

## A Systematic Review of the Safety and Effectiveness of Fast-track Cardiac Anesthesia

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COST containment and efficient resource use have forced anesthesiologists to rethink their management strategies for cardiac surgery.<sup>1-4</sup> In the late 1970s, when anesthetic practice predominantly involved inhalational anesthesia, it was possible to extubate cardiac surgical patients within a few hours after surgery. However, there was no economic pressure or incentive to practice cost-effective medicine at that time. An opioid-based anesthetic regimen gained popularity in the 1980s, when studies confirmed its ability to allow hemodynamic stability, even in patients with marginal cardiac reserve.<sup>5,6</sup> This necessitated continuation of postoperative ventilatory support for 12-24 h in cardiac surgical patients. The growing need for intensive cardiovascular and ventilatory support during the immediate postoperative period in these patients required an expansion of intensive care unit (ICU) bed availability. Until recently, this need for postoperative ICU nursing care and length of stay had continued unchecked.

The aims of "fast-tracking" cardiac surgical patients include early tracheal extubation and decreased length of ICU and hospital stay with subsequent cost reduc-

tion.<sup>2-4</sup> Fast-track cardiac anesthesia (FTCA) techniques include the use of short-acting hypnotic drugs, reduced doses of opioids, or the use of ultrashort-acting opioids, and, in some cases, the use of antifibrinolytic drugs or drugs to prevent atrial fibrillation.

There are purported benefits of early tracheal extubation and reduced duration of mechanical ventilation.<sup>7</sup> Several randomized trials have found that early tracheal extubation can be safely achieved,<sup>8-17</sup> and it may lead to reduced ICU stay<sup>10,12</sup> and costs.<sup>12,18,19</sup> Despite these findings, there are residual concerns regarding early tracheal extubation and FTCA.<sup>20-24</sup> Studies to date have not included a sufficient number of patients to detect a clinically important effect on serious morbidity or mortality. The primary objective of this systematic review was to determine whether FTCA is as safe as traditional cardiac anesthesia (TCA) based on the administration of high doses of opioids. The hypothesis tested was that there is not an increased risk of mortality or major morbidity associated with FTCA compared with TCA.

### Materials and Methods

This systematic review and meta-analysis followed a protocol that specified the aims, inclusion criteria, anesthetic regimens, and outcome assessments from previously published trials.<sup>25</sup> We chose to include all randomized trials of adult cardiac surgical patients undergoing coronary artery bypass graft (CABG) or valve surgery with cardiopulmonary bypass. Patients undergoing off-pump cardiac surgery or having major regional blockade (spinal or epidural techniques) were not included in the analysis. We compared FTCA with TCA. The former group was defined by the use of a reduced dose of opioids (fentanyl,  $\leq 20$   $\mu$ g/kg, or equivalent) and the intention to promote early ( $< 10$  h) tracheal extubation. The TCA group was defined by the use of high-dose opioids (fentanyl,  $> 20$   $\mu$ g/kg).

### Search Strategy for Identification of Studies

A systematic search for all relevant randomized controlled trials was conducted.<sup>25</sup> Relevant trials were ob-

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tained from the following sources between August and December 2000: the Cochrane Controlled Trials Register, electronic databases (MEDLINE and EMBASE) 1988–June 2000, and reference lists of relevant studies, reviews, and abstracts in major journals related to anesthesia and cardiac surgery. In addition, the following medical subject headings and text words, and their combinations, were included in a MEDLINE electronic search strategy with the assistance of a librarian: *anesthesia, coronary artery bypass surgery, postoperative complications, heart, fast-track, fast-tracking, early extubation, tracheal extubation, ventilation, intensive care, morbidity, and mortality*. No language restrictions were applied.

The quality of eligible trials was assessed independently, under open conditions.<sup>25,26</sup> Masking, losses to follow-up, method of randomization, sample size, and power calculations were recorded. The patient population, type of surgery, and anesthetic details were also collected. Data from the trial reports were independently checked by two or more investigators; disagreements were resolved by consensus. In cases in which relevant data were not presented in the original publication, the primary author was contacted by letter, and information on additional unpublished data was requested.

### Outcome Measures

Our primary outcome was 30-day all-cause mortality. Secondary outcomes were major morbidities and included the following:

myocardial infarction (*i.e.*, new Q waves on two adjacent leads of a 12-lead electrocardiogram); major sepsis (*i.e.*, patient temperature greater than 39°C or wound infection requiring surgical reexploration); stroke (*i.e.*, a new sensory or motor deficit); acute renal failure requiring dialysis or hemofiltration; prolonged ICU stay (*i.e.*, 5 or more days); major bleeding requiring surgical reexploration; time to tracheal extubation; and ICU and hospital length of stay.

The primary and secondary outcomes were chosen because they represent clinically important and reliable measures of safety and effectiveness. The definitions of the secondary outcomes were in part related to consensus guidelines.<sup>27</sup>

### Statistical Analysis

The DerSimonian and Laird random-effects model was used to combine data for continuous and dichotomous outcomes, because we anticipated that the treatments and conditions in these studies would be varied.<sup>28</sup> This model incorporates between-study (different treatment effects) and within-study (sampling error) variability.<sup>28</sup> Trials with zero events in the FTCA and TCA groups were not included in the meta-analysis. Some trials had more than one FTCA group.<sup>9,29</sup> In such cases, the FTCA groups were combined for meta-analysis. The pooled

relative risk (RR), weighted mean difference, and 95% CI were estimated for mortality and major morbidity endpoints. When the median and range were reported for continuous outcomes, the mean and SD were estimated by assuming that the mean was equivalent to the median and that the SD was one quarter of the range.<sup>30</sup>

Meta-analysis was performed using STATA, version 7.0 (Stata Corporation, College Station, TX). Because meta-analysis pools results from a variety of study populations during a broad period, heterogeneity (interstudy variation) was analyzed using the Q statistic with a threshold for the *P* value of less than 0.10. When heterogeneity was found, the trials contributing to the heterogeneity were removed and another analysis was performed to test the effect on the outcome estimates. A funnel plot of the trials was used to identify evidence of bias *via* the Egger weighted regression method with SE and log odds ratio plotted as previously recommended.<sup>31</sup> Sensitivity analyses were performed to evaluate the robustness of results according to allocation concealment (adequate *vs.* unclear or inadequate) for the primary outcome.

## Results

Our literature search identified 10 trials including 1,800 patients, which were used for the analysis.<sup>9,10,12–14,16–18,29,32,33</sup> The characteristics of the study populations are summarized in table 1. Adequate allocation concealment was used in five trials.<sup>12–14,17,29</sup> Intention-to-treat analysis and full follow-up occurred in eight trials.<sup>9,10,12–14,17,32,33</sup> There was no evidence of heterogeneity (*P* > 0.1) in any of the meta-analyses of mortality or major morbidity endpoints.

Four trials had no surgical deaths,<sup>9,17,32,33</sup> so the RR for mortality was not estimable. Hence, six trials were used to estimate effect on mortality.<sup>10,12–14,16,29</sup> There was no statistically significant difference in mortality rate between the FTCA and TCA groups (FTCA group, 12 of 968 [1.2%]; TCA group, 13 of 474 [2.7%]; RR, 0.51 [95% CI: 0.23–1.13]; *P* = 0.099) (fig. 1).

A sensitivity analysis restricting data analysis to those studies that used adequate allocation concealment<sup>12,13,17,29</sup> had a similar RR (0.57 [95% CI: 0.25–1.35]), as compared with those with unclear allocation concealment (RR, 0.25 [95% CI: 0.03–2.16]). We also removed the data from the study of Slogoff *et al.*,<sup>29</sup> but similar estimates of RR were obtained (RR, 0.37 [95% CI: 0.10–1.40]). A funnel plot showed no evidence of bias (*P* = 0.22) (fig. 2).

There was no significant difference between groups with respect to major morbidity (table 2). There was only one report of tracheal reintubation in a patient in the FTCA group,<sup>12</sup> yet this occurred late and followed the onset of postoperative pneumonia. Thus, risk estimates for tracheal reintubation could not be estimated.

**Table 1. Characteristics of the Trials Included in the Meta-analysis**

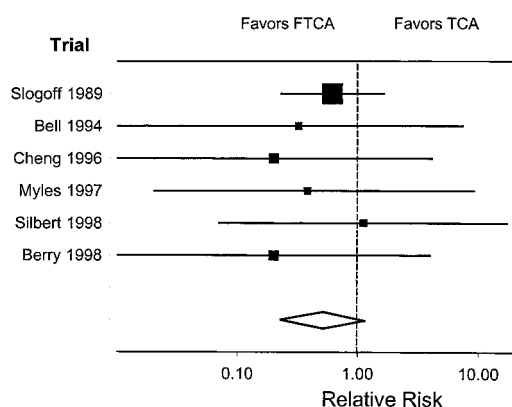
Study	Study Population	TCA Group	FTCA Group	Adjuvant Drugs
Slogoff <i>et al.</i> , 1989 <sup>29</sup>	CABG (n = 1,012); mean age, 59 y; 83% male	Sufentanil 28 ± 4.3 µg/kg	Fentanyl 10 µg/kg and enflurane, halothane or isoflurane	AF prophylaxis
Bell <i>et al.</i> , 1994 <sup>10</sup>	CABG (n = 19), valve (n = 14), CABG/valve (n = 6); mean age, 62 y; 74% male	Fentanyl 60 µg/kg and midazolam	Fentanyl 5 µg/kg and propofol	None
Ramsey <i>et al.</i> , 1994 <sup>9</sup>	CABG (n = 75); mean age, 61 y; 86% male	Sufentanil 11 µg/kg	Sufentanil 5 µg/kg and isoflurane or enflurane	AF prophylaxis
Cheng <i>et al.</i> , 1996 <sup>12</sup>	CABG (n = 120); mean age, 60 y; 78% male	Fentanyl 50 µg/kg and isoflurane, midazolam	Fentanyl 15 µg/kg and isoflurane, propofol	Antifibrinolytics
Myles <i>et al.</i> , 1997 <sup>13</sup>	CABG (n = 124); mean age, 64 y; 80% male	Fentanyl 31 µg/kg and enflurane	Fentanyl 15 µg/kg and propofol	None
Silbert <i>et al.</i> , 1998 <sup>14</sup>	CABG (n = 100)*; mean age, 62 y; 78% male	Fentanyl 50 µg/kg and propofol	Fentanyl 15 µg/kg and propofol	None
Michalopoulos <i>et al.</i> , 1998 <sup>33</sup>	CABG (n = 144); mean age, 59 y; 92% male	Fentanyl 50 µg/kg + 10–15 µg · kg <sup>-1</sup> · h <sup>-1</sup> , and isoflurane or halothane plus midazolam	Fentanyl 20–25 µg/kg and isoflurane, halothane or propofol	AF prophylaxis
Sakaida <i>et al.</i> , 1998 <sup>32</sup>	CABG (n = 27), valve (n = 13); mean age, 61 y; 75% male	Fentanyl 99 ± 5.8 µg/kg	Fentanyl 7.6 ± 1.6 µg/kg and isoflurane	
Berry <i>et al.</i> , 1998 <sup>16</sup>	CABG (n = 98)†; mean age, 59 y; 84% male	Fentanyl 50 µg/kg and isoflurane	Fentanyl 15 µg/kg and isoflurane	None
Myles <i>et al.</i> , 2002 <sup>17</sup>	CABG (n = 48); mean age, 62 y; 79% male	Fentanyl 28 µg/kg and propofol	Fentanyl 14 µg/kg and propofol	None

\* Twenty withdrawn after enrollment (not analyzed by intention-to-treat). † Thirteen withdrawn after enrollment (not analyzed by intention-to-treat).

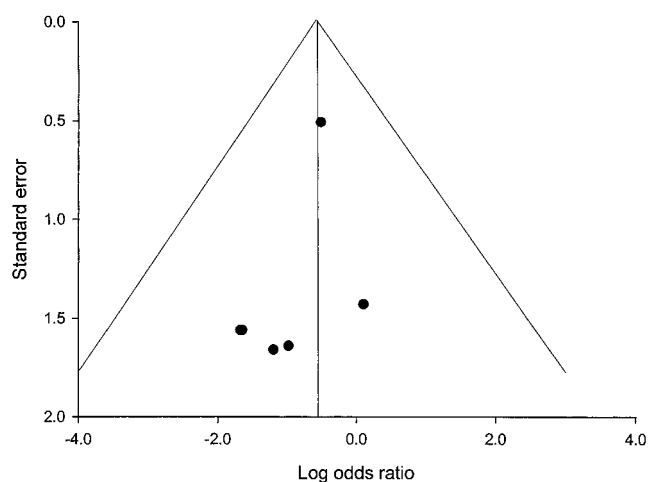
AF = atrial fibrillation; CABG = coronary artery bypass graft; FTCA = fast-track cardiac anesthesia; TCA = traditional cardiac anesthesia.

There was a marked reduction in the time to tracheal extubation<sup>12–14,16–18,31,32</sup> in the FTCA group. The FTCA group had a pooled weighted mean reduction in time to tracheal extubation of 8.1 h (95% CI: 3.7–12.5;  $P < 0.001$ ) (fig. 3). There was evidence of heterogeneity ( $P < 0.01$ ) in the meta-analyses of time data (time until tracheal extubation and ICU and hospital length of stay),

but selective inclusion and exclusion of individual studies did not alter the estimates of effect. We also removed the data from the study of Slogoff *et al.*,<sup>29</sup> but similar estimates were obtained (weighted mean reduction, 8.1 h [95% CI: 3.2–13.0];  $P = 0.001$ ). There was a reduction in the length of ICU stay in the FTCA group, with a pooled weighted mean reduction in length of ICU stay of 5.4 h (95% CI: 0.3–10.5;  $P = 0.039$ ). There was no significant reduction in the length of hospital stay, with



**Figure 1.** The relative risk of mortality comparing a low-dose opioid regimen (fast-track cardiac anesthesia [FTCA]) with a high-dose opioid regimen (traditional cardiac anesthesia [TCA]). Each trial is represented by a square, denoting the relative risk. The horizontal lines represent the 95% CI. The size of the square is proportional to the amount of information in the trial. The diamond represents the pooled relative risk and 95% CI. There was no evidence of heterogeneity ( $P = 0.93$ ). Four additional trials<sup>9,17,32,33</sup> had a zero mortality rate, so the relative risk could not be estimated.



**Figure 2.** Begg's funnel plot, with pseudo 95% confidence limits, of the estimated risk, using odds ratio for mortality in each trial. There was no evidence of bias ( $P = 0.22$ ).

**Table 2. Risk of Major Morbidities Comparing a Low-dose Opioid Regimen (Fast-track Cardiac Anesthesia) with a High-dose Opioid Regimen (Traditional Cardiac Anesthesia)**

Morbidity	FTCA		TCA		Risk Ratio (95% CI)	P Value
	No.	%	No.	%		
Myocardial infarction*	40/993	4.0	19/471	4.0	1.00 (0.52–1.94)	1.00
Major sepsis	1/98	1.0	1/102	1.0	1.05 (0.11–10.01)	0.96
Wound infection	2/84	2.4	3/84	3.6	0.78 (0.08–7.16)	0.82
Stroke	1/84	1.2	2/84	2.4	0.74 (0.05–10.56)	0.83
Acute renal failure	2/44	4.5	0/43	0	2.92 (0.32–27.1)	0.34
Prolonged ICU stay	5/160	3.1	7/171	4.1	0.84 (0.27–2.65)	0.76
Major bleeding	1/118	0.9	6/121	5.0	0.31 (0.06–1.53)	0.15

Not all relevant morbidity data were available in the original publications or from the authors. This is represented by the denominator of the incidence in each group.

\* If the Slogoff trial<sup>29</sup> is excluded, RR (95% CI) 0.91 (0.26–3.26),  $P = 0.89$ .

FTCA = fast-track cardiac anesthesia; ICU = intensive care unit; TCA = traditional cardiac anesthesia.

the FTCA group being discharged from the hospital 0.61 days (95% CI: 0.28–1.5;  $P = 0.18$ ) earlier.

## Discussion

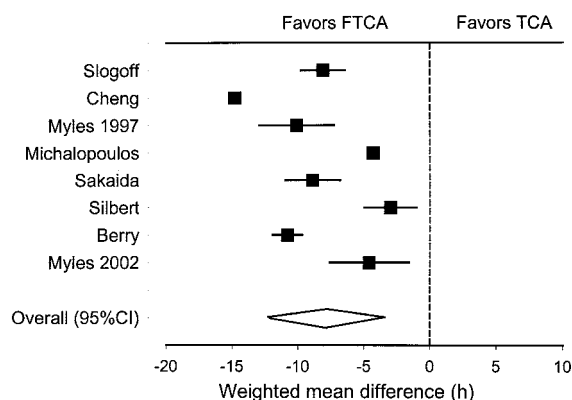
Our study found no evidence of increased mortality or major morbidity rates with FTCA. The primary purpose of many of the original studies in this review was to compare time to tracheal extubation, largely as a surrogate marker for ICU resource use. The pooled analysis of the studies clearly shows a significantly shorter duration of tracheal intubation with low-dose opioid administration. We have also shown, for the first time, a reduction in the length of stay in the ICU. Thus, this systematic review has found that FTCA is safe and effective in patients undergoing elective cardiac surgery.

Many cardiac surgical centers during the past decade have embraced the philosophy of fast-track treatment of patients. There is good reason to believe that this can have a substantial beneficial effect on costs,<sup>3,4,12,19</sup> a view supported by our ICU length of stay data. It has been argued that FTCA should not be adopted until further evidence of its safety is available, particularly because prolonged intensive analgesia can reduce postoperative myocardial ischemia.<sup>21</sup> We studied rates of myocardial infarction, but not other ischemic events. Believing that the associated neurohumoral stress ablation can optimize hemodynamic stability and reduce myocardial ischemia, many anesthesiologists have continued to use high-dose opioid-based regimens. FTCA techniques have been shown to offer similar stability,<sup>9,13</sup> and other agents, such as clonidine,<sup>15</sup> can provide similar ablation of the stress response. Hemodynamic changes and myocardial ischemia are surrogate end-points and are of little consequence if there is no effect on outcomes, such as myocardial infarction and stroke. Our study could find no evidence of increased risk of adverse outcomes associated with FTCA, but we recognize that we did not have enough patient data (*i.e.*, the

study was underpowered) to detect differences in rare events.

There has been some concern that FTCA leading to premature tracheal extubation may increase the need for reintubation in the ICU.<sup>23</sup> This can be problematic if induction of anesthesia is needed at a time of hemodynamic instability. Reported tracheal reintubation was rare in the studies we retrieved for analysis. The rate of tracheal reintubation is generally less than 2%,<sup>34–37</sup> but Rady *et al.*<sup>23</sup> reported a rate of 6.6% in a series of 11,330 unselected patients in an FTCA program that included a ventilator weaning protocol. London *et al.*<sup>38</sup> reported an initial rate of 0.7%, with reintubation for medical reasons (mostly late) of 7.7%, but this rate improved to 2.1% after institution of an FTCA program. Patients who are mechanically ventilated for a long period after surgery seem to be at particular risk for a need for reintubation,<sup>23</sup> but this is not directly related to FTCA.

There is also a concern that FTCA and early tracheal extubation may lead to suboptimal analgesia in the early postoperative period. At our institutions, we encourage multimodal analgesic techniques, using nonsteroidal an-



**Figure 3. The weighted mean difference (95% CI) in tracheal extubation times comparing a low-dose opioid regimen (fast-track cardiac anesthesia [FTCA]) with a high-dose opioid regimen (traditional cardiac anesthesia [TCA]).** One additional trial<sup>9</sup> did not report tracheal extubation times and another did not report SD or range data,<sup>10</sup> so we could not estimate the 95% CI.



tiinflammatory drugs and tramadol as opioid-sparing agents. These should reduce opioid-induced respiratory depression and favor adequate spontaneous ventilation and sputum clearance.

Cardiac surgery is among the most expensive surgical procedures.<sup>38</sup> It is estimated that approximately half a million patients undergo cardiac surgical procedures in the United States annually, costing approximately \$9 billion per year. The increased demand for cardiac surgical procedures coincides with a change in the profile of patients requiring cardiac surgery. The use of CABG surgery in the elderly population has doubled every 5 yr since 1985. With the increasing numbers of patients requiring cardiac surgery, efficient use of the limited facilities and resources available is vital for the proper delivery of medical care. Economic considerations drive the trend toward early tracheal extubation after such procedures. However, the control of perioperative costs relies on improvements in efficiency coupled with no change in the extent of morbidity and mortality experienced by the patient, compared with an individual who does not undergo fast-track surgery.

The cost savings shown with fast-tracking<sup>12,18</sup> may be illusionary if there is an associated increase in serious complications, because the costs involved in the treatment would exceed the savings achieved by early tracheal extubation.<sup>24,39</sup> Cost savings are possible in high-volume centers with flexible nurse staffing and cardiac operating room scheduling, and few emergency cases.<sup>40,41</sup> The strongest predictors of cost for cardiac surgical patients are patient age, operating room time, ICU and hospital length of stay, and the presence of postoperative complications.<sup>12,39</sup> Costs in the preoperative phase can be reduced if a same-day admission program is available. FTCA may further reduce costs. The operating room costs for personnel (*i.e.*, nurses, the perfusionist, and physicians) and supplies (*i.e.*, surgical and perfusion) are the most expensive requirements for the surgery. ICU costs rank second only to operating room costs in uncomplicated CABG surgery. The practice of early tracheal extubation allows cost shifting from the high costs of the ICU to the lower costs of the ward. This is mainly achieved by reducing the intensity of nursing care (*i.e.*, converting to part-time or less overtime), by decreasing the length of stay in the ICU, and by early mobilization in the ICU and on the ward, leading to early hospital discharge.<sup>12</sup>

Systematic review and meta-analysis are considered to provide the least biased estimates of effect, but pooling trials from a variety of institutions and countries may be inappropriate. Our meta-analysis included one large study that contained approximately 70% of the data, although this is generally considered a strength in reliable meta-analyses.<sup>42</sup> We could find no evidence of heterogeneity in the mortality and morbidity outcomes, so the results of the meta-analyses can be accepted more

readily. We did find heterogeneity with tracheal extubation time and ICU stay. This was not unexpected given the established routines and protocols that exist in each hospital, a factor known to have a marked effect on tracheal extubation times and ICU discharge practices.<sup>1,3</sup> The results of this study may not be applicable to non-elective or high-risk cardiac surgery, and we had limited valve surgery data ( $n = 33$ ). Although the mortality rate difference between FTCA and TCA groups was not statistically significant, this could represent a false negative or type II error. A meta-analysis increases power but is still limited by the total number of events in the studies included in the analysis. Mortality and major morbidity are uncommon after cardiac surgery, and trials of FTCA usually exclude patients at the highest risk. A meta-analysis of previously collected data may be incomplete because the original studies often do not collect all relevant data. If more data become available, it will be possible to obtain estimates of risk with greater precision. Alternatively, because this meta-analysis favored FTCA, it would be preferable to conduct a large, prospective, randomized trial to provide definitive evidence of reduced mortality rates.

In conclusion, this systematic review found no evidence of increased mortality or morbidity rates with FTCA techniques using lower opioid dose regimens when compared with traditional high-dose opioid techniques. Because of the known cost benefits of FTCA combined with concomitant changes in operating room scheduling and ICU nurse staffing,<sup>12,19,40,41</sup> there seems to be no compelling reason to use high-dose opioid regimens in anesthesia for elective cardiac surgery with cardiopulmonary bypass.

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