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Combined Effects of Nitrous Oxide and Propofol on the Dynamic Cerebrovascular Response to Step Changes in End-tidal P_{CO_2} in Humans

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Background: **Nitrous oxide (N_2O) and propofol exhibit directionally opposite effects on the cerebral circulation, vasodilation and vasoconstriction, respectively. The authors investigated an interaction between the two anesthetic agents on the dynamic cerebrovascular response to step changes in end-tidal pressure of carbon dioxide (P_{ETCO_2}) in humans.**

Methods: **Participants with no systemic diseases were allocated into two groups, each of which was anesthetized sequentially with two protocols. Patients in group 1 were anesthetized with 30% O_2 + 70% N_2O. A continuous intravenous infusion of propofol (7–10 mg · kg^{-1} · h^{-1}) was then added to the N_2O. Patients in group 2 were anesthetized first with continuous infusion of propofol (10 mg · kg^{-1} · h^{-1}), and then 30% O_2 + 70% N_2O was added to the propofol anesthesia. Using transcranial Doppler ultrasonography, blood flow velocity at the middle cerebral artery (FV_{MCA}) was measured during a step increase (on-response) followed by a step decrease (off-response) in P_{ETCO_2}, with P_{ETCO_2} ranging between approximately 28 and 50 mmHg. The dynamic FV_{MCA}–P_{ETCO_2} relationship was analyzed using a mathematical model that was characterized with a pure time delay, and a time constant and a gain each for the on- or off-response.**

Results: **The addition of propofol to the N_2O anesthesia increased the on-response time constant ($P < 0.01$), whereas the addition of N_2O to the propofol anesthesia increased the time constants for on- ($P < 0.01$) and off-responses ($P < 0.05$). However, the addition of either anesthetic did not affect the gains.**

Conclusions: **Propofol and N_2O, when one is added to the other, produce similar dynamic FV_{MCA} responses to sudden changes in P_{ETCO_2}. Addition of each anesthetic slows the dynamic response and produces the response whose magnitude is proportional to the baseline FV_{MCA}.**

PROPOFOL and nitrous oxide (N_2O) are known to produce directionally opposite effects on cerebral vasculature: vasoconstriction is induced by propofol,[1,2] and vasodilation is induced by N_2O.[3–8] Arterial carbon dioxide tension (Pa_{CO_2}) is a major determinant of cerebral blood flow (CBF). It has been suggested that the steady-state CBF response to changes in Pa_{CO_2} is preserved during anesthesia with N_2O,[9,10] propofol,[2,7,11] or the combination of the two.[2,12] However, to our knowledge, there has been little work on the effects of rapid changes in Pa_{CO_2} on the cerebral circulation. Therefore, in the present study we examined the actions of N_2O and propofol, alone and together, on the dynamic CBF response to rapid changes in end-tidal pressure of carbon dioxide (P_{ETCO_2}).

Materials and Methods

Thirty-five patients (20 male, 15 female; age, 15–41 yr [mean, 29.3 yr]; height, 165.2 ± 8.2 cm [mean ± SD]; weight, 62.0 ± 9.5 kg) undergoing elective surgery took part in the study. Requirements were fully explained to all participants in writing and verbally, and each gave informed consent before participating in the study. The institutional ethics committee approved the research. Participants were not taking any medication, and none had a known history of cardiovascular, cerebrovascular, respiratory, neurologic, or endocrine disease. They fasted preoperatively for 8–10 h, during which intravenous (800–1,000 ml) fluid replacement was given. No premedication was administered.

The experiment was conducted after the induction of anesthesia and before the start of surgery. To minimize experimental time, subjects were divided into two study groups. The first group was studied during anesthesia with N_2O, followed by the addition of an infusion of propofol to the N_2O anesthesia. The second group was studied during anesthesia with a propofol infusion, followed by the addition of N_2O.

A 2-MHz pulsed Doppler ultrasound system (PC-Dop 842, SciMed, Bristol, UK) was used to measure backscattered Doppler signals from the right or left middle cerebral artery (MCA). The Doppler signals were transformed to the intensity-weighted mean blood flow velocity (FV_{MCA}), which was stored on a computer for off-line analysis. FV_{MCA} was identified by an insonation pathway through the right or left temporal window using the standard search technique. The transcranial Doppler (TCD) probe was attached securely with a plastic headband at the position where the signal was maximized.

Subjects were placed in a supine position on an operating table with ambient temperature maintained at 25°C. After applying usual anesthetic monitors (pulse oxymetry, a lead II electrocardiograph, noninvasive brachial blood pressure, rectal temperature, and respired gas tensions [O_2, CO_2, and N_2O]), anesthesia was induced with a bolus injection of 2 mg/kg propofol. Tracheal intubation was facilitated by a bolus injection of

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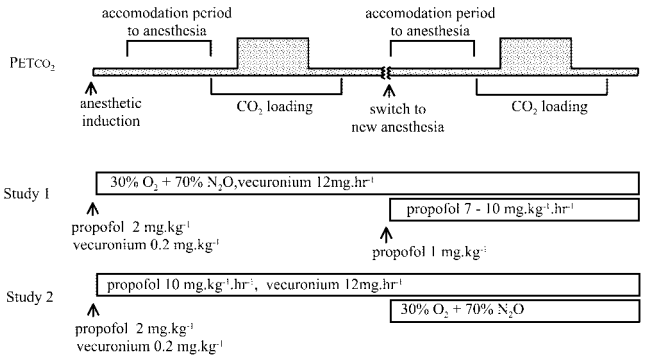

Fig. 1. Schematic presentation of experimental protocol. See text for details.

0.2 mg/kg vecuronium. Rectal temperature was maintained within the preanesthetic level ± 0.2°C with a warm air blanket and a water blanket. Expired carbon dioxide tension was monitored continuously with an infrared anesthetic gas monitor (Normocap 200 oxy, Datex, Helsinki, Finland). Airflow was measured by a flow meter to define the end-expiratory phase in the off-line analysis. Carbon dioxide tension and airflow signals were stored on a computer with the TCD signals. Brachial blood pressure was measured every 1 min with an oscillometer throughout the study.

Study 1

The experimental protocol is shown schematically in figure 1. After the induction of anesthesia, 19 subjects in group 1 were anesthetized with 30% O_2 + 70% N_2O and mechanically ventilated at a slight hypocapnic level, P_{ETCO_2} of 27–29 mmHg. Neuromuscular block was obtained with a continuous intravenous infusion of vecuronium at a rate of 12 mg/h. The slight hypocapnia was attained by adjusting a tidal volume with keeping the ventilation rate at 10 breaths/min and maintained for at least 15 min for stabilization of respiratory and circulatory condition.

After a 3-min baseline period, hypercapnia was induced suddenly by adding carbon dioxide to the inspiratory gas mixture. By closely observing P_{ETCO_2}, the CO_2 flow rate was manually adjusted breath by breath such that P_{ETCO_2} increased to approximately 45–55 mmHg within a few breaths. The target P_{ETCO_2} level was maintained for the subsequent 5 min. The CO_2 supplementation was then terminated, and the ventilatory rate was immediately increased to 16 breaths/min, keeping tidal volume constant for about 5–7 breaths to induce a rapid decrease in P_{ETCO_2}. The ventilation rate was gradually decreased such that P_{ETCO_2} remained at a constant hypocapnic level for 3 min (recovery period). This resulted in a stepwise P_{ETCO_2} decrease to the baseline P_{ETCO_2} level in several breaths. This measurement session is referred hereafter as the N_2O session.

After the N_2O session was completed, an intravenous bolus of 1 mg/kg propofol was injected, followed immediately by a continuous intravenous infusion of propofol at a rate of 10 mg · kg^{-1} · h^{-1}. The infusion rate was adjusted such that blood pressure was maintained as close to that during the N_2O session as possible. In 5 subjects, the infusion rate was reduced to 7–9 mg · kg^{-1} · h^{-1}. Once the infusion rate was determined, it was kept constant throughout the measurement run. Ventilation tidal volume was also adjusted such that the baseline P_{ETCO_2} was identical to that for the N_2O session. After a 20-min accommodation period to the new anesthesia, a series of the carbon dioxide loading with measurements was performed as in the N_2O session. This measurement run is referred hereafter as the propofol–N_2O session.

We took an extreme care to produce a step change in P_{ETCO_2} that was similar in the N_2O and propofol–N_2O sessions for each subject. However, the manual adjustment could not achieve such precise control as to attain an identical hypercapnic level across all subjects. Therefore, we had to accept interindividual variances in the hypercapnic level ranging as wide as 45–55 mmHg.

Study 2

After the anesthetic induction and tracheal intubation was performed as mentioned above, 16 subjects in group 2 were anesthetized with a continuous intravenous infusion of propofol, 10 mg · kg^{-1} · h^{-1}. Neuromuscular block was obtained as in study 1. The patients were mechanically ventilated with 30% O_2 + 70% N_2 at the slight hypocapnic level, P_{ETCO_2} of 27–29 mmHg. A series of measurements during stepwise CO_2 forcing was performed as in study 1 (propofol session). At the completion of the propofol session, the respired gas was switched to 30% O_2 + 70% N_2O. After a 20-min accommodation period to the new anesthesia, the stepwise carbon dioxide forcing was again performed with measurements (N_2O–propofol session).

Data Analysis

Data were analyzed off-line using a mathematical package (Splus 2000, MathSoft, Cambridge, MA). End-expiratory phases were determined from the airflow signal. P_{ETCO_2} was obtained from the readings in the expired carbon dioxide signal at the corresponding end-expiratory phases. Mean values of FV_{MCA} for every heartbeat and breath-to-breath P_{ETCO_2} were resampled at 1 Hz by a linear interpolation to create a uniform time base. To align interindividual variances in the absolute FV_{MCA} values, FV_{MCA} were expressed as percentages of the baseline mean FV_{MCA} value of each anesthesia session for each subject.

We rejected data obtained from subjects who did not present a stable cardiovascular condition throughout the experiment to avoid possible influence of changes in blood pressure on FV_{MCA}. The stable cardiovascular condition was defined as satisfying the following two criteria: (1) variations of the mean blood pressure remained

within a range of the value at the beginning of the experiment ±10 mmHg; and (2) heart rate variations remained within a range of the value at the beginning of experiment ±15 beats/min.

Mathematical Modeling

The mathematical model used was described previously.[6,13] The model is a simple extension of the steady-state FV_{MCA}–$PETCO_2$ relationship, in which the magnitude of change of FV_{MCA} was assumed to be proportional to the magnitude of change in $PETCO_2$. In addition, the dynamic model also considers the speed of change in FV_{MCA} in response to change in $PETCO_2$. In the model, therefore, the rate of change of FV_{MCA} is proportional to the deviation of FV_{MCA} from the value it would obtain in the steady state. Such a dynamic model produces an exponential output (FV_{MCA}) for a step input ($PETCO_2$). It is written in the form:

$$d(FV_{MCA})/dt = 1/\tau \times [G \times u(t - Td) \times FV_{MCA}^* - FV_{MCA}] \quad (1)$$

where the function u(t − Td) defines the variation of $PETCO_2$ as,

$$u(t - Td) = PETCO_2 \times (t - Td) - PETCO_2^* \quad (2)$$

where t is time (s), *d/dt* denotes a derivative in terms of time, τ (s) is a time constant, G (%/mmHg) is a gain, and Td (s) is a pure time delay. FV_{MCA}^* (%) and $PETCO_2^*$ (mmHg) are their respective steady-state values before a step change is undertaken.

To allow for asymmetry between the FV_{MCA} response to a step increase (on-response) and to a step decrease (off-response) in $PETCO_2$, separate parameter values were estimated for the on- and off-responses. This resulted in five variables for estimation: gains for the on- and off-responses (Gon, Goff), time constants for the on- and off-responses (τon, τoff), and a single time delay (Td).

Model fitting for parameter estimation was performed on the on- and off-responses separately. The on-response model was fitted to the data from duration containing the 3-min baseline period and the first 3-min hypercapnic period with a step $PETCO_2$ increase in the middle. The off-response model was fitted to the data from duration containing the last 3-min hypercapnic period and the 3-min recovery period with a step $PETCO_2$ decrease in the middle. The best fit models that minimized the sum of square of residuals between the data and model were computed using a grid search technique.[6,13]

Statistical Analysis

Statistical comparisons of FV_{MCA} and the model parameters between the two sessions in each study were performed using the paired *t* test when the normal distribution criterion for each variable or model parameter was fulfilled. Otherwise, the Mann–Whitney U test was used. $P < 0.05$ was considered significant.

Table 1. Comparison of Baseline FV_{MCA} between Two Anesthetic Conditions

	Study*	N_2O or propofol	Propofol + N_2O	*P*†
FV_{MCA} (cm/s)	1	35.2 ± 8.1	23.9 ± 5.4	<0.001
FV_{MCA} (cm/s)	2	36.4 ± 10.9	38.1 ± 12.1	NS

Values are expressed as absolute velocities (mean ± SD).

*Study 1 = N_2O alone *vs.* N_2O added with propofol. Study 2 = propofol alone *vs.* N_2O added to propofol.

†Significance levels of differences between the two anesthetic conditions.

FV_{MCA}, blood flow velocity at the middle cerebral artery.

Results

All subjects exhibited normal mean blood pressure (79 ± 6 mmHg [mean ± SD] mmHg) and heart rate (64 ± 4 beats/min [mean ± SD]) at the beginning of the experiment. Four subjects in study 1 and 1 subject in study 2 did not satisfy the stable cardiovascular condition; all of them exhibited increases in blood pressure of greater than 10 mmHg during the hypercapnic period. Therefore, they were discarded from further analysis, and the data obtained from the remaining 15 subjects in each study were analyzed.

Baseline FV_{MCA} values are presented in table 1. In study 1, the continuous infusion of propofol added to the N_2O anesthesia decreased the baseline FV_{MCA} by 31.6 ± 8.6% (mean ± SD; $P < 0.001$) compared with that for the N_2O session. In study 2, the inhalation of N_2O added to the propofol anesthesia did not affect the baseline FV_{MCA}.

Figure 2 shows the signals obtained from the subjects and the averages from the subjects. In each anesthesia condition, the manually adjusted carbon dioxide loading produced stepwise changes in $PETCO_2$, although the step magnitude ranged from 15 to 25 mmHg among the subjects. $PETCO_2$ steps tended to be faster and greater in the on-response than in the off-response.

Figure 3 shows the responses of FV_{MCA} to step changes in $PETCO_2$ and the models best fitted to the responses in a representative subject in study 1. Exponential contours in FV_{MCA} response curve to step changes in $PETCO_2$ were observed in the N_2O and propofol–N_2O sessions. Model fitting performance was good in all subjects, and the model was able to track the dynamic changes of FV_{MCA} for each anesthesia session.

Tables 2 and 3 compare the estimated values of the model parameters between the two anesthesia sessions and between the on- and off-responses. The time delay (Td) after which the FV_{MCA} responses to step changes in $PETCO_2$ started was similar in both sessions of each study. In study 1 (table 2), compared with the N_2O anesthesia, the propofol–N_2O anesthesia increased τon and did not change either Gon or Goff. In study 2 (table 3), com-

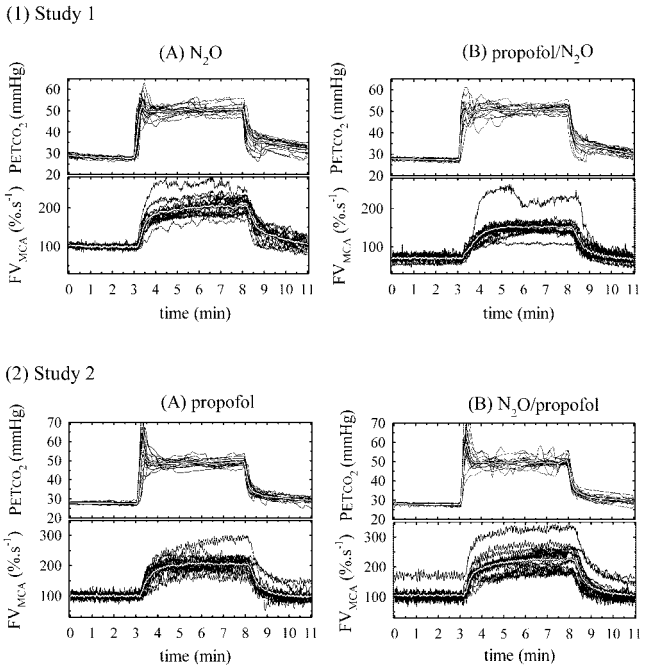

Fig. 2. Signals obtained from the subjects (thin solid lines) and the averages (thick solid lines) from the subjects. To show the effect of the addition of the second anesthetic on the baseline blood flow velocity at the middle cerebral artery (FV_{MCA}), FV_{MCA} were expressed as percentages of the baseline mean values in the first anesthesia session in each study.

pared with the propofol anesthesia, the N_2O–propofol anesthesia increased τon and τoff and did not change either Gon or Goff. In both studies, with respect to the comparison between the on- and off-responses, τon was significantly greater than τoff, and Gon was significantly smaller than Goff in any anesthesia session, indicating slower and smaller on-responses than off-responses.

Discussion

Consideration for Methodologic Limitations

Before interpreting the results of the study, the methods used should be considered. Instead of measuring the true MCA blood flow, this study used FV_{MCA} as an index

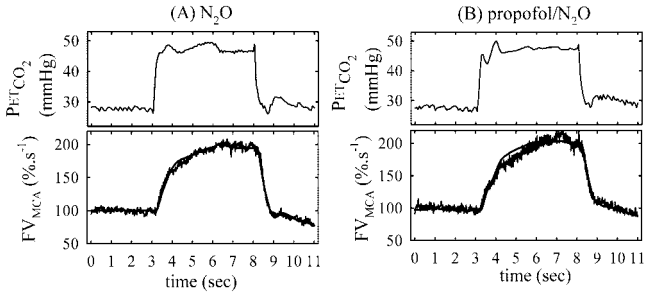

Fig. 3. Responses of blood flow velocity at the middle cerebral artery (FV_{MCA}) to step changes and the model best fitted to the data in a representative subject during the nitrous oxide (N_2O) and propofol–N_2O sessions in study 1.

Table 2. Model Parameters for Responses in Blood Flow Velocity at the Middle Cerebral Artery in Study 1: N_2O *vs.* Propofol/N_2O Anesthesia

	N_2O	Propofol/N_2O	*P**
Td, s	7.8 ± 1.4	7.5 ± 1.2	NS
τon, s	25.1 ± 9.2†	32.5 ± 10.3§	0.002
τoff, s	20.2 ± 10.8	16.1 ± 7.0	NS
Gon, %/mmHg	4.41 ± 1.15	4.73 ± 1.40‡	NS
Goff, %/mmHg	4.93 ± 1.26	5.32 ± 1.50	NS

Values are shown as mean ± SD.

*Significance levels of differences between the two anesthetic conditions (row-wise comparison).

†$P < 0.05$, ‡$P < 0.01$, and §$P < 0.001$; column-wise comparison between the on and off responses (*i.e.*, τon *vs.* τoff and Gon *vs.* Goff) in either anesthetic condition.

Td, pure time delay; τon, time constants for the on responses; τoff, time constants for the off responses; FV_{MCA}, blood flow velocity at the middle cerebral artery; Gon, gains for the on responses expressed as percent changes from the baseline FV_{MCA}; Goff, gains for the off responses expressed as percent changes from the baseline FV_{MCA}.

of MCA blood flow, which has been done in previous studies.[6,14–16] The MCA volume blood flow is theoretically the product of FV_{MCA} and the cross-sectional area of MCA. Therefore, FV_{MCA} may not necessarily represent the volume blood flow if MCA exhibits temporal changes in the cross-sectional area. However, Poulin *et al.*[13] showed that, during CO_2-loaded breathing similar to this study, changes in the MCA cross-sectional area were negligible compared with those in the FV_{MCA}.

The manually adjusted carbon dioxide loading could not produce precise step (square-shaped) changes in P_{ETCO_2} with an identical magnitude across all subjects. The nonuniformity in the carbon dioxide loading pattern among subjects may affect the results. In the previous study, we examined effects of nonuniform step P_{ETCO_2} changes on the dynamic FV_{MCA} response.[6] It indicated that the effects of the nonuniformity were negligible on

Table 3. Model Parameters for Responses in Blood Flow Velocity at the Middle Cerebral Artery in Study 2: Propofol *vs.* N_2O/Propofol Anesthesia

	Propofol	N_2O/Propofol	*P**
Td, s	6.3 ± 2.0	7.3 ± 1.8	NS
τon, s	29.4 ± 10.3‡	37.2 ± 12.1‡	0.002
τoff, s	16.5 ± 7.9	21.1 ± 10.0	0.038
Gon, %/mmHg	4.91 ± 1.12‡	4.96 ± 1.06†	NS
Goff, %/mmHg	5.87 ± 1.08	5.58 ± 1.32	NS

Values are shown as mean ± SD.

*Significance levels of differences between the two anesthetic conditions (row-wise comparison).

†$P < 0.05$, ‡$P < 0.001$; column-wise comparison between the on and off responses (*i.e.*, τon *vs.* τoff and Gon *vs.* Goff) in either anesthetic condition.

Td, pure time delay; τon, time constants for the on responses; τoff, time constants for the off responses; FV_{MCA}, blood flow velocity at the middle cerebral artery; Gon, gains for the on responses expressed as percent changes from the baseline FV_{MCA}; Goff, gains for the off responses expressed as percent changes from the baseline FV_{MCA}.

the results in this study, as long as it remained within the extent produced in this study.

We used only a single dose for each anesthetic because of limited experimental time. Furthermore, in 5 subjects in study 1, we reduced the infusion rate of additional propofol to 7–9 $mg \cdot kg^{-1} \cdot h^{-1}$ instead of 10 $mg \cdot kg^{-1} \cdot h^{-1}$ to align blood pressure as closely as possible between the two anesthesia sessions. Therefore, the results of the present study may not be interpreted as the general relationship between the two anesthetics.

Interpretation of the Results

Effects of the Combination of N_2O and Propofol on the Baseline FV_{MCA}. The continuous infusion of propofol, when added to the N_2O anesthesia, decreased the baseline FV_{MCA} by 31.6%. It indicates that propofol at the dose used decreased the baseline MCA blood flow. It was suggested that propofol further decreased CBF as a combination of direct vasoconstriction and decreased metabolism.[1,7] Although the present study neither controlled nor measured depth of anesthesia, it was likely that the infusion of propofol deepened the level of anesthesia. Therefore, both mechanisms would be responsible for the decrease in the baseline FV_{MCA} in this study.

By contrast, inhalation of 70% N_2O, when added to the propofol anesthesia, did not change the baseline FV_{MCA}. This is similar to the finding reported by Eng *et al.*[2] These results indicate that vasoconstriction induced by propofol is more potent than N_2O-induced vasodilation at the doses used, so that effects of propofol on the cerebral vasculature would manifest.

Dynamic Cerebrovascular Responses

Compared with the steady-state condition, the dynamic response not only considers the magnitude but also the speed, the gains, the pure time delay, and the time constants, respectively. Neither propofol nor N_2O affected Gon or Goff. This indicates that the magnitude of the dynamic response is proportional to the baseline FV_{MCA} level, irrespective of different anesthesia conditions. It would be similar to the steady-state response of CBF to hypocapnia in either inhalational[17–20] or intravenous anesthetia.[2,21] However, Gon and Goff are approximately twice the magnitude of the steady-state response, which was reported to be 2.1–3.5%/mmHg. This difference may be the result of sustained hypo- or hypercapnia in the steady-state studies, in which gradual adaptation of cerebral vascular regulation toward the baseline level may have occurred.[21–23] The difference in the response magnitude between the dynamic and steady-state responses may be reflected on the asymmetry between the on- and off-responses observed in this study. The on-responses were faster (τon $<$ τoff) and smaller (Gon $<$ Goff) than the off-responses in any anesthesia condition. It is comparable with the results of previous studies.[6,13] The greater Goff than Gon would be odd because it implies that CBF decreased below the baseline level during the recovery period. It could be attributed to a transient overresponse in the cerebral arteries to a step P_{ETCO_2} decrease, which then fades away in several minutes.[6,13]

As to the speed of the dynamic response, Td represents the time delay after which the FV_{MCA} responses to step P_{ETCO_2} changes start. It may be attributed mainly to a circulatory delay between the lung and the brain. The Td values obtained in this study, approximately 7 s, are comparable with those reported in previous studies.[13,24] The addition of propofol to the N_2O anesthesia increased τon, and the addition of N_2O to the propofol anesthesia increased τon and τoff. It indicates that the addition of either propofol or N_2O slowed the dynamic FV_{MCA} response to rapid changes in P_{ETCO_2}. N_2O and propofol induce mutually opposing effects on cerebral vessels, vasodilation and vasoconstriction, respectively. Therefore, the mechanisms slowing the dynamic response may differ between the two anesthetic agents. In the case of the addition of propofol, we wonder if the decrease in the baseline CBF produced by propofol would have delayed changes in the vascular and perivascular factors invoked by sudden changes in Pa_{CO_2}, leading to the slowed dynamic response of FV_{MCA}. Furthermore, cerebral metabolism may be reduced by the additional propofol,[7,25] which would also work in a direction to slow the response.

However, it is difficult to extrapolate mechanisms responsible for the slowed dynamic response produced by the addition of N_2O to the propofol anesthesia. We had anticipated that the addition of N_2O, a cerebral vasodilator, would have accelerated the dynamic FV_{MCA} response. We could only speculate that the additional N_2O might modulate carbon dioxide-induced temporal (phase) sequences arising in the vascular and perivascular factors.[21,26–28]

It is beyond the scope of the present study to specify exact mechanisms enrolled in the interaction between N_2O and propofol on the dynamic cerebrovascular response to rapid changes in P_{ETCO_2}. From a clinical viewpoint, however, the combined use of propofol and N_2O may work beneficially for the brain protection, irrespective of the order of administration, because it would dampen the immediate changes in CBF at sudden changes in Pa_{CO_2}.

In conclusion, this study examined the effects of propofol and N_2O on the cerebrovascular dynamic response to step changes in P_{ETCO_2} when added each other. Despite the directionally opposing effects of the two anesthetics on the cerebral circulation, both induced essentially similar effects. The addition of either anesthetic induced the baseline FV_{MCA}-dependent dynamic response in magnitude and slowed the dynamic response to step changes in P_{ETCO_2}.

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