Diabetic Patients Have an Impaired Cerebral Vasodilatory Response to Hypercapnia Under Propofol Anesthesia

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Background and Purpose—The purpose of this study was to examine the effects of diabetes mellitus and its severity on the cerebral vasodilatory response to hypercapnia.

Methods—Thirty diabetic patients consecutively scheduled for elective major surgery were studied. After induction of anesthesia, a 2.5-MHz pulsed transcranial Doppler probe was attached to the patient’s head at the right temporal window, and mean blood flow velocity of the middle cerebral artery (Vmca) was measured continuously. After the baselineVmca, arterial blood gases, and cardiovascular hemodynamic values were measured, end-tidal CO2 was increased by reducing ventilatory frequency by 2 to 5 breaths per minute. Measurements were repeated when end-tidal CO2 increased and remained stable for 5 to 10 minutes.

Results—Significant differences were observed in absolute and relative CO2 reactivity between the diabetes and control groups (absolute CO2 reactivity: control, 2.8±0.7; diabetes mellitus, 2.1±1.3; P<0.01; relative CO2 reactivity: control, 6.3±1.4; diabetes mellitus, 4.5±2.7; P<0.01, Mann-Whitney U test). Significant differences were also found between diabetic patients with retinopathy and those without retinopathy in absolute (P=0.002) and relative (P=0.002) CO2 reactivity, glycosylated hemoglobin (P=0.0034), and fasting blood sugar (P=0.01) (Scheffé’s test, Mann-Whitney U test). There was an inverse correlation between absolute CO2 reactivity and glycosylated hemoglobin (r=0.69, P<0.001).

Conclusions—Insulin-dependent diabetic patients have an impaired vasodilatory response to hypercapnia compared with that of the control group, and the present findings suggest that their degree of impairment is related to the severity of diabetes mellitus. (Stroke. 2003;34:2399-2403.)

Key Words: carbon dioxide ■ diabetes mellitus ■ vasodilation

It remains controversial as to whether vasoregulation in diabetic patients is intact and whether it is affected by severity of diabetes.1-7 Dandona et al1 reported that CBF decreased or was unchanged in response to the inhalation of 5% CO2 in 36 of 56 diabetic patients. In contrast, Pelligrino et al7 reported that CO2 reactivity was unchanged in streptozotocin-induced diabetic rats. In a previous study,8 we found that there was a significant difference in the mean slopes of jugular venous oxygen saturation versus cerebral perfusion pressure (CPP) for the increasing CPP between insulin-dependent diabetic patients and diabetic patients on diet therapy or glibenclamide. We hypothesized that diabetic patients have an abnormal CO2 reactivity and that this abnormality is attributable to the severity of diabetes mellitus. To date, there have been no reports describing whether severity of diabetes mellitus might be associated with cerebrovascular CO2 reactivity in diabetic patients.

In this study, we examined the effects of diabetes mellitus and its severity on the cerebral vasodilatory response to hypercapnia.

Patients and Methods

This study was approved by the ethics committee of our institution, and written, informed consent was obtained from all patients. Thirty-five diabetic patients consecutively scheduled for elective major surgery were studied.

Patients were defined as having diabetes mellitus if their medical records showed a diagnosis of type 2 diabetes and current medical treatment with antidiabetic therapy such as diet, oral, or insulin therapy. Duration of disease was defined as the duration from the start of medical treatment. Patients with a history of cerebrovascular disease, psychiatric illness, active liver disease (glutamine oxaloacetate transaminase or glutamine pyruvate transaminase >50 U/dL) were excluded. All patients were examined preoperatively for the presence of carotid artery stenosis by ultrasonography and MRI. The presence of carotid artery stenosis was defined as luminal narrowing >50%.9 Three diabetic patients had moderate or severe carotid artery stenosis and were therefore excluded. In addition, all patients were examined for the presence of silent lacunar infarction by preoperative brain CT and MR tomography. Two diabetic patients had silent lacunar infarction and were excluded. A total of 30 diabetic patients met the entry criteria. All enrolled patients had undergone ophthalmologic examination for detection of diabetic retinopathy. According to the modification...
of the Diabetic Retinopathy Study and the Early Treatment Diabetic Retinopathy grading scale, the severity of the worst affected eye was used, and patients with retinopathy were further divided into 3 categories: those with mild to moderate nonproliferative diabetic retinopathy (NPDR); those with a severe stage of NPDR; and those with proliferative diabetic retinopathy (PDR).10

Because glycosylated hemoglobin (HbA1c) (normal value, 4.5% to 5.8%) is an indicator of well-or poorly controlled diabetes mellitus, all diabetic patients were examined for preoperative HbA1c level.

As a control, 30 age-matched nondiabetic patients consecutively scheduled for elective major surgery were studied.

Anesthesia was induced by 0.1 mg/kg midazolam, 5 μg/kg fentanyl, and 0.2 mg/kg vecuronium, and the trachea was intubated. After anesthesia induction, 3 to 5 mg · kg⁻¹ · h⁻¹ propofol was infused with a syringe pump and was continued until the patients arrived at the intensive care unit. Muscular relaxation was achieved by intermittent administration of vecuronium. No volatile anesthetic was administrated. All patients were ventilated with oxygen 50% and nitrous oxide 50%, and 0.2 mg/kg fentanyl, and 0.2 mg/kg vecuronium. Muscle paralysis was achieved by intermittent administration of vecuronium. No volatile anesthetic was administrated. All patients were ventilated with oxygen 50% and nitrous oxide 50%.

The major findings of this study are that (1) diabetic patients have an impaired vasodilatory response to hypercapnia compared with the control group and (2) the impaired vasodilatory response to hypercapnia was related to the severity of diabetes mellitus. Before interpreting our results, we should discuss the validity of TCD measurement. Dahl et al11 reported that

| TABLE 1. Demographics of and CO₂ Reactivity in the 2 Study Groups |
|---------------------------|---------------------------|
|                          | Control (n=30)          | DM (n=30)        |
| Age, y                   | 63±6.0                  | 61±7             |
| Height, cm               | 159±12                  | 159±10           |
| Weight, kg               | 58±9                    | 57±11            |
| Male/female              | 18/12                   | 17/13            |
| Absolute CO₂ reactivity, |                          |                 |
| cm/s · mm Hg             | 2.8±0.7                 | 2.1±1.3*         |
| Relative CO₂ reactivity, | 6.3±1.4                 | 4.5±2.7*         |

DM indicates diabetes mellitus. Values are mean±SD.

*P<0.05 vs control group.

Results

Table 1 shows the demographic data from the 2 groups. There were no significant differences in age, height, and weight between 2 groups. A significant difference was observed in absolute and relative CO₂ reactivity between the 2 groups (Table 3). Significant differences were found in the absolute (P=0.048) and relative (P=0.024) CO₂ reactivity between the insulin group and the other 2 diabetic groups (Scheffé’s test). In addition, we subdivided the diabetes patients into 3 groups: patients with retinopathy and patients without retinopathy (Table 3). Significant differences were observed in the absolute (P=0.002) and relative (P=0.002) CO₂ reactivity, HbAlc (P=0.0034), and fasting blood sugar (P=0.01) between groups (Scheffé’s test, Mann-Whitney U test).

Discussion

The major findings of this study are that (1) diabetic patients have an impaired vasodilatory response to hypercapnia compared with the control group and (2) the impaired vasodilatory response to hypercapnia was related to the severity of diabetes mellitus. Before interpreting our results, we should discuss the validity of TCD measurement. Dahl et al11 reported that
changes in blood flow velocity measured by TCD correlated well with changes in blood flow measured by single-photon emission CT. Sugimori et al.\textsuperscript{12} examined blood flow velocity with TCD in the middle cerebral artery and cerebrovascular vasodilator responses to CO\textsubscript{2} in 22 patients with or without carotid artery occlusive disease and minor stroke. They concluded that TCD is a reliable method to evaluate decreases in the cerebral circulation in patients with hypertension or diabetes mellitus.

There have been controversial results regarding the effects of diabetes mellitus on cerebral circulation.\textsuperscript{1–7} Croughwell et al.\textsuperscript{1} examined cerebral metabolic autoregulation during the cardiopulmonary bypass period using the \textsuperscript{133}Xe-clearance method and reported that the CBF of their diabetic group remained constant despite an increase in temperature from 27°C to 37°C, in contrast to an 83% increase in CBF in the control group. They concluded that diabetic patients lose cerebral autoregulation during cardiopulmonary bypass and compensate for an imbalance in adequate oxygen delivery by increasing oxygen extraction. In a previous study,\textsuperscript{8} we found a significant difference in the mean slopes of jugular venous oxygen saturation versus CPP for increasing CPP between insulin-dependent diabetic patients and diabetic patients on diet therapy and glibenclamide therapy.

In regard to cerebrovascular CO\textsubscript{2} reactivity in diabetic patients, Griffith et al.\textsuperscript{13} reported that of 22 diabetic patients, 14 responded normally and 8 failed to show a significant increase in CBF after hypercapnia when the \textsuperscript{133}Xe-clearance method was used. Dandona et al.\textsuperscript{2,3} reported that there was a significant variation in CBF after administration of 5% CO\textsubscript{2} in insulin-dependent diabetics compared with normal subjects using the \textsuperscript{133}Xe-inhalation method, concluding that diabetics had diminished cerebrovascular reserve and were unable to compensate when necessary with an increased CBF. Rodriguez et al.\textsuperscript{14} reported that compared with control subjects, the percentage of global CBF increment measured by the \textsuperscript{133}Xe-
Anesthesia. Sieber et al5,6 reported that 4 months of hyperglycemia equivalent to those of control subjects during isoflurane anesthesia. In this way, the relative values of CO₂ reactivity in diabetic patients were significantly impaired in 4 insulin-dependent diabetic patients. In contrast, Kawata et al4 examined the effects of diabetes mellitus on the cerebral vasculature10,15 because the retina develops abnormal cerebrovascular CO₂ reactivity compared with diabetic patients without retinopathy and the control groups. It is not clear why the presence of retinopathy was associated with abnormal cerebrovascular CO₂ reactivity. However, it has been reported that retinal circulation might represent the result of diabetic vascular disease rather than hyperglycemia.

In the present study, diabetic patients with retinopathy had abnormal cerebrovascular CO₂ reactivity compared with diabetic patients without retinopathy and the control groups. It is not clear why the presence of retinopathy was associated with abnormal cerebrovascular CO₂ reactivity. However, it has been reported that retinal circulation might represent the cerebrovascular circulation10,15 because the retina develops from the forebrain.16 Abnormal cerebral microangiopathy in diabetic patients would be represented by diabetic retinopathy. In addition, Stratton et al17 reported that in patients with type 2 diabetes, the risk of diabetic complications such as macrovascular and microvascular disease was strongly associated with previous hyperglycemia. This implies that the primary cause of microvascular disease is chronic hyperglycemia itself. The fact that HbA1c was related to impaired CO₂ reactivity in our study suggests that impaired CO₂ reactivity was responsible for microvascular disease in the brain, which was induced by hyperglycemia.

This present study is the first to show that HbA1c and retinopathy are related to an impaired vasodilatory response to CO₂. This finding is inconsistent with those of Griffith et al13 and Rodriguez et al14. Rodriguez et al14 reported that duration of diabetes, serum glucose concentration, and HbA1c did not correlate with the percentage of postacetazolamide global CBF changes. This discrepancy might be due in part to differences in demographic data. The mean age of the subject of Rodriguez et al16 was 30 years; that of our subjects was 64 years. Age is a factor associated with the cerebral vasodilatory response to hypercapnia.18 Hartl et al19 reported that absolute and relative mean CO₂ reactivities in elderly subjects were markedly lower than those in young subjects. In contrast, Yamamoto et al18 examined the effect of aging on cerebral vasodilatory responses to hypercapnia and found that mean CBF in the elderly was 10% to 20% less than in young volunteers and that vasodilatory response to hypercapnia in elderly patients without risk factors was similar to that in young volunteers. Another possible mechanism might be prolonged hyperglycemia. Stratton et al17 reported that in patients with type 2 diabetes, the risk of diabetic macrovascular and microvascular complications was strongly associated with previous hyperglycemia. Klein et al19 reported that HbA1c predicted the incidence and progression of diabetic retinopathy. In addition, Pallas and Larson20 noted that hyperglycemia leads to impaired vascular function through endothelial cell function. The pathway that appears most affected by the diabetic state is that of nitric oxide. Loss of this pathway is accompanied by loss of response to Paco and lack of autoregulation related to flow-pressure relationships.

In this study, we examined the response to Paco using hyperventilation to increase middle cerebral artery velocity rather than using hyperventilation to decrease middle cerebral artery velocity. Cenic et al21 reported that cerebrovascular CO₂ reactivity was maintained during hypercapnia but was markedly diminished during hypocapnia under propofol anesthesia. We examined the cerebrovascular vasodilatory response to CO₂ in diabetic patients using hyperventilation to rule out the possibility that hyperventilation would have some effect on the cerebral vasodilatory response to hypercapnia.

**Study Limitations**
Some factors such as blood pressure, cardiac output, temperature, cerebral metabolism, and anesthetic agents are likely to

### Table 3. Comparison of the 3 Diabetic Groups

<table>
<thead>
<tr>
<th>Diabetic Group</th>
<th>Absolute CO₂ Reactivity, cm·s·mm Hg</th>
<th>Relative CO₂ Reactivity, %/mm Hg</th>
<th>HbA1c, %</th>
<th>Duration of Disease, y</th>
<th>FBS (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet therapy group (n=8 pts)</td>
<td>2.4±1.3</td>
<td>5.3±2.8</td>
<td>5.7±1.2</td>
<td>9.9±3.4</td>
<td>133±32</td>
</tr>
<tr>
<td>Glibenclamide group (n=12 pts)</td>
<td>2.1±1.4</td>
<td>4.3±3.0</td>
<td>6.0±1.2</td>
<td>7.7±3.0</td>
<td>148±46</td>
</tr>
<tr>
<td>Insulin group (n=10 pts)</td>
<td>1.6±1.1*</td>
<td>3.8±2.3*</td>
<td>6.5±1.6</td>
<td>9.1±4.6</td>
<td>139±28</td>
</tr>
<tr>
<td>Control group (n=30 pts)</td>
<td>2.8±0.7</td>
<td>6.3±1.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with retinopathy (n=14 pts)</td>
<td>1.3±1.3†</td>
<td>2.7±2.6†</td>
<td>6.9±1.5</td>
<td>8.4±4.2</td>
<td>163±43‡</td>
</tr>
<tr>
<td>Patients without retinopathy (n=16 pts)</td>
<td>2.7±0.9</td>
<td>5.9±1.9</td>
<td>5.4±0.6</td>
<td>9.0±3.3</td>
<td>122±13</td>
</tr>
<tr>
<td>Control group (n=30 pts)</td>
<td>2.8±0.7</td>
<td>6.3±1.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with mild to moderate NPDR§ (n=5)</td>
<td>1.7±1.4</td>
<td>3.6±2.9</td>
<td>6.9±2.1</td>
<td>7.4±2.7</td>
<td>169±52</td>
</tr>
<tr>
<td>Patients with severe stage of NPDR§ (n=4 pts)</td>
<td>0.8±1.0</td>
<td>1.7±2.0</td>
<td>6.9±1.0</td>
<td>11.8±6.2</td>
<td>160±26</td>
</tr>
<tr>
<td>Patients with PDR§ (n=5 pts)</td>
<td>1.3±1.5</td>
<td>2.7±3.1</td>
<td>7.1±1.4</td>
<td>6.8±7.5</td>
<td>158±52</td>
</tr>
</tbody>
</table>

FBS indicates fasting blood sugar. Values are mean±SD.

*P<0.05 vs control group; †P<0.01 vs control and diabetic patients without retinopathy; ‡P<0.01 vs diabetic patients without retinopathy; §No significant differences were found between the 3 groups.
influence CBF. In this study, no changes were observed in arterial blood pressure, tympanic membrane temperature, or anesthetic depth at pretreatment and posttreatment. Thus, we conclude that changes in CBF velocity were attributable to changes in $\text{PACO}_2$.

We examined the cerebral vasodilatory response to hypercapnia under propofol anesthesia. Propofol has been widely used for neurosurgical anesthesia and as a sedative agent in intensive care units.\textsuperscript{22} It is important for anesthesiologists and intensivists to know whether cerebrovascular $\text{CO}_2$ reactivity in diabetic patients is intact. However, there are no data describing this under propofol anesthesia. Some reports have described the effects of propofol on cerebrovascular $\text{CO}_2$ reactivity using the $133\text{Xe}$-inhalation method in 10 patients undergoing anesthesia for nonneurosurgical procedures (mean age, 37 years) and found that cerebral $\text{CO}_2$ reactivity remained intact during propofol anesthesia.\textsuperscript{10,23,24} Matta et al\textsuperscript{23} examined cerebral $\text{CO}_2$ reactivity using TCD during propofol-induced electrical silence of the electroencephalogram in 10 patients undergoing anesthesia for nonneurosurgical procedures (mean age, 37 years) and found that cerebral $\text{CO}_2$ reactivity remained intact during propofol anesthesia.\textsuperscript{25} Fox et al\textsuperscript{24} reported in 7 patients undergoing elective gynecologic or orthopedic surgery (mean age, 40.5 $\pm$ 7 years) that the slope of the CBF-$\text{CO}_2$ response measured by the $133\text{Xe}$-inhalation method was similar to that found in awake individuals and during propofol-nitrous oxide anesthesia. Myburgh et al\textsuperscript{25} reported in sheep (n = 6) that the mean slopes of the $\text{CO}_2$ reactivity curves in the sagittal sinus measured by a Doppler probe did not differ between awake conditions and propofol anesthesia. However, the possibility that propofol exerts some effect only on cerebrovascular $\text{CO}_2$ reactivity in diabetic patients cannot be ruled out.

The number of patients with nephropathy (n = 1) or neuropathy (n = 1) was too small to consider them indicators of the severity of diabetes. Further study is necessary to clarify the relationship between neuropathy and nephropathy as indicators of severity of diabetes.

Stepwise linear regression showed that only HbA1c was a factor related to absolute $\text{CO}_2$ reactivity. This finding might point to HbA1c as an indicator of the severity of diabetic microangiopathy in brain.

In conclusion, insulin-dependent diabetic patients showed an impaired vasodilatory response to hypercapnia compared with that of the control group, and our data suggest that this impaired response was related to severity of diabetes mellitus.

Acknowledgment

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References


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