A Prospective Randomized Study of the Potential Benefits of Thoracic Epidural Anesthesia and Analgesia in Patients Undergoing Coronary Artery Bypass Grafting

Nicholas B. Scott, FRCS (Ed), FFARCS(I)*, Deborah J. Turfrey, FRCA*, Dominic A. A. Ray, FRCA, MSc*, Onyukwelu Nzewi, FRCS*, Nicholas P. Sutcliffe, FRCA, MRCP*, Adarsh B. Lal, FRCA*, John Norrie, MSc†, Werner J. B. Nagels, MD*, and G. Pradeep Ramayya, FRCA*

*Department of Anaesthesia and Intensive Care, HCI International Medical Centre, Clydebank, Scotland, United Kingdom; and †Robertson Centre for Biostatistics, Boyd Orr Building, University of Glasgow, Glasgow, Scotland, United Kingdom

We performed an open, prospective, randomized, controlled study of the incidence of major organ complications in 420 patients undergoing routine coronary artery bypass graft surgery with or without thoracic epidural anesthesia and analgesia (TEA). All patients received a standardized general anesthetic. Group TEA received TEA for 96 h. Group GA (general anesthesia) received narcotic analgesia for 72 h. Both groups received supplementary oral analgesia. Twelve patients were excluded—eight in Group TEA and four in Group GA—because of incomplete data collection. New supraventricular arrhythmias occurred in 21 of 206 patients (10.2%) in Group TEA compared with 45 of 202 patients (22.3%) in Group GA ($P = 0.0012$). Pulmonary function (maximal inspiratory lung volume) was better in Group TEA in a subset of 93 patients ($P < 0.0001$). Extubation was achieved earlier ($P < 0.0001$) and with significantly fewer lower respiratory tract infections in Group TEA (TEA = 31 of 206, GA = 59 of 202; $P = 0.0007$). There were significantly fewer patients with acute confusion (GA = 11 of 202, TEA = 3 of 206; $P = 0.031$) and acute renal failure (GA = 14 of 202, TEA = 4 of 206; $P = 0.016$) in the TEA group. The incidence of stroke was insignificantly less in the TEA group (GA = 6 of 202, TEA = 2 of 206; $P = 0.17$). There were no neurologic complications associated with the use of TEA. We conclude that continuous TEA significantly improves the quality of recovery after coronary artery bypass graft surgery compared with conventional narcotic analgesia.

(Anesth Analg 2001;93:528–35)

Postoperative morbidity occurs because of factors directly related to the surgical procedure, concomitant medical disease, or the severity of the neuroendocrine response to the surgery (1), especially the sympathoadrenal reflexes (2). A review article on the prevention of perioperative myocardial ischemia after surgery recommends inhibition of sympathetic nervous system activity (4). Furthermore, there is growing evidence that for major noncardiac surgery, outcome is improved when regional anesthesia, which provides sympatholysis, is used (5).

Coronary artery bypass grafting (CABG) is associated with increased morbidity and intensive care demands. Any technique that reduces this morbidity without inherent side effects is desirable. Thoracic epidural analgesia (TEA) was among the first anesthetic techniques described for CABG (6) but became unpopular because of a perceived risk of epidural hematoma formation secondary to the heparinization required to prevent thrombus formation during cardiopulmonary bypass. However, in a number of small studies, TEA improves hemodynamic stability, reduces myocardial oxygen consumption, reduces intra- and postoperative myocardial ischemia, abolishes the catecholamine response, diminishes the cortisol response, and improves analgesia and pulmonary function (7–15). Thus patients are extubated

Accepted for publication May 4, 2001.

Address correspondence and reprint requests to Dr. Nicholas B. Scott, FRCS(Ed), FFARCS(I), HCI International Medical Centre, Beardmore St., Clydebank G81 4HX, Scotland, UK. Address e-mail to nicholas.scott@hci.co.uk.

The authors dedicate this article to the memory of Dr. Bruce Scott, who died shortly before the completion of the project. One of the acknowledged pioneers of regional anesthesia, he encouraged the principal author into the science of regional anesthesia and provided the inspiration and constant support necessary to allow the study to be completed.

0003-2999/01

earlier (16) and, if it is continued into the postoperative period, TEA may promote earlier ambulation and discharge.

These studies include only small numbers of patients, and data from a much larger number of patients are required to confirm these potential benefits. In a previous retrospective study of 218 patients, we showed that continuous TEA reduced morbidity after CABG compared with conventional analgesia (17). Therefore, our hypothesis for this prospective study was that sympathetic blockade, produced by continuous TEA, reduces morbidity after CABG.

Methods

We chose the incidence of cardiac arrhythmias to determine the power of the study on the basis of data from our previous retrospective study that showed an incidence of atrial fibrillation of 32% in the General Anesthesia (GA) group compared with 18% in the TEA group (17). With 420 subjects, the study had >90% power at a 1% level of significance to detect a change in cardiac arrhythmia from 25% to 10% by using a two-sided test of binomial proportions. Of the 420 subjects randomized into the study, 12 subjects had insufficient data as a result of incomplete documentation and were therefore excluded from analysis. The remaining 408 subjects were analyzed according to the intention-to-treat principle. Preextubation lung volume was compared by using a two-sample Student's *t*-test. Time to extubation, categorized as immediate (<4 h), <12 h, 12–24 h, and >24 h, and the outcomes of neurologic problems (stroke or acute confusion), renal failure, and bleeding were compared between the two randomized groups by using Fisher's exact test. The outcomes of 1) supraventricular arrhythmia, 2) lower respiratory tract infection, 3) significant bleeding, and 4) any complication (supraventricular arrhythmia, any pulmonary complication [lower respiratory tract infection, left lower lobe consolidation, pneumothorax, or pleural effusion], neurologic complications, acute renal failure, or bleeding) were compared between the two randomized groups by using univariate logistic regression and were then adjusted for baseline covariates by using multivariate logistic regressions (18). The covariates were age, weight, height, ejection fraction, sex, New York Heart Association class, smoking (never, former, and current), hypertension, diabetes, previous respiratory disease, and previous myocardial infarction. No adjustment was made for multiple comparisons.

Patients undergoing elective CABG with a normal coagulation screen and an ejection fraction of >0.35 were included. All patients had a routine preoperative coagulation screen that included prothrombin time, international normalized ratio, fibrinogen, platelet count, and activated partial thromboplastin time. Patients with an abnormal value for any of these were excluded. All the operations were performed by only two surgeons. The Hospital Ethics Committee approved the study, and all patients gave written informed consent. In particular, all patients were given a full explanation of the anesthetic techniques and instructed in the benefits of optimal pain management and in the need to inform the attending nurse of any pain.

Patients were randomized to one of two regimens. Group GA received GA plus postoperative opioid analgesia, and Group TEA received GA plus perioperative TEA. Randomization was performed by an independent member of staff the evening before surgery by using cards drawn from a sealed envelope.

The study was conducted in an open manner because the performance of a sham epidural insertion was considered unethical given the risk of epidural hematoma formation. Therefore, neither the anesthesiologists nor the nurses taking the measurements were blinded to the patients' treatment.

Patients receiving angiotensin-converting enzyme inhibitors had these suspended the day before surgery. Calcium-channel antagonists and β-adrenergic blocking drugs were continued until the morning of surgery. β-Blockers were not used intraoperatively or postoperatively during the study period in any patient. β-Blocker therapy was recommenced on the fifth postoperative day in all patients, except in those patients who developed a new arrhythmia that required additional therapy.

Premedication in both groups consisted of temazepam 30 mg, ranitidine 150 mg, and metoclopramide 10 mg, orally, the night before surgery; this was repeated 2 h before surgery. All patients received 1 g of cephazolin IV at the induction in Group GA or before insertion of the epidural catheter in Group TEA.

All patients received target-controlled infusions (TCIs) of propofol and alfentanil for anesthesia and analgesia, respectively. Initial plasma target levels were between 1.5 and 2.5 μg/mL for propofol and between 150 and 200 ng/mL for alfentanil. Tracheal intubation and intermittent positive pressure ventilation were facilitated with 0.1 mg/kg pancuronium or 0.15 mg/kg vecuronium given at induction only and not repeated. Central venous cannulation was performed and surgery commenced. All patients received 250 mL of 20% mannitol and 8 mmol of magnesium sulfate before bypass. After the operation, once bleeding from the surgical drains was minimal, the propofol was stopped and patients' tracheas were extubated according to strict criteria (Table 1).

In addition, patients in Group TEA had a thoracic epidural catheter sited in the operating theater immediately before surgery at the T2-3 or T3-4 interspace. Bilateral neuraxial block was established from T1 to

Table 1. Criteria for Tracheal Extubation

Sedation discontinued and patient not in pain or agitated.
Cardiovascular stability without inotropes—systolic pressure >90 mm Hg
Core temperature >36.4°C
Spontaneous ventilation with Pao_2 >12 kPa on FIO_2 <0.4 and $Paco_2$ <7 kPa
Blood loss from chest drains <60 mL/h
Urine output >1 mL · kg^{-1} · h^{-1}

FIO_2 = fraction of inspired oxygen.

T10 with an initial bolus of 5 mL bupivacaine 0.5% followed by another 5-mL bolus after 10 min.

Determination of the spread of block was performed with ethyl chloride spray. If a "bloody tap" was to occur, the operation would be postponed for 24 h and commence only if neurologic examination was completely normal the next morning. Any focal neurologic abnormality would result in an urgent magnetic resonance imaging (MRI) scan to exclude epidural hematoma. After induction of GA and when central hemodynamic status was stable, a continuous infusion of 0.125% bupivacaine and 0.0006% clonidine (300 μg in 500 mL) commenced at an initial rate of 10 mL/h.

After the administration of 300 IU/kg heparin, to achieve an activated clotting time of >450 s, cannulation of the aorta and right atrium was performed and extracorporeal bypass was commenced. Bypass flows were kept >2.4 L · min^{-1} · m^{-2}, and mean arterial pressures were maintained between 40 and 80 mm Hg with bolus doses of metaraminol or glyceryl trinitrate given to increase and decrease the pressure, respectively, to maintain these levels. Blood gas analysis was performed every 10 min while patients were on bypass.

During extracorporeal circulation, all of the patients were cooled to 28°C and received blood cardioplegia. At the end of bypass, the effects of the heparin were reversed with 0.3 mg/kg of protamine.

In Group GA, TCI of alfentanil continued for 24 h and was then converted to a patient-controlled analgesia (PCA) IV morphine pump for another 48 h by using 1-mg bolus dosing with a 3-min lockout period. The initial target plasma concentration for alfentanil after bypass was between 60 and 80 ng/mL. If the patient had a verbal pain score of 2 or more, then the infusion was increased initially by 15 ng/mL and thereafter by 10 ng/mL.

In Group TEA, the epidural infusion continued for 96 h. After surgery, the rate was titrated by the attending anesthesiologist according to clinical need; the goal was to maintain the neuraxial block between T1 and T10 throughout the infusion. "Top-up" bolus doses up to a maximum of 4 mL of 0.25% bupivacaine were administered either when the patient complained of pain (pain score of 2 or more) or whenever there was regression of the block by more than four dermatomal segments. If more than three increases to the TCI or more than three epidural "top-up" doses were required in any hour, analgesia was considered inadequate.

All patients in both groups received additional oral ibuprofen every 8 h and co-proxamol (dextropropoxyphene plus paracetamol) every 6 h for 7 days.

Patients were carefully monitored throughout their stay in the intensive care unit (ICU), the high-dependency unit (HDU), and the general ward. This included continuous electrocardiogram (ECG) monitoring and ST segment analysis in both the ICU and the HDU, 24-h telemetry in the ward, and daily 12-lead ECG analysis. The nursing staff of the ICU, HDU, and general ward collected the routine postoperative data.

Postoperative systemic complications within the first 5 days after surgery were recorded. Pulmonary complications were divided into proven lower respiratory tract infection (i.e., a combination of increased white cell count, pyrexia, productive sputum, radiologic signs, and a positive bacterial growth on culture), atelectasis or consolidation assessed on postoperative chest radiograph, and respiratory failure requiring tracheal reintubation. Arrhythmias were classified as supraventricular, ventricular, or conduction defects. Supraventricular arrhythmias were further divided into atrial flutter or fibrillation. Ventricular arrhythmias were subdivided into tachycardia, fibrillation, or multiple ventricular ectopics (>6/min). Conduction defects were classified as 1°, 2°, or 3° (complete) heart block. Postoperative myocardial infarction was diagnosed with a combination of ECG analysis (Q waves, ST segment increase of >3 mm) and a myocardial specific serum creatinine kinase level of 60 ng/mL or more. Renal failure was defined as an increase in serum creatinine to more than twice the preoperative value. Serum creatinine measurement was performed in the immediate postoperative period and daily thereafter if it was within normal limits. If the level increased above normal, it was checked twice daily until it started to decrease. A cerebrovascular accident (CVA) was defined as a new motor or sensory deficit affecting one or more limbs and that was present either on awakening from anesthesia or occurring within the next 5 days. Patients were defined as confused when, after extubation and discontinuation of propofol, they were unable either to cooperate or communicate with the nurses and were disoriented in time and place for 8 h or more. Significant bleeding was defined as bleeding necessitating treatment with blood products or a reoperation to control the bleeding surgically. Ward rounds were conducted at least twice daily by the consultant surgeon and intensivist together, and in all patients the above diagnoses were

Table 2. Baseline Characteristics in the Two Randomized Groups for Continuous Covariates

Description	TEA			GA		
	n	Mean	SD	*n*	Mean	SD
Age (yr)	206	59.2	8.94	202	58.8	9.18
Weight (kg)	203	79.3	14.5	201	76.9	13.4
Height (cm)	203	167.0	8.5	200	165.2	8.7
Body surface area (m^2)	203	1.87	0.19	200	1.84	0.18
Ejection fraction (%)	206	56.8	9.18	201	56.0	10.5
Time cross-clamp (min)	203	55.4	17.8	202	54.5	17.1
Time bypass (min)	203	86.2	27.6	202	85.6	26.8

Data shown are number of subjects (*n*), mean, and SD.
TEA = thoracic epidural analgesia; GA = general anesthesia.

confirmed by both of them after review of bedside charts, documents, and the laboratory data.

At the start of the project, it was agreed to perform interim analysis after 120 patients to determine whether or not the study should continue. This analysis was presented as a free paper at the European Association of Cardiothoracic Anaesthetists in Bergen, Norway, in 1998 and was published as an abstract. The analysis showed a 50% reduction in the incidence of proven lower respiratory tract infection ($P = 0.048$), and we subsequently attempted to measure lung volumes in all patients to try to establish an explanation for this finding. Thus, in a subset of 93 patients (47 in Group TEA and 46 in Group GA), we obtained additional prospective pulmonary data on maximal inspiratory lung volumes. Once the criteria for tracheal extubation were achieved, immediately before extubation, the patient inhaled and exhaled with maximal effort. Measurements were taken from the Servo 300 (Siemens; Stockholm, Sweden) ventilator display and reported as the mean value obtained from three recorded values.

Results

Twelve patients (5.8%) in Group TEA and 19 patients (9.4%) in Group GA were not taking β-blocking drugs before surgery because of preexisting asthma or chronic obstructive airways disease ($P = 0.19$). Tables 2 and 3 show the baseline characteristics for the two groups. Two surgeons performed all 408 procedures. Surgeon A performed 105 operations in Group TEA and 99 in Group GA. Surgeon B performed 101 operations in Group TEA and 103 in Group GA. One-hundred (49%) patients in the TEA group had no complications of any description before surgery, compared with only 73 (36%) in the GA group ($P = 0.012$).

Table 4 shows the occurrence of any complications. Eighty-four subjects in the TEA group, compared with 108 GA subjects, had a complication (odds ratio, GA to TEA, 1.67; approximate 95% confidence interval 1.13–2.47, $P = 0.011$; after adjustment for baseline covariates, 1.44 [0.95–2.19], $P = 0.089$).

Table 3. Baseline Characteristics in the Two Randomized Groups for Categorical Covariates

Description	TEA		GA	
	n	%	*n*	%
Males	179	86.9	173	85.6
NYHA class				
I	1	0.5	5	2.5
II	26	12.6	26	12.9
III	170	82.5	156	77.2
IV	9	4.4	15	7.4
Smoker				
Never	61	29.6	61	30.2
Previous[a]	133	64.6	114	56.4
Current	12	5.8	27	13.4
History of hypertension	81	39.5	77	38.1
History of diabetes	62	30.1	66	32.7
Respiratory disease	12	5.8	19	9.4
Previous MI	122	59.5	116	57.7
Inotropes	110	53.4	109	54.0
No. grafts				
≤2	25	12.1	29	14.4
3	101	49.0	96	47.8
4	63	30.6	64	31.8
≥5	17	8.3	12	6.0
Internal mammary graft	201	97.6	197	97.5

Data shown are number of subjects (*n*) and percentage (%).
TEA = thoracic epidural analgesia; GA = general anesthesia; NYHA = New York Heart Association; MI = myocardial infarction.
[a] An ex-smoker was a patient who claimed to have stopped for at least 6 mo before admission.

The incidence of lower respiratory tract infection was 31 in 206 patients (15.3%) receiving TEA compared with 59 of 202 patients (29%) in the GA group ($P = 0.0007$), odds ratio 2.33 (1.43–3.79), which after adjustment for baseline covariates was 2.06 (1.22–3.47) ($P = 0.0065$).

Patients were extubated significantly earlier in the TEA group, with only 11 of 202 patients in the GA group compared with 51 of 206 in the TEA group extubated immediately (within the first 4 h), by following the extubation criteria in Table 1 ($P < 0.001$). In

Table 4. Unadjusted and Adjusted Odds Ratios for GA Versus TEA for Various Outcomes

Outcome	TEA (n = 206), n (%)	GA (n = 202), n (%)	Unadjusted		Adjusted[a]	
			OR (95% CI)	P value	OR (95% CI)	P value
Supraventricular arrhythmia	21 (10.2)	45 (22.3)	2.53 (1.44–4.42)	0.0012	2.56 (1.41–4.66)	0.0020
Lower respiratory tract infection	31 (15.3)	59 (29.2)	2.33 (1.43–3.79)	0.0007	2.06 (1.22–3.47)	0.0065
Renal failure	4 (2.0)	14 (6.9)	3.69 (1.34–10.2)	0.016[b]	Not fitted[c]	
CVA	2 (1.0)	6 (3.0)	3.12 (0.62–15.7)	0.17[b]	Not fitted[c]	
Acute confusion	3 (1.5)	11 (5.5)	3.90 (1.07–14.2)	0.031[b]	Not fitted[c]	
Significant bleeding	35	23	0.63 (0.36–1.11)	0.11	0.52 (0.28–0.96)	0.035
Any complications	84	108	1.67 (1.13–2.47)	0.011	1.44 (0.95–2.19)	0.089

TEA = thoracic epidural analgesia; GA = general anesthesia; OR = odds ratio; CVA = cerebrovascular accident; CI = confidence interval.
[a] Data missing on some of the adjusted covariates for nine subjects.
[b] Fisher's exact tests.
[c] Adjusted model not fitted because of sparsity of events.

Table 5. Preextubation Lung Volume and Time to Endotracheal Extubation

Description	GA group		TEA group		P value
	n	Mean (SD)	n	Mean (SD)	
Maximal expiratory lung volume (mL)	46	733 (208)	47	985 (326)	<0.001
Time to extubation	n	%	n	%	
Immediate (<4 h)	11	5.5	51	25.0	<0.0001
<12 h	136	67.8	112	54.9	
12–24 h	25	12.4	19	9.3	
>24 h	29	14.3	22	10.8	

GA = general anesthesia; TEA = thoracic epidural analgesia.

the subset of 93 patients, the mean maximum inspiratory lung volume was 985 ± 326 mL in the TEA group compared with 733 ± 208 mL in the GA group ($P <$ 0.0001), a difference of 34% (Table 5).

The incidence of new supraventricular arrhythmias that necessitated treatment (Table 4) in patients receiving TEA was significantly reduced compared with those receiving GA (45 of 202 [22.3%] vs 21 of 206 [10.2%], $P = 0.0012$, odds ratio 2.53 [1.44–4.42], which after adjustment for baseline covariates was 2.56 [1.41–4.66], $P = 0.002$). There was no difference in the incidence of bradycardias, ventricular arrhythmias, conduction defects, or myocardial infarctions between the two groups. Myocardial infarction occurred in eight patients in Group GA and six patients in Group TEA, and the overall incidence in the study was 4%.

There was a significant reduction in the incidence of acute renal failure in patients receiving TEA (GA = 14 of 202, TEA = 4 of 206; $P = 0.016$) and also in the incidence of postoperative confusion (GA = 11 of 202, TEA = 3 of 206; $P = 0.031$). The incidence of CVA was less in patients receiving TEA (GA = 6 of 202, TEA = 2 of 206), but the overall number was small and the difference was not significant ($P = 0.17$).

Three deaths occurred during the study: two in the GA group and one in the TEA group. The causes of death were multiorgan failure, CVA, and incomplete revascularization.

An insignificantly larger number of patients had postoperative bleeding requiring either transfusion of blood products or chest reopening in the TEA group (35 vs 23 subjects, $P = 0.11$).

In 24 patients (11.9%) in Group GA, it was believed necessary on clinical grounds to convert to TEA within 24 h of surgery. In all patients there was decreasing arterial oxygen saturation in the presence of increasing fraction of inspired oxygen (F_{IO_2}), visual analog pain scores greater than 6 despite optimal infusion levels, or an inability to cooperate with physiotherapy. None of these 24 patients preferred PCA to epidural analgesia. All of these patients preferred the analgesia TEA provided compared with PCA morphine. In comparison, six patients (2.9%) needed to be converted from TEA to TCI alfentanil or PCA morphine as a result of catheter displacement or insufficient somatic blockade. Three of these patients preferred epidural analgesia, and three had no preference.

Discussion

Mortality and morbidity after surgery occur in direct proportion to the level of the physiologic response to the surgical stress, and postoperative complications are most frequent for all types of thoracoabdominal surgery (1). For example, after CABG surgery, the

incidence of supraventricular arrhythmias is 20%–40% (17,19). Serious and frequent morbidity is particularly important because the overall number of patients requiring CABG continues to increase and cardiac programs are an expensive drain on health resources, most notably the need for ICU beds. Any technique that helps to reduce the overall incidence of these adverse outcomes will result in a less complicated and probably prompter postoperative recovery, with a benefit both for patients and hospital. The findings of this study suggest that TEA may prove beneficial in these patients. We wanted to provide prolonged analgesia in both groups, believing that any differences would be a result of the effects of the sympathetic block and not of differences in pain relief. Most postoperative complications occur in the first three days after CABG. We therefore extended the epidural infusion beyond this to 96 hours, but virtually all of our TEA patients were mobile and out of bed by Day 2, and we believed that it was not practical or necessary to extend the infusion beyond this time. In the Control group, regular oral analgesia from Day 1 obviated the need for PCA beyond Day 3.

Our working hypothesis was that an effective epidural delivery of local anesthetic and clonidine reduces postoperative complications because of sympathetic blockade. In this study, TEA significantly reduces the incidence of new postoperative supraventricular arrhythmias, probably as a consequence of this sympathetic blockade. The use of drugs such as digoxin and warfarin, which can lead to increased length of hospital stay, is thus minimized. With regard to myocardial ischemia, cardiac sympathectomy results in slower heart rates and a reduced afterload, thereby reducing perioperative oxygen consumption (8,15). Postoperative myocardial infarction occurs in between 10% and 25% of patients after CABG. In animal models, TEA reduces myocardial infarct size (20,21). Our study failed to demonstrate a decreased incidence of myocardial infarction, but in all cases, infarction occurred secondary to incomplete revascularization, vasospasm, or acute graft occlusion. In addition, the overall incidence of myocardial infarction (4%) is small in both groups compared with that in other published data.

We have shown a 50% reduction in the incidence of lower respiratory tract infections in patients receiving TEA, and this is consistent with a previous smaller study in CABG patients (16) and with available data from other types of major surgery (5). Pulmonary function is preserved in patients receiving TEA, probably as a result of several factors, which include superior analgesia (allowing the patient to cooperate more fully with physiotherapy), the avoidance of parenteral opioids and their mood-altering effects, and the inhibition of bulbosplanchnic afferent nerve fibers (22). In a subset of patients we have also shown that maximal inspiratory lung volumes are approximately 30% larger in patients receiving TEA. Thus, in contrast to conventional opioid analgesia, during which patients have only their normal tidal volume, patients receiving TEA have 250–300 mL of reserve lung volume. This volume increases the respiratory reserve and decreases the incidence or duration of atelectasis or pulmonary infection. In turn, this leads to significantly quicker extubation times in patients receiving TEA.

There are important cost issues within this context, because we were able to discharge patients from the ICU to the HDU as soon as they were extubated and no patient required readmission to ICU. At our institution, the daily cost of a bed in the ICU is approximately $1400, with a nurse to patient ratio of 1:1, compared with $950 per day in the HDU, with a nurse to patient ratio of 1:2. Thus, TEA allows CABG patients to be fast-tracked safely while also conserving hospital and nursing costs.

We did not perform any investigations or assessments of subtle neurologic dysfunction, because other studies have failed to show any differences between regional anesthesia and GA (1). However, we have noted a significant reduction in the incidence of acute confusion after CABG in the TEA group, possibly as a result of reduced opioid requirements.

There were fewer patients with CVA in the TEA group, but because the overall incidence for both groups was only 2%, data from a much larger population are required before any conclusion can be made.

One patient in Group TEA awoke with apparent lower limb flaccidity. According to our protocol, the epidural infusion was stopped immediately, and an urgent MRI scan of the thoracic spinal cord was performed. However, the MRI scan was normal, lower-limb power and sensation steadily improved over the next few hours, and the epidural infusion was recommenced at a slower rate with no further weakness encountered.

An unexpected finding was a significant reduction in Group TEA of the incidence of renal failure, as defined by a twofold increase in serum creatinine. The two groups did not differ in the incidence of hypertension or diabetes mellitus, but 14 of the 18 patients who developed renal failure had one or both of these diseases. Moreover, fluid balance and the use of inotropic support did not differ significantly between the two groups. It may be that TEA has a benefit on renal function in the presence of mild or undiagnosed diabetic autonomic neuropathy after major surgery. Alternatively, clonidine by itself may also have exerted a protective effect on the kidney. An IV dose of clonidine (4 μg/kg) given at anesthesia induction prevents deterioration in renal function after CABG (23), which appears to be due to a direct sympathetic effect on the renal medulla (24). The doses of clonidine in

our epidural infusion (0.6 μg/mL running at a maximum of 15 mL/h, i.e., approximately 200 μg/day) are extremely small compared with those in these studies, and therefore systemic effects caused by absorption from the epidural space are probably negligible. However, there may be a further direct effect on the sympathetic supply to the kidneys at a spinal cord level from epidurally-administered clonidine.

We chose not to document pain as a specific end point for all patients in this study because we wanted to concentrate on more objective data and because we believed that the benefits of regional analgesia were more likely to be a consequence of the sustained sympathetic block. TEA is superior to other forms of analgesia for most types of surgery (25). In our retrospective study (17), we confirmed that the use of supplementary opioids with TEA was negligible (<10 mg morphine in 24 hours). TCIs of alfentanil are superior to PCA morphine for CABG (26). However, pain relief provided by TCI alfentanil was inadequate in 24 patients (11.9%) in this study. In these patients, we did perform a visual analog scale score. This was >6 in all cases, and a clinical decision was made to convert to TEA because in every case the increased pain score occurred in the presence of either a decreasing oxygen saturation with an increasing F_{IO_2} or an inability to cooperate with physiotherapy because of pain. By doing this we may have prevented several more patients in the GA group from developing a lower respiratory tract infection. Had this occurred, the data would have been even more positive in favor of TEA.

Our study is consistent with the data from other outcome studies on the use of TEA for other forms of surgery, in which it is associated with fewer postoperative complications when compared with conventional anesthesia and analgesia (1,5,27). The avoidance of opioids in the epidural infusion by using small-dose clonidine is an additional safety feature. Clonidine may also have additional effects on sympathetic activity, although the dose we have used is very small compared with that of other studies and systemic effects are, therefore, unlikely (28).

The main argument against the use of TEA for CABG surgery is that anesthesiologists are fearful of an increased risk of thoracic epidural hematoma because CABG patients receive large-dose heparin immediately before bypass. This perceived increased risk cannot be quantified, but the incidence of epidural hematoma after catheter insertion without heparinization is approximately 1 in 10,000 (29). Given the overall incidence of 4% stroke and 2% mortality for CABG and the 10-year survival, the risk may be offset by the benefits, but many more data need to be gathered before this can be established. At present, we would not support the use of this technique in an institution that did not have immediate availability of MRI scanning and surgical facilities to manage this event. In this context we also wish to emphasize the use of IV anesthetic drugs that have rapid pharmacologic onset and offset, leading to rapid awakening and thus allowing prompt neurologic monitoring. Despite these caveats, in the last four years we have performed >800 epidural catheterizations for CABG in our hospital immediately before surgery without the development of a hematoma.

We were unable to influence the surgeons' decisions regarding discharge from hospital because of the limitations of being a start-up hospital in the private sector of the United Kingdom and because 60% of the patients in the study were from North Africa and the Middle East, where cultural diversity dictates the dependence of the patient on continuing treatment and care and the time spent in hospital. Despite considerable encouragement, it was a major struggle for the surgeons to succeed in getting many patients to leave the ward or hospital as long as their government was paying them a daily allowance while they were in the hospital. The gathering of data on the duration of hospitalization is, however, extremely important in assessing the effect of this technique on the overall cost of the procedure.

This is currently the largest randomized prospective clinical trial of the use of TEA as a means of reducing postoperative morbidity after CABG. We have demonstrated a significant reduction in major postoperative complications after CABG without any cases of epidural hematoma. These findings merit a further multicenter prospective clinical trial that should focus on underlying mechanisms, long-term follow-up and outcome, and the cost-effectiveness and implications for health resource consumption for the procedure.

We wish to acknowledge the dedication and hard work of the nurses of the operating theaters, ICU, and Ward 3 East at HCI International Medical Center who collected the postoperative data on all the patients. We also wish to acknowledge the skills of Gillian Cromie and Christine Divers, who supervised the postoperative physiotherapy and rehabilitation for all patients.

References

1. Kehlet H. General versus regional anesthesia. In: Rogers MC, Tinker JH, Covino BG, Longnecker DE, eds. Principles and practice of anesthesiology. Vol 2. London: Mosby Year-Book Inc, 1992.
2. Scott NB. The effects of pain and its treatment. In: McClure JH, Wildsmith JAW, eds. Conduction blockade for postoperative analgesia. London: Edward Arnold, 1991.
3. Deleted in proof.
4. Warltier DC, Pagel PS, Kersten JR. Approaches to the prevention of perioperative myocardial ischemia. Anesthesiology 2000; 92:253–9.
5. Buggy DJ, Smith G. Epidural anaesthesia and analgesia: better outcome after major surgery? Growing evidence suggests so. BMJ 1999;319:531–2.

6. Clowes GHA, Neville WE, Hopkins A, et al. Factors contributing to success or failure in the use of a pump oxygenator for complete bypass of the heart or lungs: experimental or clinical. Surgery 1954;36:557–79.
7. Kirno K, Friberg P, Grzegorczyk A, et al. Thoracic epidural anesthesia during coronary artery bypass surgery: effects on cardiac sympathetic activity, myocardial blood flow and metabolism, and central hemodynamics. Anesth Analg 1994;79: 1075–81.
8. Blomberg S, Emanuelsson H, Kvist H. Effects of thoracic epidural anaesthesia on coronary arteries and arterioles in patients with coronary artery disease. Anesthesiology 1990;73:840–7.
9. Stenseth R, Bjella EM, Christensen O, et al. Thoracic epidural analgesia in aortocoronary bypass surgery. I. Haemodynamic effects. Acta Anaesthesiol Scand 1994;38:826–33.
10. Moore CM, Cross MH, Desborough JP, et al. Hormonal effects of thoracic extradural analgesia for cardiac surgery. Br J Anaesth 1995;75:387–93.
11. Joachimsson PO, Nystrom SO, Tyden H. Early extubation after coronary artery surgery in efficiently rewarmed patients: a postoperative comparison of opioid anesthesia versus inhalational anaesthesia and thoracic epidural analgesia. J Cardiothorac Vasc Anesth 1989;3:444–54.
12. Liem TH, Booij LH, Hasenbos MA, Gielen MJ. Coronary artery bypass grafting using two different anesthetic techniques. I. Hemodynamic results. J Cardiothorac Vasc Anesth 1992;6: 148–55.
13. Liem TH, Booij LH, Gielen MJM, et al. Coronary artery bypass grafting using two different anesthetic techniques. III. Adrenergic responses. J Cardiothorac Vasc Anesth 1992;6:162–7.
14. Stenseth R, Berg EM, Bjella L, et al. Effects of thoracic epidural analgesia on coronary haemodynamics and myocardial metabolism in coronary artery bypass surgery. J Cardiothorac Vasc Anesth 1995;9:503–9.
15. Stenseth R, Bjella L, Berg EM, et al. Thoracic epidural analgesia in aortocoronary bypass surgery. II. Effects on the endocrine metabolic response. Acta Anaesthesiol Scand 1994;38:834–9.
16. Liem TH, Hasenbos MA, Booij LH, Gielen MJ. Coronary artery bypass grafting using two different anaesthetic techniques. II. Postoperative outcome. J Cardiothorac Vasc Anesth 1992;6: 156–61.
17. Turfrey DJ, Ray DAA, Sutcliffe NP, et al. Thoracic epidural anaesthesia for coronary artery bypass graft surgery: effects on postoperative complications. Anaesthesia 1997;52:1090–113.
18. Hosmer D, Lemeshow S. Applied logistic regression. New York: Wiley, 1989.
19. Pfisterer ME, Kloter-Weber UCD, Huber M, et al. Prevention of supraventricular tachyarrhythmias after open heart operation by low-dose sotalol: a prospective, double-blind, randomized, placebo-controlled study. Ann Thorac Surg 1997;64:1113–9.
20. Davis RF, Deboer LWV, Maroko PR. Thoracic epidural anesthesia reduces myocardial infarct size after coronary artery occlusion in dogs. Anesth Analg 1986;65:711–7.
21. Groban L, Zvara DA, Deal DD, et al. Thoracic epidural anesthesia reduces infarct size in a canine model of myocardial ischemia and reperfusion injury. J Cardiothorac Vasc Anesth 1999; 13:578–85.
22. Albano JP, Garnier L. Bulbo-spinal respiratory affects originating from the splanchnic afferents. Respir Physiol 1983;51: 229–39.
23. Kulka PJ, Tryba M, Zenz M. Preoperative alpha2-adrenergic receptor agonists prevent the deterioration of renal function after cardiac surgery: results of a randomized, controlled trial. Crit Care Med 1996;24:947–52.
24. Kover G, Tost H, Darvasi A. The effects of clonidine on the kidney function in the anesthetized dog. Acta Physiol Hung 1989;74:229–41.
25. Desborough JP. Thoracic epidural analgesia in cardiac surgery. Anaesthesia 1996;51:805–7.
26. Checketts MR, Gilhooly CJ, Kenny GNC. Patient-maintained analgesia with target-controlled alfentanil after cardiac surgery: a comparison with morphine PCA. Br J Anaesth 1998;80:748–51.
27. Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000;321: 1493–7.
28. Loick HM, Schmidt C, Van Aken H, et al. High thoracic epidural anaesthesia, but not clonidine, attenuates the perioperative stress response via sympatholysis and reduces the release of troponin T in patients undergoing coronary artery bypass grafting. Anesth Analg 1999;88:701–9.
29. Sage DJ. Epidurals: spinals and bleeding disorders in pregnancy—a review. Anaesth Intensive Care 1990;18:319–26.