Posthyperventilatory Steal Response in Chronic Cerebral Hemodynamic Stress
A Positron Emission Tomography Study

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Background and Purpose—The alteration of regional cerebral blood flow (CBF) during and after hyperventilation was measured using positron emission tomography (PET) to determine the circulatory response induced by daily respiratory changes in the cerebral area under chronic hemodynamic stress.

Methods—Three normal volunteers and 12 patients with an obstruction of major cerebral arteries underwent PET measurements of the CBF after an injection of $\text{H}^\text{15} \text{O}$: (1) in the resting condition, (2) during hyperventilation (HV scan), (3) 1 to 3 minutes after hyperventilation (post-HV scan), (4) during the inhalation of 5% $\text{CO}_2$, and (5) after an injection of acetazolamide. Eleven patients also underwent a $\text{H}^\text{15} \text{O}$ gas study to measure CBF, oxygen extraction fraction (OEF), and cerebral blood volume (CBV).

Results—(1) In 9 patients, the CBF value in the post-HV scan was lower than that in the HV scan in 1 or more regions in the area of the obstructed arteries, although the $\text{Paco}_2$ level during the post-HV scan was higher than that during the HV scan in all patients. All control regions in the patients and in the normal volunteers showed an elevated CBF in the post-HV scan compared with the HV scan. (2) The negative post-HV response (posthyperventilatory steal) was prominent in 4 patients with moyamoya vessels and in another 5 patients with atherosclerotic disease who had PET evidence of hemodynamic stress (elevated CBV or OEF). (3) The regional pre- to post-HV change in CBF was significantly correlated with the CBF responses to acetazolamide and $\text{CO}_2$.

Conclusions—Vasodilatation after the termination of hyperventilation in the normal areas induces a steal response in the cerebral area suffering from hemodynamic stress and may cause profound hypoperfusion in everyday situations. This phenomenon may be important to our understanding of the clinical symptoms and the natural course of chronic cerebral occlusive disease bearing hemodynamic stress. (Stroke. 1998;29:1281-1292.)

Key Words: tomography, emission computed ▪ cerebral blood flow ▪ hyperventilation ▪ acetazolamide ▪ carbon dioxide ▪ moyamoya disease
alteration. Although such HV-induced ischemic symptoms are not observed in patients with atherosclerotic disease, the paradoxically negative blood flow response to a vasodilatory stimulus such as hypercapnia or acetazolamide challenge is observed in patients with or without moyamoya vessels. Therefore, we considered that a characteristic hemodynamic pattern may be induced by the change in PaCO₂ depending on the degree of hemodynamic stress.

In this study, we selected patients with an occlusion of major cerebral arteries and with minor or no permanent neurological deficit, and examined them with repeated measurements of the CBF to identify the changes in CBF during and right after HV. The patients were also examined with acetazolamide/C0₂ vasodilatory challenge and with an ¹⁵O gas PET study to measure CBF, OEF, and CBV. Each of these parameters was compared with each other to test the hypothesis that CBF paradoxically responds to the alteration of PaCO₂ as encountered in daily physiological conditions and that the degree of the response depends on the severity of hemodynamic stress.

Subjects and Methods

Subjects

Twelve patients with a complete obstruction of a major cerebral artery underwent the HV protocol. The patients had either a history of TIA without permanent deficit or a stroke with no or only moderate neurological deficit with a good quality of life. The patients’ profiles are listed in Table 1. All patients except 1 (case 1) had multiple cortical and subcortical infarctions in the territory of the obstructed artery. The study was done at least 6 months after the stroke event. In 3 patients (cases 1, 3, and 4) such conditions lasted more than 1 year with a consistent frequency of attack, although the study was done while the patients were suffering from frequent reversible transient motor or language deficits. Therefore, the study was done in the chronic stage when the clinical condition was stable in each patient. Three young adults (a 28-year-old male, a 22-year-old male, and a 22-year-old female) without history of neurological disease were recruited as normal volunteers to test the reliability and reproducibility of a PET CBF study during and after HV, which was developed by us for the first time in the present study. The radioactive tracers have been approved by the Radiopharmaceutical Committee of the Tokyo Metropolitan Institute of Gerontology (TMIG) regarding safety and efficacy for use with humans. The study protocol was approved by the Ethics Committee of the TMIG. Written, informed consent, in which the object of measurement, duration of study, the number of scans and the amount of radiation exposure and blood sampling were documented, was obtained from all volunteers and patients.

**PET H₂¹⁵O CBF Study**

The PET study was performed with a Headtome-IV scanner (Shimadzu Corp). An arterial catheter was inserted into the radial artery for blood sampling. The patient’s head was molded and fixed on the headrest with a customized foam head holder (Smithers Medical Products Inc) to maintain the same head position. The transmission data were acquired with a rotating germanium-68 rod source for attenuation correction. The CBF was measured using the PET autoradiographic method with an intravenous bolus injection of 1.5 GBq of H₂¹⁵O-labeled water (H₂¹⁵O) and a 2-minute data acquisition starting at the time of injection. The arterial blood was continuously drawn, and the radioactivity concentration was monitored with a beta detector equipped with a plastic scintillator (Shimadzu Corp), which was then used as an input function to compute the CBF after a correction for delay and dispersion. The concentration of end-expiratory CO₂ was continuously monitored with a blood gas analyzer (Respina, San-ei Co) to estimate the PaCO₂ during the scanning period, and calibrated with the PaCO₂ sampled before and after each scan. The CBF was sequentially measured during the resting state, during HV (HV scan), 1 to 3 minutes after the termination of another 3 to 4 minutes of HV (post-HV scan), and

### TABLE 1. Profile of the Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>Poorly or Not Perfused Vessel in Angiography</th>
<th>Moyamoya Vessels</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20/F</td>
<td>Lt ICA occlusion (intracranial)</td>
<td>Lt MCA, bil ACA</td>
<td>(+)</td>
<td>TIA (M)</td>
</tr>
<tr>
<td>2</td>
<td>22/F</td>
<td>Moyamoya disease</td>
<td>Bil MCA, bil ACA</td>
<td>(+)</td>
<td>TIA (L)</td>
</tr>
<tr>
<td>3</td>
<td>40/M</td>
<td>Moyamoya disease</td>
<td>Bil MCA, bil ACA, Lt PCA</td>
<td>(+)</td>
<td>TIA (M, L), hemianopsia</td>
</tr>
<tr>
<td>4</td>
<td>41/F</td>
<td>Lt MCA occlusion, occlusion of peripheral Lt ACA and PCA (with accessory Lt MCA)</td>
<td>Lt MCA (partially perfused by patent Lt accessory MCA), Lt distal ACA, Lt PCA</td>
<td>(+)</td>
<td>TIA (M)</td>
</tr>
<tr>
<td>5</td>
<td>48/M</td>
<td>Rt ICA occlusion (intracranial)</td>
<td>Rt MCA, rt ACA</td>
<td>(−)</td>
<td>TIA (M)</td>
</tr>
<tr>
<td>6</td>
<td>59/M</td>
<td>Rt MCA occlusion</td>
<td>Rt MCA</td>
<td>(−)</td>
<td>TIA (M)</td>
</tr>
<tr>
<td>7</td>
<td>60/M</td>
<td>Rt ICA occlusion with fetal type P-Com (cerebral)</td>
<td>Rt MCA, rt ACA, rt PCA</td>
<td>(−)</td>
<td>TIA (M)</td>
</tr>
<tr>
<td>8</td>
<td>47/M</td>
<td>Rt ICA occlusion (cerebral)</td>
<td>Rt MCA, rt ACA</td>
<td>(−)</td>
<td>Stroke (M, recovered)</td>
</tr>
<tr>
<td>9</td>
<td>68/M</td>
<td>Bil ICA occlusion (cerebral)</td>
<td>Bill MCA, bil ACA</td>
<td>(−)</td>
<td>Stroke (L, persistent)</td>
</tr>
<tr>
<td>10</td>
<td>40/M</td>
<td>Rt MCA occlusion</td>
<td>Rt MCA</td>
<td>(−)</td>
<td>Stroke (S, recovered)</td>
</tr>
<tr>
<td>11</td>
<td>66/M</td>
<td>Lt ICA occlusion (cerebral)</td>
<td>Lt MCA</td>
<td>(−)</td>
<td>Stroke (M, recovered)</td>
</tr>
<tr>
<td>12</td>
<td>67/M</td>
<td>Lt ICA occlusion (cerebral)</td>
<td>Lt MCA</td>
<td>(−)</td>
<td>Stroke (L, persistent; M, recovered)</td>
</tr>
</tbody>
</table>

Bil indicates bilateral; P-Com; posterior communicating artery; M, motor symptom; L, language symptom; S, sensory symptom.
during a second resting state, as shown in Figure 1. The percent change of CBF in the post-HV scan compared with that in the HV scan was termed the "post-HV response." After the HV protocol, all but 1 patient (case 4) underwent an acetazolamide challenge test in which the CBF was measured at 10 minutes after an intravenous injection of acetazolamide (Diamox, Lederle Japan Co). In 8 patients (cases 1 to 3 and 8 to 12), during an inhalation of 5% CO2, the CBF was also measured between the HV protocol and acetazolamide scans. The percent change of CBF caused by the acetazolamide or CO2 loading was calculated against the average resting value and termed the "acetazolamide" or "CO2" response.

**Determination of Regional OEF and CBV**

All patients but 1 (case 1) underwent an 15 O-gas study within 2 months before or after the H215O-PET study. No patients presented any change in clinical symptoms between the 2 studies. The gas study was designed to examine the flow-metabolism uncoupling and to evaluate the compensation by increased blood volume. The regional CBF and OEF were measured using continuous and consecutive inhalations of C15 O2 and 15 O2 gas with continuous arterial blood sampling, and using a table-lookup technique as described previously.19,20 In brief, the subject inhaled C15 O2 and 15 O2 consecutively, each for 9 minutes. Regional cerebral activity was monitored using a beta detector equipped with a plastic scintillator (Shimadzu Corp). The plasma radioactivity curve was created from the arterial whole blood and plasma radioactivity curves. The regional CBF and OEF were calculated with the lookup tables that were created from the arterial whole blood and plasma radioactivity curves and were corrected for delay and dispersion.21 The CBV was monitored using a beta detector equipped with a plastic scintillator (Shimadzu Corp). The plasma radioactivity curve was created from the arterial whole blood and plasma radioactivity curves. The regional CBF and OEF were calculated with the lookup tables that were created from the arterial whole blood and plasma radioactivity curves and were corrected for delay and dispersion.21 The CBV was measured by a 3-minute inhalation of C15 O2 and a 6-minute PET scan, with blood sampling after the equilibration of the radioactivity within the circulating blood.21 The OEF was corrected for the effect of regional CBV.22,23

**PET Data Analysis and Statistics**

All of the PET data were analyzed using the image analysis software system, "Dr. View" (Asahi Kasei Co, running on workstations, Indigo2 and Indy, Silicon Graphics Inc). All of the PET images of each patient were coregistered with one another using a locally developed image registration program.24,25 They were also coregistered to the subject’s MRI to obtain the morphological information for placing the ROIs in noninfarcted areas. The arterial territory was defined using a brain atlas.26 The "affected area" was defined as the arterial territory without or with only poor antegrade perfusion in the arteriogram. When the territory of the MCA was affected, 9 ROIs (each of which consisted of a series of 1-cm-diameter circles along the cortical rim) were placed over the frontal convexity, temporal cortex, medial occipital cortex, and parietal cortex on each side and the cerebellum. When an ACA or PCA was affected, additional symmetrical ROIs (frontal interhemisphere, occipital convexity, anterior or posterior watershed) were placed on the PET images. The ROIs were examined on the coregistered MRI to confirm their anatomic localization and the exclusion of the infarcted area.

The data obtained are expressed as mean ± SD of HV and post-HV CBFs for each subject with the resting value set at 100. For the statistical analysis, a general linear model was used for each subject. A linear model was designed in which the CBF within each ROI was expressed as (1) a sum of grand means (intercept), (2) the effect of "condition" (whether CBF was measured at rest, HV, or post-HV), (3) the effect of "area" (whether the ROI belongs to the control or affected area), (4) the effect of "ROI" representing the baseline CBF of each ROI, and (5) the interaction between "condition" and "area" representing the difference in the CBF response between control and affected areas, plus (6) an error term. The "ROI" was nested within "area." The error term was assumed to be normally distributed with an unknown uniform variance. When the "condition-by-area" interaction was significant, the differences in CBF between "rest" and "HV" and between "HV" and "post-HV" for each area type (control and affected) were then tested, making a total of 4 contrasts for each patient. For example, a contrast between "rest" in a "control" area and "HV" in a "control" area applies to the test for a significant CBF increase produced by HV in the control area. In the normal volunteer subjects, who had no affected ROIs, 2 comparisons were examined for each subject. Bonferroni correction was applied for multiple comparisons, and the level of significance was set at P<0.05. This statistical analysis is similar to performing a paired t test 4 times independently for each patient; however, it allows a comparison when no more than 2 or 3 ROIs belong to a specific area type, and it is more powerful because the error is estimated from all data of the patient.

The correlation between the post-HV responses and the CO2 or acetazolamide response was also examined, and statistical significance was tested in each subject with the Bonferroni correction for multiple comparisons. The significance level was set at P<0.05.

**Results**

**Results of HV Protocol**

The results of the HV protocol are summarized in Table 2. The PacO2 in the resting scans was 37.5 to 45.6 mm Hg (mean±SD, 41.1±2.4), which was reduced by 5.0 to 20.3 mm Hg (mean±SD, 11.7±4.6) in the HV scans. In the post-HV scans, performed 1 to 3 minutes after the termination of HV, the PacO2 was significantly elevated by 3.6 to 13 mm Hg (mean±SD, 7.7±3.5) from the HV scan values, but was still significantly lower than the resting values by 0.7 to 10.8 (mean±SD, 4.0±3.4). Therefore, the post-HV scan in this study was generally performed while the PacO2 was recovering from the HV value to the resting value (Figure 1).
The regional CBFs in the HV scan and in the post-HV scan in each ROI were expressed as a percent of the resting CBF. The average percentages among all ROIs in the control and affected regions were calculated for each subject and are displayed in Table 2. All subjects showed a significant reduction of CBF by HV and a significant elevation of CBF by the termination of HV in the nonaffected region (control region of patients and all regions in volunteers). However, in the affected territory, the reduction of CBF seen by the HV study was smaller than that in the control region in all but 1 patient (case 11). The reduction was not significant in 5 patients. The CBF did not increase significantly during the recovery from HV to the resting scan (Figure 2). The post-HV reduction in CBF after the termination of HV was most prominent in such regions (Figure 2; cases 1, 4, 5, and 7).

The degree of reduction in CBF was similar among the ROIs in all patients. In general, the post-HV reduction in CBF was 47.9% and the CBF increased to 70.9% in these patients compared with those without moyamoya vessels; cases 1 to 4). Both the degree of reduction in CBF and the number of ROIs with a poor reduction of CBF during HV. In cases 1 to 7, 1 or more ROIs in the affected territory ever showed paradoxically elevated CBFs in the HV scan as compared with the resting scan (Figure 2). The post-HV reduction in CBF after the termination of HV was most prominent in such regions (Figure 2; cases 1, 4, 5, and 7).

### TABLE 2. Summary of Hyperventilation Protocol Results in Patients and Normal Controls

<table>
<thead>
<tr>
<th>Case</th>
<th>Rest (mm Hg)</th>
<th>CBF, Mean±SD (Expressed as % of Mean Resting CBF; Rest=100)</th>
<th>Correlation Coefficient Between Post-HV Response and CBF, PaCO2, and Acetazolamide Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest HV Post-HV</td>
<td>HV Post-HV (n)</td>
<td>HV Post-HV (n)</td>
</tr>
<tr>
<td>1</td>
<td>45.5 37.1 40.8</td>
<td>76.1±2.3** 89.1±5.7††</td>
<td>91.9±8.8 65.8±7.6‡‡</td>
</tr>
<tr>
<td>2</td>
<td>40.9 34.1 39.0</td>
<td>84.8** 103.1††</td>
<td>105.8±8.7 96.7±5.2</td>
</tr>
<tr>
<td>3</td>
<td>44.7 29.4 43.2</td>
<td>67.8±4.5** 87.8±4.8††</td>
<td>88.6±10.7** 70.1±3.7††</td>
</tr>
<tr>
<td>4</td>
<td>40.9 30.5 40.0</td>
<td>70.3±2.9** 113.1±8.9††</td>
<td>89.4±11.5* 67.1±9.7††</td>
</tr>
<tr>
<td>5</td>
<td>37.7 32.7 37.0</td>
<td>76.8±3.2** 95.2±2.1††</td>
<td>95.9±7.5 92.5±2.7</td>
</tr>
<tr>
<td>6</td>
<td>43.3 23.0 36.0</td>
<td>70.9±4.9** 96.8±3.0††</td>
<td>97.8 94.4</td>
</tr>
<tr>
<td>7</td>
<td>40.6 30.9 35.3</td>
<td>74.2±3.5** 87.9±4.1††</td>
<td>95.6±3.7 87.3±3.0‡</td>
</tr>
<tr>
<td>8</td>
<td>41.9 26.4 34.0</td>
<td>62.3±3.1** 82.3±7.1††</td>
<td>79.8±7.7** 86.3±4.1</td>
</tr>
<tr>
<td>9</td>
<td>38.9 25.6 38.1</td>
<td>73.6±3.2** 106.5±4.7††</td>
<td>87.6±5.6** 93.7±2.2</td>
</tr>
<tr>
<td>10</td>
<td>37.5 23.1 26.7</td>
<td>60.4±2.3** 72.1±3.4††</td>
<td>67.1±4.1** 73.0±2.2</td>
</tr>
<tr>
<td>11</td>
<td>43.1 32.5 38.7</td>
<td>79.7±4.7** 91.0±3.7††</td>
<td>77.6±3.0** 83.2±2.6</td>
</tr>
<tr>
<td>12</td>
<td>42.1 28.7 38.2</td>
<td>72.8±2.2** 106.1±4.6††</td>
<td>74.3±0.9** 96.5±0.7††</td>
</tr>
<tr>
<td>Normal 1 38.2 31.7 37.7</td>
<td>70.3±4.9** 104.1±4.9††</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Normal 2 39.4 29.4 40.0</td>
<td>84.8±2.6** 104.6±4.5††</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Normal 3 41.2 21.5 34.2</td>
<td>77.4±2.2** 87.5±3.7††</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

n=number of ROIs. See text for the definitions of Post-HV, CO2, and acetazolamide response.

A general linear model with standard least squares fit was used to examine the differences between Rest and HV data and between HV and Post-HV data. Statistical significance was tested for each subject with the Bonferroni correction (number of tests=2 or 4).

The regional CBFs in the HV scan and in the post-HV scan in each ROI were expressed as a percent of the resting CBF. The average percentages among all ROIs in the control and affected regions were calculated for each subject and are displayed in Table 2. All subjects showed a significant reduction of CBF by HV and a significant elevation of CBF by the termination of HV in the nonaffected region (control region of patients and all regions in volunteers). However, in the affected territory, the reduction of CBF seen by the HV study was smaller than that in the control region in all but 1 patient (case 11). The reduction was not significant in 5 patients. The CBF did not increase significantly during the recovery from HV to the resting scan (Figure 2). The post-HV reduction in CBF after the termination of HV was encountered in the regions with a poor reduction of CBF during HV. In cases 1 to 7, 1 or more ROIs in the affected territory ever showed paradoxically elevated CBFs in the HV scan as compared with the resting scan (Figure 2). The post-HV reduction in CBF after the termination of HV was most prominent in such regions (Figure 2; cases 1, 4, 5, and 7).
scan than in the HV scan (Table 2). The CBF maps of 2 patients suffering from occlusion of a unilateral major cerebral artery with moyamoya vessels clearly indicated that in the area supplied by the occluded artery, the most profound hypoperfusion occurred not during HV but after HV, although the PaCO₂ levels in these post-HV scans were higher than those in the HV scan (Figures 3 and 4). These 2 patients (cases 1 and 4) noticed by themselves that their frequent transient hemipareses are closely related to the events that cause HV. The most prominent negative post-HV response was observed in anterior and posterior watershed ROIs (47.2% and 47.7% reduction after HV, respectively). Another patient (case 3) complained that he could not speak well when he felt fatigue after daily hard work; the most prominent negative post-HV response was observed in his left temporal cortex (34.8% reduction after HV). In the other patient with moyamoya vessels (case 2), there was no clear trigger that induced her transient hemiparesis.

Five patients with atherosclerotic disease also showed a paradoxical negative post-HV response in 1 or more ROIs (cases 5 to 9), although the degree of reduction and the number of ROIs with such a negative response were smaller than those in the patients with moyamoya vessels. The average CBF in the affected ROIs was greater in the post-HV scan than in the HV scan in 2 patients (cases 8 and 9). In them, a paradoxically negative post-HV response was observed in only 1 ROI (parietal and anterior watershed ROI, respectively; Figure 2). However, in 2 atherosclerotic patients (cases 5 and 7) who had obstruction of a vessel with an atherosclerotic origin, also showed such a paradoxical response in some regions, although the reduction rate was smaller than those of cases 1 and 4 who had moyamoya vessels. It should also be noted that many regions in the territory of the obstructed artery showed a positive post-HV response and only a few regions showed a negative post-HV response. Also, note that the negative post-HV response was closely associated with a poor reduction of CBF by HV. The regions with the largest reduction of CBF in the post-HV scan showed no reduction or even showed a paradoxical increase in the CBF by HV.

**Correlations Between the Post-HV Responses and the Acetazolamide and CO₂ Responses**

The PET subtraction images representing the post-HV response (equal to the CBF in the post-HV scan minus that in
negative post-HV response corresponds well to the area with impaired response produced by CO₂ or acetazolamide. The unit of the scales is milliliters per minute per 100 grams.

the HV scan) had a distribution pattern similar to the CBF images of the CO₂ or acetazolamide response (equal to the CBF in CO₂ or acetazolamide challenge minus rest) by visual inspection in all cases, as shown in representative cases (Figures 3 and 5 through 7). In the ROI analysis, the regional post-HV increase was significantly correlated with the acetazolamide or CO₂ response, with a high correlation coefficient in the cases with a paradoxically negative post-HV response (cases 1 to 9) (Table 2). However, in the patients without a paradoxical response and in the normal volunteers, the correlation coefficient was small and less often significant (Table 2).

The post-HV responses of all ROIs in all patients were plotted against the acetazolamide response and the CO₂ response (Figure 8A and 8B). Both the acetazolamide response and the CO₂ response were significantly correlated with the post-HV responses among all ROIs and among the affected ROIs (P<0.0001). In accordance with these plots,
the acetazolamide or CO₂ response magnitude could be used as an indicator to distinguish regions with a paradoxically negative post-HV response from those with a normal positive post-HV response. Among regions with less than a 10% response to acetazolamide, 33 of 40 (83%) regions showed a negative post-HV response. Among regions with more than a 10% response to acetazolamide, 13 of 18 (72%) regions showed a positive post-HV response. Among regions with less than a 5% response to 5% CO₂, 27 of 33 (82%) regions showed a negative post-HV response. Among regions with more than a 5% response to 5% CO₂, 11 of 15 (73%) regions showed a positive post-HV response.

Correlations Between the Post-HV Responses and the OEF, CBV, and CBV/CBF

The visual inspection of the CBF, CBV, and OEF images obtained by the ¹⁵O-gas PET study, coregistered with each other, indicated that when a focal difference of OEF or CBV was clear, paradoxical post-HV responses were encountered (Figures 4 through 6). When such a focal abnormality in OEF

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or CBV was not noted, post-HV paradoxical responses did not occur (Figure 7). However, when the OEF values in all ROIs from all patients were analyzed, the correlation between the OEF value and the post-HV responses was found to be small \((r=0.2, P=0.03)\). Moreover, there was no significant correlation between these parameters in the affected regions \((r=0.01, P=0.93)\). The regional value of CBV was significantly and highly correlated with the post-HV response among all ROIs and among the affected ROIs \((r=0.530, P=0.0001)\), respectively, and \(P<0.0001\) and \(P<0.0001\), respectively) (Figure 8C). In accordance with this plot, the CBV value could be used as an indicator to distinguish regions with a paradoxical post-HV response from those with a normal post-HV response. Among regions with CBV values greater than the mean + SD of the normal volunteers, \(22/36\) of 36 (64%) regions showed the paradoxical negative post-HV response. Among regions with CBV of less than the mean + SD, 14 of 22 (64%) regions showed a positive post-HV response (Figure 8C).

The regional CBF/CBV values were significantly correlated with the post-HV response \((r=0.65, P<0.0001)\) among all ROIs. However, among the ROIs in the affected territories, the correlation between these parameters was less good \((r=0.33, P=0.01)\), and it was not possible to determine the threshold value of CBF/CBV to classify the affected ROIs into those with paradoxical and those with normal post-HV responses (Figure 8D). The regional value of CBF/CBV seems to be influenced by the resting CBF and to have limited value in predicting the degree of post-HV response of the affected territory, which bore significantly lower resting CBF values compared to the control areas \((34.2\pm7.1\) mL \(\cdot\) min\(^{-1}\) \(\cdot\) 100 g\(^{-1}\), \(P<0.0001)\)

### Paco2 Difference Between the 2 HV Periods

The post-HV scan was done after the second period of HV, and the HV scan was done during the first HV. This procedure was necessary because we needed at least a 10-minute interval between the 2 PET scans to allow for isotope decay and to avoid continuing the HV for more than 10 minutes. Although we attempted to maintain similar levels of Paco2 during the 2 HVs by adjusting the rhythm of ventilation, the possibility that different Paco2 levels between the 2 HV periods might have affected the result was not ruled out. Thus, we reexamined and compared the Paco2 levels during the HV protocol between 2 groups of subjects: the patients who had 1 or more regions with an apparent negative post-HV response (cases 1 to 9) and the patients without a negative post-HV response and the normal volunteers (cases 10 to 12 and the 3 volunteers). There was no significant difference between the 2 groups, either in the value of Paco2 during the various scans or in the Paco2 differences from the resting values (Table 3). There was also no significant difference in Paco2 between the 2 HV periods in either group (Table 3).

### Discussion

In the present study, the cerebral area under chronically reduced perfusion pressure, which was expressed by elevated CBF, elevated OEF, or impaired vasoactivity, showed a paradoxical response in CBF during and after HV. As a result, a profound hypoperfusion occurred not during the HV but rather after the HV. The post-HV response was strongly correlated with the vascular responses to the vasodilatory stimuli of CO2 and acetazolamide. We speculate that the termination of HV acts like a vasodilatory stimulus because the reduced Paco2 recovered to the baseline level during that period. Thus, a paradoxically negative response was observed in the post-HV state and in the CO2/acetazolamide loading tests in almost identical regions.
Possible Pathophysiology of “Posthyperventilatory Steal Response”

These negative responses to vasodilatory stimuli could be explained as a “steal phenomenon” because normal vessels, which are a main source of blood supply to the impaired area through leptomeningeal collaterals or through poorly developed collaterals of the circle of Willis, promptly dilate in response to a stimulus, which reduces the blood supply to the area with an impaired vascular response. As was shown in this study, a paradoxical increase in CBF produced by reducing the PaCO2 and a paradoxical decrease in CBF produced by increasing the PaCO2 often occur in the territory of an obstructed artery. However, it is not reasonable to speculate that the vessels in such a region dilate by themselves in response to the reduced PaCO2 or that they constrict in response to the increased PaCO2. It is more reasonable to consider this a passive phenomenon caused by the vascular response in the control region by the same arterial source. Therefore, in this paper we will refer to the paradoxically negative response in CBF after the termination of HV as the “posthyperventilatory steal response.”

We postulate here that such a posthyperventilatory steal response may have some role in the clinical features of

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**TABLE 3. PaCO2 (in mm Hg) During Each Scan in Subjects With or Without ROIs With a Negative Post-HV Response**

<table>
<thead>
<tr>
<th>Subjects With One or More Regions with Negative Posthyperventilatory Response</th>
<th>Subjects Without Regions with Negative Posthyperventilatory Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=9)</td>
<td>(n=6)</td>
</tr>
<tr>
<td>Resting 1</td>
<td>41.9±2.5</td>
</tr>
<tr>
<td>Resting 2</td>
<td>41.4±2.8</td>
</tr>
<tr>
<td>HV scan</td>
<td>30.1±4.7</td>
</tr>
<tr>
<td>2nd HV (final value)</td>
<td>27.2±4.5</td>
</tr>
<tr>
<td>Post-HV scan</td>
<td>37.5±2.3</td>
</tr>
<tr>
<td>CO2 (5%) scan</td>
<td>52.0±3.8</td>
</tr>
<tr>
<td>Resting–HV scan</td>
<td>11.1±5.0</td>
</tr>
<tr>
<td>Resting–2nd HV</td>
<td>14.4±5.5</td>
</tr>
<tr>
<td>Resting–Post-HV scan</td>
<td>3.7±3.0</td>
</tr>
<tr>
<td>CO2 scan–resting</td>
<td>9.5±3.2</td>
</tr>
</tbody>
</table>

Data are mean±SD. All the values were compared between the 2 groups, and no significant difference was found in any value. The PaCO2 between the first and the second HV was also compared; no significant difference was found between the groups.
patients with chronic hemodynamic stress, because this phenomenon can be encountered in daily physiological situations. In the normal subjects and in the patients without impaired vasoreactivity, the maximum decrease in CBF occurred during HV and promptly began to recover when the HV was terminated. Homeostatic mechanisms work to eliminate excessive changes of the Paco2 level, which limit excessive cerebral hypoperfusion in normal physiological conditions. However, in patients with a hemodynamic problem, the maximum decrease in CBF occurred after the termination of HV. The degree of such a decrease cannot be controlled by physiological and intentional regulation, and unexpected hypoperfusion can thus be encountered in daily situations.

Clinical Relevance of the Posthyperventilatory Steal Response

In our series, the patients with moyamoya disease (cases 2 and 3) or unilateral cerebral arterial occlusive disease with angiographically demonstrated moyamoya vessels (cases 1 and 4) exhibited a marked posthyperventilatory steal response. It may explain why such patients often present a long-lasting but reversible TIA after a condition that leads to HV (eg, crying, eating a hot meal, or playing a wind instrument).15 In our series, the transient motor or language symptoms seen in 3 patients (cases 1, 3, and 4) could be triggered by HV. It should be noted that the reduction of CBF at post-HV was very large in these patients. A milder post-HV steal was observed in the other patient with moyamoya vessels (case 2) and in the atherosclerotic patients in whom the ischemic attack was not associated with HV. Therefore, it may be reasonable to hypothesize that the profound posthyperventilatory steal response, which may cause rather long-lasting posthyperventilatory hypoperfusion, is 1 of the triggers of well-known HV-induced ischemic symptoms. It would be worthwhile to examine the correlation between the posthyperventilatory steal response and the HV-induced abnormal electroencephalogram observed in patients with moyamoya disease.28,29 It should also be noted that such uncontrollable hypoperfusion may be closely correlated with the progressive deterioration and ischemic damage of the cerebral cortex that occurs in moyamoya patients.15

The patients with atherosclerotic occlusive disease bearing PET evidence of hemodynamic stress also showed posthyperventilatory steal responses. The relationship between this phenomenon and the clinical features of atherosclerotic disease is not clear, because ischemic attacks in atherosclerotic patients are generally independent of HV whether or not the patients show PET evidence of hemodynamic stress. In this group, the reduction of CBF after HV was smaller than that observed in the patients with moyamoya vessels, and the number of ROIs showing posthyperventilatory steal per patient was generally small. Therefore, a long-lasting and widespread posthyperventilatory hypoperfusion may occur rarely in atherosclerotic patients. However, several points suggest the contribution of posthyperventilatory steal to the clinical course of chronic atherosclerotic disease: (1) Regions with posthyperventilatory steal are closely correlated with the area of chronic misery perfusion and with a negative response to a CO2 or acetazolamide challenge. These phenomenon have been associated with a high future stroke rate.7,9–12 (2) In the patients with evidence of widespread chronic hemodynamic stress as in cases 5 and 7, the most profound negative post-HV response was observed in the frontal watershed ROI. In 6 of the 9 patients with 1 or more ROIs with a negative post-HV response, the largest negative response was observed in the frontal or posterior watershed ROI, where cortical infarction most often occurs in major cerebral arterial occlusive disease.6,11,14,30 (3) Although the CBF reduction in the post-HV scan in atherosclerotic patients was smaller than that in the patients with moyamoya vessels, the average post-HV CBF value among the ROIs with a negative post-HV response was lower in the atherosclerotic patients than in the patients with moyamoya vessels (32.8±6.0 and 38.3±11, respectively), although not to a significant degree (P=0.10). Although our protocol was performed by observing the end-expiratory CO2 level carefully to be sure not to induce too much hypocapnia, profound hypocapnia can be induced in daily situations. A more drastic CBF decrease below the critical level might be induced, which could trigger a thrombotic event in the area with a posthyperventilatory steal response. These possibilities are unproved because we did not evaluate the natural course of the patients in this study; a follow-up study of our subjects may provide some evidence concerning the contribution of the posthyperventilatory steal response to stroke evolution.

Prediction of Posthyperventilatory Steal Response from Other PET Parameters

From the standpoint of clinical practice, our HV/post-HV protocol is difficult to apply to patient diagnosis in daily clinical situations, because it requires serial quantitative measurements of CBF in short intervals with PET. Therefore, we compared the post-HV response with other parameters that can be obtained more easily. Through this analysis, we showed the possibility that the optimum threshold value for acetazolamide and CO2 responses and regional CBV could be settled to predict post-HV steal response, although the study of more patients is necessary to calculate the sensitivity and specificity of such threshold value. Because the CO2 or acetazolamide response can be measured with 133Xe single-photon emission computed tomography or cold Xe-CT, and the CBV can be imaged with 99mTc red blood cell single-photon emission tomography, these parameters may be substituted for the HV/post-HV test.

The value of regional OEF did not correlate well with the post-HV responses. This is not surprising because the value of OEF is based on the uncoupling of CBF and oxygen metabolism, and the value itself is not dependent on the vascular response.33 However, the focal elevation of OEF within a patient is a sign that compensation by increasing regional CBV has already reached a maximum level,6,8,32 and in this condition a posthyperventilatory steal was found. The use of the absolute value of CBF/CBV also requires caution in predicting whether an affected ROI would show a post-HV negative response. The side-to-side ratio of CBF/CBV may be appropriate, as has been pointed out by others.33,34 How-
ever, it imposes a limitation on the use of CBF/CBV for evaluating the hemodynamics of bilateral disease.

**Effects of Delay and Dispersion of H$_2^{15}$O on CBF Measurement**

In the present study, the regions supplied by obstructed arteries may be perfused by collateral circulation from other arteries, and may have a different delay and dispersion of tracer from other regions when CBF is measured with H$_2^{15}$O PET. 1, 18-38. To evaluate the effects on our results of regional differences in delay and dispersion, a simulation was performed using an arterial time-activity curve obtained in the present study (data not shown). Since the arterial mean transit time is related to the CBV/CBF ratio measured in this study, its within-subject regional difference was calculated for each patient (1.7 to 6.8 seconds; mean:±SD, 4.4±1.5 seconds). This simulation indicated that an arterial mean transit time of +6.8 seconds, which is the maximum value of the within-subject difference, induces an error of 15% in CBF values. As for CBF changes (either an increase or a decrease), an arterial mean transit time of +6.8 seconds induces an underestimation of 3 percentage points when the CBF is changed by 20%. Therefore, the finding of a smaller CBF response to CO$_2$ change in the affected regions than in the control regions in the present study may be partly but not totally explained by the regional difference in the delay and dispersion of tracer.

**Prospects for Further Investigation**

We reported here that the focally impaired vascular response may cause a posthyperventilatory steal response. We also proposed that this phenomenon may explain the clinical symptoms initiated by HV in selected populations of patients with obstructive cerebrovascular disease. Since the present study was done in selected patients who were screened with a PET $^{15}$O-gas study, we are still not sure how far the contribution of posthyperventilatory steal response would be seen among a whole population of patients with obstructed cerebral artery. We need to examine an extended group of patients using this protocol to further clarify this phenomenon. Another subject of further study concerning the posthyperventilatory steal response should be the correlation of this phenomenon with the risk of future stroke evolution, as we postulated. It is also important to determine whether this condition can be treated or controlled with treatment to increase the CBF by surgical revascularization. Whether or not patients are treated surgically, a follow-up study with the PET HV/post-HV protocol together with neurological examination and CT scan or MRI should provide more evidence to help clarify the nature of the posthyperventilatory steal response.

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**References**


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