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A Comparison of the Effect of High- and Low-dose Fentanyl on the Incidence of Postoperative Cognitive Dysfunction after Coronary Artery Bypass Surgery in the Elderly

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Background: **Postoperative cognitive dysfunction (POCD) after coronary artery bypass graft surgery is a common complication for which, despite many clinical investigations, no definitive etiology has been found. The current use of both high- and low-dose fentanyl as anesthetic techniques allowed us to investigate the effect of fentanyl on the incidence of POCD.**

Methods: **Three hundred fifty patients scheduled to undergo elective coronary artery bypass graft surgery were randomized to receive either high-dose fentanyl (50 μg/kg) or low-dose fentanyl (10 μg/kg) as the basis of the anesthetic. All patients underwent neuropsychological testing before surgery and at 1 week, 3 months, and 12 months after surgery.**

Results: **One hundred sixty-eight patients in the low-dose group and 158 patients in the high-dose group were included in the final analysis. Neuropsychological testing was performed on 88%, 93%, and 92% of patients at 1 week, 3 months, and 12 months, respectively. There was no difference between group mean scores at any of the three testing times. Analysis of individual patients by the 20% rule did not detect any differences between groups. The one SD rule, which has fewer false-positive results, detected significantly more patients with POCD in the low-dose group than in the high-dose group at 1 week (23.6% *vs.* 13.7%; $P = 0.03$) but not at the other testing times. Patients with POCD spent an average of 1.2 days longer in the hospital than those without POCD ($P = 0.021$).**

Conclusions: **High-dose fentanyl is not associated with a difference in the incidence of POCD at 3 or 12 months after surgery. Low-dose fentanyl leads to shorter postoperative ventilation times and may be associated with a greater incidence of POCD 1 week after surgery. Early POCD is associated with an increased duration of stay in the hospital.**

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POSTOPERATIVE cognitive dysfunction (POCD) is a well-recognized complication of coronary artery bypass graft (CABG) surgery.[1] The association of POCD with CABG surgery led early researchers to infer that the etiology was related to the cardiopulmonary bypass (CPB) pump, which was a distinguishing feature of this surgery.[2]

The introduction of CABG surgery without CPB (off-pump surgery or OPCAB surgery) provided the opportunity to compare the neuropsychological effects of CABG surgery with and without CPB and thus verify the contribution of CPB to POCD. Contrary to expectations, in a well-conducted randomized controlled trial, Van Dijk *et al.*[3] demonstrated that POCD was still common after OPCAB surgery (21% at 3 months and 30.8% at 12 months), and this was not greatly decreased from the CPB group (29% at 3 months and 33.6% at 12 months).

The conclusions drawn from this study indicated that the etiology of POCD may not be directly attributable to CPB but, at least in part, may lie elsewhere. One likely candidate may be the anesthetic itself. In patients older than 55 yr undergoing anesthesia for noncardiac surgery, POCD is present in 25% at 7 days and 10% at 3 months.[4] However, anesthesia used for cardiac surgery generally differs from that used for noncardiac operations. One type of anesthetic used commonly for cardiac surgery is unique because it relies on high-dose opioids, prompting us to investigate this as a possible cause for the high incidence of POCD after CABG surgery.

Since the demonstration in 1969 that high-dose fentanyl anesthesia could provide relative circulatory stability,[5] opioids have been the mainstay of cardiac anesthesia. This contrasted sharply to general anesthesia for other types of surgery, which was based on either volatile or intravenous agents and used opioids in analgesic doses only. When used in high doses (*e.g.*, 50–150 μg/kg fentanyl), the anesthetic is called high-dose opioid anesthesia, and patients routinely need postoperative ventilation because of prolonged opioid-induced respiratory depression. However, because postoperative ventilation was already an expectation in the cardiac arena, high-dose opioid anesthesia was adopted readily. Despite the many publications investigating POCD after CABG surgery, the type and dose of anesthetic agent are rarely mentioned; therefore, investigators who had studied POCD were directly contacted, and replies were re-

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ceived indicating they had used doses of fentanyl ranging from 10 to 100 μg/kg.

Decreasing the dose of opioids and increasing the dose of other anesthetic agents allows earlier extubation and less time in intensive care. During the past 10 yr, this practice, known as "fast-track" anesthesia, has gained popularity. Further, it has been shown to be safe[6] and economical.[7] The current clinical acceptance of both high- and low-dose opioid anesthesia provided an ideal opportunity to investigate the effect of opioids on POCD.

In addition, opioids have been shown to produce limbic system damage in rats in doses that mimic those used in humans.[8] These observations have been supported by both *in vitro* evidence of apoptosis[9] and functional brain mapping in humans.[10] Thus, an investigation into the role played by opioids in POCD is warranted both on scientific and clinical grounds. We therefore undertook a multicenter, prospective, randomized, double-blind, controlled trial to compare the incidence of POCD in patients scheduled to undergo elective first-time CABG surgery receiving either high-dose or low-dose fentanyl anesthesia.

Materials and Methods

Subjects and Study Design

Eligible patients were aged 55 yr or older, were scheduled to undergo elective first-time CABG surgery, had no previous neurologic deficit, and were able to undergo neuropsychological testing. Patients who were not suitable for fast-track anesthesia and early extubation (*e.g.*, ejection fraction [EF] $< 30\%$, major systemic illness contraindicating early extubation) or in whom it was anticipated that neuropsychological assessment would be difficult (*e.g.*, English not the prime language, psychiatric illness) were excluded. The Institutional Ethics Committee at St. Vincent's Health (Fitzroy, Victoria, Australia) and the Alfred Hospital (Prahran, Victoria, Australia) approved the study, and written informed consent was obtained from all patients. Three hospitals participated.

Patients were randomized to high-dose fentanyl anesthesia of 50 μg/kg (HD group) or low-dose fentanyl of 10 μg/kg (LD group) using random number tables and stratification by institution (three sites). We further stratified patients into on-pump and OPCAB surgery groups before being randomized, because OPCAB surgery was becoming more frequent when the study began in 2001, and it was unclear whether this would have an effect on POCD. As the study progressed, OPCAB surgery fell out of favor, and at the end of the study, only 15 patients had been assigned to this group.

In both groups, premedication consisted of oral temazepam (10–20 mg) and ranitidine (150 mg). Intravenous midazolam (up to 0.1 mg/kg) was used as sedation for insertion of peripheral intravenous, arterial, and pulmonary artery catheters. Randomization was not revealed to the anesthesiologist until after the placement of invasive monitoring lines. The LD group was induced with 10 μg/kg fentanyl, and the HD group was induced with 50 μg/kg fentanyl. In both groups, propofol was used to supplement induction if indicated (up to 1 mg/kg), and muscle relaxants (rocuronium or vecuronium) were used only at induction for intubation. Maintenance of anesthesia was with propofol infusion (either target-controlled infusion up to 3 μg/ml or fixed-rate infusion up to 300 mg/h) and with the option of supplemental boluses of fentanyl (up to 2 μg/kg/dose) in the HD group. Dose adjustments were at the discretion of the anesthesiologist, according to evaluations of depth of anesthesia and hemodynamic assessments. The lungs were ventilated with oxygen and air (fraction of inspired oxygen approximately 0.6), and volatile agents were not used at any time.

Proximal anastomoses were performed under aortic cross clamping. For CPB, the circuit was primed with 2 l heparinized crystalloid solution (Plasma-lyte® 148; Baxter Healthcare, Old Toongabbie, NSW, Australia). Standard hemodynamic management involved maintaining mean arterial pressures of 60–80 mmHg with moderate body hypothermia (nasopharyngeal temperature 30°–34°C) and α-stat pH management. Hypotension on CPB was managed by increasing flows or using phenylephrine. Myocardial preservation involved tepid blood cardioplegia (approximately 25°C) given antegrade to induce asystole with subsequent doses administered retrograde at approximately 15-min intervals. Perfusion flow rates were 2.0–2.4 $l \cdot min^{-1} \cdot m^{-2}$ using nonpulsatile flow with either a centrifugal pump head (Medtronic Bio-Pump®, model 550 with a BP-80 head; Medtronic Australasia, Sydney, NSW, Australia) or a roller pump head (using 0.5-in PVC tubing; Cobe Cardiovascular, Inc., Arvada, CO). All circuits used a Cobe® Optima membrane oxygenator (Cobe Cardiovascular, Inc.) and a 40-μm arterial line filter. Rewarming was commenced at the completion of the final distal anastomosis (before proximal aortic grafting) and adjusted to achieve a nasopharyngeal temperature of not greater than 37°C at any time before weaning. After weaning from CPB, intravenous morphine (0.1 mg/kg) was used in the LD group to decrease early postoperative pain and facilitate early extubation. In both groups, ongoing postoperative pain relief consisted of a morphine infusion for the first 24 h, acetaminophen (with or without codeine) orally, and indomethacin orally or rectally.

For both groups, the threshold for treating hypotension was a systolic blood pressure of below 100 mmHg and was to be treated unless a lower blood pressure was required for surgical reasons (*e.g.*, aortic cannulation). Hypotension was treated initially with volume replacement and then ephedrine or metaraminol as indicated. Hypertension was treated by deepening anesthesia (*vide*

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supra) or with glyceryl trinitrate. Tachycardia was treated by deepening anesthesia or a β blocker, and bradycardia was treated with atropine, ephedrine, or pacing (after CPB). Preoperative left ventricular function was graded on a five-point scale (5 = normal; 4 = EF < 60% or left ventricular hypertrophy; 3 = EF < 45% or akinetic systolic wall motion abnormality; 2 = EF < 30%; 1 = EF < 25%).

Neuropsychological Testing

All patients completed a battery of eight neuropsychological tests administered by a trained interviewer who was blinded to the patient's allocation. This was done on four occasions:

1. Baseline tests: during the week before surgery
2. Early postoperative tests: 1 week (postoperative day 6) or before discharge if earlier than this
3. Intermediate postoperative tests: 3 months after surgery
4. Late postoperative tests: 12 months after surgery

The tests were selected because they had been used commonly and recommended in an expert consensus statement.[11] The test battery consisted of the Consortium to Establish a Registry for Alzheimer's Disease Auditory Verbal Learning Test, Digit–Symbol Substitution Test, Trail Making Test Parts A and B, Controlled Oral Word Association Test, Semantic Fluency Test, and the Grooved Pegboard Test (dominant and nondominant hands). All of these tests have been described elsewhere.[12,13] A brief description of the tests is appended (see appendix).

The presence of factors such as anxiety and depression may affect the diagnosis of POCD or may be a consequence of the same. Visual analog scales were used to assess anxiety and depression at each time of testing. These are especially suitable for this situation because they offer simple, reliable, and valid techniques for measuring anxiety and depression while placing minimal demands on patients.[14,15] Patients were asked to mark an ungraded line (10 cm in length) anchored by 0 and 100 at each end.

Absolute test scores were reversed for timed tasks so that a decrease implied cognitive decline for every test.

Adjustments were made to each individual's change in score (from baseline) at each testing time to account for systematic factors such as learning and practice effects. This was done by calculating the change in population score at each testing time from baseline (systematic population change) and subtracting this value from each individual's change score.[15,16]

Parallel forms were administered for the Consortium to Establish a Registry for Alzheimer's Disease Auditory Verbal Word Learning Test, and all the tests were administered in the same order. The National Adult Reading Test was used to estimate intelligence quotient[17] and was administered at the baseline assessment.

Common rules used to define neuropsychological impairment in each test include a decrease of 20% for each individual from baseline and a decrease of an individual's score of at least 1 SD of the baseline mean for all patients for the relevant test.[16,18] We chose to use the 20% rule but also analyzed the data using the 1 SD rule to define cognitive impairment in each test because this rule has recently been shown to be associated with fewer false positives.[19,20] POCD in each patient was defined as two or more abnormal test results.[21] Tests not attempted were treated as omissions and not as failures, and if less than two tests were completed at one time point, assessment for deficit at that time point was omitted.

Statistical Analysis

The sample size was based on a conservative population incidence of POCD of 30% at 1 week after surgery.[22] Assuming a 50% reduction in deficit to be clinically significant, 348 patients would need to be randomized to achieve power of 0.9 with a type I error of 0.05.

Group comparisons were made using unpaired *t* tests for continuous variables, Mann–Whitney U test for ranked data, and chi-square or Fisher exact test for dichotomous parameters. Associations were determined using univariate and multivariate logistic regression with a *P* value of less than 0.2 set for entry into multivariate regression. Odds ratios and 95% confidence intervals were determined for individual tests and combined outcomes. Changes over time were analyzed using analysis of variance (repeated measures where appropriate). Tests were performed using STATA (version 8.0; Stata Corporation, College Station, TX). A *P* value of less than 0.05 was taken to indicate significance.

Results

From June 2001 to December 2003, 1,985 patients scheduled to undergo elective CABG surgery were screened, and 420 met inclusion criteria. Of these, 70 declined entry, and the remaining 350 consented to the investigation and were randomized. Twenty-four patients were excluded from analysis, leaving 326 patients included in the final analysis, with 168 in the LD group and 158 in the HD group. The trial profile is summarized in figure 1. The mean age ± SD was 67.9 ± 7.6 yr.

Except for a higher proportion of females in the LD group, baseline characteristics were comparable between groups (table 1).

Intraoperatively, procedural times were longer in the HD group, with mean aortic cross-clamp time, CPB time, and surgical duration longer by 5.8, 6.6, and 11.4 min, respectively (*P* values all ≤ 0.02; table 2). There were a nonsignificantly higher number of distal graft anastomo-

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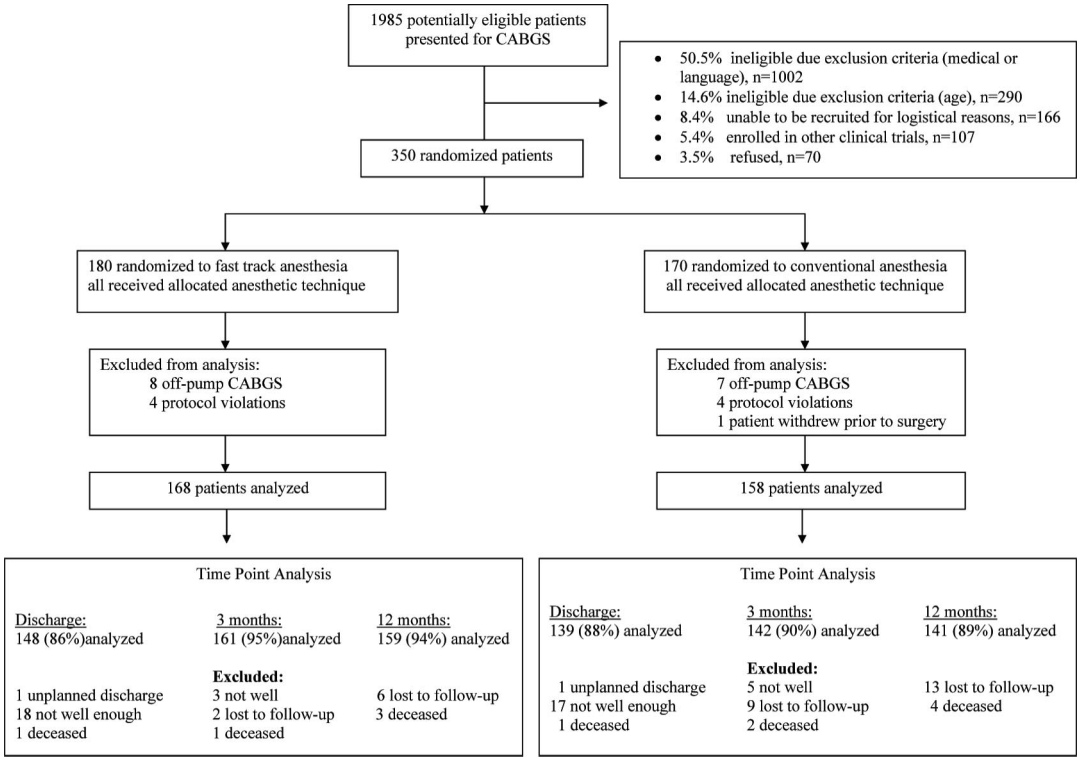

Fig. 1. Trial profile. CABGS = coronary artery bypass surgery.

ses in the HD group (table 2). There was no difference between groups in the dose of phenylephrine used to maintain blood pressure during CPB.

Doses of intraoperative fentanyl reflected treatment group. The mean intraoperative propofol dose in the LD group exceeded that in the HD group by 475 mg ($P < 0.001$; table 2).

Time to extubation was significantly longer in the HD group, with a difference in means of 4.6 h ($P = 0.004$; table 2). Time to discharge from the intensive care unit did not differ significantly between treatment groups, but the interquartile range reflects the practice of one hospital that used the intensive care unit as a step-down unit and electively kept patients there for a minimum of two nights.

There were no significant differences in testing times between groups. The mean ± SD time in days for testing at 1 week was 6.2 ± 1.7 for the LD group and 6.2 ± 1.2

Table 1. Patient Baseline Characteristics

	Low-dose Fentanyl (n = 168)	High-dose Fentanyl (n = 158)
Age, yr	68.0 ± 7.4	67.9 ± 7.8
Sex, M/F	122/46*	130/28
Height, cm	169.7 ± 9.0	170.9 ± 9.3
Weight, kg	81.3 ± 14.7	83.1 ± 14.2
Diabetes	40 (23.8)	47 (29.7)
Hypertension	117 (69.6)	115 (72.8)
Peripheral vascular disease	15 (8.9)	23 (14.6)
History of myocardial infarct	80 (47.6)	72 (45.6)
History of smoking	122 (66.7)	119 (75.3)
Hypercholesterolemia	125 (74.4)	121 (76.6)
Estimated IQ	108.4 ± 9.5	109.0 ± 10.0
Left ventricular function	4.1 ± 0.9	4.2 ± 0.9
Preoperative medications		
Aspirin	117 (70.1)	119 (75.3)
Clopidogrel	13 (7.8)	13 (8.2)
β Blocker	97 (58.1)	87 (55.1)
ACE inhibitors	54 (32.3)	62 (39.2)
Statins	103 (61.7)	102 (64.6)

Continuous variables are presented as mean ± SD, and categorical variables are presented as frequency (percentage). There were no significant differences between baseline characteristics except for sex (* $P = 0.037$).

ACE = angiotensin-converting enzyme; IQ = intelligence quotient.

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Table 2. Intraoperative Data, Perioperative Medications, and Postoperative Time Points

	Low-dose Fentanyl (n = 168)	High-dose Fentanyl (n = 158)	*P* Value
Cross clamp duration, min	75.7 ± 21.6	81.5 ± 22.1	0.020
Cardiopulmonary bypass duration, min	97.6 ± 24.6	104.2 ± 26.8	0.026
Surgery duration, min	259.5 ± 41.3	270.9 ± 44.3	0.017
Number of grafts	3 (3–4)	4 (3–4)	0.27
Midazolam, mg	2.4 ± 2.0	2.1 ± 1.8	0.11
Fentanyl, μg/kg	9.9 ± 1.1	50.0 ± 2.4	< 0.001
Propofol–intraoperative, mg	1,833 ± 648	1,358 ± 637	< 0.001
Propofol–ICU, mg	151 ± 287	300 ± 725	0.02
Propofol–total, mg	1,980 ± 703	1,663 ± 1,038	0.003
Morphine–ICU, mg	13.1 ± 15.4	8.7 ± 13.7	0.01
Time to extubation, h	7.1 (5.3–10.3)	11.1 (8.5–14.8)	< 0.001
Time to ICU discharge, h	22.0 (18.4–41.8)	22.6 (19.5–44.0)	0.11
Time to hospital discharge, days	7.0 (6.0–8.0)	7.0 (6.0–8.0)	0.68

Continuous data are presented as mean ± SD or median (interquartile range).

ICU = intensive care unit.

for the HD group, that for testing at 3 months was 102 ± 17.6 for the LD group and 101.1 ± 17.7 for the HD group, and that for testing at 12 months was 384 ± 27.3 for the LD group and 383 ± 30.0 for the HD group. The percentages of patients tested at these times were 88%, 93%, and 92%, respectively. Reasons for missed assessments are provided in figure 1.

The mean scores of each group for each test are listed in table 3. When analyzed according to group, there was a decline in both LD and HD performance in all tests at 1 week. However, there was a subsequent improvement in both LD and HD groups compared to baseline when tested at 3 and 12 months. All tests in each group changed significantly with time, but there were no significant differences in mean scores between treatment groups at each time interval.

When each individual was analyzed by the 20% rule, the incidence of POCD was equivalent in both treatment groups and higher than the 1 SD rule at all testing times. When analyzed by the 1 SD rule, the incidence of POCD was detected in significantly more patients in the LD group than the HD group at 1 week, but the incidence of

Table 3. Scores for Each Test

Test	Baseline	1 Week	3 Months	12 Months	*P* Value
AVLT, n					
LD	16.5 ± 3.7 (168)	15.8 ± 3.5 (148)	17.6 ± 3.6 (161)	17.9 ± 3.7 (159)	< 0.001
HD	16.1 ± 4.1 (158)	15.4 ± 3.8 (139)	17.1 ± 3.8 (142)	17.2 ± 3.7 (141)	< 0.001
DSST, n					
LD	34.8 ± 9.7 (168)	30.9 ± 10.2 (144)	37.5 ± 10.2 (161)	38.9 ± 10.9 (159)	< 0.001
HD	33.7 ± 10.3 (158)	29.8 ± 10.7 (138)	38.2 ± 11.1 (141)	37.1 ± 10.9 (141)	< 0.001
TMTA, s					
LD	55.0 ± 25.7 (168)	57.2 ± 30.4 (148)	50.1 ± 20.3 (161)	48.0 ± 18.1 (159)	< 0.001
HD	54.6 ± 23.6 (158)	60.3 ± 37.2 (139)	50.2 ± 19.7 (141)	50.8 ± 22.6 (140)	< 0.001
TMTB, s					
LD	125.7 ± 62.5 (168)	154.4 ± 115.3 (145)	114.8 ± 65.6 (161)	110.5 ± 58.1(158)	< 0.001
HD	127.5 ± 62.4 (158)	153.9 ± 94.7 (136)	114.3 ± 51.3 (142)	117.1 ± 58.9(141)	< 0.001
COWAT, n					
LD	33.1 ± 12.3 (168)	31.2 ± 13.4 (148)	35.2 ± 13.0 (161)	35.3 ± 12.0 (159)	< 0.001
HD	31.4 ± 11.3 (158)	30.2 ± 12.0 (137)	33.0 ± 12.2 (141)	33.4 ± 12.9 (141)	< 0.001
Sem, n					
LD	17.7 ± 4.6 (168)	15.7 ± 5.0 (146)	17.6 ± 4.7 (161)	17.4 ± 4.8 (159)	< 0.001
HD	17.1 ± 4.7 (158)	16.0 ± 5.3 (137)	17.3 ± 5.8 (141)	17.5 ± 5.1 (140)	< 0.001
GPd, s					
LD	99.7 ± 30.6 (165)	113.9 ± 49.9 (140)	92.4 ± 30.7 (157)	90.6 ± 30.7 (155)	< 0.001
HD	102.1 ± 34.5 (155)	116.2 ± 56.9 (134)	89.4 ± 26.7 (138)	91.6 ± 28.0 (138)	< 0.001
GPnd, s					
LD	110.2 ± 39.2 (166)	125.5 ± 52.7 (136)	103.5 ± 35.3 (157)	100.1 ± 34.3 (155)	< 0.001
HD	108.5 ± 37.8 (152)	124.5 ± 54.7 (129)	98.5 ± 28.8 (136)	98.6 ± 22.3 (136)	< 0.001

Test results are either number correct (n) or time taken (s). Data are presented as mean ± SD (number of patients tested). *P* value is for repeated-measures analysis of variance. There were no significant differences between treatment groups at any time point.

AVLT = Auditory Verbal Learning Test; COWAT = Controlled Oral Word Association Test; DSST = Digit–Symbol Substitution Test; HD = high-dose fentanyl group; GPd = Grooved Pegboard Dominant; GPnd = Grooved Pegboard Nondominant; LD = low-dose fentanyl group; Sem = Semantic Fluency Test; TMTA = Trail Making Test A; TMTB = Trail Making Test B.

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Table 4. Proportion of Patients with Postoperative Cognitive Dysfunction

	1 Week		3 Months		12 Months	
	20% Rule	1 SD Rule	20% Rule	1 SD Rule	20% Rule	1 SD Rule
Low-dose fentanyl	95/149	35/148	30/161	20/161	42/159	24/159
	63.8%	23.6%	18.6%	12.4%	26.4%	15.1%
High-dose fentanyl	88/139	19/139	38/142	19/142	34/141	18/141
	63.3%	13.7%	26.8%	13.4%	24.1%	12.8%
Difference (95% CI)	0.5% (−1.1 to 11.6%)	9.9% (1.1 to 18.9%)	−8.2% (−17.6 to 1.2%)	−1.0% (−8.5 to 6.6%)	2.3% (−7.5 to 12.1%)	2.3% (−5.5 to 10.2%)
P value	0.93	0.031	0.09	0.24	0.65	0.62

Data are presented as number of patients and percentage in each group with postoperative cognitive dysfunction at each time of testing.
CI = confidence interval.

POCD was equivalent at later testing times (3 and 12 months) (table 4).

Because the 1 SD rule leads to fewer false positives than the 20% rule, patients determined to have POCD by this rule were analyzed for associated factors. Stepwise multivariate logistic regression for POCD was undertaken at each time point for factors shown previously to correlate with POCD (*e.g.*, age, intelligence quotient, depression, CPB duration) and for factors that showed a *P* value for association on unpaired *t* test or Fisher exact test of less than 0.2. The results are shown in table 5. Odds ratios for factors with a *P* value of less than 0.05 on multivariate regression are also shown. The LD group had a significantly higher incidence of POCD than the HD group at 1 week ($P = 0.025$; odds ratio, 2.15 [95% confidence interval, 1.1–4.19]). This effect was not seen at the later testing times. Age was associated with POCD at 1 week and 12 months but not 3 months. At 3 months, the only factor associated with POCD was a higher total propofol dose ($P = 0.04$; odds ratio, 1.05 [95% confi-

Table 5. Predictors of Postoperative Cognitive Dysfunction

	Univariate *P* Value	Multivariate *P* Value	Odds Ratio
1 Week			
Low fentanyl dose	0.031	0.025	2.15 (1.10–4.19)
Lower left ventricular function	0.183	0.243	
High total propofol dose, mg/kg	0.593		
High ICU morphine dose	0.264		
Longer CPB time	0.239		
Increased duration of surgery	0.671		
Older age	0.003	0.030	1.05 (1.005–1.096)
IQ, NART	0.486		
Higher baseline depression score	0.071	0.158	
Midazolam dose	0.066	0.633	
3 Months			
Low fentanyl dose	0.740		
Lower left ventricular function	0.715		
High total propofol dose, mg/kg	0.076	0.040	1.05 (1.002–1.091)
High ICU morphine dose	0.817		
Longer CPB time	0.147	0.271	
Increased duration of surgery	0.184	0.830	
Older age	0.018	0.071	
IQ, NART	0.864		
Higher baseline depression score	0.728		
Midazolam dose	0.330		
12 Months			
Low fentanyl dose	0.636		
Lower left ventricular function	0.606		
High total propofol dose, mg/kg	0.417		
High ICU morphine dose	0.718		
Longer CPB time	0.360		
Increased duration of surgery	0.749		
Older age	0.101	0.043	1.05 (1.001–1.098)
IQ, NART	0.887		
Higher baseline depression score	0.346		
Midazolam dose	0.871		

CPB = cardiopulmonary bypass; ICU = intensive care unit; IQ, NART = estimated intelligence quotient from National Adult Reading Test.

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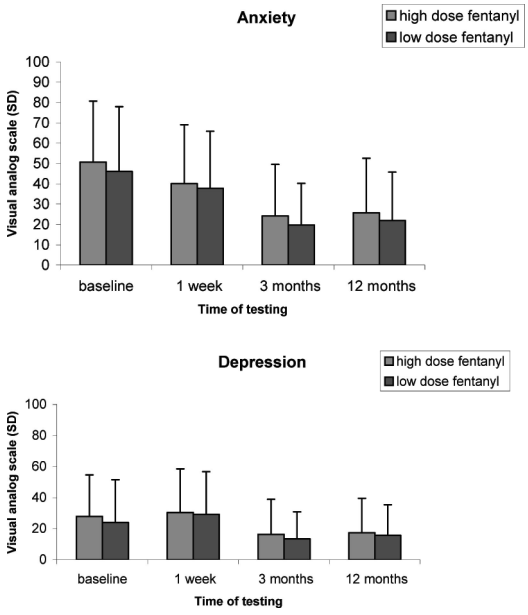

Fig. 2. Anxiety and depression visual analog scales.

dence interval, 1.002–1.091]). At 12 months, age was the only factor associated with POCD. Despite an imbalance in sex ratio between groups, neither univariate nor multivariate regression showed that sex was associated with POCD at any time.

Baseline anxiety and depression did not differ between groups (fig. 2). Patients with POCD reported higher levels of depression (mean ± SD) at 1 week (visual analog score, 38.6 ± 30.6 *vs.* 27.9 ± 26.6; $P = 0.01$) and at 12 months (visual analog score, 23.2 ± 25.2 *vs.* 15.4 ± 20.0; $P = 0.02$). Baseline depression was not predictive of POCD at any time point on univariate or multivariate regression (table 5).

Although duration of hospital stay was not significantly associated with treatment group, patients with POCD at 1 week spent an average of 1.2 days longer in the hospital (mean ± SD for no POCD 7.1 ± 3.4 *vs.* POCD 8.3 ± 4.1; $P = 0.02$).

As noted, seven patients died during the course of the study (fig. 1). Two developed acute perioperative cardiac complications and did not complete any postoperative tests and were thus excluded from analysis. The remaining five died during the postdischarge follow-up period. There were two postoperative strokes, one presenting as hemianopia at postoperative day 2 and the other as a mild hemiparesis 2 months postoperatively. Both patients were retained in the study and completed their subsequent assessments.

Discussion

We compared two common approaches to anesthesia for cardiac surgery and studied the incidence of POCD associated with each. There was no difference in the incidence of POCD as defined by either the 20% rule or the 1 SD rule at 3 and 12 months after surgery. The 1 SD rule, which leads to fewer false-positive classifications, detected a higher incidence of POCD at 1 week after surgery in patients receiving low-dose fentanyl compared with those receiving high-dose fentanyl. Early cognitive assessment is confounded by many factors relating to recent surgery, drug administration, and the stress response, making the relation to longer-term POCD difficult to interpret.[1]

We chose to analyze the test results using both the 20% rule and the 1 SD rule. A previous study on cognitive decline after CABG surgery by Van Dijk *et al.* used the 20% rule to define the incidence of POCD.[3] Recently, that group reanalyzed their data using the 1 SD rule and showed that the reported incidence of POCD at 3 months decreased from 25% to 10.5%.[19] These results are comparable to our combined group data when analyzed by each rule (22.4% and 12.8% at 3 months). We have recently shown that, in the absence of a control group, the 1 SD rule has fewer false positives than the 20% rule.[20] This explains the lower rates of POCD found when the 1 SD rule is used to define cognitive dysfunction. For this reason, we chose to use the incidence of POCD as defined by the 1 SD rule for exploratory analysis using logistic regression.

In this study, complete avoidance of volatile anesthetic agents removes the potential confounding effect of these agents as factors in the etiology of POCD.

Postoperative cognitive dysfunction after CABG surgery has been the subject of many investigations. The association of POCD with CABG surgery led early researchers to infer that the etiology was related to the CPB pump. This explanation was compatible with the concept of cerebral microemboli (platelet aggregates, atheroma, fat, or gas) leading to cerebral micropathology, which was not severe enough to cause a stroke but presumably large enough to clinically manifest as POCD. Attempts to implicate the particular facet of the CPB responsible have focused on nearly every aspect of CPB. Therefore, in turn, bubble oxygenators,[23] centrifugal pumps,[15] arterial filters,[24] hypothermia,[25] and α-stat pH management[26] have all been investigated in the etiology of POCD. Some of these studies have demonstrated factors associated with POCD, but none have been solely or consistently implicated. Although opioids have been associated with neurotoxicity, the role of fentanyl in POCD has not been studied previously.

It is unclear why the HD group showed less cognitive deficit at 1 week compared with the LD group, using the 1 SD rule. This difference was not found in individual analysis using the 20% rule. The result may be spurious, but if it is true, it contradicts the original assumption that fentanyl may compromise cognitive function. Although high-dose fentanyl has not been shown to injure the ischemic brain in rats,[27] there is no evidence in the literature to suggest that high fentanyl doses are protective. We identified significant

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differences in total perioperative drug doses of morphine and propofol between treatment groups, but these did not show an independent association with POCD, indicating the difference in POCD was unlikely to be the result of residual drug effects. A possible explanation may lie in the well-known ability of high-dose fentanyl to obtund the stress response. The International Study of Post-Operative Cognitive Dysfunction investigators have recently shown that cortisol secretion is related to POCD in noncardiac surgery.[28] If this situation is transferable to CABG surgery, fentanyl may play a preventative role on the development of early POCD. At any rate, the presence of POCD at 1 week may reflect factors that do not play a part in longer-term POCD.

Patients with early POCD spent an average of 1.2 days longer in the hospital compared with those with normal cognitive function. The delay in the hospital discharge reflects the important influence of early POCD. The results of testing were not analyzed until after study completion, and so the presence of a diagnosis of early POCD was not known to the staff caring for the patients. The association suggests that behavioral factors resulting from the presence of early POCD may have influenced hospital stay, which has both practical and economic implications. This finding may also reflect that sicker patients are more likely to have early POCD, although patients too unwell to be assessed were excluded from analysis at this time (fig. 1).

In addition to the immediate consequences of POCD on discharge times, it is important to realize that early POCD may be associated with longer-term sequelae. Newman *et al.*[18] have shown that cognitive deficit 5 yr after CABG surgery was related to POCD at discharge but not at intervening times. Therefore, the results of cognitive testing at 1 week after surgery may have implications for long-term cognition.

Multivariate analysis confirmed the association of low-dose fentanyl with POCD found at 1 week on univariate analysis. Age was associated with POCD on univariate analysis at each time point and also by multivariate analysis at 1 week and 12 months. Age has been consistently associated with POCD in most studies.[29]

The small but significant difference in procedural times between HD and LD groups related to an imbalance of the number of distal anastomoses, despite randomization. The magnitude of this prolongation was not great (mean CPB time 6.5 min greater in the HD group) and unlikely to be of clinical importance.

This trial is distinguished by a large patient sample and low losses to follow-up compared with similar studies. Many longitudinal studies involving neuropsychological testing exhibit markedly incomplete follow-up. Of 172 enrolled patients, McKhann *et al.* lost 26% to follow up after 1yr.[30] Millar *et al.*[31] were able to follow-up 81 of 120 patients over a 6-month period (a loss of 33%). The best retention rates reported are those of the Octopus study group,[3] who lost 12% and 10% of patients at 3- and 12-months of follow-up, respectively (n = 281). Clearly, loss to follow-up is a major concern because cognitive impairment cannot be ruled out as a contributing factor. This problem undermines the validity of many previous longitudinal studies, whereas our very high retention lends credibility to our results. Therefore, although we did not show a difference between groups in the incidence of POCD at 3 and 12 months, the pooled POCD incidences of 12.8% and 14% at these times provide important information.

In conclusion, we found no evidence that high-dose fentanyl is associated with an increased incidence of POCD at 3 or 12 months after CABG surgery. Low-dose fentanyl, which is the basis of fast-track anesthesia, may be associated with an increased incidence of POCD at 1 week after surgery. We have also shown that early POCD is associated with an increased duration of stay in the hospital.

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References

1. Selnes OA, McKhann GM: Cognitive changes after coronary artery bypass surgery. Curr Opin Psychiatry 2002; 15:285–90
2. Shaw PJ, Bates D, Cartlidge NE, French JM, Heaviside D, Julian DG, Shaw DA: Neurologic and neuropsychological morbidity following major surgery: Comparison of coronary artery bypass and peripheral vascular surgery. Stroke 1987; 18:700–7
3. Van Dijk D, Jansen EW, Hijman R, Nierich AP, Diephuis JC, Moons KG, Lahpor JR, Borst C, Keizer AM, Nathoe HM, Grobbee DE, De Jaegere PP, Kalkman CJ: The Octopus Study: Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: A randomized trial. JAMA 2002; 287:1405–12
4. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS: Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. Lancet 1998; 351:857–61
5. Lowenstein E, Hallowell P, Levine FH, Daggett WM, Austen WG, Laver MB: Cardiovascular response to large doses of intravenous morphine in man. N Engl J Med 1969; 281:1389–93
6. Silbert BS, Santamaria JD, O'Brien JL, Blyth CM, Kelly WJ, Molnar RR: Early extubation following coronary artery bypass surgery: A prospective randomized controlled trial. Chest 1998; 113:1481–8
7. Cheng DC, Karski J, Peniston C, Raveendran G, Asokumar B, Carroll J, David T, Sandler A: Early tracheal extubation after coronary artery bypass graft surgery reduces costs and improves resource use: A prospective, randomized, controlled trial. ANESTHESIOLOGY 1996; 85:1300–10
8. Kofke WA, Garman RH, Stiller RL, Rose ME, Garman R: Opioid neurotoxicity: Fentanyl dose-response effects in rats. Anesth Analg 1996; 83:1298–306
9. Sloviter RS, Dean E, Sollas AL, Goodman JH: Apoptosis and necrosis induced in different hippocampal neuron populations by repetitive perforant path stimulation in the rat. J Comp Neurol 1996; 366:516–33
10. Kofke WA, Attaallah AF, Kuwabara H, Garman RH, Sinz EH, Barbaccia J, Gupta N, Hogg JP: The neuropathologic effects in rats and neurometabolic effects in humans of large-dose remifentanil. Anesth Analg 2002; 94:1229–36
11. Murkin JM, Newman SP, Stump DA, Blumenthal JA: Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. Ann Thorac Surg 1995; 59:1289–95
12. Collie A, Shafiq-Antonacci R, Maruff P, Tyler P, Currie J: Norms and the effects of demographic variables on a neuropsychological battery for use in healthy ageing Australian populations. Aust N Z J Psychiatry 1999; 33:568–75
13. Lezak M: Neuropsychological Assessment. Oxford, Oxford University Press, 1995
14. McCormack H, Sheather S: Clinical application of visual analogue scales: A critical review. Psychol Med 1988; 18:1007–1019
15. Scott DA, Silbert BS, Doyle TJ, Blyth C, Borton MC, O'Brien JL, Horne DJ: Centrifugal *versus* roller head pumps for cardiopulmonary bypass: Effect on early neuropsychologic outcomes after coronary artery surgery. J Cardiothorac Vasc Anesth 2002; 16:715–22
16. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT:

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The assessment of postoperative cognitive function. Acta Anaesthesiol Scand 2001; 45:275–89

17. Nelson H: National Adult Reading Test (NART) for the Assessment of Premorbid Intelligence in Patients with Dementia: Test Manual. Windsor, England, Psychological Corporation, 1992

18. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA: Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001; 344:395–402

19. Keizer AM, Hijman R, Kalkman CJ, Kahn RS, van Dijk D: The incidence of cognitive decline after (not) undergoing coronary artery bypass grafting: The impact of a controlled definition. Acta Anaesthesiol Scand 2005; 49:1232–5

20. Lewis M, Maruff P, Silbert B, Evered L, Scott D: The sensitivity and specificity of three common statistical rules for the classification of post-operative cognitive dysfunction following coronary artery bypass graft surgery. Acta Anaesthesiol Scand 2006; 50:50–7

21. Van Dijk D, Keizer AM, Diephuis JC, Durand C, Vos LJ, Hijman R: Neurocognitive dysfunction after coronary artery bypass surgery: A systematic review. J Thorac Cardiovasc Surg 2000; 120:632–9

22. Symes E, Maruff P, Ajani A, Currie J: Issues associated with the identification of cognitive change following coronary artery bypass grafting. Aust N Z J Psychiatry 2000; 34:770–84

23. Blauth CI, Smith PL, Arnold JV, Jagoe JR, Wootton R, Taylor KM: Influence of oxygenator type on the prevalence and extent of microembolic retinal ischemia during cardiopulmonary bypass: Assessment by digital image analysis. J Thorac Cardiovasc Surg 1990; 99:61–9

24. Aris A, Solanes H, Camara ML, Junque C, Escartin A, Caralps JM: Arterial line filtration during cardiopulmonary bypass: Neurologic, neuropsychologic, and hematologic studies. J Thorac Cardiovasc Surg 1986; 91:526–33

25. Mora CT, Henson MB, Weintraub WS, Murkin JM, Martin TD, Craver JM, Gott JP, Guyton RA: The effect of temperature management during cardiopulmonary bypass on neurologic and neuropsychologic outcomes in patients undergoing coronary revascularization. J Thorac Cardiovasc Surg 1996; 112:514–22

26. Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ: A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery: I. Mortality and cardiovascular morbidity. J Thorac Cardiovasc Surg 1995; 110:340–8

27. Morimoto Y, Morimoto Y, Bart R, Pearlstein R, Dexter F, Warner D: High-dose fentanyl does not adversely affect outcome from forebrain ischemia in the rat. J Neurosurg Anesth 1997; 9:316–23

28. Rasmussen LS, O'Brien JT, Silverstein JH, Johnson TW, Siersma VD, Canet J, Jolles J, Hanning CD, Kuipers HM, Abildstrom H, Papaioannou A, Raeder J, Yli-Hankala A, Sneyd JR, Munoz L, Moller JT: Is peri-operative cortisol secretion related to post-operative cognitive dysfunction? Acta Anaesthesiol Scand 2005; 49:1225–31

29. Newman S, Stygall J: Changes in cognition following cardiac surgery. Heart 1999; 82:541–2

30. McKhann GM, Goldsborough MA, Borowicz LM, Selnes OA, Mellits ED, Enger C, Quaskey SA, Baumgartner WA, Cameron DE, Stuart RS, Gardner TJ: Cognitive outcome after coronary artery bypass: A one-year prospective study. Ann Thorac Surg 1997; 63:510–5

31. Millar K, Asbury AJ, Murray GD: Pre-existing cognitive impairment as a factor influencing outcome after cardiac surgery. Br J Anaesth 2001; 86:63–7

Appendix

The neuropsychological tests used in the current study have been discussed in detail previously, and a reference is given for each test. Briefly, eight tests were given to all patients. These were as follows:

1. The Consortium to Establish a Registry for Alzheimer's Disease Auditory Verbal Learning Test requires patients to listen to a list of 10 words read to them by the examiner and then to immediately recall as many of those words as possible. This procedure is repeated three times with the same word list, with the order of word presentation changed on each occasion. After a 10-min delay filled with other cognitive tasks, patients must recall as many words from the word list as possible. The number of words recalled at this point is measured.
2. The Digit–Symbol Substitution Test from the Wechsler Adult Intelligence Scale–Revised requires patients to reproduce on paper, within 90 s, as many coded symbols as possible in blank boxes beneath randomly generated digits, according to a coding scheme for pairing digits with symbols. The number of boxes completed in 90 s is counted, and errors are deducted from this.
3. The Trail Making Test Part A requires patients to connect numbered circles in sequence as quickly as possible. The number of seconds required to complete the task is measured.
4. The Trail Making Test Part B requires patients to connect a series of circles that contain a sequence of numbers and letters in the correct but alternating order (*i.e.*, numeric and alphabetical). The number of seconds required to complete the task is measured.
5. The Controlled Oral Word Association Test consists of presenting the patient with a letter and asking the patient to spontaneously generate as many words as possible for the given letter within 60 s. This task is repeated for three separate letters (F-A-S).
6. The Semantic Fluency test requires patients to name as many words as possible from a predefined category (*e.g.*, animals, clothing, first names) within 60 s. The number of words correctly named from the relevant category is measured.
7. The Grooved Pegboard Dominant Hand requires patients to place 25 keyed pegs in an array of holes with randomly oriented slots using only their dominant hand. The number of seconds required to complete the task is measured.
8. The Grooved Pegboard Nondominant Hand requires patients to place 25 keyed pegs in an array of holes with randomly oriented slots using only their nondominant hand. The number of seconds required to complete the task is measured.

The National Adult Reading Test was given to all patients on the first assessment to provide an estimate of intelligence. The test requires patients to read and pronounce a series of words of increasing difficulty. The correct pronunciation is taken to indicate knowledge of the meaning of that word. The number of words pronounced correctly, the number of errors made, and years of education are used to calculate a summary intelligence quotient score.

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