Effect of Intravenous Dipyridamole on Cerebral Blood Flow in Humans

A PET Study

Hiroshi Ito, MD, PhD; Tobishumi Kinoshita, MD, PhD; Yoshikazu Tamura, MD, PhD; Ikuo Yokoyama, MD, PhD; Hidehiro Iida, DSc, PhD

Background and Purpose—Dipyridamole increases the concentration of circulating adenosine, which is a potent vasodilator, by inhibition of uptake of adenosine into the erythrocytes, and hence produces coronary vasodilation. However, the effects of intravenous dipyridamole on cerebral blood flow (CBF) in humans with use of positron emission tomography (PET).

Methods—In each of 13 healthy subjects, CBF was measured using 15O-labeled water and PET at rest and during hypercapnia, hypocapnia, and dipyridamole stress; corresponding CBF values were then compared.

Results—CBF values during dipyridamole stress were significantly lower than those measured at rest. The dipyridamole stress PaCO₂ was also significantly lower than the resting PaCO₂. The change in CBF during dipyridamole stress relative to PaCO₂ closely followed the relationship between CBF and PaCO₂ during hypocapnia.

Conclusions—These results indicate that the observed decrease in CBF during dipyridamole stress was caused by a decrease in PaCO₂ rather than by any direct action of dipyridamole on CBF. The decrease in PaCO₂ during dipyridamole stress was most likely due to hyperventilation, which was a side effect of adenosine. These results support the hypothesis that circulating adenosine is largely prevented from binding to adenosine receptors of cerebral vessels by the blood-brain barrier.

Key Words: carbon dioxide • cerebral blood flow • dipyridamole • tomography, emission computed
(H$_{15}$O) and PET. The dipyridamole stress CBF values were directly compared with corresponding CBF measurements at rest and during hypercapnia and hypocapnia.

**Subjects and Methods**

**Subjects**
The study was approved by the Ethics Committees of Akita Research Institute of Brain and Blood Vessels. Thirty healthy men (age range 51 to 71 years, mean ±SD 59.4 ± 5.5 years) were recruited and gave written informed consent. The subjects were judged to be healthy on the basis of medical history, physical examination, blood screening analysis, ECG, echocardiography, MRI of the brain, and MR angiography of the brain and the neck. They did not use any medications. The body weight of subjects ranged from 50 to 79 kg. Caffeine intake and theophylline-containing foods or drugs were prohibited for 12 hours before the PET studies.

**PET Procedure**
The Headtome V dual PET (Shimadzu Corp) used for all studies provides 47 sections with center to center distances of 3.125 mm. The intrinsic spatial resolution was 4.0 mm in-plane and 4.3 mm full width at half maximum (FWHM) axially. Reconstruction with a Butterworth filter resulted in a final in-plane resolution of approximately 8 mm FWHM. The dual PET system allowed simultaneous brain and heart studies to be performed for all studies. After 1 minute of continuous inhalation of C$_{18}$O gas (approximately 5 GBq total supplied to the mouth), a 4-minute static scan was performed and 3 arterial blood samples were taken. The C$_{18}$O PET data in the heart were used to derive the arterial input function for the brain study. After the transmission scan, H$_{15}$O PET studies were performed at rest and during hypercapnia, hypocapnia, and dipyridamole stress. The interval between H$_{15}$O PET studies was at least 15 minutes. The scanning protocol consisted of a 180-second static scan of the brain and a 360-second dynamic scan of the heart after continuous intravenous infusion of H$_{15}$O over 2 minutes. The dose of radioactivity was 1.1 to 1.4 GBq at the time the scanning started. CBF was estimated with the dual PET system, as previously described. Using the arterial input function derived from the left ventricular time-activity curve measured by the PET camera ring positioned over the heart, the CBF images were calculated from the brain PET camera data by the autoradiographic method.

Forced hypercapnia was induced by inhalation of 7% CO$_2$ gas, starting 1 minute before the beginning of the scan and continuing until the end of scan. Forced hypoxemia was induced by hyperventilation using same schedule as hypercapnia. Dipyridamole (0.56 mg/kg body weight) was intravenously administered over 4 minutes from 8 minutes before the beginning of scan. Three arterial blood samples were taken during each H$_{15}$O PET scan to measure PaCO$_2$. Blood pressure and heart rate were monitored during each scan. A head fixation system with individual molds for each subject was used to minimize head movement over the period of the PET measurements. The order of the H$_{15}$O PET studies was rest, hypercapnia, hypocapnia, and dipyridamole in 7 subjects and rest, hypocapnia, hypercapnia, and dipyridamole stress conditions in the other 6 subjects.

**Data Analysis**

Region of interest for inside brain contour was drawn on a slice of CBF image, which was at the basal ganglia level. Mean CBF value in a region of interest was calculated and used for following analyses.

The vascular response to a change in PaCO$_2$ was calculated as the percent change of CBF per absolute change of PaCO$_2$ (mm Hg) in response to hypercapnia, hypocapnia, and dipyridamole, as follows:

\[
\frac{100 \times \frac{C_{BF-hyp} - C_{BF}}{C_{BF}} \times \frac{1}{[PaCO_2 - PaCO_2_{ref}]}}{\text{Hypoxemia or Dipyridamole}}
\]

**Results**

Blood pressure, heart rate, and PaCO$_2$ during each H$_{15}$O PET scan are summarized for each condition in Table 1. Dipyridamole stress PaCO$_2$ was significantly lower than resting PaCO$_2$. No change in blood pressure was observed between the dipyridamole stress and the rest conditions. Blood pressures were measured at the ankle in these studies and are thus approximately 25 mm Hg greater value than pressures measured at the brachium.

The CBF values during rest, hypercapnia, hypocapnia, and dipyridamole stress and the vascular response to PaCO$_2$ change are given in Table 2. CBF values for dipyridamole stress were significantly lower than those at rest. There was no significant difference in vascular response to PaCO$_2$ between dipyridamole stress and hypocapnia.

The percent CBF change in response to hypercapnia, hypocapnia, and dipyridamole stress are plotted versus the absolute change of PaCO$_2$ for all subjects in Figure 1. There was close agreement between the hypocapnia and dipyridamole stress regression lines, and no significant difference in regression slopes or intercepts was observed.

Typical CBF images for the rest, hypercapnia, hypocapnia, and dipyridamole stress conditions are shown in Figure 2. This figure also indicates that the observed CBF changes were global rather than regional.

**Discussion**

Although dipyridamole produces coronary vasodilation, most reports on dipyridamole effects in animals have failed to

### Table 1. Blood Pressure, Heart Rate, and PaCO$_2$ During Each H$_{15}$O PET Scan

<table>
<thead>
<tr>
<th>Condition</th>
<th>BP, mm Hg</th>
<th>HR, beats/min</th>
<th>PaCO$_2$, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>146±21/83±12</td>
<td>58±8</td>
<td>40.2±2.4</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>160±25'/85±11</td>
<td>62±9</td>
<td>43.1±2.7*</td>
</tr>
<tr>
<td>Hypocapnia</td>
<td>145±27/79±13</td>
<td>61±8</td>
<td>29.2±3.4*</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>150±33/79±14</td>
<td>73±9</td>
<td>35.7±2.6*</td>
</tr>
</tbody>
</table>

Values are mean±SD. BP indicates blood pressure (systole/diastole); HR, heart rate.

*P<0.001, † P<0.01, ‡ P<0.05 significantly different from rest studies by paired t test.

where the subscripts “r” and “a” denote the rest and activation conditions (hypercapnia, hypocapnia, or dipyridamole), respectively.

### Table 2. CBF Values During Rest, Hypercapnia, Hypocapnia, and Dipyridamole Stress and the Vascular Response to PaCO$_2$ Change

<table>
<thead>
<tr>
<th>Condition</th>
<th>CBF, mL/100 ml/min</th>
<th>Vascular Response to PaCO$_2$ Change, %/mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>39.8±5.3</td>
<td>. . .</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>48.4±10.4*</td>
<td>8.2±5.3</td>
</tr>
<tr>
<td>Hypocapnia</td>
<td>27.0±6.3*†</td>
<td>−3.0±1.1†</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>35.6±6.0*‡</td>
<td>−2.5±1.2‡</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<0.001 different from rest studies; †P<0.001, ‡P<0.01 different from hypercapnia studies; *P<0.001 different from hypocapnia studies, all by paired t test. There was no significant difference in the vascular response between dipyridamole stress and hypocapnia.
Human cerebral vessels have $A_2$ adenosine receptors. The stimulation of these $A_2$ receptors causes the relaxation of vascular smooth muscle, and this plays a role in the regulation of CBF. However, we did not observe an increase in CBF after intravenous infusion of dipyridamole in this study (Table 2 and Figure 2). The transport of adenosine through the blood-brain barrier has been investigated, and it has been reported that circulating adenosine was unable to cross the blood-brain barrier. Thus, circulating adenosine is unlikely to cause cerebral vasodilation due to its inability to bind to $A_2$ adenosine receptors of cerebral vessels. Although it is unknown whether intravenous dipyridamole is transferred across the blood-brain barrier to increase the concentration of interstitial adenosine in humans, it has been reported that dipyridamole could not be transferred across the blood brain barrier in rat and mouse, which further supports our findings.

The cerebrovascular accidents during dipyridamole stress tests have been reported and have been attributed to intracranial vascular steal phenomenon. However, because intravenous dipyridamole does not increase the CBF (Table 2 and Figure 2), the intracranial vascular steal phenomenon cannot occur. On the contrary, CBF was reduced during dipyridamole stress due to a decrease in PaCO$_2$ caused by adenosine-induced hyperventilation. Recently, posthyperventilatory steal response in chronic cerebral hemodynamic stress has been reported. If severe hypocapnia is caused by intravenous dipyridamole, a regional cerebral perfusion disturbance might be caused. In addition, it has been reported that coronary atherosclerosis is an important potential risk factor for cerebrovascular diseases. In dipyridamole stress testing to estimate coronary flow reserve, such complications should thus be considered.

SPECT studies with $^{99m}$Tc-HMPAO have shown an increased side-to-side asymmetry in occlusive carotid artery disease following intravenous dipyridamole or adenosine administration, and it was concluded that dipyridamole or adenosine was a cerebral vasodilator and was useful for estimating cerebral perfusion reserve. However, in the present study, intravenous dipyridamole decreased global CBF due to a decrease in PaCO$_2$ attributed to the hyperventilation caused by adenosine. $^{99m}$Tc-HMPAO suffers from back-diffusion from the brain to the blood, and its first-pass...
extraction fraction from the blood to the brain is limited. This causes a nonlinear relationship between radioactivity in the brain and CBF and underestimation of CBF in regions with high flow, while good linearity is observed in low CBF regions. Accordingly, a decrease in global CBF should improve the contrast in $^{99m}$Tc-HMPAO SPECT uptake between regions with different CBF values. Thus, the increase of side-to-side asymmetry in occlusive carotid artery disease introduced by intravenous dipyridamole is likely due to the observed decrease in global CBF and hence a shift toward the more linear uptake region of $^{99m}$Tc-HMPAO.

The inhalation of CO$_2$ gas has been widely used for estimation of cerebral perfusion reserve. In the present study, hypercapnia increased global CBF by 8±5% (mean ±SD) per unit PaCO$_2$ change (mm Hg) in healthy subjects (Table 2). Large interindividual variation of vascular response to hypercapnia was observed even in healthy subjects. On the other hand, the hypocapnia induced by hyperventilation decreased global CBF by 3±1% per unit PaCO$_2$ change, and the degree of this response was smaller than that for the hypercapnia (Table 2). These results are in good agreement with previous reports.

In conclusion, dipyridamole decreased CBF due to a decrease in PaCO$_2$ caused by adenosine-induced hyperventilation and did not directly change CBF, despite being a potent coronary vasodilator. Because severe hypcapnia might cause a regional cerebral perfusion disturbance, such side effects during dipyridamole stress tests to estimate coronary flow reserve should be considered.

Acknowledgments

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References

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