CEREBRAL BLOOD FLOW IN ASYMPTOMATIC INDIVIDUALS
—Relationship with Cerebrovascular Risk Factors and
Magnetic Resonance Imaging Signal Abnormalities—

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We studied the relationship between cortical grey matter flow (CBF) and age, cerebrovascular risk factors and the severity of subcortical hypersignals (HS, hyperintensity score in MRI) in 47 asymptomatic subjects with cerebrovascular risk factors. Multiple regression analysis revealed that HS was most strongly related to CBF, and that hematocrit, age and evidence of ischemic change detected in the electrocardiogram also appeared to be independent determinants of CBF. Both the severity and location of hypersignals were correlated with CBF. The most significant negative correlation observed was that between CBF and HS in the basal ganglia-thalamic region, where the degree of signal abnormality was modest. Decreased CBF in asymptomatic subjects with cerebrovascular risk factors may be related to (1) microcirculatory disturbance associated with elevated hematocrit and an increase in the number of risk factors, and (2) functional suppression of cerebral cortex due to the neuronal disconnection associated with subcortical lesions. In addition, impaired cerebral circulation may be related to MRI signal abnormalities.

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In the normal brain, cerebral blood flow (CBF) is regulated by perfusion pressure\textsuperscript{1,2} metabolic demand\textsuperscript{3} and chemical and neural mechanisms\textsuperscript{4} Previous studies comparing CBF with normal aging have demonstrated that blood flow in grey matter decreases with advancing age\textsuperscript{5–10} and that associated cerebrovascular risk factors enhance the age-related CBF decrease in certain regions of the brain\textsuperscript{6,10}.

In addition to the decrease in CBF, signal abnormalities in white matter and periventricular regions disclosed by magnetic resonance imaging (MRI) or computed tomography (CT)\textsuperscript{12} are well known changes that occur with advancing age and in association with an increasing number of cerebrovascular risk factors\textsuperscript{13–17}. Subcortical magnetic resonance hypersignals have been interpreted to be the result of a pathologic increase in tissue water content\textsuperscript{18} but their disease-related specificity and relation to CBF have not yet been fully determined.

The present study was undertaken to elucidate relationships that may exist between cortical grey matter flow (CBF) and the severity of subcortical hypersignals in asymptomatic subjects with cerebrovascular risk factors. Using multiple regression analysis, regional CBF (rCBF) was found to be related to the severity of subcortical hypersignals, age and cerebrovascular risk factors.

Key words:
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SUBJECTS AND METHODS

Cerebrovascular risk factors
We obtained the following nine sets of data from our subjects: age; sex; mean arterial blood pressure (MABP) = diastolic + (0.33 × pulse pressure); history of current or prior cigarette smoking; fasting blood glucose (FBG) concentration; total cholesterol concentration (Tch); venous hematocrit (Ht); and evidence of left ventricular hypertrophy (LVH) and ST-T change (ST-T) on electrocardiographic examination.

Subjects
Forty-seven patients with cerebrovascular risk factors, but without neurologic deficits or low intelligence, as defined by a score on Hasegawa’s dementia scale (HDS) of more than 20, were selected for study and underwent xenon CBF, MRI and laboratory examinations.

All subjects were outpatients who met the following criteria: (1) presence of one or more risk factors for cerebrovascular disease (hypertension, hyperlipidemia, diabetes mellitus, cigarette smoking or electrocardiographic abnormalities); (2) no signs or symptoms of systemic or neurologic disease; (3) not currently under treatment for chronic hypertension, diabetes mellitus or hyperlipidemia, and (4) no past history of stroke. During the study period, no treatment was given for hypertension, diabetes mellitus or hyperlipidemia.

A diagnosis of hypertension was made if blood pressure > 160/90 mmHg or if diastolic blood pressure > 95 mmHg, with use of a conventional mercury sphygmomanometer in the sitting position. Hyperlipidemia and diabetes mellitus were defined as total cholesterol concentration > 240 mg/dl, and fasting blood glucose concentration > 160 mg/dl, respectively. Electrocardiographic abnormalities (left ventricular hypertrophy and ST-T change) were evaluated and a history of current or prior cigarette smoking was obtained.

A complete clinical history was recorded and a neurologic examination was performed for each patient at the time of selection by the same neurologist.

The patients ranged in age from 31 to 85 years (mean = 67.8). Twenty-six were male and 21 were female. MABP ranged from 92 to 143 mmHg (mean = 119.9), Tch ranged from 128 to 312 mg/dl (mean = 212.4), FBG ranged from 85 to 210 mg/dl (mean = 101.9), and hematocrit ranged from 33.2 to 55.2% (mean = 43.6).

The project was reviewed and approved by the Committee on Studies Involving Human Beings of the Osaka National Hospital; informed consent was obtained in each case.

MRI
Magnetic resonance imaging (MRI) was performed using a 1.5 Tesla superconducting unit (Siemens Magnetom H15). Multiple spin-echo (SE) sequences were performed with a repetition time (TR) of 3,000 ms and an echo time (TE) of 90 ms to produce T2-weighted images. T1-weighted images were produced with a TR of 500 ms and a TE of 15 ms. Brain images were obtained parallel to the orbito meatal line (OML). All slices were 8 mm thick and there was a 2 mm gap between slices. Data acquisition time was 4 min for T1-weighted images and 13 min for T2-weighted images. Two-dimensional Fourier transformation of images and a 256 × 256 data acquisition matrix were used.

The MRI scans were reviewed by two observers who had no knowledge of the rCBF data. Special attention was directed to the region of increased signal intensity in the white matter and the deep grey matter, within which the intensity was intermediate between that of normal white matter and that of cerebrospinal fluid (CSF). A region was considered hyperintense if increased signal intensity was identified in T2-weighted images in an area which corresponded to a zone of decreased signal intensity in T1-weighted images. The severity of hyperintensity (HS, hyperintensity score) was categorized with respect to location, size, and multiplicity. Seven regions, including 6 white matter regions and the deep grey matter (on the left and right sides), of four MRI slices from each brain were evaluated at the following locations: 1) at the level of the centrum semiovale (a, anterior; b, posterior); 2) at the level of the roof of the lateral ventricles (c, anterior; d, posterior); 3) at the level of the bodies of the lateral ventricles (e, anterior; f, posterior).
ventricles (e, anterior; f, posterior); and 4) at the level of the basal ganglia (g, basal ganglia-thalamic region). A division was made between the anterior and posterior white matter regions at the center of the interhemispheric fissure for each slice. Each region was assigned a score of 0 to 3 using the following criteria: 0, no white matter lesions; 1, a single white matter lesion present; 2, multiple white matter lesions present; and 3, confluent white matter lesions present. Single lesions were defined as rounded, solitary regions of abnormally high intensity. Confluent lesions were defined as combinations of more than one rounded single, high intensity region that formed an irregularly shaped "lump" or a thick (>5 mm) linear abnormality. Scores between 0 and 42 (maximum score of 3/area×7 areas×2 hemispheres) were possible for each whole brain. The inter- and intra-observer reproducibilities of the total score obtained using this method were high, with r=0.86 (p<0.001) for the former and r=0.81 (p<0.001) for the latter. Therefore, we averaged the scores obtained from two observers.

Fig. 1 shows the MRI in a 79-year-old man who had essential hypertension, hyperlipidemia, left ventricular hypertrophy and multiple confluent signal abnormalities in the white matter and the deep grey matter. Regions "a"-"g" in the left side are indicated by lines. The average scores in the left and right sides of the brain were as follows; a, 0; b, 0; c, 2.25; d, 1.5; e, 2.75; f, 2.0; g, 2.5; and total, 22.0.

**Xe-133 CBF**
### TABLE I MULTIPLE REGRESSION ANALYSIS OF BLOOD FLOW IN THE CORTICAL GREY MATTER WITH THE SEVERITY OF SUBCORTICAL HYPERINTENSITY AND CEREBROVASCULAR RISK FACTORS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Partial regression coefficient</th>
<th>Standardized partial regression coefficient</th>
<th>Partial correlation coefficient</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS</td>
<td>-0.688</td>
<td>-0.511</td>
<td>-0.522</td>
<td>15.71</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>-0.732</td>
<td>-0.326</td>
<td>-0.381</td>
<td>7.13</td>
<td>&lt;0.025*</td>
</tr>
<tr>
<td>Age (year)</td>
<td>-0.251</td>
<td>-0.304</td>
<td>-0.318</td>
<td>4.69</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>ST-T (yes)</td>
<td>-0.234</td>
<td>-0.302</td>
<td>-0.202</td>
<td>4.22</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>MABP (mmHg)</td>
<td>-0.047</td>
<td>-0.063</td>
<td>0.16</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Male (yes)</td>
<td>-0.041</td>
<td>-0.045</td>
<td>0.08</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>0.013</td>
<td>0.018</td>
<td>0.01</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>LVH (yes)</td>
<td>-0.006</td>
<td>-0.007</td>
<td>0.00</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>TCh (mg/dl)</td>
<td>0.006</td>
<td>0.082</td>
<td>0.00</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Smoking (yes)</td>
<td>-0.002</td>
<td>-0.003</td>
<td>0.713</td>
<td>10.84</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

HS, hyperintensity score; Ht, hematocrit; ST-T, ST-T change in ECG; MABP, mean arterial blood pressure; Male, male sex; FBG, fasting blood glucose; LVH, left ventricular hypertrophy in ECG; TCh, total cholesterol; NS, not significant.

*correlation is significantly different from zero.

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**CBF was measured, with the patients lying supine in a quiet room with the eyes open and the ears unplugged, using the $^{133}$Xe injection method originally described by Obrist et al.**

A helmet-type parallel 32-detector system (Valmet, Sweden). Sodium-iodine (Na-I) scintillation detectors with 25 mm×12.5 mm crystal were placed against the subject's head with sixteen to a cerebral hemisphere and in contralaterally symmetrical pairs. The energy discriminator was set at 20 to 100 KeV in order to count both the 31- and 81-KeV photons of the $^{133}$Xe isotope.

After bolus injection of 740 MBq (20 mCi) of $^{133}$Xe in saline into an antecubital vein, the clearance curve was recorded over a 10 min period from each head detector and from a separate detector that monitored the radioactivity in expired air. Data from each detector were stored, and relative CBF was calculated based on the fast compartment (F1) data obtained using compartmental indices. Arterial CO2 levels ($P_{ET}CO_2$) were monitored as a percentage of expired air CO2 using a capnograph. CBF correction for individual PCO2 changes was not performed since all patients were normocapnic (39.2±2.8 mmHg). For data analysis, mean values were computed for the whole brain, the frontal probes (F1−F5), the central probes (C1, C2), the temporal probes (T1−T3), the parietal probes (P1−P4), and the occipital probes (01, 02).

**Statistical Analysis**

Data are presented as the mean±standard deviation (SD). Statistical analyses were performed using Kruskal-Wallis and Mann-Whitney U tests, simple regression analysis, or a multiple regression model with the stepwise forward selection method.

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RESULTS

There were no significant right-left asymmetries of regional HS (rHS) or rCBF for any of the regions tested. Therefore, the average values of the right and left sides of the brain were calculated and used for analysis (Fig. 2). MRI signal abnormalities in the white matter or in the deep grey matter were observed in 43 of 47 patients (92%), but none of the patients showed abnormalities in their cortical grey matter. HS for the brain as a whole ranged from 0 to 28.5 (mean=7.9±10.4). Regional HS had a wide distribution and included all degrees of severity. A significant difference ($\chi^2=46.5$; $p<0.001$) was observed between the 7 subcortical regions (Kruskal-Wallis test). Regional HS was highest in region “f” and lowest in region “b” (Fig. 2A). There was also a significant variation ($\chi^2=31.5$; $p<0.001$) in rCBF among the five cortical grey matter regions, with the lowest value in the occipital region and the highest value in the central region (Fig. 2B).

A multiple regression analysis was performed which treated CBF for the whole brain as a dependent variable, and HS for the whole brain, Ht, age, ST-T change, MABP, male sex, FBG, LVH, Tch, and smoking as independent variables (Table I). Of the ten initial independent variables, HS (F=15.71; $p<0.001$), Ht (F=7.13; $p<0.025$), age (F=4.69; $p<0.01$) and ST-T change (F=4.22; $p<0.01$) were found to be significant determinants of CBF. The final predictive equation obtained was: CBF=120.73−0.688×HS−0.732×Ht−0.251×age−7.389×(ST-T change). The coefficient of determination ($R^2$) was 0.507, $R^2$ adjusted for degrees of freedom was 0.461, and the multiple correlation coefficient was 0.713. The results were significant ($F=10.84$; $p<0.001$). For purposes of illustration, plots of CBF against HS in the whole brain are presented in Fig. 3.

Correlation coefficients, obtained using a simple regression analysis, were calculated between rHS and rCBF (Table II). The severity of hypersignals in regions “d”, “e”, “f” and “g” was significantly and negatively correlated with rCBF for all cortical grey matter regions, while rHS in regions “a” and “b” had no such correlation. Weaker, but still significant, inverse correlations were observed between rHS in region “c” and rCBFs in the frontal, temporal and occipital cortices. Regional HS in region “g” had the most significant negative correlations with the rCBFs of all of the regions in the cortical grey matter. Fig. 1 is an MRI of a patient with reduced CBF and severe signal abnormalities in the white matter and deep grey matter.

DISCUSSION

Our results confirm the high incidence of white matter changes and the wide range of signal abnormalities present in asymptomatic individuals with cerebrovascular risk factors. It has been generally accepted that subcortical MRI signal abnormalities are closely related to advancement in age and the presence of cerebrovascular risk factors. 

In addition, Naritomi et al. and Shaw et al.
have reported that cerebrovascular risk factors enhance the age-related decline in CBF. Therefore, multiple regression analysis is required to separate the effects of cerebrovascular risk factors on CBF from that of hypersignals. Multiple linear regression was used to analyze the complex relationships between the variables which are thought to contribute to cortical CBF. However, we did not intend to derive a rule for predicting CBF. In addition, care should be taken in extrapolating our results because our population was selected from hospitalized subjects, and the quantitative effects of cigarette smoking and electrocardiographic abnormalities on cortical CBF were difficult to analyze. However, we did find that HS, hematocrit, age and ST-T change in the electrocardiogram were each independent determinants of CBF. Hematocrit has been shown to be a major determinant of blood viscosity\textsuperscript{22} and hemorheological factors are known to play an important role in influencing brain perfusion.\textsuperscript{23} The loss of cerebral neurons\textsuperscript{24} and the decrease in synaptic density\textsuperscript{25} associated with normal aging have been thought to reduce metabolic demands and, therefore, blood flow. Ischemic change in coronary arterioles, as disclosed by histological examination, is a well known risk factor for stroke\textsuperscript{26} It is important to note that even when cerebrovascular risk factors were controlled, the degree of MRI signal abnormalities had the most significant negative correlation with CBF.

Few published reports have studied the relationship between magnetic resonance subcortical hypersignals and rCBF in asymptomatic individuals\textsuperscript{17,27} Fazekas et al\textsuperscript{17} reported that patients with white matter signal abnormalities had a lower mean grey matter blood flow (F1), and a more significant reduction in blood flow of the slow-flowing compartment (F2) than patients without such abnormalities. They interpreted the reduced F2 as an indication of microvascular disturbances associated with white matter lesions. Meguro et al\textsuperscript{27} using the oxygen-15 steady-state technique, found decreased CBF and CBF/cerebral blood volume (CBV), and an elevated oxygen extraction fraction in the grey matter of patients with severe periventricular hyperintensity (PVH). They speculated that PVH revealed by MRI is a consequence of impaired grey matter circulation.

Hyperfrontal distribution of rCBF was not seen in our subjects. Tsuda and Hartmann\textsuperscript{28} reported the disappearance of a hyperfrontal pattern in patients between 50 and 70 year old. Several mechanisms might be proposed to explain the relationship between MRI signal abnormalities and decreased flow in grey matter. The question here is whether the decrease in CBF is a cause or an effect of subcortical hyperintensities. White matter or deep grey matter ischemia occurring as a consequence of impaired cerebral circulation is one possibility. We found significant regional differences in HS. Hypersignals were frequently observed in the posterior (region "P") or anterior (region "E") white matter at the level of the bodies of the lateral ventricles. Most hyperintensities were located in the border zones between the deep cerebral branches of the anterior, middle and posterior cerebral arteries, while no signal abnormalities were detected in the cortical grey matter. Differences between the vasculature and the tolerance to ischemia of the grey and white matter have been proposed as explanations for the vulnerability of the deep white matter. However, in a middle cerebral artery occlusion model for the cat\textsuperscript{29,30} ischemic tolerance for the failure of electrical conduction was somewhat higher in the white matter than in the grey matter. The white matter and the deep grey matter may be more vulnerable to ischemia than the cortical grey matter because each of the perforating cerebral arteries which supply the periventricular white matter and the basal-ganglia thalamic region is considered an end-artery, with minimal overlap and anastomosis present in the territories of the different groups\textsuperscript{31} Progressive atherosclerosis of the small vessels may preferentially induce white matter ischemia rather than cortical grey matter ischemia.

Microvascular disturbances may not be the only explanation for the decrease in CBF. Another noteworthy hypothesis is that the decrease in CBF is caused by neuronal deactivation due to the disruption of neural pathways by subcortical lesions. This hypothesis seems probable since in our study cortical grey matter had no hypersignals and CBF had a strong negative correla-
tion with HS. If the decrease in CBF reflects only a microvascular disturbance, the negative correlation between rHS and rCBF would be strongest in the region with the highest HS. We found that in certain regions the correlation coefficient between rHS and rCBF was not necessarily dependent upon the degree of hyperintensity, and that the rHS in the basal ganglia-thalamic regions had the most significant negative correlations with the rCBFs of all of the regions in the cortical grey matter. A possible explanation for these results is that efferent projections from some regions are anatomically more prominent to the corresponding regions which have reduced rCBF. The neural deactivation may be related to the density of projections of afferent and efferent fibers between the subcortical nuclei and the cerebral cortex, and to the depth or the site of interruption of these fibers by subcortical lesions. In the basal ganglia-thalamic region, the internal capsule contains all of the efferent and afferent fibers which go to or come from the cerebral cortex. Therefore, lesions in this region may be functionally more important than those in other regions.

In the present study, we only used data which concerned compartmental indices that provide estimates of grey matter blood flow, i.e., F1 values. F2 values are of limited usefulness for the localization of CBF in deeper structures and its differentiation from the flow in overlying tissues. Positron emission tomography (PET) and cold xenon CT studies have revealed decreases in CBF and metabolism in symptomatic patients with subcortical hypersignals. Herholz et al. using 18F-fluoromethane, found that large subcortical white matter lesions induce clear focal CBF reductions in adjacent border zone cortex in patients with carotid atherosclerosis. Yao et al. in their study of patients with vascular dementia of theBinswanger type, reported that both the CBF and the cerebral metabolic rate for oxygen were reduced in the white matter in association with the presence of hypersignals, and that both were also decreased in the cortical grey matter, where no abnormalities were detected by CT or MRI. Kawamura et al. using cold xenon CT, showed that reduced cerebral perfusion in the putamen and thalamus correlated best with the severity of leukoaraiosis in patients with vascular dementia. We found that, even in asymptomatic subjects with cerebrovascular risk factors, the severity of subcortical hypersignals was closely correlated with the decrease in CBF in the cortical grey matter. In asymptomatic subjects, the use of PET for blood flow and metabolic studies may permit more precise comparisons of the rCBF changes which occur at the site of magnetic resonance abnormalities (white matter or deep grey matter) and in remote regions (cortical grey matter) which show functional suppression but remain structurally intact.

In summary, we found that major determinants of decreased CBF in asymptomatic individuals include the severity of hypersignals using MRI, the presence of microcirculatory disturbance associated with hemorheological factors and an increase in cerebrovascular risk factors. Impaired flow in cortical grey matter may be a cause of white matter ischemia and/or a result of functional suppression of cerebral cortex due to neuronal disconnection induced by subcortical lesions.

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