Cerebral Cortical and White Matter Reactivity to Carbon Dioxide

Theobald Reich, MD, and Henry Rusinek, PhD

We measured cerebrovascular reactivity to carbon dioxide in the cerebral cortex and the subcortical white matter of 12 healthy adult volunteers (four young subjects aged 21-24, four middle-aged subjects aged 34-40, and four elderly subjects aged 62-85 years). Blood flow was computed from the concentration history of xenon-133 in the volume of interest measured with an ultrapure germanium detector array. End-tidal PacO$_2$ ranged from 35.4 to 42.6 mm Hg. The mean±SD baseline blood flows in the cerebral cortex were 60±7, 51±9, and 33±4 ml/100 cm$^3$/min in the young, the middle-aged, and the elderly subjects, respectively; the corresponding subcortical white matter baseline blood flows were 21±1, 22±3, and 16±5 ml/100 cm$^3$/min.

Mean±SD cerebrovascular reactivities to carbon dioxide in the cerebral cortex were 2.03±0.58, 1.36±0.41, and 0.72±0.19 ml/100 cm$^3$/min/mm Hg PacO$_2$ for the young, the middle-aged, and the elderly subjects, respectively; the corresponding reactivities in the subcortical white matter were 0.69±0.11, 0.59±0.17, and 0.36±0.41 ml/100 cm$^3$/min/mm Hg PacO$_2$. Blood flow and cerebrovascular reactivity in the cerebral cortex of the young subjects were significantly higher than those for white matter and significantly higher than those in the elderly subjects (p<0.001).

Age vs. blood flow (for the cortex) and age vs. cerebrovascular reactivity (for both cortical gray and subcortical white matter) also showed significant linear correlation (/>0.05). However, the age-related changes in white matter blood flow and cerebrovascular reactivity were slow, and the differences among the age groups were not statistically significant. (Stroke 1989;20:453–457)

There is general agreement that hypercapnia increases blood flow (CBF) in the normal mammalian brain, whereas hypocapnia decreases it. The magnitude of the change in CBF, that is, cerebrovascular reactivity, appears to be directly proportional to the initial rate of blood flow. Blood flow in the gray matter is altered considerably more than that in the white. Though the preponderant view is that CBF decreases with normal aging, a consensus on this question has not been reached. Both the methods of study and the choice of subjects have varied greatly. Davis et al$^3$ found at least eight studies performed on humans published before 1980 that reported no significant age-related changes in CBF and 14 studies that did. The eight former studies used the NO$_2$ method to measure CBF; 10 of the latter 14 used the more accurate xenon-133 washout technique. Table 1 lists 10 studies published since 1980 that included data on age-related changes in CBF in humans.$^2$3$^5$–$^1$2 Eight of the 10 studies reported a significant reduction of gray matter blood flow, and the two that measured white matter blood flow found no significant change in it.

The question of age-related reduction of cerebrovascular reactivity also remains unsettled. Davis et al$^3$ found that age had no effect on either gray or white matter reactivity, whereas Rogers et al$^2$ found that gray matter reactivity was reduced significantly; both teams of investigators used the conventional xenon-133 washout technique (Table 1). On the other hand, Levine et al,$^1$2 using positron emission tomography, found no significant reduction in mean reactivity.

We present data on blood flow and vascular reactivity to CO$_2$ determined independently in the cortex and subcortical white matter of the cerebral hemispheres. Measurements were made in healthy young, middle-aged, and elderly adults with an array of high-purity germanium (HPGe) detectors described previously.$^1$3 The instrument makes it possible to quantify the rate of change of the concentration of xenon-133 in several anatomic subvolumes of the brain simultaneously and to compute the blood flow in each subvolume specifically.
Subjects and Methods

We studied 12 volunteers, four aged 21–24, four aged 34–40, and four aged 62–85 years. Each subject enjoyed good health, took no medications, presented no abnormal medical history or physical findings, and had normal chest x-ray, electrocardiography, and screening clinical laboratory results; each subject had a normal computed tomogram (CT scan) of the brain. The elderly subjects maintained their own homes, lived independently, and were self-sufficient.

Each subject was studied first while breathing air and then 1 hour later while breathing air mixed with 4% CO2. Measurements were made in the sitting position in a quiet, dim room. Subjects ate but refrained from smoking and drinking caffeine-containing beverages on the day of the study.

The method of measurement has been described by us.13 The instrument is a stationary array of 200 collimated HPGe detectors located about the head in a precise configuration. The output of each detector is expressed by an equation that relates count rate to the quantity of radioisotope in each subvolume of tissue. The 200 resulting linear equations are solved for the radioisotope concentration in each brain subvolume simultaneously over successive 5-second intervals. Quantification is possible owing to the high energy resolution of HPGe detectors. Gas containing 10 mCi/1 xenon-133 is inhaled for 1 minute from a shielded Douglas bag through a mouthpiece fitted with a volumetric chamber and a cadmium-telluride semiconductor detector to allow continuous monitoring of the xenon-133 concentration at the mouth over 200-msec intervals; end-tidal CO2 is also monitored continuously. The arterial concentration of xenon-133 is computed from its end-tidal concentration and the hematocrit.14

Boundaries of brain subvolumes are defined from CT scans of the subject’s head with an X–Y digitizer. In general, the subvolumes are selected according to the purpose of a study. We defined the cerebral cortex (right and left frontal, temporal [including the insula], parietal, and occipital lobes), subcortical white matter (each aforementioned lobe, including the internal and external capsules, and the corpus callosum), other brain tissue (i.e., the ventricles, basal ganglia, midbrain, cerebellum, pons, and medulla), scalp, and skull. The first two (cerebral cortex and subcortical white matter) were the subvolumes of interest; the others were needed to account for all sources of gamma radiation.

CBF is calculated from the concentration curves C(t) of each subvolume of interest in three-dimensional space13 as

\[ C(t) = \sum_{i=1}^{2} p_i \int_{0}^{t} C_i(u) e^{-k_i(u-w)} \, du \]

where \( C_i \) is the arterial concentration of the tracer, \( k_i \) are the exponential time rate constants, and \( p_i = w_i f_i \) are the linear constants for each compartment. A two-compartmental decomposition of \( C(t) \) yields \( p_1, p_2, k_1, \) and \( k_2 \). The blood flow in any subvolume is \( f = p_1 + p_2 \). A single study results in the blood flow in the two anatomic subvolumes of interest, the cerebral cortex (\( f_2 \)) and subcortical white matter (\( f_1 \)). The model is a modification of that described by Obrist et al15 for measuring regional CBF from count rate curves. The advantages of our method are that it enables three-dimensional resolution, partition coefficients are not assumed, and contamination by counts from the scalp is avoided.

The coefficient of variation of concentration based on studies of phantoms is 9% in the cerebral cortex and 10% in the white matter subvolumes.16 The error in computed CBF is even less because it is computed from 133 data points of the concentration curve.
Average CBF and reactivity to CO\textsubscript{2} of the cerebral cortex and white matter among the three age groups, as well as average CBF and reactivity in the cerebral cortex and white matter within each age group were tested by analysis of variance; Bonferroni’s multiple group comparison test was then performed to identify significant differences.\textsuperscript{17} This method of data analysis avoids the problem associated with multiple group comparisons based on repeated two-sample t-tests. Linear regression analysis was used to find the best linear fit between CBF indexes and age.

**Results**

CBF in each subject before and after inhaling CO\textsubscript{2} is presented in Table 2.

Average baseline f\textsubscript{c} was significantly higher than f\textsubscript{w} in each age group (p<0.01). The differences in f\textsubscript{c} (but not f\textsubscript{w}) of the elderly vs. the middle-aged groups as well as the elderly vs. the young groups were also significant (p<0.01). The linear regression for f\textsubscript{c} vs. age (f\textsubscript{c} = −0.49×age + 69.8) is significant (r=0.85, p<0.001; Figure 1). The relation remains significant even after correcting f\textsubscript{c} to standard 40 mm Hg Paco\textsubscript{2} according to each subject’s own cerebrovascular reactivity.

The specific reactivity to CO\textsubscript{2} (R) (ml blood flow/100 cm\textsuperscript{3} tissue/min/mm Hg Hg Paco\textsubscript{2}) is R = (f\textsubscript{a} − f\textsubscript{b}) / (C\textsubscript{a} − C\textsubscript{b}), where f\textsubscript{a} and f\textsubscript{b} are the blood flow after and before inhalation of 4% CO\textsubscript{2} in air, and C\textsubscript{a} and C\textsubscript{b} are the corresponding Paco\textsubscript{2}. Figure 2 shows the mean±SD reactivities of the cortical gray (R\textsubscript{c}) and subcortical white matter (R\textsubscript{w}) in each age group. R\textsubscript{c} was significantly higher in the young than in the elderly group (p<0.01). The differences between R\textsubscript{c} and R\textsubscript{w} in the young group were also significant (p<0.01).

Figure 3 is a graph of the correlation between R\textsubscript{c} or R\textsubscript{w} and age. For cortical gray matter, the regression equation is R\textsubscript{c} = −0.02×age + 2.35 (r=0.76, p<0.01). For subcortical white matter, the linear regression equation is R\textsubscript{w} = −0.007×age + 0.872 (r=0.61, p<0.05). Reduction of R\textsubscript{w} with age occurs slowly; the difference between the young and the elderly groups within the age span of our subjects was therefore not significant.

The mean arterial blood pressure computed from systolic and diastolic brachial blood pressure measured with a sphygmomanometer (diastolic pressure + 1/3 pulse pressure) varied by <5 mm Hg during inhalation of CO\textsubscript{2} in any subject. The pulse rate in all subjects was 71–85/min and did not change by >4/min during hypercapnia in any subject.

**Discussion**

The regional xenon-133 washout technique has made it possible to measure CBF in humans safely and noninvasively. The washout curves are most often subjected to bicompartamental analysis, yielding a fast-flow and a slow-flow component.\textsuperscript{15} Slow blood flow is difficult to measure accurately, especially when reduced, because of compartmental slippage, low count rates, contaminating counts from the scalp, and scatter.\textsuperscript{18} The paucity of studies of white matter CBF and R, particularly in the white matter of elderly subjects, appears to be the result of these difficulties.
Our method avoids the aforementioned limitations. As described in previous publications, the HPGe detector array "sees" the head as a composite structure of anatomic subvolumes and measures the concentration of radioactive tracer in each continuously. Blood flow in each subvolume is computed from the concentration (not count rate) history of xenon-133. Knowledge of the blood-brain partition coefficients, therefore, is not needed.

\[ f_g \text{ in our young and middle-aged subjects was lower than gray matter CBF measured by compartmental analysis of xenon-133 count rate curves.} \]

However, we defined the cortical subvolume anatomically and included variable quantities of white matter. The subcortical white matter compartment is more homogeneous, and our \( f_w \) is in agreement with values reported for the slow-flow compartment.

All but two studies that reported no decrease of CBF with aging measured only mean hemispheric or overall mean CBF. Fast blood flow and slow blood flow as such were not measured. On the other hand, studies that measured fast blood flow with conventional xenon-133 techniques report an age-related reduction. Mean CBF, therefore, may not be a valid index of age-related changes in CBF because averaging a significant and a nonsignificant value (i.e., \( f_g \) and \( f_w \)) may yield a nonsignificant result.

The effect of aging on R in humans is also controversial. Only two laboratories have studied R of both gray and white matter. Yamaguchi et al[21] reported a significant decline in R of the gray matter with advancing age. Davis et al[3] found no change in relative reactivity (i.e., change in CBF per millimeter of mercury PAco2 divided by the baseline CBF) for various age groups. However, inasmuch as R is proportional to baseline CBF, a ratio of the two may obscure significant changes. Furthermore, additional division required to compute relative reactivity may double the error. As expected, our computation of the relative CO2 reactivity also does not show significant age-related change.

The muting of a significant finding by averaging it with a nonsignificant one also applies to cerebrovascular reactivity. White matter does not show significant R, whereas gray matter does. Conclusions based on changes in mean R, therefore, invite Type II error.

The reason for age-related changes in baseline CBF and R have not been determined. Cerebral atrophy, reduction in metabolic activity, and increase in cerebral vascular resistance appear to play roles.

References
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**KEY WORDS** • carbon dioxide • cerebral blood flow • xenon • white matter
Cerebral cortical and white matter reactivity to carbon dioxide.
T Reich and H Rusinek

Stroke. 1989;20:453-457
doi: 10.1161/01.STR.20.4.453

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