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Effects of Increasing Concentrations of Propofol on Jugular Venous Bulb Oxygen Saturation in Neurosurgical Patients under Normothermic and Mildly Hypothermic Conditions

Masato Iwata, M.D., Masahiko Kawaguchi, M.D.,† Satoki Inoue, M.D.,† Masahiro Takahashi, M.D.,‡ Toshinori Horiuchi, M.D.,* Toshisuke Sakaki, M.D.,§ Hitoshi Furuya, M.D.‖*

Background: **Recent evidence suggested that propofol can deteriorate the cerebral oxygen balance compared with inhalational anesthetics. However, dose-related influences of propofol on cerebral oxygen balances were not clearly investigated. In the current study, the authors investigated the effects of increasing concentrations of propofol on jugular venous bulb oxygen saturation (Sjo_2) in neurosurgical patients under normothermic and mildly hypothermic conditions.**

Methods: **After institutional approval and informed consent were obtained, 30 adult patients undergoing elective craniotomy were studied. Patients were randomly allocated to either normothermic or hypothermic group (n = 15 in each group). In the normothermic and hypothermic groups, tympanic membrane temperature was maintained at 36.5° and 34.5°C, respectively. Sjo_2 was measured at predicted propofol concentrations of 3, 5, and 7 μg/ml using a target-controlled infusion system in both groups.**

Results: **At a predicted propofol concentration of 3 μg/ml, there were no significant differences in Sjo_2 values between the normothermic and hypothermic groups, although the incidence of desaturation (Sjo_2 < 50%) was significantly higher in the normothermic group than in the hypothermic group (30% *vs.* 13%; $P < 0.05$). Sjo_2 values and the incidence of desaturation remained unchanged during the changes in predicted propofol concentration from 3 to 7 μg/ml both in the normothermic and hypothermic groups.**

Conclusion: **The results indicated that the increasing concentrations of propofol did not affect Sjo_2 values in neurosurgical patients under normothermic and mildly hypothermic conditions.**

DELIBERATE mild hypothermia has been proposed as means of providing cerebral protection and treatment in neurosurgical patients and in patients with neurologic injury after cardiac arrest and head trauma. A number of investigators have demonstrated the neuroprotective efficacy of mild hypothermia in a variety of animal models.[1–3] Although recent clinical trials did not demonstrate the efficacy of mild hypothermia in patients with head trauma and subarachnoid hemorrhage, two multiple-center clinical trials conducted in Europe and Australia have shown the efficacy of mild hypothermia for 12–24 h in comatose survivors from cardiac arrest.[4–7] Because hypnotic or anesthetic agents were required during mild hypothermic therapy, it is important to know the influences of these drugs on cerebral blood flow and metabolism under mildly hypothermic conditions.

Propofol is one of the candidates for sedation or anesthesia and has been widely used during mild hypothermic therapy. It has been shown that propofol can reduce both cerebral blood flow (CBF) and cerebral metabolic rate (CMR) for oxygen.[8–11] However, during propofol anesthesia, the reduction of CBF was larger than the reduction of CMR, resulting in a decrease of the CBF/CMR ratio. Jansen *et al.*[11] reported that 50% of patients undergoing brain tumor resection have jugular venous bulb oxygen saturation (Sjo_2) values of less than 50%, an indirect indicator of cerebral hypoperfusion, during propofol–fentanyl anesthesia. Munoz *et al.*[12] demonstrated that the incidence of an Sjo_2 of less than 50% during brain tumor surgery was higher during propofol anesthesia than during sevoflurane–nitrous oxide anesthesia (60% *vs.* 20%). The data from our laboratory have also shown that Sjo_2 values were significantly lower during propofol–fentanyl anesthesia compared with those during sevoflurane–nitrous oxide–fentanyl anesthesia under mildly hypothermic conditions.[13] However, in these studies, dose-related influences of propofol on cerebral oxygen balances were not clearly investigated. In the current study, we tested the hypothesis that propofol may reduce the Sjo_2 values in a dose-dependent manner under normothermia and mild hypothermia. Effects of increasing concentrations of propofol on Sjo_2 values were investigated under normothermic and mildly hypothermic conditions.

Materials and Methods

After institutional approval at Nara Medical University, Kashihara, Nara, Japan, and informed consent were obtained, 30 patients undergoing elective craniotomy were studied. The study population size was determined based on the data in our preliminary study (Sjo_2; SD = 8). We considered the difference of Sjo_2 values by 10% (*e.g.*, 60% *vs.* 50%) between the different propofol concentrations to be clinically important. Assuming a type I error protection of 0.05 and a power of 0.90, 14 or 15 patients in each group were required for a comparison within the

* Research Fellow, † Assistant Professor, ‡ Instructor, ‖ Professor and Chair, Department of Anesthesiology, § Professor and Chair, Department of Neurosurgery, Nara Medical University.

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Address reprint requests to Dr. Kawaguchi: Department of Anesthesiology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan. Address electronic mail to: drjkawa@naramed-u.ac.jp.

group. Patients with ischemic cerebrovascular disease, symptomatic ischemic heart disease, hepatic or renal disease, or coagulopathy were excluded. Patients with a sign of increased intracranial pressure were also excluded from study.

All patients were premedicated with 75 mg oral roxatidine (H2 blocker) 2 h preoperatively. Anesthesia was induced with propofol, 1–2 μg/kg fentanyl, and 0.15 mg/kg vecuronium. Propofol was administered with a plasma target concentration of propofol of 4 μg/ml using a target-controlled infusion (TCI) device (Diprifusor TCI; Zeneca Pharmaceuticals, Macclesfield, United Kingdom). After intubation, the lungs were mechanically ventilated (0.5 fraction of inspired oxygen with air and oxygen). Arterial partial pressure of carbon dioxide ($Paco_2$) was maintained in normocapnia (35–40 mmHg). The plasma target concentration of propofol was adjusted to keep Bispectral Index (BIS) values between 40 and 60 using an A2000 BIS® monitor (software version 3.12; Aspect Medical systems, Natick, MA). Additional fentanyl was administered as necessary, and vecuronium was administered as required to maintain one or two mechanical twitches in response to supramaximal electrical stimulation of the ulnar nerve at the wrist. Routine monitoring included an electrocardiogram, a noninvasive blood pressure cuff, pulse oximetry, and a capnogram. A cannula was inserted into the radial artery to monitor arterial blood pressure and to sample the arterial blood gas analysis. The catheter was retrogradely inserted into the right jugular venous bulb through the right internal jugular vein for sampling of jugular venous bulb blood. Proper position of the tip of the jugular catheter was radiographically verified. A tympanic membrane probe was inserted in the external auditory meatus on the opposite side of surgery for temperature monitoring by using sterile copper-constantan thermocouple sensors (Mon-a-Therm thermocouples; Tyco Healthcare, Mansfield, MA). The probe was then taped in place, and the external ear was covered with a gauze pad.

All patients were randomly allocated to either the normothermic group or the mildly hypothermic group. In the normothermic group (n = 15), tympanic membrane temperature was maintained at 36.5°C. In the hypothermic group (n = 15), patients were cooled, and tympanic membrane temperature was maintained at 34.5°C. Mild hypothermia was induced as reported previously.[13–16] A water blanket (BLANKETROLII Hyper-Hypothermia; Cincinnati Sub-Zero Products, Inc., Cincinnati, OH) was placed under each patient. A polyurethane-formed pad covered with a cotton sheet (S-K pad; Asahi Medical Co., Osaka, Japan) protected the patient from direct contact with the water blanket. A convective device blanket (Warm Touch; Tyco Healthcare) was applied directly to the ventral body surface. For the active cooling, the temperature of the water blanket was set at 5°C, and room-temperature air was circulated by the convective device. Active cooling was stopped at a tympanic membrane temperature of 35°C, and body temperature was then allowed to drift downward. Temperature settings on both the water blanket and the convective device were then adjusted to maintain a target of 34.5°C (passive cooling). After the completion of major surgical procedures, such as aneurysm clipping and tumor removal, active rewarming was instituted with the water blanket set at 41°C and the convective device at its highest setting (43°C). Active rewarming was stopped at a tympanic membrane temperature of 35.5°C, and body temperature was then allowed to drift upward. Temperature settings on both the water blanket and the convective device were then adjusted to maintain a target of 36°C (passive rewarming). In both groups, amrinone was administered at 5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ with 1.0-mg/kg boluses at the beginning of cooling and rewarming to accelerate the cooling and rewarming rate, as reported previously.[14] After the operation, the patients underwent extubation in the operating room.

After tympanic temperature was maintained at a target temperature (36.5° or 34.5°C), predicted blood and effect site propofol concentrations were maintained at 3, 5, and 7 μg/ml in turn. During the administration of propofol, methoxamine was administered to maintain arterial blood pressure. At least 10 min after both predicted blood and effect site propofol concentrations were kept at each target concentration, arterial and jugular blood were sampled, and the following parameters were measured using an ABL505 analyzer (Radiometer, Copenhagen, Denmark): $Paco_2$, jugular venous partial pressure of carbon dioxide ($Pjco_2$), arterial partial pressure of oxygen (Pao_2), jugular venous partial pressure of oxygen (Pjo_2), pH, hemoglobin, arterial oxygen saturation (Sao_2), and Sjo_2. The values for pH, Pao_2, and $Paco_2$ were not corrected for temperature. To estimate cerebral oxygenation state, arteriojugular venous oxygen content difference ($AJDo_2$) and cerebral oxygen extraction rate (COER) were calculated using the following equations:

$$Cao_2 = (Sao_2 \times \text{hemoglobin} \times 1.39) + 0.0031 \times Paco_2 \quad (1)$$

$$Cjo_2 = (Sjo_2 \times \text{hemoglobin} \times 1.39) + 0.0031 \times Pjo_2 \quad (2)$$

$$AJDo_2 = Cao_2 - Cjo_2 \quad (3)$$

$$COER = 100 \times AJDo_2/Cao_2, \quad (4)$$

where Cao_2 and Cjo_2 are the arterial and jugular venous oxygen contents, respectively.

At each concentration, propofol concentration was also measured by high-pressure liquid chromatography as reported previously.[17] For the measurement of propofol concentrations, each blood sample was immediately centrifuged (3,000 rpm, 5 min), and serum was stored at −30°C until analysis. For extraction, 0.2 ml serum was

Table 1. Demographic Variables

	Normothermia (n = 15)	Hypothermia (n = 15)
Age, yr	57 ± 13	51 ± 12
Sex, F/M	11/4	9/6
Weight, kg	56 ± 10	59 ± 10
Height, cm	154 ± 10	160 ± 8
Anesthesia time, min	362 ± 92	406 ± 127
Operation, min	243 ± 70	277 ± 123
Total dose of fentanyl, mg	5.2 ± 1.0	5.2 ± 0.9
Disease		
Brain tumor	11	12
Aneurysm	4	3

Data are expressed as mean ± SD.

placed in a polypropylene test tube, and 1 ml ethyl acetate and 0.1 ml NaOH (50 mM) were added. The tube was shaken for 5 min. The mixture was centrifuged at 15,000 rpm for 5 min, and a 0.9-ml aliquot of the upper ethyl acetate phase was removed and freeze-dried. The freeze-dried pellet was redissolved by 0.05 ml mobile phase and injected into a high-pressure liquid chromatograph system: pump (655A-11; Hitachi, Tokyo, Japan), ultraviolet absorbance detector (Waters 486; Waters Associates, Milford, MA), and phenyl reverse-phase column (Micro Bondasphere 5-micro phenyl 100A; Waters Associates). The mobile phase was methanol–100 mM phosphate buffer (pH 2.8; 6:4, vol/vol), and the flow rate was 0.8 ml/h. The wavelength of ultraviolet detection was 270 nm.

To compare the demographic variables of patients between the two groups, an unpaired *t* test or chi-square test was used. Hemodynamic variables, blood gas data, and propofol concentration were expressed as mean ± SD and compared using two-way analysis of variance with repeated measures followed by the Student-Newman-Keuls test for multiple comparisons. Differences were considered significant when P was less than 0.05.

Results

Demographic variables are shown in table 1. There were no significant differences in demographic variables between the two groups. In two patients in the hypothermic group, administration of propofol at 7 μg/ml was discontinued because of a sustained reduction in mean arterial pressure regardless of the administration of methoxamine. In these patients, evaluation was performed only at predicted concentrations of 3 and 5 μg/ml. Table 2 shows the changes in mean arterial pressure, heart rate and tympanic temperature, and arterial blood gas data during the changes in predicted propofol concentration. Mean arterial pressure at a predicted concentration of 3 μg/ml was significantly higher in the hypothermic group than in the normothermic group.

Table 2. Hemodynamic Variables, Temperature, and Arterial Blood Gas Data

	Ce		
	3 μg/ml	5 μg/ml	7 μg/ml
Mean arterial pressure, mmHg			
Normothermia	73 ± 8	72 ± 8	69 ± 8†
Hypothermia	85 ± 12*	79 ± 11	74 ± 13
Heart rate, beats/min			
Normothermia	77 ± 12	78 ± 11	81 ± 9
Hypothermia	76 ± 13	78 ± 13	84 ± 14
Tympanic temperature, °C			
Normothermia	36.2 ± 0.5	36.4 ± 0.5	36.5 ± 0.5
Hypothermia	34.7 ± 0.4*	34.5 ± 0.4*	34.5 ± 0.5*
pH			
Normothermia	7.43 ± 0.03	7.43 ± 0.02	7.43 ± 0.02
Hypothermia	7.39 ± 0.04*	7.40 ± 0.03*	7.40 ± 0.03*
$Paco_2$, mmHg			
Normothermia	38 ± 2	38 ± 2	38 ± 2
Hypothermia	40 ± 2*	39 ± 1*	39 ± 2*
Pao_2, mmHg			
Normothermia	212 ± 38	203 ± 43	202 ± 39
Hypothermia	221 ± 69	222 ± 49	224 ± 53
Sao_2, %			
Normothermia	99 ± 0.4	99 ± 0.4	99 ± 0.4
Hypothermia	99 ± 0.5	99 ± 0.4	99 ± 0.4
Hemoglobin, mg/dl			
Normothermia	10 ± 2	9 ± 3	10 ± 2
Hypothermia	10 ± 2	11 ± 2	10 ± 2

* $P < 0.05$ *vs.* normothermia. † $P < 0.05$ *vs.* Ce 3.

Ce = predicted effect site concentration of propofol during target-controlled infusion; $Paco_2$ = arterial partial pressure of carbon dioxide; Pao_2 = arterial partial pressure of oxygen; Sao_2 = arterial saturation of oxygen.

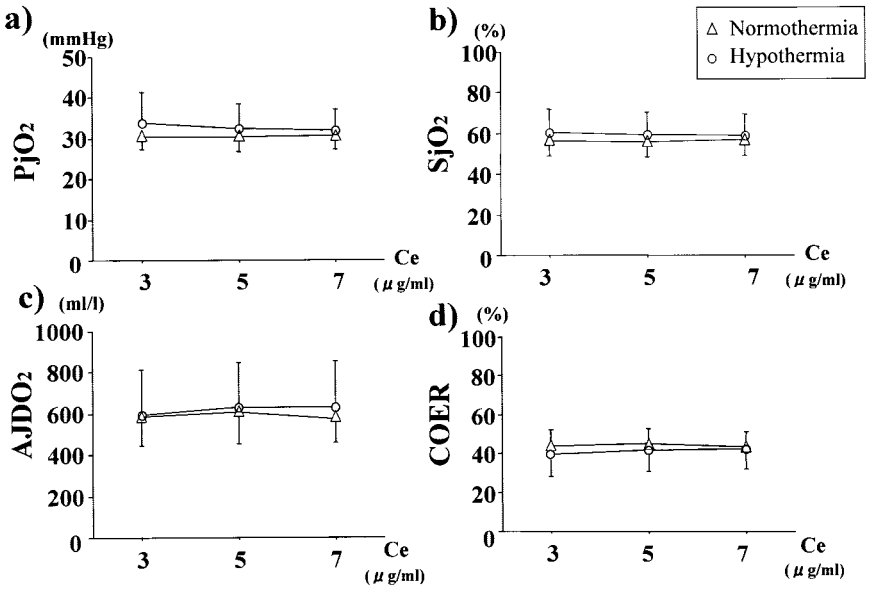

Fig. 1. Changes in jugular venous partial pressure of oxygen (Pjo_2), jugular venous oxygen saturation (Sjo_2), arteriojugular venous oxygen content difference ($AJDo_2$), and cerebral oxygen extraction rate (COER) during the administration of propofol at predicted effect site concentrations (Ce) of 3, 5, and 7 μg/ml in the normothermia group (*triangles*) and the hypothermia group (*circles*). There were no significant differences in Pjo_2, Sjo_2, $AJDo_2$, or COER between the two groups, and these variables remained unchanged during the changes in predicted propofol concentration.

Mean arterial pressure at a predicted concentration of 7 μg/ml was significantly lower than that at 3 μg/ml in the normothermic group. Tympanic temperature in the hypothermic group was significantly less compared with that in the normothermic group. Heart rate and tympanic temperature remained unchanged during the changes in predicted propofol concentration in both groups. Values of arterial pH in the hypothermic group were significantly lower compared with those in the normothermic group. Values of $Paco_2$ in the hypothermic group were significantly higher as compared with those in the normothermic group. There were no significant differences in $Paco_2$, Sao_2, and hemoglobin concentration between the groups. The values of pH, $Paco_2$, $Paco_2$, Sao_2, and hemoglobin remained unchanged during the changes in predicted propofol concentration.

Figure 1 shows the changes in Pjo_2, Sjo_2, $AJDo_2$, and COER during the changes in predicted propofol concentration. At a predicted propofol concentration of 3 μg/ml, there were no significant differences in Pjo_2, Sjo_2, $AJDo_2$, or COER between the two groups. These variables remained unchanged during the changes in predicted propofol concentration from 3 to 7 μg/ml in both groups. The incidence of desaturation (Sjo_2 < 50%) during propofol administration was summarized in table 3. At a predicted propofol concentration of 3 μg/ml, the incidence of desaturation in the normothermic group was significantly higher than that in the hypothermic group (31% *vs.* 13%; $P < 0.05$). The incidence of desaturation remained unchanged during the changes in predicted propofol concentration from 3 to 7 μg/ml in both groups.

Measured propofol concentrations and BIS values at predicted concentrations of 3, 5, and 7 μg/ml are shown in table 4. Although there were no significant differences in measured propofol concentration at predicted concentrations of 3 and 5 μg/ml between the two groups, measured propofol concentration at 7 μg/ml was significantly higher in the hypothermic group compared with that in the normothermic group. BIS values were dose-dependently reduced in both groups, and there were no significant differences in BIS values at each concentration.

Table 3. Incidence of Jugular Venous Bulb Oxygen Saturation Less Than 50%

	Ce		
	3 μg/ml	5 μg/ml	7 μg/ml
Normothermia	31% (5/15)	20% (3/15)	23% (3/13)
Hypothermia	13% (2/15)*	19% (2/15)	20% (3/15)

* $P < 0.05$ *vs.* normothermia.

Ce = predicted effect site concentration of propofol during target-controlled infusion.

Table 4. Measured Propofol Concentration and Bispectral Index

	Ce		
	3 μg/ml	5 μg/ml	7 μg/ml
Measured propofol concentration, μg/ml			
Normothermia	2.8 ± 0.8	5.8 ± 1.8†	7.5 ± 1.5†
Hypothermia	3.3 ± 0.8	6.3 ± 1.7†	8.4 ± 2.7*†
Bispectral index value			
Normothermia	57 ± 9	43 ± 12†	22 ± 13†
Hypothermia	52 ± 9	42 ± 9	22 ± 13†

* $P < 0.05$ *vs.* normothermia. † $P < 0.05$ *vs.* Ce 3.

Ce = predicted effect site concentration of propofol during target-controlled infusion.

Discussion

The results obtained in the current study show that increased concentrations of propofol from 3 to 7 μg/ml did not affect Sjo_2 values or the incidence of desaturation ($Sjo_2 < 50\%$) in the hypothermic or the normothermic group. Measured propofol concentrations were similar at target concentrations of 3 and 5 μg/ml. However, at 7 μg/ml, the measured propofol concentration was significantly higher under mild hypothermia compared with that under normothermia. These results suggest that, although a reduction in temperature can affect the accuracy of TCI techniques for propofol administration, especially at higher concentrations, cerebral oxygen balance remained unchanged during the changes in propofol concentrations ranging from 3 to 7 μg/ml in normothermic and mildly hypothermic patients.

There have been several reports on the effects of propofol on CBF and cerebral metabolic rate for oxygen ($CMRo_2$) under normothermic conditions.[8–11] Van Hemelrijick *et al.*[8] investigated the effect of propofol on CBF and $CMRo_2$ in anesthetized baboons. Propofol at infusion rates of 6 and 12 $mg \cdot kg^{-1} \cdot h^{-1}$ decreased CBF by 28% and 39%, respectively, and $CMRo_2$ by 5% and 22%, respectively. Stephan *et al.*[9] demonstrated that CBF and $CMRo_2$ were decreased by 51% and 36%, respectively, after induction of propofol anesthesia in patients undergoing coronary artery bypass surgery. Vandesteene *et al.* [10] also reported that propofol infusion reduced CBF by 28% and $CMRo_2$ by 18% in patients anesthetized with enflurane and nitrous oxide. These findings suggest that a reduction of $CMRo_2$ seems to be less than that of CBF during propofol anesthesia, indicating that the CBF/$CMRo_2$ ratio may be reduced during propofol anesthesia under normothermic conditions.

Jugular venous bulb oxygen saturation has been used as an indirect assessment of global cerebral oxygen use to guide physiologic management decisions in a variety of clinical settings.[18–20] When demand exceeds cerebral oxygen supply, the brain extracts greater oxygen, resulting in decreased Sjo_2. In contrast, when cerebral oxygen supply exceeds demand, Sjo_2 is increased. Therefore, Sjo_2 well reflects CBF/$CMRo_2$ ratio. Previous studies suggested that an Sjo_2 of less than 50% is indicative of cerebral hypoperfusion and that values of Sjo_2 of less than 40% may be associated with global ischemia.[21,22]

Jansen *et al.*[11] compared Sjo_2 values and the incidence of desaturation during propofol and isoflurane–nitrous oxide anesthesia in patients undergoing brain tumor surgery. They demonstrated that Sjo_2 values were significantly less during propofol anesthesia than during isoflurane–nitrous oxide anesthesia, with mean values of 49% and 60%, respectively, and 50% of patients had an Sjo_2 of less than 50% during propofol anesthesia. Munoz *et al.*[12] also reported that mean Sjo_2 values were 50% under propofol anesthesia during brain tumor surgery and that the incidence of Sjo_2 of less than 50% was higher under propofol anesthesia compared with sevoflurane–nitrous oxide anesthesia (60% *vs.* 20%). Kawano *et al.*[13] demonstrated that during mild hypothermia (34.5°C), Sjo_2 values during propofol anesthesia were significantly lower than those during sevoflurane–nitrous oxide anesthesia and, when hypocapnia was induced, the incidence of Sjo_2 of less than 50% reached to 80% during propofol anesthesia.

Because these previous data suggested that Sjo_2 values tend to be low during propofol anesthesia, we hypothesized that increasing doses of propofol may reduce Sjo_2 values and increase the incidence of Sjo_2 of less than 50%. However, to our knowledge, there has been little information on dose-related changes in Sjo_2 values and the incidence of Sjo_2 of less than 50% under propofol anesthesia. As a result, increasing concentrations of propofol did not affect Sjo_2 values and the incidence of Sjo_2 of less than 50% as long as propofol is used within a dosage ranging from 3 to 7 μg/ml. In addition, the incidence of Sjo_2 of less than 50% was lower (approximately 20–30%) compared with results in previous studies (> 50%), probably because normocapnia was maintained in the current study.[11–13]

In the current study, we used a recently available TCI system, Diprifusor, to infuse propofol, which consists of a pharmacokinetic model, a specific set of pharmacokinetic parameters for propofol, and infusion algorithms. This TCI device can provide a means for producing relatively stable, controllable plasma concentrations of propofol administered intravenously. Although the predictive performance of the Diprifusor TCI system has been considered acceptable for clinical purposes, several investigators have indicated the individual deviations in propofol pharmacokinetics.[23,24] In addition, the induction of hypothermia can affect the predictive performance of the Diprifusor. The results in the current study showed that measured propofol concentrations at 7 μg/ml were significantly higher under mild hypothermia than normothermia, although these are similar at 3 and 5 μg/ml between the groups. These data suggest that a reduction in temperature to 34.5°C may affect the accuracy of TCI system, especially at high concentrations of propofol.

There are several limitations in the current study. First, we evaluated Sjo_2 during the administration of propofol at 3, 5, and 7 μg/ml. These concentrations were commonly used in a clinical practice to keep the patients unconscious. However, if lower or higher concentrations of propofol were used, Sjo_2 might be changed. Second, arterial and jugular venous blood were sampled at least 10 min after both predicted blood and effect site propofol concentrations were kept at each target concentration. If propofol was administered for a longer period, the results might be different. Third, in the current study, normocapnia was maintained to avoid the

decrease in Sjo_2. However, in a clinical situation, mild hypocapnia may be applied to control the intracranial pressure. Induction of hypocapnia may affect the results. Finally, the Sjo_2 catheter was inserted in the right side in all cases because most patients have dominant right-sided drainage for the jugular vein. Because we did not examine this drainage system by angiography in each patient, variation in the drainage system might have affected the results.

In summary, we investigated the effects of increasing concentrations of propofol on Sjo_2 in neurosurgical patients under normothermic and mildly hypothermic conditions. Although the induction of mild hypothermia can affect the accuracy of TCI system, especially when high concentrations were targeted as propofol dosages, the changes in propofol concentrations did not affect Sjo_2 values as long as propofol was administered in dosages commonly used in clinical practice.

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