AJNR

Changing Topographic Patterns of Human Cerebral Blood Flow with Age Measured by Xenon CT

Hisao Tachibana, John S. Meyer, Hiroyuki Okayasu and Prasab Kandula

AJNR Am J Neuroradiol 1984, 5 (2) 139-146
http://www.ajnr.org/content/5/2/139

Changing Topographic Patterns of Human Cerebral Blood Flow with Age Measured by Xenon CT

Hisao Tachibana[1]
John S. Meyer[1]
Hiroyuki Okayasu[1]
Prasab Kandula[2]

Changes in cerebral blood flow with age have been of long-standing interest. A study of 20 normal, healthy, right-handed volunteers 20–100 years old using a noninvasive method is reported. Local cerebral blood flow (LCBF) and partition coefficients (Lλ) were measured during inhalation of 35% stable xenon gas and serial computed tomographic (CT) scanning (CT-CBF). Throughout CT-CBF measurements, subjects lay comfortably at rest, with eyes closed and ears unplugged. Environmental stimulation was limited to ambient light and only those sounds unavoidable during CT scanning. LCBF values were correlated with advancing age by cross-sectional analysis. Relatively higher LCBF values were measured bilaterally in the cortex of occipital and frontal lobes; no significant differences were noted between left and right hemispheres. Significant age-related declines in LCBF values were observed for all cortical and subcortical gray and white matter regions of interest examined ($p < 0.001$ for all three regions). Age-related declines were steepest in the cortex of the frontal lobes, particularly prefrontal cortex, caudate, putamen, and lentiform nuclei. Speech and visual cortical regions, functionally active throughout the normal life span, showed less age-related decline compared with all other regions, particularly prefrontal. So-called "hyperfrontality," ratio of mean flow values for frontal cortex to mean pooled values for total cortex, became progressively reduced with age ($p < 0.01$).

Reductions in cerebral blood flow (CBF) have long been correlated with normal aging. The well known review of the world literature by Kety [1] in 1956 was the first attempt to assess relations between advancing age and declines in CBF and metabolism. His study suggested there are rapid decreases in CBF values during early adolescence, followed by slow but progressive declines throughout later adolescence and adult life. Early measurements in CBF in relation to aging were based on the nitrous oxide inhalation technique, a method that provides average values for CBF and metabolism. The method is invasive and requires both arterial and internal jugular venous puncture. It has a reproducibility error exceeding 10% and provides no regional information. To circumvent some of these methodologic disadvantages, a number of different modifications of the Fick principle have been evaluated over the ensuing 35 years.

The first methods assessed were the intracarotid injection of radionuclides ^{85}Kr [2] and ^{133}Xe [3]. Later techniques included intracarotid injection of hydrogen [4] and intravenous injections of ^{133}Xe [5]. Each technical improvement had different advantages and disadvantages. The greatest limitation of all these methods, when considering application of CBF measurements to elderly volunteers, was that all were relatively invasive, requiring carotid and/or jugular puncture or antecubital venous catheterization. Carotid and/or jugular puncture are usually limited to hospitalized patients undergoing concurrent angiographic examinations. Even the use of repeated antecubital intravenous ^{133}Xe injections may be found stressful among elderly volunteers. For these reasons, these methods have not been considered applicable among large groups of healthy volunteers representative of normal aging populations.

This article appears in the March/April 1984 issue of *AJNR* and the May 1984 issue of *AJR*.

Received April 19, 1983; accepted after revision September 26, 1983.

[1] Department of Neurology, Baylor College of Medicine, Houston, TX 77025, and Cerebrovascular Research Center, Veterans Administration Medical Center, 20002 Holcombe Blvd., Houston, TX 77211. Address reprint requests to J. S. Meyer.

[2] Department of Radiology, Baylor College of Medicine, Houston, TX 77025, and Radiology Service, Veterans Administration Medical Center, Houston, TX 77211.

***AJNR* 5:139–146, March/April 1984**
0195–6108/84:0502–0139 $00.00

The ^{133}Xe inhalation method [6, 7] for measuring regional CBF (rCBF) has the advantage of being completely noninvasive, but it also has the disadvantage of assuming that tissue-blood partition coefficients (Lλ) remain normal, and it provides relatively poor resolution because of Compton scatter, tissue absorption, and tissue overlap. These disadvantages have been overcome by the introduction of the stable xenon CT-CBF method, which has high resolution (circa 80 mm^3) and measures both Lλ and local CBF (LCBF) for each region of interest (ROI).

A recent modification of the ^{133}Xe inhalation method for measuring rCBF has been used by Younkin et al [8]. Measurements with it indicate the high preadolescent CBF values, measured by others and included in Kety's data [1], were considerably overestimated by the nitrous oxide method. Excluding these overestimates for rCBF during adolescence, many other investigators [9–13] have confirmed reductions in CBF with advancing age among normal healthy adults, consistent with Kety's original conclusions.

Measurement of regional cerebral blood flow and metabolism has been made possible by positron emission tomography (PET) using ^{15}O-labeled O_2 and CO_2 and infusions of ^{18}Flabeled fluorodeoxyglucose. PET has the limitation of being enormously expensive, circa 4 million United States dollars for cyclotron and PET equipment, and it requires not only a cyclotron but a dedicated and sizable team of nuclear experts. The best resolution of PET is about 1 cm^3, whereas that of CT is less than 0.2 cm^3. Nuclear magnetic resonance has similar resolution, but reliable methods for CBF measurement with that equipment have yet to be attained.

Because of the two-dimensional nature and poor spatial resolution of the ^{133}Xe inhalation method, certain questions remain unanswered with respect to normal aging: Do Lλ values change with advancing age? Do LCBF values for white matter and subcortical regions of the brain share in age-related declines? Since LCBF values are calculated as the product of Lλ and the slope of clearance for xenon, if Lλ were to decrease with advancing age, this might spuriously account for apparent age-related declines of CBF. To clarify these issues, LCBF and Lλ were measured by the stable xenon CT-CBF method in normal healthy volunteers 20–100 years old. Seven to eight serial CT scans were obtained before and during inhalation of 35% stable xenon gas for 8–10 min. CT-CBF methodology takes advantage of the radiographic contrast properties of freely diffusible xenon and the high resolution and three-dimensional capabilities of the CT scanner [14–17].

Subjects and Methods

Subjects

The subjects comprised 20 normal, healthy, right-handed volunteers (15 men, five women) 20–100 years old: 20–30 years old (one subject); 31–40 (five); 41–50 (three); 51–60 (three); 61–70 (two); 71–80 (four); and 81–100 (two). Volunteers in good health were recruited from the Houston neighborhood by articles describing the project in local magazines and contacting local associations for the elderly. The subjects were all highly motivated, cooperative, self-supporting, and were carefully screened to confirm that they were all in excellent mental and physical health. All were free from any risk factors for stroke (hypertension, diabetes mellitus, hyperlipidemia, heart disease, or evidence of peripheral arteriosclerosis). None were taking drugs at the time of CBF measurement. None used addictive or "street drugs," were heavy smokers (i.e., nonsmokers or smoked less than one-half pack of cigarettes per day), or were consumers of alcohol (i.e., did not drink or consumed less than two drinks per month). All were found to be within normal limits after detailed general physical, neurologic, and psychologic examinations and standard laboratory tests. Psychologic testing was by the mini-mental scale or abbreviated modifications of it [18]. LCBF and Lλ measurements were carried out with the subjects awake but eyes closed and ears unplugged in a room with ambient low-level light. The examining room was quiet other than the noise of the CT scanner. Minimal encouragement and instructions by the investigators were carried out before CT.

Conversation with the subjects during the test was avoided. The electroencephalogram (EEG) was monitored throughout CT scanning and showed alpha and beta activity and confirmed the absence of sleep. The subjects were requested not to move or speak during the study. However, conversation with all subjects was active 15–18 min before the CT-CBF measurements. Efforts were made to acquaint each subject with the goals of the study and the nature of the methods and equipment involved. Informed consent was obtained in writing before participation. The informed consent and protocol describing these studies were approved by the Institutional Review Boards of Baylor College of Medicine and Veterans Administration Medical Center, Houston. Every effort was made for the subjects to feel relaxed and comfortable in an otherwise unfamiliar environment.

Methods

Detailed descriptions of methods used for measuring LCBF and Lλ values in small homogeneous volumes of gray or white matter using the EMI1010 CT scanner and 35% stable xenon inhalation have been described [14–17]. Oxygen was inhaled for 15 min before xenon inhalation to denitrogenate the body. After three serial scans before xenon inhalation, three to five xenon contrast scans were obtained beginning 2 min after inhalation of 35% stable xenon gas mixed with 65% oxygen. The xenon mixture was inhaled over an interval of 8–10 min. Concentrations of xenon were used that provided gradual and progressive buildup of alveolar xenon concentrations, but limitation to 35% minimized any subanesthetic effects.

Since xenon gas, like iodine, has a high atomic number, it absorbs x-rays, but, unlike iodine, it is a freely diffusible contrast agent. Tissue enhancements in selected voxels of interest, 80–220 mm^3, were directly measured by recording serial changes in Hounsfield units from the same selected voxels of homogeneous gray or white matter during the xenon buildup. End-tidal xenon gas concentrations (Pxe^s) were recorded throughout inhalation on a polygraph using a thermoconductivity gas analyzer. Since end-tidal and arterial gas concentrations have been shown to be in equilibrium, end-tidal xenon measurements were converted directly to Hounsfield units for blood using previously determined proportionality constants that corrected for different hematocrits.

Lλ and LCBF values were then calculated using a single-compartment analysis model and a computer program that provided least-square fitting to infinity of the saturation curves for both end-tidal (arterial blood) and brain tissue Hounsfield values, which were obtained from the measurements of both input functions. Blood pres-

TABLE 1: **Mean LCBF Values in Normal Healthy Volunteers**

Region	No. of Subjects	LCBF (ml/100 g brain/min)*	Lλ*	% Relative to Hemispheric Mean†
Cortical gray matter	20	73.1 ± 9.5	0.86 ± 0.04	. . .
Frontal cortex	19	73.9 ± 12.1	0.86 ± 0.06	+1.09
Prefrontal cortex	12	76.0 ± 14.0	0.88 ± 0.07	+3.97
Motor and premotor areas	12	74.0 ± 8.2	0.84 ± 0.06	+1.23
Anterior speech area	11	77.2 ± 8.1‡	0.85 ± 0.06	+5.61
Parietal cortex	9	69.6 ± 6.4‡	0.87 ± 0.08	−4.79
Temporal cortex	19	70.7 ± 10.4	0.85 ± 0.05	−3.28
Posterior speech area	12	73.6 ± 8.4	0.87 ± 0.06	+0.68
Occipital cortex	19	74.0 ± 9.4	0.84 ± 0.05	+1.23
Visual cortex	17	74.7 ± 9.2	0.85 ± 0.05	−2.19
Subcortical gray matter	17	69.7 ± 10.4	0.88 ± 0.06	−4.65
Basal ganglia	16	70.3 ± 13.0	0.86 ± 0.05	−3.83
Thalamus	17	69.4 ± 9.4	0.89 ± 0.06	−5.06
White matter	20	26.0 ± 4.9	1.38 ± 0.06	. . .
Frontal white matter	15	25.8 ± 6.2	1.42 ± 0.07	. . .
Parietal white matter	3	23.6 ± 0.7	1.32 ± 0.02	. . .
Temporal white matter	15	26.9 ± 5.2	1.38 ± 0.07	. . .
Occipital white matter	19	25.9 ± 4.1	1.37 ± 0.06	. . .
Internal capsule	15	24.6 ± 5.2	1.40 ± 0.09	. . .

* Σm LCBF (mLλ)/n, where mLCBF(mLλ) = mean of LCBF(Lλ) values for all individual regions of interest for each subject; n = number of subjects.

† Calculated by subtracting mean cortical (gray matter) flow values (73.1) from the mean values for each individual gray matter ROI and dividing the difference by the hemispheric mean values (73.1) and expressing results as percentage by multiplying by 100.

‡ $p < 0.05$.

sure, end-tidal partial pressure of carbon dioxide and oxygen, and electrocardiogram (ECG) and EEG were concurrently recorded on the polygraph.

Anatomic identification of various brain structures was performed with the aid of both neuroanatomic and CT atlases [19–23]. Cortical function ROIs were measured: prefrontal cortical area—Brodmann areas 9, 10, 11, and 12; motor and premotor area—areas 4 and 6; anterior speech area (Broca area)—areas 44 and 45; posterior speech area (Wernicke area)—area 22; and visual cortex—area 17. Data were analyzed on the basis mean ± SD and Student t test or F test.

Results

Mean Regional Patterns

Relatively high LCBF values were measured in the frontal and occipital cortices. Parietal cortex showed lower LCBF values than other regions of cortical gray matter under the recording conditions. LCBF values were higher for anterior speech ROIs compared with parietal cortex, where mean values were relatively reduced ($p < 0.05$) (table 1).

Mean LCBF values for subcortical gray matter showed trends to slightly lower values than cortical gray matter, but such differences did not reach levels of statistical significance. There were also no significant differences in mean LCBF values for different ROIs for white matter, although parietal white matter LCBF values also showed trends toward reduced values compared with other ROIs.

Mean Lλ values ± SD for cortical gray matter were 0.86 ± 0.04; for subcortical gray matter, 0.88 ± 0.06; and for white matter, 1.38 ± 0.06. There were no significant differences among gray matter Lλ values for different ROIs (table 1).

Interhemispheric Differences

As shown in table 2 there were no significant differences in mean LCBF values obtained from homologous ROIs in left and right cerebral hemispheres. This was a consistent finding for the entire series of ROIs measured from cortical gray matter, subcortical gray matter, and white matter for each of the hemispheres. A trend approaching statistical significance for increased regional LCBF values was noted between the anterior speech area on the left and corresponding Brodmann areas 44 and 45 of the right hemisphere by the paired t test ($p < 0.1$).

Analysis of Relations between Age and Mean LCBF Values

Figure 1 illustrates cross-sectional analysis of relations between advancing age and mean LCBF values for cortical and subcortical gray matter and white matter. All three regions showed highly significant negative correlations ($p < 0.001$). The slope of the regression line for mean white matter LCBF values was significantly less than for cortical gray matter ($p < 0.005$) and subcortical gray matter ($p < 0.001$) by the F test. There were no changes of Lλ values with advancing age in any ROIs. For example, the mean ± SD (0.86 ± 0.01) for gray matter in the 100- and 92-year-old male volunteers was the same as that measured among all the younger volunteers.

Table 3 displays regression lines correlating decreases of mean LCBF values with advancing age for different ROIs. In all ROIs except parietal white matter, significant age-related LCBF declines were apparent. Rates of decline with advancing age were most marked for both frontal lobes (particularly the prefrontal cortex, Brodmann areas 9, 10, 11, 12) and basal ganglia compared with declines in other regions. The

TABLE 2: **Comparison of Mean LCBF Values between Left and Right Hemispheres in Right-Handed Volunteers**

Region	No. of Subjects	Mean LCBF (ml/100 g brain/min)		Left/Right
		Left Hemisphere	Right Hemisphere	
Cortical gray matter	20	73.3 ± 10.1	72.8 ± 9.0	1.01
Frontal cortex	16	74.4 ± 10.0	73.5 ± 11.0	1.01
Prefrontal cortical area	8	71.9 ± 13.8	69.4 ± 13.6	1.04
Motor and premotor areas	10	67.4 ± 9.9	69.5 ± 8.7	0.97
Anterior speech area	9	78.3 ± 8.6	75.4 ± 7.9	1.04
Parietal cortex	7	69.0 ± 14.4	71.6 ± 5.6	0.96
Temporal cortex	17	71.3 ± 12.3	70.6 ± 10.4	1.01
Posterior speech area	7	75.6 ± 5.3	74.6 ± 9.0	1.03
Occipital cortex	18	74.3 ± 8.7	74.2 ± 9.6	1.00
Visual cortex	14	76.2 ± 10.7	75.8 ± 9.7	1.01
Subcortical gray matter	17	69.4 ± 10.9	70.1 ± 10.7	0.99
Basal ganglia	14	73.0 ± 12.7	70.4 ± 12.9	1.04
Thalamus	14	68.7 ± 10.8	70.0 ± 10.0	0.98
White matter	17	25.7 ± 4.6	26.1 ± 4.9	0.98
Frontal white matter	8	24.6 ± 8.0	25.6 ± 5.7	0.96
Parietal white matter	3	25.6 ± 3.8	22.7 ± 1.9	1.13
Temporal white matter	11	25.9 ± 6.2	27.5 ± 5.4	0.94
Occipital white matter	11	25.7 ± 4.7	25.0 ± 4.3	1.03
Internal capsule	11	25.7 ± 5.2	26.4 ± 5.5	0.97

Note.—No significant differences were apparent between left and right hemispheres in the resting nonactivated state by paired *t* test.

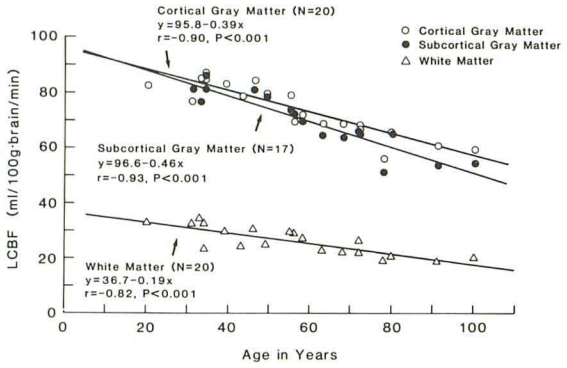

Fig. 1.—Age-related declines for LCBF values of cortical and subcortical gray matter and white matter in healthy volunteers 20–100 years old. Rate of decline for white matter is significantly less than for cortical ($p < 0.005$) and subcortical ($p < 0.001$) gray matter analyzed by *F* test.

decline with age in prefrontal cortical areas was significantly greater compared with the slopes for posterior speech regions and for visual cortex ($p < 0.05$ and $p < 0.01$, respectively). Age-related rates of LCBF decline for basal ganglia were significantly greater than those measured in parietal cortex, occipital cortex, and thalamus ($p < 0.05$, $p < 0.01$, and $p < 0.05$, respectively, estimated by the *F* test). The anterior and posterior speech areas together with the visual cortex showed least decline with advancing age. Likewise, age-related rates of LCBF declines for white matter were less prominent in the occipital lobe compared with rates of LCBF decline for other ROIs of white matter throughout both hemispheres.

Quantitative estimations of any enlargement in ventricular size and of cortical atrophy by measurements in designated regions are in progress to correlate them with measurements of LCBF. Estimates of the ventricular and/or cortical atrophy were made by three of the authors on a grading scale: 0 = no evidence of atrophy; 1 = mild; 2 = moderate; and 3 = severe. None showed severe cortical atrophy. Three, ages 72, 72, and 100 years (mean, 81 years), showed moderate atrophy; six, ages 31, 49, 63, 68, 78, and 91 (mean, 63 years), showed mild atrophy; and 11, ages 20, 33, 34, 34, 39, 43, 46, 55, 56, 58, and 80 (mean, 45 years), showed no atrophy. There is some preliminary evidence that brain atrophy with advancing age correlates with the decline in CBF. However there were many normal subjects up to age 80 without any brain atrophy, and there were some young individuals (aged 31) with brain atrophy. The decline in CBF with age appears to be more predictable than the usual estimates of brain atrophy made in routine interpretations of CT.

Effects of Advancing Age on "Hyperfrontality"

"Hyperfrontality" of CBF was originally described by Ingvar and Schwartz [24], who noted higher flows in the frontal region of resting human subjects measured by the ^{133}Xe method. Figure 2 illustrates the decline and eventual disappearance of hyperfrontality with advancing age, where the index of hyperfrontality has been expressed as a ratio of frontal cortex LCBF values to mean total cortical LCBF values.

Figure 3 illustrates, for an example, LCBF and Lλ values measured in the 100-year-old normal, healthy, right-handed male volunteer. LCBF values for caudate nuclei and frontal cortex are reduced compared with the high CBF values measured in similar ROIs among young healthy volunteers. In brief, the hyperfrontality of young normal subjects is no longer seen among the elderly.

TABLE 3: **Regression Lines Showing Decreases of LCBF Values with Advancing Age for Different Regions of Interest**

Region	No. of Subjects	Regression Line	Correlation Coefficient (r)	Significance (p)
Frontal cortex	19	$y = 101.8 - 0.50x$	−0.91	<0.001
Prefrontal cortical area	12	$y = 103.5 - 0.54x$	−0.90	<0.001
Motor and premotor areas	12	$y = 97.0 - 0.39x$	−0.90	<0.001
Anterior speech area	11	$y = 94.6 - 0.34x$	−0.67	<0.05
Parietal cortex	9	$y = 94.0 - 0.37x$	−0.87	<0.001
Temporal cortex	19	$y = 92.1 - 0.40x$	−0.81	<0.001
Posterior speech area	12	$y = 90.5 - 0.32x$	−0.81	<0.005
Occipital cortex	19	$y = 93.1 - 0.35x$	−0.83	<0.001
Visual cortex	17	$y = 92.2 - 0.31x$	−0.70	<0.005
Basal ganglia	16	$y = 103.3 - 0.57x$	−0.92	<0.001
Thalamus	17	$y = 92.7 - 0.39x$	−0.88	<0.001
Frontal white matter	15	$y = 36.2 - 0.19x$	−0.74	<0.005
Parietal white matter	3	...	−0.16	NS
Temporal white matter	15	$y = 37.6 - 0.19x$	−0.78	<0.005
Occipital white matter	19	$y = 32.4 - 0.11x$	−0.57	<0.02
Internal capsule	15	$y = 36.6 - 0.20x$	−0.80	<0.001

Note.—Rates of LCBF decline with advancing age are more marked for frontal lobes, particularly prefrontal cortex, and basal ganglia compared with rates of declines for other regions. NS = not significant.

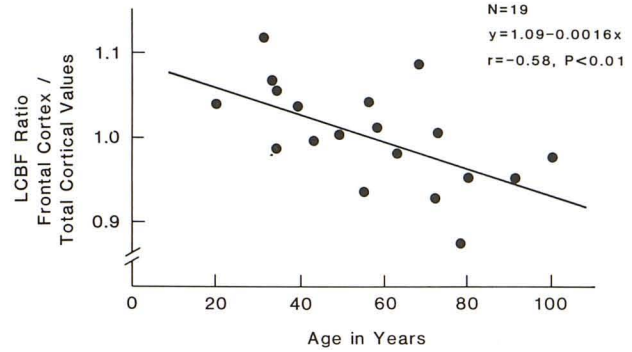

Fig. 2.—Disappearance of hyperfrontality with advancing age. Indices of LCBF hyperfrontality were calculated as ratios for frontal cortex to mean pooled values for total cortical LCBF values.

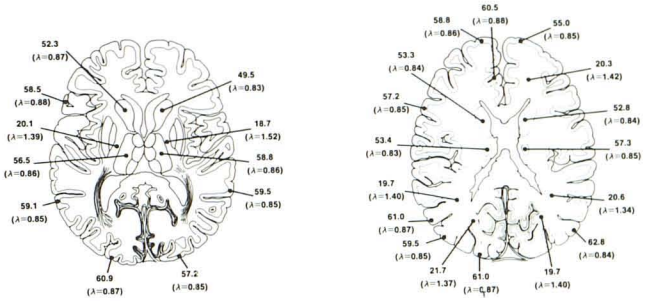

Fig. 3.—LCBF and Lλ values measured in 100-year-old normal, healthy, right-handed male volunteer resting in decubitus position with eyes closed in lighted laboratory with occasional verbal reassurance. End-tidal P_{CO_2} = 33.03 mm Hg; blood pressure = 150/90 mm Hg. Lower (*left*) and upper (*right*) sections. Neurologic and mental status were normal. There were no risk factors. All Lλ values are normal. LCBF values are diffusely reduced but to relatively greater degree in caudate and frontal cortex when compared with values for young normal volunteers. Hyperfrontality of CBF characteristic of young normal subjects is not seen.

Discussion

Relative high mean LCBF values for frontal cortex, with relatively low mean LCBF values for parietal cortex, have been demonstrated by the CT-CBF method in normal healthy volunteers when recorded in the awake, quiet, resting state with both eyes closed and both ears unplugged. These findings are consistent with previous reports measured by the ^{133}Xe inhalation method [25–27].

In addition, occipital cortex, particularly visual cortex, showed relatively high mean LCBF values despite the fact that the eyes were closed. This is taken to mean that measurements made in a lighted room, even with both eyelids closed, result in some stimulation of visual pathways. This is consonant with the well known EEG phenomenon where photic driving of EEG activity in the occipital cortex is best shown with the eyes closed.

In our study, interhemispheric LCBF asymmetries for homologous regions were not detected. Previous studies from this laboratory have reported similar symmetries of hemispheric flow under similar resting conditions measured by ^{133}Xe inhalation [26]. However, under conditions of behavioral activation, including visual and auditory stimulation such as talking and listening to others speak, marked asymmetric rCBF increases resulted. The most marked increases were seen in the visual cortex and dominant speech regions. Likewise, increases in motor regions during exercises of the hand have been measured by both ^{133}Xe and stable xenon CT-CBF methods [9, 16, 26].

Earlier studies of CBF [9, 13, 25–30] and/or metabolism [28, 31–33] in normal subjects measured in the "resting" state have produced conflicting reports with respect to left-right hemispheric asymmetries. Some investigators reported no significant differences between left and right hemispheres [13, 25–27, 29–32] and others found significant asymmetries [9, 28, 33]. Inconsistencies of such findings are best explained by differences in the so-called "resting states." For example,

resting CBF values are different whether the eyes are open or closed or whether there are repeated verbal instructions during the measurement. The resting conditions during rCBF or LCBF measurements by different authors vary with respect to amount of ambient light, noise, use of eye patches, use of ear plugs, degree of subject preparation and assurance, handedness, state of relaxation, state of motor activity, and motivation [30]. Conditions under which resting cerebral blood flow and metabolic patterns are measured should always be carefully defined, since LCBF and local metabolic patterns have been shown to vary under different conditions of sensory input, cognitive processing, and motor activity.

Age-related declines of mean cortical gray-matter flow values previously reported by the ^{133}Xe inhalation method [9–12] are confirmed by present CT-CBF measurements. Furthermore, validity is now provided for assumptions that Lλ values remain unchanged with advancing age. In addition, significant declines of mean LCBF values for subcortical gray and white matter associated with normal aging are now reported. LCBF for cortical and subcortical gray matter and for white matter are decreased, respectively, by 0.39, 0.46, and 0.19 ml/100 g brain/min/year with advancing age. Rates for gray-matter flow reduction per year of advancing age obtained by ^{133}Xe inhalation method were estimated to be 0.53 ml/100 g brain/min [9], which is comparable to mean CBF declines per year now reported by the CT-CBF.

Age-related declines for CBF measured in the gray matter of the cortex and subcortex are steeper than those measured for white matter. Lenzi et al. [34] likewise reported differences in the rates of decline of CBF and in the cerebral metabolic rates of O_2 for gray and white matter between younger and older groups of volunteers. The declines were greater for gray matter than for white matter. These conclusions were based on measurements made by the oxygen-15 inhalation method during PET scanning. Kuhl et al. [35] have also reported age-related declines in cerebral glucose utilization for cortex, caudate, thalamus, and white matter among normal subjects. These authors used the ^{18}[F]-2-fluoro-2-deoxyglucose method during PET scanning and reported that the rates of decline for gray and white matter glucose consumption with advancing age were less than for oxygen consumption. This is not surprising, since, as suggested by Kuhl et al. [35], oxygen and glucose consumption do not remain tightly coupled, and substrates other than glucose may be metabolized by the brain. There are also metabolic differences between gray and white matter. However, under normal circumstances, CBF is tightly coupled to cerebral oxygen consumption and functional activity.

When flow declines for different ROIs were compared, it was apparent that declines in gray matter flow are not homogeneous throughout the brain. Normal, age-related LCBF declines are most marked in the frontal lobes, particularly prefrontal regions, and basal ganglia, putamen, globus pallidus, and caudate nuclei. Regions resistant to LCBF declines associated with aging were the speech area and visual cortex.

Accelerated LCBF declines for prefrontal regions associated with normal aging have been reported by both cross-sectional and longitudinal analysis [12] using the ^{133}Xe inhalation method. Assuming that LCBF declines in frontal cortex and basal ganglia are associated with some functional impairment, they should correlate with minor decreases in judgment, insight, and speed of motor performance, which are known to be present in normal elderly people [37] and were recognizable, to a minor degree, in the older volunteers under discussion.

Age-dependent but selective degeneration of neuronal populations is known to occur in normal aging. Brody [37] reported from cross-sectional analysis of brains studied at autopsy from normal subjects that there were significant age-related neuronal losses in superior frontal gyrus, precentral gyrus, temporal gyrus, and striate cortex, but not in postcentral or inferior temporal cortex. Other workers [38] reported decreases in neuronal populations with advancing age in frontal poles, precentral gyrus, striate area, and cingulate gyrus.

These neuropathologic correlates are substantially consonant with measurements reported here, except that age-related LCBF declines for the visual cortex were not prominent. This exception may be accounted for by the recording conditions, which included unintentional visual stimulation. An alternative and/or additional explanation is that CBF reductions associated with advancing age are not necessarily from neuronal loss alone, but also from decreases in functional activity associated with altered neurotransmitter synthesis, which have been shown to decline with advancing age and to occur before neuronal loss [39].

To recapitulate, reductions of LCBF associated with normal aging may be considered to reflect not only numeric reductions of neuronal populations but also functional declines and decreases in metabolism in those that remain. Further, subclinical atherosclerosis of cerebral vessels is known to occur with advancing age and may contribute to CBF declines as well [10].

It is tempting to speculate regarding the relative resistance to age-related declines in LCBF measured in the visual cortex and speech areas. This may be accounted for by the continuing high functional activity of remaining cerebral neurons by continuing visual activity and frequent verbal communication, which are normal accompaniments of optimum healthy aging. Diamond [40] has reported that rat models raised in an enriched environment and supplied with numerous stimuli not only learn to solve maze tasks faster, but show measurable increases of brain weight plus dendritic branching at necropsy compared with age-matched, unstimulated controls. Evidence such as this may be adduced to advance the hypothesis that declines of LCBF values in normal aging may be minimized by sustained activity and optimal stimulation [41, 42].

Other regions showing prominent declines of LCBF with advancing age are the basal ganglia. Normal aging is known to be accompanied by slowness in performance of motor tasks and decreased motor dexterity [43, 44]. This correlates with age-related decreases in LCBF of basal ganglia, which in turn may well reflect declines in neurotransmitter synthesis, as reported by Carlsson [39] and McGeer et al. [45]. Ingvar [25] suggested that the hyperfrontal rCBF patterns noted under normal resting conditions reflect increased activity of

frontal lobes associated with stimulation of future behavior in response to anticipated tasks. Mazziotta et al. [31] reported that metabolic "hyperfrontality" was greatest in states of sensory activation and was least during sensory deprivation.

Declines of hyperfrontality associated with advancing age reported here are believed to reflect declines in neuronal function of both prefrontal cortex and basal ganglia. It is postulated that these declines may be enhanced by restricted activity and withdrawal commonly observed among the elderly.

REFERENCES

1. Kety SS. Human cerebral blood flow and oxygen consumption as related to aging. *J Chronic Dis* **1956**;3:478–486
2. Lassen NA, Munck O. The cerebral blood flow in man determined by the use of radioactive ^{85}Krypton. *Acta Physiol Scand* **1955**;33:30–49
3. Harper AM, Glass HI, Steven JL, et al. The measurement of local blood flow in the cerebral cortex from the clearance of Xe^{133}. *J Neurol Neurosurg Psychiatry* **1964**;27:255–258
4. Gotoh F, Meyer JS, Tomita M. Hydrogen method for determining cerebral blood flow in man. *Arch Neurol* **1966**;15:549–559
5. Agnoli A, Prencipe M, Priori AM, et al. Measurements of rCBF by intravenous injection of ^{133}Xe. A comparative study with intra-arterial injection method. In: Brock M, Fieschi C, Ingvar DH, Lassen NA, Schurman K, eds. *Cerebral blood flow: clinical and experimental results.* New York: Springer-Verlag, **1969**:31–34
6. Mallet BL, Veal N. Measurements of regional cerebral clearance rates in man using xenon inhalation and extracranial recording. *Clin Sci* **1965**;29:179–191
7. Obrist WD, Thompson HK, Wang HS, Wilkson WE. Regional cerebral blood flow estimated by ^{133}Xe inhalation. *Stroke* **1975**;6:245–256
8. Younkin DP, Reivich M, Jaggi J, Obrist WD, Delivoria-Papadopaulous M. Noninvasive method of estimating human newborn rCBF. *J Cereb Blood Flow Metab* **1982**;2:415–420
9. Meyer JS, Ishihara N, Deshmukh VD, et al. Improved method for non-invasive measurement of regional cerebral blood flow by ^{133}Xenon inhalation. Part 1: description of method and normal values obtained in healthy volunteers. *Stroke* **1978**;9:195–205
10. Naritomi H, Meyer JS, Sakai F, Yamaguchi F, Shaw T. Effects of advancing age on regional cerebral blood flow. Studies in normal subjects and subjects with risk factors for atherothrombotic stroke. *Arch Neurol* **1979**;36:410–416
11. Meyer JS, Shaw T. Cerebral blood flow in aging, the dementias and depression. In: Burrows GD, Kay DW, eds. *Handbook of studies of psychiatry and old age.* Amsterdam: Biomedical Press, **1984** (in press)
12. Shaw TG, Mortel KF, Meyer JS, Hardenberg J, Okabe T, Okayasu H. Four year longitudinal (prospective) analysis of age related changes in cerebral blood flow measured in normal healthy and risk factored volunteers. In: *Cerebrovascular diseases 4*, 11th Salzburg Conference, International Congress Series. Amsterdam: Excerpta Medica, **1983**:15–21
13. Melamed E, Lavy S, Bentin S, Cooper G, Rinot Y. Reduction in regional cerebral blood flow during normal aging in man. *Stroke* **1980**;11:31–35
14. Meyer JS, Hayman LA, Yamamoto M, Sakai F, Nakajima S. Local cerebral blood flow measured by CT after stable xenon inhalation. *AJNR* **1980**;1:213–225, *AJR* **1980**;135:239–251
15. Meyer JS, Hayman LA, Nakajima S, Amano T, Lauzon P. Local cerebral blood flow and tissue solubility measured by stable xenon-enhanced computerized tomography. *Adv Neurol* **1981**;30:73–84
16. Meyer JS, Hayman LA, Amano T, et al. Mapping local blood flow of human brain by CT scanning during stable xenon inhalation. *Stroke* **1981**;12:426–436
17. Amano T, Meyer JS, Okabe T, Shaw T, Mortel KF. Stable xenon CT cerebral blood flow measurements computed by a single compartment–double integration model in normal aging and dementia. *J Comput Assist Tomogr* **1982**;6:923–932
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state," a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **1975**;12:189–198
19. Schaltenbrand G, Bailey P. *Introduction to stereotaxis with atlas of the human brain*, vol 2. Stuttgart: Springer-Verlag, **1959**
20. Naeser MA, Hayward RW. Lesion localization in aphasia with cranial computed tomography and the Boston diagnostic aphasia exam. *Neurology* (NY) **1978**;28:545–555
21. Gado M, Hanaway J, Frank R. Functional anatomy of the cerebral cortex by CT. *J Comput Assist Tomogr* **1979**;3:1–19
22. Shipps FC, Jones JM, D'Agostino A. *Atlas of brain anatomy for CT scans.* Springfield, IL: Thomas, **1977**
23. Matsui T, Hirano A. *An atlas of the human brain for computerized tomography.* Tokyo: Igaku-Shain, **1978**
24. Ingvar DH, Schwartz M. Blood flow patterns induced in the dominant hemisphere by speech and reading. *Brain* **1974**; 97:273–288
25. Ingvar DH. "Hyperfrontal" distribution of the cerebral gray matter flow in resting wakefulness; on the functional anatomy of the conscious state. *Acta Neurol Scand* **1979**;60:12–25
26. Meyer JS, Sakai F, Naritomi H, Grant P. Normal and abnormal patterns of cerebrovascular reserve tested by ^{133}Xe inhalation. *Arch Neurol* **1978**;35:350–359
27. Knopman DS, Rubens AB, Klassen AC, Meyer MW, Niccum N. Regional cerebral blood patterns during verbal and nonverbal auditory activation. *Brain Lang* **1980**;9:93–112
28. Finklestein S, Alpers NA, Ackerman RH, et al. Positron imaging of the normal brain: regional patterns of cerebral blood flow and metabolism. *Trans Am Neurol Assoc* **1980**;105:8–10
29. McHenry LC Jr, Merory J, Bass D, et al. Xenon-133 inhalation method for regional cerebral blood flow measurements: normal values and test-retest results. *Stroke* **1978**;9:396–399
30. Risberg J, Halsey JH, Wills E, Wilson EM. Hemispheric specialization in normal man studied by bilateral measurements of regional cerebral blood flow. *Brain* **1975**;98:511–524
31. Mazziotta JC, Phelps ME, Miller J, et al. Tomographic mapping of human cerebral metabolism: normal unstimulated state. *Neurology* (NY) **1981**;31:503–516
32. Phelps ME, Mazziotta JC, Kuhl DE, et al. Tomographic mapping of human cerebral metabolism: visual stimulation and deprivation. *Neurology* (NY) **1981**;31:517–529
33. Mazziotta JC, Phelps ME, Carson RE, Kuhl DE. Tomographic mapping of human cerebral metabolism: sensory deprivation. *Ann Neurol* **1982**;12:435–444
34. Lenzi GL, Frackowiak RSJ, Jones T, et al. $CMRO_2$ and CBF by the oxygen-15 inhalation technique. Results in normal volunteers and cerebrovascular patients. *Eur Neurol* **1981**;20:285–290
35. Kuhl DE, Metter EJ, Riege WH, Phelps ME. Effects of human aging on patterns of local cerebral glucose utilization determined by the ^{18}F-fluorodeoxyglucose method. *J Cereb Blood Flow Metab* **1982**;2:163–171
36. Smith BH, Sethi PK. Aging and the nervous system. *Geriatrics* **1975**;30:109–112
37. Brody H. An examination of cerebral cortex and brain stem aging. In: Terry RD, Gershon S, eds. *Neurobiology of aging.* New

York: Raven, **1976**:177–181
38. Colon EJ. The elderly brain. A quantitative analysis of the cerebral cortex in two cases. *Psychiatr Neurol Neurochir* **1972**;75:261–270
39. Carlsson A. Aging and brain neurotransmitters. In: Crook T, Gershon S, eds. *Strategies for the development of an effective treatment for senile dementia.* New Canaan, CT: Mark Powley, **1981**:93–104
40. Diamond M. Extensive cortical depth measurements and neuron size increases in the cortex of environmentally enriched rats. *J Comp Neurol* **1967**;131:357–364
41. Bortz WM. Disuse and aging. *JAMA* **1982**;248:1203–1208
42. Hamburger V, Oppenheim RW. Naturally occurring neuronal death in vertebrates. *Neurosci Commentaries* **1982**;1:39–55
43. Barbeau A. Aging and the extrapyramidal system. *J Am Geriatr Soc* **1973**;21:145–149
44. Hassler R. Extrapyramidal control of the speed of behaviour and its change by primary age process. In: Welford AT, Birren JE, eds. *Behavior, aging and the nervous system.* Springfield, IL: Thomas, **1965**;284–306
45. McGeer PL, McGeer EG, Suzuki JS. Aging and extrapyramidal function. *Arch Neurol* **1977**;34:33–35