Regional Difference in Cerebral Blood Flow and Oxidative Metabolism in Human Cortex

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We sought to determine if there are regional differences in cerebral blood flow (CBF) and cerebral metabolic ratio for oxygen ($CMRO_2$) in normal subjects during the resting state. **Methods:** Regional CBF, $CMRO_2$ and oxygen extraction fraction (OEF) in 15 normal volunteers (mean age 58.8 ± 8.2 yr) were measured during rest using PET and a ^{15}O-gas steady-state technique. **Results:** CBF and $CMRO_2$ in the visual cortex were significantly higher than those in other cortices. Additionally, OEF in the sensorimotor cortex was significantly lower than that in other cortical regions. **Conclusion:** CBF and $CMRO_2$ in the visual cortex are always high, and low OEF in the sensorimotor cortex exists even in a resting state in normal subjects. We hypothesize that these regional functional differences would result in different resistances to degeneration.

Key Words: cerebral blood flow; cerebral oxygen metabolism; primary visual cortex; primary sensorimotor cortex; PET

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Relation between regional cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) or cerebral metabolic rate for glucose (CMRGlu) have been reported to be constant in normal brain in the resting state (*1,2*). On the other hand, Fox and Raichle (*3*) reported on focal uncoupling of CBF and $CMRO_2$ during somatosensory stimulation using ^{15}O-water and ^{15}O-oxygen gas PET imaging. Fukuyama et al. (*4*) reported that the temporoparietal metabolic ratio ($CMRO_2$/CMRglu) was higher in the resting state in Alzheimer's disease patients compared to healthy controls. This implicates a metabolic shift from glycolytic to oxidative metabolism in the temporoparietal regions of Alzheimer's disease patients. This phenomenon suggests that the temporoparietal oxygen extraction fraction (OEF) is high in OEF images of Alzheimer's disease patients. In routine PET studies, we often see increased parietal OEF compared to that of the primary sensorimotor cortex in the patients with Alzheimer's disease. We sometimes observe this contrast between the primary sensorimotor and parietal cortical OEF in normal aged subjects. In Alzheimer's disease, perfusion and metabolism in temporal, parietal and frontal regions are reduced and those of visual and sensorimotor cortices are preserved. We speculated that there might be a functional difference between the affected regions and the preserved ones. The aim of this study was to evaluate the regional difference of CBF and $CMRO_2$ and to elucidate the differences in regional OEF in normal subjects in a resting state using PET and steady-state technique (*5*).

MATERIAL AND METHODS

Subjects

We studied 15 healthy normal volunteers (11 women, 4 men; age 42–73 yr; mean age 58.8 ± 8.1 yr) who were recruited from social activist groups and had no clinical evidence of cognitive deficits or neurological disease. All subjects had no abnormal findings except age-related brain atrophy on magnetic resonance (MR) images. Informed consent was obtained from all subjects and the PET study was approved by our institution's Ethical Committee.

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MRI

Before PET scanning, all subjects underwent MRI for diagnosis and anatomical references for the PET study. The MR scanner has a circularly polarized head coil as both transmitter and receiver. Sagittal, coronal and axial Tl-weighted SE images (repetition time [TR] msec/echo time [TE] msec = 550/15, two excitations, 5 mm thickness, 2.5 mm gap) and axial T2-weighted fast SE images (3000/21,105, two excitations) were used for diagnosis. Three-Dimensional Spoiled Gradient Echo images (TR 14 msec, TE 3 msec, flip angle 20°, 1.5 mm thickness by 124 slices) served as references for posthoc anatomical analysis of PET. These MR images were obtained days before PET examination (range: 0–14 days).

Immediately before the PET examination, sagittal gradient-echo images (TR/TE = 60/2.9, 10 mm thickness) were obtained to determine the coordinates for positioning the patient's head on the PET table. A headholder was used and the subject's head was positioned horizontally on the MR table. Three landmarks indicating the iso-center of the field of view (FOV) were placed on the headholder. On the midsagittal section, the angle of the anterior commissure-posterior commissure (AC-PC) plane to the horizontal plane and the distance between the AC-PC plane and the iso-center of FOV were determined. These parameters were used to determine the coordinates of the head on the PET table.

PET

The PET scanner has four rings located 13 mm apart and yields a transverse resolution of 4.5 mm FWHM (*6*). The slice interval was 6.5 mm when the z-motion mode was used.

The subject's head was placed horizontally on the PET scanner table and the gantry and scanner table were adjusted according to the coordinates determined during the MRI study, so that scans were taken parallel to the AC-PC plane from 32.5 mm below to 52.0 mm above the AC-PC plane at 6.5-mm intervals.

Cross-calibration between the scanner and the well counter and the cross-planes of the scanner was obtained before each study. A transmission scan was obtained using $^{68}Ga/^{68}Ge$ for absorption correction after subject positioning. PET studies were performed under resting conditions with eyes closed and ears unplugged. CO_2 and O_2 labeled with ^{15}O were inhaled continuously at 200 MBq/200 ml/min and 500 MBq/200 ml/min, respectively. Emission scans were performed during inhalation of $C^{15}O_2$ and $^{15}O_2$ after equilibrium was reached and confirmed with the head activity curve measured by the detector banks of the scanner. The $C^{15}O$ emission scan started 2-3 min after a 1-min inhalation of 2000 MBq/200 ml $C^{15}O$. Scanning took 10 min for $C^{15}O_2$ and $^{15}O_2$ and 4 min for $C^{15}O$. Arterial blood sampling was performed from a catheter placed in the radial artery three times during the scan session (at the start of scan, at the midpoint and 30 sec before the end of the scan) to determine radioactivity and blood gas analysis.

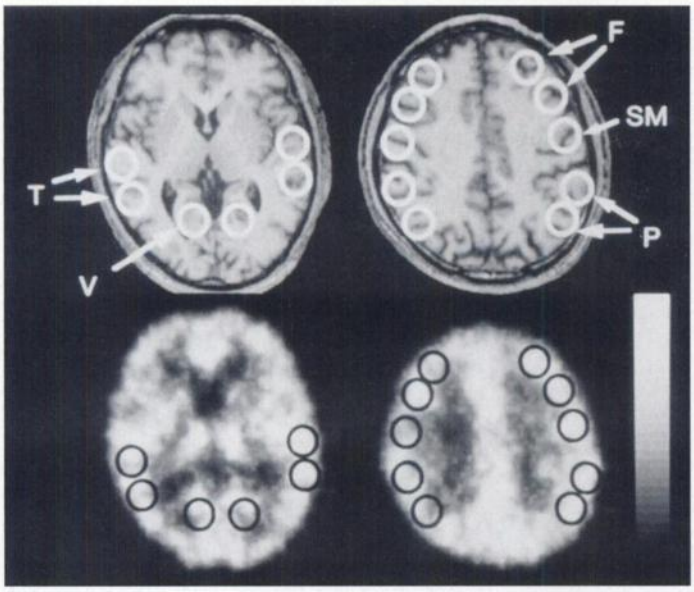

FIGURE 1. MR image and CBF image from a 54-yr-old healthy man with overlaid ROIs. T = temporal; V = visual; F = frontal; SM = sensorimotor; P = parietal cortex.

During the examination, head stability was monitored by laser marker.

Calculations. CBF, $CMRO_2$ and OEF were calculated with the data obtained by the steady-state method using ^{15}O-labeled gases (*5*). Cerebral blood volume (CBV) was calculated by the 1-min inhalation of ^{15}O-labeled carbon monoxide and was incorporated in the correction of the vascular space for $CMRO_2$ and OEF (*7*).

Data Analysis

PET and MR image datasets were directly transmitted to a workstation from the PET and MRI units and analyzed using image analyzing software. MR three-dimensional spoiled gradient echo images were reconstructed in parallel to the AC-PC plane as references. Both PET and MR images were displayed side-by-side and one or two circular regions of interest (ROIs, 3.14 cm^2) were determined on the cortical ribbon of each region on CBF image (Fig. 1). We took care not to include the sinus in the ROIs by comparing the CBF image with the CBV image. The same ROIs were transferred to the OEF, $CMRO_2$ and CBV images and regional OEF, $CMRO_2$ and CBV were measured.

Statistical Analysis

The calculated data were compared for regional differences among the temporal, visual, frontal, sensorimotor and parietal regions by repeated measures one-way analysis of variance (ANOVA) with posthoc Scheffé's tests. A probability value less than 0.05 was statistically significant.

RESULTS

Mean regional CBF, $CMRO_2$, OEF and CBV in the temporal, visual, frontal, sensorimotor and parietal cortex are shown in Table 1. The CBF, $CMRO_2$ and CBV in the visual cortex were significantly higher than other regional CBF, $CMRO_2$ and CBV, although there were no significant differences among the temporal, frontal, sensorimotor and parietal CBF, $CMRO_2$ and CBV. On the other hand, the mean OEF in sensorimotor cortex was significantly lower than any other regional OEF, and there was no significant difference among other regional OEF.

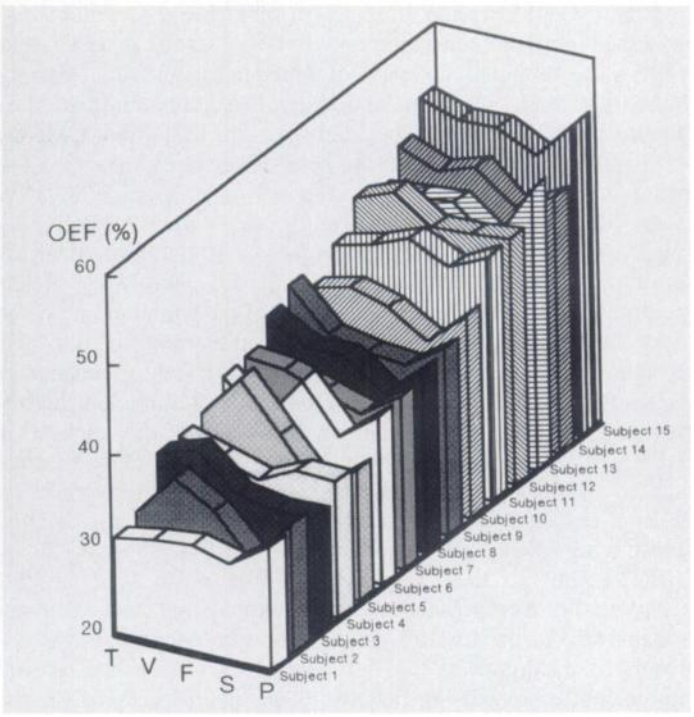

FIGURE 2. Individual regional OEF. T = temporal; V = visual; F = frontal; S = sensorimotor; P = parietal cortex. OEF in the sensorimotor cortex was the lowest in every subject except in Subject 4.

Figure 2 shows the individual regional OEF in the temporal, visual, frontal, sensorimotor and parietal cortex of each subject. Except in Subject 4, the OEF in the sensorimotor cortex was the lowest in each individual regional OEF.

DISCUSSION

The hypothesis that a tight coupling exists between cerebral metabolism and perfusion has been widely accepted (*8*). Increased neuronal metabolic activity will result in accumulation of vasoactive catabolites, which decrease vascular resistance and thereby increase blood flow until normal homeostasis is reestablished. However, Lou et al. (*9*) reported that the concept of coupling blood flow to brain function might need reevaluating, since direct anatomical or functional evidence for local neurogenic control of perfusion is still lacking.

Fox and Raichle (*3*) investigated the coupling of blood flow and metabolism during focal, physiological increase in neuronal activity in humans. Rapid-sequence serial measurements of the

TABLE 1
Regional CBF, $CMRO_2$, OEF and CBV in Normal Healthy Subjects

Parameter	Temporal	Visual	Frontal	Sensorimotor	Parietal
CBF (ml/100 ml/min)	56.3 ± 8.8	66.1 ± 12.9*	54.8 ± 8.9	55.2 ± 10.3	52.2 ± 9.1
$CMRO_2$ (ml/100 ml/min)	3.79 ± 0.72	4.36 ± 1.03*	3.59 ± 0.60	3.40 ± 0.56	3.49 ± 0.64
OEF (%)	41.3 ± 6.6	41.3 ± 6.1	40.6 ± 6.5	38.4 ± 6.5*	41.2 ± 6.9
CBV (ml/100 ml)	5.33 ± 0.74	7.01 ± 1.05†	4.71 ± 0.61	4.86 ± 0.81	4.80 ± 0.82

Values are mean and standard deviation. CBF, $CMRO_2$ and CBV in the visual cortex is significantly higher than those in other cortices. The OEF in the sensorimotor cortex is significantly lower than that in other cortices. Significantly different from others (*$p < 0.05$, †$p < 0.01$).

regional $CMRO_2$ were made in nine healthy volunteers. Matched regional measurement of CBF, $CMRO_2$, CBV and OEF were obtained for each of four states: an initial resting state followed by three sets of unilateral vibratory stimulation of finger pads. Discrete focal increases in CBF and $CMRO_2$ occurred in every subject in the hemisphere contralateral to the stimulation. These increases were not in proportion to each other. CBF increased significantly more than $CMRO_2$, as measured during identical conditions of stimulation in identical brain regions in the same subject. Similarly, a highly significant decline in OEF occurred. The duration of the stimulation did not alter the results. The discrepancy between increases of flow and metabolism cannot be explained by any transient overshoot in CBF or any transient lag in $CMRO_2$. The findings are highly focal. Throughout the remainder of the brain, the relation of CBF and $CMRO_2$ was unchanged. In our study, we demonstrated a significantly low OEF in the sensorimotor cortex in 15 normal subjects during a resting state. We could not demonstrate a significant difference in either mean CBF, $CMRO_2$ or CBV except in the visual cortex. The mean CBF in the sensorimotor cortex was not the lowest in the cortical areas examined, but the $CMRO_2$ in the sensorimotor cortex was the lowest. This slight low $CMRO_2$ caused the OEF in the sensorimotor cortex to be significantly lower than the other regional OEF, although there was no significant difference among the other regional OEF. We speculate that the OEF in the sensorimotor cortex is usually lower than that in other cortices, even in the resting state. When this cortical area is activated (e.g., under somatosensory stimulation) the decline of OEF will be enhanced, as Fox and Raichle reported (*3*).

The neocortex presents several minor differences in various parts of the brain. These differences were shown histologically by Brodmann (*10*) and von Economo (*11*). Brodmann distinguished some 50 different areas by the varying thickness, varying densities of cells and differences with regard to the size and types of cells in the neocortex. On the other hand, von Economo's cytoarchitectural map is simpler than that of Brodmann. He arranged the different areas in five fundamental groups. They were distinguished as: type 1: angular cortex; 2: frontal type cortex; 3: parietal type; 4: polar type; and 5: granular cortex, koniocortex.

The regions, sensorimotor, frontal, parietal, temporal and occipital area, in which we placed ROIs are adapted to the regions in von Economo's map: type 1, type 2, type 3 and type 4, respectively. The cortex of type 1 is distinguished by its lack of distinct granular layers (II and IV), whereas layers III and V are well developed. Between the larger pyramids in the fifth layer, the giant pyramids of Betz are found. Our study revealed that a slight decline in OEF was found in the type 1 area, whereas in type 2, 3 and 4 areas the level of OEF was higher than that of the type 1 area. In the type 4 area, the occipital lobe, the CBF, $CMRO_2$ and CBV were much larger than those in other areas. This would be due to the cytoarchitecture of the type 4 area and the amount of gray matter. Sensorimotor area and visual cortex are minimally affected in Alzheimer's disease (*12*) because of the difference in perfusion, metabolism and cytoarchitecture. Therefore, the sensorimotor cortex has a decline in OEF and construction of type 1, and the visual cortex has large CBF and $CMRO_2$ and construction of type 4. However, the temporal, frontal and parietal lobes, mainly consisting of types 2 and 3 areas, have the same level of CBF, $CMRO_2$, CBV and OEF. These regional differences indicate that the primary sensorimotor cortex and visual cortex should be resistant to the neuronal degeneration that occurs in Alzheimer's disease.

CONCLUSION

The CBF and $CMRO_2$ in the visual cortex were high and the OEF in the sensorimotor cortex was significantly lower compared to that in other regions during rest. This suggests that these cortices have resistance to degeneration.

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