Regional Cerebral Blood Flow and Oxygen Consumption in Human Aging

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SUMMARY **The oxygen-15 continuous inhalation technique and PET were used to study the age-related changes in regional CBF and $CMRO_2$. Twenty-seven patients, aged 19 to 76 years, free of any history of cerebral disease and vascular risk factors were examined in "resting state."**

CBF, $CMRO_2$ and oxygen extraction fraction (OEF) values were calculated in seven different brain structures as well as in mean gray matter. Left-right ratios were also computed for all symmetrical structures analyzed.

Mean gray CBF, but not mean gray $CMRO_2$, decreased linearly with age ($p < 0.02$). However, when younger subjects (≤50 yrs) were compared to older subjects (>50 yrs), an age-related matched decrease in CBF and $CMRO_2$ was observed in mean gray matter (18% and 17%, $p < 0.05$) and in all gray matter regions analyzed, particularly in frontal, temporo-sylvian and parieto-occipital cortex. White matter CBF and $CMRO_2$ remained remarkably stable with advancing age.

Although the possibility of methodological artifacts was considered, we favor progressive loss of cortical neurones and/or diminished activity of those remaining to explain our findings. In addition, age-related changes in cognitive activities might also be involved.

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DESPITE NUMEROUS STUDIES,[1-14] the effects of aging on cerebral circulation and metabolism still remain largely unsettled. Studies on global hemispheric cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) have so far provided discrepant results: some[3-6] concluded that CBF and $CMRO_2$ did not decrease with advancing age except when vascular risk factors were present, while other authors[1,2] found a parallel decline in both CBF and $CMRO_2$. These discrepancies may be partially explained by different criteria for normality used. In his review on this subject, Kety[7] favored the idea that there was a rapid fall of both CBF and $CMRO_2$ around puberty which continued to the third decade and was followed by a more gradual decline in middle and old age.

Although atherosclerosis of the cerebral vessels was held by some[3-6] as the main factor causing the $CMRO_2$ decrease observed in human aging (as a consequence of long-standing diminished perfusion and oxygen supply), others,[1,2,7] in view of the lack of any consistent increase in the oxygen arteriovenous difference, considered concomitant cellular alterations and/or loss due to aging per se.

More recently, ^{133}Xe non-invasive studies[8-14] repeatedly reported a decline in *mean* gray CBF with age, but did not provide any clue to the above question since $CMRO_2$ was not concurrently measured.

In addition, very little is still known concerning the *regional* CBF and $CMRO_2$ and their interrelationship in normal human aging. It is conceivable that the effects of aging affect preferentially circumscribed brain areas.

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The recent development of positron emission tomography (PET) and the ^{15}O continuous inhalation technique[15] provides the opportunity to obtain quantitative tomographic maps of CBF and $CMRO_2$. We felt it important to apply this new tool to study the effects of normal human aging on both hemispheric and regional CBF and $CMRO_2$.

Patients and Methods

1) Patients

Twenty seven hospitalized patients, free of any history of brain disease and of general vascular risk factors (that is, no history of arterial hypertension, diabetes or hypercholesterolemia) were studied. There were 19 males and 8 females, all but one right-handed and aged 19 to 76 years (mean 46 ± 15). Although no formal psychological tests were performed, a careful inquiry from family about intellectual decline and a neurological assessment by an experienced academic neurologist ruled out overt dementia in this patient sample.

For data analysis, the patients were divided into two groups: the "young" group, consisting of 18 subjects (13 males and 5 females) aged 19 to 50 years, and the "old" group, consisting of 9 subjects (6 males and 3 females) aged 55 to 76 years. The age limit of 50 years was chosen to allow comparison with previous reports on the effects of aging on CBF and $CMRO_2$, since most of these used the same (arbitrary) threshold.

2) Methods

The ^{15}O continuous inhalation technique was employed. The principle[15] and the mathematical model[15,16] on which it is based, as well as its theoretical[17,18] and statistical[19,20] limitations, have been published in detail elsewhere. Its validity has been confirmed by experimental studies[21,22] and by results obtained in normal subjects.[23,24] Thus, in this context, only the

details pertaining to the present work will be described.

In this entire group, the PET study was performed in "resting" state. Before the study, each subject was informed about the procedure to minimize anxiety and was asked to keep the eyes closed but to avoid sleeping or moving. The ears were not plugged. During the study external stimuli were reduced to a minimum; the subject was not touched or spoken to; the only intermittent noise was the sound of motion of the positron detectors.

Each subject was studied in the supine position. The subject's head was positioned by means of a laser beam projected on the lowest of three parallel skin lines previously marked at 2, 4 and 6 cm above and drawn at a 5° angle rostral to the orbito-meatal line (OM).

The patient continuously inhaled the radioactive gas at tracer doses by means of a standard oxygen mask; a connection with a CO_2 analyzer (Beckmann LB2) allowed the monitoring of end-tidal CO_2 content during the study.

$C^{15}O_2$ and $^{15}O_2$ scans, each of them at the three parallel planes, were performed only after equilibrium (that is, constant radioactivity levels) was reached. Immediately following the end of each scan, an arterial blood sample was drawn by direct puncture of the femoral artery, which had been previously anesthetized locally (lidocaine). Duplicate measurements of $H_2{}^{15}O$ and Hb-$^{15}O_2$ as well as $PaCO_2$, PaO_2, pH, hematocrit and total oxygen content (Lex O_2 Con device) were obtained in most of studies and averaged for further use.[24]

The tissue ^{15}O activity was detected by an ECAT II (Ortec) single slice tomograph, with a spatial resolution of 16 × 16 mm in the lateral plane and 19 mm in the axial one (slice thickness). Tissue ^{15}O concentration was carefully quantified relatively to arterial concentration, by means of: 1) correction for attenuation using ^{68}Ge-^{68}Ga transmission scanning performed on the same planes prior to study; 2) normalization of detector sensitivity; and 3) cross calibration between the ECAT system and well-counter. The $C^{15}O_2$ and $^{15}O_2$ images were reconstructed by a medium filtered back-projection algorithm, and thereafter transformed, pixel by pixel, into CBF, OEF (oxygen extraction fraction) and $CMRO_2$ images using published equations.[5, 16] Thus, for each study, a set of 3 images, each one for CBF, OEF and $CMRO_2$, was obtained, for a total of 9 images.

In this work, only the planes at OM + 4 cm and OM + 6 cm were analyzed; the lower level (OM + 2 cm) was not used because of marked and variable partial averaging of bony vascular structures at the base of skull.

3) Data Analysis

Regional CBF, OEF and $CMRO_2$ were calculated, using a standardized protocol[24] by means of 22 bilateral symmetrical and 4 single medial circular (4 cm^2) ROIs. The ROIs were first placed on the CBF image and then automatically copied on corresponding $CMRO_2$ and OEF images. Symmetrical positioning of ROIs was achieved by mirror-copying of one-sided ROIs with respect to the vertical axis, the proper location of the latter being verified by 20% isocountour superimposition (ROI 1 in fig. 1). The ROI value used was the mean of 113 matrix pixels contained within its boundaries.

Ten symmetrical ROIs and 2 medial ones were placed on the OM + 4 cm plane, and 12 symmetrical ROIs and 2 medial ones were used on the OM + 6 cm plane (see fig. 1 for details). Thus, regional values were obtained on 7 different brain structures (frontal, temporo-sylvian, sensory-motor, parieto-occipital, occipital cortex, thalamus and centrum semiovale), each of them being calculated as the average of 2 to 6 ROIs. In addition, frontal and occipital values were also analyzed separately as lateral and medial cortex.

Mean gray CBF, OEF and $CMRO_2$ were calculated by averaging all gray structures analyzed (24 ROIs), and global and regional right to left ratios were computed for each symmetrical structure. Finally, frontal to sensory-motor cortex ratios were obtained by divid-

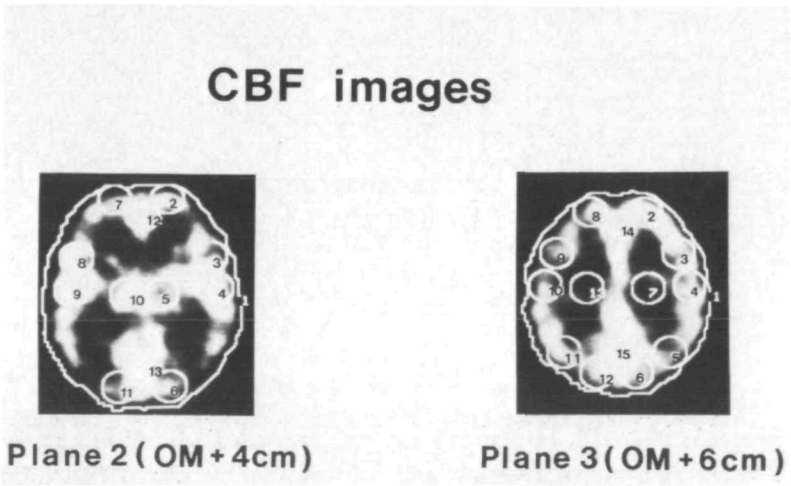

FIGURE 1. *Twenty six circular ROIs (4 cm^2) were used for regional data analysis. Regional CBF, $CMRO_2$ and OEF values were obtained for 7 different cerebral structures, averaging a varying number of ROIs, as following: 1) Frontal cortex (2, 7, 12 on plane 2 and 2, 8, 14 on plane 3), also considered as lateral (2, 7 on plane 2 and 2, 8 on plane 3) and medial (12 on plane 2 and 14 on plane 3) structures. 2) Temporo-sylvian cortex (3, 4, 8, 9 on plane 2). 3) Sensory-motor cortex (3, 4, 9, 10 on plane 3). 4) Parieto-occipital cortex (5, 11 on plane 3). 5) Occipital cortex (6, 11, 13 on plane 2 and 6, 12, 15 on plane 3) also considered as lateral (6, 11 on plane 2 and 6, 12 on plane 3) and medial (13 on plane 2 and 15 on plane 3) structures. 6) Thalamus (5, 10 on plane 2). 7) Centrum semiovale (7, 13 on plane 3).*

ing frontal cortex values by corresponding sensory-motor values. Linear regression and t-test were used for data analysis.

Results

No significant differences in $PaCO_2$, arterial oxygen content or arterial blood pressure were observed between young and aged subjects (see table 1).

Mean Gray Values

Mean gray CBF ($\overline{CBF}g$) was significantly linearly correlated with age ($p < 0.02$) (that is, the null hypothesis was outside the 95% confidence limits of the calculated slope), whereas mean gray $CMRO_2$ ($\overline{CMRO_2}g$) was not ($p > 0.10$) (fig. 2).

Despite this lack of significant linear correlation for $\overline{CMRO_2}g$, the comparison between the two groups by t-test showed that both $\overline{CBF}g$ and $\overline{CMRO_2}g$ were similarly affected: $\overline{CBF}g$ declined from 50.7 ± 10 ml/100 ml/min to 41.8 ± 9 ml/100 ml/min (18%, $p < 0.05$) and $\overline{CMRO_2}g$ declined from 4.1 ± 0.7 ml/100 ml/min to 3.4 ± 0.8 ml/100 ml/min (17%, $p < 0.05$) (table 2, fig. 3). Separation according to age into 3 samples of 9 subjects each, provided similar trends of decrease with age.

Mean gray OEF was 0.483 ± 0.09 in the "young" group and 0.51 ± 0.10 in the "old" group, showing only an insignificant increase of 7% (table 2).

White Matter Values

As shown in table 2 and figure 3, white matter CBF, $CMRO_2$ and OEF did not differ between the two groups.

Regional Gray Matter Values

In the "old" group, all gray matter structures showed a decrease in rCBF and $rCMRO_2$, ranging from 10% to 26% and from 10% to 25%, respectively (table 2, fig. 3). However, only in frontal, temporo-sylvian and parieto-occipital cortex, did the decrease in both CBF and $CMRO_2$ (ranging from 18% to 26%) reach statistical significance (table 2, fig. 3). The CBF and $CMRO_2$ decrease was more marked in lateral than in medial frontal cortex, whereas the opposite was true in occipital cortex (table 2). The less prominent decrease in CBF and $CMRO_2$ was observed in sensory-motor and lateral occipital cortex (table 2).

Frontal to sensory-motor cortex ratio decreased from 1.14 ± 0.17 in the "young" group to 1.01 ± 0.14 in the "old" group for CBF ($0.06 > p > 0.05$) and from 1.11 ± 0.16 to 1.01 ± 0.11 for $CMRO_2$ ($p > 0.10$).

TABLE 1 *Miscellaneous Data in "Young" and "Old" Subjects*

	"Young" (n = 18)	"Old" (n = 9)
$PaCO_2$ (mm Hg)	37.1 ± 2.0	37.5 ± 2.8
Total arterial oxygen content (ml/100 ml)	0.175 ± 0.03	0.164 ± 0.02
Systolic pressure (mm Hg)	125 ± 16	135 ± 7.5
Diastolic pressure (mm Hg)	78 ± 12	85 ± 11
Age	38 ± 10	63 ± 6

"Young" group < 50 years, n = 18.
"Old" group > 50 years, n = 9.
Mean ± SD.

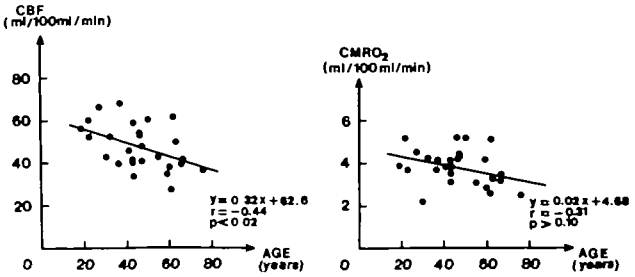

FIGURE 2. *Plot of mean gray CBF and mean gray $CMRO_2$ values versus age in 27 control subjects. Significant linear relationship with age was found only for CBF* ($p < 0.02$).

Age-related correlations (linear regression) were significant only in frontal ($p < 0.01$) and temporo-sylvian cortex ($p < 0.01$) for CBF and only in temporo-sylvian cortex ($p < 0.02$) for $CMRO_2$ (see table 3).

Right to Left Ratios

CBF and $CMRO_2$ right to left ratios for all the structures analyzed are shown in table 4. No significant asymmetry was found for $\overline{CBF}g$ and $\overline{CMRO_2}g$. Although frontal CBF and $CMRO_2$ and parieto-occipital $CMRO_2$ were found significantly higher on the left side for the entire group of subjects, no significant differences between young and old subjects in their regional right-left ratios were found (table 4).

Discussion

Significant negative correlations ($p < 0.02$) were found between $\overline{CBF}g$ and advancing age, with a decrease of 3.2 ml/100 ml/min/decade, whereas the correlation between $\overline{CMRO_2}g$ and age did not reach statistical significance, presumably because of the spread in individual values (fig. 2). However, further analysis by age groups showed a significant decrease in $\overline{CMRO_2}g$ (17%, $p < 0.05$) in the "old" group with respect to the "young" one, that was matched to the $\overline{CBF}g$ decrease (18%, $p < 0.05$). Thus, the decrease in $CMRO_2$ with age appears true, although not strictly linearly correlated with age.

No significant age-related changes either in global or in regional oxygen extraction fraction (OEF) were observed. In white matter, CBF and $CMRO_2$ did not show any tendency toward a decrease with advancing age. In the "old" group, rCBF and $rCMRO_2$ were found decreased in all gray structures analyzed, with a more marked and significant decrease in frontal, temporo-sylvian and parieto-occipital regions. Right-left symmetry in $\overline{CBF}g$ and $\overline{CMRO_2}g$ was found, but higher $rCMRO_2$ in left frontal and parieto-occipital cortex and higher rCBF in left frontal cortex were observed in both age groups.

Before discussing the physiological relevance of these findings, the possibility that they might be affected by methodological limitations must be considered.

TABLE 2 *Global (mean gray matter) and Regional CBF, $CMRO_2$ and OEF Values (mean ± SD) in 27 Control Subjects, Also Divided into Two Groups with Respect to Age*

Regions	CBF			$CMRO_2$		
	All	"Young" group	"Old" group	All	"Young" group	"Old" group
Mean gray matter	47.7 ± 10.9	50.7 ± 10.3	41.8 ± 9 9*	3 9 ± 0 8	4.1 ± 0.7	3 4 ± 0.8*
Frontal	46.3 ± 10.4	49 9 ± 10.3	39 4 ± 6.9†	3 6 ± 0.7	3.9 ± 0 7	3.1 ± 0 7†
Lateral frontal	43.4 ± 10.1	46.6 ± 10.2	40.0 ± 6.5†	3.4 ± 0 7	3.7 ± 0.7	3.0 ± 0.6†
Medial frontal	52.6 ± 12.7	55 7 ± 12.9	46.5 ± 10 3	3.9 ± 1.0	4.2 ± 0.9	3.4 ± 1.0*
Temporo-sylvian	54.7 ± 16.8	59.9 ± 16.2	44.4 ± 13.5†	4.4 ± 1 2	4.8 ± 1.0	3.6 ± 1 0‡
Sensory-motor	42.5 ± 10.1	44.0 ± 9 1	39.5 ± 11.6	3 4 ± 0.7	3.5 ± 0.6	3 1 ± 0.7
Parieto-occipital	40.0 ± 10 2	45.0 ± 10 3	35.9 ± 7.0*	3.5 ± 0 8	3.7 ± 0 7	3.0 ± 0.8*
Occipital	53.9 ± 13.2	56.5 ± 13.5	48.6 ± 11.5	4 7 ± 1.1	4 9 ± 1.1	4.2 ± 1.1
Lateral occipital	47 5 ± 11 9	49.2 ± 12 3	44 1 ± 10.2	4.2 ± 1.0	4.3 ± 1.1	3.9 ± 0.9
Medial occipital	66.0 ± 19.2	70 3 ± 20 5	57 5 ± 13 2	5.7 ± 1.6	6.1 ± 1 7	4.9 ± 1.2
Thalamus	43.6 ± 13.3	46 0 ± 12.0	38.8 ± 14.1	3 4 ± 0 9	3.5 ± 0.8	3.0 ± 1.0
White matter	24.7 ± 5.3	24.5 ± 4.1	25.0 ± 6.9	1 9 ± 0.4	1.9 ± 0.3	1.9 ± 0 6

"Young group ≤ 50 yrs, n = 18
"Old" group > 50 yrs, n = 9.
*$p < 0.05$.
†$p < 0.02$
‡$p < 0.01$ with respect to "young" group.

Among the theoretical limitation of the ^{15}O steady-state model, one is due to the tracer present in the cerebral blood volume[17] (correction for this variable, though possible,[17] was not undertaken here because of the additional scanning-time and exposure required), but there is no available evidence for a change in cerebral blood volume with age. Likewise, there is no known alteration in brain water content, and hence, in brain-blood water partition coefficient with aging in man.

A major technical limitation of PET is the partial volume effect.[25] This leads to inevitable and unpredictable averaging of gray and white matter, and results in an underestimation of the CBF and $CMRO_2$ values of gray matter and in an overestimation of those of white matter.[24] If the present study, as well as other reports[8, 14, 26] are correct in showing that the decrease in CBF and $CMRO_2$ with advancing age selectively affects gray matter and spares white matter, then our findings, as a result of this averaging effect, would underestimate true age-related changes in gray matter.

Conversely, simply because the PET technology cannot reliably differentiate cerebral from non-cerebral tissue or gray from white matter, the occurrence of cortical atrophy in aged subjects might result in a greater proportion of slowly or non-perfused tissue in the ROIs analyzed, and hence in an overestimation of the true age-related changes in gray matter CBF and $CMRO_2$. Since CT scans were not performed in our population, we cannot estimate if and how much cortical atrophy would have affected our data. Although

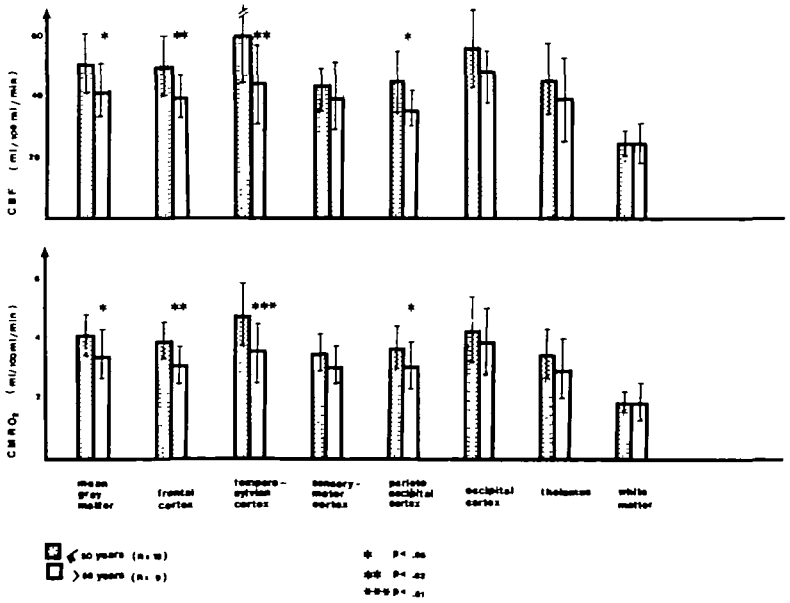

FIGURE 3. *Regional patterns of CBF and $CMRO_2$ in young and aged subjects. Mean values and one standard deviation are indicated for each brain region studied.*

TABLE 2 *(Continued)*

OEF		
All	"Young" group	"Old" group
0.49±0.10	0.48±0.09	0.52±0.10
0.48±0.10	0.47±0.09	0.50±0.10
0.48±0.10	0.47±0.10	0.51±0.10
0.47±0.10	0.46±0.10	0.48±0.11
0.49±0.11	0.48±0.11	0.52±0.10
0.48±0.09	0.47±0.09	0.50±0.10
0.50±0.09	0.49±0.09	0.53±0.10
0.53±0.10	0.52±0.10	0.55±0.11
0.54±0.11	0.52±0.11	0.56±0.11
0.53±0.11	0.53±0.10	0.53±0.11
0.46±0.10	0.45±0.10	0.48±0.09
0.46±0.08	0.45±0.08	0.48±0.08

several CT scan studies[27-30] suggested that normal aging may be accompanied by sulci widening, some histological studies[31,32] found that the thickness of the cortical ribbon remained unchanged with aging. Finally, the fact that our results are in agreement with earlier studies[1,2,8-14] that used CBF and $CMRO_2$ techniques largely insensitive to cerebral atrophy (because measurement of tissue volume is not needed in the calculations) would tend to further reduce the importance of such artifact.

In our group of normals without vascular risk factors, we found a moderate but significant parallel reduction in $\overline{CBF}g$ and $\overline{CMRO_2}g$ with aging (18% and 17%, respectively). In roughly similar population, Fazekas et al[1] and Scheinberg et al[2] reported an age-related decline in whole brain CBF and $CMRO_2$ of a magnitude close to that of our results; mean hemispheric CBF has been repeatedly shown to decrease with age in several ^{133}Xe non-invasive studies.[8-14]

It has been reported, however, that elderly subjects selected for their unusually healthy intellectual and physical state had hemispheric values not different from those of young subjects,[4,5] but that aged people with multiple vascular risk factors had decreased values.[3-5] The variability in social, intellectual and vascular conditions seen in aged people seems to be reflected in the observed variability in CBF and $CMRO_2$,[6] but, on the average, a decline in the latter variables has been generally accepted.[7]

The age-related decreases in gray matter CBF and $CMRO_2$ reported here are roughly similar to, although less prominent than, those previously published by Lenzi et al.,[26] who also used the ^{15}O steady-state technique and PET.

In addition, we found that white matter values were not affected by aging, in agreement with Lenzi et al' study[26] and with two ^{133}Xe rCBF studies.[8,14] Since the decline seems to affect only gray matter flow and metabolism, one could infer that glial cells are less involved by the aging process, as also suggested by histological data.[32]

Neuronal cell depopulation and/or diminished activity that are associated with normal human aging[31-33] stand out as the most likely hypothesis to explain the observed decrease in metabolic rate of oxygen, and, in turn, in perfusion.

This hypothesis is further borne out by our finding an essentially matched reduction in CBF and $CMRO_2$ in older subjects, as found also by Lenzi et al[26] and by most Kety-Schmidt technique studies,[1-4] indicating that the regulatory mechanism which adjusts oxygen supply to metabolic demand remains essentially unaffected by the aging process. However, relatively maintained $CMRO_2$ with decreased CBF, suggesting reduced perfusion as a primary factor, has been reported in atherosclerotic aged subjects.[5] Although it remains conceivable that a *primary* CBF reduction, if long-standing, may progressively lead to *secondary* metabolic alterations and reduction in $CMRO_2$, some increase in the OEF should nevertheless result from this process, particularly in its early phase; however, the OEF increase in the old group (7%) found in the present study was not significant, suggesting that primary

TABLE 3 *Linear Regression ($y = ax + b$) of Regional CBF and $CMRO_2$ Versus Age*

	CBF			$CMRO_2$		
Regions	a	b	r	a	b	r
Mean gray matter	−0.32	62.6	−0.44*	−0.01	4.68	−0.31
Frontal	−0.36	63.3	−0.52†	−0.02	4.48	−0.36
Lateral frontal	−0.31	57.8	−0.47†	−0.01	4.05	−0.27
Medial frontal	−0.42	72.1	−0.50*	−0.02	5.04	−0.35
Temporo-sylvian	−0.61	82.8	−0.55†	−0.03	6.01	−0.45*
Sensory-motor	−0.15	49.3	−0.22	−0.01	3.70	−0.15
Parieto-occipital	−0.25	53.7	−0.37	−0.01	4.13	−0.26
Occipital	−0.29	67.2	−0.33	−0.02	5.46	−0.21
Thalamus	−0.30	57.6	−0.34	−0.01	3.95	−0.22
White matter	−0.005	24.9	−0.02	−0.002	1.78	−0.01

*$p < 0.02$.
†$p < 0.01$.
$n = 27$.

TABLE 4 *Global (mean gray matter) and Regional Right to Left Ratios (mean ± SD) in 27 Control Subjects, Also Divided into Two Groups with Respect to Age*

Regions	CBF			$CMRO_2$		
	All	"Young" group	"Old" group	All	"Young" group	"Old" group
Mean gray matter	0.994 ± 0.05	0.998 ± 0.06	0.988 ± 0.04	0.990 ± 0.05	0.992 ± 0.05	0.989 ± 0.04
Frontal	0.970 ± 0.07*	0.968 ± 0.06	0.974 ± 0.07	0 964 ± 0.06†	0.959 ± 0.07†	0.974 ± 0 06
Temporo-sylvian	1.003 ± 0.11	1.009 ± 0.12	0.992 ± 0 08	1.011 ± 0.09	1 015 ± 0.10	1.003 ± 0.08
Sensory-motor	1.003 ± 0.10	0.972 ± 0.08	0.993 ± 0.10	0.977 ± 0.08	0.972 ± 0.08	0.993 ± 0.10
Parieto-occipital	0.967 ± 0.12	0.947 ± 0.13	0.984 ± 0.06	0.959 ± 0.11*	0.947 ± 0.13	0.984 ± 0 06
Occipital	1.018 ± 0.09	1.033 ± 0.08	0.997 ± 0.09	1.021 ± 0.08	1 033 ± 0.08	0.997 ± 0.09
Thalamus	0.995 ± 0.15	0.979 ± 0 14	1.027 ± 0.17	1.001 ± 0.13	0.975 ± 0.12	1.053 ± 0 14
White matter	0.998 ± 0.12	0.983 ± 0.11	1.028 ± 0.13	1.002 ± 0.14	0.978 ± 0.12	1.058 ± 0 17

"Young" group ≤ 50 yrs, n = 18.
"Old" group > 50 yrs, n = 9.
*$p < 0.05$.
†$p < 0.02$.
Significantly different from 1.00.

hypoperfusion was not an important factor. Rather, our data would indicate that the observed CBF declines with aging are largely or exclusively a consequence of reduced metabolic needs.

Consonant with earlier PET studies of cerebral glucose metabolism,[34] and with ^{133}Xe non-invasive rCBF studies,[13, 14] we found no right-left asymmetry in overall gray CBF and $CMRO_2$ either in young or in aged subjects studied with eyes closed and ears unplugged; other PET studies, not specifically addressing the aging issue, also reported no asymmetry in cerebral metabolic rate of glucose (CMRglu) in young subjects,[35, 36] except perhaps in conditions of marked sensory deprivation.[36]

On a regional basis, however, we found a small but significant left prevalence for both CBF and $CMRO_2$ in the frontal cortex, as reported in the ^{133}Xe inhalation rCBF studies of Thomas et al[11] and Gur et al[37] and apparent also in the ^{15}O steady-state PET study of Lenzi et al,[26] and a left prevalence for $CMRO_2$ in the parieto-occipital region. In Finklestein et al' PET study,[38] it was the left perisylvian area that had higher flow and metabolism than the right, but the environmental conditions may have been different from those of our study. Although the reasons for such asymmetries — anatomical, functional or artifactual — remain obscure, the latter were not significantly affected by the aging process in our population.

In general agreement with most earlier studies using PET[26, 34] or ^{133}Xe inhalation,[10, 39] we found that the age-related decline in grey matter rCBF and $rCMRO_2$ was diffuse but affected preferentially the frontal and temporo-sylvian cortex, as well as the parieto-occipital regions. On the other hand, white matter appeared remarkably spared by the aging process. Although it is difficult to precisely estimate to what extent regional variations in the gray-white ratio or/and brain atrophy may, through the partial volume effects, have affected our regional CBF and $CMRO_2$ data, the fact that neuronal loss has been found maximal in prefrontal, precentral and temporal cortex[31-33] would lend some indirect support to our findings.

Alternatively, the CBF and $CMRO_2$ decline observed in frontal cortex, as well as the decrease found in the frontal/sensory-motor cortex ratio (see results), may be related to the functional changes in programming activities[40] and in conditioning of emotional reactions[41] that occur in the elderly.

To sum up, the functional changes of aging seem to affect preferentially the frontal cortex as well as temporo-sylvian and parieto-occipital areas. More detailed studies using new-generation PET devices of higher spatial resolution, and performed both at rest and during various activation procedures, should refine the present findings.

References

1. Fazekas JF, Alman RW, Bessman AN: Cerebral physiology of the aged. Am J Med Sci **223:** 245–257, 1952
2. Scheinberg P, Blackburn I, Rich M, Saslaw M: Effects of aging on cerebral circulation and metabolism. Arch Neurol Psychiat **70:** 77–85, 1953
3. Shenkin HA, Novak P, Goluboff B, Soffe AM, Bortin L: The effects of aging, arteriosclerosis, and hypertension upon the cerebral circulation. J Clin Invest **32:** 459–465, 1953
4. Schieve JF, Wilson WP: The influence of age, anesthesia and cerebral arteriosclerosis on cerebral vascular reactivity to CO2. Am J Med **15:** 171–174, 1953
5. Dastur DK, Lane MH, Hansen DB, Kety SS, Butler RN, Perlin S, Sokoloff L: Effects of aging on cerebral circulation and metabolism in man *In* Birin JE, Butler RN, Greenhouse SW, et al (eds): Human Aging: A Biological and Behavioral Study. US Public Health Service Publication N. 986, 59–76, 1963
6. Gottstein U: Effects of aging on cerebral circulation and metabolism in man. Acta Neurol Scand **60** (s72): 54–55, 1979
7. Kety SS: Human cerebral blood flow and oxygen consumption as related to aging. J Chron Dis **3:** 478–486, 1956
8. Meyer JS, Ishihara N, Deshmukh VD, Naritomi H, Sakai F, Ming-Chang Hsu, Pollak P: Improved method for non-invasive measurement of regional cerebral blood flow by 133Xenon inhalation. Stroke **9:** 195–205, 1978
9. Shaw T, Meyer JS, Mortel K, Cutaia M, Sakai F, Yamaguchi F, Yamamoto M: Effects of normal aging, sex and risk factors for stroke on regional cerebral blood flow in normal volunteers. Acta Neurol Scand **60** (s72): 462–463, 1979
10. Naritomi H, Meyer JS, Sakai F, Yamaguchi F, Shaw T: Effects of advancing age on regional cerebral blood flow. Arch Neurol **36:** 410–416, 1979
11. Thomas DJ, Zilkha E, Redmond S, Du Boulay GH, Marshall J, Ross Russel RW, Symon L: An intravenous 133Xenon clearance

technique for measuring cerebral blood flow. J Neurol Sci **40:** 53–63, 1979
12. Yamamoto M, Meyer JS, Sakai F, Yamaguchi F: Aging and cerebral vasodilator responses to hypercarbia Arch Neurol **37:** 489–496, 1980
13. Melamed E, Lamy S, Bentin S, Cooper G, Rinot Y: Reduction in regional cerebral blood flow during normal aging in man Stroke **11:** 31–35, 1980
14. Davis SM, Ackerman RH, Correia JA, Alpert NM, Chang J, Buonanno F, Kelley RE, Rosner B, Taveras J: Cerebral blood flow and cerebrovascular CO2 reactivity in stroke-age normal controls. Neurology **33:** 391–399, 1983
15. Jones T, Chesler DA, Ter-Pogossian MM· The continuous inhalation of oxygen-15 for assessing regional oxygen extraction in the brain of man. Br J Radiol **49:** 339–343, 1976
16. Subramanyam R, Alpert NM, Hoop B Jr, Brownell GL, Taveras JM: A model for regional cerebral oxygen distribution during continuous inhalation of 1502, C150 and C1502. J Nucl Med **19:** 48–53, 1978
17 Lammertsma AA, Jones T, Frackowiak RSJ, Lenzi GL: A theorical study of the steady-state model for measuring cerebral blood flow and oxygen utilization using oxygen-15 J Comput Assist Tomogr **5:** 544–550, 1981
18 Steinling M, Baron JC: Mesure du debit sanguin cerebral local par inhalation continue de C1502 et tomographie d'emission etude des limites du modele. J Biophys Med Nucl **6:** 89–95, 1982
19. Lammertsma AA, Heather JD, Jones T, Frackowiak RSJ, Lenzi GL: A statistical study of the steady-state technique for measuring regional cerebral blood flow and oxygen utilization using 150. J Comput Assist Tomogr **6:** 566–573, 1982
20 Jones SC, Greenberg JH, Reivich M: Error analysis for the determination of cerebral blood flow with the continuous inhalation of 150-labeled carbon dioxide and positron emission tomography. J Comp Assist Tomogr **6:** 116–124, 1982
21 Rhodes CG, Lenzi GL, Frackowiak RSJ, Jones T, Pozzilli C Measurement of CBF and CMRO2 using the continuous inhalation of C1502 and 1502. J Neurol Sci **50:** 381–389, 1981
22 Baron JC, Steinling M, Tanaka T, Cavalheiro E, Soussaline F, Collard P Quantitative measurement of CBF, oxygen extraction fraction (OEF) and CMRO2 with the 150 continuous inhalation technique: experimental evidence and normal values in man J Cereb Blood Flow Metab **1** (suppl 1): S5–S6, 1981
23. Frackowiak RSJ, Lenzi GL, Jones T, Heather JD: Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man, using 150 and positron emission tomography: theory, procedure and normal values. J Comput Assist Tomogr **4:** 727–736, 1980
24. Lebrun-Grandie P, Baron JC, Soussaline F, Loc'h C, Sastre J, Bousser MG: Coupling between cerebral blood flow and oxygen utilization in the normal human brain. Arch Neurol **40:** 230–236, 1983
25 Hoffman EJ, Huang SC, Phelps ME Quantification in positron emission computed tomography: 1-Effect of object size. J Comput Assist Tomogr **3:** 299–308, 1979
26 Lenzi GL, Frackowiak RSJ, Jones T, Heather JD, Lammertsma AA, Rhodes CG, Pozzilli C: CMRO2 and CBF by oxygen-15 inhalation technique. Europ Neurol **20:** 285–290, 1981
27. Earnest MP, Heaton RK, Wilkinson WE, Manke WF: Cortical atrophy, ventricular enlargement and intellectual impairment in the aged. Neurol **29:** 1138–1143, 1979
28. Roberts MA, Caird FI, Grossart KW, Steven JL: Computerized tomography in the diagnosis of cerebral atrophy. J Neurol, Neurosurg Psychiatry **39:** 909–915, 1976
29. Gyldensted C: Measurements of the normal ventricular system and hemispheric sulci of 100 adults with computed tomography Neuroradiology **14:** 183–192, 1977
30 Gonzales CF, Lantieri RL, Nathan RJ: The CT scan appearance of the brain in the normal elderly population. a correlative study. Neuroradiology **16:** 120–122, 1978
31. Shefer VF: Absolute number of neurones and thickness of the cerebral cortex during aging, senile and vascular dementia and Pick's and Alzheimer's diseases. Neurosc Behav Physiol **6:** 319–324, 1973
32. Henderson G, Tomlinson BE, Gibson PH: Cell counts in human cerebral cortex in normal adults throughout life using an image analysing computer. J Neurol Sci **46:** 113–136, 1980
33. Brody H: Organisation of the cerebral cortex. III-A study of aging in the human cerebral cortex J Comp Neurol **102:** 511–556, 1955
34 Kuhl DE, Metter EJ, Riege WH, Phelps ME: Effects of human aging on patterns of local cerebral glucose utilization determined by the [18F]Fluorodeoxyglucose method J Cereb Blood Flow Metab **2:** 163–171, 1982
35. Reivich M, Alavi A, Wolf A, Greenberg JH, Fowler J, Christman D, MacGregor R, AJones SC, London J, Shine C, Yonekura Y. Use of 2-deoxy-D[1-11C]glucose for the determination of local cerebral glucose metabolism in humans: variation within and between subjects J Cereb Blood Flow Metab **2:** 307–319, 1982
36 Mazziotta JC, Phelps ME, Carson RE, Kuhl DE. Tomographic mapping of human cerebral metabolism: sensory deprivation. Ann Neurol **12:** 435–444, 1982
37. Gur RC, Parker IK, Hungerbuhler JP, Reivich M, Obrist W, Amarnek WS, Sackeim HA: Differences in the distribution of gray and white matter in human cerebral hemispheres. Science **207:** 1226–1228, 1980
38 Finklestein S, Alpert NM, Ackerman RH, Buonanno FS, Correia JA, Chang J, Kulas S, Brownell GL, Taveras JM: Positron imaging of the normal brain. Regional patterns of cerebral blood flow and metabolism. Trans Am Neurol Assoc **105:** 8–10, 1980
39. Bes A, Guell A, Fabre N, Dupui P, Victor G, Geraud G. Cerebral blood flow studied by Xenon-133 inhalation technique in parkinsonism: loss of hyperfrontal pattern. J Cereb Blood Flow Metab **3:** 33–37, 1983
40. Ingvar DH: "Hyperfrontal" distribution of the cerebral gray matter flow in resting wakefulness; on the functional anatomy of the conscious state Acta Neurol Scand **60:** 12–25, 1979
41. Risberg J, Maximillian VA, Prohvnik I. Changes in cortical activity patterns during habituation to a reasoning test. Neuropsychologia **15:** 793–798, 1977