Thoracic Epidural Anesthesia for Cardiac Surgery: A Randomized Trial

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ABSTRACT

Background: The addition of thoracic epidural anesthesia (TEA) to general anesthesia (GA) during cardiac surgery may have a beneficial effect on clinical outcomes. TEA in cardiac surgery, however, is controversial because the insertion of an epidural catheter in patients requiring full heparinization for cardiopulmonary bypass may lead to an epidural hematoma. The clinical effects of fast-track GA plus TEA were compared with those of with fast-track GA alone.

Methods: A randomized controlled trial was conducted in 654 elective cardiac surgical patients who were randomly assigned to combined GA and TEA *versus* GA alone. Follow-up was at 30 days and 1 yr after surgery. The primary endpoint was 30-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke.

Results: Thirty-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke was 85.2% in the TEA group and 89.7% in the GA group ($P = 0.23$). At 1 yr follow-up, survival free from myocardial infarction, pulmonary complications, renal failure, and stroke was 84.6% in the TEA group and 87.2% in the GA group ($P = 0.42$). Postoperative pain scores were low in both groups.

Conclusions: This study was unable to demonstrate a clinically relevant benefit of TEA on the frequency of major complications after elective cardiac surgery, compared with fast-track cardiac anesthesia without epidural anesthesia. Given the potentially devastating complications of an epidural hematoma after insertion of an epidural catheter, it is questionable whether this procedure should be applied routinely in cardiac surgical patients who require full heparinization.

What We Already Know about This Topic

- Thoracic epidural anesthesia and analgesia has been suggested in small studies to benefit patients after cardiac surgery

What This Article Tells Us That Is New

- In a randomized, controlled trial of more than 600 cardiac surgery patients, addition of thoracic epidural anesthesia to general anesthesia did not result in improvement in 30-day or 1-yr morbidity or mortality

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HIGH thoracic epidural anesthesia (TEA) during cardiac surgery promotes sympathicolysis and attenuates the stress response to surgery.[1,2] TEA may also enhance coronary perfusion.[3] TEA may therefore improve myocardial oxygen balance and reduce the incidence of tachyarrhythmias.[1] Through the same mechanism, the incidence of perioperative myocardial infarction could be reduced.[4] Moreover, the excellent analgesia that is associated with TEA facilitates early tracheal extubation and may prevent respiratory complications.[5–7] Along with these potential benefits of TEA, however, there is a risk for potential harm caused by an epidural hematoma that may develop after an epidural puncture and catheter insertion, especially in patients who need full heparinization for cardiopulmonary bypass.[8] An epidural hematoma may compress the spinal cord and lead to permanent neurologic injury including paraplegia if not detected and evacuated promptly.

Most randomized controlled studies on TEA in cardiac surgery have compared TEA with traditional opioid-based general anesthesia (GA). Over the last two decades, however, fast-track cardiac anesthesia has gained widespread popularity. Fast-track cardiac anesthesia is based on lower doses of shorter acting opioids and hypnotics than conventional cardiac anesthesia. Like TEA, fast-track cardiac anesthesia therefore facilitates early tracheal extubation and may decrease length of intensive care and hospital stay, but without the need to insert an epidural catheter.[9–11]

Despite the apparent advantages of both techniques separately, few studies have directly compared TEA and fast-track cardiac anesthesia. We therefore designed a randomized controlled trial to compare the effect of fast-track GA with TEA *versus* fast-track GA alone on major complications in patients undergoing elective cardiac surgery.

Materials and Methods

Study Population

The study was designed as a randomized clinical trial and is reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement.[12] The local human research ethics committees of the two participating centers (METC Isala Clinics, Zwolle, The Netherlands and METC MST, Enschede, The Netherlands) approved of the study, and written informed consent was obtained from all patients. Patients were eligible if scheduled for elective cardiac surgery, including off-pump procedures. Exclusion criteria were age less than 18 yr, patient refusal, severe aortic valve stenosis, active neurologic disease, cutaneous disorders at the epidural insertion site, and preoperative impaired coagulation status precluding safe insertion of an epidural catheter (see appendix 1). Patients were randomly assigned the day before surgery to the GA group or the combined GA and TEA group. The random-allocation sequence was concealed and computer-generated in permuted unequal blocks, accessible through an Internet site. It was not possible for either the patient or the care providers to be blinded for treatment allocation. Major sensory differences are associated with epidural block, which are readily apparent to the patient, that preclude the patient from being blinded. Inserting a thoracic epidural catheter and treating the GA group with placebo infusion and the TEA group with bupivacaine/morphine infusion, "sham epidural," was rejected because of ethical and practical reasons.

Anesthetic and Operative Management

Patients allocated to the epidural group received a thoracic epidural catheter at least 4 h before heparinization. The epidural catheter was inserted in the thoracic 2–3 or thoracic 3–4 intervertebral space. The location of the catheter was verified before induction of GA with a test dose of lidocaine (Xylocain 2%, 3 ml). Before the start of GA, an epidural injection of 0.1 ml/kg was administered of a solution of 0.08 mg/ml morphine and 0.125 mg/ml bupivacaine, followed by a continuous infusion of 4–8 ml/h of the same solution. The GA technique for both groups consisted of 0.1–0.3 mg/kg etomidate, 0.15 mg/kg pancuronium, and 100–200 μg remifentanil at induction, followed by a continuous infusion of 1–4 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol or 1–1.5% sevoflurane, and 0.01 $mg \cdot kg^{-1} \cdot h^{-1}$ remifentanil. Hypnotic depth was monitored electroencephalographically with a bispectral index monitor. The bispectral index was kept between 40 and 60.

All patients underwent surgery through a median sternotomy. During cardiopulmonary bypass (CPB), myocardial protection was achieved with antegrade blood or crystalloid cardioplegia. One surgeon used a combination of retrograde and antegrade crystalloid cardioplegia for aortic valve surgery. CPB was managed using nonpulsatile flow applied by a centrifugal pump and with the α-stat principle. A 40-μm filter was placed in the arterial line. Activated clotting time was kept more than 480 s throughout CPB. Body temperature was reduced to 28°–34°C during CPB, followed by rewarming to a temperature of 36°C before separation from CPB. After weaning from CPB protamine 300 U/kg was administered. At the conclusion of surgery, all patients were transported to the intensive care unit (ICU).

In the ICU sedation was continued until the patient had complied with the criteria for stopping the sedation listed in appendix 2. Postoperative analgesia in the TEA group was continued through the epidural catheter with continuous infusion of bupivacaine/morphine. The GA group received an injection of 0.2 mg/kg morphine 1 h before the end of the operation. In the ICU an infusion of 1–4 mg/h morphine was continued. The patients were extubated as soon as the extubation criteria listed in appendix 2 were met. In the TEA group, the epidural catheter was removed before transfer to the general ward and after infusion of a 0.15-mg/kg morphine bolus. Postoperatively, all patients received paracetamol, 1 g every 6 h.

Outcomes

The primary endpoint was defined as 30-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke. The definitions of these complications are listed in appendix 3. All components of the primary endpoint were evaluated by an independent event committee blinded for randomization, consisting of a cardiologist, cardiothoracic surgeon, nephrologist, pulmonologist, and a neurologist. Secondary outcome measures were the combined endpoint at 1 yr and the occurrence of each component of the primary endpoint separately at 1 and 12 months. We also compared postoperative cardiac arrhythmias, resternotomy, transient ischemic attack, postoperative cardiac enzyme release, duration of mechanical ventilation, length of stay in the ICU, and total length of stay in the hospital. In addition, the time needed for a patient to meet the criteria of being nursed at the Medium Care level (appendix 4) was evaluated. A 10-cm visual analog scale[13] was used to assess patient comfort and pain control. Finally, we used the Euroquol[14] and ShortForm-36[15] questionnaires to assess quality of life 30 days after the operation.

Sample Size

The power calculation was based on the following: The primary endpoint was 30-day survival free from major complications, *i.e.*, survival free from myocardial infarction, pulmonary complications, renal failure, and stroke. Based on the complication rate in our institution in 2003 and our experience during a pilot study in 30 patients, it was estimated that this would be present in the GA group in 85% of patients. An improvement to 92.5% with use of epidural block was considered clinically relevant and possibly achievable considering previously published studies.[3,16,17] With the (two-sided) α error set at 0.05 and the β error set at 0.2 (power of 80%), 304 patients per treatment group were needed. Taking into account a 5% loss to follow-up, we decided to recruit 320 patients per group.

Statistical Analysis

The aim of the main analysis was to compare the incidence of the primary outcome measure (30-day survival free from major complications) in both patient groups. Kaplan–Meier curves were used for graphic comparison. The primary outcome was compared using the chi-square statistic and presented as relative risk (RR) with 95% CI.

The secondary analyses included the comparison of each component of the primary outcome at 1 and 12 months and in-hospital complications, again by means of the chi-square test. The comparison of postoperative cardiac enzyme release was performed using linear mixed models for repeated measures. Continuous outcome measures include length of stay in the ICU, costs of care, and quality of life. Normally distributed data are presented as means with SD and were compared with a two-sample *t* test. Nonnormally distributed data are presented as medians with 10th and 90th percentile, and were compared using the Wilcoxon nonparametric test.

All data were analyzed according to the intention-to-treat principle, *i.e.*, based on randomization. Statistical analysis was performed with SPSS software version 15 (SPSS Inc., Chicago, IL).

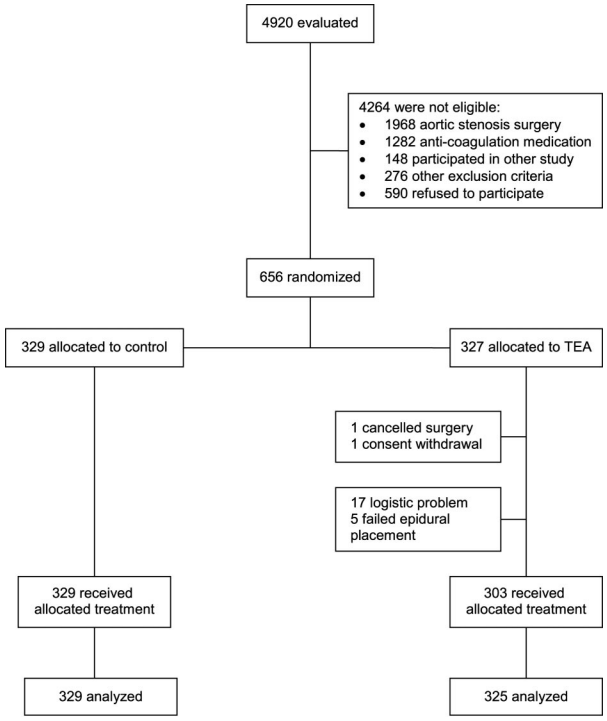

Fig. 1. Trial profile. TEA = thoracic epidural anesthesia.

Results

From March 2004 to September 2007, we evaluated 4,920 patients for study participation in two hospitals. Six hundred fifty-six patients were randomly assigned, and 632 patients received the allocated treatment (fig. 1). One patient was excluded because his surgery was canceled, and one patient withdrew his consent after randomization. Twenty-two patients allocated to the TEA group did not have an epidural catheter placed: 17 patients because of logistic reasons and five patients because the attending anesthesiologist was unable to place the catheter in the epidural space. These 22 patients were analyzed according to their random assigments. The number of isolated coronary artery bypass graft patients in the TEA group was 236, of whom 47 underwent an off-pump procedure. The number of isolated coronary artery bypass graft patients in the GA group was 241, of whom 41 underwent an off-pump procedure. No patient suffered an epidural hematoma or abscess. Patient and surgical characteristics are listed in table 1.

Primary Outcome Measure

Thirty-day follow-up was complete. The frequency of events is shown in table 2 and illustrated by the Kaplan–Meier curve

Table 1. Baseline Characteristics and Intraoperative Data

	TEA Group n = 325	GA Group n = 329	Missing Data, %
Age (yr)	65 (52–77)	64 (52–77)	0.4
Sex, male	266 (82)	277 (84)	0.3
Euroscore	3 (0–7)	3 (1–7)	2.3
Weight (kg)	85 (66–102)	83 (67–100)	0
COPD	51 (16)	46 (14)	0
Hypertension	185 (57)	170 (52)	0
Diabetes mellitus	71 (22)	74 (22)	0
Peripheral vascular disease	33 (10)	27 (8)	0
Renal failure	2 (0.6)	1 (0.3)	0
Neurological disease*	8 (2)	10 (3)	0
LVEF < 20%	12 (4)	12 (4)	0.5
CABG	297 (91)	293 (89)	0
CABG off pump	47 (14)	41 (12)	0
Number of anastomoses	4 (2–5)	4 (2–5)	0
Aortic valve replacement	18 (6)	12 (4)	0
Mitral valve replacement	61 (19)	52 (16)	0
Other cardiac surgical procedure	13 (4)	12 (4)	0
CPB time (min)	87.5 (56–165)	92 (58–165)	0
Aortic cross clamp time (min)	58 (36–110)	61 (39–123)	0

Data are n (%) or median (interquartile range).

* History of stroke or other neurological dysfunction severely affecting ambulation or day-to-day functioning.

CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; GA = general anesthesia; LVEF = left ventricular ejection fraction; TEA = thoracic epidural anesthesia.

(fig. 2). Thirty-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke was 85.2% in the TEA group and 89.7% in the GA group (RR 0.95; $P = 0.23$).

Secondary Outcome Measures

At 30-day follow-up, two patients had died in the TEA group and one in the GA group ($P = 0.56$). Thirty patients in the TEA group and 19 patients in the GA group had suffered a pulmonary complication ($P = 0.12$), and in both groups, 16 patients had a myocardial infarction ($P = 0.98$). Renal failure occurred in five patients in the GA group and in 12 patients in the TEA group ($P = 0.14$). Two patients in the TEA group and one patient in the GA group suffered a stroke ($P = 0.56$). At 1-yr follow-up, two patients were lost to follow-up. Fifty (15.4%) patients in the TEA group had died or had at least one complication, compared with 42 (12.8%) in the GA group ($P = 0.42$).

The incidence of cardiac arrhythmias was similar across the two groups (table 3). A total of 156 (48%) patients in the TEA group and 173 (53%) in the GA group developed supraventricular arrhythmia postoperatively ($P = 0.24$). This was 32 (10%) *versus* 46 (14%) for ventricular arrhythmia ($P = 0.12$). None of the patients in the TEA group suffered a transient ischemic attack *versus* 6 (2%) patients in the GA group ($P = 0.04$). Resternotomy was

Table 2. Primary Endpoint and Separate Components after 30-Day and 1-yr Follow-up

	30-Day Follow-up				1-yr Follow-up			
Endpoint	TEA Group (n = 325), n (%)	GA Group (n = 329), n (%)	RR (95% CI)	*P* Value*	TEA Group (n = 325), n (%)	GA Group (n = 327), n (%)	RR (95% CI)	*P* Value*
Postoperative death	2 (0.6)	1 (0.3)	2.02 (0.18–22.2)	0.56	3 (0.9)	7 (2.1)	0.43 (0.11–1.65)	0.21
Pulmonary complications	30 (9.2)	19 (5.8)	1.60 (0.92–2.78)	0.12	33 (10.2)	21 (6.4)	1.58 (0.94–2.67)	0.11
Acute myocardial infarction	16 (4.9)	16 (4.9)	1.01 (0.52–1.99)	0.98	17 (5.2)	18 (5.5)	0.95 (0.50–1.81)	0.88
Renal failure	12 (3.7)	5 (1.5)	2.43 (0.87–6.82)	0.14	12 (3.7)	5 (1.5)	2.41 (0.86–6.78)	0.10
Stroke	2 (0.6)	1 (0.3)	2.02 (0.18–22.2)	0.56	5 (1.5)	4 (1.2)	1.26 (0.34–4.64)	0.73
Any event	48 (14.8)	34 (10.3)	1.43 (0.95–2.16)	0.23	50 (15.4)	42 (12.8)	1.20 (0.82–1.75)	0.42

* Chi-square test. A risk ratio of > 1.00 indicates an increased risk in the TEA group.

CI = confidence interval; GA = general anesthesia; RR = relative risk; TEA = thoracic epidural anesthesia.

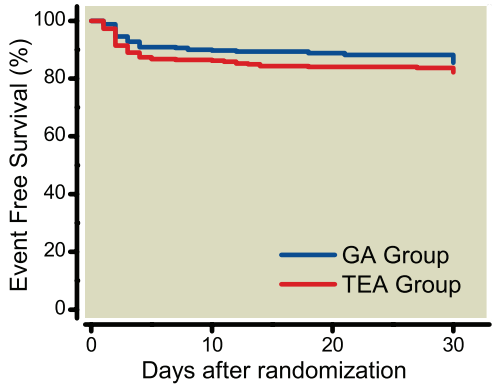

Fig. 2. Thirty-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke, $P = 0.22$ by the log-rank test. GA = general anesthesia; TEA = thoracic epidural anesthesia.

necessary in seven (2%) patients in the TEA group and 13 (4%) patients in the GA group. No significant difference of creatine kinase muscle-brain isoenzyme plasma concentration was found (the difference of GA in comparison with TEA group for all measurements was 0.32 U/l, $P = 0.52$).

The duration of mechanical ventilation, length of stay in the ICU, total length of stay in the hospital, and the time until the patient met the criteria of being nursed at the Medium Care level were similar for both groups and are listed in table 4.

Median pain scores on the first postoperative day were 2 in the TEA group and 3 in the GA group ($P < 0.001$). On the second and third day after surgery, the median pain scores were 2 in both groups (table 4). There were no marked differences in self-reported quality of life at 1 month between the TEA and GA group (data not presented).

Our per protocol analysis showed results similar to the intention-to-treat analysis: 30-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke was 85.7% in the TEA group and 88.4% in the GA group (RR 0.97; 95% CI 0.92–1.03; $P = 0.40$).

We have performed an additional subgroup analysis for the coronary artery bypass graft patients who underwent an off-pump procedure. In the TEA group, there were 47 off-pump procedures, and in the GA group, 41 off-pump procedures; in each group, there were four events that resulted in RR of 0.88 (95% CI 0.23–3.33; $P = 0.84$) for survival free from events.

Discussion

This randomized trial in 654 cardiac surgical patients evaluated the effect of TEA on major clinical outcomes at 1- and 12-month follow-up. The principal finding was that we were not able to show a measurable benefit of TEA combined with GA, compared with GA alone. There was even a trend toward a higher number of major complications in the TEA group. In addition, the duration of mechanical ventilation, length of stay in the ICU, length of stay in the hospital, and quality of life at 30-day follow-up were similar for the two groups. Statistically significant lower pain scores were observed in the TEA group on the first and second postoperative days, but the absolute pain scores were very low in both study groups.[18]

The use of TEA in cardiac surgery is controversial because the need for systematic heparinization during cardiopulmonary bypass may increase the risk of epidural hematoma.[8] This devastating complication is believed to be rare, but the incidence is likely to be underreported.[19,20] Furthermore, hypotension due to TEA-associated sympathicolysis, both intraoperatively and postoperatively, might have deleterious effects for patients with carotid artery stenosis. The use of TEA also has logistic and manpower implications because of the need to insert the epidural catheter several hours before surgery, more postoperative monitoring, and consequently increased costs.

The use of TEA for cardiac surgery is nevertheless still being advocated, because a trial by Scott *et al.*[1] in 420 patients and a systematic review by Liu *et al.*[21] reported benefits of TEA on pulmonary complications and cardiac arrhythmias. There are several plausible explanations as to why the current study could not confirm the benefits of TEA that were found in older studies. This includes the play of chance and publication bias.

A more likely explanation, however, is that the older studies compared TEA with a light GA to conventional anesthe-

Table 3. The Effect of TEA *versus* GA on Secondary Endpoints

Endpoint	TEA Group (n = 325), n (%)	GA Group (n = 329), n (%)	RR (95% CI)	*P* Value
VT	32 (10)	46 (14)	0.73 (0.48–1.12)	0.12*
SVT	156 (48)	173 (53)	0.91 (0.78–1.06)	0.24*
Cardiac arrest	1 (0.3)	3 (0.9)	0.34 (0.04–3.23)	0.62*
TIA	0 (0)	6 (2)	0.50 (0.46–0.54)	0.04†
Resternotomy	7 (2)	13 (4)	0.55 (0.22–1.35)	0.26*
Epidural hematoma or abscess	0	0		

* Chi-square test. † Fisher exact test. A risk ratio of > 1.00 indicates an increased risk in the TEA group.

CI = confidence interval; GA = general anesthesia; RR = relative risk; SVT = supraventricular tachycardia; TEA = thoracic epidural anesthesia; TIA = transient ischemic attack; VT = ventricular tachycardia.

Table 4. The Effect of TEA *versus* GA on Duration of Mechanical Ventilation, ICU and Hospital Stay, and Pain at Rest

	TEA Group (n = 325), Median (Interquartile Range)	GA Group (n = 329), Median (Interquartile Range)	*P* Value*
Duration of mechanical ventilation, h	5 (3–12)	5 (3–11)	0.58
Duration of ICU hospitalization, h	22 (17–46)	22 (17–44)	0.21
MC level reached, h	5 (3–16)	5 (3–21)	0.82
Duration of hospitalization, days	6 (4–10)	6 (4–11)	0.62
VAS day 1	2 (0–6)	3 (0–7)	< 0.001
VAS day 2	2 (0–5)	2 (0–6)	< 0.001
VAS day 3	2 (0–5)	2 (0–5)	0.86

* Wilcoxon rank sum test.

GA = general anesthesia; ICU = intensive care unit; MC = medium care; TEA = thoracic epidural anesthesia; VAS = visual analog scale pain score.

sia with high-dose, long-acting opioids. In contrast, the current study compared TEA with fast-track general cardiac anesthesia that is based on lower doses of short-acting opioids and showed that both anesthetic techniques offer the same benefits of early extubation and a low rate of pulmonary complications. The fact that early tracheal extubation with a reduction in pulmonary complications can also be achieved using fast-track general cardiac anesthesia[22] without TEA, makes TEA less relevant. Although TEA is also thought to reduce the incidence of perioperative myocardial infarction through sympathicolysis,[1–4] our results do not confirm these previously reported cardioprotective effects of TEA.

Although this study is the largest randomized clinical trial to date evaluating TEA in cardiac surgery, there are several limitations. First, to facilitate early mobilization of the patients, we removed the epidural catheter within 48 h after surgery. This time span is shorter than in most previous study protocols, in which the epidural catheter remained *in situ* for 4 days. As a result, one might argue that we provided insufficient perioperative sympathicolysis, although most ischemic complications occur within the first 48 h postoperatively. This may also explain the absence of a positive effect on the incidence of tachyarrhythmias, although one could also argue that there are better and less invasive alternatives for preventing postoperative arrhythmias, such as β-blockers or amiodarone.[23] A second limitation of the study is that the median Euroscore in both groups was low, representing a relatively healthy population of cardiac surgical patients. Sicker patients are thought to benefit more from TEA,[24] but unfortunately, these patients also most often have contraindications for the application of this technique, in particular because of an impaired coagulation status. Twenty-six percent of our patient population was not eligible for the TEA technique because their clinical condition required the perioperative continuation of their anticoagulation therapy. Another 40% was not eligible owing to severe aortic valve stenosis, leaving only 34% of our patient population eligible for TEA.

The study was powered for a combined endpoint, survival free from major complications. The validity of combined endpoints depends on similarity in patient importance, treatment effect, and number of events across the components of the combined endpoint. Pulmonary complications occurred more frequently, but repeating the analyses without the pulmonary complication component, resulted in a point estimate that reflects no benefit of TEA (RR 1.14; 95% CI 0.61–2.13; $P = 0.61$). However, because of the lower number of events in this analysis, the CI is even wider and therefore an actual benefit of TEA still cannot be excluded with these data. This also applies to the subgroup analysis of the coronary artery bypass graft patients who underwent an off-pump procedure: the CI is wide and an actual benefit of TEA in off-pump patients cannot be excluded. A final limitation of the current study is that the definitions of myocardial infarction and renal failure, which were prospectively set at the time of the study design, are now considered outdated. When we applied the newer definitions in a *post hoc* analysis, this did not change the results.[25,26]

In conclusion, we were unable to demonstrate a clinically relevant benefit of TEA on the frequency of major complications after elective cardiac surgery, compared with fast-track cardiac anesthesia without epidural anesthesia. Given the potentially devastating complications of an epidural hematoma after insertion of an epidural catheter, it is questionable whether this procedure should be applied routinely in cardiac surgical patients who require full heparinization.

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Appendix 1. Impaired Coagulation Status Precluding Safe Insertion of an Epidural Catheter

Insertion of an epidural catheter is not allowed if a patient meets any of the following criteria:

1. History of a bleeding disorder
2. Preoperative laboratory investigations:
   - International normalized ratio > 1.8
   - Platelet count $< 80 \times 10^9$/l
   - Activated partial thromboplastin time > 1.5 normal value
   - Ureum > 15 mM
3. Use of any of the following medications:
   - Platelet aggregation inhibitors
     - Clopidogrel administered in the last 120 h
     - Acetylsalicylic acid administered in the last 72 h or, if combined with low-molecular-weight heparin
   - GPIIB/IIIa-receptor antagonists administered in the last 48 h
   - Coumarine derivatives associated with an international normalized ratio > 1.8
   - Low-molecular-weight heparin
     - Therapeutic dosage administered in the last 24 h
     - Prophylactic dosage administered in the last 10 h
   - Intravenous heparin infusion associated with an activated partial thromboplastin time > 1.5 times the normal value
   - Thrombolytic/fibrinolytic agents

A patient may be included in the trial if it is expected that his or her coagulation status is restored at the time of catheter insertion. The criteria listed in this appendix were checked again at the time of catheter insertion, if a patient was randomly assigned to the thoracic epidural anesthesia group.

Appendix 2. Intensive Care Unit Protocols

Criteria for discontinuing the sedation in the intensive care unit

- Core temperature > 36°C
- Difference core/skin temperature < 5°C
- Hemodynamic stability without the use of major doses of vasoactive medication
- Chest drain output < 1.5 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}

Criteria for extubation

- Presence of deglutition reflex
- Breathing minute volume > 80 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}
- Breathing frequency > 10 min^{-1} and < 20 min^{-1}
- Oxygen saturation $> 94\%$ with fraction of inspired oxygen $\leq 40\%$

Appendix 3. Definitions of the Components of the Primary Endpoint

Endpoint	Definition
Postoperative death	Death from any cause within 30 days of surgery
Pulmonary complication	• Pneumonia: clinical symptoms consistent with pneumonia *and* (1) positive microbiologic criteria of pneumonia, *or* (2) positive radiographic criteria of pneumonia[27]: 1. Clinical symptoms: chest pain, cough, or typical ausculatory findings, with or without fever or leukocytosis 2. Microbiologic criteria: (a) purulent expectorated sputum with identification by microscopy or culture of a predominant suspected pathogen; or (b) transtracheal aspirate with identification by microscopy or culture of a predominant suspected pathogen; or (c) pleural fluid or direct lung aspirate with identification by microscopy or culture of a predominant suspected pathogen; or (d) positive blood culture with identification by microscopy or culture of a predominant suspected pathogen, in absence of another source of bacteremia 3. radiographic criteria: the presence of a new infiltrate on chest radiograph • Prolonged artificial ventilation: patient intubated for $>$ 24 h postoperatively
Acute myocardial infarction	Creatine kinase muscle–brain isoenzymes $>$ 75 U/l (5 times upper limit of normal level) and peak creatine kinase muscle–brain isoenzymes/creatine kinase ratio of $>$ 10% or a new Q-wave infarction
Renal failure	Rise in serum creatinine of 50% of the preoperative value, or need for hemofiltration or dialysis
Stroke	A new motor or sensory deficit of central origin, persisting more than 24 h, preferably confirmed by computed tomography, resulting in a drop of two points on the Rankin scale

Appendix 4. Intensive Care and Medium Care Level Criteria

	Intensive Care		Medium Care		Time
Breathing					
Detubation	NO	☐	YES	☐	___:___
Saturation $>$ 92%	NO	☐	YES	☐	___:___
Hemodynamics					
According level Dobutamine $<$ 25 mg/h Dopamine $<$ 20 mg/h Noradrenaline $<$ 120 μg/h Milrinone $<$ 0.4 mg/h Nitroglycerin $<$ 2 mg/h Nicardipine $<$ 4 mg/h Ketanserin $<$ 4 mg/h	NO	☐	YES	☐	___:___
Temperature					
$>$ 36°C	NO	☐	YES	☐	___:___
Drain production					
$<$ 1 ml · h^{-1} · kg^{-1}	NO	☐	YES	☐	___:___
Urine production					
$>$ 0.5 ml · h^{-1} · kg^{-1}	NO	☐	YES	☐	___:___
Consciousness					
Ramsey score 2–3	NO	☐	YES	☐	___:___
Each of the 7 criteria "YES" patient has reached the "Medium care level"					___:___

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