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Effects of Induced Hypotension on Cerebral Vasomotor Response to Carbon Dioxide in Humans

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Summary. **The purpose of the present study was to evaluate the effects of nicardipine (NIC), nitroglycerin (NTG), and prostaglandin E_1 (PGE_1) on cerebrovascular CO_2 reactivity during propofol-fentanyl anesthesia in humans. Cerebrovascular CO_2 reactivity was evaluated with transcranial Doppler sonography (TCD) in 30 patients. The patients were randomly allocated to NIC, NTG or PGE_1 groups. Anesthesia was induced and maintained with a bolus, followed by a continuous infusion of propofol (6.73 ± 0.45 mg/kg/hr) and fentanyl (1.72 ± 0.54 μg/kg/hr). Time-mean blood flow velocity in the right middle cerebral artery (Vmca) was measured with TCD at an end-tidal CO_2 tension ($P_{ET}CO_2$) of 50, 45, 40, 35, 30, and 25 mmHg during normotension and hypotension. Induced hypotension of mean arterial pressure 55-60 mmHg was maintained with a continuous infusion of NIC (6.99 ± 0.73 μg/kg/min), NTG (2.98 ± 1.10 μg/kg/min) or PGE_1 (0.103 ± 0.052 μg/kg/min). The CO_2 reactivity of Vmca was determined by linear or exponential regression analysis and was compared between normotension and induced hypotension with repeated measures ANOVA. There was a significant close linear and exponential regression between Vmca and $P_{ET}CO_2$ during normotension and hypotension in each subject ($r>0.95$, $p<0.05$). Absolute slopes and exponents were significantly attenuated during drug-induced hypotension, when compared with normotension ($p<0.05$). These results strongly suggest that the cerebrovascular CO_2 reactivity is preserved. However, the cerebrovascular sensitivity to CO_2 is attenuated during NIC, NTG, and PGE_1-induced hypotension.**

Key words—induced hypotension, cerebrovascular CO_2 reactivity, transcranial Doppler ultrasonography.

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INTRODUCTION

Cerebral blood flow (CBF) varies in direct relationship to arterial carbon dioxide tension ($PaCO_2$). The greatest effect of $PaCO_2$ on CBF has been observed within the physiologic range of 25-60 mmHg.[1)] CBF changes linearly[2)] or exponentially[3)] in response to $PaCO_2$ within the these physiologic variations. Hypotensive drugs affect not only the systemic blood vessels but also the cerebral ones and may influence the responses of CBF to $PaCO_2$ by changing the vascular tonus. An implication of possible impaired cerebrovascular CO_2 reactivity during induced hypotension is of great clinical importance because application of hyperventilation to reduce CBF, and hence cerebral blood volume and intracranial pressure during induced hypotension, is the so-called "gold standard" in the field of neuroanesthesia. There have been several studies indicating that cerebrovascular CO_2 reactivity remains intact during nicardipine[4,5)], nitroglycerin[6)], or prostaglandin E_1[6-9)]-induced hypotension. However, prior to this investigation, these relationships have been studied within a narrow range of $PaCO_2$ to hypocapnia.

Transcranial ultrasound Doppler (TCD) recording represents a noninvasive, on-line, and continuous means of assessing blood flow velocity in the basal intracerebral arteries. As demonstrated angiographically,[10)] the blood vessel diameters of large basal intracerebral arteries remain relatively constant during changes in $PaCO_2$. Therefore, changes in CBF induced by alterations of the $PaCO_2$ should also be proportional to changes in blood flow velocity in the basal cerebral arteries. We can thereby assess the cerebral vascular CO_2 reactivity by measuring blood flow velocity by TCD without a direct measurement

of CBF.

The present study employed TCD to investigate the influences of nicardipine (NIC), nitroglycerin (NTG), and prostaglandin E_1 (PGE_1)-induced hypotension on cerebrovascular CO_2 reactivity over a wide range of end-tidal CO_2 tension ($P_{ET}CO_2$: 25-50 mmHg) in patients under propofol-fentanyl anesthesia.

SUBJECTS AND METHODS

Subjects and anesthesia

Thirty adults, ASA (American Society of Anesthesiologists) physical status 1 or 2, who were scheduled for non-neurologic surgery were enrolled in the present study. A written, informed consent was obtained from each patient. Patients with neurologic disease, uncontrolled hypertension, or diabetes mellitus were excludcd from the study. The patients were randomly allocated to one of three groups (NIC, NTG or PGE_1). Preanesthetic medication was administered via an intramuscular injection of 0.5 mg atropine and 50 mg hydroxyzine approximately 1 h before induction of anesthesia. Anesthesia was induced with a bolus injection of propofol (2-2.5 mg/kg), fentanyl (2-2.5 μg/kg) and vecuronium (0.1 mg/kg), and was maintained with a continuous infusion of propofol (6 -7 mg/kg/hr) and fentanyl (1.5-2.5 μg/kg/hr). After the tracheal intubation, patients were mechanically ventilated with a mixture of air and 100% oxygen ($FiO_2 = 0.5$). The radial artery was cannulated for continuous measurement of arterial blood pressure. Electrocardiography, pulseoximetry, $P_{ET}CO_2$, and rectal temperature were also continuously monitored.

Measurements of middle cerebral artery blood flow velocity

The portion of the right middle cerebral artery (MCA) near its juncture with the ipsilateral anterior cerebral artery was isonated at a depth of 45-60 mm to obtain the best signal through the right temporal window using TCD (Multidop T, DWL Elecreonische, Sipplingen, Germany). The Doppler probe was positioned with a custom-designed frame to keep a constant isonation angle throughout the study. Confirmation of MCA was performed by an ispilateral carotid artery compression test[11] or by the depth of its signals. Time-averaged mean MCA velocity (Vmca) was recorded by fine-tuning of the Doppler gain so that the spectral envelope was as noise free as possible.

Experimental protocol

$P_{ET}CO_2$ was increased to 50 mmHg by hypoventilation (mainly by reduced respiratory rate); thereafter, $P_{ET}CO_2$ was gradually reduced to 25 mmHg by the adjustment of minutes ventilation. Consecutive measurements of Vmca were performed at a stable $P_{ET}CO_2$ of 50, 45, 40, 35, 30, and 25 mmHg during normotension and induced hypotension. $P_{ET}CO_2$ was regarded as stable when the same value of $P_{ET}CO_2$ was obtained for at least 10 respiratory cycles. Induced hypotension was induced with a continuous infusion of NIC, NTG or PGE_1, (for doses, see Table 1). Mean arterial blood pressure (MAP) was maintained at 55-60 mmHg during induced hypotension. The sequence of normotension or hypotension was randomized in order to eliminate the time-bias. The study was completed before surgery to avoid

Table 1. Demographic and anesthetic data

	Nicardipine	Nitroglycerin	Prostaglandin E_1
Age (yr)	42.1±5.3	38.±16.6	36.6±8.3
Sex (F/M)	4/6	6/4	5/5
BW (kg)	60.6±7.8	55.6±6.6	64.5±12.5
HT (cm)	164.8±10.0	161.6±8.7	163.0±6.3
Hemoglobin (g/dl)	13.5±1.4	13.8±1.3	14.3±1.0
Hematocrit (%)	41.1±3.6	41.3±4.7	42.7±2.8
Propofol (mg/kg/hr)	6.9±0.3	6.5±0.5	6.8±0.4
Fentanyl (μg/kg/hr)	1.68±0.26	1.82±0.23	1.61±0.32
Infusion rate (μg/kg/min)	6.99±0.73	2.98±1.10	0.103±0.052
Infusion range (μg/kg/min)	5.81−7.94	1.44−4.46	0.04−0.218

All values are means ±SD.

surgical stimulation.

Data analysis

A total of six paired Vmca and $P_{ET}CO_2$ measurements were performed during normotension and induced hypotension in each subject. Linear and exponential regression analyses were applied to determine the best fit for the individual relationship of Vmca and $P_{ET}CO_2$. Because both methods yielded almost identical correlation coefficients (Table 3), both were adopted for subsequent comparison. The derived absolute slopes and exponents were regarded as the variables. All values are expressed as mean± SD. Comparisons of intergroup or intragroup variables were performed using one-way analysis of variance (ANOVA) or repeated measures ANOVA, respectively. When a significance was found, Fisher's protected least significant difference test was used as *a post hoc* multiple comparison procedure. A p value of less than 0.05 was considered statistically significant.

RESULTS

There were no significant intergroup differences in age, body weight, body height, gender distribution, hemoglobin, hematocrit, dose of propofol, or dose of fentanyl except for the infusion rate of the hypoten-

Table 2. Changes of mean arterial blood pressure and heart rate during normotension and induced hypotension

Mean arterial blood pressure (mmHg)

$P_{ET}CO_2$	50 mmHg		45 mmHg		40 mmHg		35 mmHg		30 mmHg		25 mmHg	
	Normo	Hypo	Normo	Hypo	Normo	Hypo	Normo	Hypo	Normo	Hypo	Normo	Hypo
Nicardipine	82±15	58±3	79±12	56±5	76±9	57±3	74±11	56±3	74±9	56±3	77±10	57±3
Nitroglycerin	77±8	60±10	76±10	59±7	78±11	58±6	75±12	58±6	75±11	59±7	74±11	59±7
Prostaglandin E_1	77±10	59±5	75±9	58±4	77±11	58±4	75±9	58±5	76±12	58±4	75±12	58±5

Heart rate (beats/min)

$P_{ET}CO_2$	50 mmHg		45 mmHg		40 mmHg		35 mmHg		30 mmHg		25 mmH	
	Normo	Hypo	Normo	Hypo	Normo	Hypo	Normo	Hypo	Normo	Hypo	Normo	Hypo
Nicardipine	74±14	82±11	68±11	83±13	67±10	85±12	67±11	88±13	68±11	88±16	71±13	92±15
Nitroglycerin	78±15	89±11	75±14	86±13	74±15	86±14	74±15	85±15	75±14	87±15	75±14	87±12
Prostaglandin E_1	81±12	96±20	77±12	92±14	81±10†	95±16	80±12†	92±17	79±11	98±20	79±14	98±15

All values are expressed as mean±SD. $P_{ET}CO_2$, end-tidal CO_2 (mmHg); normo, during normotension; hypo, during induced hypotension.
†$p<0.05$ vs nicardipine group.

Table 3. The absolute slope and exponent during normotension and induced hypotension

	Absolute slope (cm/sec/mmHg)		Exponent (x 10^{-3}) (/mmHg)	
	Normotension	Hypotension	Normotension	Hypotension
Nicardipine	1.74±0.55	1.16±0.45†	43.3±7.0	32.9±7.7†
	(.950−.999)	(.974−.997)	(.978−.997)	(.956−.995)
Nitroglycerin	1.97±0.74	1.43±0.48†	45.3±6.5	38.6±8.3†
	(.952−.988)	(.950−.999)	(.980−.995)	(.989−.998)
Prostaglandin E_1	2.04±1.24	1.39±0.74†	41.5±9.1	34.2±8.2†
	(.961−.997)	(.969−.999)	(.979−.997)	(.956−.995)

All values are expressed as mean±SD. †indicates a significant ($p<0.05$) difference from normotension. Parentheses indicate the range of correlation coefficient.

sive drugs (Table 1). Rectal temperature was maintained at 35.5-37.0 C° in all subjects. Pulse oximetry showed 99%-100% throughout the study in all subjects. MAP was maintained at 55-60 mmHg during induced hypotension in each group (Table 2). There were no significant intergroup differences in MAP between normotension and hypotension (Table 2). Heart rate in the NIC-group during normotension was significantly decreased when compared with the PGE_1-group at $P_{ET}CO_2$ of 40 mmHg and 35 mmHg ($p<0.05$) (Table 2). Vmca at a $P_{ET}CO_2$ of 50 mmHg during NIC, NTG, and PGE_1-induced hypotension was significantly decreased when compared with values during normotension ($p<0.05$) (Fig. 1). Both linear and exponential regression when analyses demonstrated significant close relationships between Vmca and $P_{ET}CO_2$, with correlation coefficients ranging from 0.950 to 0.999 ($p<0.05$) (Table 3). Absolute slopes and exponents during drug-induced hypotension were significantly reduced when compared with values during normotension ($p<0.05$) (Table 3).

DISCUSSION

CBF at a given $PaCO_2$ ranging from 25 to 60mmHg has been found to change in a linear or exponential fashion, and CBF changes by approximately 3-4% per mmHg of $PaCO_2$ in these variations of $PaCO_2$.[1] The response of CBF to $PaCO_2$ has been indirectly evaluated by using TCD without a direct measurement of CBF. Kirkham et al.[2] showed a linear relationship between relative Vmca (%changes of Vmca at $P_{ET}CO_2$ of 40 mmHg) and $P_{ET}CO_2$ with a mean slope of 2.9% per mmHg of $P_{ET}CO_2$, and Markwalder et al.[3] showed an exponential relationship between relative Vmca and $P_{ET}CO_2$ with a mean exponent of 0.035 per mmHg of $P_{ET}CO_2$ in awake humans with TCD. The slope or exponent is generally accepted as an index of the cerebrovascular CO_2 reactivity.

The present study demonstrates that NIC, NTG and PGE_1-induced hypotension preserved the responsiveness of the cerebral vasculature to CO_2. However, they did attenuate the sensitivity of the cerebral vasculature to CO_2, regardless of which drugs were used. These findings completely contradicted previous studies. Abe et al. showed that cerebrovascular CO_2 reactivity and CO_2 sensitivity, measured by the thermal gradient method, remained unchanged during NIC,[4] NTG,[6] and PGE_1-[6,7,8] induced hypotension. Kawaguchi et al. also showed the persistence of cerebral vascular CO_2 reactivity and sensitivity, measured by TCD, during NIC[5] and PGE_1-[9] induced hypotension. These divergent findings can be explained by the fact that the number of data points generated and the range of altered $PaCO_2$ values were minimal. The CO_2 reactivity was calculated at 2 points within a narrow $PaCO_2$ range in these previous studies. In contrast, in the present study, the CO_2 reactivity was evaluated with an absolute slope and an exponential exponent was determined at 6 data points over a wide $P_{ET}CO_2$ range of 25-50 mmHg.

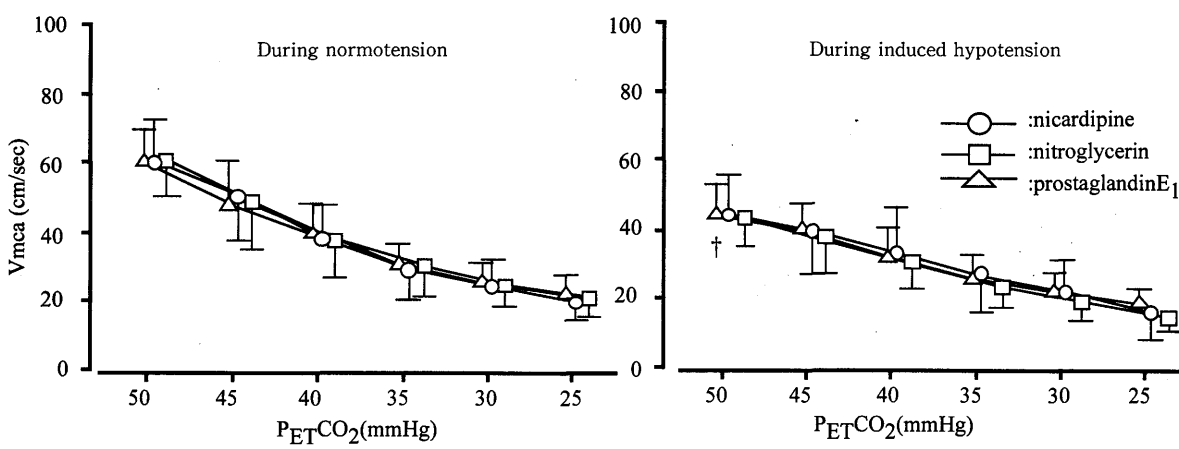

Fig. 1: Vmca during normotension and induced hypotension in 3 groups. Values are means±SD. Vmca, time averaged mean blood flow velocity in the middle cerebral artery; $P_{ET}CO_2$, end-tidal CO_2 tension. †indicates a significant ($p<0.05$) difference from normotension, respectively.

Matta et al.[12] recently showed similar findings to the present study during sodium nitroprusside-induced hypotension. They demonstrated an attenuated slope, which was determined by linear regression analysis over 5 data points of $PaCO_2$ ranging from 25 to 50 mmHg.[12]

Vmca decreased significantly during drug induced-hypotension at a $P_{ET}CO_2$ of 50 mmHg, regardless of the hypotensive drugs used, when compared with values during normotension ($p<0.05$) (Fig. 1). These findings suggest that the cerebral vasculature dilates submaxi-mally or maximally, and that CBF becomes passive to perfusion pressure at a $P_{ET}CO_2$ of 50 mmHg by blunting cerebral vascular autoregulation. The cerebrovascular CO_2 reactivity depends on the ability of the vasculature to dilate or constrict, which in turn is dependent on the presence of the vascular tonus. In the present study, an attenuated sensitivity of cerebral vessels to CO_2 during induced hypotension may be ascribed primarily to the loss of the vascular tonus at a $P_{ET}CO_2$ of 50 mmHg.

Propofol is a relatively new intravenous anesthetic. The cerebrovascular CO_2 reactivity in humans during propofol anesthesia has been previously assessed by TCD in several studies. Eng et al. demonstrated that propofol anesthesia without nitrous oxide slightly decreased the Vmca in comparison with the awake state; however, the CO_2 reactivity, as determined by linear regression analysis, was maintained.[13] Strebel et al. reported similar findings regarding propofol anesthesia.[14] These observations may validate the notion that propofol without nitrous oxide is a suitable anesthetic for comparing the effects of some drugs or physiologic changes on the cerebrovascular CO_2 reactivity in humans.

One potential criticism of the present study is that the cerebrovascular CO_2 reactivity was evaluated based only on $P_{ET}CO_2$, and not on $PaCO_2$. Young and associates demonstrated comparable CBF response slopes, calculated using either $PaCO_2$ or $P_{ET}CO_2$, because of stable $PaCO_2$-$P_{ET}CO_2$ gradients.[15] However, it is well recognized that hypotension possibly increases the gradient between $PaCO_2$ by increasing the ratio of physiological dead space to tidal volume (VD/VT).[16] Invasive measurements of $PaCO_2$ were not performed in the present study. However, there were no significant differences in Vmca between normotension and drug induced hypotension, except at a $P_{ET}CO_2$ of 50 mmHg (Fig. 1). These findings indirectly suggest that the $PaCO_2$-$P_{ET}CO_2$ gradients during normotension and induced hypotension were negligible, so that the CO_2 reactivity could be correctly evaluated in the present study.

In summary, we conclude that NIC, NTG and PGE_1 have similar effects on cerebral vasculature. They preserve the responsiveness to CO_2; however, they attenuate the sensitivity to CO_2.

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