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Evaluation of cerebrovascular carbon dioxide reactivity in patients with diabetes mellitus under sedative doses of propofol

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Abstract
The present study compared cerebrovascular CO_2 reactivity in diabetic patients on different treatment modalities under sedative doses of propofol. Fifteen patients with diabetes mellitus (on three different antidiabetic treatment modalities) who required mechanical ventilation during intensive care therapy were studied, sedation during mechanical ventilation being maintained using propofol. As controls, 6 patients without diabetes were monitored. A 2.5-MHz pulsed transcranial Doppler probe was attached to the head of the patient at the right temporal window for continuous measurement of mean blood flow velocity in the middle cerebral artery (Vmca). After establishing baseline values of Vmca and cardiovascular hemodynamics, end-tidal CO_2 was decreased by increasing ventilatory frequency by 5–8 breaths·min^{-1}. Values for absolute and relative CO_2 reactivity in insulin-treated patients were lower than those in the other three groups (absolute CO_2 reactivity [means ± SD]: control, 3.1 ± 0.6 cm·s^{-1}·mmHg^{-1}, diet, 3.8 ± 1.4 cm·s^{-1}·mmHg^{-1}; oral antidiabetic drug 3.2 ± 0.9 cm·s^{-1}·mmHg^{-1}; insulin, 1.1 ± 0.6 cm·s^{-1}·mmHg^{-1}; $P = 0.002$).

The present study shows that insulin-treated diabetic patients probably have lower cerebrovascular CO_2 reactivity under propofol anesthesia than control patients or diabetics treated with dietary therapy or oral hypoglycemics.

Key words Cerebrovascular CO_2 reactivity · Diabetes mellitus · Propofol · Sedation dose

Introduction

The control of arterial CO_2 levels (Pa_{CO_2}) is often used to control cerebral blood flow (CBF) and cerebral blood volume (CBV) during surgery and in intensive care units (ICUs) [1–4]. Alteration of CBF in response to changes in Pa_{CO_2} is defined as cerebrovascular CO_2 reactivity [5].

Many different sedative drugs are administered to mechanically ventilated patients in the ICU [6–8]. We previously showed that different sedatives, such as propofol and dexmedetomidine, had different effects on cerebrovascular CO_2 reactivity in patients with septic shock [9]. In another study, we reported that different doses of propofol exerted different vasoconstrictive effects in elderly subjects as compared to the effects in younger patients [10]. Moreover, Eng et al. [11] found that propofol had vasoconstrictive properties on the cerebral vasculature and induced impaired cerebrovascular CO_2 reactivity. These findings indicate that cerebrovascular CO_2 reactivity under the sedative doses of propofol usually used in the ICU may differ from the reactivity under anesthetic propofol doses.

The prevalence of diabetes mellitus has been steadily rising throughout the world for the past 20–30 years. Inevitably, the number of diabetic patients requiring ICU care is also gradually increasing [12]. In previous studies, we [2, 13, 14] found that diabetic patients had impaired cerebrovascular CO_2 reactivity under anesthesia. These findings strongly suggest that diabetic patients would also have impaired cerebrovascular CO_2 reactivity under sedation in the ICU. Clinical situations in patients in the ICU are very different from those encountered during anesthesia. For example, organ dysfunction in ICU patients, especially liver and kidney dysfunction, may affect drug metabolism, potentiating the effect of sedative drugs. Further, the use of catecholamines induces vasoconstrictive effects on the endothelium, affecting endothelial cell function.

Although it is important for physicians to know whether the cerebrovascular CO_2 reactivity in diabetic patients in ICU situations may differ from that under anesthesia, there are no data available to confirm this. This study was designed to test this hypothesis.

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Patients and methods

After obtaining approval from the ethics committee of our institution, we obtained written informed consent from the patients' families. The study subjects were 15 patients with diabetes mellitus within 96 h of admission to the ICU. As controls, 6 patients without diabetes mellitus were also monitored. Patients from both groups required mechanical ventilation for the management of respiratory failure. Patients were considered to have diabetes mellitus if medical records showed that they had been diagnosed as having type 2 diabetes and were receiving medical antidiabetic therapy, such as diet, oral hypoglycemics, or insulin therapy. Because glycosylated hemoglobin (HbA1c; normal value, 4.5%–5.8%) is one of the indicators of the adequacy of control of blood sugar levels in diabetic patients, all patients, including the control group individuals, had their HbA1c levels measured. Patients' families were questioned about the patient's medical and smoking histories. A history of prior stroke was ruled out in all study subjects.

Routine monitoring was applied to all patients, including electrocardiography, invasive arterial pressure, central venous pressure, end-tidal CO_2 (Pet_{CO_2}), and pulse oximetry.

All subjects, diabetics and controls, received a 1.0-mg·kg^{-1} intravenous bolus of propofol over 10 min, followed by a continuous infusion at the rate of 1–3 mg·kg^{-1}·h^{-1}. To maintain hemodynamic stability, all patients in both groups received inotropic agents such as dopamine and dobutamine. Target systolic arterial blood pressure for all patients was more than 80 mmHg. All patients received mechanical ventilation using a Servo 300 ventilator (Siemens, Danvers, MA, USA) in volume-controlled ventilation mode with a positive end-expiratory pressure (PEEP) of 5–10 cmH_2O. Target oxygenation variables were Pa_{O_2} more than 60 mmHg and arterial oxygen saturation more than 90%. Permissive hypercapnia with a low tidal volume ventilatory strategy was employed for all patients to avoid ventilator-induced lung injury. Measurement of cerebrovascular CO_2 reactivity was performed 1 h or more after the hemodynamic and respiratory variables had stabilized.

To assess the severity of disease and organ dysfunction, the Acute Physiology and Chronic Health Evaluation II (APACHE II), multiple organ dysfunction syndrome (MODS), and systemic inflammatory response syndrome (SIRS) scores were registered [15].

The target sedation level in all patients in both groups was Ramsay score 4 sedation. A bispectral index (BIS) monitor (Aspect Medical Systems, Natic, MA, USA) was used to assess the effects of equipotent doses in each group.

A 2.5-MHz pulsed transcranial Doppler probe was attached to the head of the patient at the right temporal window, and mean blood flow velocity in the middle cerebral artery (Vmca) was measured continuously, using a SONOS 5500 2.5-MHz transducer (Hewlett Packard, Andover, MA, USA). After signals were identified at a depth of 45–60 mm, the probe was fixed using a probe folder, to avoid changing the insonating angle. Vmca values at end-expiration were recorded.

After the measurement of baseline Vmca and cardiovascular hemodynamic values, Pet_{CO_2} was decreased by increasing the ventilatory frequency by 5–8 breaths·min^{-1}. This decreased Pet_{CO_2} by approximately 10–12 mmHg, from 52 ± 2 mmHg to 38 ± 3 mmHg, within several minutes. All measurements were repeated after Pet_{CO_2} had decreased and remained stable for 5–10 min. To confirm alterations in Pa_{CO_2} resulting from increased ventilatory frequency, Pa_{CO_2} was also measured.

The cerebral vasoconstrictive response to hypocapnia in each patient was calculated as both the absolute change in Vmca and the percentage change from baseline Vmca per millimeter of mercury change in Pa_{CO_2}, using the following formulae [2,3]:

$$\text{Absolute } CO_2 \text{ reactivity} = (\text{Vmca at baseline} - \text{Vmca at hypocapnia})/\Delta Pa_{CO_2}$$

$$\text{Relative } CO_2 \text{ reactivity} = (\text{absolute } CO_2 \text{ reactivity}/\text{baseline Vmca}) \times 100,$$

where ΔPa_{CO_2} is the difference between final and baseline Pa_{CO_2}. The normal value of absolute CO_2 reactivity under anesthesia is a 2.0 to 5.0 · cm change in flow velocity per second per millimeter of mercury change in Pa_{CO_2}, while that for relative CO_2 reactivity is a 2.5%–6.0% change in flow velocity per millimeter of mercury change in Pa_{CO_2}.

The pulsatile index (PI) and Vmca were calculated for all study participants, using the following formulae [2,3]:

$$PI = (\text{systolic velocity} - \text{diastolic velocity})/\text{mean velocity}$$

$$\text{Vmca} = \frac{\text{systolic velocity} - \text{diastolic velocity}}{3} + \text{diastolic velocity}$$

Examiners who measured MCA flow velocity were blinded to each patient. Data obtained in this study were analyzed later by an independent researcher who was likewise blinded to each patient.

All data values are expressed as means ± SD. Following confirmation of equal variance among groups using the Bartlett test, one-way factorial measure analysis of variance was performed with multiple comparisons. When the F value was significant, the Bonferroni method was used for multiple comparisons. Values of $P < 0.05$ were considered statistically significant. All calculations

were performed on a Macintosh computer with SPSS (SPSS, Chicago, IL, USA) and StatView 5.0 software (Abacus Concepts, Berkeley, CA, USA).

Results

Table 1 shows the demographic data for each group. All patients in the control and diabetic groups displayed readily detectable MCA flow velocities. All groups were well matched for age; weight; height; and APACHE II, MODS, and SIRS scores. No significant differences in mean arterial pressure (MAP), heart rate (HR), and central venous pressure (CVP) were identified between groups. Fractional inspired oxygen ($F_{I_{O_2}}$) and PEEP were well matched between control and diabetic patients, as were the dosages of vasopressor drugs that they received.

Table 2 shows cerebrovascular CO_2 reactivity data in each group. The PI, baseline Vmca, BIS, blood sugar level, propofol infusion dosage to maintain Ramsay score 4 level, baseline Pa_{CO_2}, and Pa_{CO_2} under conditions of hypocapnia were essentially identical in all groups. HbA1c levels in the insulin-treated patients were higher than those in the other three groups (Table 2). Values of Vmca at hypocapnia in diabetic patients treated with insulin were higher than those in the other three groups.

Values for absolute and relative CO_2 reactivity in the insulin-treated patients were lower than those in the other three groups (absolute CO_2 reactivity: control, 3.1 ± 0.6 $cm \cdot s^{-1} \cdot mmHg^{-1}$; diet, 3.8 ± 1.4 $cm \cdot s^{-1} \cdot mmHg^{-1}$, oral antidiabetic drug, 3.2 ± 0.9 $cm \cdot s^{-1} \cdot mmHg^{-1}$; insulin, 1.1 ± 0.6, $cm \cdot s^{-1} \cdot mmHg^{-1}$; $P = 0.002$).

Discussion

The present study showed that cerebrovascular CO_2 reactivity in insulin-treated diabetic patients was lower than that in control patients and those on dietary or oral antidiabetic therapies.

The American College of Critical Care Medicine and the Society of Critical Care Medicine practice guidelines for the optimal use of sedatives and analgesics, published in 1995 and revised in 2000, recommend a tiered approach to the use of sedatives and analgesics [7]. These guidelines recommend that the drugs of choice in patients more than 12 years old requiring prolonged sedation and analgesia during mechanical venti-

Table 1. Demographic data for each group

		Diabetic patients			
	Control ($n = 6$)	Diet ($n = 5$)	Oral AD ($n = 5$)	Insulin ($n = 5$)	P value
Age (years)	60 ± 7	63 ± 8	64 ± 4	62 ± 6	0.81
Height (cm)	155 ± 3	157 ± 5	159 ± 7	162 ± 5	0.28
Weight (kg)	58 ± 10	54 ± 3	63 ± 6	60 ± 9	0.36
Hypertension	2	1	2	2	0.89
Smoking	1	1	0	1	0.77
SIRS score	2.1 ± 0.8	2.6 ± 0.5	2.2 ± 0.9	2.2 ± 0.8	0.76
APACHE II	23 ± 2	22 ± 2	21 ± 2	20 ± 3	0.30
MODS score	7.6 ± 1.5	6.0 ± 1.5	7.4 ± 2.4	6.6 ± 1.3	0.41
Baseline					
MAP (mmHg)	92 ± 13	104 ± 11	95 ± 4	91 ± 8	0.25
HR ($beats \cdot min^{-1}$)	90 ± 12	96 ± 15	88 ± 12	82 ± 4	0.35
CVP (mmHg)	6 ± 2	7 ± 1	5 ± 2	7 ± 1	0.47
During hypocapnia					
MAP (mmHg)	93 ± 12	104 ± 10	95 ± 7	92 ± 8	0.25
HR ($beats \cdot min^{-1}$)	90 ± 10	94 ± 12	89 ± 11	82 ± 4	0.34
CVP (mmHg)	6 ± 2	7 ± 1	5 ± 2	7 ± 1	0.33
Inspired $F_{I_{O_2}}$	0.53 ± 0.04	0.59 ± 0.05	0.54 ± 0.04	0.59 ± 0.08	0.15
PEEP (cmH_2O)	8 ± 2	10 ± 2	9 ± 2	8 ± 1	0.22
Catecholamine dosage					
Dopamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	5.8 ± 1.2	7.6 ± 1.6	5.8 ± 1.9	7.2 ± 0.8	0.16
Dobutamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	6.6 ± 1.2	8.4 ± 1.5	8.0 ± 0.7	8.4 ± 1.1	0.07

Values are expressed as means ± SD

SIRS, systemic inflammatory response syndrome; oral AD, oral antidiabetic drug; APACHE II, Acute Physiology and Chronic Health Evaluation II; MODS, multiple organ dysfunction syndrome; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure; PEEP, positive end-expiratory pressure

Table 2. Comparison of cerebrovascular CO_2 reactivity in the four groups

		Diabetic patients			
	Control ($n = 6$)	Diet ($n = 5$)	Oral AD ($n = 5$)	Insulin ($n = 5$)	P value
HbA1c (%)	4.5 ± 0.3	5.2 ± 0.4	6.5 ± 0.6	8.3 ± 0.4*	<0.001
Blood sugar level ($mg \cdot ml^{-1}$)	98 ± 16	111 ± 14	118 ± 28	101 ± 18	0.34
Propofol dosage ($mg \cdot kg^{-1} \cdot h^{-1}$)	2.4 ± 0.5	2.4 ± 0.4	2.3 ± 0.5	2.3 ± 0.6	0.99
BIS value	60 ± 3	59 ± 2	58 ± 3	60 ± 2	0.41
Baseline Pa_{CO_2} (mmHg)	50 ± 2	52 ± 2	53 ± 2	52 ± 2	0.38
Pa_{CO_2} at hypocapnia (mmHg)	37 ± 2	39 ± 3	38 ± 3	36 ± 3	0.55
Baseline Vmca ($cm \cdot s^{-1}$)	85.3 ± 5.4	86.2 ± 4.7	86.2 ± 3.9	80 ± 5.4	0.69
Vmca at hypocapnia ($cm \cdot s^{-1}$)	44.1 ± 2.0	42.4 ± 2.4	43.8 ± 2.6	63.8 ± 3.0*	<0.001
PI	1.14 ± 0.07	1.11 ± 0.09	1.10 ± 0.06	1.15 ± 0.08	0.73
Absolute CO_2 reactivity ($cm \cdot s^{-1} \cdot mmHg^{-1}$)	3.1 ± 0.6	3.8 ± 1.4	3.2 ± 0.9	1.1 ± 0.6*	0.002
Relative CO_2 reactivity ($\% \cdot mmHg^{-1}$)	7.1 ± 1.2	8.8 ± 2.9	7.1 ± 1.9	2.7 ± 1.6*	0.001

*$P < 0.05$ compared with other groups
Values are expressed as means ± SD
Oral AD, oral antidiabetic drug; HbA1c, glycosylated hemoglobin; BIS, bispectral index; Vmca, mean blood flow velocity in the middle cerebral artery; PI, pulsatile index

lation include morphine and fentanyl for intravenous opiate analgesia and propofol for rapid awakening from sedation.

Several studies have evaluated the effects of propofol on cerebrovascular circulation and CO_2 reactivity [11, 16–20]. These studies, were however, all conducted with anesthetic rather than sedative doses of propofol. Moreover, several clinical differences in patient demographics existed in these studies, such as the doses of catecholamines used, inspired oxygen concentrations, and infusion rates of propofol while in the ICU and during anesthesia. Matta et al. [16] examined cerebral CO_2 reactivity during propofol-induced electrical silence of the electroencephalogram in ten patients, and found that cerebral CO_2 reactivity remained intact during propofol anesthesia. In a study on sheep, Myburgh et al. [17] reported that although a constant propofol infusion of $15\ mg \cdot min^{-1} \cdot kg^{-1}$ significantly decreased cerebral blood flow compared with that in awake conditions, CO_2 reactivity remained intact. Harrison et al. [18] examined the effects of target-controlled infusion (TCI) of propofol (mean target concentration was 6.7 ± $1.1\ \mu g \cdot ml^{-1}$), and found that propofol had no effect on CO_2 reactivity. Conti et al. [19] showed that total intravenous anesthesia (TIVA) with propofol-remifentanil preserved cerebrovascular CO_2 reactivity at a BIS level of 50, in which the TCI rate of propofol was 2.7 ± $0.5\ \mu g \cdot ml^{-1}$, and that of remifentanil was 0.18 ± $0.06\ \mu g \cdot kg^{-1}$. In contrast, Eng et al. [11] examined the effects of propofol on cerebral CO_2 reactivity. Anesthesia was induced with $2.5\ mg \cdot kg^{-1}$ of propofol followed by an infusion of $150\ \mu g \cdot kg^{-1} \cdot min^{-1}$ while patients were breathing 100% oxygen. They showed that, compared to the CO_2-reactivity slope of $3.2 \pm 0.2\% \cdot mmHg^{-1}$ during the awake state, the slope under propofol anesthesia was $2.1 \pm 0.2\% \cdot mmHg^{-1}$, implying impaired cerebrovascular CO_2 reactivity. Steiner et al. [20] showed that the cerebrovascular effects of propofol in head-injured patients were different from those observed in healthy individuals. Our results showed that, in the ICU setting, cerebrovascular CO_2 reactivity under propofol sedation was lower in diabetic patients treated with insulin than that in control patients or diabetic patients treated with dietary therapy or oral hypoglycemics.

Several mechanisms should be considered to explain the apparently contradictory effects of propofol on cerebrovascular CO_2 reactivity. First, many reports differ in the anesthetic regimens employed, such as the use of nitrous oxide, additional opiate use, and the rate of propofol infusion. In particular, the use of different propofol dosages compared with those in our study may have yielded different effects. Indeed, we have previously shown that different dosages of propofol exert different effects on CO_2 reactivity [10]. Altering the dose of propofol used in our study may thus have resulted in different effects on CO_2 reactivity. Second, patient demographics may have affected our results. In our previous study, noted above [10], we found that cerebrovascular CO_2 reactivity was lower in elderly versus young patients. Hartl et al. [21] reported markedly lower absolute and relative mean CO_2 reactivities in elderly compared to young subjects, suggesting that aging might have some effects on cerebrovascular CO_2 reactivity.

The present study has clinical implications for hypercapnic lung-protective ventilation, a currently widely accepted ventilatory strategy for acute respiratory distress syndrome in the ICU. Hypercapnic lung-protective ventilation may increase intracranial pressure (ICP) in patients with brain injury. To decrease ICP,

hyperventilation is sometimes used in these patients. In patients without diabetes mellitus or in diabetic patients on dietary or oral hypoglycemic therapy, hyperventilation would be an effective means to control ICP under sedative doses of propofol. However, in diabetic patients treated with insulin, hyperventilation would have little beneficial effect in controlling ICP with the patients under sedative doses of propofol.

Large doses of catecholamines were used to maintain adequate hemodynamics in our study. These large doses of catecholamines may have had some effects on our results [22,23]. Strebel et al. [22] showed that noradrenaline and phenylephrine infused to increase arterial pressure in anesthetized patients failed to show any significant vasoconstrictor effect on the cerebral circulation. In addition, Myburgh et al. [24] showed that, in an ovine model, catecholamine infusions decreased propofol concentrations during continuous propofol infusion. Although the catecholamine dosages were almost identical in our study groups, the vasoconstrictor effects of catecholamines on the cerebral circulation cannot be ignored. Another potential criticism of our study is that some of our patients had hypertension, which, by itself, affects cerebrovascular CO_2 reactivity. McCulloch et al. [25] showed that small differences in mean arterial pressure (MAP) could affect cerebrovascular CO_2 reactivity during sevoflurane anesthesia. However, we previously found no differences in cerebrovascular CO_2 reactivity between control and hypertensive patients [26].

In the present study, we focused on a comparison of cerebrovascular CO_2 reactivity in diabetic patients with different treatments under sedative doses of propofol. Further studies are needed to clarify the differences, if any, between cerebrovascular CO_2 reactivities in diabetic patients in the awake state and under sedation with propofol.

There have been some reports regarding the effects of cytokines on cerebral endothelial cells. Papadopoulos et al. [27] suggested that inflammatory mediators released by leukocytes during sepsis had profound effects on cerebral endothelial cell functions. In the present study, we did not measure plasma cytokine levels in each group, and hence cannot rule out the possibility that plasma cytokines may have had some effects on our results, although the SIRS scores were identical in all groups.

The number of patients in the present study was small, so that further studies with more patients are required to confirm the results observed in this study.

In conclusion, we found that, in patients under propofol sedation in the ICU, cerebrovascular CO_2 reactivity in diabetic patients treated with insulin was impaired compared with that in patients without diabetes and compared with that in diabetic patients receiving dietary or oral hypoglycemic therapy.

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