Neuroanesthesia and Intensive Care

Changes in cerebral blood flow velocity elicited by surgical stimulation are dependent on the $PaCO_2$ level

[Les changements de vitesse du flux sanguin cérébral, déclenchés par la stimulation chirurgicale, dépendent du niveau de $PaCO_2$]

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Purpose: To investigate the influence of $PaCO_2$ manipulation on the cerebral hemodynamic response to surgical stimulation.

Methods: Twenty-one female patients undergoing elective gynecological surgery performed through a lower median abdominal incision were enrolled. After obtaining steady general anesthesia with 1.7% sevoflurane and 60% nitrous oxide, the patients were randomly assigned to three groups, hypocapnia ($PaCO_2$=30 mmHg), normocapnia ($PaCO_2$=38 mmHg), and hypercapnia ($PaCO_2$=44 mmHg) groups. The changes in mean blood flow velocity in the middle cerebral artery (Vmca) were evaluated using transcranial Doppler ultrasonography during nine minutes after surgical incision.

Results: The change in Vmca (Δ Vmca) with surgical incision during hypercapnia (30–36 cm·sec^{-1}) was significantly greater than during normocapnia (20–22 cm·sec^{-1}) and hypocapnia (13–15 cm·sec^{-1}). The Δ Vmca in the hypocapnia group was significantly smaller than in the normocapnia group. Arterial blood pressure increased with incision but there was no significant difference among the three groups.

Conclusion: Cerebral hemodynamic changes evoked by surgical stimulation are attenuated by hypocapnia and are augmented by hypercapnia, even within a clinically relevant range of $PaCO_2$.

Objectif : *Rechercher l'influence de la manipulation de la $PaCO_2$ sur la réaction hémodynamique cérébrale à la stimulation chirurgicale.*

Méthode : *Vingt et une patientes devant subir une intervention gynécologique, réalisée par incision médiane abdominale basse, ont été recrutées. L'anesthésie générale étant stabilisée avec du sévoflurane à 1,7 % et du protoxyde d'azote à 60 %, nous avons réparti les patientes en trois groupes : hypocapnie ($PaCO_2$ = 30 mmHg), normocapnie ($PaCO_2$ = 38 mmHg) et hypercapnie ($PaCO_2$ = 44 mmHg). Les changements de vitesse du flux sanguin moyen de l'artère cérébrale médiane (Vacm) ont été évalués en utilisant l'échographie Doppler transcrânienne pendant neuf minutes après l'incision chirurgicale.*

Résultats : *Les changements de Vacm (Δ Vacm) provoqués par l'incision chirurgicale pendant l'hypercapnie (30–36 cm·sec^{-1}) ont été significativement plus importants que pendant la normocapnie (20–22 cm·sec^{-1}) et l'hypocapnie (13–15 cm·sec^{-1}). La Δ Vacm a été significativement plus faible avec hypocapnie qu'avec normocapnie. La tension artérielle a augmenté avec l'incision, mais il n'y a pas eu de différence intergroupe significative.*

Conclusion : *Les changements hémodynamiques cérébraux provoqués par la stimulation chirurgicale sont atténués par l'hypocapnie et augmentés par l'hypercapnie, même en se confinant dans des limites cliniques acceptables de $PaCO_2$.*

NOCICEPTIVE stimulation provokes an increase in cerebral blood flow (CBF), which has been attributed to the cerebral vasodilation coupled with functional/metabolic activation.[1,2] The increase in CBF

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may be accompanied by an increase in intracranial pressure (ICP) in patients with central nervous system pathology and, hence, is undesirable.

The arterial partial pressure of carbon dioxide ($PaCO_2$) is an important regulator of cerebral vascular tone and an alteration of $PaCO_2$ may interact with several physiologic processes in the brain.[3] However, little is known whether altering cerebral vascular tone via manipulation of $PaCO_2$ influences the response of CBF to nociceptive stimulation.

We hypothesized that the CBF response elicited by nociceptive stimulation can be attenuated by prior constriction of cerebral vessels through hypocapnia and be augmented by dilatation of them through hypercapnia. We tested this hypothesis in surgical patients by measuring blood flow velocity in the middle cerebral artery using noninvasive transcranial Doppler ultrasonography (TCD).

Methods

Twenty-one patients scheduled for elective gynecological surgery performed through a lower median abdominal incision were enrolled in the study. Patients were all classified as American Society of Anesthesiologists physical status I or II. Patients with an apparent history of cerebrovascular disease were excluded. The study protocol was approved by the Institutional Review Board of the Yamaguchi University Hospital, and informed consent was obtained from each patient. The patients were premedicated with 0.5 mg atropine and 50 mg hydroxyzine or 3 mg midazolam administered intramuscularly 30 min before entering the operating room. In the operating room, a lumbar epidural catheter was inserted in all patients but no drug was administered epidurally until all study measurements were obtained. While the patients were awake, heart rate (HR), noninvasive arterial blood pressure (Life Scope 14; Nihon Koden, Japan), end-tidal carbon dioxide tension ($P_{ET}CO_2$) (Capnomac; Ultima, Datex- Ohmeda, Helsinki, Finland) were measured and recorded. $P_{ET}CO_2$ was obtained by attaching the sampling line close to the nares while the patient breathed spontaneously. The mean blood flow velocity of the middle cerebral artery (Vmca) while awake was measured using a 2-MHz pulsed TCD probe (TC 2-64; EME, Uberlingen, Germany) through the patient's left "temporal window". After the appropriate signals were identified at a depth of 45–55 mm, the probe was fixed using a probe holder (model IMP-F/536B; EME), so as not to change the insonating angle.

General anesthesia was induced with 4 $mg \cdot kg^{-1}$ thiopentone and 0.15 $mg \cdot kg^{-1}$ vecuronium administered intravenously and was deepened with inhalation of 3.0% sevoflurane in 60% nitrous oxide and oxygen. After intubation of the trachea, the lungs were ventilated mechanically with 1.7% sevoflurane (end-tidal) in 60% nitrous oxide and oxygen (total 1.6 MAC). The patients were randomly assigned to three groups, a hypocapnia group ($PaCO_2$=30 mmHg), a normocapnia group ($PaCO_2$=38 mmHg) and a hypercapnia group ($PaCO_2$=44 mmHg). Mechanical ventilation was adjusted (tidal volume of 8–10 $mL \cdot kg^{-1}$ and respiratory rate of 6–10 $times \cdot min^{-1}$) to maintain a $P_{ET}CO_2$ 2–3 mmHg lower than target $PaCO_2$ values. After anesthesia induction, attachment of TCD probe was reconfirmed and care was taken to obtain the values continuously throughout the study period. Blood samples for analysis of blood gases, hemoglobin, blood glucose, and electrolyte concentrations were obtained by an arterial puncture. The nasopharyngeal temperature was monitored continuously and was maintained at normothermia (36.0–36.5°C) using a water blanket (Medi-Therm II, Gaymar, New York, NY, USA) and a convective warming blanket (Warm touch, Mallinckrodt Medical, Eden Prairie, MN, USA).

Vmca, arterial blood pressure, HR, and $P_{ET}CO_2$ were measured and recorded at the following time points: just before surgical incision and one, three, five, seven, and nine minutes after surgical incision.

The increase in flow velocity (Δ Vmca) and the increase in mean arterial blood pressure (Δ MABP) at the different time points were calculated as the difference between preincisional Vmca and postincisional Vmca [Δ Vmca=(post-Vmca) – (pre-Vmca)] and the difference between preincisional MABP and postincisional MABP [Δ MABP=(post-MABP) – (pre-MABP)], respectively.

Data analysis

All data are reported as mean ± standard deviation (SD). An analysis of variance was used for intergroup comparisons of patients' clinical data and preincisional blood gases, hemoglobin, glucose, temperature, and Vmca data. A repeated measure analysis of variance was used for intergroup comparisons of Δ Vmca change and Δ MABP change. Fisher's protected least significant difference was used for post hoc test. A *P* value less than 0.05 was considered to be statistically significant.

Results

Table I shows patients' characteristics. There were no significant differences among the three groups in age, height, weight, awake values of $P_{ET}CO_2$, Vmca, MABP, and HR.

Table II shows the values of preincisional blood gases, hemoglobin, blood glucose, and nasopharyngeal temperature and Vmca. There were no significant

TABLE I Patient characteristics

	Hypocapnia (n=7)	*Normocapnia (n=7)*	*Hypercapnia (n=7)*
Age (yr)	37 ± 10	43 ± 8	45 ± 8
Height (cm)	160 ± 3	158 ± 6	159 ± 5
Weight (kg)	54 ± 4	53 ± 7	54 ± 7
Awake values			
- $PETCO_2$ (mmHg)	37 ± 1	38 ± 2	38 ± 1
- Vmca ($cm \cdot sec^{-1}$)	73 ± 17	59 ± 10	69 ± 8
- MABP (mmHg)	91 ± 11	85 ± 11	91 ± 11
- HR ($beats \cdot min^{-1}$)	75 ± 11	75 ± 11	75 ± 10

Values are mean ± SD. $PETCO_2$=end-tidal carbon dioxide tension; Vmca=velocity in the middle cerebral artery; MABP=mean arterial blood pressure; HR=heart rate.

TABLE II Preincisional blood gases, hemoglobin and glucose concentrations, temperature and Vmca

	Hypocapnia (n=7)	*Normocapnia (n=7)*	*Hypercapnia (n=7)*
$PaCO_2$ (mmHg)	30 ± 2**	38 ± 2	44 ± 2*
PaO_2 (mmHg)	241 ± 23	232 ± 28	215 ± 29
Hemoglobin ($g \cdot L^{-1}$)	110 ± 6	109 ± 14	110 ± 12
Glucose ($mmoL \cdot L^{-1}$)	4.3 ± 0.5	4.9 ± 1.1	4.7 ± 0.5
Temperature (°C)	36.0 ± 0.4	36.2 ± 0.2	36.4 ± 0.5
Vmca ($cm \cdot sec^{-1}$)	46 ± 20	50 ± 8	84 ± 19*

Values are mean ± SD. *=significantly different from hypocapnia and normocapnia groups; **=significantly different from normocapnia group.

differences among the three groups except for $PaCO_2$ and Vmca values. The Vmca in the hypercapnia group was significantly greater than in the normocapnia and hypocapnia groups and the Vmca in the hypocapnia group, though it was numerically smaller, was not significantly different from the normocapnia group.

The Figure shows the changes in flow velocity and MABP after surgical incision calculated as Δ Vmca and ΔMABP. The Δ Vmca in the hypercapnia group was significantly greater than in the normocapnia and hypocapnia groups. The Vmca in the hypocapnia group was significantly smaller than in the normocapnia group. The MABP significantly increased with incision in all three groups but there was no significant difference among the groups.

Discussion

The flow velocity determined by TCD is not equivalent to CBF. However, an excellent correlation between changes in flow velocity and changes in CBF has been reported.[4] In the present study, we evaluated the cerebrovascular response to surgical stimulation by using this noninvasive technique. We chose the study period

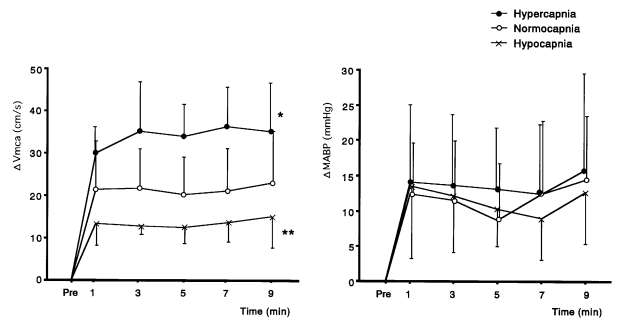

FIGURE Changes in Δ Vmca and Δ MABP after surgical incision. Left: The Δ Vmca change in the hypercapnia group was significantly greater than in the normocapnia and hypocapnia groups (*P <0.05). The Δ Vmca in the hypocapnia group was significantly smaller than in the normocapnia group (**P <0.05). Right: There was no significant difference in blood pressure change among the three groups.

at skin incision because we thought that skin incision would cause a substantial change in cerebral hemodynamics and could be most easily detected and followed without bias. As the size of the skin incision and the time from skin incision to incision of the peritoneum were almost identical in all patients, we think the surgical stimulation was similar among the patients.

We found that changing the basal cerebral vascular tone by $PaCO_2$ manipulation influenced the increase in Vmca elicited by surgical stimulation: the increase in Vmca elicited by surgical incision was attenuated by prior constriction of cerebral vessels through hypocapnia ($PaCO_2$=30 mmHg) and was augmented by dilatation of cerebral vessels through hypercapnia ($PaCO_2$=44 mmHg). This observation may be important in the management of patients with a decreased intracranial compliance because $PaCO_2$ elevation, even if it is mild, would not only increase steady state CBF but also augment CBF response to surgical stimulation and hence increase ICP, whereas hypocapnia provides an opposite effect, which is favourable for these patients.

The aim of anesthesia is to attenuate the undesirable response to various nociceptive stimuli. However, 1.6 MAC anesthesia used in the present study did not prevent an increase in Vmca induced by surgical incision. Many, but not all, stressful events are accompanied by increases in CBF and/or cerebral metabolism.[5] Although we did not measure cerebral metabolism in the present study, it is possible that increases in Vmca elicited by surgical stimulation might be due in part to

the activation of cerebral metabolism. In awake humans, somatosensory stimulation has been reported to increase CBF but not cerebral metabolic rate for oxygen ($CMRO_2$) in the sensorimotor cortex,[6] and visual stimulation raised CBF and cerebral metabolic rate for glucose with little change in $CMRO_2$.[7] It is uncertain whether normal functional activation in the brain is supported by energy derived from aerobic or anaerobic metabolism. Assuming aerobic metabolism is the case, CBF increases in excess of O_2 demand. Indeed, in humans, Inada *et al.* reported a decrease in cerebral arteriovenous oxygen content difference from 6.5 vol% to 5.3 vol% with surgical incision under 1.2% sevoflurane and 65% nitrous oxide anesthesia.[8] This suggests that stimulation altered the flow-metabolism coupling balance to a state of relative hyperemia in this anesthetic condition. Thus, it seems acceptable to attenuate the increase in CBF elicited by nociceptive stimulation without decreasing cerebral metabolism.

Kuramoto *et al.* reported in dogs that, under deep halothane anesthesia, CBF increased significantly after stimulation of the sciatic nerve, while $CMRO_2$ did not increase.[9] Thus, increases in CBF elicited by stimulation may not always be associated with an increase in cerebral metabolism or the magnitude of increases in CBF and metabolism may not always be parallel. With morphine given with nitrous oxide, the increase in CBF induced by stimulation was augmented.[9] At a plasma thiopentone concentration over 37 $\mu g \cdot mL^{-1}$, responses of CBF, $CMRO_2$ and electroencephalography to stimulation were completely abolished.[10] Taken together, these results suggest that the increase in CBF is more pronounced when subjects are anesthetized with drugs possessing vasodilatory properties than when anesthetized with drugs having vasoconstrictive properties. In the present study, hypocapnia, which induces cerebral vasoconstriction, attenuated CBF response to surgical stimulation and hypercapnia, which induces vasodilation, augmented the response. It might therefore be possible to control the CBF response to surgical stimulation by prior regulation of cerebral vascular tone, either chemically or pharmacologically.

To block the sympathoadrenal response to stimuli, more than 1.5 MAC is required (MAC BAR).[11] In the present study, while patients were anesthetized at 1.6 MAC, surgical incision increased arterial blood pressure and HR and the observed increase in Vmca may be due, in part, to increased arterial blood pressure. von Knobelsdorff *et al.* investigated the effects of surgical stimulation on blood flow velocity using TCD in isoflurane anesthetized patients.[12] They reported that noradrenaline-induced increases in arterial blood pressure, which were greater than those induced by surgery, did not change blood flow velocity significantly. They concluded that increases in blood flow velocity with surgical stimulation were not a function of changes in arterial blood pressure.[12] However, if the increase in arterial blood pressure elicited by surgical stimulation is abrupt, it will cause a transient increase in CBF because cerebral autoregulation is not instantaneous. $PaCO_2$ also modifies cerebral autoregulation. Hypocapnia maintains autoregulation better, while hypercapnia tends to cause dysautoregulation.[13,14] Thus, the increase in CBF may be more pronounced in hypercapnia than in hypocapnia, even if the increases in arterial blood pressure are almost the same. In this context, though the magnitude of arterial blood pressure elevation elicited by surgical stimulation in the present study was very similar in the three groups, the possibility that the differences in Vmca responses may be related, in part, to the change in arterial blood pressure cannot be excluded.

Another concern is that CO_2 itself has effects on central nervous system function. Extreme hypocapnia (respiratory alkalosis pH >7.50) and hypercapnia ($PaCO_2 \geq$ 245 mmHg) can cause narcosis,[15] and can likely influence anesthetic depth. Recently, Zhou *et al.* reported that hypercapnia and hypocapnia at more clinically relevant levels ($P_{ET}CO_2$ of 25 and 45 mmHg) affected spinal motor neuron excitability during isoflurane anesthesia.[16] Spinal cord neuron excitability was determined by measuring the posterior tibial nerve H-reflex amplitude and F-wave persistence. Not only hypercapnia, but also hypocapnia decreased H-reflex amplitude and F-wave persistence, which may affect motor response to surgical stimulation. It is uncertain whether cerebral cortical neuronal excitability was affected and hence the functional/metabolic response to surgical stimulation were influenced at the $PaCO_2$ levels (30–44 mmHg) examined in the present study.

The subjects of the present study were female patients with no brain pathology. Extrapolation of these findings to a mixed population of patients with intracranial pathology deserves consideration. A recent report has demonstrated that regional CBF during visual stimulation increased more in women than in men.[17] Therefore, it is possible that the magnitude of response to nociceptive stimulation could be less in men than women. In patients with various intracranial pathologies, it would be difficult to perform a study like ours. We suggest that our results may be applicable to diseased brain, provided the cerebrovascular response to CO_2 is preserved.

In conclusion, increases in Vmca evoked by surgical stimulation were attenuated by hypocapnia and were augmented by hypercapnia, even within a clinically

relevant range of $PaCO_2$. Our findings suggest that hypocapnia should be achieved prior to nociceptive stimulation in patients at risk of complications from increased CBF.

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