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An induction dose of propofol does not alter cerebral blood flow determined by single-photon-emission computed tomography

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Abstract
Purpose. To examine the effect of propofol per se on cerebral blood flow (CBF), we measured CBF by single-photon-emission computed tomography (SPECT) using a technetium-99m ethyl cysteinate dimer before and after propofol administration.
Methods. Ten healthy adult male volunteers were studied. Ten minutes after isotope injection, CBF was measured using a SPECT system. After this first SPECT scan, 1.5 mg·kg^{-1} of 1% propofol was administered over 30 s and the same dose of isotope was injected 2 min thereafter. Ten minutes later, a second SPECT scan was carried out. A subtraction SPECT image was obtained by reducing the first SPECT image from the second SPECT image. Based on these SPECT images, various regions of interest (ROI) were traced. Changes in regional CBF to each ROI were analyzed by a comparison of the total γ-ray counts in each ROI between the first and subtraction SPECT images.
Results. The total γ-ray counts in each ROI did not change significantly after propofol administration. At this time, end-tidal carbon dioxide concentration and heart rate did not change, but blood pressure and oxygen saturation decreased slightly.
Conclusion. The present result suggests that the induction dose of propofol does not alter CBF.

Key words: Propofol, Cerebral blood flow, Single-photon-emission computed tomography, SPECT, Technetium-99m-ECD

Introduction

Propofol is known to decrease cerebral blood flow (CBF) when it is infused along with other anesthetics in humans [1] or animals [2]. Since propofol decreases cerebral metabolism [3], the coupling hypothesis that CBF decreases as cerebral metabolism is suppressed [4,5] has been used to explain these results. However, as far as we know, there have been no reports describing the effect of infusion of propofol alone on human CBF. Regarding the effect of anesthetics on CBF, two factors should be considered: the effect on cerebral autoregulatory ability and the direct effect on cerebral vessels (constriction or dilatation). Propofol has been demonstrated not to impair cerebral autoregulatory ability [2,6,7], whereas there have been two conflicting reports [8,9], regarding the direct cerebrovascular effect of propofol. Thus, the effect of infusion of propofol alone on CBF cannot be estimated. The present study was designed to examine the changes in regional CBF after a single bolus injection of propofol by single-photon-emission computed tomography (SPECT) in healthy volunteers.

Materials and methods

Ten healthy adult male volunteers were enrolled into this study after approval of the study protocol by the Institutional Committee. All volunteers were requested to take no drugs and to fast for 12 h before the study.

A 22-G intravenous catheter was placed into the left cubital vein, and acetated Ringer's solution was infused at a rate of 5 ml·kg^{-1}·h^{-1}. An auto-sphygmomanometer, a cardioscope, and instruments for monitoring of oxygen saturation (SpO_2) and end-tidal carbon dioxide concentration ($ETco_2$) were attached. The subject was placed in the recumbent position with eyes masked, while $ETco_2$ was measured by sealing a mask on his face. Subsequently, technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD) 500 MBq was administered intravenously. Ten minutes later, CBF was measured with a SPECT system, which took about 20–30 min. After this

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first SPECT scan, 1.5 mg·kg^{-1} of 1% propofol was injected over 30 s. A second injection of ^{99m}Tc-ECD 500 MBq was made 2 min after completion of the propofol injection. After propofol injection, ventilation was assisted manually by the face mask with room air to maintain the $ETco_2$ within ±2 mmHg of the control value measured before the first SPECT scan. Assisted ventilation was continued and $ETco_2$ was recorded every 1 min until sufficient spontaneous breathing resumed. Ten minutes after injection of the isotope, a second SPECT scan was performed in the same way. During this experiment, blood pressure, heart rate, and SpO_2 were recorded every 1 min.

The SPECT system used in this study was a ring type for the head (Shimadzu Headtome SET-031, Shimadzu, Kyoto, Japan). SPECT images were expressed as a horizontal section parallel to the orbitomeatal line, and a total of six tomograms from the parietal to the cerebellar regions were obtained (Fig. 1). The γ-ray energy of ^{99m}Tc-ECD incorporated into the brain during the first SPECT scan remained in the second SPECT scan. This energy has been demonstrated to be almost retained, in which no washout of the energy from the brain is observed until 20 min, and a maximum of 6% of the energy is washed out per hour for 6 h [10–13]. This characteristic of ^{99m} Tc-ECD results in the generation of almost the same SPECT image at any time from 5 min to several hours after isotope injection, and these images depict CBF at the time 1 min after isotope injection. Thus, the γ-ray counts obtained from the second SPECT included the γ-ray counts obtained from the first SPECT, so that the net SPECT image after

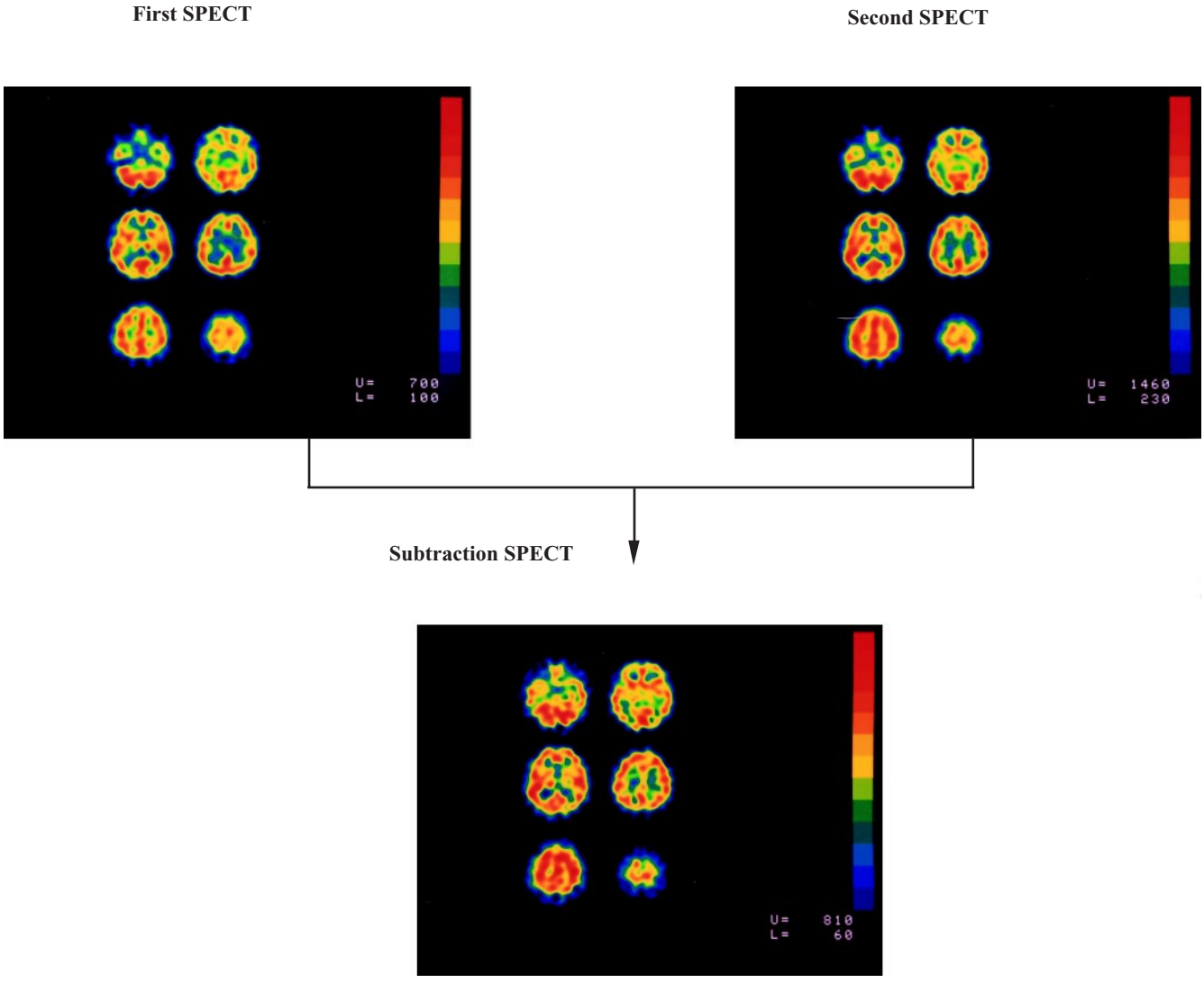

Fig. 1. Images of single-photon-emission computed tomography (SPECT). In a single scan, a total of six horizontal tomograms from the parietal to the cerebellar regions are obtained. The subtraction SPECT is obtained by reducing the first SPECT from the second SPECT. The first SPECT shows the CBF image under nonanesthetized conditions, and the subtraction SPECT shows the CBF image under propofol-anesthetized conditions

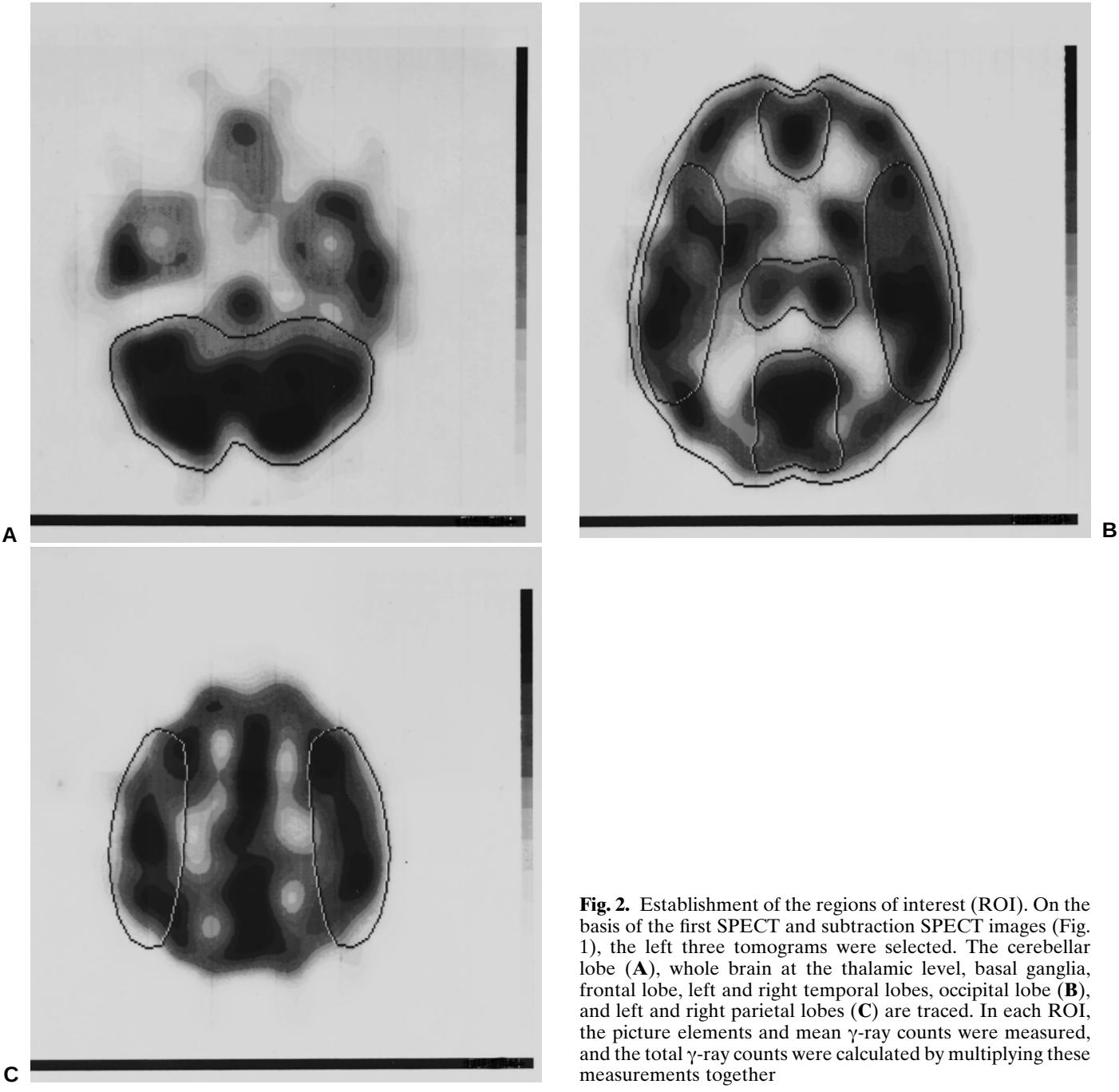

Fig. 2. Establishment of the regions of interest (ROI). On the basis of the first SPECT and subtraction SPECT images (Fig. 1), the left three tomograms were selected. The cerebellar lobe (**A**), whole brain at the thalamic level, basal ganglia, frontal lobe, left and right temporal lobes, occipital lobe (**B**), and left and right parietal lobes (**C**) are traced. In each ROI, the picture elements and mean γ-ray counts were measured, and the total γ-ray counts were calculated by multiplying these measurements together

propofol injection could be calculated by subtraction of the first SPECT image from the second SPECT image (Fig. 1). The principle of this measurement technique as the repeated isotope injection has been commonly applied to the estimation of acetazolamide activation test in various patients with stroke [14,15].

To establish the regions of interest (ROI), the cerebellar lobe (Fig. 2A), whole brain at the thalamic level, basal ganglia, frontal lobe, left and right temporal lobes, occipital lobe (Fig. 2B), and left and right parietal lobes (Fig. 2C) were traced from the first SPECT image (nonanesthetized condition) and the subtraction SPECT image (propofol-injected condition). The picture elements and mean γ-ray counts in each ROI were measured, and the total γ-ray counts were calculated by multiplying these measurements together. Since total γ-ray counts have been demonstrated to correlate linearly with CBF [12,16,17], this calculated value can be regarded as the regional CBF in each ROI.

Data are presented as means ± SD (range). Differences in $ETco_2$ before the first SPECT scan and after propofol injection were analyzed by the paired Student's *t* test. Comparisons of the mean blood pressure (MBP), heart rate (HR), and SpO_2 over time were analyzed by repeated-measure analysis of variance (ANOVA). Statistical comparison at each measurement time between groups was made by the unpaired Student's *t* test. Comparison within groups was made by repeated-measure one-way ANOVA followed by Fisher's PLSD for multicomparison, in which each value was compared with the control value. Changes in the total γ-ray counts in each ROI from the first SPECT to the subtraction SPECT images were analyzed by the paired Student's *t* test. $P < 0.05$ was considered significant.

Results

The subjects' age, weight, and height were 33 ± 5 (26–42) yr, 71 ± 7 (62–88) kg, and 173 ± 5 (163–181) cm, respectively. $ETco_2$ before the first SPECT scan was 30.7 ± 1.6 (28–33) mmHg. The time taken to resume sufficient spontaneous breathing after propofol injection was 6.5 ± 2.0 min (4–10 min). The values of $ETco_2$ immediately and 1, 2, 3, and 4 min after the propofol injection were 34.8 ± 1.6 (32–37), 30.4 ± 1.9 (28–35), 30.2 ± 1.9 (27–34), 29.9 ± 1.7 (28–33), and 29.8 ± 1.6 (28–33) mmHg, respectively. Compared with the $ETco_2$ measured before the first SPECT scan, $ETco_2$ increased significantly after propofol injection and returned to the same levels 1 min later. All volunteers showed a slight response to our verbal command before the second SPECT scan. The time taken to complete the second SPECT scan from the isotope injection for the first SPECT was 73 ± 5 (65–80) min.

Changes in MBP, HR, and SpO_2 during the first and second SPECT scan are shown in Fig. 3. MBP did not change significantly in the first SPECT, but decreased significantly in the second SPECT. Compared with the first SPECT, MBP decreased significantly in the second SPECT just before and after isotope injection. HR did not change significantly in either the first or the second SPECT, and no significant difference was seen between the values in both SPECTs. SpO_2 decreased significantly from 8 min in the first SPECT but decreased significantly immediately after propofol injection in the second SPECT. There were significant differences between the values in both SPECTs at all times except for 0, 10, and 13 min.

The results of the total γ-ray counts in each ROI in the first SPECT and subtraction SPECT images are shown in Table 1. No differences between the first SPECT and subtraction SPECT images were observed in any region.

Discussion

The isotopes used to measure CBF by SPECT are divided into dispersion-type tracers and accumulation-type tracers, depending on their intracerebral behavior. The dispersion-type and accumulation type-tracers include xenon-133 and technetium-99m hexamethyl propylene amine oxime (^{99m}Tc-HMPAO), iodine-123 isopropyl iodoamphetamine (^{123}I-IMP), and ^{99m}Tc-ECD, respectively. Xenon-133 has a low resolution for the head even in the SPECT system because of its low γ-ray energy, resulting in inaccurate CBF measurement, although previous reports [1,2] describing CBF reduction during propofol infusion used this isotope. On the other hand, ^{99m}Tc-HMPAO, ^{123}I-IMP, and ^{99m}Tc-ECD have high γ-ray energy, providing a CBF distribution image with high resolution. In particular, ^{99m}Tc-ECD has the following characteristics [10–13]: safety when administered at high doses; little remaining background compared with ^{99m}Tc-HMPAO and ^{123}I-IMP, as a result of

Table 1. Total γ-ray counts in each region of interest (ROI)[a]

ROI	Total γ-ray count	
	First SPECT	Subtraction SPECT
Cerebellar lobe	682059 ± 67904	679147 ± 81005
Whole brain at thalamic level	3271942 ± 265111	3261140 ± 182430
Basal ganglia	775728 ± 107171	775712 ± 106602
Frontal lobe	1792081 ± 193362	1783810 ± 192884
Left temporal lobe	1708858 ± 146014	1713889 ± 144429
Right temporal lobe	1707171 ± 146169	1707917 ± 145960
Occipital lobe	2134244 ± 189750	2127727 ± 181596
Left parietal lobe	414374 ± 30274	415891 ± 22735
Right parietal lobe	414022 ± 30110	415863 ± 22662

[a] Data are means ± SD. SPECT = single-photon-emission computed tomography

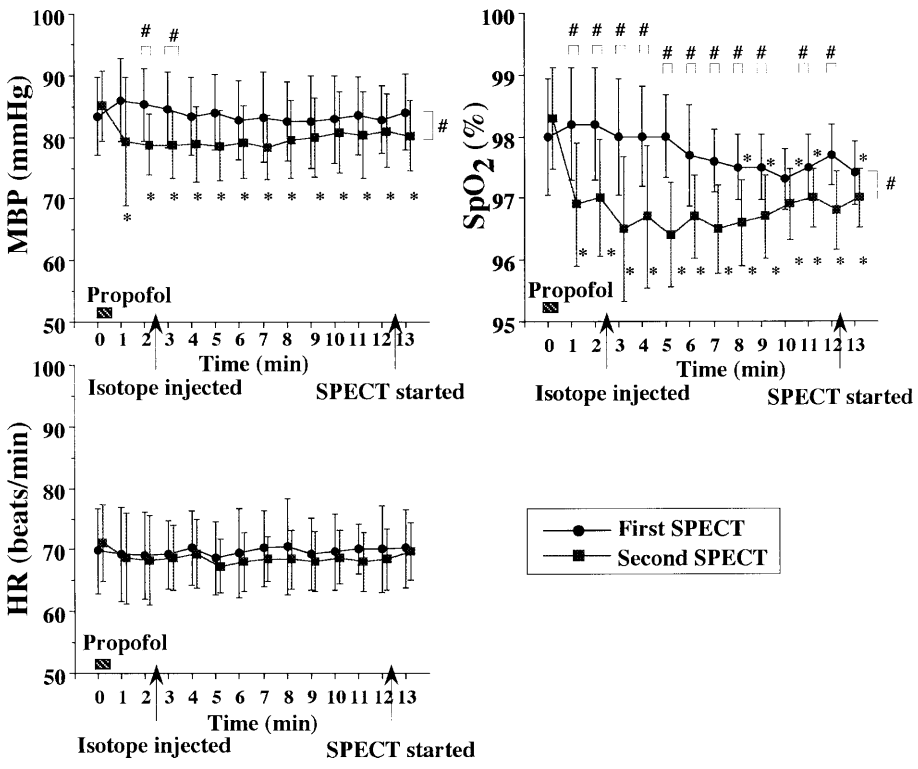

Fig. 3. Changes in mean blood pressure (*MBP*), heart rate (*HR*), and oxygen saturation (SpO_2) before the first and second single-photon-emission computed tomographic (*SPECT*) scans. Propofol was injected before the second SPECT scan. Data are means ± SD. $^*P < 0.05$ *vs* 0 min value, $\#P < 0.05$ between groups

less accumulation in soft tissues and rapid clearance from the blood; good affinity for the brain as a result of water solubilization with hydrolysis on the ester site of the ECD after passing the blood-brain barrier; stable and fixed imaging for several hours; and accurate determination of its CBF image about 1 min after isotope injection. Since the first SPECT image in this study showed CBF 1 min after intravenous administration of ^{99m}Tc-ECD, it was possible to visualize CBF under nonanesthetized conditions. During the second SPECT scan to measure CBF under propofol-anesthetized conditions, the γ-ray energy of ^{99m}Tc-ECD in the first SPECT scan remained. Since the duration from the first isotope injection to completion of the second SPECT was 65–80 min, the energy was assumed to be almost retained [10–13], so that the subtraction SPECT image obtained by reducing the first SPECT from the second SPECT should show CBF under propofol-anesthetized conditions.

The present results showed that the total γ-ray counts in each ROI did not change significantly after administration of 1.5 mg·kg^{-1} of propofol. At this time, $ETco_2$ and HR did not change, but MBP and SpO_2 decreased slightly. If these physiological parameters did not affect the CBF, the results can suggest that the induction dose of propofol does not alter CBF. Since propofol does not impair cerebral autoregulatory ability [2,6,7], this small change in MBP probably did not affect CBF. Despite maintenance of $ETco_2$ levels with manually assisted ventilation after propofol injection, SpO_2 before the second SPECT scanning decreased mildly. This finding could be attributed to increased venous admixture caused by a decrease in functional residual capacity or in the ventilation-blood perfusion ratio caused by a transient stopping of diaphragm movement. However, the depression in SpO_2 was minimal, suggesting no influence on CBF. In artificial ventilation, dead space increases so that the carbon dioxide concentration in the blood may increase slightly even when $ETco_2$ does not change. However, since we performed assisted ventilation after propofol injection, this effect would be minimal. Since CBF in this study was determined around 1 min after isotope injection, subsequent changes in physiological parameters from the time of isotope injection would have actually affected the CBF measurement. After isotope injection in the second SPECT, MBP and SpO_2 decreased mildly without change in $ETco_2$. Therefore, such small changes in physiological parameters would not have affected the CBF measurement.

According to computer simulation (PK-SIM, the pharmacokinetic simulator, Specialized Data Systems, Jenkintown, PA, USA), blood propofol levels in the cerebral circulation reach a peak 3–4 min after injection of 1.5 mg·kg^{-1}·30 s^{-1} of propofol, indicating levels of approximately 2500 ng·ml^{-1}. Since it is believed that the

maximum depth of anesthesia is obtained at this time, the isotope was injected 2 min after completion of propofol injection in this study in order to set the CBF measurement at a time when the propofol concentration in the cerebral circulation was at a maximum. The results have revealed no significant change in the total γ-ray counts in each ROI between the nonanesthetized and propofol-anesthetized conditions, suggesting that a propofol concentration up to 2500 ng·ml^{-1} has little effect on CBF.

The dose of propofol used in the present study is approximately the standard initial dose, and the blood propofol concentrations of 2500 ng·ml^{-1} are comparable to those obtained when a maintenance dose of 5–6 mg·kg^{-1}·h^{-1} is administered. We consider, therefore, that the standard dose of propofol does not affect CBF, although it has been thought that propofol decreases CBF [1,2,8]. In one report [1], propofol was administered after thiopentone injection and under low concentrations of enflurane, in which the effects of these drugs on the results were not considered. Furthermore, in this report on humans [1] and in another on animals [2], xenon-133 was used to measure CBF, although this isotope provides low-resolution images. A study using positron-emission tomography has proven that cerebral metabolism is suppressed by approximately 55% when the blood concentration of propofol is 3400 ng·ml^{-1} [3]. Although the coupling hypothesis between CBF and cerebral metabolism [4,5] has been used often to explain CBF reduction, whether this occurs during infusion of propofol alone has not been demonstrated. Propofol has recently been reported to have a cerebral vasodilatating action [9]. Even if there is coupling during propofol infusion, it is possible that CBF does not change due to the vasodilatating effect of propofol as a counterbalance. There is similar evidence from inhalational anesthetics, which increase CBF [18–20] while decreasing cerebral metabolism [21]. Since inhalational anesthetics have a greater cerebral vasodilatory action, they are considered to increase CBF as a whole, in spite of the existence of coupling in the regional brain tissue [22].

In conclusion, the present study examined changes in CBF after propofol injection by SPECT using ^{99m}Tc-ECD in healthy humans. The results showed that an induction dose of propofol at 1.5 mg·kg^{-1} has little effect on CBF. Although further study to elucidate the effects of greater concentrations or a continuous infusion of propofol on CBF are needed, we conclude that the standard induction dose of propofol does not alter CBF as long as the factors influencing cerebral autoregulation are maintained.

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