Regional Cerebral Blood Flow and Oxygen Consumption in Human Aging

PATRIZIA PANTANO, JEAN-CLAUDE BARON, M.D., PHILIPPE LEBRUN-GRANDIÉ, NATHALIE DUQUESNOY, MARIE-GERMAINE BOUSSER, M.D., AND DOMINIQUE COMAR

SUMMARY The oxygen-15 continuous inhalation technique and PET were used to study the age-related changes in regional CBF and CMRO2. Twenty-seven patients, aged 19 to 76 years, free of any history of cerebral disease and vascular risk factors were examined in a resting state. CBF, CMRO2, 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 CMRO2, 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 CMRO2 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 CMRO2 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.

The recent development of positron emission tomography (PET) and the 15O continuous inhalation technique provides the opportunity to obtain quantitative tomographic maps of CBF and CMRO2. We felt it important to apply this new tool to study the effects of normal human aging on both hemispheric and regional CBF and CMRO2.

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 CMRO2, since most of these used the same (arbitrary) threshold.

2) Methods

The 15O continuous inhalation technique was employed. The principle and the mathematical model on which it is based, as well as its theoretical and statistical limitations, have been published in detail elsewhere. Its validity has been confirmed by experimental studies and by results obtained in normal subjects. 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 CO₂ analyzer (Beckmann LB2) allowed the monitoring of end-tidal CO₂ content during the study.

CI5O₂ and O₂ 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 H₂O and Hb-15O₂ as well as PaCO₂, PaO₂, pH, hematocrit and total oxygen content (Lex O₂ Con device) were obtained in most of studies and averaged for further use.

The tissue ¹⁵O 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 ¹⁵O concentration was carefully quantified relatively to arterial concentration, by means of: 1) correction for attenuation using ⁶⁷Ge-⁶⁸Ga 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 CI5O₂ and O₂ images were reconstructed by a medium filtered back-projection algorithm, and thereafter transformed, pixel by pixel, into CBF, OEF (oxygen extraction fraction) and CMRO₂ images using published equations. Thus, for each study, a set of 3 images, each one for CBF, OEF and CMRO₂, 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 CMRO₂ were calculated, using a standardized protocol by means of 22 bilateral symmetrical and 4 single medial circular (4 cm²) ROIs. The ROIs were first placed on the CBF image and then automatically copied on corresponding CMRO₂ 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 I 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 CMRO₂ 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-
Results

No significant differences in PaCO₂, arterial oxygen content or arterial blood pressure were observed between young and aged subjects (see table 1).

Mean Gray Values

Mean gray CBF (CBFg) 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 CMRO₂ (CMRO₂g) was not (p > 0.10) (fig. 2).

Despite this lack of significant linear correlation for CMRO₂g, the comparison between the two groups by t-test showed that both CBFg and CMRO₂g were similarly affected: CBFg declined from 50.7 ± 10 ml/100 ml/min to 41.8 ± 9 ml/100 ml/min (18%, p < 0.05) and CMRO₂g 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, CMRO₂ 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 rCMRO₂, 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 CMRO₂ (ranging from 18% to 26%) reach statistical significance (table 2, fig. 3). The CBF and CMRO₂ 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 CMRO₂ 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 CMRO₂ (p > 0.10).

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 CMRO₂ (see table 3).

Right to Left Ratios

CBF and CMRO₂ right to left ratios for all the structures analyzed are shown in table 4. No significant asymmetry was found for CBFg and CMRO₂g. Although frontal CBF and CMRO₂ and parieto-occipital CMRO₂ 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 CBFg and advancing age, with a decrease of 3.2 ml/100 ml/min/decade, whereas the correlation between CMRO₂g 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 CMRO₂g (17%, p < 0.05) in the “old” group with respect to the “young” one, that was matched to the CBFg decrease (18%, p < 0.05). Thus, the decrease in CMRO₂ 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 CMRO₂ did not show any tendency toward a decrease with advancing age. In the “old” group, rCBF and rCMRO₂ 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 CBFg and CMRO₂g was found, but higher rCMRO₂ 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, CMRO₂, and OEF Values (mean ± SD) in 27 Control Subjects, Also Divided into Two Groups with Respect to Age

<table>
<thead>
<tr>
<th>Regions</th>
<th>CBF</th>
<th>CMRO₂</th>
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<tbody>
<tr>
<td></td>
<td>All</td>
<td>&quot;Young&quot; group</td>
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<tr>
<td>Mean gray matter</td>
<td>47.7 ± 10.9</td>
<td>50.7 ± 10.3</td>
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<tr>
<td>Frontal</td>
<td>46.3 ± 10.4</td>
<td>49.9 ± 10.3</td>
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<tr>
<td>Lateral frontal</td>
<td>43.4 ± 10.1</td>
<td>46.6 ± 10.2</td>
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<tr>
<td>Medial frontal</td>
<td>52.6 ± 12.7</td>
<td>55.7 ± 12.9</td>
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<tr>
<td>Temporo-sylvian</td>
<td>54.7 ± 16.8</td>
<td>59.9 ± 16.2</td>
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<tr>
<td>Sensory-motor</td>
<td>42.5 ± 10.1</td>
<td>44.0 ± 9.1</td>
</tr>
<tr>
<td>Parieto-occipital</td>
<td>40.0 ± 10.2</td>
<td>45.0 ± 10.3</td>
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<tr>
<td>Occipital</td>
<td>53.9 ± 13.2</td>
<td>56.5 ± 13.5</td>
</tr>
<tr>
<td>Lateral occipital</td>
<td>47.5 ± 11.9</td>
<td>49.2 ± 12.3</td>
</tr>
<tr>
<td>Medial occipital</td>
<td>66.0 ± 19.2</td>
<td>70.3 ± 20.5</td>
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<tr>
<td>Thalamus</td>
<td>43.6 ± 13.3</td>
<td>46.0 ± 12.0</td>
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<tr>
<td>White matter</td>
<td>24.7 ± 5.3</td>
<td>24.5 ± 4.1</td>
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* p < 0.05,
‡ p < 0.02
* p < 0.01 with respect to "young" group.

Among the theoretical limitation of the ¹⁵O steady-state model, one is due to the tracer present in the cerebral blood volume (correction for this variable, though possible, 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. This leads to inevitable and unpredictable averaging of gray and white matter, and results in an underestimation of the CBF and CMRO₂ values of gray matter and in an overestimation of those of white matter. If the present study, as well as other reports, are correct in showing that the decrease in CBF and CMRO₂ 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 CMRO₂. Since CT scans were not performed in our population, we cannot estimate if and how much cortical atrophy would have affected our data. Although

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**FIGURE 3.** Regional patterns of CBF and CMRO₂ in young and aged subjects. Mean values and one standard deviation are indicated for each brain region studied.
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selected for their unusually healthy intellectual and with age in several \textsuperscript{14} non-invasive studies.\textsuperscript{14} Zekas et al\textsuperscript{1} and Scheinberg et al\textsuperscript{2} reported an age-related decrease in CBFg and CMRO\textsubscript{2}g with aging (18\% and magnitude close to that of our results; mean hemispheric CBF and CMRO\textsubscript{2} of a torsions) 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 CBFg and CMRO\textsubscript{2}g with aging (18\% and 17\%, respectively). In roughly similar population, Fazekas et al\textsuperscript{7} and Scheinberg et al\textsuperscript{8} reported an age-related decline in whole brain CBF and CMRO\textsubscript{2} of a magnitude close to that of our results; mean hemispheric CBF has been repeatedly shown to decrease significantly with aging. Finally, the fact that our results are in agreement with earlier studies\textsuperscript{1"4} that used CBF and CMRO\textsubscript{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 CBF and CMRO\textsubscript{2} with aging (18\% and 17\%, respectively). In roughly similar population, Fazekas et al\textsuperscript{7} and Scheinberg et al\textsuperscript{8} reported an age-related decline in whole brain CBF and CMRO\textsubscript{2} of a magnitude close to that of our results; mean hemispheric CBF has been repeatedly shown to decrease with age in several \textsuperscript{133}Xe non-invasive studies.\textsuperscript{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,\textsuperscript{4"5} but that aged people with multiple vascular risk factors had decreased values.\textsuperscript{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\textsubscript{2},\textsuperscript{6} but, on the average, a decline in the latter variables has been generally accepted.\textsuperscript{7}

The age-related decreases in gray matter CBF and CMRO\textsubscript{2} reported here are roughly similar to, although less prominent than, those previously published by Lenzi et al.\textsuperscript{26} who also used the \textsuperscript{18}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's study\textsuperscript{26} and with two \textsuperscript{133}Xe rCBF studies.\textsuperscript{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.\textsuperscript{11}

Neuronal cell depopulation and/or diminished activity that are associated with normal human aging\textsuperscript{13"15} 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\textsubscript{2} in older subjects, as found also by Lenzi et al\textsuperscript{26} and by most Kety-Schmidt technique studies,\textsuperscript{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\textsubscript{2} with decreased CBF, suggesting reduced perfusion as a primary factor, has been reported in atherosclerotic aged subjects.\textsuperscript{3} Although it remains conceivable that a primary CBF reduction, if longstanding, may progressively lead to secondary metabolic alterations and reduction in CMRO\textsubscript{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 2** (Continued)

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<th>Regional CBF and CMRO\textsubscript{2} Versus Age</th>
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<td>Regions</td>
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**Table 3** Linear Regression (y = ax + b) of Regional CBF and CMRO\textsubscript{2} Versus Age

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<td>White matter</td>
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\( *p < 0.01. \)

\( **p < 0.05. \)

\( n = 27. \)

(Continued)
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, and with 133Xe non-invasive rCBF studies, we found no right-left asymmetry in overall gray CBF and CMRO2 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, except perhaps in conditions of marked sensory deprivation.

On a regional basis, however, we found a small but significant left prevalence for both CBF and CMRO2 in the frontal cortex, as well as the decrease found in frontal-sensory-motor cortex ratio (see results), and in conditioning of emotional reactions 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.

Alternatively, the CBF and CMRO2 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 and in conditioning of emotional reactions that occur in the elderly.

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

<table>
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<tr>
<th>Regions</th>
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<td>&quot;Young&quot; group</td>
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<tr>
<td>Mean gray matter</td>
<td>0.994 ± 0.05</td>
<td>0.998 ± 0.06</td>
</tr>
<tr>
<td>Frontal</td>
<td>0.970 ± 0.07*</td>
<td>0.968 ± 0.06</td>
</tr>
<tr>
<td>Temporo-sylvian</td>
<td>1.003 ± 0.11</td>
<td>1.009 ± 0.12</td>
</tr>
<tr>
<td>Sensory-motor</td>
<td>1.003 ± 0.10</td>
<td>0.972 ± 0.08</td>
</tr>
<tr>
<td>Parieto-occipital</td>
<td>0.967 ± 0.12</td>
<td>0.947 ± 0.13</td>
</tr>
<tr>
<td>Occipital</td>
<td>1.018 ± 0.09</td>
<td>1.033 ± 0.08</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.995 ± 0.15</td>
<td>0.979 ± 0.14</td>
</tr>
<tr>
<td>White matter</td>
<td>0.998 ± 0.12</td>
<td>0.983 ± 0.11</td>
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"Young" group ≤ 50 yrs, n = 18.
"Old" group > 50 yrs, n = 9.
*p < 0.05.
†p < 0.02.
Significantly different from 1.00.

References
Regional cerebral blood flow and oxygen consumption in human aging.
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Stroke. 1984;15:635-641
doi: 10.1161/01.STR.15.4.635

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