Comparison of Intracarotid and Intravenous Propofol for Electrocerebral Silence in Rabbits

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Background: The high lipid solubility that permits rapid transfer across the blood–brain barrier makes propofol attractive for intracarotid injection. The authors hypothesized that intracarotid injection produces electrocerebral silence at a fraction of the intravenous dose and with less adverse systemic and cerebrovascular side effects.

Methods: The authors compared the systemic and cerebrovascular effects of intracarotid and intravenous propofol during transient (10 s) and sustained (1 h) electrocerebral silence in anesthetized New Zealand White rabbits. Hemispheric electrocerebral activity, mean arterial blood pressure, ipsilateral and contralateral cerebral blood flow, tympanic temperature, and end-tidal carbon dioxide were continuously monitored in these animals. Changes in outcome variables were analyzed at four time points: at baseline, during electrical silence, during burst suppression, and after recovery of electrocerebral activity. Propofol (1%) was injected as intracarotid (0.1 ml) or intravenous (0.5 ml) boluses.

Results: Intracarotid propofol produced electrocerebral silence at one fifth (sustained silence) to one tenth (transient silence) of the intravenous dose. Compared with baseline values, the mean arterial pressure and ipsilateral cerebral blood flow remained unchanged or decreased transiently during electrocerebral silence with intracarotid propofol. In contrast, intravenous propofol resulted in systemic hypotension and a decrease in ipsilateral cerebral blood flow.

Conclusions: Intracarotid propofol resulted in electrocerebral silence at a fraction of the intravenous dose that was not associated with systemic hypotension or a sustained decrease in the cerebral blood flow. Intracarotid propofol could be potentially useful for providing electrocerebral silence when cerebral perfusion is at risk.

INTRAVENOUS anesthetic drugs, when used to produce electroencephalogram silence, result in a significant depression of the cardiovascular system.[1–3] There is extensive anecdotal evidence that intraarterial injection of propofol does not result in vascular injury.[4–6] Further, intracarotid propofol has been used in humans for local-izing neurologic functions (Wada test).[7,8] The high lipid solubility of propofol (octanol–water partition coefficient of $\approx$ 7,000) that facilitates rapid transfer of drugs across the blood–brain barrier makes it particularly attractive for intracarotid delivery.[9] Computer modeling suggests that compared with intravenous injections, substantially high cerebral tissue concentrations can be achieved by intracarotid injection of drugs.[10] However, when intracarotid infusions are delivered over a prolonged period, the intracarotid–intravenous dose advantage decreases due to redistribution of the drugs.[11] Computer simulation studies must be interpreted with caution because kinetic models frequently fail to predict free drug concentrations after intracarotid injection.[9,12]

We hypothesized that it is feasible to sustain electrocerebral silence by intracarotid injection of propofol. Further, suppression of electrocerebral activity with intracarotid propofol can be achieved at a fraction of the intravenous dose. Such doses are unlikely to have adverse systemic or cerebrovascular side effects and will result in a prompt recovery of electrocerebral activity after cessation of drug infusion. Rabbits, like primates, have near-complete separation of the intracranial and extracranial arterial irrigation, thus providing a convenient model for investigating the effects of intracarotid drugs.[13] Further, in rabbits, propofol results in a spiking pattern during recovery from electrical silence that provides a consistent marker for injection of repeated doses of the drug. These spikes are $\approx$ 100 μV in amplitude and less than 100 ms in duration.[14] The goal of this study was to compare the dose requirements and hemodynamic side effects of intracarotid and intravenous propofol for transient (at least 10 s) and sustained (1 h) electrocerebral silence.

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Materials and Methods

After approval by the institution's animal care and use committee, the study was conducted on New Zealand White rabbits (weight, 3 to 4 lb). Animals were given full access to food and water before the experiment. The animals were sedated with intramuscular ketamine (50–100 mg/kg). Intravenous access was obtained through an earlobe vein. Surgery on rabbits has often been associated with infection that requires prophylactic antibiotics.[15] However, because of the relatively short duration of our experiments, 3 to 4 h, we used 10 mg intravenous hydrocortisone as an alternative to antibiotics to prevent hypotension due to surgical interventions. We have observed that administration of hydrocortisone results in

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greater hemodynamic stability of our preparation; therefore, we routinely use it during our experiments. After intravenous access was achieved, the animal received intravenous propofol (5- to 10-mg bolus) (Diprivan, 1%; AstraZeneca Pharmaceutical LP, Wilmington, DE) as needed for inducing adequate anesthesia. Anesthesia was subsequently maintained with continuous intravenous infusion of propofol at 1–3 ml/h. Intravenous propofol infusion was targeted at keeping the heart rate at less than 250 beats/min and the blood pressure at 90–100 mmHg.

After infiltration of the incision site with local anesthetic, bupivacaine (0.25%) with epinephrine at 1:200,000, a tracheotomy was performed for placement of an endotracheal tube and mechanical ventilation by a Harvard small animal ventilator (Harvard Apparatus, Inc., South Natick, MA). End-tidal carbon dioxide was continuously monitored with a Novametrix Capnomac monitor (Novametrix Medical Systems, Inc., Wallingford, CT). A femoral arterial catheter was placed for monitoring the mean arterial pressure (MAP). The right common carotid artery was dissected in the neck and cannulated using a 20-cm-long PE-50 tubing (Becton Dickinson and Company, Sparks, MD). The catheter tip was located ≈ 3–5 mm below the putative origin of the internal carotid artery (ICA). We have observed that ICA occlusion in rabbits tends to decrease the distal cerebral pressure within 80–90% of the MAP, which is clearly above the normal autoregulatory range. Experiments suggest that although occlusion may decrease hemispheric cerebral blood flow (CBF), unilateral ICA occlusion alone in these animals is unlikely to cause injury.[16-18] There are profound anatomic variations in the size and origin of rabbit ICA.[19,20] Therefore, rather than attempt retrograde cannulation, our approach was to isolate the ICA by cannulating the common carotid and ligating all branches other than the ICA. Correct identification of the ICA and its isolation was confirmed by the retinal discoloration test.[21] Briefly, this test entails injection of 0.1–0.2 ml indigo carmine blue (0.05%). Injection of indigo carmine blue changes the retinal reflex from red to blue when the ICA is correctly identified.

CBF was measured by a laser Doppler device (Periflux PF 5001; Perimed, Inc., Jarfalla, Sweden). Two probes (Probe 407–1; Perimed, Inc.) were placed on either hemisphere. For probe placement, the animals were turned prone and positioned on a stereotactic frame. The skull was exposed through a mid-line incision. A 5 × 4-mm area of the skull was shaved with an air-cooled drill just anterior to the bregma and 1 mm lateral to the mid-line. The skull was shaved to expose the inner table such that the cortical vessels could be seen through a fine layer of the bone as described in the literature.[22] The probes were maneuvered to obtain a laser Doppler blood flow reading of 50–250 perfusion units. Once the optimal site of placement was identified, the probes

were secured within plastic retainers and glued to the skull. Satisfactory probe placement was judged by an abrupt increase in probe reading during intracarotid injection of a small volume of saline (0.2 ml). The laser Doppler blood flow measurement technique provides a relative measure of blood flow changes in the tissue; therefore, laser Doppler blood flow values were normalized to the baseline value and were expressed as the percentage change from the baseline value. Cerebrovascular resistance was calculated in two ways. The absolute cerebrovascular resistance was calculated by dividing the MAP by the laser Doppler blood flow value (mmHg/the raw laser Doppler blood flow value). The relative cerebrovascular resistance was calculated by dividing the MAP by the percentage change in the laser Doppler blood flow value from the baseline value (mmHg/the percentage change in the laser Doppler blood flow value).

A hemispheric electroencephalogram was obtained on the side of drug infusion using stainless steel needle electrodes (impedance, < 10 kΩ) placed subcutaneously at the right frontal and parietal regions with the neutral electrode placed behind the ear. Frontoparietal electroencephalographic signals were recorded by a bioamplifier (ML136; AD Instruments, Grand Junction, CO), with a range of 100 mV and an electroencephalogram recording mode with a 0.3- to 60-Hz passband. Analog data were sampled at 40 Hz per channel with an analog to a digital converter and displayed using the Chart 4.0 program (AD Instruments). Electrocerebral silence was defined operationally, using a reference recording obtained with an identical recording technique from a known brain-dead preparation after administration in intravenous KCl.[18] Burst suppression was defined as the onset of spiking activity with 2 to 3 s of intervening electroencephalogram silence. Electroencephalogram recovery was defined as the return of electrocerebral activity with amplitudes and frequency composition comparable with those at baseline.[23] Duration of electrocerebral silence was the period between the onset of silence after the last injection and the onset of spiking activity. Recovery time was defined as the time between the onset of electrocerebral silence after the last injection and the recovery of regular electrocerebral activity comparable with that at baseline.

A tympanic temperature probe was used to monitor brain temperature (Mon-a-therm, 400H; Mallinckrodt Anesthesia Products, St. Louis, MO). The animal's temperature was kept constant at 37 ± 0.2°C using an electrically heated blanket. An intravenous infusion of fluid was given at $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ through an IVAC pump (IVAC 599 volumetric pump; IVAC Company, San Diego, CA). The intravenous infusion consisted of three fluids: lactated Ringer's solution, dextrose (5%), and albumin (5%) mixed in a ratio of 3:1:1, respectively. Electroencepha-

lographic recording, MAP, inspired and expired carbon dioxide concentrations, and laser Doppler blood flow values were continuously recorded on a computer using Powerlab software (AD Instruments).

During preliminary studies on two animals, we established the approximate dose requirements for intracarotid propofol (Diprivan, 1%). In these animals, electrocerebral silence was achieved with 0.2 and 0.3 ml (2 to 3 mg) of propofol, whereas the corresponding intravenous doses were 3 and 4.2 ml (30 and 42 mg), respectively. On this basis, we delivered propofol in boluses of 0.1 and 0.5 ml per injection with intracarotid and intravenous doses, respectively. We preferred bolus delivery of intraarterial propofol over continuous infusion because it was less susceptible to streaming, which causes uneven distribution of drugs.[24] Intravenous propofol results in a typical spiking pattern with a spike width of less than 100 ms and an amplitude of 100–200 μV.[14] The preliminary studies also revealed a similar spiking pattern with intracarotid and intravenous propofol during recovery from electrocerebral silence. The recordings during electrocerebral silence after propofol administration were identical to those observed after death—*i.e.*, a loss of detectable electroencephalogram signals and a background noise level less than 10 μV.

We undertook two experimental protocols: transient electrocerebral silence and sustained electrocerebral silence.

Transient Electrocerebral Silence

Animals in this group were tested twice with intracarotid and intravenous injections of propofol. First, they randomly received boluses of intracarotid or intravenous propofol and then crossed over to the alternate mode of drug delivery. The boluses were administered every 30 s, until electrocerebral silence was evident for at least 10 s. The animals were allowed to recover until electrocerebral activity returned to that at baseline as judged by its amplitude and frequency. Thereafter, the preparation was allowed to rest for 30 min. The baseline data were collected again, and propofol was injected by the alternate route to achieve at least 10 s of electrocerebral silence. Systemic and cerebral hemodynamic parameters were evaluated at four time points: at baseline; during electrocerebral silence; on return of intermittent spiking (burst suppression); and on (intravenous) return of electroencephalogram activity with amplitudes and frequency composition comparable with those at baseline.[23]

Sustained Electrocerebral Silence

The object of this arm of the study was to compare the dose requirements of intracarotid and intravenous propofol for producing electrocerebral silence for 1 h by repeated bolus injections of the drug (fig. 1). To avoid the effects of cumulative doses of the drug, the animals
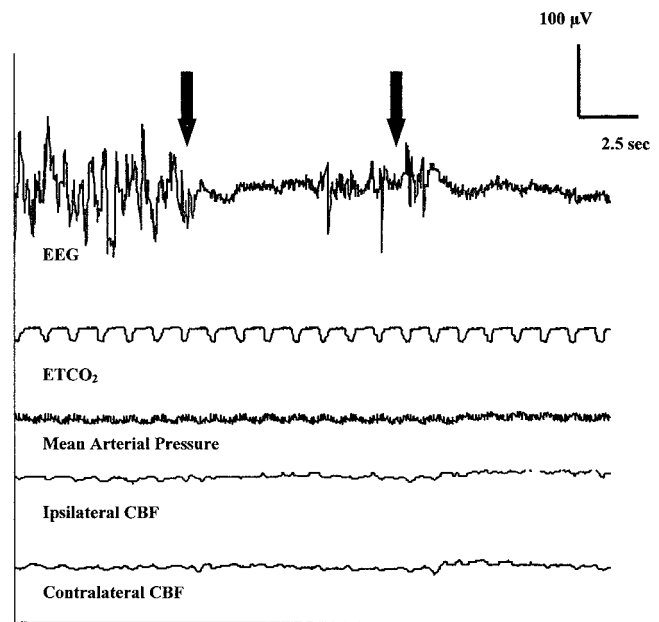

Fig. 1. Real-time data screen of an experimental study showing sustained suppression of electrocerebral activity after the first two intracarotid injections of propofol (0.1 ml) (*solid vertical arrows*). Data track changes in electrocerebral activity (EEG), end-tidal carbon dioxide (ETCO₂), mean arterial pressure (mmHg), and ipsilateral and contralateral cerebral blood flow (CBF) recorded by laser Doppler probes.

received either intracarotid or intravenous propofol. The surgical preparation was identical to the protocol described above. The only difference in the experimental protocol was that the repeated doses of the drug were administered whenever electrical spikes were evident on the electroencephalographic trace, so as to maintain electrocerebral silence for 1 h. The total dose of the drug required for the entire duration of the procedure was recorded. However, because electrocerebral silence was for a long duration, the lowest stable MAP and corresponding laser Doppler blood flow values were recorded to represent electrocerebral silence.

Histologic Examinations

Four animals in the intracarotid group were ventilated for 4 h after cessation of intracarotid propofol infusion. After these animals were killed with an overdose of saturated KCl, their brains were immediately obtained for histologic examination. Evidence of any gross neural injury was examined on hematoxylin–eosin-stained 7-μm-thick coronal forebrain sections.

Statistical Analysis

The data are presented as mean $\pm$ SD. The hemodynamic and laser Doppler blood flow data recorded at the four time points were analyzed by repeated-measures ANOVA. The Bonferroni–Dunn *post hoc* test was used to correct for multiple comparisons; accordingly, $P < 0.0083$ was considered significant. Comparisons be-

Table 1. Changes in Hemodynamic and Cerebrovascular Parameters during Transient (10 s) Electrocerebral Silence (n = 7)

	Intravenous Propofol				Intracarotid Propofol			
Dose (mg)	30 ± 10				3.5 ± 1.0*			
Duration of silence (s)	41 ± 50				21 ± 16			
Recovery time (s)	241 ± 83				110 ± 29*			

	Base	Silence	Burst Suppression	Recovery	Base	Silence	Burst Suppression	Recovery
ETco$_2$	36 ± 13	36 ± 13	36 ± 13	36 ± 13	36 ± 14	35 ± 14	36 ± 14	35 ± 14
MAP (mmHg)	85 ± 23	66 ± 15†‡	67 ± 15†‡	84 ± 23	97 ± 10	101 ± 18	91 ± 8	95 ± 7
%-Δ LDI	100 ± 0	75 ± 13†‡	73 ± 12†‡	97 ± 7	100 ± 0	96 ± 24	91 ± 13	98 ± 12
%-Δ LDC	100 ± 0	91 ± 21	88 ± 20‡	108 ± 19	100 ± 0	95 ± 13	93 ± 8	99 ± 7
Relative CVRI	0.8 ± 0.2	0.9 ± 0.3	0.8 ± 0.3	0.9 ± 0.3	1.0 ± 0.1	1.1 ± 0.3	1.0 ± 0.1	1.0 ± 0.2
Relative CVRC	0.8 ± 0.2	0.8 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	1.1 ± 0.1	1.1 ± 0.2	1.0 ± 0.1	1.0 ± 0.1
Absolute CVRI	1.3 ± 0.7	1.4 ± 0.8	1.4 ± 0.8	1.4 ± 0.9	1.3 ± 0.6	1.5 ± 0.9	1.4 ± 0.8	1.3 ± 0.6
Absolute CVRC	0.7 ± 0.3	0.6 ± 0.3	0.7 ± 0.3	0.6 ± 0.3	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.3

Significant differences: between intracarotid and intravenous groups; † from baseline; ‡ from recovery.

Absolute CVRC = cerebrovascular resistance (mmHg/laser Doppler blood flow value) contralateral to carotid cannulation; absolute CVRI = cerebrovascular resistance (mmHg/laser Doppler blood flow value) ipsilateral to carotid cannulation; ETco$_2$ = end-tidal carbon dioxide concentration; %-Δ LDC = percentage change of laser Doppler blood flow values from baseline in contralateral to carotid cannulation; %-Δ LDI = percentage change of laser Doppler blood flow values from baseline in ipsilateral to carotid cannulation; MAP = mean arterial pressure; relative CVRC = cerebrovascular resistance contralateral to carotid cannulation (mm Hg/%-Δ LDC); relative CVRI = cerebrovascular resistance (mm Hg/%-Δ LDI) ipsilateral to carotid cannulation.

tween the intravenous and intracarotid groups were performed by factorial ANOVA; $P < 0.05$ was considered significant. Statistical analysis was done by using Statview 5.0 software (SAS Institute, Inc., Cary, NC).

Results

The study included a total of 23 animals. All animals completed the experiment protocol (transient electrocerebral silence, n = 7; sustained electrocerebral silence, n = 16).

Transient Electrocerebral Silence

Seven animals were used for crossover comparisons between dose requirements for intracarotid and intravenous propofol for transient electrocerebral silence. The mean dose of intracarotid propofol (3.5 ± 1 mg) was significantly less than that of the intravenous dose (30 ± 10 mg, n = 7, $P < 0.0001$; table 1). Baseline MAP was comparable during intracarotid and intravenous propofol infusions. The MAP showed no significant change during intracarotid injection of propofol at all four stages. However, during intravenous injection, MAPs

during electrocerebral silence and burst suppression (66 ± 15 and 67 ± 15 mmHg, respectively) were significantly lower than the baseline and recovery values (85 ± 23 and 84 ± 23 mmHg, respectively; fig. 2). Ipsilateral CBF, expressed as the percentage change from the baseline value, did not decrease during intracarotid infusion. With intravenous propofol, the percentage change in the CBF during electrocerebral silence and burst suppression was significantly lower than the baseline and recovery values. There was no significant difference in the duration of electrocerebral silence after 10 s of electrocerebral inactivity between intravenous and intracarotid injections (41 ± 50 and 21 ± 16 s, respectively; $P = 0.3$). The recovery time was significantly longer after intravenous injection than after intracarotid injection (241 ± 83 vs. 110 ± 29 s, respectively; $P < 0.002$).

Sustained Electrocerebral Silence

Eight animals each received intravenous or intracarotid boluses of propofol to maintain electrocerebral silence for 1 h. The mean dose of propofol required in the intravenous and intracarotid groups was significantly different (258 ± 58 vs. 52 ± 13 mg, respectively, $P <$

Fig. 2. Changes in mean arterial pressure (mmHg) during transient (*left*) and sustained (*right*) electrocerebral silences. ● = intracarotid infusion; ○ = intravenous infusion; Burst Supp = burst suppression. Significant differences: *from baseline; @from recovery; #between intracarotid and intravenous groups.
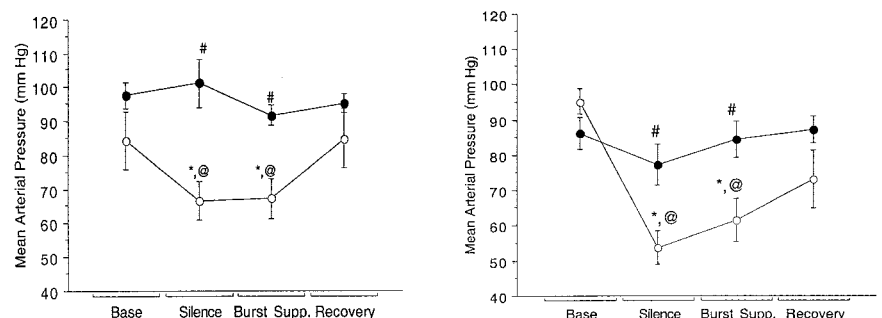
Table 2. Changes in Hemodynamic and Cerebrovascular Parameters during Sustained (1 h) Electrocerebral Silence

	Intravenous Propofol (n = 8)				Intracarotid Propofol (n = 8)			
Dose (mg)	258 ± 58				52 ± 13*			
Duration of silence (s)	55 ± 45				38 ± 31			
Recovery time (s)	510 ± 297				330 ± 148			

	Base	Silence	Burst Suppression	Recovery	Base	Silence	Burst Suppression	Recovery
ET$_{CO_2}$	38 ± 10	38 ± 10	38 ± 10	38 ± 10	33 ± 4	34 ± 5	33 ± 6	33 ± 6
MAP (mmHg)	95 ± 10	53 ± 13†	62 ± 17†	73 ± 23†	86 ± 12	77 ± 16*	85 ± 14†	87 ± 11
%-Δ LDI	100 ± 0	81 ± 7†	85 ± 18†	89 ± 17	100 ± 0	79 ± 17†‡§	99 ± 13	104 ± 15
%-Δ LDC	100 ± 0	84 ± 7	92 ± 29	93 ± 36	100 ± 0	97 ± 24	104 ± 20	116 ± 25
Relative CVRI	1.0 ± 0.1	0.7 ± 0.2†	0.7 ± 0.2	0.9 ± 0.3	0.9 ± 0.1	1.0 ± 0.3*	0.9 ± 0.2	0.8 ± 0.2
Relative CVRC	1.0 ± 0.1	0.7 ± 0.3	0.7 ± 0.3	0.9 ± 0.4	0.9 ± 0.1	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
Absolute CVRI	1.5 ± 0.8	1.1 ± 0.8	1.3 ± 0.9	1.4 ± 1.1	1.2 ± 0.7	1.5 ± 1.1	1.3 ± 0.7	1.2 ± 0.7
Absolute CVRC	1.1 ± 0.4	0.8 ± 0.3†	0.8 ± 0.3	1.0 ± 0.5	1.1 ± 0.6	1.1 ± 0.6	1.1 ± 0.6	1.0 ± 0.6

Significant differences: * between intracarotid and intravenous groups; † from baseline; ‡ from burst suppression; § from recovery.

Absolute CVRC = cerebrovascular resistance (mmHg/laser Doppler blood flow value) contralateral to carotid cannulation; absolute CVRI = cerebrovascular resistance (mmHg/laser Doppler blood flow value) ipsilateral to carotid cannulation; ET$_{CO_2}$ = end-tidal carbon dioxide concentration; %-Δ LDC = percentage change of laser Doppler blood flow values from baseline in contralateral to carotid cannulation; %-Δ LDI = percentage change of laser Doppler blood flow values from baseline in ipsilateral to carotid cannulation; MAP = mean arterial pressure; relative CVRC = cerebrovascular resistance contralateral to carotid cannulation (mmHg/%-Δ LDC); relative CVRI = cerebrovascular resistance (mmHg/%-Δ LDI) ipsilateral to carotid cannulation.

0.0001; table 2). Intravenous infusion of anesthetic drugs substantially decreased the MAP during electrocerebral silence, burst suppression, and recovery compared with that at baseline. The CBF on the side of drug infusion was low compared with that at baseline and during electrocerebral silence and burst suppression with intravenous infusion. However, the decrease in ipsilateral CBF during recovery was not significant compared with that at baseline. During intracarotid administration, the decrease in the CBF was transient and only lasted the duration of electrocerebral silence. There was no difference in the duration of electrocerebral silence or the time required for electroencephalographic recovery between intravenous and intracarotid groups.

Histopathologic Examination

The brains from four animals that received intracarotid infusion of propofol showed no evidence of any acute neuronal injury.

Discussion

There were four main results of this study: (1) intracarotid injection of propofol can achieve transient and sustained electrocerebral silence at a fraction of the intravenous dose; (2) intracarotid propofol sufficient to produce electrocerebral silence does not decrease the MAP; (3) the CBF was maintained despite electrocerebral silence with intracarotid infusion of propofol; and (4) compared with intravenous administration, recovery from an intracarotid anesthetic was faster during transient electrocerebral silence but not after sustained electrocerebral silence.

It is generally assumed that, irrespective of its kinetic properties, intracarotid infusion of a drug does not offer more than a twofold dose advantage over an intravenous infusion.[10,11] However, investigations into the kinetics of intracarotid drug delivery remain largely confined to antineoplastic agents.[10,25,26] Furthermore, the kinetics of repeated bolus injections of drugs that circumvent the problem of streaming have not yet been evaluated.[24,27,28] Few studies have addressed the kinetics of intracarotid anesthetics, which are highly lipid soluble and can easily penetrate the blood–brain barrier. Jones et al.[9] investigated the kinetics of intracarotid benzodiazepines. They observed that penetration of this class of drug into the brain is a function of lipid solubility, protein binding, molecular size, and degree of ionization. Reichenthal et al.[29] compared the dose requirements of intracarotid and intravenous amobarbital for electrical silence on electroencephalograms in rats. They observed that intracarotid administration was 10 times more efficacious than intravenous administration. This is similar to the intracarotid–intravenous dose ratio that was observed for transient electrocerebral silence with propofol in the current study.

The high lipid solubility and relative lack of endothelial toxicity of propofol make it suitable for intracarotid infusion.[10] Yet, this high lipid solubility also results in rapid elimination of the drug from the brain. Therefore, although electrocerebral silence could be rapidly achieved with intracarotid propofol, sustaining it would require frequent administration of the drug and hence a greater dose. In theory, this could explain the difference in the intracarotid–intravenous dose ratios for transient and sustained electroencephalogram suppressions in the present study. During transient electrocerebral silence, the intracarotid–intravenous dose ratio was ≈ 1:10 com-

pared with a dose ratio of 1:5 required for sustaining electrocerebral silence for 1 h.

The major advantage of intracarotid propofol was a relative lack of systemic hypotension during electrocerebral silence. The MAP did not change during intracarotid administration of propofol during transient electrocerebral silence and decreased minimally during sustained electrocerebral silence. In contrast, the MAP decreased significantly during intravenous injection of propofol during both transient and sustained electrocerebral silences. Human data also suggest a significant decrease in the MAP during burst suppression by intravenous propofol.[1-3] Systemic hypotension due to propofol is largely attributed to peripheral vasodilation, a decrease in preload, and a mild degree of myocardial depression.[30,31] The extent to which systemic hypotension after intravenous injection of propofol is due to its effect on the central nervous system remains undetermined.

A possible explanation for the relative lack of hypotension after intracarotid injection of propofol could be due to the distribution of the intracarotid drug. The distribution of intracarotid drugs in rabbits has been demonstrated by injection of crystal voilet.[20] Intracarotid bolus injection of dye stains not only the ipsilateral cerebral cortex but also the dorsomedial aspect of the contralateral cerebral cortex. Such observations suggest that the effects of intracarotid propofol in this study were not confined to the ipsilateral cerebral cortex alone. Furthermore, intracarotid injection of dye does not stain medulla, pons, thalamus, and the mamillary bodies.[20] Our results suggest that intracarotid propofol probably fails to reach medullary vasomotor centers and that higher cortical regions of the brain play a minimal role in systemic hypotension due to propofol.

The third significant observation in this study was the relative lack of effect of intracarotid propofol on the CBF during transient electrocerebral silence. The decrease in the CBF after sustained electrocerebral silence with intracarotid propofol resulted in prompt recovery of blood flow once drug injections were stopped. The magnitude of the decrease in ipsilateral CBF during electrocerebral silence was between 20% and 25% of that at baseline. Measurements of the CBF and cerebral metabolic rate for comparable human subjects revealed that during electroencephalographic silence–induced steady-state intravenous infusions of propofol, the mean CBF was 44% and the cerebral metabolic rate for O_2 was 42% below the control values.[32] However, blood flow measurements during intracarotid injection of drugs must be interpreted with caution. The CBF in such situations can be influenced by a number of factors, including the effect of ICA occlusion,[33] suppression of brain metabolism,[34] direct vasodilator effects of the drug,[35] the method of measuring the CBF, hematocrit change during intracarotid drug injection, and biomechanical effects of drug injection. To the best of our knowledge, this is the first study to use laser Doppler probes on the inner table of the rabbit skull, a method that is frequently used in rodents.[22] Additional studies will be necessary to further investigate these observations.

The fourth significant observation of this study was that intracarotid infusion of propofol resulted in a rapid recovery of electrocerebral activity after transient silence. There was no significant difference in recovery time during sustained electrocerebral silence. However, there were wide individual variations in the duration of electrocerebral silence and recovery after intracarotid and intravenous infusion of propofol. One possibility is that the total dose of the drug used during sustained electrocerebral silence impacts recovery of electroencephalogram functions. Our baseline intravenous infusions of propofol were 1–3 ml/h, which generally have a minimal effect on electrocerebral activity and systemic and cerebral hemodynamics. However, the cumulative effect of the baseline propofol infusion cannot be discounted during sustained electrocerebral silence. Alternatively, there might be pharmacokinetic and pharmacodynamic differences between individual animals that could become significant over time. For example, Newman *et al.*[1] observed wide variations in the predicted target effect site concentrations of propofol required for burst suppression in human subjects (4,500–11,000 ng/ml).

This study reveals the potential benefits of intraarterial propofol with regard to decreasing the dose requirements, lack of systemic side effects, and maintaining the CBF. Advances in interventional neuroradiology provide unprecedented access to human cerebral circulation that compels us to further investigate the pharmacology of anesthetics delivered by the intraarterial route.

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