Meta-analysis of Thoracic Epidural Anesthesia *versus* General Anesthesia for Cardiac Surgery

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ABSTRACT

Background: A combination of general anesthesia (GA) with thoracic epidural anesthesia (TEA) may have a beneficial effect on clinical outcomes after cardiac surgery. We have performed a meta-analysis to compare mortality and cardiac, respiratory, and neurologic complications in patients undergoing cardiac surgery with GA alone or a combination of GA with TEA.

Methods: Randomized studies comparing outcomes in patients undergoing cardiac surgery with either GA alone or GA in combination with TEA were retrieved from PubMed, Science Citation index, EMBASE, CINHAL, and Central Cochrane Controlled Trial Register databases.

Results: The search strategy yielded 1,390 studies; 28 studies that included 2,731 patients met the selection criteria. Compared with GA alone, the combined risk ratio for patients receiving GA with TEA was 0.81 (95% CI: 0.40–1.64) for mortality, 0.80 (95% CI: 0.52–1.24) for myocardial infarction, and 0.59 (95% CI: 0.24–1.46) for stroke. The risk ratios for the respiratory complications and supraventricular arrhythmias were 0.53 (95% CI: 0.40–0.69) and 0.68 (95% CI: 0.50–0.93), respectively.

Conclusions: This meta-analysis showed that the use of TEA in patients undergoing cardiac surgery reduces the risk of postoperative supraventricular arrhythmias and respiratory complications. The sparsity of events precludes conclusions about mortality, myocardial infarction, and stroke, but the estimates suggest a reduced risk after TEA. The risk of side effects of TEA, including epidural hematoma, could not be assessed with the current dataset, and therefore TEA should be used with caution until its benefit-harm profile is further elucidated.

What We Already Know about This Topic

- Whether the addition of thoracic epidural anesthesia to general anesthesia provides an overall benefit to patients undergoing cardiac surgery is controversial

What This Article Tells Us That Is New

- In a meta-analysis of more than 2,700 cardiac surgery patients in 28 studies, the addition of thoracic epidural anesthesia significantly reduced supraventricular arrhythmias and respiratory complications, but not mortality, myocardial infarction, or stroke
- Because epidural hematoma did not occur in these small studies, overall benefit to harm could not be calculated

OUTCOMES after cardiac surgery have been markedly improved over recent decades because of advances in anesthesiology, surgery, cardiopulmonary bypass, and postoperative care.[1,2] A combination of general anesthesia (GA) with thoracic epidural anesthesia (TEA) may have an additional beneficial effect on outcomes after cardiac surgery,[3–5] compared with GA alone. TEA may enhance coronary perfusion, improve myocardial oxygen balance, and reduce the incidence of tachyarrhythmias and perioperative myocardial ischemia through sympathycolysis.[6,7] The excellent analgesia

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that is associated with TEA facilitates early tracheal extubation and may prevent respiratory complications.[8,9]

TEA in cardiac surgery is controversial, considering possible complications of TEA, including spinal cord compression caused by a hematoma or abscess. Systematic anticoagulation needed during cardiopulmonary bypass could increase the incidence of epidural hematoma related to the use of an epidural catheter.[10] More commonly, the intense sympathycolysis may lead to systemic hypotension, which can be difficult to correct. The majority of studies comparing GA with the combination of GA and TEA were insufficiently powered to quantify the effect of TEA on clinical outcome measures. A previous meta-analysis by Liu *et al.*[11] was published in 2004 and included 1,178 patients. This meta-analysis found no difference in rates of mortality or myocardial infarction after cardiac surgery for patients receiving TEA *versus* GA alone. Since then, several new randomized studies evaluating TEA in cardiac surgery have been published.

The purpose of this study was to update the meta-analysis and explore reasons for discrepancies between the clinical trials that have evaluated the effects of TEA on mortality and cardiac, respiratory, or neurologic complications in patients undergoing cardiac surgery.

Materials and Methods

Search Process

We combined various synonyms for cardiac surgical procedures and epidural anesthesia to retrieve studies comparing GA and TEA from CENTRAL, PubMed, EMBASE, CINAHL, and Web of Science (SCI/SSCI). For EMBASE and PubMed, we combined our topical search filter with a sensitive evidence-based search query for effectiveness studies. Bibliographies and references of selected publications and systematic reviews and editorials on cardiac surgery and epidural anesthesia were screened using Web of Science (SCI/SSCI).[7,8,11] The complete search strategy is presented in appendix 1. The current study only used published literature data, and no institutional review board approval was required by our institute.

Only randomized clinical studies published before January 1, 2010, that included adult patients (*i.e.*, 18 yr or older) undergoing cardiac surgery, comparing the outcomes of the patients undergoing cardiac surgery with GA or the combination of GA and TEA, were considered for inclusion in the review. We applied no restrictions with respect to language.

Risk of Bias Assessment

All publications found during the search were manually and independently reviewed by the same two authors (V. S. and M. P. P.), using the risk of bias assessment tool[12] (appendix 2). Criteria that were used for assessing the risk of bias of the included studies were: method of randomization; concealed treatment allocation; blinding during pre-, peri-, and postoperative care; blinded data collection and analysis; blinded adjudication of study endpoints; and completeness of (follow-up) data. The decision on the suitability of a study for our analysis was compared by two authors (V. S. and M. P. P.). Discrepancies were resolved by discussion, where necessary, with the help of a third reviewer (D. v. D.).

Data Extraction and Principal Endpoints

Data were extracted from the full-text article of each included study, using a standardized data-extraction form (appendix 2). The principal endpoints for the current analysis were mortality, acute myocardial infarction, supraventricular tachyarrhythmia, and respiratory or neurologic complications (*e.g.*, stroke, epidural hematoma, or abscess). These endpoints were chosen because of their clinical importance and frequency of reporting. More recent studies have also assessed the lengths of stay in the intensive care unit and in the hospital, but not enough data were available to pool a reliable estimate. From all included studies, data on the number of events for the endpoints were extracted for both the TEA and the GA groups. Because the endpoints were analyzed separately, it is possible that studies attributed information to one, two, or more endpoints. The definition of myocardial infarction and stroke were those used in each study, although a sensitivity analysis was performed with an endpoint combining the two. The endpoint respiratory complication was defined as respiratory insufficiency requiring reintubation, prolonged ventilation, or a ventilatory-associated pneumonia, according to the reported data in the studies.

Statistical Methods

Meta-analysis was performed with MIX 2.0 Pro (release 2.0.0.9; BiostatXL, Tokyo, Japan) and Stata (release 10.0; StataCorp., College Station, TX). Patients who only had GA were treated as control groups, and patients with TEA were treated as intervention groups. For each trial, we calculated the risk per treatment group by dividing the number of events by the number of patients randomized. Subsequently, risk ratio (RR) and the corresponding 95% CIs were calculated for each trial, where a risk ratio less than 1 indicates an effect in favor of TEA. For trials without events in the control group, the RR and its SE could not be calculated. To deal with this problem, it is common to add 0.5 or a smaller value to each cell in the contingency table of these trials. This is, nevertheless, known to cause bias[13] when treatment arm sizes are unequal, as was the case with a number of the included studies. We therefore used a treatment arm–dependent approach, in which the correction was proportional to the size of the relevant treatment arm.[14] Sensitivity analyses were planned to assess the impact of different continuity corrections and weighting methods. To provide readers with information about control (baseline) risks and experimental group risks, L'Abbe plots were created for each outcome.

The presence of heterogeneity of outcomes across trials was assessed using the I^2 measure and the DerSimonian–Laird two-step between-study variance estimate, t^2.[15] The

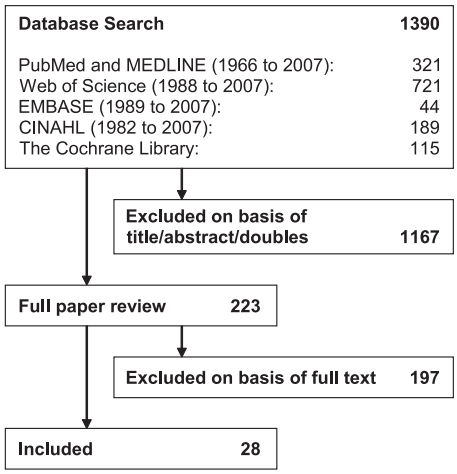

Fig. 1. Flowchart of the database search and selection process.

dataset was graphically explored by forest, Galbraith, L'Abbe, and funnel plots. We intended to use random-effects models, while anticipating that they effectively become fixed-effect syntheses when the between-study variance t^2 is estimated as being 0. The Mantel–Haenszel method was used for the fixed-effect syntheses.

Although a complete synthesis of the dataset was planned, it was anticipated that time to extubation as well as other factors that vary over time could be varying between studies and causing heterogeneity in the estimates. A metaregression as well as subgroup analyses based on year of publication and time to extubation were therefore planned *a priori*. In addition, the presence of small study effects, indicative of biases related to selective reporting and selective publication of studies, was assessed with plots and Peters regression test.[16]

Results

Results of our search strategy are shown in figure 1. We have identified 1,390 titles, of which 1,167 studies did not satisfy the selection criteria or were duplicate publications retrieved from the five different databases. Full review was performed on 223 studies, of which 28 publications met all inclusion criteria. These 28 publications reported on a total of 2,731 patients: 1,416 patients with GA and 1,315 patients with GA plus TEA. Characteristics of the included trials are presented in table 1.

Mortality

All 28 studies reported mortality. None of the studies showed significant reduction in risk with TEA. The reported events were extremely sparse, with 25 studies reporting no events in either the TEA or the GA arms and 15 studies reporting no events at all. A total of 9 events were reported in the TEA arm, compared with 13 events in the GA arm. In the primary analysis, the 15 studies that did not report any events were excluded, resulting in 13 studies with a total number of 1,906 patients contributing to the dataset. The statistical heterogeneity was small (I^2: 0% [95% CI: 0–57%]; t^2 = 0). Combining the data from 13 studies yielded a fixed-effect estimate of the RR of 0.81 (95% CI: 0.40–1.64). Results of the primary meta-analysis for mortality are presented in table 2 and figure 2. Different continuity corrections and weighting methods had little effect on the results and yielded in RRs ranging from 0.79 to 0.81. Using mortality and myocardial infarction as combined outcome (assuming independence of the events) led to an RR of 0.79 (95% CI: 0.54–1.16).

Myocardial Infarction

Fifteen studies with 2,041 patients reported on myocardial infarction. Of the 15 studies, two studies reported no events in both the TEA and the GA arms and they were excluded from the primary analysis. The analysis dataset contained 1,849 patients with 33 events in the TEA arm and 43 events in the GA arm. The I^2 statistic (I^2: 0%; 95% CI: 0–57%), as well as the t^2 statistic (t^2: 0), indicated that the statistical heterogeneity was low. Synthesis of the 13 studies showed no evidence for a difference in the risk of acute myocardial infarction between groups of patients receiving TEA, compared with patients receiving GA alone (RR: 0.80; 95% CI: 0.52–1.24; see table 2 and fig. 3). Sensitivity analyses with different continuity corrections and weighting methods had little effect on the results, with RRs ranging from 0.79 to 0.81.

Supraventricular Tachyarrhythmias

Fourteen studies with 2,194 patients reported on supraventricular tachyarrhythmias, with 300 events in the TEA and 410 events in the GA arms. There were no studies without events. Heterogeneity was substantial (I^2: 62% [95% CI: 33–79%]; t^2 = 0.21), and we applied a random-effects model for the synthesis. The resulting RR was 0.68 (95% CI: 0.50–0.93), showing that combining TEA with GA may be associated with a lower risk of supraventricular tachyarrhythmias than the use of GA alone. The 95% prediction interval ranges from 0.25 to 1.83. Meta-analysis results are shown in table 2 and figure 4.

Respiratory Complications

A total of 13 studies with 1,886 patients presented data on the number of patients who had had respiratory complications. The respiratory complications were rare, with five studies reporting no events in one of the treatment arms and one study reporting no events at all. The primary synthesis was performed on the 12 studies that had one or more events in the study. There were 67 events in the TEA and 128 events in the GA arms. The I^2 statistic was low (I^2: 0%; 95% CI: 0–57%), and the t^2 statistic also showed no evidence of statistical heterogeneity (t^2: 0). Combined fixed-effect analysis of data from 1,858 patients of 12 studies showed a lower risk of respiratory complications for patients receiving TEA and GA during surgery, compared with those receiving GA

Table 1. Characteristics of the Studies Contributing Data to this Meta-analysis

Author	Year of Publication	Participants: TEA+GA	Participants: GA	Concealed Allocation	Blinding	Lost to Follow-up (n)	Reported Outcome Measures	Interventions (Epidural Medication)
El Baz[29]	1987	30	30	+	–	0	Mortality	Morphine
	—	—	—	—	—	—	Respiratory complications	—
	—	—	—	—	—	—	Neurologic complications	—
Rein[30]	1989	8	8	+	?	0	Mortality	Bupivacaine (bolus plus infusion)
Liem[31]	1992	27	27	+	+	4	Mortality	Bupivacaine/sufentanil (bolus plus infusion)
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Supraventricular tachycardias	—
—	—	—	—	—	—	—	Respiratory complications	—
—	—	—	—	—	—	—	Neurologic complications	—
Kirno[20]	1994	10	10	+	–	0	Mortality	Mepivacaine
—	—	—	—	—	—	—	Neurologic complications	(Bolus)
Stenseth[32]	1994	18	10	+	?	2	Mortality	Bupivacaine (bolus plus infusion)
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Neurologic complications	—
Moore[34]	1995	9	9	+	?	—	Mortality	Bupivacaine (bolus plus infusion)
Stenseth[9]	1996	26	26	+	?	2	Mortality	Bupivacaine
—	—	—	—	—	—	—	Myocardial infarction	(Bolus plus infusion)
Brix-Christensen[35]	1998	8	8	+	+	0	Mortality	Bupivacaine/sufentanil (bolus plus infusion)
Loick[36]	1999	25	25	+	–	2	Mortality	Bupivacaine/sufentanil (bolus plus infusion)
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Supraventricular tachycardias	—
—	—	—	—	—	—	—	Neurologic complications	—
Tenling[37]	1999	14	14	+	–	2	Mortality	Bupivacaine/sufentanil (bolus plus infusion)
—	—	—	—	—	—	—	Respiratory complications	—
Scott[6]	2001	206	206	+	+	12	Mortality	Bupivacaine (bolus plus infusion)
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Supraventricular tachycardias	—
—	—	—	—	—	—	—	Respiratory complications	—
—	—	—	—	—	—	—	Neurologic complications	—
Bach[38]	2002	13	13	+	+	0	Mortality	Bupivacaine (bolus plus infusion)
Fillinger[39]	2002	30	30	+	+	0	Mortality	Bupivacaine/morphine (bolus plus infusion)
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Supraventricular tachycardias	—
—	—	—	—	—	—	—	Respiratory complications	—
—	—	—	—	—	—	—	Neurologic complications	—
Priestley[5]	2002	50	50	+	–	0	Mortality	Ropivacaine/fentanyl (bolus plus infusion)
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Supraventricular tachycardias	—
—	—	—	—	—	—	—	Respiratory complications	—
—	—	—	—	—	—	—	Neurologic complications	—
Vries[40]	2002	30	30	+	?	5	Mortality	Bupivacaine.sufentanil (bolus plus infusion)
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Supraventricular tachycardias	—
—	—	—	—	—	—	—	Respiratory complications	—
—	—	—	—	—	—	—	Neurologic complications	—
Berendes[41]	2003	36	36	+	+	0	Mortality	Bupivacaine.sufentanil (bolus plus infusion)
—	—	—	—	—	—	—	Respiratory complications	—
—	—	—	—	—	—	—	Neurologic complications	—
Royse[17]	2003	37	37	+	?	4	Mortality	Ropivacaine/fentanyl (bolus plus infusion)
—	—	—	—	—	—	—	Supraventricular tachycardias	—
—	—	—	—	—	—	—	Respiratory complications	—
—	—	—	—	—	—	—	Neurologic complications	—
Kendall[42]	2004	8	8	+	?	3	Mortality	Bupivacaine/fentanyl (bolus plus infusion)
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Neurologic complications	—
Nygard[6]	2004	79	79	+		0	Mortality	Bupivacaine/morphine (bolus plus infusion)
—	—	—	—	—	—	—	Supraventricular tachycardias	—

(*continued*)

Table 1. Continued

Author	Year of Publication	Participants TEA+GA	Participants GA	Concealed Allocation	Blinding	Lost to Follow-up (n)	Reported Outcome Measures	Interventions (Epidural Medication)
Barrington[43]	2005	60	60	+	+	0	Mortality	Ropivacaine/fentanyl (boluses)
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Supraventricular tachycardias	—
—	—	—	—	—	—	—	Respiratory complications	—
—	—	—	—	—	—	—	Neurologic complications	—
Lundstrom[44]	2005	26	26	+	?	4	Mortality	Bupivacaine/morphine (bolus plus infusion)
—	—	—	—	—	—	—	Respiratory complications	—
Hansdottir[20]	2006	58	58	+	+	16	Mortality	Bupivacaine/fentanyl (bolus plus infusion)
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Supraventricular tachycardias	—
—	—	—	—	—	—	—	Respiratory complications	—
—	—	—	—	—	—	—	Neurologic complications	—
Kilickan[18]	2006	40	40	+	–	0	Mortality	Bupivacaine (bolus plus infusion)
—	—	—	—	—	—	—	Supraventricular tachycardias	—
Langunilla[45]	2006	25	25	+	?	2	Mortality	Ropivacaine/fentanyl (bolus plus infusion)
Bakhtiary[46]	2007	66	66	+	+	0	Mortality	Ropivacaine.sufentanil (bolus plus infusion)
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Supraventricular tachycardias	—
—	—	—	—	—	—	—	Neurologic complications	—
Heijmans[47]	2007	15	15	+	+	0	Mortality	Bupivacaine/morphine (bolus plus infusion)
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Neurologic complications	—
Caputo[48]	2009	36	38	+	+	0	Mortality	—
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Supraventricular tachycardias	—
—	—	—	—	—	—	—	Neurologic complications	—
Svircevic[49]	2010	325	329	+	+	0	Mortality	Bupivacaine/morphine
—	—	—	—	—	—	—	Myocardial infarction	—
—	—	—	—	—	—	—	Supraventricular tachycardias	—
—	—	—	—	—	—	—	Respiratory complications	—
—	—	—	—	—	—	—	Neurologic complications	—
Total	—	1,315	1,416	—	—	—	—	—

GA = general anesthesia; TEA = thoracic epidural anesthesia.

alone (RR: 0.53; 95% CI: 0.40–0.69). Alternative continuity corrections and weighting models yielded RRs of 0.52–0.55.

Neurologic Complications

None of the trials reported events of epidural hematoma or abscess. Thirteen trials with 1,986 patients reported on stroke events. However, because of the extremely low event rate, seven studies reported no events at all, and only six studies with 1,469 patients were used for the primary analysis. There were 6 events in the TEA and 11 events in the GA arms. There was no evidence of statistical heterogeneity (I^2: 0%; 95% CI: 0–75%). Formal synthesis yielded an RR of 0.59 (95% CI: 0.24–1.46), indicating that the use of TEA was associated with a lower risk of stroke that may be substantial. However, the risk ratio estimate was not statistically

Table 2. Effect of TEA *versus* GA on Mortality, Myocardial Infarction, Supraventricular Tachyarrhythmia, Respiratory Complications, and Stroke

Outcome	Studies	RR	95% CI		Events TEA	Events GA	Patients TEA	Patients GA
Mortality	28	0.81	0.40	1.64	9	13	931	975
Myocardial infarction	13	0.80	0.52	1.24	33	43	899	950
Supraventricular tachyarrhythmias	14	0.68	0.50	0.93	300	410	1,069	1,125
Respiratory complications	12	0.53	0.40	0.69	67	128	915	943
Stroke	6	0.59	0.24	1.46	6	11	735	734

A risk ratio of > 1.00 indicates an increased risk in the TEA group.
GA = general anesthesia; RR = risk ratio; TEA = thoracic epidural anesthesia.

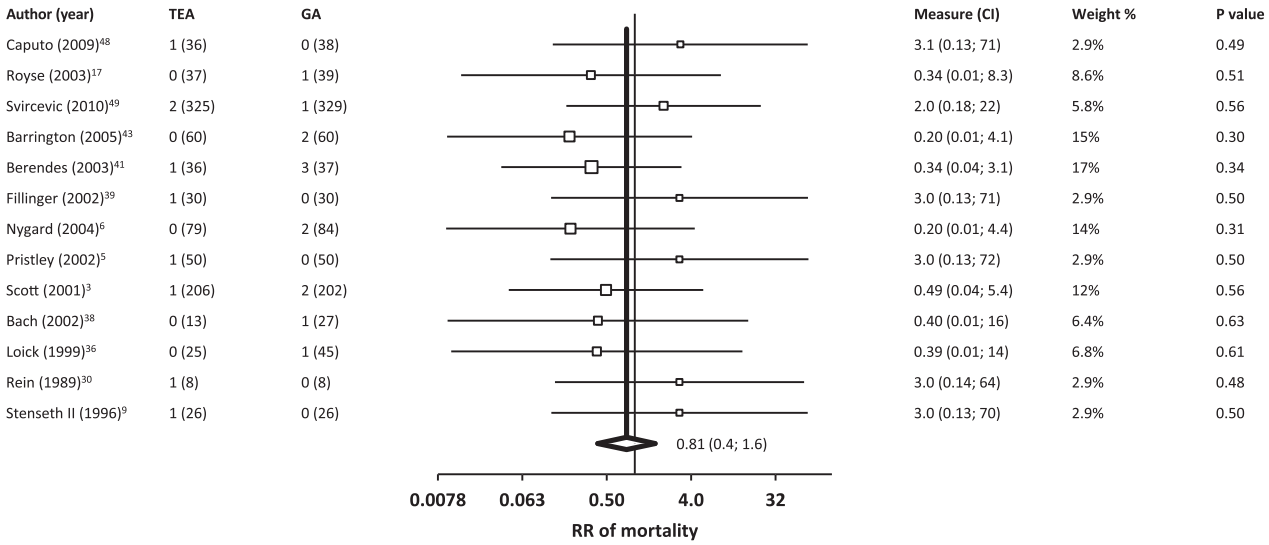

Fig. 2. Risk ratios and forest plot for mortality in the first 2 weeks after surgery. GA = general anesthesia; RR = risk ratio; TEA = thoracic epidural anesthesia.

significant and was based on a small number of events. Alternative weighting models had little impact on the results, but alternative continuity corrections that integrated the excluded studies yielded RRs from 0.52 to 0.77.

Additional Evaluations

Metaregression did not show likely associations between the study outcome and factors varying over the years of execution of the individual studies or risk of bias items for any of the outcomes. Neither graphical explorations nor formal regression tests showed evidence of small study effects due to selective dissemination of studies or study results for any of the above-mentioned endpoints. Figure 5 contains risk-based L'Abbé plots, showing the per-study control group (baseline) risks, index group risks, and their relationship for all endpoints in a single graph.

Discussion

We have conducted a meta-analysis of clinical trials comparing the effects of cardiac surgery with and without TEA on mortality and cardiac, respiratory, and neurologic complications. Our meta-analysis showed statistically significant reductions in the incidence of supraventricular tachyarrhythmias and respiratory complications after TEA. There were no significant differences in the incidences of mortality, myocardial infarction, and stroke.

The potential of TEA for decreasing tachyarrhythmias has been reported before[3,17,18] and was confirmed in this meta-analysis. However, the included studies were heterogeneous, and the confidence intervals around the risk ratio estimates were wide. The study by Scott *et al.*[3] in 420 patients was contributing the most to this result. In this study,

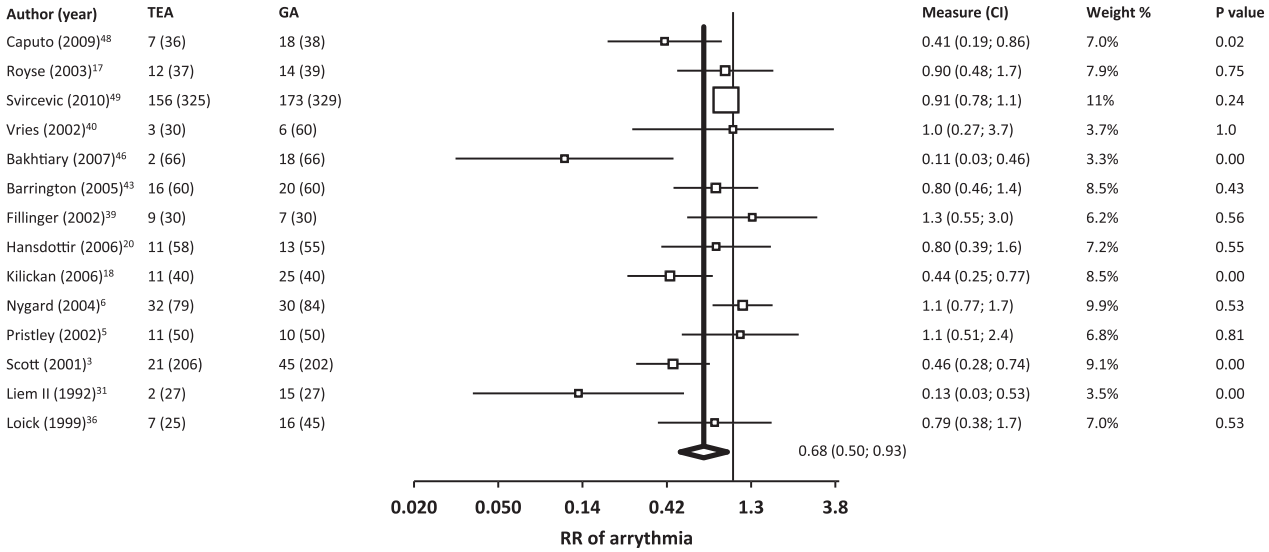

Fig. 3. Risk ratios and forest plot for supraventricular tachyarrhythmias in the first 2 weeks after surgery. GA = general anesthesia; RR = risk ratio; TEA = thoracic epidural anesthesia.

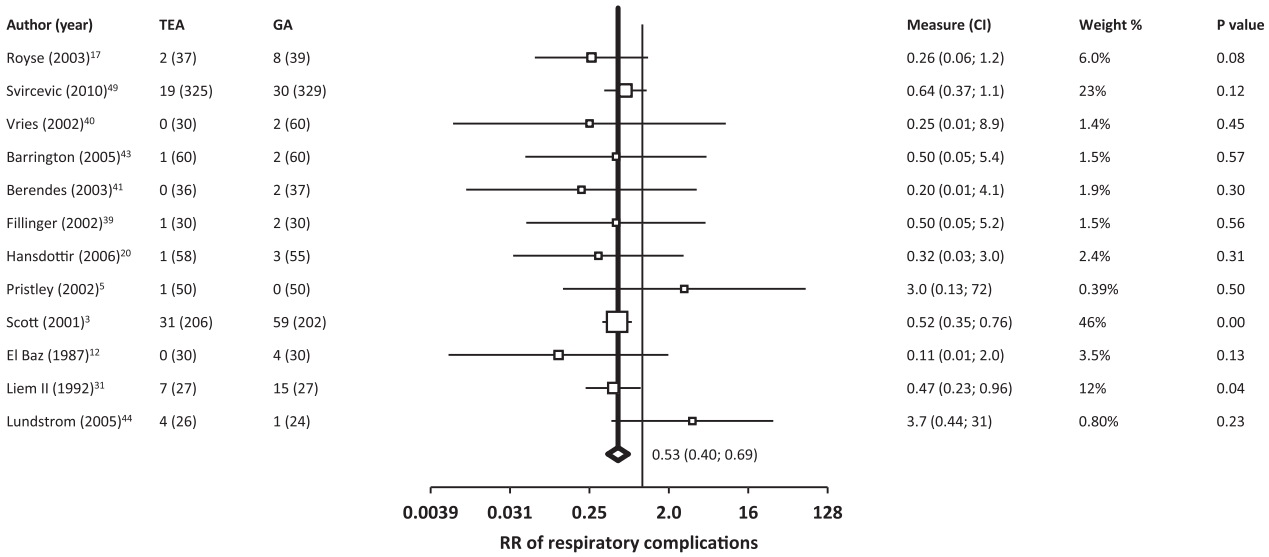

Fig. 4. Risk ratios and forest plot for respiratory complications in the first 2 weeks after surgery. GA = general anesthesia; RR = risk ratio; TEA = thoracic epidural anesthesia.

β-blockers were discontinued 5 days perioperatively. Moreover, the patients randomized to TEA received the cardioprotective drug, clonidine, through their epidural catheter. This cardioprotective drug[19] was not administered to the control patients. The withdrawal of β-blockers in all study patients and the selective use of clonidine in the patients randomized to TEA may explain the large benefit of TEA on supraventricular arrhythmias found in this trial. Although the Scott study was encouraging, most studies published since then were unable to repeat its results. A recent, well-designed study by Hansdottir[20] revealed no benefits of TEA on the incidence of tachyarrhythmias, plus a 17% failure of epidural catheter insertion. Recent studies showed that postoperative supraventricular tachyarrhythmias can also be reduced with less invasive treatments, such as β-blockers and amiodarone.[6,21,22] The majority of the studies included in this meta-analysis did not report whether the patients also used drugs to prevent postoperative arrhythmias. It is therefore unclear whether TEA has an additional preventive effect in patients who are also administered prophylactic antiarrhythmic drugs after their operation.

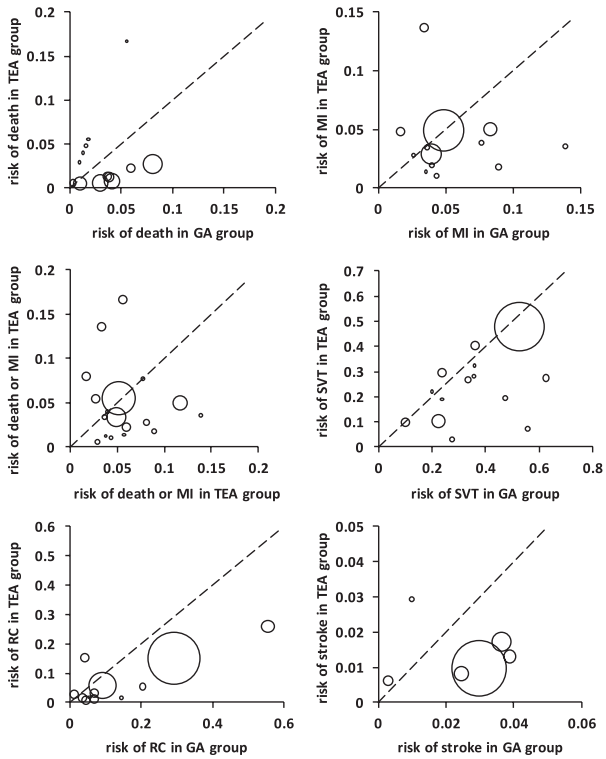

Fig. 5. Risk-based L'Abbé plots for baseline, index group risks, and relationship for endpoints. GA = general anesthesia; MI = myocardial infarction; RC = respiratory complications; SVT = supraventricular tachyarrhythmias; TEA = thoracic epidural anesthesia.

Our meta-analysis also showed that TEA results in a statistically significant reduction in postoperative respiratory complications, which is consistent with previous meta-analyses.[8,11] This may be explained by the superior analgesia after TEA, which facilitates earlier spontaneous respiration in the intensive care unit and faster tracheal extubation. It has been shown, however, that other strategies that allow earlier tracheal extubation can also reduce respiratory complications.[23–25] A previous meta-analysis by Liu[11] showed that pulmonary complications after cardiac surgery can also be reduced with spinal anesthesia. Interestingly, this benefit was not explained by a shorter time to extubation. As the risk of an epidural hematoma is considerably lower after a single spinal injection than after insertion of an epidural catheter, spinal anesthesia might be a viable option for cardiac surgical patients with a high risk of pulmonary complications.

There are several limitations associated with the included randomized studies that warrant caution in the interpretation of the results of this meta-analysis. First, the time period in which the studies were undertaken spanned 30 yr. The

quality of anesthesiological and intensive care has clearly improved over these years. It is possible that some beneficial effects of TEA, such as earlier extubation, are currently also achieved with modern general anesthetics. Second, most of the included studies were designed to evaluate the effect of TEA on intermediate or surrogate outcome measures, instead of clinical endpoints. Third, the nonstandardized coverage of clinical outcomes in most studies carries a high risk of observer bias, in particular when the endpoint adjudication was not blinded.

Our findings are largely comparable with those of the two previous meta-analyses.[8,11] Because we were able to include 28 studies including 2,731 patients, which is substantially more patients than in the two previous meta-analyses, the effect estimates are more precise with narrower confidence intervals. Although the number of patients in the current meta-analysis is more than twice the number of patients in previous meta-analyses, the events were extremely sparse, and the current meta-analysis is still not sufficiently powered to detect small beneficial or harmful effects of TEA on mortality, myocardial infarction, paraplegia, and stroke. To demonstrate statistical significance for the reduction in the incidence of myocardial infarction from 3.8% after GA to 2.8% after TEA (as found in this meta-analysis), a sample size of at least 10,000 patients is required. It is obvious that such a large trial would be extremely difficult to perform.

Despite the benefit of TEA on supraventricular tachyarrhythmias and respiratory complications, our findings must be viewed with caution. Thoracic epidural anesthesia in cardiac surgery remains controversial in the absence of a sufficiently large, statistically significant effect on mortality, stroke, or myocardial infarction while possible hazardous complications of TEA, such as epidural hematoma or abscess, must be taken into account. Systematic anticoagulation needed during cardiopulmonary bypass could increase the incidence of epidural hematoma related to the use of an epidural catheter.[10] More commonly, the intense sympathycolysis may lead to systemic hypotension, which can be difficult to correct.

In the included studies, no cases of epidural hematoma were reported, but this devastating complication is too rare to evaluate in randomized studies. There are a few reports[26,27] on neuraxial hematoma in cardiac surgery, of which some have directly been linked to TEA.[28] The benefit-harm tradeoff could not be explored in the current framework of meta-analysis of randomized trials. However, given the severity of this complication and the lack of a clear beneficial effect on mortality, stroke, or myocardial infarction, the potential benefits of TEA in cardiac surgery may not be worth the potential risks.

In conclusion, this meta-analysis showed that the use of TEA in patients undergoing cardiac surgery reduces the risk of postoperative supraventricular arrhythmias and respiratory complications. The sparsity of events precludes conclusions about mortality, myocardial infarction, and stroke, but the estimates suggest a reduced risk after TEA. The risk of side effects of TEA, including epidural hematoma, could not be assessed with the current dataset, and therefore TEA should be used with caution until its benefit-harm profile is further elucidated.

Appendix 1. Search Strategy

Database

PubMed and MEDLINE (1966–2010)

Searchfilter

(("Cardiac Surgical Procedures"[MeSH] or cardiac surgery[tiab] or heart surgery[tiab] or cardiac surgical procedures[tiab] or cardiopulmonary bypass[tiab] or cardiothoracic*[tiab] or CABG[tiab]) not Pulmonary Surgical Procedures[MeSH]) and ("Analgesia, Epidural"[MeSH] or "Anesthesia, Epidural"[MeSH] or "Anesthesia, Spinal"[MeSH] or epidural*[tiab] or peridural*[tiab] or extradural*[tiab] or spinal*[tiab] or subarachnoid*[tiab] or intrathecal*[tiab] or neuraxial*[tiab]) and ((randomized controlled trial [pt] or controlled clinical trial [pt] or randomized controlled trials [mh] or double-blind method [mh] or single-blind method [mh] or clinical trial [pt] or clinical trials [mh] or ("clinical trial" [tw])) or ((singl* [tw] or doubl* [tw] or trebl* [tw] or tripl* [tw]) and (mask* [tw] or blind* [tw])) or (placebos [mh] or placebo* [tw] or random* [tw] or research design [mh:noexp] or comparative study [mh] or evaluation studies [mh] or follow-up studies [mh] or prospective studies [mh] or control* [tw] or prospective* [tw] or volunteer* [tw] not (animals [mh] not human [mh])))

Database

Science Citation Index Expended and Social Sciences Citation Index (1988–2010)

Searchfilter

1988–2004/07TI = ((epidural* or peridural* or extradural* or spinal* or subarachnoid* or intrathecal* or neuraxial*) and (anesthes* or anaesthes* or analges*) and (card* surg* or heart surg* or CABG or coronar* arter* bypass* or coronar* bypass* or heart* valv* surg*) and (metaanalysis or meta-analysis or review or consensus or guideline or random* or trial* or control* or ((singl* or doubl* or trebl* or tripl*) and (blind* OR mask*))))

Database

EMBASE (1989–2010)

Searchfilter

(((heart-surgery in su) or (cardiopulmonary-bypass in su)) or ((coronary artery bypass surgery or coronary artery surgery or coronary bypass graft surgery or coronary artery bypass graft or coronary bypass graft or coronary artery bypass graft* or coronary bypass graft* or CABG or ((off pump or offpump or off-pump) and (coronary surgery)) or open heart surgery or heart

surgery or heart valve surgery or cardiopulmonary bypass) and ((xrec = ab) or (xrec = ti)))) and (((epidural or peridural or extradural or spinal or subarachnoid or intraspinal or intrathecal or neuraxial) and ((xrec = ab) or (xrec = ti))) or ((spinal-anesthesia or intraspinal-drug-administration or epidural-anesthesia) in su)) and (((controlled study or controlled trial or clinical study or major clinical study or clinical trial or randomized controlled trial or random* or trial*) and ((xrec = ab) or (xrec = ti))) or ((clinical study or controlled study) in su))

Database

CINAHL (1982–2010)

Searchfilter

(((heart-surgery in de)or(cardiopulmonary-bypass in de)) or (((coronary artery bypass surgery or coronary artery surgery or coronary bypass graft surgery or coronary artery bypass graft or coronary bypass graft or coronary artery bypass graft* or coronary bypass graft* or CABG or ((off pump or off-pump or off-pump) and coronary surgery) or open heart surgery or heart surgery or heart valve surgery or cardiopulmonary bypass)) and ((xrec = ab) or (xrec = ti)))) and (((epidural or peridural or extradural or spinal or subarachnoid or intrathecal or neuraxial) and ((xrec = ab) or (xrec = ti))) or (((anesthesia-spinal in de)or(injections-intraspinal in de)or(infusions-intraspinal in de)) or ((analgesia-epidural in de)or(anesthesia-epidural in de)or(epidural-analgesia-administration in de)))) and (((clinical-trials in de) or ((Randomized controlled trial or clinical trial or explode clinical trial/all topical subheadings/all age subheadings or (control* or prospectiv* or volunteer*) or ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)) or placebo* or random* or explode evaluation studies/all topical subheadings/all age subheadings or prospectieve study) and ((xrec = ab) or (xrec = ti)))) or (clinical-trials in de))

Database

Cochrane Anaesthesia Review Group trials register and CENTRAL (the current issue of The Cochrane Library)

Searchfilter

1. ANALGESIA EPIDURAL explode all trees (MeSH)
2. ANESTHESIA EPIDURAL explode all trees (MeSH)
3. ANESTHESIA SPINAL explode all trees (MeSH)
4. INJECTIONS SPINAL explode all trees (MeSH)
5. (epidural* or peridural* or spinal* or intraspinal* or intrathecal* or neuraxial*)
6. (1 or 2 or 3 or 4 or 5)
7. CARDIAC SURGICAL PROCEDURES explode all trees (MeSH)
8. CARDIOPULMONARY BYPASS explode all trees (MeSH)
9. (6 and (7 or 8))
10. ((coronary next artery next bypass next surgery) or (coronary next artery next surgery) or (coronary next bypass next graft next surgery) or (coronary next artery next bypass next graft) or (coronary next bypass next graft) or (coronary next artery next bypass next graft*) or (coronary next bypass next graft*) or cabg or (((off next pump) or offpump or off-pump) and (coronary next surgery)) or (open next heart next surgery) or (heart next surgery) or (heart next valve next surgery) or (cardiopulmonary next bypass))
11. (7 or 8 or 10)
12. (11 and 6) 74

Appendix 2. Processing-form "Epidural *versus* Nonepidural Anesthesia in Cardiac Surgery"

Article nr:
Date: .../.../.....
Name reviewer: Svircevic Passier van Dijk
First author's name .....
Year of publication .....
Study Quality
1 Group size
- Neuraxial N =
- Control N =

2 Randomized allocation Yes No Method unclear
3 Concealed allocation Yes No Method unclear
4 Number of crossovers
- Neuraxial N =
- Control N =

5 Maximum number of dropouts
- Neuraxial N =
- Control N =

6 Maximum number lost to follow-up
- Neuraxial N =
- Control N =

7 Intention to treat analyses Yes No Unclear
8 Blinded analyses Yes No Unclear
9 Blinding pre- and postsurgery care Yes No Unclear
10 Standardized pre- and postsurgery care Yes No Unclear
11 Blinding endpoints Yes No Unclear
12 Standardization endpoints Yes No Unclear
Preoperative data
13 Age
- Neuraxial mean = SD =
- Control mean = SD =

14 Males
- Neuraxial N =
- Control N =

15 Prior vascular surgery
- Neuraxial N =
- Control N =

16 Diabetic status: type 1 2 dialysis
- Neuraxial N = N = N =
- Control N = N = N =

17 Preoperative risk score: French score Parsonnet score Euro score
- Neuraxial mean = SD =
- Control mean = SD =

18 Type(s) of surgery .....
19 Type of neuraxial anesthesia: intrathecal epidural
20 Type of general anesthesia: traditional fast track < 12 h fast track < 6 h
21 Outcome measures
- Primary endpoint .....
- Secondary endpoints .....

22 Time to follow-up .....
23 Main Outcomes of this Study (give absolute numbers, no percentages)

Outcome	Neuraxial group	Control group	*P*
Mortality	—	—	—
MI	—	—	—
SVT	—	—	—
Respiratory complications	—	—	—

Other important outcomes:
.....
.....
Main conclusion(s) (see last paragraph discussion):
.....
.....
Remarks:
.....
.....

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