J Anesth (2007) 21:125–130
DOI 10.1007/s00540-007-0500-7

Journal of
Anesthesia

Original articles

Effects of nicardipine-induced hypotension on cerebrovascular carbon dioxide reactivity in patients with diabetes mellitus under sevoflurane anesthesia

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Abstract
Purpose. The purpose of this study was to examine the effects of nicardipine-induced hypotension on cerebrovascular CO_2 reactivity in patients with diabetes mellitus under sevoflurane anesthesia.
Methods. Nineteen diabetic patients, and 11 nondiabetic patients (serving as controls), undergoing elective orthopedic, cardiovascular, or thoracic surgery were included in the study. The diabetic patients were divided into three groups according to the antidiabetic therapy they were receiving, i.e., diet therapy ($n = 6$), oral antidiabetic drugs ($n = 7$), and insulin ($n = 6$). Anesthesia was maintained with 1.0 minimum alveolar concentration of sevoflurane. Absolute and relative cerebrovascular CO_2 reactivity was calculated using a 2.5-MHz pulsed transcranial Doppler (TCD) probe for the continuous measurement of mean blood flow velocity in the middle cerebral artery (Vmca). The cerebrovascular CO_2 reactivity was measured both at baseline and during hypotension by increasing the ventilatory frequency by 4 to 7 breaths·min^{-1}. Nicardipine was used to induce hypotension.
Results. We found that values for the Bispectral index (BSI), baseline mean blood pressure, endtidal CO_2 (Pet_{CO_2}), and Vmca were essentially identical in all patients, irrespective of the type of antidiabetic treatment being taken. Values for absolute and relative CO_2 reactivity in insulin-dependent patients, at both baseline blood pressure and during hypotension, were lower than those in patients in the antidiabetic drug, diet, and control groups (during hypotension, absolute CO_2 reactivity: diet group: 3.2 ± 0.9; oral antidiabetic drug group: 3.2 ± 0.7; insulin group: 1.5 ± 0.6; control group: 3.4 ± 0.8 cm·s^{-1}·mmHg^{-1}, [$P < 0.05$ insulin group vs the other groups]; relative CO_2 reactivity: diet group, 6.3 ± 1.0; oral antidiabetic drug group, 6.5 ± 0.8; insulin group, 3.5 ± 0.8; control group, 6.5 ± 0.7%·mmHg^{-1}, [$P < 0.05$ insulin group vs the other groups].
Conclusion. We concluded that cerebrovascular CO_2 reactivity in insulin-dependent patients is impaired during nicardipine-induced hypotension under sevoflurane anesthesia.

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Received: August 2, 2006 / Accepted: January 4, 2007

Key words Cerebrovascular CO_2 reactivity · Diabetes mellitus · Transcranial Doppler sonography · Hypotension

Introduction

Intraoperative cerebral blood flow (CBF) and cerebral blood volume (CBV) are often controlled by altering arterial carbon dioxide (Pa_{CO_2}) levels [1–3]. A change in CBF in response to changes in Pa_{CO_2} is defined as cerebrovascular carbon dioxide (CO_2) reactivity [3].

Hyperventilation and induced hypotension are useful techniques during anesthesia and surgery, with hyperventilation reducing CBF and CBV, and induced hypotension decreasing intraoperative blood loss [4,5]. Hypotensive drugs can, however, affect cerebral blood vessels and may influence CO_2 reactivity by changing vascular tone during induced hypotension [4].

Nicardipine, a calcium channel blocker that has potent systemic vasodilatory effects without negative inotropic, chronotropic, and dromotropic effects, and that does not increase intracranial pressure, is sometimes used for induced hypotension [6–9]. Abe et al. [7] examined the effects of nicardipine (initial infusion rate, 0.5 μg·kg^{-1}·min^{-1}) on CO_2 reactivity in nondiabetic patients under isoflurane anesthesia, and found that CO_2 reactivity did not change during the hypotension induced by nicardipine.

The prevalence of diabetes mellitus has been steadily rising throughout the world for the past 20–30 years. Inevitably, the number of diabetic patients undergoing surgery is also gradually increasing [10], making it important for anesthesiologists to know about the integrity of cerebrovascular CO_2 reactivity in diabetic patients during induced hypotension. Kawaguchi et al. [6] reported that cerebrovascular CO_2 reactivity was maintained during induced hypotension under fentanyl/diazepam/nitrous oxide anesthesia in patients without

diabetes mellitus. In previous studies [11–13], we found that diabetic patients had impaired CO_2 reactivity under propofol anesthesia. Dandona et al. [14] reported that there was a significant variation in CBF after the administration of 5% CO_2 in insulin-dependent diabetics compared with normal subjects, concluding that diabetic patients had diminished cerebrovascular reserve. These findings indicate that diabetic patients may also have impaired cerebrovascular CO_2 reactivity during induced hypotension under anesthesia. No data, however, exist describing cerebrovascular CO_2 reactivity during induced hypotension in patients with diabetes mellitus.

The purpose of this study was to examine the effects of nicardipine-induced hypotension on cerebrovascular CO_2 reactivity under sevoflurane anesthesia in patients with diabetes mellitus.

Patients and methods

After obtaining the approval of the ethics committee of our institution, written informed consent was obtained from 11 control nondiabetic patients and 20 diabetic patients scheduled consecutively for elective orthopedic, cardiovascular or thoracic surgery who were studied.

Patients were considered to have diabetes mellitus if medical records showed that they were diagnosed as having type 2 diabetes and were receiving antidiabetic therapy, such as diet, oral hypoglycemics, or insulin therapy. The duration of the disease was defined as the time period from the start of antidiabetic treatment until the start of the study.

Patients with a history of cerebrovascular disease, psychiatric illness, or active liver disease (glutamine oxaloacetate transaminase or glutamine pyruvate transaminase >50 $U \cdot dL^{-1}$) were excluded from the study. Patients with hypertension were defined as those taking antihypertensive medication.

All patients were examined for the presence of carotid artery stenosis, by ultrasonography and magnetic resonance imaging performed preoperatively. The presence of carotid artery stenosis was defined as luminal narrowing of more than 50% (insignificant or no disease, luminal narrowing of ≦50%; moderate disease, narrowing of >50% but <80%; severe disease, narrowing of ≧80% but ≦99%, defined by the arc of the short-axis view of the carotid artery [15]). None of the patients in this study had carotid artery stenosis. In addition, all patients were examined for the presence of silent lacunar infarction by, preoperative brain computed tomography and magnetic resonance tomography. One diabetic patient who had a silent lacunar infarction was excluded from the study. A total of 19 diabetic patients satisfied all the criteria and were included in the study. These 19 patients were divided into three groups according to the type of antidiabetic therapy they were receiving, i.e., diet therapy (n = 6), oral antidiabetic drugs (n = 7), and insulin (n = 6). As controls, 11 patients without diabetes mellitus were also examined. Because glycosylated hemoglobin (HbA1c; normal value, 4.5%–5.8%) is one of the indicators for the adequacy of control of blood sugar levels in diabetic patients, all the patients had their preoperative HbA1c levels measured.

Anesthesia was induced with 2 $mg \cdot kg^{-1}$ propofol, 5 $\mu g \cdot kg^{-1}$ fentanyl, and 0.2 $mg \cdot kg^{-1}$ vecuronium, followed by endotracheal intubation. Muscular relaxation was achieved by the intermittent administration of vecuronium. All patients were ventilated with 33% oxygen and 67% nitrous oxide, with the continuous monitoring of endtidal carbon dioxide (Pet_{CO_2}; Ultima; Datex, Helsinki, Finland). The tympanic membrane temperature was continuously monitored with the Mon-a-Therm (Mallinckrodt, St. Louis, MO, USA). Anesthesia was maintained with 1.0 minimum alveolar concentration (MAC) sevoflurane in 33% oxygen and 67% nitrous oxide (1 MAC = 1.71% for sevoflurane). A bispectral index (BIS) monitor (ASPECT Medical Systems, Natic, MA, USA) was used to assess the effects of sevoflurane in the control and diabetic groups.

The study was started after the induction of anesthesia and before the start of surgery, during a stable hemodynamic period (approximately 20–30 min after the induction of anesthesia) under 1.0 MAC sevoflurane anesthesia. A 2.5-MHz pulsed transcranial Doppler (TCD) probe was attached to the patient's head at the right temporal window, and mean blood flow velocity in the middle cerebral artery (Vmca) was continuously measured (SONOS 5500; 2.5-MHz transducer; Hewlett Packard, Andover, MA, USA). After the signals were identified at a depth of 45–60 mm, the probe was fixed, using a probe folder, so as not to change the insonating angle. The Vmca value at end-expiration was recorded. After the measurement of baseline Vmca and cardiovascular hemodynamic values, Pet_{CO_2} was decreased by increasing the ventilatory frequency by 4–7 $breaths \cdot min^{-1}$. This resulted in a decrease in the Pet_{CO_2}, by approximately 6–9 mmHg, within several minutes. All measurements were repeated when the Pet_{CO_2} decreased and remained stable for 5–10 min.

After finishing the measurement of cerebrovascular CO_2 reactivity under baseline conditions, hypotension was induced with a continuous infusion of nicardipine. The target blood pressure during hypotension was a 20% decrease in the baseline value. After the target hypotension was reached by using nicardipine infusion, cerebrovascular CO_2 reactivity during hypotension was measured by the same methods as those described above.

The cerebral vasoconstriction response to hypocapnia in each patient was calculated as both the absolute change in Vmca ($cm \cdot s^{-1} \cdot mmHg^{-1}$) and the relative percentage change in Vmca (percentage of baseline $Vmca \cdot mmHg^{-1}$) for each millimeter of mercury change in Pa_{CO_2}, using the following formulae [13]:

$$\text{Absolute } CO_2 \text{ reactivity} = \Delta Vmac / \Delta Pa_{CO_2}$$
$$\text{Relative } CO_2 \text{ reactivity} = (\text{absolute } CO_2 \text{ reactivity} / \text{baseline Vmca}) \times 100$$

where Δ Vmca is the difference between the flow velocity after Pa_{CO_2} decrease and the baseline flow velocity, and Δ Pa_{CO_2} is the difference between the baseline and final Pa_{CO_2}.

Statistical analysis

All data values are expressed as means ± SD. Following the confirmation of equal variance among groups by 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 to make multiple comparisons. To eliminate a type II error, each individual *P* value was adjusted. Statistical significance was set at $P < 0.05$. All calculations were performed on a Macintosh computer with SPSS (SPSS, Chicago, IL, USA) and Stat View 5.0 software packages (Abacus Concepts, Berkeley, CA, USA).

Results

Table 1 shows the demographic data of the groups. All patients, in both the diabetic and control groups, had easily detectable MCA flow velocities. No significant differences in demographic data existed between the diabetic and control groups. In addition, the diabetic subgroups were well matched for age, weight, awake baseline mean blood pressure (BP), fasting blood sugar (FBS), and duration of disease. The HbA1c of patients in the insulin group as a whole was higher than that of patients in the antidiabetic drug or diet groups.

Table 2 shows cerebrovascular CO_2 reactivity data in the groups. Values for BIS, and baseline mean BP, Pet_{CO_2}, and Vmca were essentially identical among the groups. Values for absolute and relative CO_2 reactivity in insulin-dependent patients were lower than those in the antidiabetic drug, diet, or control groups, under both normotensive and hypotensive conditions (Table 2).

There were no significant intragroup differences in any groups in regard to absolute or relative CO_2 reactivity between normotension (baseline BP) and during hypotension.

Discussion

The present study showed that cerebrovascular CO_2 reactivity in patients with diabetes mellitus with dietary control or receiving oral ant-diabetic drugs was maintained during nicardipine-induced hypotension under sevoflurane anesthesia. In contrast, in the patients on insulin therapy, impaired cerebrovascular CO_2 reactivity was observed during both nicardipine-induced hypotension and at baseline blood pressure.

There have been contradictory data regarding the effects of induced hypotension on cerebrovascular CO_2 reactivity under anesthesia in animal studies and in studies of patients without diabetes mellitus [5,16–18]. Artru and Colley [4] and Artru [5] reported that cerebral vascular responses to hypocapnia during

Table 1. Demographic data of the two groups

	Diabetic patients			Controls
	Diet ($n = 6$)	Oral AD ($n = 7$)	Insulin ($n = 6$)	($n = 11$)
Age (years)	61 ± 8	63 ± 9	65 ± 6	63 ± 11
Height (cm)	162 ± 5	163 ± 6	159 ± 6	161 ± 7
Weight (kg)	58 ± 8	58 ± 8	57 ± 7	57 ± 6
Hypertension (no.)	4	5	4	5
ACE blocker (no.)	3	4	2	3
Ca. blocker (no.)	1	1	2	2
Beta-blocker (no.)	0	0	0	0
Awake mean BP(mmHg)	95 ± 12	94 ± 12	96 ± 13	95 ± 12
FBS ($mg \cdot ml^{-1}$)	110 ± 18	119 ± 19	123 ± 23	95 ± 6
HbA1c (%)	5.6 ± 1.1	5.9 ± 1.4	6.6 ± 0.8*	4.6 ± 0.2
Duration of disease (years)	4 ± 3	4 ± 3	5 ± 3	

* $P < 0.05$ compared with the other groups
Values are means ± SD
Oral AD, Oral antidiabetic drug; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; BP, blood pressure; ACE, angiotensin-converting enzyme; Ca. blocker, calcium channel antagonist; No., number of patients

Table 2. Effects of nicardipine-induced hypotension on cerebrovascular CO_2 reactivity during sevoflurane anesthesia in the two groups

	Diabetic patients			Controls ($n = 11$)
	Diet ($n = 6$)	Oral AD ($n = 7$)	Insulin ($n = 6$)	
BIS value	52 ± 4	52 ± 4	50 ± 4	52 ± 4
Baseline values				
Normocapnia				
Mean BP (mmHg)	90 ± 9	88 ± 11	91 ± 11	87 ± 10
Pet_{CO_2} (mmHg)	36 ± 4	37 ± 3	37 ± 3	36 ± 4
Vmca ($cm \cdot s^{-1}$)	43.3 ± 4.3	43.1 ± 4.1	37.0 ± 3.3	44.3 ± 2.4
Hypocapnia				
Mean BP (mmHg)	88 ± 7	89 ± 10	90 ± 10	89 ± 11
Vmca ($cm \cdot s^{-1}$)	36.7 ± 4.4	36.7 ± 4.0	34.8 ± 3.3	35.9 ± 2.2
Pet_{CO_2} (mmHg)	30 ± 2	30 ± 3	30 ± 3	29 ± 3
Absolute CO_2 reactivity ($cm \cdot s^{-1} \cdot mmHg^{-1}$)	3.0 ± 0.9	2.9 ± 0.7	1.7 ± 0.7*	3.3 ± 0.8
Relative CO_2 reactivity ($\% \cdot mmHg^{-1}$)	5.7 ± 0.7	5.5 ± 0.9	3.8 ± 0.7*	5.6 ± 0.7
Values during hypotension				
Nicardipine dosage ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	4.9 ± 0.5	5.3 ± 0.7	5.5 ± 0.7	5.3 ± 0.7
Normocapnia				
Mean BP (mmHg)	70 ± 8	71 ± 12	70 ± 11	71 ± 10
Pet_{CO_2} (mmHg)	36 ± 3	37 ± 4	37 ± 4	36 ± 4
Vmca ($cm \cdot s^{-1}$)	42.9 ± 5.1	44.2 ± 4.9	40.1 ± 4.0	45.2 ± 2.9
Hypocapnia				
Mean BP (mmHg)	71 ± 10	70 ± 11	72 ± 10	69 ± 11
Pet_{CO_2} (mmHg)	29 ± 4	30 ± 3	29 ± 4	30 ± 3
Vmca ($cm \cdot s^{-1}$)	36.0 ± 4.1	37.1 ± 3.5	36.8 ± 3.0	36.1 ± 3.0
Absolute CO_2 reactivity ($cm \cdot s^{-1} \cdot mmHg^{-1}$)	3.2 ± 0.9	3.2 ± 0.7	1.5 ± 0.6*	3.4 ± 0.8
Relative CO_2 reactivity ($\% \cdot mmHg^{-1}$)	6.3 ± 1.0	6.5 ± 0.8	3.5 ± 0.8*	65 ± 0.7

* $P < 0.05$ compared with the other groups
Values are means ± SD
Oral AD, Oral antidiabetic drugs; BIS, bispectral index; Vmca, mean blood flow velocity in the middle cerebral artery; BP, blood pressure

nitroglycerin or trimethoaphan-induced hypotension (mean arterial pressure, 50 mmHg) were absent in animal studies. Okuda et al. [16] showed the absence of cerebrovascular CO_2 responsiveness after halothane-induced hypotension at a systolic blood pressure of 60 mmHg in baboons. Regarding the effects of nicardipine-induced hypotension on cerebrovascular CO_2 reactivity in humans, Kawaguchi et al. [6] examined the effects of nicardipine on cerebral vascular responses to hypocapnia (manipulation of the Pa_{CO_2} level during hypocapnia, 36 ± 1 mmHg), and showed that cerebrovascular CO_2 reactivity was maintained during nicardipine-induced hypotension under fentanyl/diazepam/nitrous oxide anesthesia in patients without diabetes mellitus. Abe et al. [7] found no changes in CO_2 reactivity after nicardipine infusion (manipulation of the Pa_{CO_2} level during hypocapnia was not shown). In contrast, Endoh et al. [8] showed that nicardipine-induced hypotension attenuated human cerebrovascular CO_2 reactivity during propofol-fentanyl anesthesia in patients without diabetes mellitus (manipulation of the Pa_{CO_2} level during hypocapnia was not shown). The discrepancy between these studies may, in part, be attributable to the range of altered Pa_{CO_2} values, as suggested by the report of Endoh et al. [8]. They speculated that the range of Pa_{CO_2} used for the calculation of the slope of CO_2 reactivity may have had some effects on the results. Another possibility is that the different anesthetic agents used in these studies, such as propofol, sevoflurane, or isoflurane, may themselves have had some effects on cerebral circulation. Nishiyama et al. [19] showed that cerebrovascular CO_2 reactivity was greater with isoflurane anesthesia than with sevoflurane anesthesia.

Our present study is the first of its kind to have examined the effects of nicardipine on cerebrovascular CO_2 reactivity in patients with diabetes mellitus. In previous studies [11–13], we found that insulin-dependent diabetic patients had impaired cerebrovascular CO_2 reactivity and cerebral autoregulation at baseline BP, as compared to findings for patients on dietary control or oral antidiabetic drug therapy. Dandona et al. [14] and Griffith et al. [20] also showed impaired cerebrovascular CO_2 reactivity in insulin-dependent diabetic patients. The present study showed that insulin-dependent patients had impaired cerebrovascular CO_2 reactivity during hypotension induced by nicardipine as well.

Manipulation of Pa_{CO_2} is a common practice in clinical situations [3], with hypocapnia being used to control intracranial pressure. The loss of cerebrovascular reactivity in patients on insulin therapy in the present study indicates the probable inability of the cerebral vasculature in these patents to meet oxygen demand and supply, especially under conditions of hypotension under anesthesia. Indeed, Matta et al. [17] showed that the hypocapnia-induced reduction of CBF was attenuated during hypotension induced with isoflurane, but that it was preserved during hypotension induced with other hypotensive agents. Our findings suggest that, in diabetic patients on insulin therapy, there may be a risk associated with inducing hypotension and simultaneously controlling Pa_{CO_2} during sevoflurane anesthesia.

Stratton et al. [21] reported that, in patients with type 2 diabetes, the risk of diabetic vascular complications was strongly associated with previous hyperglycemia. In addition, Pallas and Larson [22] noted that hyperglycemia led to impaired vascular function through endothelial cell dysfunction. The pathway that appears most affected by the diabetic state is that of nitric oxide. Loss of this pathway is accompanied by a loss of responsiveness to Pa_{CO_2}, and by a lack of autoregulation related to flow/pressure relationships. From these reports, we speculated that, in diabetic patients treated with insulin, nicardipine was unable to have any effects on the cerebral circulation, due to impaired vascular function.

Study limitations

We examined CO_2 reactivity during anesthesia with sevoflurane used together with nitrous oxide. Although the effect of nitrous oxide was ignored in our study, because nitrous oxide was administered at the same concentration in both the diabetic and the control groups, it is possible that nitrous oxide may have differential effects on cerebral circulation when used in combination with different anesthetics, such as isoflurane or propofol.

Another potential criticism of our study is that most of our patients had hypertension, which, by itself, affects cerebrovascular CO_2 reactivity [23]. McCulloch et al. [24] showed that small differences in mean arterial pressure could affect cerebrovascular CO_2 reactivity during sevoflurane anesthesia. Thus, the possibility that, in the present study, hypertension had some effects on cerebrovascular CO_2 reactivity cannot be ruled out.

The number of diabetic patients included in our study was relatively small, so that further, larger, studies are necessary to clarify whether cerebrovascular CO_2 reactivity in insulin-dependent patients is impaired during conditions of hypotension.

Although Mielck et al. [25] and Kitaguchi et al. [26] showed no effect of 1 MAC sevoflurane on CO_2 reactivity, it is still possible that sevoflurane had some effects on CO_2 reactivity in the patients on insulin therapy in our study.

In conclusion, cerebrovascular CO_2 reactivity in insulin-dependent patients is impaired during nicardipine-induced hypotension under sevoflurane anesthesia.

Acknowledgments. The authors thank Forte Inc. (Tokyo, Japan) for assistance with the manuscript. This study was supported by grants (to Dr. Kadoi, no. 18591688) from the Japanese Ministry of Science, Education, and Culture and the Mitsubishi Pharma Research Foundation.

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