Age-Matched Normal Values and Topographic Maps for Regional Cerebral Blood Flow Measurements by Xe-133 Inhalation

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SUMMARY The relationship between normal aging and regional cerebral blood flow (rCBF) computed as initial slope index (ISI) by Fourier method was investigated in 105 right-handed healthy volunteers (132 measurements) by Xe-133 inhalation method, and age-matched normal values were calculated. Mean brain ISI values showed significant negative correlation with advancing age (r = -0.70, p < 0.001), and the regression line and its 95% confidence interval was \( Y = -0.32 (X-19) + 63.5 \pm 11.2 \) (19 \( \leq X \leq 80 \)). Regional ISI values also showed significant negative correlations for the entire brain (p < 0.001). The regional reductions of ISI values with advancing age were significantly greater in the regional distribution of the middle cerebral arteries bilaterally, compared with regions in the distribution of the other arteries (p < 0.05). Therefore, measured rCBF values for patients must be compared to age-matched normal values for mean hemispheric and each region examined. Two kinds of topographic maps, brain map showing rCBF compared to age-matched normal values and showing hemispheric differences were made by dividing patient’s values by the 95% confidence limits for age-matched normal values and displaying laterality index calculated as follows, respectively.

\[
\text{Laterality index} = 100 \left( 1 + \frac{(\text{Right flow} - \text{Left flow})}{(\text{Right flow} + \text{Left flow})} \right)
\]

These maps were useful for evaluating significantly decreased or increased regions and regional hemispheric differences.

Since Cerebral Blood Flow (CBF) measurements in man were reported by Kety and Schmidt in 1945,1 influences of aging on CBF has often been a subject of controversy. Kety and others mentioned that there were progressive reductions of CBF with aging in normal subjects free from clinical evidence of hypertension or arteriosclerosis.2-3 By contrast, Shenkin and others said that there were no reductions of CBF associated with aging unless accompanied by hypertension, arteriosclerosis and dementia.6-8 In these reports, however, such invasive methods as nitrous oxide and Kr-85 inhalation, or Xe-133 intra-carotid injection were used for measurements of CBF. Therefore, subjects were limited mainly to hospitalized patients and it was hard to say whether or not the measurements were carried out in the resting state. While, Xe-133 inhalation method for measuring regional cerebral blood flow (rCBF) is noninvasive, it also offers the opportunity to simultaneously study both hemispheres and the entire brain. Therefore, this method is more suitable for investigation of relations between normal aging and rCBF. The present study was designed to investigate these relationships by measuring age-matched normal rCBF values and defining brain maps which would allow comparison of patient’s values with these regional values measured by Xe-133 inhalation method.

Materials and Methods

One hundred and thirty two measurements of rCBF were performed in 105 right-handed (judged by Edinburgh handedness questionnaire9-10) healthy volunteers free from cardiovascular and pulmonary diseases and risk factors of atherothrombotic stroke including hypertension, diabetes mellitus and hyperlipidemia.11 There were 57 males and 48 females, aged 19 to 80 years old (mean 42 years) (table 1). The old age group above 60 was subjected to psychometrical testing (Hasegawa scale12) and diagnosed normal. Hematocrit was determined in all subjects.

The measurements were carried out in a room where the ambient noise level was 61 db (A) derived from inhalation system and blowers and illumination intensity was 3 lux at rest and in the eye closed state. Xe-133 inhalation system (Meditronic Novo Diagnostic Systems, Inhalation Cerebrograph, Denmark) consists of 32 scintillation detectors placed in parallel. One pair of the detectors was mounted in a position over the brain stem and cerebellar region (fig. 1).

The data were analyzed by Fourier method,13-15 and initial slope index (ISI, computed on the period 30 to 90 seconds from the beginning of inhalation)13-16 was used in this presentation as the index of rCBF. The relation between age and regional hemispheric percent values, which are obtained by dividing the regional values by hemispheric mean values, was also studied. Besides, two kinds of topographic maps, brain map showing rCBF compared to age-matched normal values and showing hemispheric differences were made for the purpose of evaluating significantly decreased or increased regions and regional hemispheric differences, respectively. These maps were made by divid-
ing patient’s values by the 95% confidence limits for age-matched normal values and displaying laterality index calculated as follows.

\[
\text{Laterality index} = \frac{\text{Total}}{100} \times \left( \frac{\text{Right flow} - \text{Left flow}}{\text{Right flow} + \text{Left flow}} \right)
\]

The values of laterality index more and less than 100 denote the dominancies of the right and left hemisphere, respectively.

End expired air PCO₂ (PECO₂, calculated as follows) \(^{17}\) was recorded from the face mask during the measurements along with the mean arterial blood pressure (MABP). PECO₂ = (Barometric pressure – 47) \(\text{mmHg} \times \%\text{CO}_2\). ISI values were not corrected for changes in PECO₂.

**Results**

PECO₂ and MABP were 37.8 ± 2.9 and 83.7 ± 12.0 \(\text{mmHg}\) (mean ± 1 standard deviation (s.d.)) respectively, and didn’t significantly correlate with aging \((r = 0.03\) and \(r = 0.18\), respectively, \(p > 0.05\)). Mean brain ISI values showed significant negative correlations with advancing age \((r = -0.70)\) total, \(r = -0.72\) males, \(r = -0.61\) females, \(p < 0.001\), and the regression lines were \(Y = -0.32 (X-19) + 63.5\) (total), \(Y = -0.37 (X-19) + 64.1\) (males) and \(Y = -0.26 (X-19) + 62.5\) (females) \((19 \leq X \leq 80)\). The number of subjects was so large that the 95% confidence interval of the regression line (total) was able to approximate to \(\pm 1.96 \sqrt{\frac{V}{n}} \approx 11.2\) (VE: mean residual square) (fig. 2). There were no significant differences in the correlation coefficients between males and females \((p > 0.05)\). Regional ISI values also showed significant negative correlations with advancing age for the entire brain \((p < 0.001)\) (fig. 3). Regional regression lines and their 95% confidence intervals were also calculated (fig. 4). There were no significant differences in the correlation coefficients obtained from parallel regions between the right and left hemispheres \((p > 0.05)\). The regional reductions of ISI values with advancing age were significantly greater in the regional distribution of the middle cerebral arteries (MCA, corresponding detectors are 4, 5, 6, 7, 9, 10, 11, 13, 15, 20, 21, 22, 23, 25, 26, 27, 29, 31, see fig. 3) bilaterally, compared with regions in the distribution of the anterior cerebral (detectors, 1, 3, 17 and 19), the posterior cerebral (detectors, 8, 12, 16, 24, 28, 32) and verteobasilar (detectors, 2, 18) arteries \((p < 0.05)\). Regional hemispheric percent values for frontal lobe (mean value of detectors, 1, 3, 4, 5, 6, 7, and 9, or of detectors, 17, 19, 20, 21, 22, 23 and 25) were greater than that of either parietal (mean value of 7, 9, 11, 13 and 15, or 23, 25, 27, 29 and 31), temporal (mean value of 6, 8, 10, 12 and 14, or 22, 24, 26, 28 and 30), occipital lobe (mean value of 14, 15 and 16, or 30, 31 and 32), or brain stem and cerebellar region (2 or 18) for the entire age (fig. 5). But, this hyperfrontal distribution became gradually lost with advancing age, because reductions of ISI values with aging were greater in the frontal lobe than in other regions.

Topographic patterns of rCBF as a brain-map, were made on a 64-year-old patient who suffered from left angular artery infarction after 102 days from the onset (fig. 6a) by dividing patient values with the lower 95% confidence limits for the age-matched normal values (fig. 6b, c, d). According to this map, it became clear that rCBF of extensive regions except for part of frontoparietal and brain stem and cerebellar regions fell within the lower normal limits or showed significant decreases for the left hemisphere \((p < 0.05)\), while all regions were within normal limits for the right hemisphere.

There were no significant differences in the hemispheric mean ISI values between the right and left hemispheres \((p > 0.05)\), on the other hand significant regional hemispheric differences were observed in superior frontal (right dominancy) and posterior inferior temporal (left dominancy) regions for these normal right-handed subjects (Student’s t-test, \(p < 0.05\)). Mean and 1 s.d. values for laterality indices of hemispheric mean values were 100.3 ± 1.2 (fig. 7). Mean values for regional laterality indices were less than 100 (left dominancy) between the pairs of detectors at positions (see fig. 1) 7 and 23, 8 and 24, 10 and 26, 12 and 28, and 13 and 29, on the other hand more than 100 (right dominancy) between the other pair detectors, while 1 s.d. values for regional laterality indices were below 3 in all regions. In the patient mentioned above,
regional laterality indices showed significantly greater values ($p < 0.05$), that is the right hemisphere was dominant, in all regions except for part of frontal and temporal lobes (fig. 8).

**Discussion**

In analyzing head clearance curves by the Xe-133 inhalation technique, Fourier method has been reported to have the following three advantages in comparison with the conventional Obrist method. In Obrist method, delayed start fit time has been used to avoid the artifacts from the air passages. The main disadvantage of this method is the omission of the first part of the clearance curve which contains information about the flow of the fast clearing gray matter. By contrast, Fourier method provides complete informa-
The method has a faster computation time. We compared the reproducibilities of flow parameters, F, and ISI between Fourier and Obrist methods by back-to-back measurements. The coefficient variations (C.V.) of the change from first to second measurement were 5.1%, 3.3%, 6.4%, 3.4% for hemispheric mean values, 9.1%, 5.0%, 13.0%, 6.6% on average for regional absolute values, and 7.9%, 3.9%, 12.2%, 5.5% on average for regional hemispheric percent values in F, by Fourier method, ISI by Fourier method, F, by Obrist method and ISI by Obrist method, respectively. ISI by Fourier method showed the best reproducibility.

Naritomi et al. and Davis et al. reported significant negative correlations (r = -0.70 and -0.69) between aging and mean brain F, values by Obrist method in 46 and 53 normal subjects, respectively. Melamed et al. also reported significant negative correlations (r = -0.46) between age and mean brain ISI values by Obrist method in 44 normal subjects. In the present study, significant negative correlation (r = -0.70) were obtained between age and mean brain ISI values using the Fourier method in 105 normal subjects. Regional reductions were significantly greater in the regional distribution of the MCA than in the distribution of other arteries, bilaterally. This greater reduction in the MCA territory was also pointed out by Naritomi et al. and Melamed et al.

As for the differences in mean brain flow between the male and female groups, Davis et al. reported that mean flow for the female group below age 50 was higher than the mean male flow and that the mean flows for both groups were similar above age 50. There were no significant differences in the correlation coefficients of the mean brain ISI values with aging between male and female groups in the present study, although the mean age for the male group (36 years) was 14 years less than that for the female group (50 years). Further investigation should be continued on this point.

As factors for progressive reductions of rCBF with advancing age, firstly, there is a loss of brain substance and hence decreased cerebral metabolism. In pathological findings of normal brains established to be free of disease by careful neurological examination shortly before death, it has been reported that populations of cerebral cortical neurones progressively decrease in number with aging, especially in superior temporal and precentral regions. Some brains showed softening and changes of senile type (senile plaques, Alzheimer's neurofibrillary change and granulovacuolar degeneration) either alone or in combination. A gradual increase in ventricular size with advancing age in X-ray CT findings also indicates progressive reduction of brain parenchyma. These changes of brain parenchyma correlate well with reductions of cerebral blood flow and metabolism. Secondly, atherosclerotic changes may be considered. In autopsy studies of the patients dying without morphologic evidence of atherosclerotic disease, it has been reported that the MCA and basilar arteries had the most atherosclerosis, which caused vascular narrowing and increased resistance.

In resting wakefulness, cerebral gray matter flow is reported to show a hyperfrontal distribution. Ingvar reported that the hyperfrontal distribution of gray matter flow suggested the activity of the brain with an anticipatory “stimulation of behavior.” Though these high frontal flow values were seen in all age groups in the present study, it was gradually reduced with advancing age so that only small differences were noted compared to the other regions in old age.
It is concluded that measured rCBF values for patients with disease must be compared to age-matched normal values for mean hemispheric and each region examined, because rCBF inhomogeneously becomes reduced with advancing age. The brain map showing rCBF compared to age-matched normal values is useful for evaluating significantly decreased or increased regions.

Regarding hemispheric differences for CBF in normal subjects, opinions vary. Ingvar said that there were no significant hemispheric differences in hemi-

![Brain map showing rCBF compared to age-matched normal values.](image-url)
Mean and 1 s.d. values for hemispheric mean and regional laterality indices in right-handed healthy volunteers. Laterality index is calculated as follows: Laterality index = 100 (Right) flow - (Left) flow / (Right) flow + (Left) flow. The values of the index more and less than 100 denote the dominancies of the right and left hemisphere, respectively.

Concerning regional hemispheric differences, Blauenstein et al reported that rCBF in the inferior frontal region was higher in the right hemisphere of the right-handed, while Prohovnik et al reported that rCBF in the superior frontal and posterior temporal regions were higher in the right hemisphere, and rCBF in the inferior temporal region higher in the left hemisphere of the right-handed. In our normal right-handed subjects, there were no significant differences between the right and left hemispheric mean values, though the mean value of laterality indices was slightly above 100. The result of regional hemispheric differences was similar to that of Prohovnik et al. Laterality index is stable regardless of the values of rCBF, moreover significant abnormal values were obtained in a study of our patients with cerebral infarction.

Topographic map for rCBF was made by dividing the rCBF values for this 64-year-old patient with left angular artery infarction by the lower 95% confidence limits for age-matched normal values. Right and left hemispheric mean values of the patient were 117% and 101% of the lower limits, respectively. Topographic map showed regional percentages above or below the lower limits using the clock symbols in the circles (90° = 25% and 100° = 25%). In the left hemisphere, all regions except for part of frontoparietal and brain stem and cerebellar regions fell within the lower normal limits or showed significant decreases (p < 0.05). Regional laterality indices show significantly greater values, that is the right hemisphere is dominant, in all regions except for part of frontal and temporal lobes.

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a. X-ray CT of the patient. Low density area was observed in left parieto-occipital region.
b. rCBF of the patient.
c. The lower 95% confidence limits of age-matched normal values.
d. Regional brain map showing flow reductions compared to age-matched normal values.
References

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