# Comparative Effects of Propofol Versus Fentanyl on Cerebral Oxygenation State During Normothermic Cardiopulmonary Bypass and Postoperative Cognitive Dysfunction

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*Background.* **The purpose of this study was to examine the comparative effects of propofol and fentanyl on cerebral oxygenation during normothermic cardiopulmonary bypass and postoperative cognitive dysfunction.**

*Methods.* **One hundred eighty patients scheduled for elective coronary artery bypass grafting were randomly divided into two groups: propofol group (n = 90) and fentanyl group (n = 90). After induction of anesthesia, a fiberoptic oximetry oxygen saturation catheter was inserted into the right jugular bulb to monitor jugular venous oxygen hemoglobin saturation continuously. Hemodynamic measurements and arterial and jugular venous blood gases were measured at seven time points. All patients underwent a battery of neurologic and neuropsychological tests on the day before the operation and at 6 months after the operation.**

*Results.* **Cerebral desaturation (defined as a jugular venous oxygen hemoglobin saturation value less than 50%) during cardiopulmonary bypass was more frequent in the fentanyl group than in the propofol group. Cerebral desaturation time (duration when jugular venous oxygen hemoglobin saturation was less than 50%) and the ratio of cerebral desaturation time to total cardiopulmonary bypass time in the fentanyl group differed significantly from those in the propofol group (fentanyl group: 27 ± 14 minutes, 20% ± 9%; propofol group: 18 ± 11 minutes, 14% ± 7%, respectively, $p < 0.05$). There was no significant difference in postoperative cognitive dysfunction at 6 months after operation between the two groups (propofol group: 5 of 77, 6%; fentanyl group: 5 of 75, 7%).**

*Conclusions.* **Propofol preserved cerebral oxygenation state estimated by jugular venous oxygenation during cardiopulmonary bypass compared with the fentanyl group. However, propofol did not affect postoperative cognitive dysfunction.**

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Central nervous system complications continue to be a major cause of morbidity and mortality after cardiac surgical procedures [1]. Neuropsychological dysfunction after cardiopulmonary bypass (CPB) has been reported in as many as 79% of patients during the early postoperative period [2].

Several studies have attempted to identify intraoperative factors of cognitive change after CPB [3, 4]. Two possible mechanisms of postoperative cognitive dysfunction are cerebral ischemia and cerebral desaturation as a result of hypoperfusion during CPB [1]. Croughwell and colleagues [3] reported that lower values for internal jugular venous oxygen hemoglobin saturation ($SjvO_2$) at the end of rewarming were associated with cognitive deficits 4 to 8 days after operation. They suggested the importance of assessing the cerebral oxygenation state estimated by $SjvO_2$ during CPB.

Recently, several studies have attempted to improve cerebral oxygenation during CPB. Hanel and associates [5] reported that mild hypercapnia (arterial carbon dioxide pressure from 43.6 mm Hg to 48.6 mm Hg) during the rewarming period could prevent the cerebral desaturation state. However, they did not examine whether this hypercapnia during the rewarming period could improve postoperative cognitive dysfunction. Roach and coworkers [6] reported that a propofol-induced burst suppression did not lead to better neurologic or neuropsychological outcome than did opiate-based anesthesia in patients undergoing valve operations. Subjects in the study by Roach and associates [6] were undergoing cardiac valve operations, not coronary artery bypass grafting (CABG). It is generally accepted that the incidence of postoperative cognitive dysfunction differs between valve operation patients and CABG patients [1]. Inasmuch as the number of patients undergoing CABG is increasing [1], it would be more important to determine whether an anesthetic regimen could improve cerebral oxygenation during CPB.

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There have been two reports describing the comparative effects of propofol anesthesia and opiate-based anesthesia on postoperative cognitive dysfunction during hypothermic CPB [7, 8]. However, there has been no comparative study regarding the effects of propofol anesthesia and opiate-based anesthesia on $SjvO_2$ and postoperative cognitive dysfunction during normothermic CPB, which has been widely used in recent years during cardiac surgical procedures [2].

The purpose of this study was to examine the comparative effects of propofol and fentanyl on cerebral oxygenation during normothermic CPB and postoperative cognitive dysfunction.

## Patients and Methods

The study protocol was approved by the ethics committee of our institution, and written informed consent was obtained from all patients. One hundred eighty patients consecutively scheduled for elective CABG were studied. Patients with a history of cerebrovascular disease, diabetes, psychiatric illness, renal disease (creatinine concentration $>$ 2.0 mg/dL), or active liver disease (glutamine oxaloacetate transaminase or glutamine pyruvate transaminase $>$ 40 U/dL) were excluded. Patients with moderate or severe atherosclerotic lesions in the ascending aorta or carotid artery stenosis confirmed by preoperative ultrasonography and magnetic resonance imaging were also excluded.

Patients were randomly divided into two groups; a propofol group (n = 90), in which patients received 4 to 6 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol infusion using a syringe pump continuously until arriving in the intensive care unit, and a fentanyl group (n = 90), in which patients received 40 to 70 $\mu$g/kg (mean average, 58.1 $\pm$ 15.2 $\mu$g/kg, $\pm$ standard deviation) of fentanyl infusion. A bispectral index (BIS) monitoring (Aspect Medical Systems, Natick, MA) electrode was attached to the forehead of the patient as instructed by the manufacturer. The anesthetic dosage for each group was defined as that which did not induce hypotension, but which produced an equivalent anesthetic depth during CPB in each group, as measured by BIS monitoring. We did not induce burst-suppression in the propofol group, because the burst-suppression dosage of propofol induced massive hypotension.

All patients received 10 mg of diazepam by mouth 1 hour before anesthesia. Anesthesia was induced by 0.3 mg/kg midazolam, 10 $\mu$g/kg fentanyl, and 0.2 mg/kg vecuronium, and the trachea was intubated. After induction of anesthesia, a pulmonary arterial catheter (Vigilance, Swan-Ganz CCO Thermodilution Catheter, Baxter, Irvine, CA) was inserted through the right internal jugular vein. For continuous monitoring of $SjvO_2$, a 4.0F fiberoptic oximetry oxygen saturation catheter (dual-lumen oximetry catheter, Baxter) was inserted into the right jugular bulb using a modified Seldinger technique. This catheter was connected to an analysis system (Explorer System, Baxter) and calibrated in vivo by drawing a blood sample from the catheter. The position of the jugular bulb catheter was verified by roentgenogram. The correctly positioned catheter tip should be placed cranial to a line extending from the atlantooccipital joint space and caudal to the lower margin of the orbit. Jugular venous oxygen hemoglobin saturation was collected and processed in a monitor–computer interface and displayed and stored every 5 seconds on an Apple Macintosh computer (Apple Computer, Cupertino, CA).

Partial pressures of the arterial and jugular venous blood gases were analyzed using CO-oximeter (OSM3, Hemoximeter, Radiometer Co, Copenhagen). All patients were ventilated with oxygen 50% and nitrogen 50%. End-tidal carbon dioxide was monitored (Ultima, Datex, Helsinki, Finland) and maintained between 35 and 40 mm Hg. Muscular relaxation was maintained by intermittent administration of vecuronium. No volatile anesthetic was administrated. After the onset of CPB, 0.2 mg/kg midazolam was infused into all patients. The tympanic temperature was continuously monitored by Mon-a-Therm (Mallinckrodt Co, St. Louis, MO).

Cardiopulmonary bypass was primed with a crystalloid, nonglucose-containing solution, and a nonpulsatile pump flow rate of 2.2 to 2.5 $L \cdot min^{-1} \cdot m^{-2}$ was maintained. A membrane oxygenator and a 40-$\mu$m arterial line filter were used, and arterial carbon dioxide tension uncorrected for temperature was adjusted to normocapnic levels (35 to 40 mm Hg) by varying fresh gas flow to the membrane oxygenator ($\alpha$-stat regulation).

Target nasopharyngeal temperatures during CPB were more than 35°C. The limit on maximal inflow temperature was set at 37.5°C.

Hematocrit was maintained at more than 20% on CPB, with the addition of blood as necessary. Phenylephrine infusions were used during CPB to maintain mean arterial pressure at 50 to 80 mm Hg. Intermittently, antegrade blood cardioplegia was administrated at 37°C. Distal coronary anastomoses and proximal anastomoses were performed during a single aortic cross-clamp.

During the CPB period, BIS scores were measured continuously as a monitor of depth of anesthesia. Hemodynamic measurements and arterial and jugular venous blood gases were measured at the following times: (1) after induction of anesthesia and before the start of the surgical procedure, (2) at the onset of CPB, (3) 20 minutes after the onset of CPB, (4) 40 minutes after the onset of CPB, (5) 60 minutes after the onset of CPB, (6) at the cessation of CPB, and (7) at the end of the operation.

Intraoperative epiaortic ultrasonography confirmed that none of the patients had moderate or severe atherosclerotic lesions in the ascending aorta.

Critically low SjvO2 values ($<$50%) found in normothermic, awake humans account for cerebral dysfunction and electroencephalographic slowing [9, 10]. In addition, Gopinath and associates [11] showed that an $SjvO_2$ less than 50% for more than 10 minutes during intensive therapy care of patients with severe head injuries was strongly associated with a poor neurologic outcome. Thus, we defined cerebral desaturation as a $SjvO_2$ less than 50%.

### *Neurologic and Neuropsychologic Assessments*

All patients underwent a battery of neurologic and neuropsychological tests on the day before the operation and at 6 months after the operation, administered by trained specialists. The examiners who administrated the cognitive tests were unaware of the patient's intraoperative treatment assignment (propofol or fentanyl).

The neuropsychological portion of the study design followed the consensus statements on the assessment of central nervous system disorders after cardiac surgery [12].

Cognitive functioning was assessing using the following tests: (1) Mini-Mental Test, (2) Rey Auditory Verbal Learning Test, (3) Trail-Making Test (part A), (4) Trail-Making Test (part B), (5) digit span forward, and (6) grooved pegboard.

### *Statistical Analysis*

All data are expressed as mean ± standard deviation. After confirmation of equal variance among the groups by the Bartlett test, two-way repeated measures analysis of variance was performed for multiple comparisons. With a significant $F$ value, the Bonferroni method was used for multiple comparisons. To eliminate a type II error, each individual $p$ value was adjusted. Cerebral desaturation states in the two groups were analyzed using an unpaired Student's $t$ test. Difference between the preoperative values and those at 6 months after the operation on neuropsychologic tests was assessed with a paired Student's $t$ test. To obtain an indicator of outcome overall, significant impairment was defined as a decline from preoperative testing of more than one standard deviation on more than 20% of test measures (at least two of six). A multivariable logistic regression with odds ratio was used to examine the predictive variables of adverse outcome at 6 months. After the study was completed, the sample size was evaluated. Based on our previous report [4, 13], we considered a 20% reduction of cognitive dysfunction to be clinically important. The sample size provides 80% power to detect a 20% difference between groups with a 5% probability of a type I error.

Statistical significance was set at $p$ less than 0.05. All calculations were performed on a Macintosh computer with SPSS (SPSS, Inc, Chicago, IL) and StatView 5.0 software packages (Abacus Concepts, Inc, Berkeley, CA).

## Results

Table 1 shows demographic data from the two groups. There were no significant differences between the two groups except for phenylephrine dosage.

Table 2 shows variables from the two groups. Mean arterial pressure and hemoglobin concentration decreased during the CPB period in the two groups. There were no differences in mean arterial pressure, cardiac index, arterial carbon dioxide tension, or hemoglobin between the two groups during the study. Figure 1 shows the time course for changes in $SjvO_2$ values in the two groups. The $SjvO_2$ value in the fentanyl group had decreased at 20 minutes after the onset of CPB compared with at the induction of anesthesia ($p < 0.05$). Also, there was a significant difference in $SjvO_2$ value between the two groups ($p < 0.05$).

*Table 1. Demographic Data*[a]

| Characteristic | Propofol Group | Fentanyl Group | $p$ Value |
|---|---|---|---|
| Age (year) | 64 ± 8 | 66 ± 10 | 0.79 |
| Height (cm) | 163 ± 11 | 164 ± 10 | 0.81 |
| Weight (kg) | 63 ± 7 | 62 ± 10 | 0.88 |
| LVEF (%) | 59 ± 8 | 62 ± 9 | 0.44 |
| Male/female | 69/21 | 67/23 | |
| Hypertension | 56 (62%) | 61 (67%) | 0.37 |
| Smoking | 31 | 33 | 0.66 |
| Preoperative hemoglobin (g/dL) | 13.9 ± 2.0 | 14.1 ± 1.9 | 0.62 |
| Phenylephrine dosage (mg) | 4.9 ± 3.1 | 3.9 ± 2.9 | 0.005[b] |
| Total CPB time (min) | 129 ± 28 | 132 ± 31 | 0.49 |
| Aortic clamping time (min) | 100 ± 26 | 108 ± 22 | 0.50 |

[a] Values are mean ± standard deviation. [b] $p < 0.05$ compared with propofol group.

CPB = cardiopulmonary bypass; LVEF = left ventricular ejection fraction.

Table 3 shows cerebral desaturation data from patients whose $SjvO_2$ values decreased to less than 50% during CPB. Cerebral desaturation (defined as an $SjvO_2$ value below 50%) during CPB was more frequent in the fentanyl group than in the propofol group. Cerebral desaturation time (duration when $SjvO_2$ was <50%) and the ratio of cerebral desaturation time to total CPB time in the fentanyl group differed significantly from those in the propofol group (fentanyl group, 27 ± 14 minutes, 20% ± 9%; propofol group, 18 ± 11 minutes, 14% ± 7%; $p < 0.05$; Table 3).

Oxygen saturation values measured by the optical catheter ($SjvO_2$) and in sampled blood measured by the blood gas analyzer were compared. Jugular venous oxygen hemoglobin saturation and oxygen saturation in sampled blood correlated well ($y = 12.771 + 0.716x$; $r^2 = 0.606$; $p < 0.0001$).

There was no significant difference in BIS between groups during the CPB period (fentanyl group, 50 ± 11; propofol group, 47 ± 9; $p = 0.53$).

Major neurologic defects (defined as clinical evidence of focal cerebral infarction including hemiparesis, visual or gait disturbance, mental changes, or a combination of these) were observed in 3 patients after the operation (propofol group, 3 of 90 [3.3%]; fentanyl group, 3 of 90 [3.3%]; total 6 of 180 [3.3%]).

Table 4 shows the assessment during the intensive care unit period in two groups. There were significant differences in extubation time after CPB and emergence time from the anesthesia between the two groups. However, there were no significant differences in reintubation for pneumonia, length of intensive care unit stay, postoperative renal dysfunction (creatinine concentration > 3.0 mg/dL), postoperative liver dysfunction (glutamine oxaloacetate transaminase or glutamine pyruvate transam-

*Table 2. Variables in Two Groups During Perioperative Period*[a]

| Variable | Groups | Measurement Period 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| CI ($L \cdot min^{-1} \cdot m^{-2}$) | propofol | 2.7 ± 0.8 | 2.2 ± 0.2 | 2.2 ± 0.2 | 2.2 ± 0.2 | 2.1 ± 0.2 | 3.2 ± 0.9 | 2.9 ± 0.8 |
| | fentanyl | 2.7 ± 0.8 | 2.1 ± 0.2 | 2.2 ± 0.2 | 2.2 ± 0.2 | 2.3 ± 0.2 | 3.4 ± 0.8 | 3.0 ± 0.7 |
| MAP (mm Hg) | propofol | 87 ± 10 | 76 ± 9 | 60 ± 7[b] | 60 ± 9[b] | 64 ± 11[b] | 78 ± 14 | 80 ± 13 |
| | fentanyl | 89 ± 11 | 77 ± 10 | 59 ± 8[b] | 61 ± 10[b] | 60 ± 12[b] | 77 ± 13 | 86 ± 14 |
| $Paco_2$ (mm Hg) | propofol | 35 ± 8 | 33 ± 5 | 35 ± 6 | 36 ± 4 | 35 ± 4 | 33 ± 8 | 37 ± 7 |
| | fentanyl | 34 ± 6 | 34 ± 4 | 33 ± 4 | 36 ± 5 | 34 ± 5 | 34 ± 7 | 33 ± 8 |
| Hb ($g/dL^{-1}$) | propofol | 13.8 ± 2.1 | 8.0 ± 2.1[b] | 7.7 ± 2.2[b] | 8.0 ± 1.9[b] | 7.9 ± 2.0[b] | 8.7 ± 3[b] | 9.8 ± 2.0[b] |
| | fentanyl | 14.0 ± 1.9 | 8.2 ± 2.0[b] | 7.3 ± 2.4[b] | 8.1 ± 1.7[b] | 7.6 ± 1.9[b] | 8.9 ± 2.0[b] | 9.6 ± 2.0[b] |
| TT (°C) | propofol | 35.9 ± 0.6 | 35.5 ± 0.9 | 35.8 ± 0.7 | 36.1 ± 0.7 | 35.5 ± 0.7 | 35.7 ± 0.7 | 35.9 ± 1.0 |
| | fentanyl | 36.0 ± 0.7 | 35.6 ± 0.9 | 35.7 ± 0.8 | 36.1 ± 0.8 | 35.5 ± 0.6 | 35.8 ± 0.9 | 35.8 ± 1.0 |
| $SjvO_2$ (%)[d] | propofol | 59 ± 7 | 58 ± 7 | 58 ± 7 | 60 ± 6 | 60 ± 6 | 60 ± 7 | 62 ± 7 |
| | fentanyl | 58 ± 8 | 56 ± 5 | 48 ± 6[bc] | 54 ± 8 | 57 ± 6 | 58 ± 6 | 58 ± 5 |
| *p* value | | 0.89 | 0.88 | 0.01 | 0.08 | 0.35 | 0.62 | 0.21 |

[a] Values are mean ± standard deviation. [b] $p < 0.05$ compared with period 1. [c] $p < 0.05$ compared with propofol group at the following measurement periods: (1) after induction of anesthesia and before the start of the operation, (2) at the onset of CPB, (3) 20 min after the onset of CPB, (4) 40 min after the onset of CPB, (5) 60 min after the onset of CPB, (6) at the cessation of CPB, and (7) at the end of the operation. [d] The $SjvO_2$ values are measured from samples of jugular venous blood.

CI = cardiac index; Hb = hemoglobin concentration; MAP = mean arterial pressure; $Paco_2$ = arterial carbon dioxide tension; $SjvO_2$ = jugular venous oxygen hemoglobin saturation; TT = tympanic temperature.

inase > 100 U/dL), or catecholamine dosage between the two groups.

We could not examine neuropsychologic assessments for 28 patients (propofol group, 13; fentanyl group, 15) at 6 months after the operation. Fifteen patients (including patients with major neurologic defects) had incomplete cognitive data, and 13 patients refused follow-up. Cognitive impairment at 6 months was observed in 6.6% of patients (10 of 152). There was no significant difference in cognitive decline between the two groups (propofol group, 5 of 77, 6%; fentanyl group, 5 of 75, 7%; Tables 5 and 6).

A multivariate logistic regression analysis showed that no factors were correlated with cognitive impairment at 6 months after the operation (Table 7).

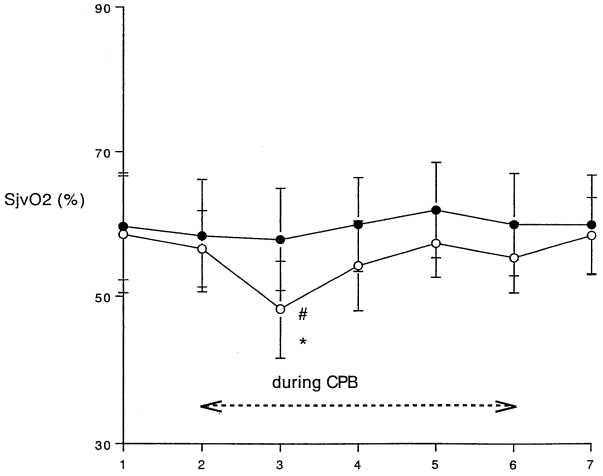


*Fig 1. Time course of changes in jugular venous oxygen hemoglobin saturation ($SjvO_2$) in two groups. Jugular venous oxygen hemoglobin saturation in the fentanyl group (○) had decreased at 20 minutes after cardiopulmonary bypass (CPB) compared with at the induction of anesthesia. Moreover, there was a significant difference in jugular venous oxygen hemoglobin saturation between the two groups. *$p < 0.05$ compared with period 1; #$p < 0.05$ compared with the propofol group (●) after induction of anesthesia and before the start of the operation (1), at the onset of CPB (2), 20 minutes after the onset of CPB (3), 40 minutes after the onset of CPB (4), 60 minutes after the onset of CPB (5), at the cessation of CPB (6), and at the end of the operation (7).*

## Comment

The principal findings of this study were that (1) the fentanyl group had a greater incidence and duration of $SjvO_2$ less than 50% than the propofol group, and (2) the fentanyl and propofol groups did not differ in cognitive

*Table 3. Analysis of Jugular Venous Oxygen Hemoglobin Saturation by Oximetric Catheter*[a]

| Variable | Propofol | Fentanyl |
|---|---|---|
| Number of patients whose $SjvO_2$ was <50% | 19 | 32[b] |
| Duration when $SjvO_2$ was <50% (desaturation time; min) | 18 ± 11 | 27 ± 14[b] |
| Ratio of desaturation time to total CPB time (%) | 14 ± 7 | 20 ± 9[b] |
| Integrated area under $SjvO_2$ of <50% | 423 ± 51 | 625 ± 68[b] |

[a] Values are mean ± standard deviation. [b] $p < 0.05$ compared with propofol group.

CPB = cardiopulmonary bypass; $SjvO_2$ = jugular venous oxygen hemoglobin saturation.

*Table 4. Assessment in Intensive Care Unit Period in the Two Groups*[a]

| Variable | Propofol | Fentanyl |
|---|---|---|
| Extubation time (h) | 6.1 ± 3.6 | 15.2 ± 7.7[b] |
| Reintubation for pneumonia | 3 | 2 |
| Length of ICU stay (d) | 5 ± 3.9 | 6 ± 3.4 |
| Postoperative renal dysfunction | 2 | 3 |
| Postoperative liver dysfunction | 6 | 5 |
| Dopamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$) | 6.4 ± 2.9 | 6.0 ± 2.4 |
| Dobutamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$) | 4.8 ± 2.3 | 5.0 ± 1.9 |
| Emergence time from the anesthesia (h) | 4.1 ± 2.7 | 10.8 ± 5.9[b] |

[a] Values are means ± standard deviation. [b] $p < 0.05$ compared with propofol group.

ICU = intensive care unit.

outcome at 6 months after operation. This suggested that $SjvO_2$ differences between the two groups did not affect cognitive dysfunction.

### *Comparative Effects of Propofol and Fentanyl on Jugular Venous Oxygen Hemoglobin Saturation*

Several studies have investigated the effects of anesthetic agents on $SjvO_2$ during CPB [6–8, 14]. Nandate and coworkers [14] examined the effects of isoflurane, sevoflurane, and propofol on $SjvO_2$ during CPB in patients undergoing CABG and found that reduced $SjvO_2$ was more often observed in the propofol group than in the isoflurane or sevoflurane groups. This finding is inconsistent with our results, but the discrepancy might be attributable in part to the propofol dosage and anesthetic protocol. Nandate and associates [14] used 15 μg/kg fentanyl as an induction agent. Moreover, they did not measure $SjvO_2$ continuously, nor examine postoperative cognitive dysfunction.

Newman and colleagues [7] reported that $SjvO_2$ values were equivalent between propofol-based (burst-suppression) and opiate (sufentanil)-based anesthesia during both hypothermic and normothermic (rewarming) bypass. Similarly, Souter and coworkers [8] found no $SjvO_2$ differences between propofol-based (burst-suppression) and an opiate-benzodiazepine–based anesthetic during hypothermic or normothermic (rewarming) bypass. In contrast, in the present study, we found $SjvO_2$ to be greater with propofol during steady-state normothermic bypass. Both the studies by Newman and colleagues [7] and Souter and coworkers [8] used a much greater dose of propofol than that used in this study (approximately 250 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [7]; approximately 125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [8]; approximately 85 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [present study]). Both Newman and colleagues [7] and Souter and coworkers [8] also reported significant hypotension and greater vasoconstrictor use in patients receiving propofol versus control subjects. In contrast, propofol patients in this study did not receive significantly greater doses of vasoconstrictor than control subjects. Hypotension and vasoconstrictors may have altered cerebral blood flow. Johnston and associates [15] reported that phenylephrine did not reduce cerebral blood flow in animal models. However, we recently found that increasing mean arterial pressure has some effect on $SjvO_2$ in patients without diabetes during tepid CPB [16]. Therefore, it is possible that differences in propofol dosage and hemodynamics and vasoconstrictor use between the studies by Newman and colleagues [7] and Souter and coworkers [8] and the present study might explain the different findings regarding the effect of propofol versus opiate on $SjvO_2$. The present study findings did not explain why propofol could prevent the reduction of $SjvO_2$ during normothermic CPB. We speculated that because propofol decreased cerebral blood flow and metabolism in parallel, as demonstrated by Newman and colleagues [7], mismatch of flow or metabolism, which was often observed at the initiation of CPB [17], did not occur in the propofol group.

*Table 6. Number of Cognitive Impairments at 6 Months After the Operation*

| Propofol Group | Fentanyl Group | Total |
|---|---|---|
| 5/77 (6%) | 5/75 (7%) | 10/152 (6.6%) |

### *Comparative Effects of Propofol and Fentanyl on Postoperative Cognitive Dysfunction*

Several reports have described the effects of propofol on postoperative cognitive dysfunction [6–8]. Roach and associates [6] reported that a burst-suppression dose of propofol during cardiac valve operation did not reduce

*Table 5. Raw Neurocognitive Test Scores at Baseline and 6 Months After the Operation*[a]

| | Fentanyl | | | Propofol | | |
|---|---|---|---|---|---|---|
| Test | Baseline | 6 months | *p* Value | Baseline | 6 months | *p* Value |
| Mini-Mental Test | 47.7 ± 5.7 | 45.0 ± 6.4 | 0.22 | 46.4 ± 5.6 | 45.0 ± 5.9 | 0.18 |
| Trail Making Test (A) | 43.2 ± 5.6 | 45.4 ± 6.9 | 0.11 | 42.5 ± 6.6 | 44.1 ± 5.7 | 0.09 |
| Trail Making Test (B) | 156.3 ± 50.3 | 176.0 ± 57.0 | 0.12 | 154.2 ± 51.1 | 164.0 ± 63.4 | 0.17 |
| Digit span forward | 7.5 ± 2.2 | 7.7 ± 2.4 | 0.41 | 7.6 ± 2.0 | 8.0 ± 2.2 | 0.33 |
| Grooved pegboard | 22.0 ± 3.5 | 23.2 ± 4.3 | 0.51 | 21.9 ± 3.0 | 23.2 ± 4.0 | 0.30 |
| Immediate recall | 42.7 ± 5.6 | 45.1 ± 11.7 | 0.09 | 40.6 ± 6.6 | 43.1 ± 7.7 | 0.10 |
| Delayed recall | 23.1 ± 3.5 | 25.6 ± 7.7 | 0.08 | 22.4 ± 3.9 | 25.2 ± 5.4 | 0.07 |

[a] Values are mean ± standard deviation.

*Table 7. Analysis of Risk Factors in Relation to 6-Month Cognitive Impairment*

| Variable | OR (95% CI) | *p* Value |
|---|---|---|
| Age | 1.0 (0.8–1.4) | 0.18 |
| Preoperative Hb | 1.1 (0.7–2.0) | 0.7 |
| Hypertension | 0.3 (0.1–1.2) | 0.09 |
| Smoke | 0.7 (0.1–2.9) | 0.6 |
| Weight | 0.9 (0.9–1.1) | 0.7 |
| Sex | 3.1 (0.2–12) | 0.2 |
| $Paco_2$ | 0.9 (0.6–1.5) | 0.8 |
| TT | 0.7 (0.2–2.0) | 0.6 |
| Anesthetic regimen | 0.9 (0.7–1.4) | 0.3 |
| Ventilation-supported time | 0.7 (0.5–1.7) | 0.5 |
| Emergence time | 0.8 (0.7–1.6) | 0.4 |
| IAU MAP | 0.6 (0.8–1.1) | 0.3 |
| CPB time | 0.9 (0.7–1.1) | 0.6 |
| Preoperative EF | 0.9 (0.8–1.3) | 0.5 |
| IAU desaturation | 1.0 (0.8–1.2) | 0.21 |

CI = confidence interval; CPB = cardiopulmonary bypass; EF = left ventricular ejection fraction; Hb = hemoglobin; IAU desaturation = integrated area under $SjvO_2$ of less than 50%; IAU MAP = integrated area under MAP of less than 50 mm Hg; MAP = mean arterial pressure; OR = odds ratio; $Paco_2$ = lowest arterial carbon dioxide tension during CPB; $SjvO_2$ = jugular venous oxygen hemoglobin saturation; TT = tympanic temperature of the highest value during CPB.

the incidence or severity of neurologic or neuropsychologic dysfunction during hypothermic CPB. Souter and coworkers [8] reported that propofol did not attenuate the frequency or extent of reductions of $SjvO_2$ less than 50% during the rewarming period or postoperative cognitive decline. Both studies were conducted under hypothermic conditions. The present study examined the effects of propofol and fentanyl on $SjvO_2$ and postoperative cognitive dysfunction during normothermic CPB and is consistent with the other two reports. Our study confirmed that $SjvO_2$ during hypothermic or normothermic CPB did not appear to affect long-term cognitive outcome.

### *Clinical Implications*

Early tracheal extubation and the fast-track clinical care pathways are thought to be an acceptable approach to reduce the cost of CABG and possibly improve the physiologic status of patients [18]. Although we did not assess the costs of CABG in propofol-based anesthesia, propofol-based anesthesia is useful for the fast-track method.

Hanel and coworkers [5] reported that mild hypercapnia prevented reduced $SjvO_2$ during the rewarming period. However, they did not examine the effects of mild hypercapnia during rewarming on postoperative cognitive dysfunction. Grigore and colleagues [19] in a recent study from Duke University reported that slower rewarming rates were better than standard rewarming techniques for improving neurocognitive outcome, possibly because of the amelioration of reduced $SjvO_2$. If we prevent reduced $SjvO_2$ during CPB, as was done in the present study and that by Hanel and coworkers [5], will cognitive outcome be improved? Unfortunately, there have been no clear reports regarding the effect of amelioration of reduced $SjvO_2$ on postoperative cognitive dysfunction in patients undergoing CABG. The present study examined the effect of amelioration of reduced $SjvO_2$ on postoperative cognitive decline in patients undergoing CABG. Our data indicate that prevention of reduced $SjvO_2$ during normothermic CPB cannot improve long-term postoperative cognitive dysfunction.

### *Study Limitations*

Because a burst-suppression dose of propofol might induce massive hypotension, which would in turn lead to myocardial ischemia in patients undergoing CABG, we did not use a burst-suppression dose of propofol during the study. Therefore, this dosage of propofol might be not enough for brain protection. However, a recent study found that burst suppression was not necessary for maximal neuroprotection with pentobarbital [20].

It remains controversial whether reduced $SjvO_2$ during the CPB period is a predictor of postoperative cognitive dysfunction. Croughwell and associates [3] reported that lower normothermic $SjvO_2$ (at the end of rewarming) were associated with short-term cognitive deficits (4 to 8 days after operation). Subsequent work by Newman and colleagues [21], which included most of the patients reported in Croughwell and coworkers [3], found that $SjvO_2$ had an extremely small independent association with cognitive impairment 7 to 10 days after operation in hypothermic CPB, when baseline cognitive status, age, and years of education were considered in the analysis. Finally, Robson and associates [22] found averaged $SjvO_2$ during hypothermic bypass, and in the early postoperative phase, had no association with cognitive status 3 months after operation in normothermic CPB. In contrast, Yoshitani and coworkers [23] reported that high $SjvO_2$ were associated with cognitive dysfunction after the operation. Further prospective, randomized studies are necessary to identify the association between low or high $SjvO_2$ during CPB and cognitive dysfunction. In addition, we cannot rule out the potential problem in this study. Jugular venous oxygen hemoglobin saturation differences between the two groups were so small, and of such a short duration, that outcome was not likely to be affected. Therefore, we concluded that cerebral venous desaturation of the magnitude observed in this study was not sufficient to influence cognitive outcome.

Because of the limited time available for neuropsychological testing preoperatively, we could not cover all major cognitive domains. Moreover, there were no specific domains concerning the cognitive tests in this study. Further studies are needed to determine whether any correlation exists between $SjvO_2$ reduction and all major cognitive domains.

Robson and colleagues [22] provided evidence that jugular bulb catheters were not very accurate during bypass, possibly because of increased vessel wall contact. However, in previous [17] and present studies, we assessed the accuracy of our oximetric catheter system and found an excellent correlation between oximetry catheter

values for $SjvO_2$ and simultaneous $SjvO_2$ values obtained from samples of jugular venous blood measured in a CO-Oximeter.

Because $SjvO_2$ indicates the global balance of cerebral blood flow and metabolism, it is possible that an $SjvO_2$ monitor could not be sensitive enough to detect the regional cerebral oxygenation. However, in a previous study [17], we found a good correlation ($r^2 = 0.49$) between $SjvO_2$ and regional cerebral oxygenation measured by near infrared spectroscopy.

In the present study, we used BIS score as an indicator of anesthetic depth. There have been some controversial results regarding the use of BIS score to represent anesthetic depth [24]. Thus, we cannot rule out the possibility of a difference in anesthetic depth between the two groups.

In the present study, we selected a dichotomous outcome analysis. Controversy exists regarding which analysis would be more meaningful, a dichotomous outcome or continuous outcome measures [25, 26]. Grigore and colleagues [19] found that the analysis of neurocognitive performance as a continuous measure was more sensitive. Blumenthal and associates [26] reported that although the arbitrariness of categorical boundaries was avoided in continuous outcome measures, it was difficult to ascertain with this type of analysis the clinical significance of changes. Statistical analysis does not mean clinical importance [25]. There is no clear agreement whether linear regression is better than logistic regression analysis as a statistical method for assessing the relationship between risk factors and cognitive dysfunction [25]. We must consider what type of analysis is the most appropriate method for assessing cognitive dysfunction.

In conclusion, the fentanyl group had a reduced $SjvO_2$ compared with the propofol group during normothermic CPB. However, this reduced $SjvO_2$ was not associated with long-term cognitive dysfunction.

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