Changes in Hyperfrontality of Cerebral Blood Flow and Carbon Dioxide Reactivity With Age

Yoshiyasu Tsuda, MD, PhD, and Alexander Hartmann, MD

We evaluated the topographic distributions of regional cerebral blood flow in 51 normal subjects (mean age 41 years) by the xenon-133 inhalation technique. Forty-five of these subjects were divided by age into young normals <30 years old (mean age 24 years), middle-aged normals 30–50 years old (mean age 40 years), and elderly normals >50 years old (mean age 62 years); there were 15 subjects in each group. The distributions of vascular CO2 reactivity to hypocapnia were also evaluated in 20 of the normal subjects (mean age 34 years), including 11 younger normals <30 years old (mean age 24 years) and nine older (middle-aged or elderly) normals ≥30 years old (mean age 45 years). The hyperfrontal distribution of regional cerebral blood flow observed in the young and middle-aged normals was not observed in the elderly normals. The hyperfrontal distribution of vascular CO2 reactivity observed in the younger normals was absent in the older normals. In addition, the correlation between regional cerebral blood flow and vascular CO2 reactivity observed in the younger normals was disturbed in the older normals. The data show a hyperfrontal distribution of regional cerebral blood flow in normal subjects that diminishes during the fifth and sixth decades, along with a distribution of vascular CO2 reactivity in younger normal subjects that is not homogeneous throughout the frontoparietal regions. It is also suggested that evaluation of the correlation between the regional cerebral blood flow and vascular CO2 reactivity can provide an accurate assessment of the functional capacity of the cerebral vasculature to constrict in normal subjects of varying ages. (Stroke 1989;20:1667–1673)

The xenon-133 inhalation technique is one of the most established methods used to measure two-dimensional regional cerebral blood flow (rCBF) in normal subjects and in patients with cerebrovascular disorders.1–5 However, a full understanding of the topographic distributions of rCBF and vascular CO2 reactivity in connection with vascular supply areas in normal subjects is still lacking. This understanding is considered essential for the precise interpretation of physiologic and pathophysiologic conditions in the cerebral circulation. Analysis of the distributions of rCBF and vascular CO2 reactivity in the brain cortex could represent a steady-state vascular supply; it could also provide a functional topography of the vasomotor reactivity relating to the changes of Paco2 in normal subjects and its disturbances in both elderly subjects and in patients with cerebrovascular diseases.

From the study of various forms of ischemic cerebrovascular disease, we have reported significant decreases of rCBF and vascular CO2 reactivity as determined by the intra-arterial xenon-133 injection method.6–10 Using the xenon-133 inhalation method, it is difficult to express the significance of the results from individual patients,11,12 but it is possible to provide quantitative information about rCBF from a group of patients. In this study, we attempt to determine the topographic distributions of rCBF and vascular CO2 reactivity as related to vascular supply areas and to show the functional distribution of brain activity in normal subjects compared with disturbances occurring with advanced age.

Subjects and Methods

The topographic distribution of rCBF was evaluated in both hemispheres for 51 normal subjects...
Table 1. Summary of Subjects in Resting Regional Cerebral Blood Flow Study

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Women</th>
<th>Men</th>
<th>Range (yr)</th>
<th>Mean±SD (yr)</th>
<th>( P_{E\text{CO}_2} ) at rest (mean±SD mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects</td>
<td>51</td>
<td>25</td>
<td>26</td>
<td>19-77</td>
<td>40.5±16.0</td>
<td>37.7±4.2</td>
</tr>
<tr>
<td>Young normals</td>
<td>15</td>
<td>11</td>
<td>4</td>
<td>19-29</td>
<td>24.3±3.5</td>
<td>37.3±4.7</td>
</tr>
<tr>
<td>Middle-aged normals</td>
<td>15</td>
<td>5</td>
<td>10</td>
<td>32-47</td>
<td>39.8±5.3</td>
<td>36.1±2.8</td>
</tr>
<tr>
<td>Elderly normals</td>
<td>15</td>
<td>7</td>
<td>8</td>
<td>51-77</td>
<td>61.5±7.8</td>
<td>37.6±3.5</td>
</tr>
</tbody>
</table>

\( P_{E\text{CO}_2} \), end-expiratory CO2 tension.

(Table 1) who had no history of neurologic abnormalities, showed no risk factors, and were not on any medication. Subjects with hypertension (blood pressure of ≥150/95 mm Hg) and those with chronic pulmonary disease were excluded from the study so that accurate rCBF measurements could be obtained as part of the routine vascular evaluation in healthy subjects. Informed consent was obtained from each subject prior to evaluation. Forty-five of the normal subjects were categorized by age as 15 young normals <30 years old, 15 middle-aged normals 30-50 years old, and 15 elderly normals >50 years old (Table 1).

The distribution of vascular CO2 reactivity was also evaluated in both hemispheres for 20 of the normal subjects, 11 younger normals <30 years old and nine older normals ≥30 years old (Table 2).

rCBF was measured using the atraumatic design proposed by Veall and Mallett,1 further developed by Obrist et al2 and slightly modified by us.3 The examinations took place in a quiet, darkened room with the subjects instructed to close both eyes and refrain from moving or talking. CO2 volume percentage of the expired air was continuously recorded by >1,500 detectors and of vascular CO2 reactivity study. rCBF was calculated from the initial slope index (ISI) as proposed by Risberg et al and modified by Prohovnik et al; that is, ISI was defined as 100 times the monoeponential slope during the interval between 0.5 and 1.5 minutes after the beginning of desaturation of the clearance curves.

To evaluate vascular CO2 reactivity, rCBF was measured a second time 20 minutes after the end of the first rCBF study to ensure clearance of residual xenon-133 activity, and the background activities were subtracted from data in the second study when calculating rCBF during hypocapnia. Voluntary hyperventilation was started 2 minutes prior to the initiation of the xenon-133 inhalation and continued for 5 minutes. Vascular CO2 reactivity was evaluated as the percentage change in rCBF divided by the absolute change in \( P_{E\text{CO}_2} \) between the resting steady state and hyperventilation; rCBF during hyperventilation might be less influenced by resting rCBF itself.

To evaluate the distributions of rCBF recorded by >1,500 detectors and of vascular CO2 reactivity recorded by nearly 600 detectors, data for several detector pairs were combined. rCBF and vascular CO2 reactivity values were averaged for the anterior precentral region (comprising seven detector pairs: P1-5 [frontal], C2 [central], and T2 [temporal]) and the postcentral temporo-occipital region (comprising eight detector pairs: C1, P1-4 [parietal], T3, and O1 and O2 [occipital], which were approximately bordered by the rolandic fissure.13 Each cerebral hemisphere was also divided into four vascular territories: the anterior cerebral artery (ACA) territory (comprising four detector pairs: F1-3 and F5), the anterior aspect of the middle cerebral artery (A-MCA) (comprising three detector pairs: F2, C2,

Table 2. Summary of Subjects in Vascular CO2 Reactivity Study

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Women</th>
<th>Men</th>
<th>Range (yr)</th>
<th>Mean±SD (yr)</th>
<th>( P_{E\text{CO}_2} ) (mean±SD mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects</td>
<td>20</td>
<td>9</td>
<td>11</td>
<td>20-64</td>
<td>33.6±13.3</td>
<td>39.8±4.1</td>
</tr>
<tr>
<td>Younger normals</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td>20-29</td>
<td>24.3±3.6</td>
<td>41.0±4.1</td>
</tr>
<tr>
<td>Older normals</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>32-64</td>
<td>45.2±11.6</td>
<td>38.5±3.7</td>
</tr>
</tbody>
</table>

\( P_{E\text{CO}_2} \), end-expiratory CO2 tension.
and T2), the posterior aspect of the middle cerebral artery (P-MCA) (comprising four detector pairs: C1 and P1-3), and the posterior cerebral artery (PCA) territory (comprising three detector pairs: P4 and O1 and O2) (Figure 1); rCBF and vascular CO2 reactivity values were also averaged for each territory. One detector pair (T1, not shown) was omitted from the evaluation because of frequent artifacts caused by radioactivity in the air passages and in an attempt to avoid the arterial artifact, as previously reported.14-15

We applied one-way analysis of variance and F statistics to the continuous data to test the null hypothesis that there were no differences between the two regions nor among the four territories; these evaluations were done separately for rCBF and vascular CO2 reactivity of all seven groups. Regional and territorial rCBF and vascular CO2 reactivity values were then compared using an independent t test. For the 20 normal subjects, the correlation coefficients between rCBF and vascular CO2 reactivity for the 15 detector pairs were calculated by the conventional method. Regression lines for vascular CO2 reactivity versus rCBF for each detector pair of the 20 normal subjects, the 11 younger normals, and the nine older normals were obtained using the least-squares method.

Results

Among the 51 normal subjects, rCBF and vascular CO2 reactivity were greater in the anterior precentral region than in the postcentral temporocipital region (showed hyperfrontal and hyperfrontoparietal distributions) ($F_{1,151}=48.64$ and $F_{1,576}=7.04$, $p<0.001$ and $p<0.005$, with differences of 5.6% and 5.5%, respectively). Comparisons of rCBF and vascular CO2 reactivity for the four vascular territories also showed significant differences ($F_{3,140}=15.75$ and $F_{3,536}=3.12$, $p<0.001$ and $p<0.025$, respectively). In particular, in the middle cerebral artery territories, rCBF and vascular CO2 reactivity were higher in the A-MCA than in the P-MCA ($p<0.001$ and $p<0.01$ by independent t tests, with differences of 6.4% and 7.6%, respectively; Figure 2). rCBF was greater in the anterior than in the posterior region and greater in the A-MCA than in the P-MCA territory (hyperfrontal and hyperfrontoparietal distributions were observed) in the young and middle-aged normals ($F_{1,442}=61.20$, $p<0.001$; $F_{3,440}=22.21$, $p<0.001$; and $F_{1,444}=7.00$, $p<0.001$; $F_{3,412}=7.61$, $p<0.001$; with regional differences of 8.5% and 6.2%, respectively), but the distributions disappeared in the elderly normals (for regions $F_{3,444}=2.09$), particularly in the middle cerebral artery territories ($F_{3,412}=1.14$) (Figure 3).

Among the 20 normal subjects, vascular CO2 reactivity in the younger normals also showed these hyperfrontal and hyperfrontoparietal distributions;
reactivity was greater in the anterior than in the posterior region ($F_{1,16}=9.55, p<0.005; F_{3,20}=4.56, p<0.005$) and greater in the A-MCA than in the P-MCA territory ($p<0.001$ by independent $t$ test), with differences of 7.2% and 11.3%, respectively. However, these regional and territorial differences in vascular CO$_2$ reactivity were not observed in the older normals ($F_{1,29}=0.81, F_{3,24}=0.44$) (Figure 4).

**Figure 4.** Distributions of vascular CO$_2$ reactivity in (a) 11 younger normal subjects and (b) 9 older normal subjects. Regional and territorial values are expressed as mean±SD. Dark circled detectors show significantly higher values than shaded and open circles by independent $t$ test. ACA, anterior cerebral artery territory; A-MCA, anterior aspect of middle cerebral artery (MCA); P-MCA, posterior aspect of MCA; PCA, posterior cerebral artery territory.
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FIGURE 5. Changes in correlations between regional cerebral blood flow (ISI) and vascular CO₂ reactivity in 15 detector pairs (c), two regions (a), and four territories (a) of (a) 20 normal subjects, including (b) 11 younger normals and (c) 9 older normals. ANT, anterior precentral region; POST, postcentral temporo-occipital region; ACA, anterior cerebral artery territory; A-MCA, anterior aspect of middle cerebral artery (MCA); P-MCA, posterior aspect of MCA; PCA, posterior cerebral artery.

ranges 0.7–0.9 and 0.05–0.06, respectively) correlated significantly (p<0.01) (Figure 5a). In addition, the two regions had obviously different rCBF values, which also showed hyperfrontal and hyperfrontoparietal distributions. The relation between rCBF and vascular CO₂ reactivity in the 11 younger normals (Figure 5b) (SEM ranges 0.7–0.9 and 0.05–0.07, respectively) was compared with that in the nine older normals (SEM ranges 1.4–1.6 and 0.08–0.10, respectively) (Figure 5c). In the younger normals the relation was more highly significant (p<0.005) than in the older normals (p<0.05). In the older normals, however, the hyperfrontal distribution became undistinguishable. The hyperfrontal distribution in the younger normals was characterized by ISI values of >59 and vascular CO₂ reactivity values of >2.8–3.0%/mm Hg, as shown by the dotted lines in Figure 5, b and c. Mean P₅ CO₂ at rest was 41.0 mm Hg in the younger normals and 38.5 mm Hg in the older normals, and no significant differences were demonstrated (Table 2). We also compared regional and territorial rCBF in the younger and older groups (Figure 6). The results showed a trend in rCBF similar to that in vascular CO₂ reactivity (see Figure 4); that is, significant age differences in the anterior precentral region were diminished in the postcentral temporo-occipital region.

Discussion

rCBF data obtained by xenon-133 inhalation should be interpreted with caution because the differences detected by this method may be caused by artifacts and may not represent existing pathophysiologic differences in blood flow. In our study, airway artifacts were markedly reduced by using a...
mouthpiece instead of a face mask. If any artifacts were detected by visual inspection of the clearance curves or if any insufficient peak count rates or inadequate curve fitting standard deviations were noticed, the data from that detector and its corresponding detector on the other side were deleted. Fourteen detector pairs in the rCBF study (six in the anterior and eight in the posterior region) and 22 detector pairs in the vascular CO2 reactivity study (12 in the anterior and 10 in the posterior region) were deleted. No differences in the regional distribution of the deleted detector pairs by age were found in either the rCBF study (young normals: 4 and 2, middle-aged normals: 0 and 4, elderly normals: 2 and 2 in the anterior and posterior regions, respectively) or in the vascular CO2 reactivity study (younger normals: 6 and 6, older normals: 6 and 4 in the anterior and posterior regions, respectively). In addition, due to the frequent artifacts caused by radioactivity in the air passages and to avoid the arterial artifact,14,15 one detector pair in the temporal region (T1) was omitted from the evaluation. Averaging the values from more than one detector pair enabled us to reduce the variation and provided an additional degree of statistical significance, as previously reported.12 We used ISI to evaluate rCBF because the index is stable and it primarily reflects the clearance rate from rapidly perfused blood flow compartments of the gray matter.3,4 We evaluated vascular CO2 reactivity by the vasoconstrictive responses to hypocapnia because the procedure is easy and safe and can be accurately repeated without causing respiratory difficulties. Also, it is considered to be a more physiologic procedure than the artificial hypercapnia induced by inhalation of 5% CO2, which is more likely to disturb cardiovascular dynamics.16 With respect to an "order effect," we first evaluated resting rCBF and then obtained the hypocapnic rCBF in each subject according to vascular CO2 reactivity. The decline in rCBF with hypocapnia, however, has been found regardless of whether the process is carried out in the manner described above or whether the hypocapnic values are obtained first.17

With respect to the estimation of hyperfrontality, we found a regional difference in rCBF of 6-9%, closer to that found by Risberg et al18 (5-15%) and Mamo et al19 (10-15%) than to that found by Ingvar20 (20-40%). These variations might be due to technical differences in measurement methods. It has been suggested19 that rCBF in the frontal region is inhomogeneous due to a slightly lower rate of blood flow in its motor and premotor frontal areas than in its most anterior aspect. In our study, greater rCBF in the prerolandic, premotor, and Rolandic somatosensory areas were found than in the postrolandic somatosensory areas. Such distributions of rCBF might be important since they indicate high levels of flow not only in the territory of the ACA but also in the A-MCA compared with the P-MCA and the remainder of the brain hemisphere. Such inhomogeneous distributions of rCBF in the same vascular territory must be taken into consideration before interpreting the rCBF data in physiologic and pathophysiologic conditions of the cerebral circulation.

Vascular CO2 reactivity also showed hyperfrontal distributions, with a difference of 6-11% in the anterior precentral region and the A-MCA territory. However, we could not find any other reports that mentioned these differences in normal subjects. Maximilian et al21 reported a homogeneous increase of blood flow to 6% CO2 inhalation regardless of whether the pattern was present at rest or was elicited by a cognitive task, whereas we found regional inhomogeneity to variations in CO2 tension. However, it should be noted that voluntary hyperventilation could increase relative frontal blood flow due to the vigilance component, thereby contributing to a systemic change in rCBF pattern during hypocapnia. Moreover, the correlation between rCBF and vascular CO2 reactivity was significant for all subjects in our study, although vascular CO2 reactivity was evaluated as the percentage change in rCBF divided by the absolute change in PeCO2 determined during rest and hypocapnia. These percentage reactivities of rCBF to PeCO2 changes might be less influenced by resting rCBF values.

Our findings agree with previous data from 22 normal subjects22 and suggest a rationale for the law of initial value first described by Wilder in 1953.23 The law states that the higher the initial rCBF, the smaller the response to function-raising agents, such as CO2 inhalation, and the greater the response to function-depressing agents, such as hyperventilation. The greater response expected by this law supports the fact that in our study, vascular CO2 reactivity was evaluated by vasoconstrictive responses to hypocapnia. Ackerman et al24 also reported that the resting rCBF value influences vasomotor CO2 reactivity. These findings might explain our results of hyperfrontal and hyperfrontoparietal distributions of vascular CO2 reactivity associated with similar distributions of rCBF and the significant rCBF-CO2 reactivity correlations. On the other hand, Davis et al16 found a linear decline in blood flow in the gray matter with age but no corresponding change in vascular CO2 reactivity in 55 normal volunteers; however, that work did not evaluate the correlations between gray matter blood flow and vascular CO2 reactivity.

Significant regional and territorial differences in rCBF and vascular CO2 reactivity disappeared in our older normal subjects. These results agree with findings in 105 healthy volunteers previously reported25 in whom the regional reduction in ISI with advancing age was significantly greater in the territory of the middle cerebral artery than in the territories of other arteries (p<0.05). As a result, hyperfrontality of rCBF disappeared in our older normal subjects.
Our results suggest that the hyperfrontal distribution of rCBF disappears during the fifth and sixth decades, as previously reported. The rCBF–CO₂ reactivity correlation in our younger normal subjects showed a clear separation of regional rCBF and vascular CO₂ reactivity values. In our older normal subjects, however, the correlation showed decreased hyperfrontality in both measures because of more decreased values of rCBF and vascular CO₂ reactivity in the anterior precentral region than in the postcentral temporoparietal region. As a result, each regional value of rCBF and vascular CO₂ reactivity in our older normal subjects decreased to those values in the postcentral temporoparietal region of our younger normal subjects.

The age separation (i.e., <30 vs. ≥30 years) that we used in our correlation study of normal subjects might be too strict; nevertheless, we did observe considerable decreases in hyperfrontality in our subjects ≥30 years old. Based on these results, we suggest that evaluation of this correlation between hyperfrontality and age could accurately assess the changes in functional capacity of the cerebral vasculature to constrict. Further, the evaluation could be used as a predictor of the atherosclerotic changes that begin to occur even after age 30.

References


Key Words: aging · cerebral blood flow · xenon
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