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Cerebral Blood Flow Affects Dose Requirements of Intracarotid Propofol for Electrocerebral Silence

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Background: **The authors hypothesized that cerebral blood flow (CBF) changes will affect the dose of intracarotid propofol required to produce electrocerebral silence.**

Methods: **The authors tested their hypothesis on New Zealand White rabbits. The first group of 9 animals received intracarotid propofol during (1) normoventilation, (2) hyperventilation, and (3) hypoventilation. The second group of 14 animals received intracarotid propofol with or without concurrent intraarterial verapamil, a potent cerebral vasodilator. The third group of 8 animals received bolus injection of propofol during normotension, during severe cerebral hypoperfusion, and after hemodynamic recovery.**

Results: **In the first group, there was a linear correlation between the dose of intracarotid propofol and percent change (%Δ) in CBF from the baseline due to changes in the minute ventilation, Total Dose (y) = 0.17 + 0.012 * %Δ CBF (x), n = 27, r = 0.76. In the second group, the dose of propofol was also a function of CBF change after verapamil, Total Dose (y) = 0.98 + 0.1 * %Δ CBF (x), n = 14, r = 0.75. In the third group, the duration of electrocerebral silence after intracarotid propofol (3 mg) was significantly increased with concurrent cerebral hypoperfusion compared with prehypoperfusion and posthypoperfusion values (141 ± 38 *vs.* 19 ± 24 and 16 ± 12 s, respectively, P < 0.0001).**

Conclusions: **The authors conclude that CBF affects the dose requirements of intracarotid propofol required to produce electrocerebral silence. Furthermore, the manipulation of CBF might be a useful tool to enhance the efficacy of intracarotid drugs.**

INTRAARTERIAL drugs have been anecdotally used to treat a variety of brain diseases such as brain tumors,[1,2] cerebral vasospasm,[3] and thromboembolic strokes.[4] Experiments in the 1980s suggested that conventional intracarotid drug infusions do not offer sufficient dose advantage that would justify their potential complications, such as embolic strokes.[5] Therefore, except in diagnostic radiology, where intraarterial anesthetics are routinely used to localize brain functions, intraarterial delivery is seldom the preferred route of drug delivery.[6]

With systemic administration of drugs, any increase in cerebral blood flow (CBF) increases the regional distribution of flow to the brain, hence the delivery of drug to the brain. To the contrary, computer simulations suggest that with intracarotid injections, regional drug delivery is enhanced with low regional blood flows.[7] However, to our best knowledge, these theoretical models have not been tested in *in vivo* experiments. In clinical settings, CBF can be manipulated by changing minute ventilation, inducing systemic hypotension below the lower limit of autoregulation, or injecting intraarterial vasodilators. We hypothesized that changes in CBF induced by the above means would affect the dose requirements of intracarotid drugs.

To test our hypothesis, we conducted our study in New Zealand White rabbits, which have a primate-like separation of the internal and external cerebral circulations.[8] We assessed how changes in CBF affected the electroencephalographic response to intracarotid propofol. Propofol is a highly unionized, lipid-soluble anesthetic drug, with an octanol:water partition coefficient of approximately 7,000:1.[9] Intraarterial injection of propofol is well tolerated by the vascular endothelium.[10] If CBF significantly affects the dose response of intracarotid propofol, then flow manipulation could be used in clinical setting to enhance the efficacy of intraarterial drugs.

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Materials and Methods

After the approval of the protocol by the institution's animal care and use committee (Columbia University, New York, NY), the study was conducted on New Zealand White rabbits (1.5–2.0 kg). The animals were given full access to food and water before the experiment. The animals were sedated with an intramuscular ketamine (50 mg/kg). Intravenous access was obtained through an earlobe vein. Hydrocortisone, 10 mg, was given after the placement of an intravenous line because it prevents hypotension, which sometimes occurs after surgical intervention in this animal species. Subsequently, the animal received 0.2-ml boluses of intravenous propofol (1% Diprivan; AstraZeneca Pharmaceutical LP, Wilmington, DE) as needed for maintaining adequate depth of anesthesia before tracheostomy. After infiltration of the incision site with local anesthetic, 0.25% bupivacaine with

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1:200,000 epinephrine, a tracheotomy was undertaken for placement of an endotracheal tube for mechanical ventilation by a Harvard small animal ventilator (Harvard Apparatus Inc., South Natick, MA). End-tidal carbon dioxide ($ETco_2$) was continuously monitored with a Novametrix Capnomac monitor (Novametrix Medical Systems Inc., Wallingford, CT). After securing the airway, anesthesia was maintained with intravenous infusion of 2–3 $ml \cdot kg^{-1} \cdot h^{-1}$ propofol. A femoral arterial line was placed for monitoring mean arterial blood pressure.

The right common carotid artery was dissected in the neck and cannulated using 20-cm-long PE-50 tubing (Becton Dickinson and Co. Spark, MD). Correct identification of the internal carotid artery (ICA) and its isolation was confirmed by the retinal discoloration test.[8] 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. Before the start of the experiment, when all leads and probes had been placed, we further tested the preparation with intracarotid injection of 0.3 ml propofol. If the internal carotid artery is correctly isolated, this dose should produce transient electrocerebral silence (approximately 10 s) or significantly attenuate electrocerebral activity. The preparation is then allowed to recover over the next 15 min.

An esophageal temperature probe was used to monitor core temperature (Nova Therm; Novamed Inc., Rye, NY). The animal's temperature was kept constant between 36° and 38°C using an electrically heated blanket. An intravenous infusion of fluid was given at 10 $ml \cdot kg^{-1} \cdot h^{-1}$ through an IVAC pump (IVAC 599 volumetric pump; IVAC Co., San Diego, CA). The intravenous infusion consisted of three fluids: lactated Ringer's solution, 5% dextrose, and 5% albumin mixed in a ratio of 3:1:1, respectively. Electroencephalographic recording, mean arterial blood pressure, end-tidal carbon dioxide, and laser Doppler flows were continuously recorded on a computer using Powerlab software (AD Instruments Inc., Grand Junction, CO).

To measure CBF, Doppler probes (probe No. 407-1; Perimed Inc., Jarfalla, Sweden) were placed on each hemisphere. For probe placement, the animals were turned prone and positioned on a stereotactic frame. The skull was exposed through a midline incision. A 5 × 4-mm area of the skull was shaved with a drill, slightly anterior to the bregma and 1 mm lateral to the midline. The skull was shaved to expose the inner table, such that the cortical vessels could be seen through a fine layer of bone as described in the literature.[11,12] The laser Doppler blood flow measurement technique measures the changes in tissue hematocrit and particle velocity in a small volume of tissue, approximately 1 mm^3. The baseline values can be affected by the site, the angle of probe placement, and the ambient light. It is recommended by the manufacturer that the normal probe reading on the brain should be around 100 perfusion units at baseline. We maneuvered the probes to obtain a baseline value of 50–250 perfusion units. We accepted a lower value because the ICA was occluded on the side. The higher value was limited to 250 such that any hyperemic response was well within the measuring range of the instrument, which is limited to 999 perfusion units. When the optimum site of placement was identified, the probes were secured within plastic retainers and glued to the skull. The probes were secured in plastic retainers to minimize any movement artifacts. Satisfactory probe placement was judged by an abrupt increase in the probe reading during intracarotid injection of a small volume of saline (0.1 ml). This 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 percent change (%Δ) from baseline value.

Frontoparietal leads were placed and used to monitor the bilateral electrocerebral activity. Electrocerebral activity was monitored using standard stainless steel needle electrodes (impedance is < 10 kΩ). The frontal and the parietal needle electrodes were secured to the skull by small stainless steel screws. The neutral electrode was placed in the temporalis muscle. Frontoparietal electroencephalographic signals were recorded using bioamplifier (ML136; AD Instruments, Grand Junction, CO) with a range of 100 mV and an electrocerebral activity recording mode having a pass-band of 0.3–60 Hz. Analog data were sampled at 100 Hz/channel with an analog-to-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 potassium chloride.[13] A burst suppression pattern was evident during recovery from electrocerebral silence that was characterized by transient bursts of electrocerebral activity within the 30- to 50-μV range spaced with intervening period of electrocerebral silence. Electrocerebral recovery was defined as the return of electrocerebral activity with amplitudes and frequency compositions comparable to baseline as judged by visual inspection. Injection of intracarotid propofol in the rabbit produces a typical spiking pattern on recovery from electrocerebral silence. These spikes are 50–200 μV in amplitude. Repeat doses of intracarotid drugs were given whenever the spikes were evident on the ipsilateral electroencephalographic tracings. The spikes appear earlier in the contralateral hemisphere than in the ipsilateral hemisphere and provide a consistent and reliable dosing endpoint. Injections were made by the same operator (J. J. E.) to maintain consistency with repeat dosing.

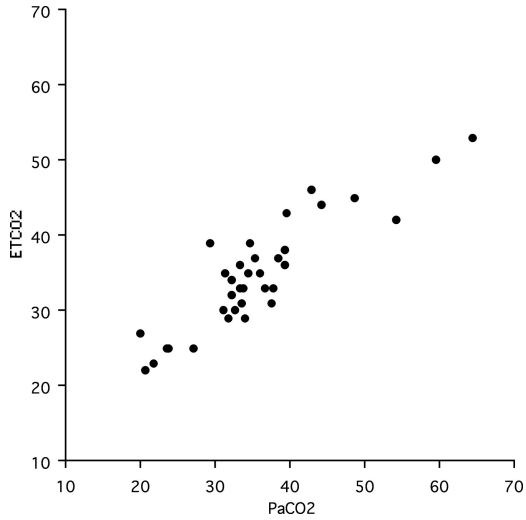

Fig. 1. Bivariate scattergram showing the linear correlation between partial pressure of carbon dioxide ($Paco_2$) in arterial blood and the end-tidal carbon dioxide ($ETco_2$) in the rabbit model. Thirty-five simultaneous measurements yielded an *R* value of 0.895, $P < 0.0001$.

Group 1

In the first arm of this study, we obtained baseline measurements of physiologic parameters under normocapnic conditions, 15 min after preparation had been challenged with 0.3 ml intracarotid propofol to verify isolation of the ICA. Animals were then randomly subjected to (1) normocapnic ventilation with an $ETco_2$ of 30–35 mmHg; (2) hyperventilation, $ETco_2$ of 20–25 mmHg; and (3) hypoventilation, $ETco_2$ of 45–50 mmHg. We tailored our ventilation to $ETco_2$ because of the robust correlation between $ETco_2$ and partial pressure of carbon dioxide in arterial blood ($ETco_2$ = 10.6 + 0.7 partial pressure of carbon dioxide in arterial blood, n = 35, $R = 0.895$; fig. 1). We altered the $ETco_2$ by changing the respiratory rate. Ventilation was maintained for 5 min before intracarotid propofol was injected.

To determine the loading dose, propofol (1% Diprivan, 0.1 ml) was injected every 10 s until electrocerebral silence was evident for at least 10 s. Thereafter, repeat doses of the drug (maintenance dose) were administered whenever electrocerebral activity was evident or when burst of electrocerebral activity returned. The silence was maintained for 10 min. Then, the preparation was allowed to recover without altering the ventilation. The total dose of anesthetic drug required for electrocerebral silence was the sum of loading and maintenance doses. When electrocerebral activity, CBF, and mean arterial blood pressure had returned to predrug levels, the ventilation was altered for the next ventilatory challenge.

Group 2

In the second set of animals, we undertook preliminary studies with intraarterial verapamil to establish the dose of verapamil that would increase CBF by approximately 100% for 10 min. Five animals received 0.1, 0.2, and 0.4 mg verapamil. An intraarterial dose of 0.4 mg was found to have the desired duration of effect. The definitive experiments were conducted in 14 animals, in which we first determined the dose of propofol required to produce 10 min of electrocerebral silence. After a 30-min period of rest, we determined the dose of propofol required to produce 10 min of electrocerebral silence with verapamil pretreatment.

Group 3

The third arm of the study required comparisons between the effects of intracarotid propofol with normal CBF and during hypoperfusion in the brain, secondary to severe systemic hypotension with contralateral ICA occlusion. Severe hypotension required large doses of esmolol (20 mg) and adenosine (30 mg). The use of such large doses of systemic drugs could alter the reactivity of the preparation. Therefore, we did not randomize the interventions but assessed the effects of propofol before and after the hypotensive challenge. The preparation was challenged three times with intracarotid propofol, *i.e.*, prehypoperfusion, hypoperfusion, and posthypoperfusion. For each challenge, the data were recorded at three time points, *i.e.*, before propofol injection, during electrocerebral silence with intracarotid propofol, and after propofol injection. For the first and third challenges, we obtained baseline measurements of physiologic parameters; then, the animal received a standard injection of 0.5 ml propofol, 1%. Considering that the dead space of the catheter and the stopcock was 0.2 ml, a 3-mg bolus of propofol was effectively delivered with each injection. Systemic hemodynamic, cerebrovascular, and electrocerebral effects of the drugs were continuously monitored. The preparation was allowed to recover for 45 min. In the hypoperfusion challenge after baseline measurement, intravenous esmolol and adenosine were injected as a bolus. This dose is sufficient to decrease CBF by 60–70% but does not result in electrocerebral silence.[14] At the peak of hypotension, 3 mg of 1% propofol injection was given through ICA. Electrophysiologic and hemodynamic parameters were assessed thereafter. The posthypoperfusion challenge was similar to the prehypoperfusion challenge that was undertaken 45 min later when a repeat bolus of 3 mg propofol was injected *via* the intracarotid route.

Data Analysis

The data are presented as mean ± SD. The hemodynamic and laser Doppler flow data, recorded at the three time points (baseline, silence, and recovery), were normalized to baseline value and analyzed by repeated-measures analysis of variance. A Bonferroni-Dunn *post hoc* test to correct for multiple comparisons was undertaken to determine significance, and a *P* value of less than 0.0167 was considered as significant. The correla-

Table 1. Changes in Parameters during Hyperventilation, Hypoventilation, and Normoventilation

n = 9	Challenge	Predrug	Drug	Recovery
Temperature, °C	Hypoventilation	36 ± 1	36 ± 1	36 ± 1
	Hyperventilation	36 ± 1	36 ± 1	36 ± 1
	Normal ventilation	37 ± 1	37 ± 1	36 ± 1
Respiratory rate, breaths/min	Hypoventilation	24 ± 5*	24 ± 5*	25 ± 5*
	Hyperventilation	74 ± 7*	74 ± 7*	74 ± 7*
	Normal ventilation	44 ± 6*	45 ± 6*	44 ± 6*
Heart rate, beats/min	Hypoventilation	219 ± 34	218 ± 30	221 ± 27
	Hyperventilation	265 ± 24*	254 ± 23*†	252 ± 27*†
	Normal ventilation	264 ± 29*	262 ± 21*	254 ± 32*
MAP, mmHg	Hypoventilation	88 ± 14	79 ± 17†	89 ± 13
	Hyperventilation	83 ± 18	72 ± 19*†	82 ± 24
	Normal ventilation	93 ± 12	85 ± 16†	91 ± 13
ET_{CO_2}, mmHg	Hypoventilation	47 ± 3*	49 ± 3*	49 ± 2*
	Hyperventilation	24 ± 3*	23 ± 3*	22 ± 2*
	Normal ventilation	36 ± 1*	36 ± 2*	34 ± 3*
LDF, PU	Hypoventilation	200 ± 71	175 ± 83	146 ± 68†
	Hyperventilation	140 ± 65	112 ± 51†	104 ± 49†
	Normal ventilation	135 ± 80	125 ± 70	110 ± 62†
CLD, PU	Hypoventilation	250 ± 163	194 ± 140†	174 ± 126†
	Hyperventilation	176 ± 164*	124 ± 95*	129 ± 104*
	Normal ventilation	187 ± 130*	160 ± 107*	148 ± 101*†
%Δ-ILD	Hypoventilation	157 ± 54	129 ± 29	107 ± 20†
	Hyperventilation	104 ± 22*	84 ± 12*	81 ± 23*†
	Normal ventilation	101 ± 19*	93 ± 14*	82 ± 6*†
%Δ-CLD	Hypoventilation	176 ± 50*	133 ± 40	113 ± 22
	Hyperventilation	101 ± 47	77 ± 15	79 ± 15
	Normal ventilation	105 ± 27	86 ± 19†	82 ± 19†

* Significant *post hoc* differences between ventilatory challenges ($P < 0.0167$). † Significant *post hoc* differences between stages of each drug challenge ($P < 0.0167$).

%Δ-CLD = percent change in contralateral laser Doppler from baseline; %Δ-ILD = percent change in ipsilateral laser Doppler from baseline value at the start of experiment; CLD = contralateral laser Doppler; ET_{CO_2} = end-tidal carbon dioxide concentration; ILD = ipsilateral laser Doppler; MAP = mean arterial pressure; PU = perfusion units.

tion coefficient (r) was determined by simple linear regression analysis, using Statview 5 software (SAS Institute, Cary, NC). The dose was the dependent variable and changes in CBF (x) were the independent variable (y). The P value was generated using regression analysis of variance.

Results

The study was conducted in a total of 32 New Zealand White rabbits, weighing 1.5 ± 0.5 kg, of which 31 yielded satisfactory data. In addition, we studied the response to intraarterial verapamil alone in five animals. Test injection of 0.3 ml propofol produced transient electrocerebral silence in all animals, suggesting adequate isolation of the ICA at the start of the experiments.

Group 1

In this group, we determined the effects of ventilation-induced changes in CBF on the dose requirements of intracarotid propofol. Satisfactory data could be collected from 9 of the 10 animals. Therefore, 27 data points were available from 9 animals. The mean ET_{CO_2} was significantly different during normal ventilation, hyperventilation, and hypoventilation (36 ± 1, 24 ± 3, and 47 ± 3 mmHg, respectively, n = 9, $P < 0.0001$). The temperature remained constant during the study (table 1). Hypoventilation was associated with a significant increase in CBF. Despite significant differences in ET_{CO_2}, there was no difference in blood flow during hyperventilation and normal ventilation (104 ± 22 and 101 ± 19, respectively, n = 9, not significant; table 1). The dose requirements of intracarotid propofol were significantly affected by the changes in ventilation. The total dose of the drug was the highest for hypoventilation (1.8 ± 0.3 mg) compared with both hyperventilation (1.0 ± 0.3 mg) and normal ventilation (1.4 ± 0.3 mg) (n = 27, $P < 0.0001$ from hypoventilation and 0.0062 from normal ventilation; table 2). There was a significant correlation between the total, loading, and maintenance doses

Table 2. Effect of Ventilation on Dose Requirements of Intracarotid Propofol

n = 9	Hypoventilation	Hyperventilation	Normal Ventilation
Total dose, mg	1.8 ± 0.3	1.0 ± 0.3*	1.4 ± 0.3†
Loading dose, mg	0.6 ± 0.2	0.3 ± 0.1*	0.4 ± 0.1†
Maintenance dose, mg	1.2 ± 0.3	0.7 ± 0.3*	1.0 ± 0.3

Significant differences between challenges ($P < 0.0167$): * between hypoventilation and hyperventilation; † between hypoventilation and normoventilation.

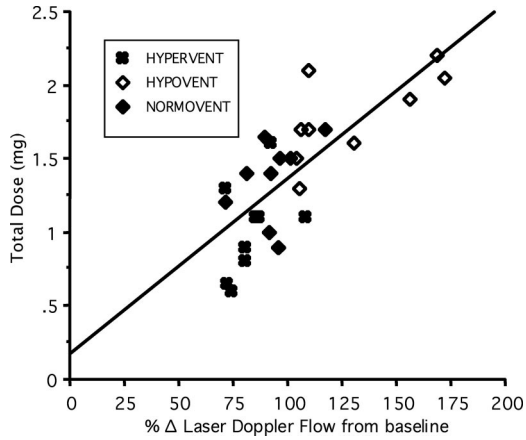

Fig. 2. Bivariate scattergram showing the effect of change in laser Doppler flow with ventilation on the dose requirements of intracarotid propofol (mg) to produce 10 min of electrocerebral silence.

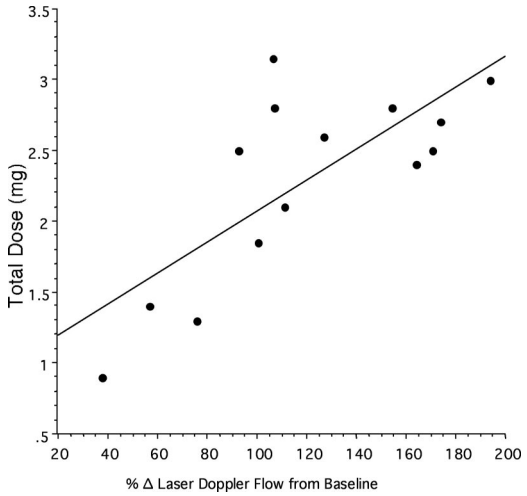

Fig. 3. Bivariate scattergram showing the effect of change in laser Doppler flow after intraarterial verapamil on the dose requirement of intracarotid propofol (mg) to produce 10 min of electrocerebral silence.

and the percent change in blood flow from baseline (table 2 and fig. 2).

Group 2

In preliminary experiments in 5 animals, we determined the dose of verapamil that would augment CBF by approximately 75–100%. These animals received 0.1, 0.2, and 0.4 mg verapamil in four divided doses, 10 s apart. At the highest dose, these animals demonstrated a sustained increase in peak increase in CBF of 75–100%, the increase in CBF that lasted at least for 10 min. Subsequently, in 14 animals, we undertook propofol followed by the verapamil–propofol challenge. The injection of 0.4 mg verapamil followed by the injection of propofol only modestly increased CBF. In 3 animals, verapamil pretreatment and concurrent propofol injection resulted in a decrease in laser Doppler blood flow after propofol. Compared with intracarotid propofol alone, verapamil pretreatment resulted in an increase in blood flow from baseline during propofol injection (84 ± 12% *vs.* 128 ± 41%, n = 14, $P < 0.05$; table 3). The total dose of intracarotid propofol was 15.9 ± 0.5 mg (n = 14) and was significantly increased after verapamil pretreatment to 22.9 ± 07 mg (n = 14, $P = 0.04$). After verapamil pretreatment, there was a strong linear relation between the increase in blood flow from baseline and the total dose of propofol (y = 0.1 * %Δ CBF (x) + 0.98, $r = 0.75$, $P = 0.002$; fig. 3).

Table 3. Changes in Parameters during Intracarotid Propofol and Verapamil and Propofol

n = 14	Drug Challenge	Predrug	Drug	Recovery
Temperature, °C	Propofol	37 ± 1	37 ± 1	37 ± 1
	Verapamil–propofol	37 ± 1	37 ± 1	37 ± 1
Respiratory rate, breaths/min	Propofol	35 ± 10	35 ± 10	35 ± 10
	Verapamil–propofol	32 ± 7	32 ± 7	32 ± 7
Heart rate, beats/min	Propofol	265 ± 16	244 ± 21†	243 ± 20†
	Verapamil–propofol	256 ± 21	228 ± 22†	228 ± 22†
MAP, mmHg	Propofol	96 ± 15	81 ± 15†	93 ± 17‡
	Verapamil–propofol	94 ± 13	72 ± 12†	86 ± 9‡
ET_{CO_2}, mmHg	Propofol	36 ± 3	35 ± 3	35 ± 4
	Verapamil–propofol	35 ± 3	35 ± 3	34 ± 4
ILD, PU	Propofol	143 ± 47	123 ± 50	128 ± 52
	Verapamil–propofol	143 ± 46	188 ± 82†	146 ± 67‡
CLD, PU	Propofol	131 ± 43	100 ± 36†	107 ± 29†
	Verapamil–propofol	134 ± 42	124 ± 50	110 ± 32†
%Δ-ILD	Propofol	100 ± 0	84 ± 12*†	81 ± 23†
	Verapamil–propofol	100 ± 0	128 ± 41†	99 ± 33‡
%Δ-CLD	Propofol	100 ± 0	77 ± 17†	90 ± 11‡
	Verapamil–propofol	100 ± 0	92 ± 21	84 ± 16‡

* Significant differences between (propofol *vs.* verapamil–propofol) challenges ($P < 0.05$). Significant *post hoc* differences between stages of each drug challenge ($P < 0.0167$): † from silence; ‡ from recovery.

%Δ-CLD = percent change in contralateral laser Doppler from baseline; %Δ-ILD = percent change in ipsilateral laser Doppler before challenge; CLD = contralateral laser Doppler; ET_{CO_2} = end-tidal carbon dioxide concentration; ILD = ipsilateral laser Doppler; MAP = mean arterial pressure; PU = perfusion units.

Table 4. Changes in Physiological Parameters during the Three Propofol Challenges

n = 8	Challenge	Baseline	Propofol/ Electroencephalographic Silence	Recovery
Temperature, °C	Prehypoperfusion	36.5 ± 0.8	36.5 ± 0.8	36.6 ± 0.7
	Hypoperfusion	36.6 ± 0.7	36.5 ± 0.8	36.4 ± 0.7
	Posthypoperfusion	36.4 ± 0.7	36.4 ± 0.7	36.5 ± 0.8
Respiratory rate, breaths/min	Prehypoperfusion	27 ± 4	27 ± 4	26 ± 4
	Hypoperfusion	27 ± 4	26 ± 4	26 ± 4
	Posthypoperfusion	27 ± 4	27 ± 4	26 ± 4
Heart rate, beats/min	Prehypoperfusion	239 ± 38	232 ± 32	237 ± 35
	Hypoperfusion	245 ± 34	134 ± 38*†	222 ± 23
	Posthypoperfusion	256 ± 24	231 ± 56	252 ± 26
MAP, mmHg	Prehypoperfusion	98 ± 14	97 ± 9	97 ± 13
	Hypoperfusion	97 ± 9	37 ± 13*†	89 ± 17
	Posthypoperfusion	96 ± 11	97 ± 14	96 ± 11
ET_{CO_2}, mmHg	Prehypoperfusion	32 ± 5	32 ± 5	32 ± 5
	Hypoperfusion	33 ± 5	27 ± 5*†	33 ± 5
	Posthypoperfusion	32 ± 5	32 ± 5	32 ± 5
ILD, PU	Prehypoperfusion	136 ± 73	183 ± 114†	91 ± 22
	Hypoperfusion	140 ± 46	86 ± 42†	78 ± 30†
	Posthypoperfusion	137 ± 30	168 ± 36†	82 ± 30†
CLD, PU	Prehypoperfusion	119 ± 70	137 ± 112	108 ± 63
	Hypoperfusion	127 ± 77	67 ± 46†	106 ± 65†
	Posthypoperfusion	109 ± 38	130 ± 39†	84 ± 29
%Δ-ILD	Prehypoperfusion	100 ± 0	130 ± 31*	93 ± 59
	Hypoperfusion	100 ± 0	61 ± 19*†	67 ± 40†
	Posthypoperfusion	100 ± 0	125 ± 25†	65 ± 32†
%Δ-CLD	Prehypoperfusion	100 ± 0	106 ± 45	92 ± 19
	Hypoperfusion	100 ± 0	55 ± 15†	84 ± 7†
	Posthypoperfusion	100 ± 0	122 ± 22†	77 ± 4†

* Significant *post hoc* differences between the three propofol challenges that were undertaken before, during, and after the hypoperfusion challenge, $P < 0.0167$. † Significant *post hoc* differences between stages of each challenge (baseline, propofol/electrocerebral silence, and recovery, $P < 0.0167$).

%Δ-CLD = percent change in contralateral laser Doppler flow; %Δ-ILD = percent change in ipsilateral laser Doppler from baseline; CLD = contralateral laser Doppler; ET_{CO_2} = end-tidal carbon dioxide concentration; ILD = ipsilateral laser Doppler; MAP = mean arterial pressure; PU = perfusion units.

Group 3

In 8 animals, we assessed the effect of injecting intracarotid propofol during cerebral hypoperfusion on the duration of electrocerebral silence. Systemic hypotension and contralateral ICA occlusion were associated with a significantly decreased ipsilateral laser Doppler blood flow during propofol injection by greater than 50% (130 ± 31, 125 ± 25, and 61 ± 19% for prehypoperfusion, posthypoperfusion, and hypoperfusion challenges, respectively, n = 8, $P < 0.0167$; table 4). There was a significant increase in the duration of electrocerebral silence when the injection of propofol was made during cerebral hypoperfusion compared with the injections made before and after the hypoperfusion challenge. Injection of propofol (3 mg) with normal cerebral perfusion resulted in 19 ± 24 and 16 ± 12 s for prehypoperfusion and posthypoperfusion, respectively, that were not statistically different (fig. 4). However, injection of propofol during hypoperfusion produced 141 ± 38 s of electrocerebral silence that was significantly greater that prehypoperfusion and posthypoperfusion values of 19 ± 24 and 16 ± 12 s, respectively ($P < 0.0001$, n = 8). Similarly, the recovery time was significantly prolonged when propofol was injected during cerebral hypoperfusion as compared with the prehypoperfusion and posthypoperfusion challenges (298 ± 54 *vs.* 130 ± 75 and 116 ± 61 s, respectively, n = 8, $P < 0.0167$).

Discussion

This study reveals that changes in blood flow due to altered minute ventilation, intraarterial vasodilators, or with induced hypotension significantly affect the dose response of intracarotid propofol. There was a strong linear correlation between the changes in blood flow due to changes in minute ventilation or with injection of intraarterial verapamil on the dose of intracarotid propofol required to produce 10 min of electrocerebral silence. Similarly, injection of propofol during severe systemic hypotension prolonged the duration of drug effect by approximately eightfold. This study supports the concept that an increase in CBF adversely affects the dose requirements of intraarterial drugs. Furthermore, it suggests that methods to safely decrease CBF could enhance the efficacy of intraarterial drugs.

The most outstanding finding of this study was that the dose of intracarotid propofol increase is linearly related to the increase in CBF. This is in contrast with studies that use intravenous delivery of drugs that show a decrease in dose requirement for intravenous anesthetics

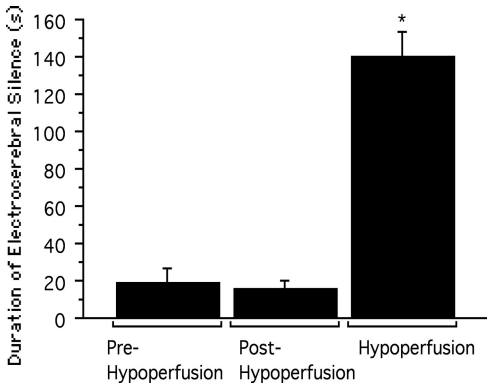

Fig. 4. Bar chart showing the effect of cerebral hypoperfusion with severe systemic hypotension on the duration of electrocerebral silence after bolus intracarotid injection of propofol (3 mg). Injection of propofol during severe systemic hypotension and cerebral hypoperfusion significantly prolonged the duration of electrocerebral silence compared with injection before and after hypoperfusion. * Significant difference between prehypoperfusion and posthypoperfusion propofol challenge.

with the increase in CBF.[15,16] During intravenous delivery, a greater proportion of the systemically administered drug is delivered to the brain with a proportional increase in blood flow. In contrast, during intracarotid delivery, when the delivery of the drug to the brain is an independent operator controlled variable, the uptake of the drug by the brain is a function of (1) drug extraction by the brain and (2) CBF.[7] The higher CBF, the greater is the dilution of the drug, the shorter the transit time, and the more rapid washout. Therefore, increase in CBF adversely affects dose requirements of intracarotid drugs by decreasing uptake and enhancing redistribution of the drug from the brain. Therefore, the findings of this study bear well with the theoretical predictions by Dedrick.[7] Based on computer simulations, Dedrick proposed that intraarterial drug delivery would be particularly suitable in three specific situations: (1) injection of drugs with high brain extraction, (2) those with high systemic clearance, and (3) injection of drugs in low regional blood flow states.

One of the fundamental problems with intraarterial drug delivery is streaming.[17,18] Streaming refers to uneven distribution of drugs within an arterial irrigation at low rates of drug infusion and injections in the distal branches of the cerebral arteries. Bolus injection of drugs particularly timed with diastole can avoid maldistribution of drugs due to streaming.[19] Few studies have addressed the kinetics of intracarotid bolus drug injections.[20] In a rat model, Jones *et al.*[21] observed 5- to 25-fold higher benzodiazepine concentrations in the brain than those predicted by conventional kinetic models of drug–protein binding. Propofol is a very lipid-soluble drug with an octanol:water partition coefficient of 6,871. It is highly nonionized and is very protein bound (98%).[9] In theory, high protein binding of propofol would decrease its uptake by the brain and could explain a prolonged equilibrium time with the brain and blood, 4–5 min, based on intravenous infusions.[15,22,23] However, during intracarotid bolus injections, protein binding is a less significant factor. It has been estimated that the blood volume in the rabbit brain is 1.89 ml/100 g.[24] Assuming the ICA irrigates 5 g of brain tissue, the effective blood volume will be less than 0.1 ml, equivalent to the bolus volume of the injected drug. Therefore, during our experiments, relatively concentrated drug was being delivered to the brain. We believe that, during bolus intracarotid injections, the CBF is transiently overwhelmed, and virtually pure drug is delivered to the brain. Delivery of pure drug could explain the failure of conventional kinetic models.

It is challenging to investigate the kinetics of intracarotid bolus drug delivery. Techniques such as microdialysis are difficult to apply in this situation because of low volume yield of microdialysate, which is approximately 2 μl/min. Such a low yield may be insufficient to detect changes in drug concentration when drug bolus is delivered over a few seconds. The high octanol:water partition coefficient of propofol, in theory, also poses technical problems during microdialysis of the drug. A possible method of measuring tissue drug concentration in real time noninvasively is elastic spin spectroscopy, which measures the changes in reflected light spectrum during drug injection.[25] However, elastic spin spectroscopy is not applicable to all drugs and has not yet been extensively validated *in vivo*. We have therefore used electrocerebral activity changes as a surrogate measure of tissue concentration. Plasma and brain tissue concentrations of propofol correlate well with electrocerebral activity.[26,27] Therefore, we believe our model provides a useful insight into the kinetics of intracarotid drug delivery.[28] One of the limitations to using electrocerebral to assess the tissue concentrations is acute tolerance to the effects of the drug. There are experimental data to suggest that there can be tolerance to the effects of propofol in acute animal preparation,[29] but the significance of acute tolerance to propofol has been challenged in other studies.[30]

A limitation of our model is the possible cerebral vascular effects of intraarterial anesthetic drugs that could alter blood flow and thereby affect drug kinetics. However, cerebrovascular effects of intracarotid propofol are usually benign. CBF is maintained during transient electrocerebral silence with intracarotid propofol and declines modestly when used to produce sustained electrocerebral silence. Blood flow changes after intracarotid drug injections are usually complex because they are affected by the mechanical artifacts from drug injection, the direct effects of the drug on the vascular endothelium, the distribution of intracarotid drugs, and the systemic responses to the recirculating drug. However,

drug flow is usually well maintained with intracarotid anesthetics, and it is unlikely to be a significant factor in influencing the outcome of this study.[20]

Finally, we would like to point to some issues related to the design of our experiments. First with regard to group 1, we altered the minute ventilation to alter CBF but did not use the alternate approach by altering inspired carbon dioxide. In our model, we have observed that the best way to alter CBF is by decreasing minute ventilation and not by altering inspired carbon dioxide. We have also observed that increasing minute ventilation in our model only minimally affects CBF despite significant decreases in partial pressure of carbon dioxide in arterial blood as well as $ETCO_2$. This could in part be explained by the unilateral occlusion of the ICA that results in some degree of baseline compensatory vasodilation that impairs response to hypocapnia. The baseline arterial tone affects cerebrovascular responses to dynamic challenges. It is also possible that injection of propofol could have impaired vasoconstrictor response in the preparation. This study focused on how blood flow changes affected intracarotid propofol dose requirements; therefore, we did not focus on why the response to hypocapnia was impaired in the preparation. If we did not observe a decrease in CBF with hyperventilation, how do we explain the decrease in dose requirement? One possible explanation might be that hyperventilation resulted in a decrease in cardiac output as is evidenced by a greater decrease in mean arterial blood pressure during electrocerebral silence (table 1). Changes in cardiac output could have altered the recirculating concentration of propofol. The mean arterial pressure was lower during hyperventilation (table 1), which would suggest a greater systemic effect of the recirculating drug.

With regard to the group 2, we did not randomize the propofol or the propofol–verapamil challenge. This decision was based on the observation that there was a very sustained increase in CBF with intraarterial verapamil (0.4 mg) in three of the five animals in the preliminary studies that lasted over 30–45 min. In contrast, both the hemodynamic and electrocerebral recovery effects of intraarterial propofol were exceedingly transient and occurred within 5 min of cessation of intracarotid drug injections. Therefore, it was logical to undertake the propofol challenge first, wait for a sufficient recovery period of time for recovery, and then undertake the propofol–verapamil challenge.

We conclude that the dose of intracarotid propofol needed to achieve electrocerebral silence is linearly related to the increase in CBF. Judiciously decreasing blood flow could enhance the efficacy of intracarotid drugs. The pharmacokinetic profile of carmustine, a drug approved by the US Food and Drug Administration for intraarterial chemotherapy of brain tumors, is similar to that of propofol. Therefore, results of this study could be applied for enhancing intraarterial delivery of antineoplastic drugs. In clinical settings, CBF can be altered by altering minute ventilation, inducing systemic hypotension, or by mechanical means, such as by small balloon occluding arterial catheters that can be floated into distal cerebral circulations. Therefore, any of these clinical tools for manipulating CBF could be used to enhance the efficacy of intraarterial drugs.

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