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The Influence of Propofol with and without Nitrous Oxide on Cerebral Blood Flow Velocity and CO_2 Reactivity in Humans

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The cerebrovascular response to CO_2 has been reported to be preserved during propofol anesthesia, but no comparison with awake control values has been made, and the additional influence of N_2O has not been investigated. Using the noninvasive technique of transcranial Doppler ultrasonography, this study investigated the cerebrovascular response to varying levels of Pa_{CO_2} while awake and during anesthesia with propofol and propofol/N_2O. Seven adults without systemic diseases undergoing nonneurologic surgery were studied. A pulsed-wave Doppler monitor was used to measure the mean middle cerebral artery flow velocity (V_{mca}) during varying levels of Pa_{CO_2} (25–55 mmHg) under the following conditions: 1) awake; 2) propofol 2.5 mg·kg^{-1} bolus followed by continuous infusion of 150 μg·kg^{-1}·min^{-1}; and 3) propofol as in the condition above plus 70% N_2O. During the awake study condition, hypocapnia was induced by voluntary hyperventilation, and hypercapnia was induced with rebreathing of 7% CO_2 in a closed circuit. During the anesthetized study conditions, hypocapnia and hypercapnia were induced by adjustment of minute ventilation. A minimum of five to six simultaneous V_{mca} and Pa_{CO_2} measurements were obtained under each of the study conditions. Systemic blood pressure was monitored *via* a radial arterial catheter, and phenylephrine was administered if mean arterial blood pressure decreased below 60 mmHg (phenylephrine was used in three of five patients in the propofol–N_2O group). Linear regression and analysis of covariance were used for statistical analysis of V_{mca}–Pa_{CO_2} relationships. At all levels of Pa_{CO_2}, the V_{mca} recorded during propofol alone and propofol–N_2O was significantly less than that recorded during the awake state (the reduction ranged from 36% during hypercapnia to 45% during hypocapnia). Compared to the CO_2-reactivity slope during the awake state of 3.2 ± 0.2% mmHg^{-1} (mean ± SE, n = 7), the slopes during propofol (n = 7) and propofol–N_2O (n = 5) were 2.1 ± 0.2% and 2.5 ± 0.2% respectively ($P < 0.05$ compared to awake). We conclude that propofol has vasoconstrictive properties on the cerebral vasculature and that the addition of N_2O does not influence the vasoconstriction or the CO_2 reactivity. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: propofol. Brain: blood flow; blood flow velocity; carbon dioxide response; intracranial pressure. Carbon dioxide: hypercapnia; hypocapnia. Measurement techniques: transcranial Doppler ultrasonography.)

CO_2 IS AN IMPORTANT determinant of blood flow to the brain, and in healthy patients cerebral blood flow (CBF) changes by approximately 3–4% per mmHg change in Pa_{CO_2}. This normal cerebral vascular response to CO_2 or CO_2 reactivity is used clinically by anesthesiologists to decrease CBF and, by inference, cerebral blood volume and hence intracranial pressure. Previous studies on CO_2 reactivity in humans have demonstrated that the response is preserved during administration of thiopental,[1] halothane,[2] midazolam,[3] etomidate,[4,5] sufentanil,[6] and a diazepam–fentanyl mixture.[7] Experimental studies in animals similarly have demonstrated the presence of CO_2 reactivity during inhalation anesthesia[8–10] as well as during synthetic opioid administration.[11,12] Few studies, however, have quantified the influence of anesthetic agents on CO_2 reactivity by comparing the observations made during anesthesia to awake values.

Propofol is a recently introduced short-acting anesthetic agent used for induction as well as maintenance of anesthesia. It has been shown to reduce cerebral metabolic activity in a dose-dependent manner and decreases both CBF[13–15] and intracranial pressure.[15,16] Only one study has investigated the effect of propofol on CO_2 reactivity, and those investigators reported that it is preserved.[14] However, the awake reactivity was not measured, so no comparative analysis could be made.

The introduction of transcranial Doppler ultrasonography (TCD) makes it possible to measure CBF velocity in a noninvasive and continuous manner. Accordingly, we evaluated the influence of propofol on cerebral vascular dynamics by measuring middle cerebral artery (MCA) flow velocity and CO_2 reactivity in the awake state and comparing this to the anesthetized state with propofol. In addition, the influence of N_2O was studied, not only because N_2O is frequently used with propofol clinically, but also because the cerebral vasodilatory action of N_2O may vary with the background anesthetic.[8,17–19]

Materials and Methods

The study was approved by the University of Washington Human Subjects Review Committee. Seven adults, mean age 31 ± 5 yr (SD), mean weight 80 ± 8 kg, ASA physical status 1 or 2, who were scheduled for nonneurologic surgery were studied after written informed con-

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sent was obtained. Patients who had neurologic disease or who were medicated with psychoactive drugs were excluded.

Preanesthetic medication was not administered. Monitors were placed to measure noninvasive blood pressure, continuous electrocardiography, and pulse oximetry. In addition, a radial artery catheter was inserted percutaneously during local anesthesia to allow direct arterial blood pressure measurements as well as sampling for blood gas determinations. An esophageal stethoscope/temperature probe was placed after induction of anesthesia. End-tidal CO_2 tension and N_2O concentration were monitored using a dedicated mass-spectrometer (Perkin-Elmer 1100) that was calibrated before the study. Temperature was maintained greater than 36° C by regulating ambient temperature and using warming blankets.

Determination of Mean Middle Cerebral Artery Flow Velocity

The methodology has been reported previously.[20] Briefly, the transcranial Doppler (Transpect, Medasonics, Fremont, CA) monitor probe, which transmits a 2-MHz pulsed wave, was positioned over the left temporal bone window and anchored using a head harness so that the angle of insonation remained constant throughout the study. Doppler signals from the left MCA were identified and measured at a depth of 45–50 mm. The shift in frequency spectra of the Doppler signals converted into velocity was displayed on a video monitor, and peak systolic and diastolic MCA flow velocities in centimeters per second were obtained by manually manipulating the cursor to read the average value from two to three cardiac cycles. When respiratory fluctuations were evident, care was taken to obtain the values only during end-expiration. The time-mean flow velocity (V_{mca}), considered to be the most physiologic measure of flow velocity,[21] was calculated from systolic and diastolic velocities using the formula: V_{mca} = (systolic velocity − diastolic velocity)/3 + diastolic velocity. The monitor automatically calculates and displays this value in a continuous manner, but the value it displays can be unreliable because of electrical artifact contamination in the operating room; therefore it was not used.

Experimental Protocol

Change in V_{mca} in response to change in Pa_{CO_2} (CO_2 reactivity) was determined three times in each patient: 1) Awake; 2) propofol 2.5 $mg \cdot kg^{-1}$ bolus followed by continuous infusion of 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with 100% O_2; and 3) propofol as in the second condition, but with 70% N_2O substituted for 100% O_2. Because of time constraints, in two patients the influence of N_2O was not studied.

Awake control CO_2 reactivity was obtained with the subject breathing through a mouthpiece and wearing a nose clip. End-tidal CO_2 was monitored in the expiratory limb of the breathing circuit distal to a nonrebreathing valve. All subjects were given 10–15 min to adapt to the breathing apparatus. After determination of V_{mca} during normocapnia, progressive hypocapnia was induced by slow voluntary hyperventilation. Additional V_{mca} determinations were made after a steady end-tidal CO_2 was obtained for at least five breaths. A blood sample was always withdrawn for determination of Pa_{CO_2} simultaneous to V_{mca} determination. A minimum of three measurements were made during hypocapnia, with the lowest end-tidal CO_2 ranging from 25 to 30 mmHg. All patients were breathing room air during the hypocapnic portion of the awake condition. Ventilation was then allowed to return to normal, and after 5 min of normal ventilation, hypercapnia was induced by having the subject breathe into a closed circuit with a 70-l bag previously filled with 7% CO_2 and 93% O_2. The subject then was instructed to take three large breaths and thereafter resumed a normal breathing pattern. Progressive increase of the end-tidal CO_2 plateau was monitored closely, and an increase of approximately 10–15 mmHg was allowed, during which at least three simultaneous V_{mca} determinations and blood gas samples were performed.

The patient then was allowed to recover from hypercapnia, after which anesthesia was induced with propofol 2.5 $mg \cdot kg^{-1}$ followed by 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with 100% O_2. After 20 min, V_{mca} measurements in response to progressive hypocapnia and hypercapnia were again determined during propofol infusion. The patient was returned to a normocapnic level, and 70% inspired N_2O was introduced. After at least 15 min of steady 70% end-tidal N_2O with continuous infusion of propofol, additional V_{mca} measurements were similarly determined. In both anesthetic conditions, hypocapnia and hypercapnia were induced by adjusting the minute ventilation, primarily by altering the respiratory rate. A minimum of five paired V_{mca}–Pa_{CO_2} determinations were obtained for each CO_2-reactivity response during the anesthetic conditions. Systemic blood pressure was continuously monitored, and phenylephrine infusion (0.2%) was administered intravenously if mean arterial blood pressure (MAP) was less than 60 mmHg. To avoid the confounding influence of surgical stimulation, the entire study was completed before surgery was allowed to begin.

Data Analysis

The data collected were analyzed using two approaches: 1) absolute V_{mca} values and 2) relative V_{mca} values.

Absolute V_{mca} Values

The paired V_{mca}–Pa_{CO_2} determinations were fitted to both exponential and linear regression analyses to deter-

mine the best fit for the relationship. Because both methods yielded almost identical correlation coefficients, linear regression analysis was used for subsequent comparisons. The derived slope was treated as the variable, and comparisons among the three experimental conditions in patients with complete data were made using analysis of variance for repeated measures. When significance was found ($P < 0.05$), a *post hoc* multiple comparison procedure (Fisher's protected least significant difference) was used to delineate where the significant difference lay. This method allowed the comparison of slope in flow velocity change per mmHg in Pa_{CO_2} between the experimental conditions. Because the Pa_{CO_2} values at the time of V_{mca} determinations varied among patients as well as between experimental conditions, it was difficult to make direct comparisons at any specific Pa_{CO_2} level. Therefore, to allow comparative analysis between the study conditions during normocapnia, hypocapnia, and hypercapnia, normalization of data was achieved by calculating the V_{mca} for Pa_{CO_2} at 30, 40, and 50 mmHg from each individual linear regression equation. These derived values allow comparison between the different experimental considerations, taking into account the change in both slope and intercept.

Relative V_{mca} Values

V_{mca} was also expressed as a percentage of the V_{mca} at a Pa_{CO_2} of 40 mmHg during the awake state for all patients and study conditions. All relative flow values were then analyzed using analysis of covariance,[22] with the experimental condition as the independent variable, Pa_{CO_2} as the covariate, and relative V_{mca} as the dependent variable. When significant difference was found, Tukey's test was used for individual comparisons.

Results

The MAP and heart rate recorded during the study are tabulated in table 1. The hypocapnia and hypercapnia data represent values recorded during the minimum and maximum Pa_{CO_2} values attained. During hypercapnia, MAP was lower with propofol alone compared to the awake state; otherwise, there was no significant difference in blood pressure between the awake and propofol conditions. However, when N_2O was added, MAP was significantly decreased at all levels of Pa_{CO_2}, and a continuous intravenous infusion of phenylephrine was required in three of five patients in the propofol–N_2O group to maintain MAP greater than 60 mmHg. There was no significant difference in the heart rate. The temperature of the patients was kept between 35.5 and 36.5° C, and there was no difference between the study groups. The mean hematocrit in arterial blood measured during the awake state, propofol alone, and propofol–N_2O were 39 ± 1 (SD), 38 ± 1, and 36 ± 2%, respectively, with no significant difference among them.

The partial pressures of O_2 in arterial blood are listed in table 2. Because of the experimental design with different inspiratory O_2 concentrations at different phases of the study, Pa_{O_2} values during hypercapnia in the awake state and with propofol alone were significantly higher than those during propofol–N_2O, and Pa_{O_2} values during propofol–N_2O were different from those measured during the awake state.

Linear regression analysis demonstrated a tight relationship between V_{mca} and Pa_{CO_2}, with correlation coefficients varying from 0.94 to 0.99. Propofol and propofol–N_2O reduced V_{mca} from awake values at all levels of Pa_{CO_2}, with no discernible difference between them (table 3). The actual TCD recordings of a subject during hypocapnia, normocapnia, and hypercapnia for all study conditions are shown in figure 1. Compared to the CO_2-reactivity slope derived by linear regression analysis during the awake state of 2.1 ± 0.3 $cm \cdot s^{-1} \cdot mmHg^{-1}$, the slopes of propofol and propofol–N_2O were significantly reduced, by 27% and 24%, respectively ($P < 0.05$) (table 4). Analysis of the relative V_{mca} (V_{mca} expressed as a percentage of the respective awake V_{mca} at a Pa_{CO_2} of 40 mmHg) using analysis of covariance similarly showed a small but significant reduction of the regression slope during propofol and propofol–N_2O. The plot of relative V_{mca} *versus* Pa_{CO_2} for all paired data and their respective linear regression lines with 95% confidence intervals (slope) are shown in figure 2. The addition of N_2O to

TABLE 1. Mean Arterial Blood Pressure and Heart Rate during Hypocapnia, Normocapnia, and Hypercapnia under the Three Experimental Conditions

	Awake (n = 7)			Propofol (n = 7)			Propofol–N_2O (n = 5)		
	Hypocapnia	Normocapnia	Hypercapnia	Hypocapnia	Normocapnia	Hypercapnia	Hypocapnia	Normocapnia	Hypercapnia
Mean blood pressure (mmHg)	93 ± 3	97 ± 4	104 ± 5	86 ± 5	87 ± 5	76 ± 3*	75 ± 6*	72 ± 5*	72 ± 4*
Heart rate (beats/min)	81 ± 3	70 ± 3	74 ± 4	80 ± 5	75 ± 5	71 ± 4	69 ± 4	71 ± 6	62 ± 6

All values are expressed as mean ± SE.

* Significantly different from awake values ($P < 0.05$).

TABLE 2. Mean Pa_{O_2} during Hypocapnia, Normocapnia, and Hypercapnia under the Three Experimental Conditions

Condition	Hypocapnia	Normocapnia	Hypercapnia
Awake (n = 7)	123 ± 3	107 ± 1	418 ± 25
Propofol (n = 7)	504 ± 19*	505 ± 22*	482 ± 28
Propofol–N_2O (n = 5)	199 ± 7†	199 ± 9†	160 ± 17†

All values are expressed as mean ± SE in mmHg and are computed from blood gases obtained when Pa_{CO_2} most closely approximated 30, 40, and 50 mmHg, respectively.
* Significantly higher than awake and propofol–N_2O.
† Significantly different from awake and propofol.

propofol had no appreciable effects on either the absolute flow velocity value or the CO_2 reactivity.

Discussion

CBF reactivity to CO_2 is one of the most important physiologic determinants of CBF and is central to the practice of neuroanesthesia in the manipulation of CBF and, by inference, cerebral blood volume and intracranial pressure. CO_2 reactivity is thought to be preserved during anesthesia with volatile agents as well as with intravenous agents, and in normal, nonpathologic states as well as in conditions of intracranial pathology.[1–12,23,24] Because the volatile agents tend to increase CBF[25] and intravenous agents tend to decrease CBF, it has been suggested that the CO_2-reactivity curve is enhanced by halothane and decreased or unchanged during intravenous anesthesia.[26] This enhancement has also been demonstrated by Drummond and Todd in cats[8] and by Scheller *et al.* in rabbits.[10]

In contrast, the influence of intravenous agents is not as well defined. Although numerous studies[1,3–7,11,12] have demonstrated the preservation of CO_2 reactivity during intravenous anesthesia, most of them either have lacked awake control values for comparison or have had experimental design problems. Pierce *et al.* observed a reduction of CBF from 50 to 27 ml · 100 g^{-1} · min^{-1} with thiopental anesthesia and noted a further and profound decrease to 16 ml · 100 g^{-1} · min^{-1} when Pa_{CO_2} was decreased from 40 to 20 mmHg.[1] Because both CBF and jugular bulb O_2 saturation measured during this profound hypocapnia approximated values obtained during awake conditions at similar levels of Pa_{CO_2}, they concluded that the CO_2 reactivity was unchanged by thiopental. However, because there were no intermediate measurements and because near maximal vasoconstriction can be expected to occur at a Pa_{CO_2} of 20 mmHg, the CO_2 reactivity at higher values of Pa_{CO_2} cannot be determined. Renou *et al.*[4] and Vernhiet *et al.*[7] demonstrated that CO_2 reactivity was preserved during both etomidate and diazepam–fentanyl anesthesia. However, in both studies, only one CBF measurement was made during anesthesia in each patient, and the reactivity was determined by plotting CBF against Pa_{CO_2}, which were deliberately varied among the patients studied. To be valid, this analysis must assume that the CO_2 reactivity is homogeneous within the entire group of patients studied, and that their awake CBF values were the same, which was false.

Forster *et al.*[3] reported the only quantitative assessment of intravenous anesthesia on CO_2 reactivity. On two separate occasions, the subjects received either intravenous placebo or 0.15 mg · kg^{-1} midazolam, and CBF was determined during normocapnia and hypercapnia. Compared to placebo, CBF was decreased by midazolam at both levels of Pa_{CO_2}. However, the reduction was greater during normocapnia than during hypercapnia. Consequently, based on the two-data point analysis, an enhanced CO_2 reactivity with midazolam was observed.

Propofol is a relatively new intravenous anesthetic agent, and the cerebrovascular response to changes in Pa_{CO_2} during propofol anesthesia has not been extensively studied. In patients undergoing coronary artery bypass surgery who had been anesthetized with propofol, Stephan *et al.* observed a decrease in CBF after the administration of propofol and a further decrease after hyperventilation.[14] However, the patients also received their scheduled β-adrenergic blockers, calcium channel antagonists, and/or nitrates and benzodiazepines. Although the combination of these medications may not have significantly influenced the observations, it at least renders them less conclusive. In addition, common to most studies on CO_2 reactivity during anesthesia, they did not have awake CO_2-reactivity slopes for comparison. In the current study, we determined the awake CO_2-reactivity slope in each patient and evaluated the effects of propofol and propofol/N_2O anesthesia. We induced anesthesia with propofol 2.5 m/kg followed by an infusion rate of 150 μg · kg^{-1} · min^{-1} propofol. The infusion rate was chosen to ensure anesthesia: it was given in excess of the minimal infusion rate that suppresses movement in response to the initial surgical incision in 50% of patients[27] and that has

TABLE 3. The Calculated Middle Cerebral Artery Flow Velocities at Pa_{CO_2} of 30, 40, and 50 mmHg during the Awake State and During Anesthesia with Propofol and Propofol–N_2O

	Vmca 30 (cm · s^{-1})	Vmca 40 (cm · s^{-1})	Vmca 50 (cm · s^{-1})
Awake	42 ± 4	63 ± 5	84 ± 5
Propofol	23 ± 2*	38 ± 3*	54 ± 5*
Propofol–N_2O	23 ± 2*	39 ± 3*	55 ± 4*

All values are expressed as mean ± SE. Vmca = middle cerebral artery flow velocity.
Vmca 30 = Vmca at Pa_{CO_2} of 30 mmHg; Vmca 40 = Vmca at Pa_{CO_2} of 40 mmHg; and Vmca 50 = Vmca at Pa_{CO_2} of 50 mmHg.
Vmca 50 > Vmca 40 > Vmca 30 for all study conditions ($P < 0.05$).
* Significantly different from awake values ($P < 0.05$).

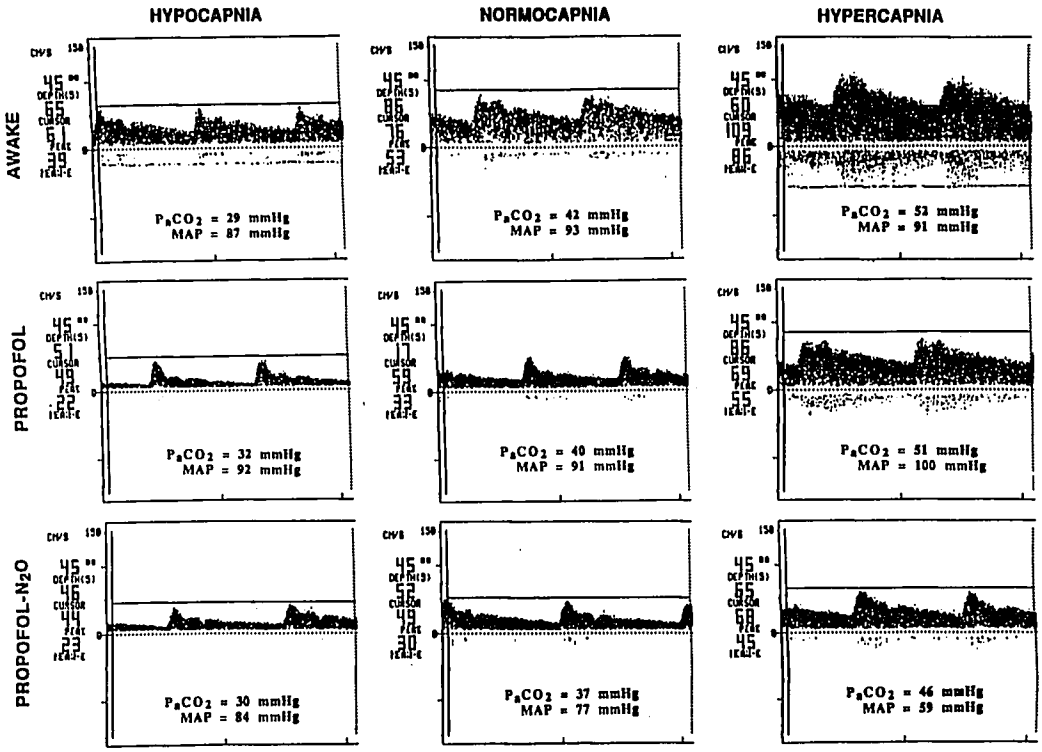

FIG. 1. The middle cerebral artery blood flow velocity (Vmca) waveform of a typical subject during hypocapnia, normocapnia, and hypercapnia under all experimental conditions. The corresponding Pa_{CO_2} and mean arterial blood pressure are shown.

been shown previously to achieve a blood concentration ensuring a near-pharmacologic steady state and a stable depth of anesthesia.[28] Our results for the blood pressure and heart rate response are in accordance with published studies.[29,30]

We also studied the influence of the addition of N_2O to propofol, not only because this is a common anesthetic technique, but also because N_2O has been demonstrated to be a potent cerebral vasodilator in a number of studies.[9,17–19] Hansen *et al.* observed in rats that the combination of 0.5 MAC N_2O + 0.5 MAC halothane resulted in flows similar to that produced by 1.0 MAC halothane alone, and that 0.5 MAC N_2O + 0.5 MAC isoflurane resulted in flows greater than that of 1.0 MAC isoflurane alone; they concluded that the use of N_2O in combination with volatile agents does not attenuate the increase in CBF and offers no advantage over an equipotent concentration of volatile agents.[17] Todd noted that the CO_2 reactivity to halothane-anesthetized rabbits was intact, and although the addition of N_2O did not change the reactivity, the CBF during the combination was greater than with halothane alone.[9] Similar results on isoflurane–N_2O have been reported in humans recently.[18,19] It is therefore important to delineate the CO_2 reactivity during propofol as well as during propofol–N_2O anesthesia.

TABLE 4. The Absolute and Relative Slopes of CO_2 Reactivity during the Awake State and during Anesthesia with Propofol and Propofol–N_2O

Conditions	Absolute Slope ($cm \cdot s^{-1} \cdot mmHg^{-1}$)	Relative Slope ($\% \cdot mmHg^{-1}$)
Awake	2.1 ± 0.1	3.2 ± 0.1 (2.9–3.5)
Propofol	1.5 ± 0.2*	2.1 ± 0.1* (1.8–2.5)
Propofol–N_2O	1.6 ± 0.2*	2.5 ± 0.2* (2.0–2.9)

All values are expressed as mean ± SE. Brackets denote 95% confidence interval. Relative slope is derived from analysis of covariance using relative middle cerebral artery flow velocity.

* Significant difference compared to the awake values, $P < 0.05$. There was no significant difference between the slopes under anesthetized conditions of propofol and propofol–N_2O.

To ensure that CBF velocity did not change as a result of a change in blood pressure, we used an infusion of phenylephrine whenever necessary to maintain the MAP within the autoregulatory range. This proved to be frequently necessary during propofol–N_2O anesthesia (three of five patients). Although the MAP during propofol–N_2O remained significantly less than that of awake and propofol anesthesia alone, it was greater than the lower limit of autoregulation. Moreover, it has been shown that the autoregulatory response to MAP changes remains in-

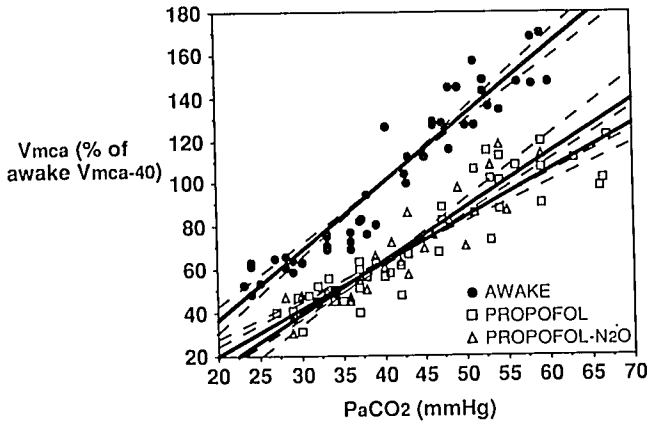

FIG. 2. A composite diagram plotting the relative middle cerebral artery flow velocity (Vmca) against corresponding Pa_{CO_2} for all patients studied. Relative Vmca are calculated by expressing all flow velocity values as a percentage of awake Vmca at Pa_{CO_2} of 40 mmHg. The respective linear regression and 95% confidence intervals for all experimental conditions are shown. Propofol and propofol–N_2O significantly reduced flow velocity at all levels of Pa_{CO_2} with no differences among them. Although the CO_2 reactivity slope was reduced equally by both anesthetic conditions, the vasoconstrictive response to reduction in Pa_{CO_2} was clearly preserved.

tact in baboons after administration of a propofol bolus of 1 mg/kg followed by infusions of 3, 9, and 12 $mg \cdot kg^{-1} \cdot min^{-1}$.[31]

Because the patients were studied before their scheduled surgery and there was a concern that not all phases of the study could be completed in all patients, we did not randomize the study sequence and always studied the influence of N_2O last. Because the blood pressure was always lowest during propofol–N_2O anesthesia, we cannot rule out the possibility that there was a time-related bias. However, the anesthetic phase of the study was completed within 60–70 min, a period that we considered to be too short to introduce significant bias. More importantly, the interaction of N_2O with propofol resulting in hypotension was not unexpected, because Van Hemelrijck *et al.* had made similar observations in their baboon study, the experimental sequence of which was randomized.[31] They also had observed no increase in CBF with the addition of N_2O to propofol infusion, supporting our contention that the lack of change in V_{mca} during propofol–N_2O compared to propofol alone in our study was not likely the result of a time-related bias. Therefore, we believe that our nonrandomized design did not introduce significant error to our observations and analysis.

TCD makes it possible to measure CBF velocity in a noninvasive and continuous manner. However, the TCD method of recording changes in the cerebral vasculature is not a direct measurement of CBF but rather is a measurement of flow velocity. Although techniques to measure CBF, such as radioactive xenon, are available, these techniques are cumbersome and slow; require a condition of steady state; and allow only a limited amount of measurements. TCD recording, on the other hand, is noninvasive and can be followed in a repetitive, continuous manner. Although correlation between absolute flow velocity and CBF in any given population is poor, largely because of the variation in MCA diameter, good correlation between relative changes in flow velocity and CBF has been demonstrated.[32] Moreover, TCD studies[20,34] on CO_2 reactivity indicated that this may be a particularly suitable tool for such studies, since multiple paired measurements can be taken and linear regression lines can therefore be constructed in a more accurate manner than with conventional blood flow measurements, with which only limited number of measurements can be made. The validity of the TCD method rests on the assumption that the MCA diameter does not change with changes in Pa_{CO_2}. Because the MCA is a conductance and not a resistance vessel, changes in cerebral vascular resistance occur primarily through dilation of arterioles and not the arteries of the Circle of Willis.[21] Consequently, the MCA as a conductance vessel is unlikely to be affected by cerebral vasoactive agents. Though not extensively studied, in at least one angiography study by Huber and Handa, CO_2 was reported to have negligible influence on the MCA diameter.[33] If we accept the assumption that the region of the MCA where the TCD insonates does not change in diameter, then the blood flow velocity should be directly proportional to the CBF. Indeed, Kirkham *et al.* compared volunteers' CO_2 reactivity determined with TCD to reactivity reported using direct methods of measuring CBF; they found the slopes to be very similar and concluded that velocity changes in the MCA reflect changes proportionally to CBF.[34]

Another potential criticism of our experimental protocol was that the inspired O_2 concentration was not constant during the study. Hypoxemia increases CBF significantly, and though not to the same extent, hypoxemia causes cerebral vasoconstriction.[35] Nakajima *et al.*[36] reported that inhalation of 100% O_2 can reduce CBF by 13% in healthy awake volunteers, although some of this decrease may be due to a simultaneous reduction in endtidal CO_2 tension. Thus, our flow velocity may have been underestimated during hypoxemic conditions. Considering that Pa_{O_2} values during propofol alone were significantly higher than those during propofol–N_2O, any potential vasodilatory influence of N_2O should have been exaggerated. However, we observed no increase in flow velocity with the addition of N_2O to propofol, and these findings were similar to those of Van Hemelrijck *et al.*,[31] who studied baboons under constant inspired O_2 concentrations. Moreover, the difference in inspired O_2 concentration should not influence the determination of CO_2-reactivity slope during propofol and propofol–N_2O be-

cause Pa_{O_2} levels were relatively constant within each of these two experimental conditions. The minimal scatter of the V_{mca}–Pa_{CO_2} regression indirectly supports this argument. Our major findings in this study therefore should remain valid.

Hematocrit can also affect flow velocity as hemodilution decreases viscosity and increases CBF and flow velocity. However, this occurs primarily when hematocrit declines below 35%.[37] Hematocrit was always higher than 35% in our patients, and there was no significant difference between experimental conditions.

The normal V_{mca} varies from 35 to 90 $cm \cdot s^{-1}$, with an average value of about 60 $cm \cdot s^{-1}$ during awake and resting states.[38] This range in V_{mca} probably reflects the individual's difference in MCA vessel diameter, baseline CBF, and the angle of insonation. Our results are consistent with these reported values as the V_{mca} in our awake state at normocapnia ranged from 52 to 77 $cm \cdot s^{-1}$, with an average of 63 $cm \cdot s^{-1}$. Because of this variation, we performed analysis using two methods. The absolute V_{mca}–Pa_{CO_2} relationship for each patient during each experimental condition was analyzed by linear regression, and the derived slope then was treated as a variable for comparison between experimental conditions. This assumes that the CO_2-reactivity slope (change in flow velocity per mmHg change in Pa_{CO_2}) is a parameter that follows a normal distribution pattern; this is not an unreasonable assumption, because the variation in flow velocity and MCA diameter are probably normally distributed. To allow comparison with previous published studies using other methods of CBF determinations, we normalized all V_{mca} by expressing them as percentage of awake V_{mca} at a Pa_{CO_2} of 40 mmHg. This allowed us to use analysis of covariance to compare the regression slopes derived during the three experimental conditions. The results of the two methods of analysis are in close agreement. Our awake CO_2-reactivity slope of 3.2% per mmHg is consistent with the value previously reported using the xenon washout technique.[39]

One other aspect of the analysis deserves comment. Although most investigators used linear regression analysis for the CBF–CO_2 relationship, some have used exponential regression.[8] Because near maximal vasoconstriction is reached at a Pa_{CO_2} of 20 mmHg, exponential analysis is appropriate if such severe hypocapnia is used. However, within the range of 25 to 55 mmHg, a linear regression more closely reflects the relationship. We in fact fitted our data to both exponential and linear regression analyses and found very similar correlation coefficient values. We elected to use the linear regression model to facilitate comparison with published series.

Our results show that in healthy patients with normal CO_2 reactivity, propofol anesthesia decreases CBF velocity, and the addition of N_2O has no discernible effect. Furthermore, although both anesthetic techniques (propofol and propofol–N_2O) decreased the CO_2-reactivity slopes, the CO_2 reactivity nevertheless was preserved. The observations we made with propofol were not unexpected and are consistent with the cerebral vasoconstrictive nature of propofol. However, they are in direct contrast to Forster *et al.*'s study[3] on midazolam, in which an enhanced CO_2 reactivity was observed. The observation with N_2O, however, was somewhat unexpected. Unlike previous findings with combinations of N_2O and volatile agents,[8,17–19] the addition of N_2O to propofol did not change the V_{mca} and, by inference, CBF. It is conceivable that N_2O may have cause dilation of the MCA and increase its diameter, thus increasing flow while decreasing the flow velocity. However, we considered this to be highly unlikely because an increase in V_{mca} with N_2O had been previously observed when isoflurane was the background anesthetic.[18] Moreover, our results are consistent with those of Van Hemelrijck *et al.*, who also observed no change in CBF in baboons when N_2O was added to propofol anesthesia.[31] The current findings thus suggest that the cerebral vasoconstrictive effects of propofol can offset or override the vasodilatory effects of N_2O.

We conclude that propofol has cerebral vasoconstrictive properties and that the addition of N_2O influences neither the vasoconstriction nor the CO_2 reactivity. Because we did not study patients with increased intracranial pressure, we are unable to extrapolate directly these findings to the care of such neurosurgical patients. However, the vasoconstrictive property of propofol in head-injured patients have been demonstrated previously.[15] The influence of propofol on CO_2 reactivity in neurosurgical patients with intracranial pathology must await confirmation.

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