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Combined effects of propofol and mild hypothermia on cerebral metabolism and blood flow in rhesus monkey: a positron emission tomography study

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Abstract
Purpose. Propofol reduces the cerebral metabolic rate for oxygen ($CMRO_2$), regional $CMRO_2$ ($rCMRO_2$), cerebral blood flow (CBF), and regional CBF (rCBF), but maintains the coupling of cerebral metabolism and blood flow. Under mild to moderate hypothermia, the coupling is maintained, while rCBF is reduced, but no direct measurement of $rCMRO_2$ has yet been reported. This study aimed to evaluate the effects of propofol under normothermic and mild hypothermic temperatures upon $rCMRO_2$, rCBF, and their regional coupling, through direct measurement by positron emission tomography.
Methods. Rhesus monkeys were anesthetized with 65% nitrous oxide and propofol. Then rCBF and $rCMRO_2$ were measured under four sets of conditions: infusion of a low-propofol dose ($12\,mg \cdot kg^{-1} \cdot h^{-1}$) at normothermic temperatures (38°C), a high dose ($25\,mg \cdot kg^{-1} \cdot h^{-1}$) at normothermic temperatures, a low dose under mild hypothermia (35°C), and a high dose under mild hypothermia. The ratio of $rCBF/rCMRO_2$ was calculated from these data.
Results. Reductions in $CMRO_2$ and $rCMRO_2$ in most regions were associated with two factors: the higher propofol dose and the induction of hypothermia, but there was no interaction between these factors. Concerning blood flow, no significant reduction was observed, except for CBF by the induction of hypothermia. The ratio of $rCBF/rCMRO_2$ was constant in this study setting.
Conclusion. During propofol anesthesia, it is possible to reduce cerebral metabolism throughout the entire brain as well as in any brain region by increasing the propofol dose or inducing hypothermia. The concurrent use of these two interventions has an additive effect on metabolism, and can be considered as safe, as their combination does not impair the coupling of cerebral metabolism and blood flow.

Key words Propofol · Mild hypothermia · Cerebral metabolism · Cerebral blood flow · Coupling of cerebral metabolism and blood flow

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Introduction

Most intravenous anesthetics have an inhibitory effect on the central nervous system by suppressing cerebral electrophysiologic function [1], which results in a reduction in cerebral metabolism accompanied by decreased cerebral blood flow (CBF) [1]. In humans, administration of propofol results in reductions in the cerebral metabolic rate of oxygen ($CMRO_2$) [2,3], regional $CMRO_2$ ($rCMRO_2$) [4], CBF [2,3,5], and regional CBF (rCBF) [6], but the coupling of cerebral metabolism and blood flow is maintained at anesthetic doses [3]. In animal studies, propofol also decreases $rCMRO_2$ [7] and rCBF [7–9], but does not inhibit their coupling [7]. It has been suggested that propofol preserves both cerebral autoregulation [10–12] and carbon dioxide responsiveness [11–14].

Hypothermia reduces $CMRO_2$ [1,15,16] by suppressing cerebral electrophysiologic activity and decreasing cerebral metabolic activity, thereby working to maintain cellular homeostasis [1]. This reduction makes it useful for protecting the brain during cardiovascular surgery and as a therapeutic measure in patients with cerebral ischemia. Under mild to moderate hypothermia, the coupling of cerebral metabolism and blood flow is maintained [17,18], while rCBF is reduced [17]. However, to the best of our knowledge, no direct measurement of hypothermic $rCMRO_2$ has yet been reported.

The mechanisms by which intravenous anesthetics and hypothermia inhibit central nervous system activity are known to be different [1]. But the nature and extent of the interactions between these two interventions and those of the coupling of cerebral metabolism and blood flow remain poorly understood. We believe that elucidating the effect of the interaction between intravenous anesthetics and hypothermia upon $rCMRO_2$ and the coupling of cerebral metabolism and blood flow will lead us to a better understanding of

the safe management of general anesthesia under hypothermia.

Positron emission tomography (PET) is a nuclear imaging technique, used to measure gamma ray activity from chemical compounds labeled with positron-emitting isotopes. This technique enables the direct and noninvasive measurement of the regional distribution and kinetics of the labeled compounds in the body and brain, and the very short half-lives of the labeled isotopes allows for repeated measurements at brief intervals. These characteristics seemed to make PET the ideal method for this study, which required multiple measurements of $rCMRO_2$ and rCBF.

The aim of this study was to evaluate the effects of propofol under varying temperatures upon regional cerebral metabolism and blood flow, and their regional coupling in particular, through the direct measurement of $rCMRO_2$ and rCBF by PET in rhesus monkeys.

Materials and methods

The protocol of this experiment was approved by the Animal Ethics Committee, Central Research Laboratory, Hamamatsu Photonics.

General procedure

Three adult rhesus monkeys (*Macaca mulatta*), weighing 4.2–6.4 kg, were studied; in the first one, experiments were done three times, in the second, one time, and in the third, two times. These experiments were done on separate days at least 4 weeks apart. The animals were maintained and handled in accordance with United States National Institutes of Health recommendations on animal care and the guidelines of the Central Research Laboratory, Hamamatsu Photonics.

The animals were fasted but allowed free access to water for at least 12 h before the induction of anesthesia; 0.02–0.05 $mg \cdot kg^{-1}$ of atropine sulfate was given intramuscularly as premedication.

General anesthesia was induced by the intramuscular injection of 7.5–10 $mg \cdot kg^{-1}$ of ketamine hydrochloride. The animals were intubated using an endotracheal tube equipped with a cuff (Lo-Pro; Mallinckrodt, Athlone, Ireland), and mechanically ventilated to strictly maintain normocapnia (arterial partial pressure of CO_2 [Pa_{CO_2}], 39–41 mmHg).

During surgical procedures, anesthesia was maintained with 65% nitrous oxide (N_2O) and 2% sevoflurane. A cephalic vein was cannulated with a 24-G catheter, and lactated Ringer's solution was infused at 4 to 5 $ml \cdot kg^{-1} \cdot h^{-1}$. A femoral artery was cannulated with a 20-G catheter, and an intravascular probe, used for monitoring continuous blood gas (Paratrend 7; Diametrics Medical, St. Paul, MN, USA), was inserted into the artery through this catheter. After these procedures, sevoflurane was terminated, and anesthesia was maintained with 65% N_2O and propofol. An initial 25-mg bolus of propofol (3.9–6.0 $mg \cdot kg^{-1}$) was administered, followed by continuous infusion of propofol at 12 $mg \cdot kg^{-1} \cdot h^{-1}$. Vecuronium bromide was injected intermittently.

Arterial blood pressure, electrocardiograph, and rectal temperature were monitored throughout the study (Nihon Kohden, Tokyo, Japan). Pa_{CO_2} and Pa_{O_2} were monitored using a continuous blood gas monitoring system, and endtidal concentrations of inhalation anesthetics and CO_2 were monitored using an anesthesia machine (Cato, Dräger, Germany).

After the surgical procedures, the animal was kept in a supine position and its head was immobilized using an acrylic resin restraint developed by the study team. The orbito-meatal (OM) line was adjusted to the zero point of the PET scanner; 30-min-transmission scan data were collected before the first measurement.

After the measurements were completed, the animal was extubated and treated, following the animal care guidelines, after recovery from anesthesia.

PET scan

Data were collected using a high-resolution animal PET scanner (SHR-7700; Hamamatsu Photonics, Hamamatsu, Japan), with transaxial resolution of 2.6 mm full width at half maximum in the center of the scan field, and a center-to-center distance of 3.6 mm [19]. The PET camera allowed 16 to 17 slices for imaging to be recorded simultaneously.

Measurements

In this study, ^{15}O (half-life, 2.04 min) was used as the positron-emitting isotope.

For the measurement of rCBF and $rCMRO_2$, 2.3 $GBq \cdot min^{-1}$ of ^{15}O-CO_2 gas was used as a tracer to measure rCBF, and 2.0 $GBq \cdot min^{-1}$ of ^{15}O-O_2 gas was used to measure $rCMRO_2$. Each gas was continuously supplied through a gas administration system (Sumitomo Heavy Industry, Tokyo, Japan), and mixed into the oxygen and nitrous oxide in the anesthesia circuit. After the activity of gamma rays radiating from the cranium reached equilibrium, a 6-min scan was initiated. At the end of the scan, the delivery of gas was terminated, and an interval of more than 15 min was allowed before the next measurement to permit the isotope radioactivity to decay.

For the calculation of rCBF and $rCMRO_2$, the partition coefficient and hematocrit ratio were set at 0.95 and 0.85, respectively [19].

Conditions

In each experiment, rCBF and $rCMRO_2$ were measured under the following four sets of conditions, in the following order, at least 30 min apart.

Low-dose/Normo. Infusion of propofol given at 12 $mg \cdot kg^{-1} \cdot h^{-1}$ at normothermic temperatures (rectal temperature, ~38°C).

High-dose/Normo. Infusion of propofol given at 25 $mg \cdot kg^{-1} \cdot h^{-1}$ at normothermic temperatures.

Low-dose/Hypo. Infusion of propofol given at 12 $mg \cdot kg^{-1} \cdot h^{-1}$ under mild hypothermia (rectal temperature, ~35°C).

High-dose/Hypo. Infusion of propofol given at 25 $mg \cdot kg^{-1} \cdot h^{-1}$ under mild hypothermia.

In this study, we regarded low-dose/normo as the control condition; a low dose of anesthetic was necessary, as surgically treated animals require some form of sedation. During the experiments, blood pressure was maintained at the level of low dose/normo by the continuous infusion of angiotensin II (AT II; Sigma Chemical, St. Louis, MO, USA), as necessary.

The normal body temperature of the rhesus monkey is 38°C; this temperature was regarded as normothermia, and 35°C as hypothermia. Body temperature was maintained using a blanket, an electric warming mat, and disposable pocket warmers. Hypothermia was maintained by ventilating the air with a fan.

Statistical analysis

Areas in the frontal cortex, temporal cortex, parietal cortex, occipital cortex, cerebellar cortex, thalamus, and white matter were selected as regions of interest (ROI). The areas of these ROIs were chosen (or sectioned) in reference to magnetic resonance images ([MRI]; MRT-50A/II; Toshiba, Tokyo, Japan), and the stereotaxic coordination of PET and MRI was adjusted based on the OM reference line.

Datum for whole brain was calculated as the average of data from all slices, and datum for each ROI was calculated as that of two data from different slices. The ratio of $rCBF/rCMRO_2$ was calculated using the rCBF and $rCMRO_2$ data.

Two-way analysis of variance was used for statistical comparisons. The Student Newman-Keuls test was used as a post hoc test. In this study, $P < 0.05$ was considered to indicate statistical significance.

Results

Physiological variables (Table 1)

Mean arterial pressure (MAP) and heart rate (HR) varied in each subject, but in most cases, MAP was

Table 1. Physiological variables

		Normothermia		Hypothermia	
Experiment no.	Parameters	Low-dose propofol	High-dose propofol	Low-dose propofol	High-dose propofol
1	MAP/HR	130/160	130/150	130/130	125/130
	Pa_{CO_2}/RT	40.6/38.3	39.7/37.8	40.0/35.0	39.9/35.0
	AT II	0	13.0	5.0	15.0
2	MAP/HR	140/125	135/145	160/115	130/105
	Pa_{CO_2}/RT	39.6/37.5	40.4/37.8	40.5/34.9	39.9/35.0
	AT II	0	6.0	4.0	8.0
3	MAP/HR	125/150	135/145	135/120	125/130
	Pa_{CO_2}/RT	39.6/38.3	39.9/38.1	40.1/35.1	40.0/35.0
	AT II	0	2.5	0.5	1.5
4	MAP/HR	75/140	70/140	100/100	75/100
	Pa_{CO_2}/RT	40.0/38.1	40.2/38.1	39.6/34.8	39.7/34.9
	AT II	0	0.8	0	0.8
5	MAP/HR	75/120	70/120	80/100	70/90
	Pa_{CO_2}/RT	40.1/38.1	39.9/38.3	40.4/35.4	39.5/35.3
	AT II	0	0	0	0
6	MAP/HR	80/110	70/100	85/80	70/80
	Pa_{CO_2}/RT	39.7/38.2	39.7/38.4	40.1/35.1	40.2/35.3
	AT II	0	0	0.4	0.6

The condition of "hypothermia" was a significantly affecting factor for HR ($P = 0.003$)
Under the condition of "normothermia", body temperature was maintained at approximately 38°C, and under the condition of "hypothermia" body temperature was maintained at approximately 35°C. Under the condition of "Low-dose propofol", 12 $mg \cdot kg^{-1} \cdot h^{-1}$ of propofol was administered, and under the condition of "high-dose propofol", 25 $mg \cdot kg^{-1} \cdot h^{-1}$ of propofol was administered
MAP, mean arterial blood pressure (mmHg); HR, heart rate (bpm); Pa_{CO_2}, arterial partial pressure of carbon dioxide (mmHg); RT, rectal temperature (°C); AT II, dose of angiotensin II ($ng \cdot kg^{-1} \cdot min^{-1}$)

maintained at the same level as in low-dose/normo, the control value in this study. The maximum dose of AT II required to maintain MAP was 15 ng·kg^{-1}·h^{-1}. We did not attempt to maintain HR, which showed a significant reduction on the induction of mild hypothermia (P = 0.0026), but not on the increase of the propofol dose from 12 mg·kg^{-1}·h^{-1} to 25 mg·kg^{-1}·h^{-1} (P = 0.8752). In all cases, the rectal temperature of the subjects was maintained at approximately 38°C in the normothermic conditions, and at approximately 35°C in the hypothermic conditions. Pa_{CO_2} was maintained between 39 and 41 mmHg throughout all of the studies.

CBF and $CMRO_2$ in whole brain (Table 2)

$CMRO_2$ showed a significant reduction on the increase of the propofol dose from 12 mg·kg^{-1}·h^{-1} to 25 mg·kg^{-1}·h^{-1}, as well as on the induction of hypothermia. CBF significantly decreased under hypothermia. With the increased propofol dose, CBF decreased by 22% under normothermia and by 15% under hypothermia, but these changes were not statistically significant. There were no significant changes in CBF/$CMRO_2$.

Values of rCBF and $rCMRO_2$ (Table 3)

The $rCMRO_2$ values in all ROIs showed significant reductions on the induction of mild hypothermia. In all ROIs, except for the occipital and cerebellar cortexes, $rCMRO_2$ decreased significantly under the higher propofol dose, but rCBF was not significantly reduced by either the increased propofol dose or by hypothermia, the only exception being the frontal cortex, in which rCBF was reduced at the higher propofol dose. There was no significant change in regional CBF/$CMRO_2$ in any ROI, as was the case in the whole brain.

Discussion

The main findings of this study were: (1) reductions in whole brain $CMRO_2$ and $rCMRO_2$ in most ROIs were associated with two factors: the higher propofol dose and the induction of hypothermia, but there was no interaction between these two factors; (2) whole brain CBF decreased under hypothermia, but not at the higher propofol dose in this study setting; (3) no rCBF showed significant reduction under either higher propofol dose (except for that in the frontal cortex) or mild hypothermia; and, (4) CBF/$CMRO_2$ in both the whole brain and in all ROIs was unaffected by these factors.

In this study, $CMRO_2$ in the whole brain decreased in response to two factors, higher propofol dose and mild hypothermia, which was in line with findings from

Table 2. CBF and $CMRO_2$ in whole brain

	Normothermia		Hypothermia		*P* value		
	Low-dose propofol	High-dose propofol	Low-dose propofol	High-dose propofol	Propofol dose	Body temperature	Interaction
CBF	23.6 ± 7.1	18.5 ± 3.4	18.0 ± 4.7	15.6 ± 3.8	0.08	0.048*	0.51
$CMRO_2$	2.3 ± 0.3	1.8 ± 0.3	1.7 ± 0.4	1.4 ± 0.3	0.01*	0.003*	0.43
CBF/$CMRO_2$	10.4 ± 2.7	10.6 ± 1.9	10.6 ± 2.3	10.9 ± 1.9	0.77	0.80	0.95

*Factor that significantly affected CBF or $CMRO_2$ ($P < 0.05$)
Data values are presented as means ± SD
Under the condition of "normothermia", body temperature was approximately 38°C and under the condition of "hypothermia", it was approximately 35°C. Under the condition of "low-dose propofol", 12 mg·kg^{-1}·h^{-1} of propofol was administered, and under the condition of "high-dose propofol", 25 mg·kg^{-1}·h^{-1} of propofol was administered
CBF, cerebral blood flow (ml·min^{-1}·100 g tissue^{-1}); $CMRO_2$, cerebral metabolic rate of oxygen (ml·min^{-1}·100 g tissue^{-1}); interaction, interaction between the two factors of propofol dose and body temperature

Table 3. Values of rCBF and $rCMRO_2$

Region of interest	Parameters	Normothermia		Hypothermia		*P* value		
		Low-dose propofol	High-dose propofol	Low-dose propofol	High-dose propofol	Propofol dose	Body temperature	Interaction
Frontal cortex	rCBF	22.6 ± 7.4	16.7 ± 2.8	17.6 ± 4.6	14.5 ± 3.6	0.03*	0.09	0.50
	$rCMRO_2$	2.1 ± 0.4	1.5 ± 0.4	1.6 ± 0.5	1.3 ± 0.4	0.01*	0.048*	0.63
	$rCBF/rCMRO_2$	11.0 ± 4.1	11.4 ± 3.5	11.1 ± 3.5	11.9 ± 4.1	0.74	0.84	0.89
Temporal cortex	rCBF	25.5 ± 9.8	18.8 ± 3.8	18.9 ± 6.0	15.9 ± 5.2	0.08	0.09	0.49
	$rCMRO_2$	2.3 ± 0.5	1.7 ± 0.4	1.7 ± 0.5	1.4 ± 0.3	0.02*	0.02*	0.55
	$rCBF/rCMRO_2$	11.1 ± 3.4	11.0 ± 2.0	10.8 ± 2.0	11.0 ± 1.8	0.96	0.90	0.84
Parietal cortex	rCBF	22.1 ± 6.9	17.3 ± 3.4	17.2 ± 4.6	15.1 ± 3.7	0.10	0.09	0.50
	$rCMRO_2$	2.0 ± 0.4	1.5 ± 0.4	1.5 ± 0.5	1.3 ± 0.3	0.04*	0.02*	0.39
	$rCBF/rCMRO_2$	10.9 ± 3.0	11.7 ± 3.1	12.3 ± 3.9	12.3 ± 3.3	0.76	0.48	0.77
Occipital cortex	rCBF	22.0 ± 6.5	19.5 ± 5.1	17.8 ± 5.3	16.6 ± 5.0	0.43	0.13	0.77
	$rCMRO_2$	2.1 ± 0.4	1.7 ± 0.4	1.4 ± 0.2	1.4 ± 0.3	0.12	0.002*	0.21
	$rCBF/rCMRO_2$	10.5 ± 2.3	11.6 ± 2.5	12.4 ± 3.0	12.0 ± 2.3	0.72	0.27	0.47
Cerebellar cortex	rCBF	21.1 ± 5.7	18.7 ± 4.9	17.4 ± 5.3	15.8 ± 4.9	0.36	0.13	0.85
	$rCMRO_2$	2.1 ± 0.4	1.7 ± 0.3	1.5 ± 0.3	1.5 ± 0.3	0.16	0.002*	0.12
	$rCBF/rCMRO_2$	9.8 ± 2.1	10.7 ± 2.2	12.0 ± 3.5	10.5 ± 1.7	0.78	0.33	0.25
Thalamus	rCBF	24.1 ± 6.3	19.7 ± 5.7	18.9 ± 5.9	16.1 ± 4.6	0.13	0.07	0.74
	$rCMRO_2$	2.4 ± 0.3	2.0 ± 0.4	2.0 ± 0.6	1.6 ± 0.4	0.02*	0.03*	0.88
	$rCBF/rCMRO_2$	9.9 ± 2.6	10.1 ± 2.0	9.5 ± 2.4	10.3 ± 1.5	0.58	0.91	0.77
White matter	rCBF	24.5 ± 9.6	17.6 ± 3.5	17.5 ± 5.0	14.9 ± 3.7	0.06	0.06	0.40
	$rCMRO_2$	2.2 ± 0.4	1.8 ± 0.4	1.7 ± 0.4	1.5 ± 0.3	0.02*	0.01*	0.50
	$rCBF/rCMRO_2$	10.7 ± 3.6	10.0 ± 2.1	10.1 ± 2.1	10.1 ± 1.9	0.78	0.75	0.74

*Factor that significantly affected rCBF or $rCMRO_2$ ($P < 0.05$)
Data values are presented as means ± SD
Under the condition of "normothermia", body temperature was approximately 38°C and under the condition of "hypothermia", it was approximately 35°C. Under the condition of "low-dose propofol", 12 mg·kg^{-1}·h^{-1} of propofol was administered, and under the condition of "high-dose propofol", 25 mg·kg^{-1}·h^{-1} of propofol was administered
rCBF, regional cerebral blood flow (ml·min^{-1}·100 g tissue^{-1}); $rCMRO_2$, regional cerebral metabolic rate of oxygen (ml·min^{-1}·100 g tissue^{-1}); interaction, interaction between the two factors propofol dose and body temperature

numerous previous reports [2,3,15–18,20,21]. The $rCMRO_2$ values in all ROIs showed significant reductions under hypothermia, as expected [1]. The increased propofol dose was associated with significant reductions in $rCMRO_2$ in all ROIs except for the occipital and cerebellar cortexes. This exception arose from the results that $rCMRO_2$ in these two ROIs was not diminished by increasing propofol dose under mild hypothermia. It might be suggested that even mild hypothermia suppresses not only the energy requirement for the maintenance of cellular homeostasis but also a great amount of the requirement for electrophysiologic activity, so that increasing the propofol dose has little effect on $rCMRO_2$ in these ROIs.

One of our new findings is that there was no interaction between the effects of increased propofol dose and mild hypothermia on either $CMRO_2$ or $rCMRO_2$ in most of the ROIs, suggesting that the suppressive effect of these two factors on both the entire brain and specific brain regions under our experimental conditions was neither synergistic nor antagonistic, but simply additive. It is known that hypothermia causes reductions in cerebral metabolism by suppressing electrophysiologic activity and metabolic activity in the maintenance of cellular homeostasis, while propofol causes similar reductions by its inhibition of electrophysiologic activity [1]. It can be seen that electrophysiologic function is well maintained under mild hypothermia, so additional propofol may further suppress this function.

In this study, whole brain CBF was reduced on the induction of mild hypothermia, as has been reported elsewhere [15–17,22]. The higher propofol dose was associated with a 22% reduction of CBF under normothermia and a 15% reduction under hypothermia; however, these decreases were not statistically significant, and such findings are different from those reported in previous studies [2,3,5,20,21]. The rCBF did not show significant reductions in any ROIs either at the higher propofol dose or under hypothermia, with only one exception—the frontal cortex. It can be considered that the wide variation of rCBF and CBF values made it difficult to define the statistical significance of these decreases in rCBF and CBF.

In order to evaluate the coupling of cerebral metabolism and blood flow, CBF must be observed under stable cardiovascular conditions, while the cerebral metabolism is changed. But this method of observation could not be done in our study design; thus, we calculated $CBF/CMRO_2$ and used this ratio as the index of the coupling. In both the whole brain and specific brain regions, this ratio showed a wide range of variation in each subject, but did not show specific, statistically significant changes. We concluded that the coupling of cerebral metabolism and blood flow was not affected by either an increased dose of propofol or the induction of mild hypothermia. It has been reported in studies using the Kety-Schmidt method [3] or PET scans [7] that this coupling is maintained under propofol anesthesia. It has also been shown in studies using the colored microsphere method [17] or PET scans [18] that the coupling is maintained under mild to moderate hypothermia. Our findings are consistent with these previous studies.

Six experiments, using the PET technique, were performed on three rhesus monkeys in our study, which was rather small in number. But it should be noted that this technique is an expensive method because of the requirement for a cyclotron, and also it is difficult to keep a large number of primates in one facility. In spite of the limitation in sample numbers, using the PET technique in primates brings us many important findings, which cannot be obtained by ordinary methods, or from other species.

We induced anesthesia with ketamine hydrochloride, and it is well known that this agent increases $CMRO_2$, followed by an increase in CBF [1]. But as we found that the blood concentration of ketamine could not be detected at the time of the first measurement of PET in our previous study [23], we regard the influence of ketamine as negligible. We maintained anesthesia with sevoflurane during surgical procedures. In another previous study, we found that sevoflurane decreased $rCMRO_2$, but did not change rCBF or affect coupling [24]. However, in the present study, the endtidal concentration of sevoflurane was zero at least 30 min before the first PET measurement, and we have also regarded the influence of sevoflurane as negligible.

We used N_2O throughout this experiment, because analgesia was necessary to minimize the wound pain after the surgery. The lack of pharmacokinetic information for the rhesus monkey precluded the use of intravenous analgesics, including opiates, as it would have been impossible to maintain stable effect site concentrations throughout the study. It has been shown that N_2O increases CBF [25–28], and its effect plateaus at an inhalation concentration of approximately 30% [28]. But it has also been reported that the inhalation of 20% N_2O does not affect the coupling of cerebral metabolism and blood flow [27]. Given these data, it was our belief that the effects of an increased propofol dose and hypothermia on rCBF and $rCMRO_2$ could be evaluated, as long as the concentration of N_2O was kept constant throughout the study.

In the study reported by Enlund et al. [7], the basic dose of propofol in the rhesus monkey was $6\,mg \cdot kg^{-1} \cdot h^{-1}$, while our low-dose control was $12\,mg \cdot kg^{-1} \cdot h^{-1}$. In our pilot study, we observed changes in blood pressure and heart rate in response to weak auditory stimulation, at propofol doses of less than $10\,mg \cdot kg^{-1} \cdot h^{-1}$, which led us to conclude that $10\,mg \cdot kg^{-1} \cdot h^{-1}$ was the minimal anesthetic dose. Target-

controlled infusion provides an excellent method to maintain constant plasma and effect site concentrations of propofol, but the pharmacokinetic and dynamic parameters of propofol are not available for the rhesus monkey. Even mild hypothermia would have a suppressive effect on the metabolism of propofol, but its nature in this species is not well understood. Thus, we used constant dosage infusion in our study.

In conclusion, it is possible to reduce cerebral metabolism throughout the entire brain, as well as in any brain region, by increasing the propofol dose or by inducing hypothermia during propofol anesthesia. When these two interventions are combined, the reduction in metabolism is additive, and the coupling of cerebral metabolism and blood flow is not impaired. We consider the concurrent use of these two interventions as a superior alternative to either overdosage of propofol or profound hypothermia for the reduction of CBF and $CMRO_2$ without increasing the risk of complications.

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