Reduction in Regional Cerebral Blood Flow During Normal Aging in Man

ELDAD MELAMED, M.D., SYLVAN LAVY, M.D., SHLOMO BENTIN, M.Sc., GERALD COOPER, PH.D., AND YOSEF RINOT, PH.D.

SUMMARY Regional cerebral blood flow (rCBF) was measured by the 133Xenon inhalation method in a selected group of 44 normal non-hospitalized, normotensive subjects aged 19 to 79 years. rCBF was computed as the initial slope index value (ISI). Advancing age was associated with significant reductions in the mean brain and mean hemispheric ISI as well as in individual ISI levels measured from all areas in both hemispheres. Our findings suggest that decline of rCBF is not limited to normal elderly subjects but that it is a progressive phenomenon which begins at an earlier age.

REGIONAL CEREBRAL BLOOD FLOW (rCBF) in man has been studied extensively in a variety of pathological and physiological conditions during the last 2 decades. However, little and conflicting information is available on the effect of normal aging on the rCBF. A few studies showed decline of CBF in normal elderly subjects. Kety suggested that progressive CBF reduction occurs through adolescence, adulthood and senescence. By contrast, others did not find significant differences in CBF between young and old normal subjects. These studies and others suggested that normal aging per se is not associated with decreases in CBF, unless it is accompanied by conditions such as hypertension, arteriosclerosis and mental deterioration.

Settlement of the dispute concerning the natural history of rCBF during normal aging is important. Many studies, designed to determine rCBF in various conditions, compare the results in a given group of subjects with those obtained in normal controls, usually a rather small group of young patients or volunteers. However, if rCBF reduction indeed occurs with advancing age, rCBF levels should be compared with those obtained in age-matched normal controls.

This lack of basic data is probably related in part to the traumatic and invasive nature of the techniques which are used in the study of rCBF in man. The most common method, using intracarotid injection of 133Xenon, is limited mainly to hospitalized patients undergoing carotid angiography. Understandably, such methods could not be applied to large series of normal ambulatory subjects. In addition, criteria for normality were not always rigid and elderly hospitalized patients were often included in most studies dealing with the effect of aging on the CBF.

The development of a non-invasive atraumatic technique for simultaneous bihemispheric measurement of rCBF by the inhalation of 133Xenon now permits a new and safe approach to this problem. We have measured the rCBF by this method in a relatively large series of normal, non-hospitalized subjects in order to determine the effect of age on rCBF.

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Method

Forty-four normal subjects (26 males, 18 females) with ages ranging from 19 to 79 (mean 42 years), were included in the present study. Some were volunteers; the others came from various outpatient clinics in the hospital. Each subject gave informed consent for the procedure after its nature had been fully explained. All were fully active, independent and non-hospitalized. Each subject underwent a detailed interview and general physical and neurological examinations. Chest roentgenogram and an electroencephalographic recording were obtained in every subject above 40. There was no evidence of central nervous system pathology, dementia or focal neurological deficit in any of the subjects. Those with hypertension, coronary and peripheral vascular disease and pulmonary abnormalities were excluded.

rCBF was measured by the 133Xenon inhalation method which was developed and described in detail by Obrist et al. Briefly, the study was conducted with subjects at rest and ears plugged in a quiet, semidarkened room. 133Xenon in a concentration of 2.5 mCi per liter mixed with air, was breathed by the subject for one minute through a close-fitting face mask with a one-way valve. The clearance of the radioisotope from the brain was monitored for 10 minutes by 16 NaI collimated scintillation detectors applied perpendicularly over homologous regions in both hemispheres (8 over each hemisphere) with the head relating to the probes in a standard position (see figure 1 for location of probes). Each detector was incorporated into an on-line computer. Air, drawn directly from the face mask by a vacuum pump, was continuously monitored for 133Xenon concentration and CO2 content. The rCBF was calculated according to Risberg et al. as the initial slope index (ISI), derived from the initial slope of the wash-out curves between the second and third minute. Paco2 levels, calculated from the CO2 content in the expired air, were 37 ± 3 mm Hg. However, for several reasons we have chosen to present ISI values which were not corrected for changes in Paco2. The effects of induced hypo- and hypercapnia on rCBF using the inhalation method have not been studied in detail and, therefore, the normalization constant for Paco2 alterations is still not well established. Also, the need for normalization of
The mean hemispheric and individual flow values (calculated as ISI) for the whole group of 44 normal subjects are shown in figure 1. ISI values were higher in the anterior than in the posterior regions of both hemispheres. There were no significant differences in the mean hemispheric and in individual ISI values obtained from parallel regions, between the right and left hemispheres. There were no significant differences in flow values between males and females in this series.

Figure 2 presents the correlation between mean brain ISI (calculated for each subject from 16 bihemispheric ISI values) and age. There is a statistically significant reduction of CBF with advancing age \( r = -0.46; p < 0.001 \). This figure also shows the computed regression line through the scattergram, which best describes the progressive, age-related CBF decline.

Subjects were divided into 4 age groups: A) 19 to 30 years, 14 subjects; B) 31 to 50 years, 12 subjects; C) 51 to 60, 8 subjects; D) 61 to 79 years, 10 subjects. Mean right and left hemispheric ISI were calculated for each age group (fig. 3). There were no significant differences in the mean flow values between right and left hemispheres and in the mean \( \text{Paco}_2 \) values, in the various groups. Mean hemispheric ISI decreased from one age group to the next. A significant reduction of 12 percent was observed between groups B and A \( (p < 0.01) \). A significant decrease of 11 percent occurred between groups C and B \( (p < 0.05) \). Group D showed a reduction of 6 percent from the former age group which was not statistically significant. However, the mean hemispheric ISI in group D were significantly reduced by 27 and 17 percent when compared with groups A and B, respectively \( (p < 0.01; p < 0.01) \).

The table shows the computed linear functions best describing the regression of individual ISI values obtained from different regions in the right and left hemispheres with advancing age. In the left hemisphere, the age-related ISI decreases are more

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**Figure 1.** Mean right and left hemispheric and individual ISI values in a series of 44 normal subjects aged 19–79 (mean 42 years).

**Figure 2.** Mean brain ISI values plotted against age of subjects. The computed regression line shows decline of ISI with advancing age.
marked in the anterior regions and less pronounced in the posterior areas. However, such regional predilection was not clearly observed in the right hemisphere, and areas showing more marked ISI reductions during aging were rather scattered.

Discussion

The present study shows that normal aging is associated with rCBF reduction. These decreases were observed in mean brain and mean left and right hemispheric blood flows as well as in regional flow values. Although in the left hemisphere, these changes were more prominent in the anterior regions, the age-related regional pattern of flow reduction warrants further study in a larger series of normal subjects. This study also suggests that reduction of the rCBF is not limited to elderly normal subjects. It seems, in agreement with Kety, that the age-related decline of rCBF is a progressive phenomenon which continues from youth through adulthood, middle age and old age.

The $^{133}$Xenon inhalation technique for measurement of rCBF presents several methodological problems such as the recirculation of the radioisotope and contamination of extracerebral tissues. $^{12,13}$ rCBF values measured by this technique may be less accurate than flow data obtained by carotid injection of the radioisotope, although a good correlation has been reported. $^{17}$ We have chosen to compute the ISI as an index of the rCBF. $^{14,15}$ The ISI is derived mainly from the first component of the clearance curve and is dominated by washout of $^{133}$Xenon in rapidly perfused tissues with less influence of slowly perfused tissues. It was suggested by Risberg $^{14}$ that the ISI consists mainly of gray matter flow, less of white matter flow and of negligible flow in extracerebral tissues. It was also reported $^{14}$ to be more stable than other flow parameters calculated in the inhalation method. Even if ISI values do not exactly equal true rCBF levels, they represent the clearance rates of $^{133}$Xenon from cerebral tissues and permit at least a close estimate of the rCBF. We believe, therefore, that in the present study, the age-related decreases of the ISI, indicate genuine rCBF reduction during normal aging.

A basic assumption in the $^{133}$Xenon inhalation method is that the end-tidal air is in equilibrium with the arterial blood at the alveolar surface, and that the end-tidal concentration of $^{133}$Xenon is analogous to its concentration in the arterial blood. Therefore, monitoring of $^{133}$Xenon end-tidal concentration in the expired air is used for correcting the recirculation of the inhaled radioisotope. $^{13,17}$ It may be argued that with advancing age, pulmonary changes occur which interfere with the exchange of $^{133}$Xenon between alveoli and blood. Such age-related changes may in turn influence the washout curves of $^{133}$Xenon in the expired air. Since the latter curves are used for correction of recirculation, the computed ISI values may be distorted with a resultant artificial rCBF decline during aging. However, this possibility is remote since

Table: Regression Lines Showing Decreases of rCBF (ISI) in Various Areas of Right and Left Hemispheres During Aging*

<table>
<thead>
<tr>
<th>Detector</th>
<th>Left hemisphere</th>
<th>Right hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>-0.33</td>
<td>67.4</td>
</tr>
<tr>
<td>7</td>
<td>-0.31</td>
<td>74.1</td>
</tr>
<tr>
<td>12</td>
<td>-0.28</td>
<td>66.8</td>
</tr>
<tr>
<td>6</td>
<td>-0.27</td>
<td>62.8</td>
</tr>
<tr>
<td>4</td>
<td>-0.23</td>
<td>66.3</td>
</tr>
<tr>
<td>8</td>
<td>-0.22</td>
<td>57.2</td>
</tr>
<tr>
<td>3</td>
<td>-0.22</td>
<td>61.9</td>
</tr>
<tr>
<td>1</td>
<td>-0.17</td>
<td>61.5</td>
</tr>
</tbody>
</table>

*Regression lines were computed from individual ISI values plotted against age (ISI = B X Age + A). The intercept A represents the expected ISI at the hypothetical age of 0 years. The slope B indicates the average yearly change in ISI. For location of detectors see fig. 1. In both hemispheres, regression lines are arranged in a descending order of ISI decline. All slopes are significant at $p < 0.01$. 

Figure 3. Mean right and left hemispheric ISI values in four age groups of normal subjects. ISI decreases are observed in successive age groups.
subjects with clinical or roentgenographic evidence for pulmonary abnormalities were excluded from the present study. More important, we have studied the effect of various physiological factors, including that of age, on the washout of inhaled \(^{133}\)Xenon in the expired air in a series of 87 subjects (age range 15 to 87 years) with no clinical and roentgenographic evidence for pulmonary diseases, undergoing rCBF measurements.\(^{18}\) This series included the 44 subjects described in the present report. Among the various age groups, there were no significant differences in the clearance rates of \(^{133}\)Xenon from the lungs. The configuration of the expired air \(^{133}\)Xenon curves did not change significantly with age. Furthermore, Obrist’s\(^{19}\) preliminary findings suggested that in an aging population a substantial deviation of the air curve from the arterial \(^{133}\)Xenon concentration curve is necessary before rCBF values are affected. It seems therefore that possible age-dependent pulmonary changes have no or negligible effect on the observed decreases of the clearance rates of \(^{133}\)Xenon from cerebral tissues during aging.

It is feasible that even in normal subjects with no evidence of intellectual deterioration or focal neurological phenomena, the reduction of rCBF may be due to subclinical structural or functional cerebral disorders. It is known that brains of elderly non-demented subjects may show various and multiple cerebral parenchymatous abnormalities including softenings, senile plaques and neurofibrillary tangles.\(^{18}\) It is possible that rCBF decreases in the elderly group may reflect a higher prevalence of arteriosclerotic or other age-dependent changes\(^{50}\) in cerebral arterial vessels which produce vascular narrowing and increased resistance. Alternatively, rCBF reduction in this group may be secondary to age-related loss of brain substance.\(^{21, 22}\) Decreased cerebral metabolism and an adaptation to diminished metabolic demands.\(^{23}\) The mechanisms underlying the reduction of rCBF in the younger age groups are unclear because detailed qualitative and quantitative pathological studies of brains in younger subjects are lacking. Nevertheless, these rCBF decreases may be due to onset and progression of more subtle cerebral changes at an earlier age. For instance, it has been shown that various pathological alterations in the cerebral microvasculature are not limited to old age and may occur earlier.\(^{50}\) In addition, a computerized tomography study has recently demonstrated in normal subjects a gradual increase in ventricular size from the first through the sixth decades indicating early and progressive loss of brain substance.\(^{24}\)

The present investigation shows that the \(^{133}\)Xenon inhalation method may be a useful and safe tool to study rCBF behavior in man, particularly in physiological conditions which do not justify a carotid puncture. Our findings suggest that since rCBF decreases with advancing age, future studies should compare flow data with rCBF values obtained in age-matched normal controls.

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Effect of Chronic Atrial Fibrillation on Regional Cerebral Blood Flow

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SUMMARY The development of a non-invasive technique for simultaneous bihemispheric measurement of regional cerebral blood flow (rCBF) by inhalation of 133Xenon made available a safe method for evaluation of cerebral circulation under various cardiac conditions. Regional cerebral blood flow was measured by 133Xenon inhalation in 31 patients with chronic atrial fibrillation without symptoms of heart failure and free from neurological diseases. Their age ranged from 35 to 80 (mean 60.3 years). In 27 out of the 31 patients rCBF was found to be lower than for age-matched normal control subjects. A reduction in cerebral blood flow from 17.5% to 5.5% in various age groups was found. The highest reduction in mean rCBF (17.5%) was found in the younger age group (35–50 years). In the group of patients between 51–65 years, the reduction was 13.4% and in the patients above 65, only 5.5%. The reduction of rCBF observed in our patients apparently did not reach the level required to produce cerebral manifestations. However, it is plausible to assume that any superimposed rhythm or rate pathology and/or cerebral arteriosclerosis may further compromise the cerebral circulation.

Although cerebral emboli are a frequent cause of cerebral manifestations in cardiac arrhythmia, a chronic reduction in cerebral perfusion consequent to rate or rhythm disturbances in patients with cerebral vascular diseases should be considered. Early recognition and therapy of chronic arrhythmia with reduced cerebral perfusion may prevent neurological complications at a later stage.

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