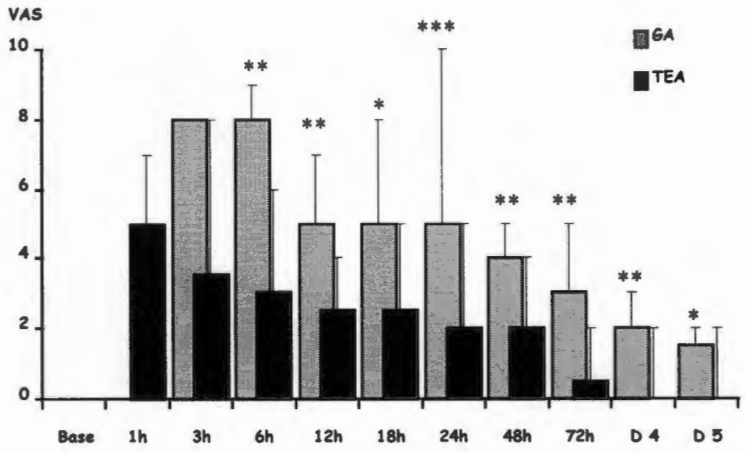


Figure 14. Visual analog pain score.
No error bar is seen at 3- h post cardiopulmonary bypass in the GA group - this is because only one patient was extubated in this group, at this time point. Data is presented as median + upper range. * = p< 0.05; ** = p< 0.02; *** = p< 0.01; Wilcoxon two sample test.
Abbr. Base, pre-cardiopulmonary bypass; h, hours following cessation of cardiopulmonary bypass.

2. Fast-track parameters:

Ability to wean the patient from ventilation in the intensive care, as assessed by a scoring system at 4- h following CPB, did not differ between the TEA and GA groups.
Despite similar weaning assessment scores (3.8 ± 1.3 *vs.* 3.5 ± 0.3) and similar **gas exchange** (PaO_2/FiO_2 : 48.3 ± 5.7 *vs.* 56.4 ± 10.6) in the TEA and GA groups, respectively the TEA group showed significantly improved time to extubation (3.7 ± 0.6 h *vs.* 6.9 ± 1.2 h; $p < 0.05$).

This improved time to extubation may be attributed to;

- the opioid free anaesthetic technique,

- significantly improved analgesia,
- and a trend towards improved alertness in the TEA group, as assessed by a **mini-mental test** conducted at 6- h following CPB (87.8 ± 10.7 % vs. 61.4 ± 13.7 %).

No difference was shown between groups with respect to time to discharge from ITU and time to discharge from hospital.

V. DISCUSSION

In this pilot study, both the TEA and GA groups were well matched for demographic data, surgical intervention and for the duration of ischaemia (aortic cross-clamp time) and therefore groups can be regarded as being comparable. The differences in the demographic data were balanced out by other factors in each group, e.g. 3 *vs.* 0 patients were in a NYHA functional class III status; 6 *vs.* 9 patients were on beta-blockers; 2 *vs.* 1 were on ACE-inhibitors; 5 *vs.* 7 had previous MI's; 7 *vs.* 5 had triple vessel disease, in the TEA and GA groups, respectively.
Ischaemia-reperfusion injury is the single most important factor that can detrimentally influence outcome of myocardial function following cardiac surgery and this correlates closely with aortic cross clamp duration. Importantly, the duration of aortic cross clamp was similar between the TEA and GA groups. A difference was observed in the duration of CPB, however, no factor was identified that could have contributed to this, for example more difficult vessels. This observed difference in cardiopulmonary bypass duration between the groups may relate to the relatively small size (n = 10) of both groups, and it would be expected to become insignificant in a follow-up study with a larger population.

We as anaesthesiologists aim to induce sympatholysis, suppress the stress response and provide superlative analgesia in an attempt to prevent perioperative complications e.g. myocardial infarction.
This trial was designed as a pilot study to investigate the following **hypothesis: that TEA provides a more favourable perioperative physiological milieu in the setting of cardiac surgery.**
In an attempt to prove or disprove this hypothesis we investigated the impact that TEA may have on sympatholysis, stress response attenuation and perioperative analgesia, specifically in the setting of patients undergoing cardiac surgery for coronary artery disease.

Does TEA induce sympatholysis, suppress the stress response and improve analgesia in the cardiac patient ?.

Based on the fact that myocardial ischaemia is the single most important, potentially reversible risk factor for cardiovascular complications, we use surrogate markers of ischaemic injury e.g. ST-segment changes and echocardiography, for the detection of regional wall motion abnormalities. These surrogate markers are used in an attempt to allow early detection of metabolic derangement, and thereby facilitate reversal of the process through timely therapeutic interventions.

Myocardial ischaemia is a state of coronary supply/demand imbalance and two principle factors have been identified that contribute to the majority of postoperative ischaemic events, these include;

- an exaggerated sympathetic response and,
- endothelial dysfunction.

The impact of TEA on sympatholysis and stress response was explored in this trial, however we did not explore the impact of TEA on endothelial dysfunction (associated with atherosclerosis and ischemia-reperfusion injury).

Haemodynamic instability (tachycardia, hypertension) can result in increased myocardial oxygen demand, which especially in the presence of restricted supply (coronary artery atherosclerosis) may promote myocardial ischaemia. Most experimental and clinical [Blomberg et. al, 1989; Liem et. al, 1989; Stenseth et. al, 1994] studies agree that TEA provides greater haemodynamic stability and in particular, results in a reduction in the incidence of hypertension during CPB and in the early postoperative period, with fewer pharmacological interventions being required.

Our data confirmed these findings to a certain degree, as was evidenced by lack of a significant increase in heart rate, when compared to baseline values in the TEA group. The GA group showed a significant increase in heart rate in the early postoperative period, when compared to baseline. In keeping with these previous studies, the greater haemodynamic stability by TEA is further suggested by the requirement for less perioperative pharmacologic intervention in this group; e.g. vasodilators (TEA *vs.* GA = 4 : 10 patients), and inotropes (TEA *vs.* GA = 1 : 5 patients). These pharmacological therapies

were used in order to maintain acceptable perioperative systemic perfusion pressures.

Our data, however, showed no differences, at the designated measuring time points, between the groups as a whole, with regards to other haemodynamic variables e.g. mean arterial blood pressure, and thermodilution-derived indices e.g. cardiac index, LVSWI, SVRI (table 2.). This may be due to;

- the unrestricted use of anaesthetic, vasodilator and inotropic agents in order to maintain haemodynamic stability in both groups
- the fact that haemodynamic measurements were not made at the time points known to be stimulating, that is, at intubation, surgical incision, sternotomy, aortic cannulation, and extubation.

Previous fears have been expressed that epidural analgesia and other neuraxial techniques may reduce coronary perfusion pressure, thereby predisposing to myocardial ischaemia. It is important to note that our technique, of providing a selective (T1-4) epidural blockade, maintained cardiac output and systemic vascular resistance, when compared to the GA group. This suggests that our TEA technique maintained coronary perfusion pressure and emphasises the importance of a high TEA approach, thereby avoiding vasodilation of the splanchnic bed.
This preservation of coronary perfusion pressure is also subsequently reflected by the absence of ST-segment changes on perioperative Holter ECG monitoring (figure 7.) in the TEA group. The ST-segment changes observed in the GA group were suggestive of postoperative coronary artery vasoconstriction occurring in the early postoperative period. These ST-segment changes occurred despite all GA patients (vs. only 4 patients in the TEA group) receiving prophylactic nitroglycerine infusions. These infusions were maintained throughout the perioperative period and maintained for 24- to 48- hours into the postoperative period. The nitroglycerine was administered in the GA group as part of our standardised intra- and post-operative care protocols used in out institution. The TEA group was in fact biased against because nitroglycerine infusions were only used in the 4 TEA patients for blood pressure control in the postoperative period. It was noted that patients with epidurals tended to reset their postoperative blood pressures towards their pre-operative values.

If we remember that epicardial coronary arteries are predominantly innervated by α-receptors and sympathetic stimulation of these receptors reduces myocardial oxygen delivery through arterial vasoconstriction and

redistribution of blood flow away from the subendocardium. It is therefore not surprising that coronary vasoconstriction is abundant in the early postoperative period of the GA group. This sympathetic response can be overridden by metabolic autoregulation in patients with a normal intact endothelium, resulting in regional vasodilation. However, as shown by Nabel et. al [1990], this post-stenotic vasodilator reserve is lost in patients with endothelial dysfunction e.g. atherosclerosis, hypercholesterolaemia, hypertension and diabetes mellitus. This was confirmed by Johannsen et al. [1982] who showed that despite infusing adenosine into atherosclerotic vessels they were unable to overcome sympathetic-induced vasoconstriction.

It is suggested that endothelial dysfunction proceeds the development of macroscopic atherosclerotic lesions [Ross, 1993]. This is characteristic of unstable atherosclerotic lesions, which tend to have non-critical stenoses - with impaired vasodilation and an exaggerated response to sympathetic stimulation, and unstable lipid bullae below the plaque surface.
The presence of sympathetic activation, coronary vasoconstriction and increased shear stress may predispose to plaque fissuring, thereby exposing the subendothelial collagen and lipids (known strong activators of the coagulation cascade). This leads to thrombus formation and subsequent reduction in myocardial metabolic supply. During CABG surgery these unstable lesions may be bypassed, but this does not prevent this dynamic pathological process from being triggered by the sympathetic activation and increased shear stress that occurs during the perioperative period and thus an evolving plaque and / or thrombus may embolise, resulting in perioperative morbidity and mortality. Clearly, this is a process that could benefit from the sympatholysis.

Endothelial dysfunction is characteristic of the group of patients we studied, and this dysfunction presents with an imbalance in the endothelial regulated vasodilator/constrictor and pro/anticoagulant equilibrium. Characteristically there is a decreased response to vasodilatory mediators e.g. serotonin, bradykinin and shear stress, as well as an exhibition of an exaggerated response to α-agonists, and an attenuated response to β-agonists.
Apart from the disease process, other perioperative factors are known to promote and exaggerate this endothelial dysequilibrium. These include;

- surgical trauma with intimal injury and endothelial denudation at the site of the vascular anastomosis - with a resultant focal loss of endothelial-dependent endogenous vasodilators, e.g. nitric oxide (EDRF) and prostacyclin (PGI_2).

- an increase in sympathetic neural outflow and increased systemic stress response mediated by CPB and postoperative pain.

In addition to the exaggerated sympathetic response and endothelial dysfunction witnessed in the perioperative period of patients undergoing CABG surgery, any one and more commonly a combination of various postoperative factors could contribute to myocardial ischaemia. An example may be poor postoperative analgesia resulting in intermittent episodes of tachycardia, thereby **increasing myocardial oxygen consumption**. This poor postoperative analgesia may further result in a reluctance to inspire adequately, promoting the development of postoperative atelectasis, V/Q mismatching and impaired oxygenation. This impaired oxygenation and the reduction in diastolic filling time by tachycardia, combined with possible postoperative anaemia and stress-response induced hypercoagulability may all contribute to a **reduction in myocardial oxygen delivery**. These factors may therefore result in subsequent ischaemia.

Our data, suggests that TEA promotes sympatholysis, stress response attenuation and improved analgesia and thereby facilitates an improved intra- and postoperative physiological milieu. This is supported by the following results obtained in our pilot study;

- improved haemodynamic stability
- direct selective coronary artery vasodilation (figure 7.),
- reduced systemic circulating catecholamines (figure 10, 11.)
- reduced inhibition of fibrinolysis by plasminogen activator (figure 13.)
- reduced postoperative tachycardia, V/Q mismatch and impaired oxygenation through improved analgesia (table 2, figure 14.).

Will the more favourable perioperative physiological milieu provided by TEA translate into improved patient outcome ?.

It is our goal as anaesthetists to prevent poor perioperative cardiac outcome (e.g. P-MI) in patients undergoing cardiac surgery, as well those at increased risk of CAD undergoing non-cardiac surgery. Poor perioperative cardiac outcome can potentially compromise the patient's life or quality of life after surgery, as well result in an increase in the cost of patient care.

Whether TEA may potentially confer a better postoperative cardiac outcome following CABG surgery requires further study in a larger population of patients. However, this pilot study suggests that TEA may have a role in attenuating the vasodilator/constrictor, pro/anticoagulant imbalance that occurs in the perioperative period (as discussed above) and therefore may potentially impact,

- the incidence of P-MI
- the incidence of early graft occlusion.

- ***Perioperative myocardial infarction.***

The importance of preventing ischaemic injury was highlighted by Guiteras Val et. al [1983]. They reported that 49 % of patients who suffered a P-MI following CABG surgery had either re-infarcted or died at the time of their 2- year follow up, as opposed to 4 % in patients in those who did not develop a new P-MI. Furthermore, it has been shown that survivors of complications following cardiac surgery result in annual additional costs estimated at US$750 million for in-hospital treatment and US$500 million for follow-up care [Harrison, 1985].

This data is supported by Slogoff et. al, [1985], who showed a 3-fold increase of P-MI in patients who developed perioperative ischaemia in patients undergoing CABG surgery. Hence, the increase in P-MI in our GA group correlates with the increased ST-segment changes in this group.

The incidence of P-MI in CABG surgery varies according to the diagnostic methods and criteria used. Slogoff et. al [1985] using ECG and enzymatic criteria estimated the incidence of P-MI at 4.1%, compared to Cheng et. al [1978], who with the addition of technetium-pyrophosphate scanning (SPECT) showed a 25% incidence of P-MI, of which 2.8% were Q-wave infarctions.

Using more sensitive enzyme studies (cardiac isoform of troponin-I - discussed below), we showed a similar incidence of P-MI in our GA group, compared to that seen by Cheng et. al. Using the predefined criteria (see discussion below) to diagnose non-Q and Q-wave myocardial infarctions we showed that 3 patients (30 %) in the GA group suffered non-Q wave myocardial infarctions as opposed to 1 patient in the TEA group. Neither group suffered any new Q-wave myocardial infarction. Arguably, no statistical difference is shown between the GA and TEA groups in this small study and it will need to be repeated in a larger group of patients. The reduction in the incidence of P-MI in the TEA group, however, holds promise and suggests that a more favourable perioperative physiological milieu is conducive to an improved / preserved outcome of myocardial function.

No clear consensus exists regarding the criteria that should be applied to creatine kinase-MB isoenzyme (CK-MB) or the cardiac isoform of troponin-I (cTn-I) with regards to the diagnosis of Q- and non-Q wave P-MI following CABG surgery.
The numerous factors that make the choice of threshold for P-MI difficult include;

- lack of cardiospecificity - despite higher sensitivity and specificity CK-MB and Troponin-T are still not 100 % cardiospecific. It is suggested that Troponin I has the most cardio-specificity.
- a peak is evidenced in both CK-MB activity (between 4- to 8-h after CABG surgery) [Olthof et. al, 1983] and in cTn-I (between 6 to 12-h after CABG surgery) due to surgical trauma and postbypass washout. These factors produce a short-term liberation of enzymes into the circulation in all patients, including those without P-MI.
- the lack of standardisation of the assays currently available. This yields different reference ranges, hence, making the comparison among different studies difficult. This is true for both CK-MB and cTn-I.
  (The reference ranges for CK-MB (using an immunoinhibition technique [Merck, Darmstadt, Germany]) are as follows : <10.0 IU/L at 25 °C, <14.4 IU/L at 30 °C, and <24.0 IU/L at 37 °C. The latter value is the upper limit of the normal reference range in our laboratories, where CK-MB activity is measured with a similar immunoinhibition technique at 37 °C rather than at 25 or 30 °C.)

It is suggested that using CK-MB activity levels (immunoinhibition technique) >50 IU/L (twice the upper reference range), occurring 21- h after CABG surgery [Farah et. al, 1984], and lasting more than 12 to 18- h are diagnostic

of P-MI [Lee et. al, 1986], and that cTn-I levels (immunoassay technique) >15 μg/L occurring within 24 to 48- h after CABG surgery are diagnostic of P-MI [Alyanakian et. al, 1998].

With the addition of the more sensitive and specific cardiac isoform of troponin-I to our diagnostic armamentarium we may now be able to monitor the incidence of P-MI following CABG more accurately, without the need for more advanced and less accessible technologies like SPECT as used by Cheng et. al [1978]. Troponins are a complex of regulatory proteins that regulate the calcium-mediated interaction of actin and myosin and are uniquely present in striated muscle. Unlike Troponin-T, cTn-I is highly specific for myocardial injury (Opus 2 site cTn-I immunoassay vs. Opus CK-MB sensitivity is 93.9% and 95.9%, respectively and specificity is 97.4% and 85.3%, respectively) and furthermore, unlike other cardiac markers (CK-MB) cTn-I levels may remain elevated in serum for several days before returning to normal. Perioperative necrosis results in a more prolonged and slower release of enzyme, with a delayed (10 to 16- h) peak in postoperative CK-MB activity and cTn-I levels, aiding the ability to distinguish P-MI from enzymatic rise associated with brief ischaemia-reperfusion injury and surgical trauma associated with cardiac surgery.

Gao et. al [1997] identified cTn-I proteolysis as the cause of the reversible cardiac dysfunction in myocardial stunning, with a subsequent report by McDonough et. al [1999] suggesting that severe ischaemia/reperfusion injury is associated with proteolysis on N-terminal amino acids of cTn-I. What is intriguing is that proteolysis of cTn-I may be an initial or triggering insult in engaging the hypertrophic process through unknown transcriptional and translational mechanisms. This is supported by extensive evidence that mutations in sarcomeric proteins are genetically linked to familial hypertrophic cardiomyopathy [Kimura et. al, 1997]. To what degree this is true for cTn-I release following cardiac surgery is not known, however, it seems prudent that all attempts to reduce an ischaemia-reperfusion injury and subsequent cTn-I release are warranted.

- ***Coronary artery graft occlusion***

Current experience in peripheral vascular surgery suggests that patients requiring re-operation for graft thrombosis have higher circulating concentrations of noradrenaline [Parker et. al, 1993] and plasminogen activator inhibitor-1 (with impaired fibrinolytic activity) in the perioperative period. Circulating levels of both these substances [Rosenfeld et. al, 1993]

and the incidence of peripheral vascular graft occlusion [Rosenfeld et. al, 1993; Tuman et. al, 1991] have been shown to be reduced by epidural anesthesia. Whether this demonstrates a cause and effect relationship is debatable. Furthermore and in contrast, other groups [Cook et. al, 1986; Pierce et. al, 1997] have failed to show any benefit of regional anaesthesia in reducing the incidence of graft thrombosis after peripheral vascular surgery. This point was debated in an earlier section of this text.

In our experience, post-operative catecholamine concentrations (especially noradrenaline - figure 10.) are elevated up to 72 hours following CABG surgery. Postoperative catecholamine levels values exceed those values obtained under controlled intraoperative conditions, suggesting that postoperative analgesia is sub-optimal and that it may well be the most important factor influencing the frequency of thrombotic complications and early postoperative graft occlusion.
Our data suggests that TEA significantly attenuates the increase in intraoperative noradrenaline levels, and maintains this effect up to 24- hours (vs. 3 hours in the GA group - figure 10.) following CPB. Although greater significance would possibly become evident in a larger study population, TEA also attenuates the increase in plasminogen-activator-1 levels (figure 13.).
The beneficial effect of TEA on PAI-1 levels warrants further investigation into the impact of TEA on the dynamic effect of thrombus formation, as measured by thromboelastography (see section titled ... future).

TEA may impact the incidence of early phase graft occlusion. This postulation is based on the knowledge that a combination of factors exist in the immediate peri-operative period that promote early graft occlusion. These include; surgical technique that exposes the sub-endothelium and thus promote thrombus formation, the promotion of a stress response induced by surgery - resulting in postoperative hypercoagulability, and high levels of catecholamines that may promote vasoconstriction with resultant poor run-off from distal coronary vessels.

The use of the internal mammary artery to the left anterior descending coronary artery is associated with patency rates of greater than 90%. Whether other arterial conduits will yield a similar patency rate is still not known, however, the use of multiple arterial grafts may be associated with an increase in perioperative morbidity related to increased reactivity of these arterial conduits to circulating catecholamines, with the development of spasm and ischaemia.

These and other data suggest that TEA may have a role in prevention of early graft occlusion through the reduction in circulating catecholamines and preventing the postoperative hypercoagulability. The possibility that TEA may reduce the incidence of early graft occlusion, especially in patients undergoing multiple arterial grafts and those with poor distal vessels, thereby reducing the need for re-operation coronary surgery, still needs to be explored and may warrant angiographic studies in the postoperative period to confirm this.

Does TEA facilitate fast tracking ?.

Both financial and clinical considerations have prompted many anaesthetists to advocate early extubation after uncomplicated revascularisation instead of traditional prolonged respiratory support.
The studies by Joachimsson et al. [1989] and Liem et al. [1992], comparing the influence of a general anaesthetic technique using intravenous opioids with a combined regional and general anaesthetic technique showed that TEA provides superlative analgesia, thereby; obviating the need for opioids, reducing the duration of mechanical ventilation, facilitating improved respiratory function with early extubation and enhanced control of blood pressure in the postoperative period.
Our data suggests that - through the facilitation of earlier extubation, improved respiratory function, improved alertness (as assessed by a mini-mental test) and improved analgesia (figure 14.) in the TEA group, that TEA is suited as an anaesthetic technique for 'fast-tracking' suitable CABG patients. These data support the findings of Joachimsson et. al [1989] and Liem et. al [1992].
The newer ultra-short acting opioids e.g. remifentanil, through superlative stress response attenuation and allowing almost immediate awakening and extubation, are also ideally suited to facilitate 'fast-tracking' of suitable CABG patients. However, these opioids lack postoperative analgesic properties, and therefore it may be advisable to explore the combination of TEA with these newer opioids, as a potential mechanism to overcome their limitation.

It is important that our anaesthetic techniques also attempt to prevent injury to the skeletal muscle and other end-organs, so that the strive to early mobilisation and discharge from hospital is facilitated. The non-pulsatile flow of CPB and increase in circulating stress hormones during and after CPB may result in an ischaemia-reperfusion injury to the skeletal muscle bed. This is evidenced as an elevation in total creatine kinase (figure 9.), peaking at 72- hours following CABG surgery. The use of TEA was associated with significant reductions in the total creatine kinase levels, together with an earlier peak at 24- hours following CPB. This may be suggestive of improved perfusion of the skeletal muscle bed that is probably facilitated by reduced levels of circulating catecholamines (especially noradrenaline) in the TEA group, and this supports the feasibility of earlier mobilisation and fast tracking by TEA.

The role of TEA in minimally invasive coronary artery bypass graft (MIDCAB) surgery ?.

The increasing interest in the use of minimally invasive coronary artery bypass graft (MIDCAB) surgery is driven by two motives. Firstly, improved patient care - attempting to reduce CPB-related morbidity e.g. inflammatory response and secondly, pressures to reduce medical resource consumption - attempting to expedite postoperative recovery and reduce the duration of hospital stay [Hensley.

MIDCAB surgery is done on a beating heart. This maintenance of myocardial contraction facilitates lymphatic removal of interstitial fluid, thereby avoiding post-arrest ventricular dysfunction due to edema. During MIDCAB surgery, however, regional ischaemia (15 - 20 minutes) is still induced in order to facilitate anastomosis of the distal end of the internal mammary artery to the LAD on the beating heart. This inevitably predisposes to myocardial ischaemia and a ischaemia-reperfusion injury may occur e.g. postischemic myocardial dysfunction (stunning). This myocardial dysfunction may be counter productive to the original objective of this surgical procedure, namely rapid convalescence and home-discharge.
The inability to use conventional myocardial protective strategies that are used during CPB (cardioplegia-induced electromechanical arrest) in MIDCAB surgery necessitates we search for other methods of myocardial protection. Three possible techniques used in conventional CABG surgery may prove useful in MIDCAB surgery. These include; ischaemic preconditioning [Jacobsohn et. al, 1997], pre-treatment with intravenous substrate (s) and thoracic epidural anaesthetic techniques.

Experimental data showing improved recovery of systolic thickening following ischaemia (reduced stunning) [Rolf et. al, 1996] and a reduction in myocardial infarct size [Klassen et. al, 1980; Davis et. al, 1986] support the myocardial protective properties of TEA and suggest that TEA is ideal as a method of myocardial protection during MIDCAB surgery, where conventional protection by electromechanical arrest cannot be used. This is further supported by our data, showing a preserved state of inotropy in the TEA group, when compared to the GA group - see left ventricular function curves (figure 6.).

The controversy of the impact of epidural analgesia on the incidence of cardiac morbidity in non-cardiac surgery.

"Impressed by the association of operation and coronary artery occlusion in patients over 50 years of age" Master et. al [1937] of Mount Sinai Hospital in New York, provided the first evidence for surgical interventions precipitating coronary occlusion. In this series of 35 patients who suffered perioperative myocardial infarction (P-MI), during the period 1931 to 1937, characteristically more than 50% of these P-MI's occurred within three days of surgery, 60% were silent, associated with a high (66%) mortality and post-mortem findings suggested that thrombosis occurred on underlying atherosclerotic plaques.

Sixty years on, in the 1990's, we are still plagued with the increased risk of peri-operative morbidity and mortality associated with coronary artery disease (CAD). This is evidenced by the strong correlation between recent myocardial infarction and re-infarction or death following non-cardiac surgery. Mangano et al. [1990] estimated a 41% incidence of postoperative myocardial ischemia in patients who were at risk of or with known CAD following non-cardiac surgery. In this study, postoperative myocardial ischaemia was the only multivariate predictor of an adverse post-operative cardiac event, with a 9.2 odds ratio for an adverse ischaemic event (myocardial infarction or unstable angina) within 6 months of surgery and an 18% reported incidence of adverse cardiac events within the first 6 months following surgery. The inability to show history of a recent myocardial infarction, pre-operative or intra-operative ischaemia, as independent predictors of adverse cardiac events following non-cardiac surgery in this study may reflect the improved pre-operative work up and stratification of patients who are at risk, or known to have CAD, with appropriate referral of the patients for revascularisation prior to their non-cardiac surgery, according to the recent American College of Cardiology / American Heart Association (ACC/AHA) Task Force on practice guidelines [1996], as well as optimal intra-operative anaesthetic management.

Ischaemic injury is, furthermore, also responsible for a significant delay in extubation and hospital discharge, an impaired quality of life and the consumption of a disproportionate amount of health resources. These increased expenses in the non-cardiac surgical patients who suffers P-MI

is estimated at an additional hospital cost estimated at US$10,000 - $20,000 per patient [Kalish et. al, 1995].

The optimal anaesthetic and analgesic management of patients at risk of a cardiac event following surgery still remains undefined. However, if we are to continue making an impact on reducing the incidence of adverse perioperative ischaemic events in patients with CAD who undergo non-cardiac surgery, then we as anaesthetists should assume the role of perioperative physicians and place emphasis of patient management on the entire peri-operative and especially the post-operative period.

Management should focus on risk stratification, a multimodal therapeutic approach to prophylaxis and treatment of ischaemia and improved detection of peri-operative myocardial ischaemia to allow prompt therapeutic intervention. The fact that the majority of atherosclerotic coronary lesions are dynamic in nature [Blomberg et. al, 1990] and that vasoconstriction and increased shear stress induced by sympathetic activation may rupture unstable coronary lesions exposing the underlying lipid and collagen, leading to secondary activation of the coagulation cascade, motivates us to place emphasis on two areas of peri-operative management in the patient at risk of an adverse peri-operative ischaemic event, namely a reduction in sympathetic activation and a reduction in secondary platelet and coagulation cascade activation.
Modulation of the sympathetic nervous system can be done with pre-operative medication using α_2-agonists, peri-operative use of β-antagonists [Mangano et. al, 1996], superlative peri-operative analgesia with the use of opioids and regional anaesthetic techniques.
Separate to the indirect effect of analgesia on limiting sympathetic outflow, there is now increasing evidence that opioids may have a direct myocardial protective effect, through the mediation of ischaemic preconditioning by delta 1-opioid receptors [Schultz, 1998].
Therapies aimed at preventing postoperative hypercoagulability include the use of regional anaesthetic techniques [Rosenfeld et. al, 1993], the postoperative use of non-steroidal anti-inflammatory agents e.g. ketorolac [Beattie et. al, 1997], aspirin and possibly more specific platelet antagonists, e.g. glycoprotein IIb/IIIa receptor antagonists.

Do the experimental and clinical data regarding high-TEA (T1-4) techniques in CABG surgery shed any light on the continued controversy of whether

regional anesthetic techniques have the ability to reduce cardiac morbidity in non-cardiac surgery or not?.

A full discussion of this topic falls outside the realm of this paper.
Sympathectomy by epidural anaesthesia in the low thoracic (e.g. $T_{7/8}$) or lumbar segments may result in diastolic hypotension, with a reduction in coronary perfusion pressure. Furthermore, the T_{1-4} segments may remain unanaesthetised when this lower epidural route is used. In addition to the reduction in coronary perfusion pressure, hypotension may also induce a baroreceptor reflex-induced compensatory hyperactivity of these unanaesthetised sympathetic nerve segments [Taniguchi et. al, 1997]. Remembering that these last two mentioned changes may be detrimental, it is then not that surprising that studies [Baron et. al, 1991; Bode et. al, 1996; Bois et. al, 1997] have failed to show any benefit by regional anaesthesia in reducing the incidence of peri-operative myocardial morbidity. This is in contrast to the earlier studies by Yeager et. al [1987] and Tuman et. al [1991] who did show a reduction in cardiac morbidity with regional anaesthetic techniques. These earlier trials have also been criticised for their methodological limitations.
There is clearly no substantial, consistent evidence from these clinical trials to support benefit by regional anaesthesia in reducing the incidence of peri-operative myocardial morbidity and in fact the largest prospective, randomised trial to-date by Bode et al. [1996] showed an increasing trend in cardiac morbidity in those patients randomised to neuraxial regional anaesthetic techniques. As a consequence controversy continues to surround the role of epidural analgesia in the prevention of perioperative cardiac morbidity in non-cardiac surgery.

The increased sympathetic outflow and increased shear stress associated with unanaesthetised sympathetic segments (T_{1-4}) during lumbar or low-thoracic epidural techniques may result in an exaggerated response to adrenergic stimuli, with excessive vasoconstriction in the presence of pre-existent endothelial dysfunction. This vasoconstriction may cause plaque fissuring in atherosclerotic lesions that have an **unstable angina-prone anatomical composition**, i.e. unstable lipid bullae. This primary event then exposes subendothelial collagen and lipids which are known potent activators of the coagulation cascade (secondary event).

The suggestion that non-critical, unstable lesions may predispose to P-MI and that major peri-operative myocardial morbidity following non-cardiac

surgery is at least partly due to coronary thrombosis, suggests that highly selective cardiac sympathectomy (T_{1-4}), through selective vasodilation of atherosclerotic vessels and through the reduction of increased shear stress may prevent the primary incident, namely plaque fissuring - and therefore play a role in the prevention of P-MI in non-cardiac surgery. Fujita et. al [1996] showed that TEA lessened regional ischaemia induced by intracoronary injection of endothelin, in a dog model. This suggests that TEA at a high-thoracic level may provide protection against increased circulating levels of endogenous stress factors, precipitated by surgery at a site removed from the epidural.

With regards to the attempt to reduce cardiac morbidity in high risk patients undergoing non-cardiac surgery, it may be that epidural catheters have been "***malpositioned***" in these previous studies, and that the ideal location of an epidural in these patients needs reconsideration.
Positioning the epidural at T_{1-4}, away from the site of surgery, for a highly selective cardiac sympathectomy, may be more suited for the prevention of cardiac morbidity than current neuraxial techniques in non-cardiac surgery, where the epidural is sited at the level of the surgical incision. This high-TEA should then be combined with a general anaesthetic technique that uses the newer more potent opioids e.g. remifentanil for attenuation of the surgically-induced intra-operative stress response, or even more controversial, the high-TEA should be combined with a second epidural at the level of surgery (in an attempt to maintain the other beneficial effects of neuraxial techniques that are known to occur in non-cardiac surgery - namely, increased vascular graft patency, reduced pulmonary dysfunction and decreased rate of infection etc.).
We await trials that provide highly selective cardiac sympathectomy by TEA at T_{1-4} (distant from the surgical site), in the high-risk non-cardiac surgical patient population in the hope that this will finally resolve the controversial issue of whether or not regional anaesthetic techniques reduce cardiac morbidity in patients undergoing non-cardiac surgery.

VI. FUTURE

The promising results obtained in this pilot study have lead to the implementation of a larger (n = 90), prospectively randomised clinical trial investigating the role of TEA in the setting of coronary artery bypass graft surgery.

This trial has been designed with emphasis on;

- finding the optimal local anaesthetic dose, as well as the comparison of bupivacaine to the newer local anaesthetic agent, ropivacaine
- utilising more concrete endpoints that will reflect whether TEA may impact patient outcome and patient quality of life - these endpoints include;
    - * **peri-operative myocardial infarction**
    - * **peri-operative hypercoagulability** as assessed by thromboelastographic studies and its possible contribution to **early graft occlusion** as assessed by coronary angiography at 4-6 weeks post-surgery.

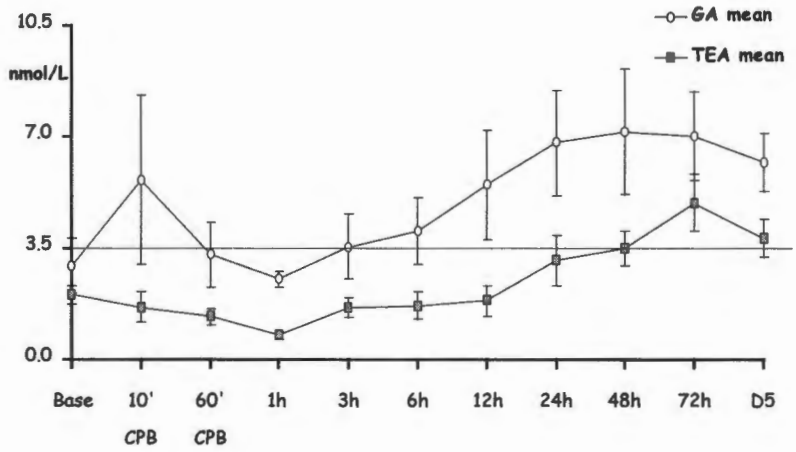
In our pilot study Holter monitoring showed an increased incidence of post-operative ventricular arrhythmia (VPBs) formation compared to pre-operative values. This may be related to ischaemia-reperfusion and was evidenced in both the TEA (17.9 vs. 1517.4 VPBs) and the GA groups (651.2 vs. 932.7 VPBs). No statistical difference was, however, shown between the groups. We intend to compare bupivacaine with ropivacaine in TEA, as it may be that ischaemia-reperfusion injury following aorta cross-clamping may benefit from the lower cardiotoxicity profile of ropivacaine and therefore a reduction in the incidence of these postoperative arrhythmias.

A more selective group of patients will be investigated in this larger trial. This group will include patients undergoing coronary artery bypass graft surgery using one or more arterial anastomosis (i.e. left and / or right internal mammary artery and / or radial artery). The reasoning behind this is that traditionally multiple arterial bypass grafts have been regarded to be at increased risk of peri-operative morbidity. This is due to a propensity for the thicker walled, muscular arterial grafts to develop vasospasm, and subsequent ischaemia. The superior patency rates of the left internal mammary artery graft, however, suggests that arterial grafts

should remain patent for a longer period than saphenous vein grafts and therefore warrants studies of anaesthetic and surgical techniques that may reduce the incidence of arterial graft spasm.

A "sneak preview" of the data collected to date, in this larger trial will be discussed below, but please note that it is incomplete, and that no statistical analysis has been done. These preliminary data suggest that;

- intraoperative control of noradrenaline release is less well controlled in the GA group. Furthermore, despite an increase in the local anaesthetic infusion dose from 0.1% to 0.125% bupivacaine we still show a similar profile in post-operative noradrenaline levels, with noradrenaline levels rising above the upper reference range at 72-hours following CPB. Whether this is tachyphylaxis, or increased stress with active mobilisation remains to be elucidated.

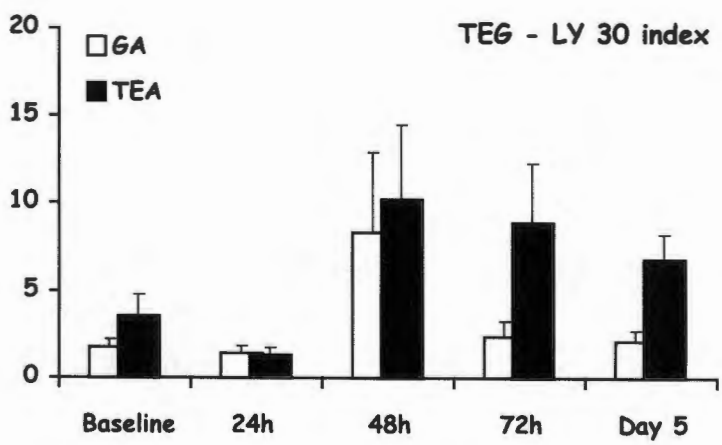


- With the use of peri-operative thromboelastography we investigated the influence of TEA on the dynamic coagulation process. The maximal amplitude component of a TEG correlates with fibrinogen levels and platelet activity. It was our expectation to find an increase in the fibrinogen, an acute phase protein, component in the GA group. In an attempt to differentiate the contribution by the platelet and fibrinogen components to postoperative hypercoagulability, and an increased maximum amplitude, we added Reopro® [platelet glycoprotein IIb/IIIa antagonist] to a duplicate TEG cup. We, however, observed no difference in maximal amplitude components between groups.
  A striking observation was however made and that was that there was a significant hyperfibrinolytic process (as measured by a lysis index at 30- minutes) in the TEA group during the late postoperative period

(after 24- hours - see figure below). This effect was maintained above baseline values for the first 5 post-operative days in which TEG's were performed. In comparison the GA group shows rapid loss of this fibrinolytic process after 48- hours.

This **hyper**fibrinolytic pattern witnessed in the TEA group is suggestive of an active process. It may be that a repair process is activated and maintained in the TEA group, but not evidenced in or rapidly lost in the GA group. The origins of this is yet unknown - but we suspect neutrophilic activity may contribute to this. Neutrophils are often described as possessing 'two-faces'. When activated in the immediate per-operative period become "aggressor" cells and promote the inflammatory response. However, in the later post-operative period these aggressor cells now become "repairer" cells and may promote fibrinolysis. This repair process may be through the secretion of a possible fibrinolytic agent and the stepped process of fibrinolysis on a TEG recording suggests that a these agents are released in little boluses, possibly from granules.

In the GA group, we see a greater stress response to surgery, with resultant increased levels of PAI-1 or other yet-unknown antagonists that oppose this hyperfibrinolytic process induced by repair cells. Whether this promotion of a hyperfibrinolytic process by TEA will translate into improved graft patency rates, and whether this is the process whereby epidural analgesia promotes graft patency in peripheral vascular surgery, is not established yet. However, it seems to hold promise.



On reviewing the literature and studying the results of our pilot study, it seems that numerous subgroups of patients undergoing cardiac surgery may benefit from TEA, and would warrant further investigation. These include the following groups of patients;

- patients undergoing MIDCAB surgery - where the inability to arrest the heart and thus an inability to use conventional myocardial protective methods is seen due to not using CPB
- patients with poor distal run-off in their native coronary arteries - these patients show a high propensity to occlude their bypass grafts
- patients with exaggerated endothelial dysfunction - e.g. diabetic patients, who would benefit from direct vasodilatory effects of TEA
- patients with left ventricular hypertrophy (e.g. aortic stenosis) - regional anaesthesia has traditionally been regarded as a contra-indication for in these patients undergoing non-cardiac surgery. In cardiac surgery, these patients often exhibit poor postoperative outcome due to the difficulty to provide adequate myocardial protection of the hypertrophic myocardium. The improved distribution of myocardial blood flow towards the subendocardium by TEA may prove valuable during administration of cardioplegia in this group of patients.
- congenital heart disease - the high incidence of pulmonary hypertensive crises evidenced in the postoperative period of children having undergone congenital heart surgery may also benefit from sympatholysis, and from stress response attenuation that is maintained into the postoperative period. Furthermore, patients with spelling episodes (e.g. Tetrallogy of Fallot) may also benefit from the sympatholytic effects of TEA.

VII. CONCLUSION

The choice of anaesthetic technique may significantly benefit and impact the continual strive to improve patient care and meet the economic constraints placed on health care resources. This choice has the potential of reducing the incidence of adverse haemodynamic, metabolic, immunologic, and hemostatic alterations, and thereby potentially reducing morbidity and mortality rates. The choice of anaesthetic technique may, furthermore, facilitate early extubation, accelerate convalescence and promote early discharge of the patient following both cardiac and non-cardiac surgery.

The optimal anaesthetic technique in cardiac and non-cardiac surgery, however, still remains undefined. This dissertation suggests that regional anaesthetic and analgesic techniques, when used correctly, in the immediate per-operative setting and probably even more importantly in the post-operative period of cardiac surgery may, in addition to the provision of superlative analgesia, reduce surgical stress-induced alterations of organ function and thereby contribute to reduced peri-operative morbidity and accelerated recovery from cardiac surgery.

VIII. REFERENCES

1. Alyanakian M-A, Dehoux M, Chatel D et al.: Cardiac troponin I in diagnosis of perioperative myocardial infarction after cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 1998, 12: 288--294.
2. American Heart Association Task Force on Practice Guidelines. *Anesth Analg* 1996, 82: 854—860.
3. Anand KJS, Hickey PR. Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. *N Engl J Med* 1992, 326: 1--9.
4. Baron JF, Bertrand M, Barre E, et al.: Combined epidural and general anesthesia versus general anesthesia for abdominal aortic surgery. *Anesthesiology* 1991, 75: 611--618.
5. Beattie WS, Warriner CB, Etches R, et al.: The addition of continuous intravenous infusion of Ketorolac to a Patient-controlled analgetic morphine regime reduced postoperative myocardial ischemia in patients undergoing elective total hip or knee arthroplasty. *Anesth Analg* 1997, 84: 715—722.
6. Beilin Y, Zahn J, Comerford M: Safe epidural analgesia in thirty parturients with platelet counts between 69,000 and 98,000 mm^{-3}. *Anesth Analg* 1997, 85: 385--388.
7. Blackburn H, Keys A, Simonson E, et al.: The electrocardiogram in population studies: A classification system. *Circulation* 1960; 21: 1160--1165.
8. Blomberg S, Emanuelsson H, Kvist H, et al.: Effects of thoracic epidural anesthesia on coronary arteries and arterioles in patients with coronary artery disease. *Anesthesiology* 1990; 73: 840--847.
9. Blomberg S, Emanuelsson H, Ricksten S-E: Thoracic epidural anesthesia and central haemodynamics in patients with unstable angina. *Anesth Analg* 1989, 69: 558—562.
10. Blomberg S, Ricksten SE. Thoracic epidural anaesthesia decreases the incidence of ventricular arrhythmias during acute myocardial ischaemia in the anaesthetized rat. *Acta Anaesthesiol Scand* 1988, 32: 173--178.
11. Blomberg S, Ricksten S-E: Effects of thoracic epidural anesthesia on central haemodynamics compared to cardiac beta adrenoceptor blockade in conscious rats with acute myocardial infarction. *Acta Anaesthesiol Scand* 1990, 34: 1--7.

12.Blomberg SG: Long-term home self-treatment with high thoracic epidural anesthesia in patients with severe coronary artery disease. *Anesth Analg* 1994, 79: 413--421.
13.Bode RH Jr, Lewis KP, Zarich SW, et al.: Cardiac outcome after peripheral vascular surgery: Comparison of general and regional anesthesia. *Anesthesiology* 1996, 84: 3—13.
14.Bois S, Couture P, Boudreault D, et al.: Epidural analgesia and intravenous patient-controlled analgesia result in similar rates of postoperative myocardial ischemia after aortic surgery. *Anesth Analg* 1997, 85: 1233--9.
15.Brown BG: Response of normal and diseased epicardial coronary arteries to vasoactive drugs: Quantitative arteriographic studies. *Am J Cardiol* 1985, 56: 23E--29E.
16.Caplan RA, Ward RJ, Posner K, et al.: Unexpected cardiac arrest during spinal anesthesia: A Closed claims analysis of predisposing factors. *Anesthesiology* 1988, 68: 5--11.
17.Chaitman BR, Alderman EL, Sheffield LT: Use of survival analysis to determine the clinical significance of new Q waves after coronary artery bypass surgery. *Circulation* 1983, 67: 302--309.
18.Chan KK, Welch KJ: Cardiac arrest during segmental thoracic epidural anesthesia. *Anesthesiology* 1997, 86: 503--505.
19.Chaney MA: Intrathecal and epidural anesthesia and analgesia for cardiac surgery. *Anesth Analg* 1997, 84: 1211--1221.
20.Cheng DC, Chung F, Burns R, et al.: Postoperative MI documented by technetium pyrophosphate scan using SPECT: Significance of intraoperative ischemia and haemodynamic control. *Anesthesiology* 1978, 71: 818—826.
21.Christopherson R, Beattie C, Frank SM et al.: Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery: Perioperative Ischemia Randomised Anesthesia Trial Study Group. *Anesthesiology* 1993, 79: 422—34.
22.Clagett GP, Anderson FA Jr, Heit J, et al.: Prevention of venous thromboembolism. *Chest* 1995, 108: 312--34S.
23.Cook PT, Davies MJ, Cronin KD, et al.: A prospective randomized trail comparing spinal anaesthesia using hyperbaric cinchocaine with general anaesthesia for lower limb vascular surgery. *Anaesth Intensive Care* 1986, 14: 373--380.
24.Dahlgren N, Tornebrandt K. Neurological complications after anaesthesia. A follow-up of 18,000 spinal and epidural anaesthetics performed over three years. *Acta Anaesthesiol Scand* 1995, 39: 872--80.

25.Davis RF, DeBoer, LW, Maroko PR: Thoracic epidural anaesthesia reduces myocardial infarct size after coronary artery occlusion in dogs. *Anesth Analg* 1986, 65: 711--717.
26.De Swiet M, Redman CWG: Aspirin, extradural anaesthesia and the MRC collaborative low dose aspirin study in pregnancy (CLASP). *Br J Anaesth* 1992, 69: 109--110.
27.Delva E, Maille JG, Solymoss BC. Evaluation of myocardial damage during coronary artery grafting with serial determination of serum CPK MB isoenzyme. *J Thorac Cardiovasc Surg.* 1978, 73: 467--75.
28.Desborough JP, Hall GM, Hart GR, et al.: Hormonal responses to cardiac surgery: effects of sufentanil, somastatin and ganglion block. *British Journal of Anesthesia* 1990, 64: 688--695.
29.Dickman CA, Shedd SA Spetzler RF, et al.: Spinal hematoma associated with epidural anesthesia: Complications of systemic heparinization in patients receiving peripheral vascular thrombolytic therapy. *Anesthesiology* 1990, 72: 947--50.
30.Euler DE, Nattel S, Spear JF, et al.: Effect of sympathetic tone on ventricular arrhythmias during circumflex coronary occlusion. *Am J Physiol* 1985, 249: H1045--H1050.
31.Farah S, Moss DW, Ribeiro P, et al.: Interpretation of changes in the activity of creatine kinase MB isoenzyme in serum after coronary artery bypass grafting. *Clin Chem Acta.* 1984, 141: 219--25.
32.Feigl ED: Coronary physiology. *Physiol Rev* 1982, 63: 1--205.
33.Flatley KA, DeFily DV, Thomas JX: Effects of cardiac sympathetic nerve stimulation during adrenergic blockade on infarct size in anesthetised dogs. *J Cardiovasc Pharmacol* 1985, 4: 673--679.
34.Fredericks RL, Campbell J, Bassell JM: Psychologic cardiac arrest during extensive sympathetic blockade. *Anesthesiology* 1988, 68: 943--944.
35.Fujita S, Tsuchida H, Kanaya N, et al.: Effects of thoracic epidural anesthesia on changes in ischemic myocardial metabolism induced by intracoronary injection of endothelin in dogs. *Journal of Cardiothoracic and Vascular Anesthesia* 1996; 10: 903--908.
36.Fuster V, Badimon L, Badimon JJ, et al.: The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992, 326: 242--250.
37.Gao WD, Atar D, Liu Y, et al.: Role of troponin I proteolysis in the pathogenesis of stunned myocardium. *Circ Res* 1997, 80: 393--9.
38.Giebler RM, Schere RU, Peters J: Incidence of neurologic complications related to thoracic epidural catheterization. *Anesthesiology* 1997, 86: 55--63.

39.Gild W, Crilley P: Sudden cardiac arrest during epidural anesthesia (letter). *Anesthesiology* 1990, 73: 1296.
40.Goertz A, Heinrich H, Seeling W: Baroreflex control of heart rate during high thoracic epidural anaesthesia. *Anaesthesia* 1992, 47: 984--987.
41.Gould KL: Dynamic coronary stenosis. *Am J Cardiol* 1980, 45: 286--292.
42.Graeber GM, Shawl FA, Head HD, et al.: Changes in serum creatine kinase and lactate dehydrogenase cause by acute perioperative myocardial infarction and by transatrial cardiac surgical procedures. *J Thorac Cardiovasc Surg.* 1986, 92: 63--72.
43.Gray RJ, Matloff JM, Conkin CM: Perioperative myocardial infarction: late clinical course after coronary artery bypass surgery. *Circulation* 1982, 66: 1185--1189.
44.Guiteras Val PG, Pelletier LC, Hernadex MG, et al.: Diagnostic criteria and prognosis of perioperative myocardial infarction following coronary bypass. *J Thorac Cardiovasc Surg* 1983, 86: 878—886.
45.Harrison DC: Cost containment in medicine: why cardiology? American *Journal of Cardiology* 1985, 56: 10C--15C.
46.Hendriks GWH, Hasenbos MAWM, Gielen MJM, et al.: Evaluation of thoracic epidural catheter position and migration using radio-opaque catheters. *Anesthesia* 1997, 52: 457--459.
47.Hensley FA Jr: Minimally invasive myocardial revascularisation surgery : Here to stay ? *J Cardiothorac Vasc Anesth* 1996, 10: 445—446 (editorial).
48.Hirsh J, Levine MN. Low molecular weight heparin: laboratory properties and clinical evaluation. *Eur J Surg* 1994, 571: (Suppl): 9—22.
49.Hogan QH, Novalija E, Kulier AH, et al.: Effect of thoracic epidural anesthesia on spontaneous postinfarction ventricular dysrhythmia in awake dogs. *Regional anesthesia* 1997, 22: 318 --324.
50.Hopf HB, Weissbach B, Peters J: High thoracic segmental epidural anesthesia diminishes sympathetic outflow to the legs, despite restriction of sensory blockade to the upper thorax. *Anesthesiology* 1990, 73: 882--889.
51.Horlocker TT, Wedel DJ. Spinal and epidural blockade and perioperative low molecular weight heparin: smooth sailing on the Titanic. *Anesth Analg.* 1998, 86: 1153--1156.
52.Horlocker TT, Heit JA. Low molecular weight heparin: biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anesthetic management. *Anesth Analg.* 1997, 85: 874--885.
53.Horlocker TT, Wedel DJ, Offord KP: Does perioperative anti-platelet therapy increase the risk of hemorrhagic complications associated with regional anesthesia? *Anesth Analg* 1990, 70: 631--634.

54.Jacobsohn EJ, Young CJ, Aronson S, et al.: The role of ischemic preconditioning during minimally invasive coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 1997, 11: 787—792.

55.Joachimsson PO, Nystrom SO, Tyden H: Early extubation after coronary artery bypass surgery in efficiently rewarmed patients: a postoperative comparison of opioid anesthesia versus inhalation anesthesia and thoracic epidural analgesia. *J Cardiothorac Anesth* 1989, 3: 444--454.

56.Johannsen UJ, Mark AL, Marcus ML: Responsiveness to coronary sympathetic nerve stimulation during maximal coronary dilation produced by adenosine. *Circ Res* 1982, 50: 510—517.

57.Kalish RL, Daley CC, Davis RB, et al.: Costs of potential complications of care for major surgery patients. *American Journal of Medical Quality* 1995, 10: 48—54.

58.Kamibayashi T, Hayashi Y, Mammoto T, et al.: Thoracic epidural anesthesia attenuates halothane-induced myocardial sensitization to dysrhythmogenic effects of epinephrine in dogs. *Anesthesiology* 1995, 82: 129--134.

59.Kane RF: Neurodeficits following epidural or spinal anesthesia. *Anesth Analg* 1981, 60: 150--161.

60.Kehlet H: Surgical stress: the role of pain and analgesia. *Br J Anaesth* 1989, 63: 189--195.

61.Kereiakes DJ: Preferential benefit of platelet glycoprotein IIb/IIIa receptor blockade: specific considerations by device and disease state. *Am J Cardiol* 1998, 81: 49E--54E.

62.Kimura A, Harada H, Park JE, et al.: Mutations in the cardiac troponin I gene associated with hypertrophic cardiomyopathy. *Nat Genet* 1997, 16: 379--82.

63.Klassen GA, Bramwell RS, Bromage PR, et al.: Effect of acute sympathectomy by epidural anesthesia on the canine coronary circulation. *Anesthesiology* 1980, 52: 8--15.

64.Kleinman B: Thoracic epidural anesthesia for treatment of angina - Con: Thoracic epidural anesthesia is not indicated in the treatment of unstable angina. *J Cardiothorac Vasc Anesth* 1997, 11: 109--111.

65.Krukenkamp IB, Silverman NA, Pridjian A, et al.: Correlation between the linearized Frank-Starling relationship and myocardial energetics in the ejecting heart. Afterload independence and sensitivity to inotropic state. *J Thorac Cardiovasc Surg* 1987, 93: 728—740.

66.Lee TH, Goldman L. serum enzyme assays in the diagnosis of acute myocardial infarction. *Ann Intern Med.* 1986, 105: 221--33.

67.Liem TH, Booij LH, Hasenbos MA, et al.: Coronary artery bypass using two different anesthetic techniques: Part 1: Haemodynamic results. *Journal of Cardiothoracic and Vascular Anesthesia* 1992, 6: 148--155.

68.Liem TH, Hasenbos MA, Booij LH, et al.: Coronary artery bypass using two different anesthetic techniques: Part 2: Postoperative outcome. *Journal of Cardiothoracic and Vascular Anesthesia* 1992, 6: 156--161.

69.Liem TH, Booij LH, Gielen MJ, et al.: Coronary artery bypass using two different anesthetic techniques: Part 3: Adrenergic responses. *Journal of Cardiothoracic and Vascular Anesthesia* 1992, 6: 162--167.

70.Liu SL, Carpenter RL, Neal JM: Epidural anesthesia and analgesia. Their role in postoperative outcome. *Anesthesiology* 1995, 82: 1474--1506.

71.Macdonald IA, Lake DM. An improved technique for extracting catecholamines from body fluids. *Journal of Neuroscience Methods* 1985, 13: 239--248.

72.Mangano D: Biventricular function after myocardial revascularisation in humans: Deterioration and recovery patterns during the first 24 hours. *Anesthesiology* 1985, 62: 571--577.

73.Mangano DT, Browner WS, Hollenberg M, et al.: Association of perioperative ischemia with cardiac morbidity and mortality in men undergoing non cardiac surgery. *N Engl J Med* 1990, 323: 1781—8.

74.Mangano DT, Siliciano D, Hollenberg M, et al.: Postoperative myocardial ischemia: therapeutic trials using intensive analgesia following surgery. *Anesthesiology* 1992, 76: 342--353.

75.Mangano DT, Layug EL, Wallace A, et al.: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med* 1996, 335: 1713—20.

76.Master AM, Dack S, Jaffe HL: Postoperative coronary artery occlusion. *JAMA* 1937, 110: 1415—1418.

77.McDonough JL, Arrell DK, Van Eyk JE. Troponin I degradation and covalent complex formation accompanies myocardial Ischemia/Reperfusion injury. *Circ Res* 1999, 84: 9—20.

78.McEnvoy GK. American Hospital Formulary Service. *Drug information* 1997, 1086.

79.Meissner A, Weber TP, Van Aken H et al.: Thoracic epidural anesthesia does not affect functional recovery from myocardial stunning in sevoflurane-anesthetised dogs. *Journal of Cardiothoracic and Vascular Anesthesia* 1998, 12: 662--667.

80.Miller DC, Stinson EB, Oyer PE: Detection of myocardial injury after coronary bypass grafting using a hypothermic cardioplegia technique. *Ann Thor Surg* 1982, 33: 139--144.

81.Moore CM, Cross MH, Desborough JP, et al.: Hormonal effects of thoracic extradural analgesia for cardiac surgery. *British Journal of Anesthesia* 1995, 75: 387--393.
82.Nabel EG, Selwyn AP, Ganz P: Paradoxical narrowing of atherosclerotic coronary arteries induced by increases in heart rate. *Circulation* 1990, 81: 850—859.
83.National Confidential Enquiry into Perioperative Deaths. Report of the national confidential enquiry into perioperative deaths 1993/4. London: NCEPOD, 1996.
84.Olthof H, Middelhof C, Meijne NG, et al.: The definition of myocardial infarction during aortocoronary bypass surgery. *Am Heart J* 1983, 106: 631.
85.Onishchuk JL, Carlsson C. Epidural hematoma associated with epidural anesthesia: complications of anticoagulant therapy. *Anesthesiology* 1992, 77: 1221--1223.
86.Orlikowski CE, Payne AJ, Moodley J, et al.: Thromboelastography after aspirin ingestion in pregnant and non-pregnant subjects. *Br J Anaesth* 1992, 69: 159--161.
87.Parker SD, Breslow MJ, Frank SM, et al.: Catecholamine and cortisol responses to lower extremity revascularisation: Correlation with outcome variables. *Critical care Medicine* 1995, 23: 1954--1961.
88.Pierce ET, Pomposelli FB, Stanley GD, et al.: Anesthesia type does not influence early graft patency or limb salvage rates of lower extremity arterial bypass. *J Vasc Surg* 1997, 25: 226--233.
89.Podrid PJ, Fuchs T, Candinas R: Role of sympathetic nervous system in the genesis of ventricular arrhythmias. *Circulation* 1990, 82: I-103--I-113.
90.Report on the confidential enquiry into maternal deaths in the United Kingdom 1991-1993. London: HMSO, 1996.
91.Roizen MF: Should we all have a sympathectomy at birth? Or at least preoperatively? [editorial]. *Anesthesiology* 1988, 68: 482--484.
92.Rolf N, Meissner A, Van Aken H, et al.: The effect of thoracic epidural anesthesia on functional recovery from myocardial stunning in propofol-anesthetised dogs. *Anesthesia Analgesia* 1996; 84: 723--729.
93.Rolf N, Mollhoff T: Epidural anaesthesia for patients undergoing coronary artery bypass grafting. *Current Opinion in Anaesthesiology* 1997, 10: 17--20.
94.Rolf N, Van de Velde M, Wouters PF, et al.: Thoracic epidural anesthesia improves functional recovery from myocardial stunning in conscious dogs. *Anesth Analg* 1996, 83: 935--940.

95.Rosenfeld BA, Beattie C, Christofferson R, et al.: The effects of different anesthetic regiments on fibrinolysis and the development of postoperative arterial thrombosis. *Anesthesiology* 1993, 79: 435--443.
96.Ross R: The pathogenesis of atherosclerosis: a perspective for the 1990's. *Nature* 1993, 362: 801-809.
97.Sakura S, Saito Y, Kosaka Y: The effects of epidural anesthesia on ventilatory response to hypercapnia and hypoxia in elderly patients. *Anesth Analg* 1996, 82: 306--311.
98.Schmidt A, Nolte H: Subdural and epidural hematomas following epidural anesthesia: A literature review. *Anaesthetist* 1992, 41: 276--284.
99.Schultz JE, Hsu AK, Gross GJ. Ischemic preconditioning in the intact rat heart is mediated by delta1- but not mu- or kappa-opioid receptors. *Circulation* 1998, 97: 1282—9.
100.Seth J, Brown LM. A simple RIA for cortisol. *Clinica Chimica Acta* 1988, 86: 109--120.
101.Skilton RWH, Justice W. Epidural haematoma following anticoagulant treatment in a patient with an indwelling epidural catheter. *Anaesthesia.* 1998, 53: 691--701.
102.Slogoff S, Keats A: Does perioperative myocardial ischemia lead to a postoperative myocardial infarction? *Anesthesiology* 1985, 62: 107—14.
103.Sorensen RM, Pace NL: Mortality and morbidity of regional versus general anaesthesia: a meta-analysis. *Anesthesiology* 1991, 75: A1053.
104.Sprung J, Abdelmalak B, Schoenwald P. Vaso-vagal cardiac arrest during the insertion of an epidural catheter and before the administration of epidural medication. *Anesth Analg* 1998, 86: 1263--5.
105.Staats PS, Panchal SJ: Thoracic epidural anesthesia for treatment of angina - Pro: The anesthesiologist should provide epidural anesthesia in the coronary care unit for patients with severe angina. *J Cardiothorac Vasc Anesth.* 1997, 11: 105--108.
106.Stenseth R, Bjella L, Berg EM, et al.: Thoracic epidural analgesia in aorto-coronary bypass surgery I: Haemodynamic effects. *Acta Anaesthesiologica Scandinavica* 1994, 38: 826--833.
107.Stenseth R, Bjella L, Berg EM, et al.: Thoracic epidural analgesia in aorto-coronary bypass surgery II: effects on the endocrine metabolic response. *Acta Anaesthesiologica Scandinavica* 1994, 38: 834--839.
108.Stenseth R, Bjella L, Berg EM, et al.: Effects of thoracic epidural analgesia on pulmonary function after coronary artery bypass surgery. *Eur J Cardiothorac Surg* 1996, 10: 859--65.
109.Stephanov S, de Preux J: Lumbar epidural hematoma following epidural anesthesia. *Surg Neurol* 1982, 18: 351--351.

110.Suga H, Goto Y, Futaki S, et al.: Systolic pressure-volume area (PVA) as the energy of contraction in Starling's law of the heart. *Heart Vessels* 1991, 6: 65--70.

111.Taniguchi M, Kasaba T, Takasaki M: Epidural anesthesia enhances sympathetic nerve activity in the unanesthetised segments in cats. *Anesth Analg* 1997, 84: 391--397.

112.Tekkok IH, Catalepe O, Tahta K, et al.: Extradural haematoma after continuos extradural anaesthesia. *British Journal of Anaesthesia* 1991, 112—5.

113.Theroux P, Quinet H, McCans J, et al.: Aspirin, heparin or both to treat acute unstable angina. *N Engl J Med* 1988, 319: 1105--1111.

114.Tryba M, Wedel DJ. Central neuraxial block and low molecular weight heparin: Lessons learned from different dosage regimes in two continents. *Acta Anaesthesiologica Scandinavia* 1997; 41 (Suppl. 111): 100-3.

115.Tsuchida H, Omote T, Miyamoto M, et al.: Effects of thoracic epidural anesthesia on myocardial pH and metabolism during ischaemia. *Acta Anaesthesiol Scand* 1984, 28: 132--137.

116.Turfrey DJ, Ray DA, Sutcliffe NP, et al.: Thoracic epidural anaesthesia for coronary artery bypass graft surgery. Effects on postoperative complications. Anaesthesia 1997, 52: 1090--5.

117.Tuman KJ, McCarthy RJ, March RJ, et al.: Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. *Anesth Analg* 1991, 73: 696--704.

118.Usubiaga JE. Neurological complications following epidural anesthesia. *Int Anesthesiol Clin* 1975, 13: 1--153.

119.Vandermeulen EP, van Aken H, Vermylen J: Anticoagulants and spinal-epidural anesthesia. *Anesthesia and analgesia* 1994, 79: 1165--1177.

120.Wiessman C: The metabolic response to stress: an overview and update. *Anesthesiology* 1990, 73: 308--327.

121.Wildsmith JA, McClure JH. Anticoagulant drugs and central nerve blockade. *Anaesthesia* 1991, 46: 613--614.

122.Wulf H. Epidural anaesthesia and spinal haematoma. *Can J Anaesth.* 1996, 43: 1260--1271.

123.Wysowski DK, Talarico L, Bacsanyi J, et al.: Spinal and epidural hematoma and low-molecular-weight heparin. *NEJM* 1998, 338: 1774--5.

124.Yeager MP, Glass DD, Neff RK, et al.: Epidural anesthesia and analgesia in high risk surgical patients. *Anesthesiology* 1987, 66: 729--736.

125.Young MA, Vatner SF: Regulation of large coronary arteries. *Circ Res* 1986, 59: 579--596.