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CEREBRAL BLOOD FLOW, BLOOD VOLUME AND OXYGEN UTILIZATION

NORMAL VALUES AND EFFECT OF AGE

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SUMMARY

Regional cerebral blood flow (CBF), oxygen extraction ratio (OER), oxygen utilization ($CMRO_2$) and blood volume (CBV) were measured in a group of 34 healthy volunteers (age range 22–82 yrs) using the ^{15}O steady-state inhalation method and positron emission tomography. Between subjects CBF correlated positively with $CMRO_2$, although the interindividual variability of the measured values was large. OER was not dependent on $CMRO_2$, but highly negatively correlated with CBF. CBV correlated positively with CBF. When considering the values of all the regions of interest within a single subject, a strict coupling between $CMRO_2$ and CBF, and between CBF and CBV was found, while OER was constant and independent of CBF and $CMRO_2$. In 'pure' grey and white matter regions $CMRO_2$, CBF and CBV decreased with age approximately 0.50% per year. In other regions the decline was less evident, most likely due to partial volume effects. OER did not change or showed a slight increase with age (maximum in the grey matter region 0.35%/yr). The results suggest diminished neuronal firing or decreased dendritic synaptic density with age.

INTRODUCTION

Several studies concerning cerebral energy metabolism in vivo in healthy volunteers have been reported. Their aim was to determine the effects of age or to obtain normal values to compare with results in patients. The results have been partially conflicting and each new report seems to contribute to the confusion. Cerebral blood flow (CBF), cerebral metabolic rates of glucose (CMRglu) and oxygen ($CMRO_2$) are the functions which have been measured, either separately or in different combinations. Under physiological steady-state conditions CBF is coupled to the level of cerebral oxygen and glucose consumption (Sokoloff *et al.*, 1977). It is still unclear what mechanisms are responsible for the coupling between blood flow and energy requirements (Lou *et al.*, 1987).

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Both global and regional values have been determined using various techniques. Kety and Schmidt (1948) developed a technique using nitrous oxide to measure blood flow, oxygen and glucose utilization in brain globally. Kety (1956) reported a global decline of CBF, CMRglu and $CMRO_2$ with age. Most studies using in vivo techniques such as nitrous oxide, ^{133}Xe wash-out measurements or positron emission tomography (PET) show a decline of CBF with age. An exception is the study of Yamaguchi *et al.* (1986). With respect to oxygen or glucose utilization the situation is less clear: some studies have reported a decline with age (Kety, 1956; Kuhl *et al.*, 1982; Lebrun-Grandié *et al.*, 1983; Pantano *et al.*, 1984; Yamaguchi *et al.*, 1986), whereas others showed no such change (Duara *et al.*, 1983, 1984; De Leon *et al.*, 1983, 1984). Previous studies from our group (Frackowiak and Lenzi, 1982; Lenzi *et al.*, 1983) indicated a decline of $CMRO_2$ with age but with a more pronounced decrease of CBF.

Since these reports the ^{15}O steady-state technique has been refined through the introduction of a correction for intravascular signal in the $^{15}O_2$ scan (Lammertsma *et al.*, 1983*a*, *b*) and multiple arterial blood sampling during all scans (Lammertsma *et al.*, 1988). We now report new data using the improved oxygen-15 steady-state inhalation technique and PET in a group of 34 healthy subjects. We measured regional CBF, $CMRO_2$, OER (oxygen extraction fraction) and CBV (cerebral blood volume) to obtain normal values for comparison with our patient studies and to study the effect of age.

SUBJECTS

The group of healthy volunteers consisted of 16 female and 18 male subjects, who were equally represented across the age range (22–82 yrs; mean ± SD 45.1 ± 15.2; median 45). From the second to the sixth decades at least 5 subjects were included for each decade. In the seventh and eighth decades only 1 subject was available in each. The volunteers were recruited from hospital staff and relatives of patients studied in our clinical research protocols. The selection criteria were an unremarkable past medical and family history, no use of drugs, and a normal clinical examination with no signs of mental or physical abnormality. Only 1 examiner was involved in history taking and investigation. Neither CT nor MRI scans were performed. No standardized formal mental state questionnaire supplemented the clinical examination. The subjects were nonsmokers and had normal body weights.

Systolic and diastolic blood pressures were 121 ± 16 mmHg and 77 ± 10 mmHg, respectively. The pulse was 72 ± 11 per min. Blood samples were taken as part of the scanning procedure (*see* below) to measure haemoglobin, arterial oxygen content and pCO_2. The haemoglobin (Hb) concentration was 13.5 ± 1.1 g/dl, the arterial oxygen content 0.1835 ± 0.0140 ml/ml and the pCO_2 5.466 ± 0.324 kPa (41 ± 2.4 mmHg).

The project was approved by the Research Ethics Committee of the Hammersmith Hospital and permission for use of the appropriate radionuclides was obtained from the UK Administration of Radioactive Substances Advisory Committee. All volunteers gave their written informed consent.

METHODS

Radionuclides

The positron emitting radionuclides used in this study were oxygen-15 (2.1 min radioactive half-life) and carbon-11 (20.3 min radioactive half-life). The radionuclides were produced by a 16 Mev deuteron

cyclotron, situated close to the scanning unit. The radiolabelled gaseous tracers ($C^{15}O_2$ and $^{15}O_2$) were produced 'on-line' (Clark and Buckingham, 1975) and continuously administered during the scanning procedure. The carbon-11 labelled tracer (^{11}CO) was produced in a batch before administration.

Scanning procedure

PET scans were performed using a whole body single slice positron emission tomograph (ECAT II, EG and G ORTEC) (Phelps *et al.*, 1978; Williams *et al.*, 1979). Data were collected in the medium resolution mode (FWHM = 16×16×16 mm). The ^{15}O steady-state inhalation technique was applied to measure regional CBF, CBV, OER, and $CMRO_2$. The advantages, limitations and improvements of the steady state inhalation technique have been described in detail elsewhere (Jones *et al.*, 1976; Frackowiak *et al.*, 1980; Lammertsma *et al.*, 1981, 1982, 1983*a*, *b*). In brief, the subjects sequentially inhaled trace doses of oxygen-15 labelled $C^{15}O_2$ and $^{15}O_2$ and carbon-11 labelled ^{11}CO through a small plastic face mask. The tracers were delivered continuously in a constant flow of air (0.5 l/min) and at a constant concentration for $C^{15}O_2$ and $^{15}O_2$; ^{11}CO was delivered as a bolus but in a constant flow of air. The radioactive doses of the delivered air were 20.8, 60.9 and 86 mCi/min for $C^{15}O_2$, $^{15}O_2$ and ^{11}CO, respectively. A plastic hood covering the face was connected to an air extraction device to remove to waste redundant and expired radioactivity.

The subjects were positioned on the scan couch without plugging the ears. They were instructed to close their eyes. Typically, 3 cross-sections (planes) through the brain were scanned. The 3 planes were chosen in relation to the orbitomeatal line (OM line) which was lined up with a laser beam after positioning the subject on the scanning couch. The lower plane (plane 1) was 2 cm above the OM line (OM+2) 'cutting through', the cerebellum. The middle plane (plane 2) was 4 cm (OM+4) and the higher plane (plane 3) 6 cm (OM+6) above the OM line, 'cutting through' insular grey matter and planum temporale, repectively. Adjustable cushions supporting both cheeks helped to keep the head immobile. The position of the head was checked throughout the scanning procedure with the help of a grid of light projected on the forehead of the scanned subject. With constant supervision, movement was immediately detectable. When deviations from the original position were noted, immediate correction was performed manually. Such corrections were rarely necessary.

When $C^{15}O_2$ is inhaled, rapid transfer of the oxygen-15 label to $H_2{}^{15}O$ takes place in the lung (West and Dollery, 1962). Continuous steady breathing of $C^{15}O_2$ results in a steady supply of radiolabelled $H_2{}^{15}O$ in the arterial blood, which distributes through the body. At steady-state, the level of $H_2{}^{15}O$ accumulated in a region of brain tissue in relation to that being delivered to the brain via the arterial blood is directly (although not linearly) proportional to the blood flow to that region (Jones *et al.*, 1976). When a steady-state was reached, usually between 8 and 10 min after the start of tracer inhalation, three 5 min emissions scans (each scanning the cross-sections (planes 1, 2 and 3) of the brain described above) were performed. Steady-state of brain radioactivity was checked using a continuous readout of the total count rate. Typically between 1 and 2 million counts were collected for each of the 3 planes. The total time that $C^{15}O_2$ was breathed amounted to 25 min. When data had been collected for plane 3, tracer administration was stopped. While the cerebral radioactivity decayed rapidly, the next tracer ($^{15}O_2$) was prepared and the procedure was repeated as for the $C^{15}O_2$ inhalation. At steady-state, the regional radioactivity in the brain during $^{15}O_2$ inhalation is determined by the oxygen extraction and its conversion into metabolic $H_2{}^{15}O$, recirculating $H_2{}^{15}O$ of metabolism, and intravascular $^{15}O_2$ (the fraction not extracted from haemoglobin) (Frackowiak *et al.*, 1980; Lammertsma *et al.*, 1981). Oxygen extraction can be calculated since it is possible to correct both for the recirculating water (using the $C^{15}O_2$ perfusion scan data), and for the intravascular component (an additional ^{11}CO scan; *see* below).

To correct the emission scans for tissue attenuation, transmission scans (330 s duration each) were performed using an external ring source of ^{68}Ge resulting in the collection of 5×10^6 counts per scan. The last part of the procedure consisted of breathing ^{11}CO tracer for 2−3 min. The tracer was then allowed to equilibrate (checked again using the chart recorder) in the blood compartment for about 4 min. This was followed by 5 min scans of each of the 3 planes. Typically, 200−300 × 10^3 counts per plane were

obtained. Since ^{11}CO is bound to haemoglobin only, the measured regional brain radioactivity allows calculation of regional CBV by comparing tissue concentration of tracer to that in the arterial blood (Phelps *et al.*, 1979; Lammertsma *et al.*, 1983*a*, *b*; Pantano *et al.*, 1985) and subsequent correction of tissue OER for nonextracted intravascular activity.

The total duration of scanning, including transmission scan, was almost 2 h. The average effective dose equivalent for all subjects was 26.31 mSv (range 18.93 – 38.53 mSv).

During both steady-state emission scans, 3 arterial blood samples were taken via a short radial artery catheter (Teflon-R gauge 21), which was inserted, using a long-acting local anaesthetic, before the scanning procedure. The taking of blood samples was painless and hardly noticed by the scanned subject. The samples (both whole blood and plasma) were measured in a well-counter that was cross-calibrated with the tomograph. An additional blood sample was taken during steady-state to determine blood gases (pCO_2, pO_2) pH and Hb content. The values obtained were used to calculate arterial oxygen concentration (ml/ml). During the ^{11}CO emission scans, 3 arterial blood samples in total were taken and whole bood radioactivity was measured in the well-counter.

DATA ANALYSIS

Reconstruction

After data collection, radioactivity distribution across the 3 planes was determined by a standard (filtered back projection) tomographic reconstruction technique resulting in quantitative images. All transmission and emission scans were reconstructed with the medium resolution reconstruction filter (16 mm FWHM) (Phelps *et al.*, 1978). Transmission scans were used to correct for tissue attenuation. After reconstruction of the radioactivity distribution, images were converted pixel by pixel into absolute units of blood flow, blood volume, oxygen extraction and oxygen utilization. This was achieved by solving the appropriate mathematical equations which relate cerebral tissue radioactivity to arterial blood radioactivity. CBF was expressed as ml blood/100 ml brain/min; CBV as ml blood/100 ml brain; OER as percentage, and $CMRO_2$ as ml oxygen/100 ml brain/min. For calculation of CBV a ratio of 0.85 (Grubb *et al.*, 1978) for small vessel versus large vessel hematocrit was used. $CMRO_2$ was calculated according to the formula: $CMRO_2$ = CBF × OER × arterial oxygen content.

Regions of interest

After image reconstruction of the 3 planes and the calculation of functional distributions of CBF, OER, $CMRO_2$ and CBV, regions of interest (ROIs) were drawn in a standardized manner on a visual display unit. Fourteen ROIs, distributed over the 3 planes were determined (*see* footnote to Table 1) on the $CMRO_2$ image and subsequently transposed on the other functional images.

All ROIs (except the 'cortical ribbon' ROIs) were circular with a diameter of 8 pixels (= 20 mm). The left and right cerebellar, temporal pole, frontal cortex, occipital cortex and 'insular grey matter' ROIs were determined by placing the centre of the ROI over the maximum value for these territories on the right and left sides of the midline using a joystick. The 'insular grey matter' ROI (ING) is considered to be the purest sample of grey matter given the resolution characteristics of the tomograph. The position of the white matter ROIs was found by selecting the lowest value with lowest SD in anterior and posterior parts of the centrum semiovale between frontal and occipital lobe cortices in the highest plane (plane 3). The 2 ROI values were averaged to obtain right and left-sided white matter values.

Particularly for the occipital cortex and cerebellar ROIs care was taken to avoid proximity of venous sinuses. This was checked by inspection of the CBV scans.

The cortical ROIs were determined using a 'cortical ribbon' of small rectangular boxes (6×3 pixels each) placed by the computer on the images (*see* fig. 1). The rectangular boxes were plotted by the computer over the ribbon of peak values along the edge of the brain. Middle cerebral artery ROIs (MCA) were arbitrarily defined as the mean of 12 rectangular boxes located centrally in the 'cortical ribbon' on each

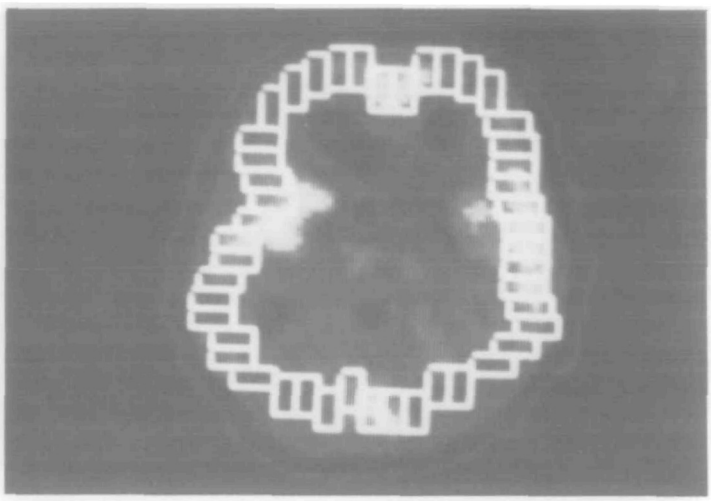

FIG. 1. Visualization of the 'cortical ribbon' as generated by the computer on the visual display unit. The several cortical ROIs are taken from this ribbon. *See* text for explanation.

side. The posterotemporal cortex ROI was defined as the 6 boxes on the middle plane (plane 2) 'cortical ribbon', starting posteriorly with the fourth box from the midline. The parietal cortex ROI was determined on the superior plane (plane 3) by taking 4 boxes, starting posteriorly with the fourth box from the midline. The parietal cortex ROI was determined on the superior plane (plane 3) by taking 4 boxes, starting posteriorly with the fourth box from the midline. No CT or MRI scans were available to compare the positions of the ROIs on the functional images. However, sufficient anatomical information is provided by the PET scan images to determine in a standardized manner the ROIs as described above (for discussion, *see* Duara, 1985).

Brain size

A brain size index was measured for each subject (Hatazawa *et al.*, 1987*a*, *b*) to be able to determine a possible influence of brain size on energy metabolism.

Statistics

The 4 functional values for each ROI were tabulated for the 34 subjects for right and left sides separately. Right and left hemisphere values were then averaged and regressions with age calculated. Regressions with age of the $\log_{10}$ values were also determined, yielding a percentage decrease per annum. In addition, for each ROI and each function, mean values and SDs were obtained across all subjects.

RESULTS

The mean values and SDs for each function calculated for all 14 ROIs (average of left and right sides) are given in Table 1. The values were not available for all 34 subjects in several categories. The actual number of measurements is also given in Table 1. The reasons for the missing values were twofold. On the one hand, it sometimes proved difficult or impossible to determine the localization of some of the ROIs, mainly in the white matter (Table 1). On the other hand, in some studies, because of technical difficulties, a steady-state could not be achieved or a CBV scan could not be obtained

TABLE 1. MEAN VALUES (±SD) FOR ALL SUBJECTS (LEFT AND RIGHT ROI VALUES AVERAGED)

	CBF	*$CMRO_2$*	*OER*	*CBV*
Plane 1				
CBL	49.4± 9.9 (n = 28)	3.37±0.49 (n = 24)	39.9±6.8 (n = 24)	4.7±2.0 (n = 24)
TMP	35.7± 8.6 (n = 26)	2.26±0.29 (n = 24)	38.7±7.6 (n = 22)	6.6±1.9 (n = 22)
Plane 2				
FRC	44.8±10.4 (n = 33)	3.18±0.46 (n = 32)	40.0±5.9 (n = 32)	4.3±0.8 (n = 32)
ING	54.5±12.3 (n = 33)	3.69±0.54 (n = 32)	38.5±5.6 (n = 32)	5.2±1.4 (n = 32)
OCC	46.8± 8.40 (n = 33)	3.59±0.46 (n = 32)	43.2±5.9 (n = 32)	8.6±3.6 (n = 32)
BGN	42.4± 7.60 (n = 33)	3.07±0.41 (n = 32)	40.4±4.9 (n = 32)	3.5±0.7 (n = 32)
MCA	44.3± 7.50 (n = 33)	3.11±0.36 (n = 32)	39.8±4.9 (n = 32)	4.7±0.7 (n = 32)
HCX	42.8± 7.00 (n = 33)	3.11±0.31 (n = 32)	40.9±4.9 (n = 32)	5.0±4.7 (n = 32)
PTC	38.0± 5.90 (n = 33)	2.96±0.31 (n = 32)	43.4±5.1 (n = 32)	4.7±1.2 (n = 32)
Plane 3				
WMR	22.2± 4.90 (n = 29)	1.43±0.24 (n = 28)	36.6±5.3 (n = 28)	2.7±0.6 (n = 28)
FRC	46.4±10.7 (n = 29)	3.16±0.44 (n = 28)	39.2±6.9 (n = 28)	4.0±0.6 (n = 28)
OCC	44.0± 7.60 (n = 29)	3.37±0.42 (n = 28)	43.2±7.4 (n = 28)	5.9±1.7 (n = 28)
MCA	42.0± 8.00 (n = 29)	3.00±0.41 (n = 28)	42.6±6.4 (n = 28)	3.8±0.5 (n = 28)
PAC	36.6± 6.60 (n = 29)	2.78±0.32 (n = 28)	43.3±6.7 (n = 28)	3.5±0.4 (n = 28)

ROI descriptions: lower plane (plane 1: OM+2); CBL = cerebellum; TMP = temporal pole. Middle plane (plane 2: OM+4); FRC = frontal cortex; ING = insular grey matter; OCC = occipital cortex; BGN = basal ganglia; MCA = middle cerebral artery territory cortical ribbon; HCX = hemicortical ribbon; PTC = posterotemporal cortical ribbon. Higher plane (plane 3: OM+6); WMR = white matter; FRC = frontal cortex; OCC = occipital cortex; MCA = middle cerebral artery cortical ribbon; PAC = parietal cortical ribbon. n = number of available values for each ROI for the specified function.

during scanning of a particular plane, excluding the corresponding ROIs.

For the 'insular grey matter' ROI (ING of plane 2), 'white matter' ROI (WMR of plane 3) and 'cerebellar' ROI (CBL plane 1), the values are listed separately for all 34 subjects in Tables 2−4. The % SDs between the subjects for the grey matter ROI (ING) was 22.6 for CBF, 14.6 for $CMRO_2$, 14.6 for OER and 26.9 for CBV (Table 1). Fig. 2 shows, for one ROI, scatter diagrams correlating the four functions. $CMRO_2$ is positively correlated with CBF ($P < 0.001$) and CBF is negatively correlated wtih OER ($P < 0.001$). No correlation is apparent between $CMRO_2$ and OER ($P > 0.05$) and a weak positive correlation between CBF and CBV ($P < 0.01$). Fig. 3 illustrates the relationships between the four functions for all 14 ROIs in 1 individual (Subject 10) as an example.

Regression coefficients of the logarithmically-transformed values for the four functions in all 14 ROIs vs age are given in Table 5 yielding the percentage change per year. Scatter diagrams for the absolute 'insular grey matter' ROI are presented in fig. 4. For this ROI a significant decrease in $CMRO_2$ with age was found (0.0158 ml oxygen/100 ml brain/min/yr) paralleled by a significant decrease of CBF (0.257 ml/100 ml brain/min/yr) and CBV (0.046 ml/100 ml/yr). OER increased significantly with age (0.133/yr). The same changes with age were also found for the other ROIs, but statistical significance was reached only for some (Table 5).

Of note is that the cerebellar values did not show any change with age for any function.

TABLE 2. INSULAR GREY MATTER (ING-ROI) VALUES

Subjects	*Age (yrs)*	*CBF*	*$CMRO_2$*	*OER*	*CBV*
1	22	48.7	3.83	38.6	6.0
2	23	57.4	4.21	36.1	6.1
3	27	75.0	4.65	33.0	5.2
4	27	88.8	4.56	27.6	8.3
5	29	50.0	3.67	41.8	4.3
6	30	–	–	–	–
7	30	43.9	3.34	37.3	4.1
8	32	45.7	3.49	41.1	6.2
9	33	63.5	3.75	30.0	5.3
10	33	53.1	4.09	38.3	8.6
11	35	58.1	38.1	33.7	5.1
12	35	61.8	4.14	37.9	5.8
13	35	71.6	4.41	34.4	8.0
14	37	51.1	3.49	40.7	4.8
15	38	53.9	3.77	36.1	5.9
16	39	46.4	4.14	43.6	4.8
17	44	48.4	3.21	40.1	4.8
18	46	65.3	4.92	44.4	6.1
19	47	54.3	3.01	36.4	5.3
20	48	31.4	2.93	50.3	4.1
21	49	54.5	3.98	37.6	3.3
22	51	59.3	3.79	37.6	4.9
23	54	68.4	3.51	30.7	4.1
24	54	60.7	3.85	37.6	4.3
25	54	40.8	2.93	43.0	5.1
26	55	52.1	3.67	36.0	5.9
27	57	51.3	3.36	36.9	3.8
28	61	46.9	3.41	39.4	6.4
29	62	40.6	2.89	43.5	3.4
30	62	65.0	3.12	27.3	5.5
31	63	56.4	3.85	40.7	4.8
32	64	67.5	3.80	34.9	4.7
33	75	35.7	3.17	49.7	3.0
34	82	40.0	3.51	48.4	3.6

– = missing values.

The absolute values of the cerebellar ROI were the same on average as the 'insular grey matter' ROI (Tables 1, 2, 4).

Some 'cortical ribbon' ROIs (MCA, HCX and PTM) showed significantly higher values ($P < 0.01$) on the right side for CBF and $CMRO_2$, but no other consistent right-left differences were seen. No correlations were found between right-left differences and age. The average right-left ratio for OER was 0.999 ± 0.016 and for CBV 1.005 ± 0.03. For CBF and $CMRO_2$ these were 1.024 ± 0.034 and 1.021 ± 0.025, respectively.

The ratio of CBF/CBV (mean ± SD: 10.9 ± 2.6; Table 6), which is a measure of mean flow velocity (reciprocal of mean vascular transit time) and thought to be a useful index of perfusion reserve on the basis of studies in cerebrovascular disease (Gibbs *et al.*, 1984), did not change with age in any ROI (fig. 5B). Neither systolic nor diastolic blood pressure, nor pulse frequency, correlated with CBV or the CBF/CBV ratio in any of the ROIs. No clear correlations of Hb or arterial oxygen concentration values were

TABLE 3. WHITE MATTER (WM-ROI) VALUES OF ALL SUBJECTS

Subjects	*Age (yrs)*	*CBF*	*$CMRO_2$*	*OER*	*CBV*
1	22	26.1	1.69	33.4	3.37
2	23	–	–	–	–
3	27	24.4	1.53	35.6	3.42
4	27	20.8	1.59	37.1	2.94
5	29	–	–	–	–
6	30	27.7	1.95	36.2	3.59
7	30	18.7	1.33	42.4	1.87
8	32	21.6	1.44	39.8	3.22
9	33	33.1	1.64	27.7	3.66
10	33	18.1	1.54	40.9	1.71
11	35	24.8	1.55	41.3	2.22
12	35	21.0	1.33	35.4	2.47
13	35	17.2	1.26	36.1	2.19
14	37	31.4	1.73	29.3	2.86
15	38	32.9	1.56	28.3	2.16
16	39	24.6	1.29	32.7	2.4
17	44	22.7	1.49	38.9	2.18
18	46	20.1	1.45	40.7	2.78
19	47	27.0	1.54	34.9	3.09
20	48	22.5	1.7	39.0	2.6
21	49	–	–	–	–
22	51	–	–	–	–
23	54	–	–	–	–
24	54	21.5	1.27	31.8	2.89
25	54	23.2	1.14	27.9	2.43
26	55	17.5	1.27	36.9	3.01
27	57	23.3	1.74	38.6	1.73
28	61	18.1	1.05	34.4	2.59
29	62	22.8	1.32	32.3	2.68
30	62	23.9	1.38	34.9	2.22
31	63	14.2	1.33	50.4	2.92
32	64	16.1	1.09	37.4	2.7
33	75	16.2	1.34	44.3	2.74
34	82	16.1	1.11	39.6	2.22

– = missing values.

found with the four functions, although for $CMRO_2$ a significant positive correlation ($P < 0.01$) was found for ING and MCA ROIs. pCO_2 did not correlate with CBF across subjects. None of the physiological variables by themselves (pulse, blood pressure, Hb and pCO_2) showed dependence on age. Brain size did not correlate with the functional values of the ROIs except for global CBF ($P < 0.01$).

DISCUSSION

This study applies the steady-state oxygen inhalation technique, with multiple arterial sampling and correction of OER for nonextracted intravascular oxygen, to a new group of 34 healthy subjects. Normal values from the third to eighth decade for CBF $CMRO_2$, OER and CBV were established for 14 regions. Table 1 and fig. 2 show that the interindividual variability is wide, in the order of 15% for $CMRO_2$. This implies that

TABLE 4. CEREBELLAR TISSUE (CBL-ROI) VALUES OF ALL SUBJECTS

Subjects	*Age (yrs)*	*CBF*	*$CMRO_2$*	*OER*	*CBV*
1	22	–	–	–	–
2	23	–	–	–	–
3	27	50.4	–	–	–
4	27	52.8	–	–	–
5	29	–	–	–	–
6	30	43.9	–	–	–
7	30	72.9	–	–	–
8	32	56.0	3.95	42.0	3.61
9	33	52.9	3.13	32.9	4.16
10	33	45.9	3.86	40.9	4.61
11	35	59.2	3.25	36.0	3.58
12	35	50.2	3.17	35.1	6.00
13	35	42.0	2.98	34.9	6.15
14	37	49.1	3.35	36.1	2.98
15	38	56.7	3.72	39.1	6.01
16	39	52.6	3.19	37.5	7.11
17	44	76.7	4.81	37.2	10.25
18	46	41.2	3.36	46.2	3.56
19	47	38.9	3.36	52.2	6.21
20	48	47.9	3.19	34.4	4.33
21	49	–	–	–	–
22	51	–	–	–	–
23	54	–	–	–	–
24	54	38.7	2.79	43.9	3.75
25	54	52.9	2.96	31.8	4.26
26	55	38.7	3.14	40.9	4.11
27	57	44.0	3.13	36.7	4.31
28	61	50.1	3.00	35.1	3.47
29	62	45.7	2.85	35.0	3.83
30	62	57.0	3.73	39.4	3.60
31	63	36.3	3.95	58.3	4.88
32	64	43.9	3.86	47.7	4.85
33	75	47.9	3.51	39.4	7.33
34	82	37.5	3.00	44.7	6.20

– = missing values.

cohort comparisons with a patient group will only yield statistically significant differences when there are small but real changes caused by a disease if large groups are considered. At present this is not easily achieved in studies using PET.

It is obvious that the scanner available for this study did not allow a finer regional analysis such as is possible with the new high resolution multiple plane scanners now coming into use. Reasonable functional resolution between grey and white matter and major anatomically based regions was nevertheless readily achievable. The mean values found in our study correspond well with the literature values. For the 'grey matter' ROI (ING) the values were: CBF = 55 ml/100 ml/min; $CMRO_2$ = 3.70 ml/100 ml/min; OER = 38% and CBV = 5.2 ml/100 ml. The interrelationship between the four functions for the 'insular grey matter' ROI is shown in figs 2 and 3. $CMRO_2$ is not determined by CBF, but each value of $CMRO_2$ corresponds to a range of CBF values. Nevertheless a coupling between the two functions is observed across individuals.

TABLE 5. REGRESSION COEFFICIENTS OF LOGARITHMICALLY-TRANSFORMED VALUES VERSUS AGE

	CBF	*$CMRO_2$*	*OER*	*CBV*
CBL	−0.18	+0.05	+0.32	+0.53
TMP	−0.55	−0.22	+0.27	+0.34
FRC	−0.47*	−0.47**	+0.25	−0.53**
ING	−0.51*	−0.47**	+0.35*	−0.53**
OCC	−0.26	−0.21	+0.32*	−0.72
BGN	−0.10	−0.19	+0.19	−0.19
MCA	−0.29	−0.35**	+0.21	−0.46**
HCX	−0.26	−0.31**	+0.22	−0.43**
PTC	−0.06	−0.12	+0.21	−0.50*
WMR	−0.49	−0.64**	+0.07	−0.20
FRC	−0.56	−0.60**	+0.17	−0.33
OCC	−0.27	−0.18	+0.23	−0.06
MCA	−0.40	−0.50**	+0.12	−0.31*
PAC	−0.11	−0.22	+0.11	−0.26

* $P < 0.05$; ** $P < 0.01$. Units are in % change per year.
See footnote to Table 1 for explanation of abbreviations.

A higher $CMRO_2$ is associated with a correspondingly higher rate of CBF values. $CMRO_2$ does not determine OER. The latter adjusts itself to the value of CBF, which may vary within a subject or differ between subjects due to alterations in breathing patterns or other physiological factors. The OER compensates reciprocally for different values of CBF. CBV was positively correlated with CBF within and between individuals. This indicates that the vascular space is larger where tissue perfusion is highest. Although care was taken to avoid placing ROIs close to venous sinuses, this was apparently less successfully done for the occipital ROI, resulting in an artefactually large value of occipital CBV ($8.6 \pm 3.6\%$) (Table 1). The observed relations between CBF and $CMRO_2$, CBF and CBV, and between OER and $CMRO_2$ across individuals (fig. 2), become more evident when comparing the 14 ROI values in one subject (fig. 3). In addition, OER is then not dependent on CBF because of the close coupling of CBF to $CMRO_2$. It is remarkable how constant OER is across all regions in any one healthy subject's brain (fig. 5A and Table 6).

Global brain glucose utilization was reported to correlate with brain size (Hatazawa *et al.*, 1987*a*, *b*) but no such correlation was found in our data for $CMRO_2$, either for the specified ROIs or for total image values. For CBF, only global flow showed an inverse correlation with brain size ($P < 0.01$). We therefore did not adjust our values for a brain size effect.

In this study CBF, CBV and $CMRO_2$ decreased significantly with age in the frontal cortex and insular grey matter ROIs (Table 5). In other ROIs (white matter and cerebrocortical regions) $CMRO_2$ and CBV also decreased significantly. The decline in CBF in these regions did not reach significance, presumably owing to the larger variance of this variable. Nevertheless, a consistent negative trend of CBF decrease with age was observed for all other ROIs. OER showed a nonsignificant upward trend

TABLE 6. MEAN AND SD OF OER AND CBF/CBV FOR ALL ROIs IN EACH SUBJECT

		CBF/CBV		OER	
Subjects	*Age (yrs)*	*Mean*	*SD*	*Mean*	*SD*
1	22	10.5	2.8	41.1	3.48
2	23	9.0	3.3	44.3	1.80
3	27	9.6	2.4	39.9	1.81
4	27	8.5	1.9	40.9	2.66
5	29	7.1	3.2	43.7	1.82
6	30	9.2	2.1	45.5	5.38
7	30	9.9	1.2	43.6	2.95
8	32	9.1	2.8	43.4	4.48
9	33	11.2	3.0	28.2	3.21
10	33	9.4	2.4	44.9	1.77
11	35	10.0	3.5	41.4	5.13
12	35	9.6	2.0	38.8	3.94
13	35	8.3	2.5	38.9	3.74
14	37	12.3	3.5	34.2	1.99
15	38	12.9	2.6	35.6	3.18
16	39	11.3	2.8	36.0	4.12
17	44	11.3	2.7	39.9	2.60
18	46	9.4	2.9	46.8	2.37
19	47	8.9	2.9	44.8	4.08
20	48	9.0	2.5	37.7	2.55
21	49	8.3	2.9	43.2	4.81
22	51	7.3	1.7	40.7	3.89
23	54	9.2	2.1	31.0	2.72
24	54	9.4	2.4	43.9	5.15
25	54	10.8	1.7	31.2	1.20
26	55	8.6	1.7	40.1	2.56
27	57	6.7	2.1	37.2	–
28	61	9.9	2.9	39.7	3.10
29	62	9.5	3.1	37.5	4.10
30	62	10.4	2.2	40.2	1.78
31	63	6.3	1.6	56.1	5.61
32	64	9.4	2.9	49.2	4.47
33	75	7.2	1.9	46.3	3.53
34	82	9.1	1.9	46.1	2.05

– = missing value.

for all ROIs, except for 'pure' grey matter regions (ING and OCC), where the increase reached statistical significance ($P < 0.05$). Since OER essentially did not change in our study (fig. 5A), the decline of CBF and $CMRO_2$ with age (both approximately 0.5%/yr) must be coupled and does not appear to result from ischaemic factors. In addition, a parallel reduction of CBF and CBV was found. Thus the ratio CBF/CBV, which may be used to indicate perfusion reserve (Gibbs *et al.*, 1984) did not decrease with age (Table 6, fig. 5B). Since CBF determines the number of perfused capillaries (Diemer, 1968), our findings suggest that any loss of capillary density that might occur in the ageing brain is not in excess of decreased tissue energy demand. The increase with age of OER in the ING ROI would suggest that for that region additional vascular factors may play a role (for discussion, *see also* Frackowiak *et al.*, 1984). However, the OER increase was slight when compared with values seen in pathological ischaemic conditions (Wise *et al.*, 1983; Gibbs *et al.*, 1984).

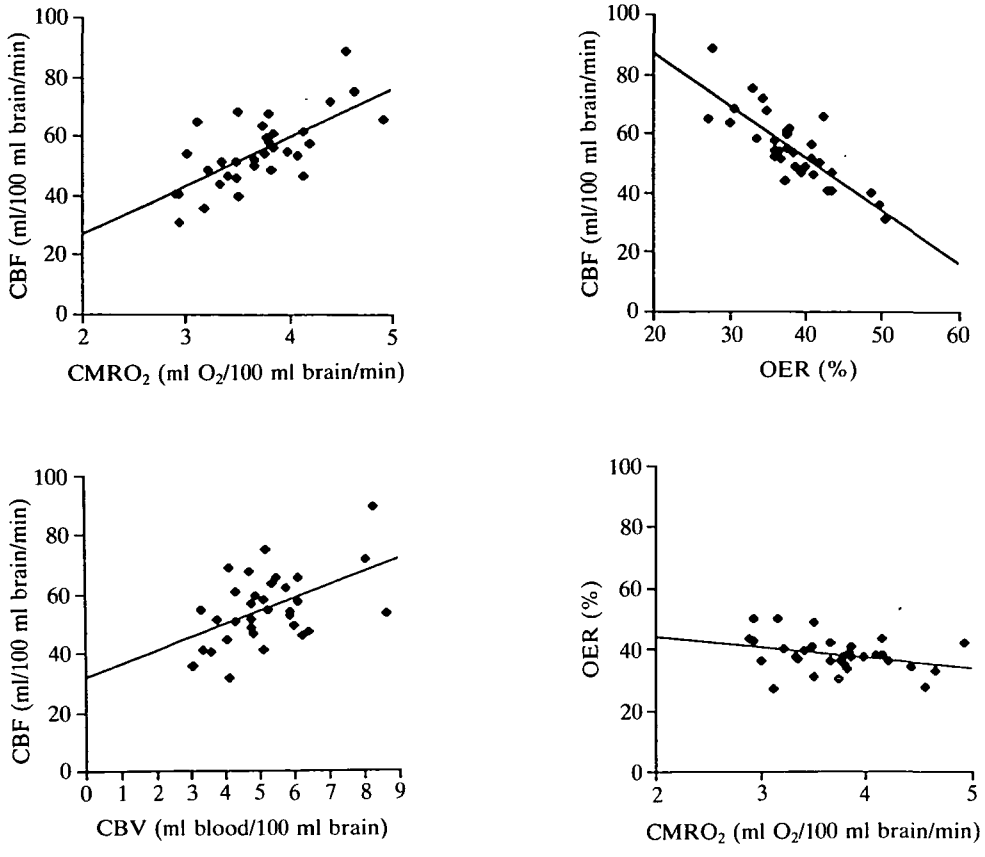

FIG. 2. Scatter-diagrams relating CBF to $CMRO_2$, CBF to OER, CBF to CBV and OER to $CMRO_2$. Each point is the value measured in a different healthy subject for the 'insular grey matter' ROI (ING). Linear regression lines were: CBF vs $CMRO_2$, $y = -5.4+16.2x$; $r = 0.69$**; CBF vs OER, $y = 123-1.8x$; $r = 0.82$**; CBF vs CBV, $y = 32+4.4x$, $r = 0.50$*; OER vs $CMRO_2$, $y = 52-3.6x$, $r = 0.33$ (n.s.). (* = $P < 0.05$; ** = $P < 0.01$; n.s. = not significant.)

We have compared our findings with results obtained using the steady-state technique without CBV correction for OER and with single arterial sampling (Frackowiak *et al.*, 1982; Lenzi *et al.*, 1983). CBF was reported to decline significantly with age but $CMRO_2$, although showing a downward trend, did not reach statistical significance. OER showed an upward trend. The absolute and relative decreases of CBF and $CMRO_2$ with age are similar in our previous and present reports. The findings are also of the same magnitude as the original hemisphere measurements revealed by Kety (1956), which also suggested a small increase of hemisphere arteriovenous (O_2) difference with age.

Equally, Pantano *et al.* (1984) showed that CBF and $CMRO_2$ declined with age. A significant linear correlation with age was only found for CBF. $CMRO_2$ showed a matched decrease, but significance was only reached when dividing the population into a 'young' and 'old' group. OER showed no statistically significant changes with age,

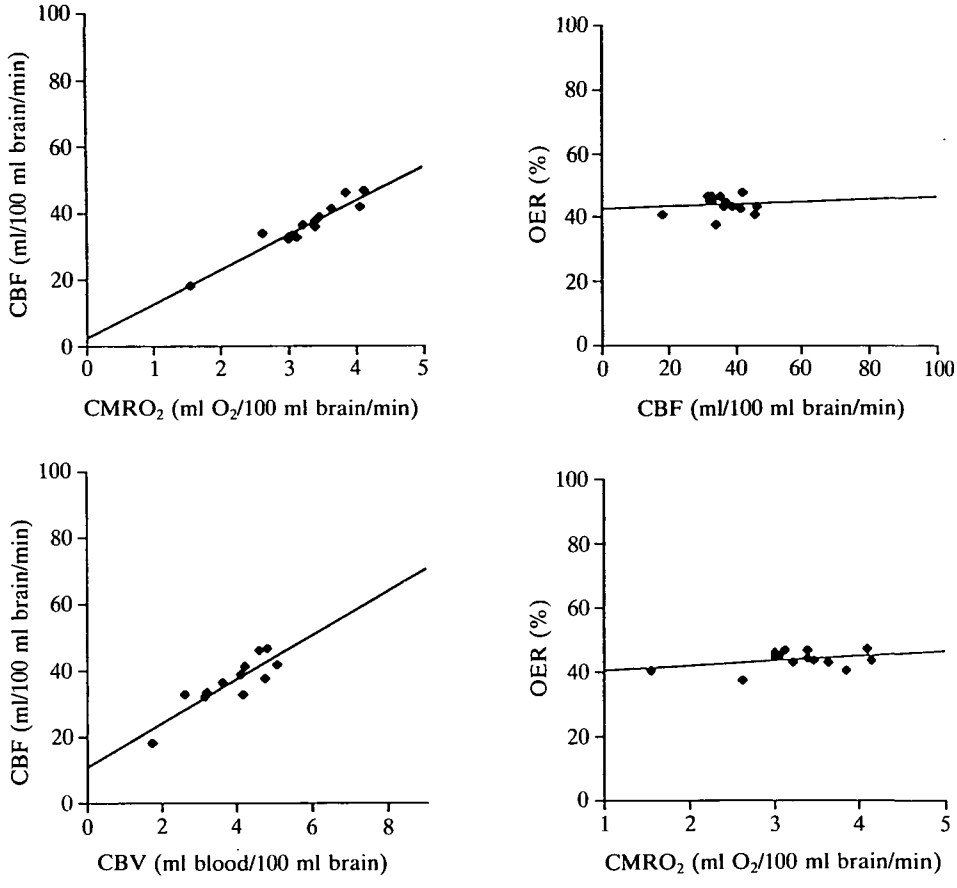

FIG. 3. Scatter-diagrams of relations between the 4 measured functions in all 14 ROIs in subject 10. Linear regression lines were: CBF vs $CMRO_2$, y = 2.46+10.3x, r = 0.96**; OER vs CBF, y = 42.6+0.037x, r = 0.09 (n.s.); CBF vs CBV, y = 11+6.6x, r = 0.88**; OER vs $CMRO_2$, y = 39+1.6x, r = 0.38 (n.s.). (* = $P < 0.05$; ** = $P < 0.01$; n.s. = not significant.)

although a small upward trend was present. Because in that study the steady-state oxygen-15 inhalation technique was performed without CBV correction, OER, and thus $CMRO_2$, were slightly overestimated.

More recently, a study from Japan (Yamaguchi *et al.*, 1986), using the same technique as in the present investigation (including CBV scans), demonstrated a significant reduction with age for mean $CMRO_2$ in grey matter, but CBF and OER did not show any correlation with age. In several regions a significant decline of CBV with age was found. These results are difficult to interpret since it is unusual not to find a decrease of CBF with age, particularly in the light of a decline of $CMRO_2$. In such a situation a parallel decrease of OER would also be expected, but this was not found.

Measurements of cerebral glucose metabolism using FDG (^{18}F-fluorodeoxyglucose) PET scan techniques have yielded conflicting results in the literature. Kuhl *et al.* (1982)

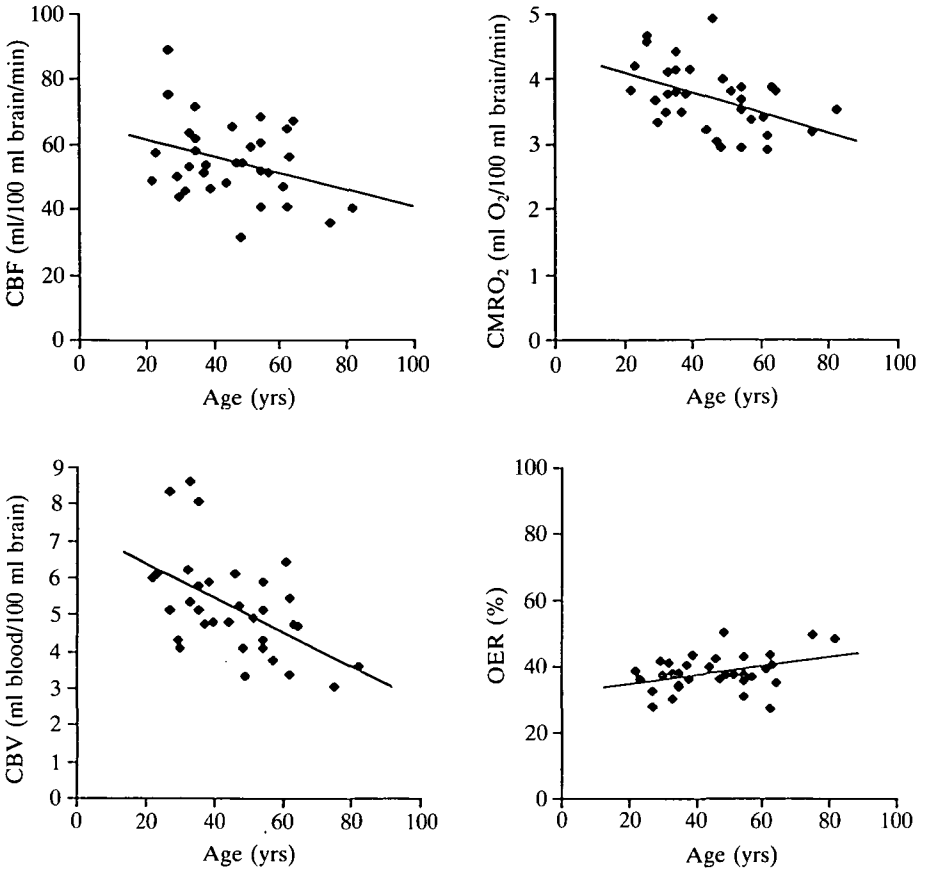

FIG. 4. Scatter-diagrams of absolute values for CBF, $CMRO_2$, CBV and OER against age for one ROI (ING) in 33 of the subjects. The regression equations are: $y = 66.5-0.26x$, $r = 0.35^*$ for CBF; $y = 4.42-0.0158x$, $r = 0.47^{**}$ for $CMRO_2$; $y = 32.2+0.13x$, $r = 0.37$ for OER*; $y = 7.3-0.046x$, $r = 0.52^{**}$ for CBV. (* = $P < 0.05$; ** = $P < 0.01$; n.s. = not significant). *See* Table 3 for significance of other regression coefficients.)

reported a decline of mean CMRglu with age. This decline was larger than for $CMRO_2$ previously reported (Lammertsma *et al.*, 1981). The authors suggested an altered utilization of substrates for energy metabolism in elderly subjects. This hypothesis had already been advanced by Sokoloff (1973) and Gottstein and Held (1979) using Kety-Schmidt techniques. The latter authors found a decrease of hemisphere CBF, oxygen and glucose consumption with age in 137 patients without neurological deficits. Glucose consumption decreased on average more than oxygen utilization, but the variance was large for both functions and the number of younger subjects was small. Dastur *et al.* (1963) also found that CBF, $CMRO_2$ and CMRglu are decreased in the healthy elderly and that $A-V(O_2)$ tends to increase with age. However, the CBF and $CMRO_2$ changes were not statistically significant.

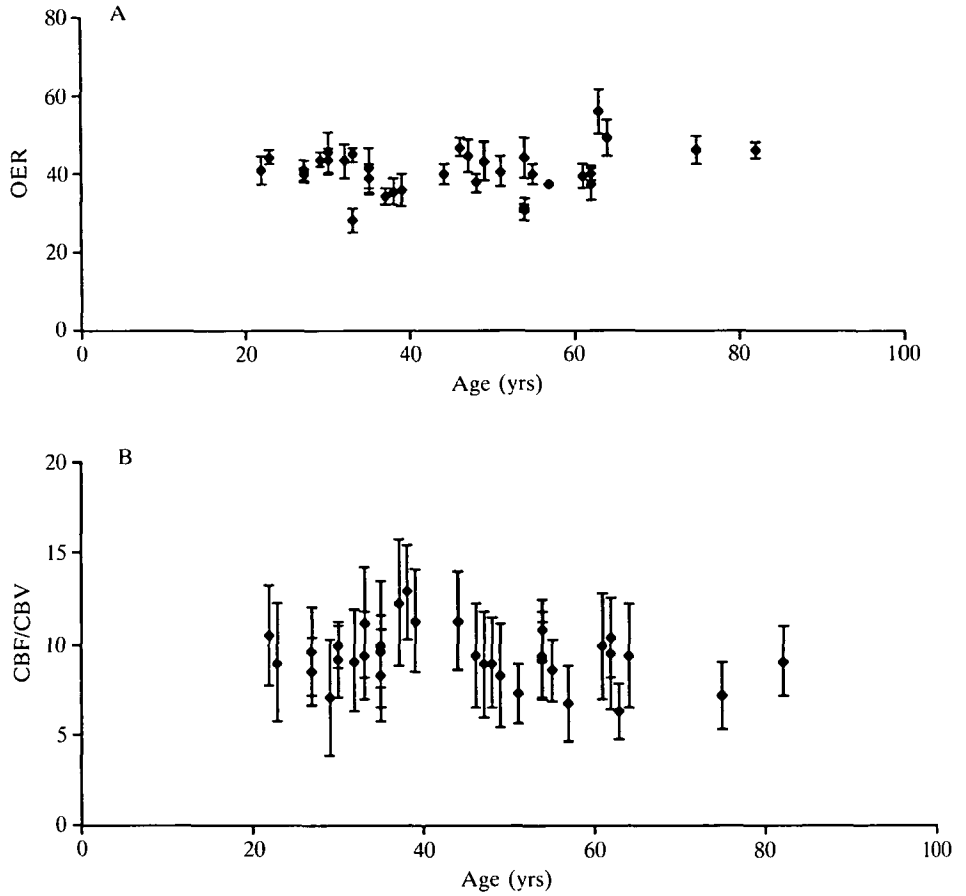

FIG. 5. A, mean and SD of all OER ROI values (minus white matter and cerebellar ROIs) for each subject plotted against age (linear regression: $r = 0.27$; n.s.). B, mean and SD of CBF/CBV for all ROIs in each subject plotted against age (linear regression: $r = 0.19$; n.s.).

Duara *et al.* (1984) and De Leon *et al.* (1983, 1984), using PET, showed no decline of CMRglu with age. These authors claim that careful screening of healthy volunteers had resulted in a particularly healthy group of elderly subjects. In our study, the subjects were evenly distributed according to age over several decades of life. On grounds of clinical and social history and clinical and neurological examination, the subjects in this study represent both completely healthy and asymptomatic elderly individuals. The blood pressure was not correlated with age, nor with the ratio CBF/CBV. This suggests that our subject population was not compromised by subclinical vascular disease. It is not clear who in the general healthy population should be considered to be 'really' healthy. The authors of the published reports to date differ in their opinion about this. It seems questionable whether more rigorous screening would yield a better or more representative sample of healthy people.

All our subjects were examined in the same resting condition, which is a more 'normal' state than the more artificial sensory deprivation used by other authors. Duara *et al.* (1983) suggested that sensory deprivation achieved in their studies by plugging ears and covering eyes did lower their measured values, particularly in the younger subjects. If this were true it would imply that energy metabolism in the brains of younger people is indeed different from that in elderly subjects. In a later study from the same group (Yoshii *et al.*, 1988) cerebral glucose utilization measured in a group of 76 subjects was reported. Mean cerebral glucose metabolism was significantly lower in the elderly group and appeared to be related to frontal, parietal and temporal reductions. Brain volume and atrophy was estimated using MRI in 58 subjects and accounted for 21% of the variance of the glucose utilization. When correcting the metabolic values for brain volume and atrophy, the effect of age or gender was no longer significant in their data. The authors suggested that the remainder of the measured metabolic values is probably due to differences in physiological arousal.

In contrast to the findings in the predominantly grey matter ROI (ING), we did not find an effect of age on cerebellar ROI values, although this region also contains predominantly grey matter, reflected in the high values for CBF $CMRO_2$ (Table 1). Hemisphere cerebellar atrophy in healthy elderly subjects has not been demonstrated on CT scans, although Koller *et al.* (1981) have reported selective atrophy of the cerebellar vermis with ageing. Counts of cerebellar Purkinje cells showed wide individual variations and a reduction of 2.5% per decade, after the sixth decade, has been reported (Hall *et al.*, 1975). Yamaguchi *et al.* (1986) found only a supratentorial decrease of $CMRO_2$. Kushner *et al.* (1985) reported in a short abstract no significant difference in cerebellar glucose metabolism between young and old healthy subjects. It is intriguing that the cerebellum apparently follows a different pattern of functional and anatomical change in life compared with the cerebral hemispheres.

In white matter, significant $CMRO_2$ decrease only was found, although CBF also decreased by 0.5% per year with age. No effect of age on white matter was found by Pantano *et al.* (1984) and Yamaguchi *et al.* (1986).

It is well recognized that partial volume effects play an important role, accounting for varying recovery of signal because of different shapes and sizes of brain structures in relation to the necessarily large ROIs (Mazziotta *et al.*, 1981). Basal ganglia ROI values are likely to have been influenced by the proximity of the lateral ventricles; the thinness of the parietal cortex inevitably results in a lowering of values in the corresponding ROI by white matter; and the temporal pole ROI may have been influenced by the surrounding skull. A related factor is the possible influence of brain atrophy on the values measured with PET. Moderate to gross ventricular enlargement can be detected on the functional PET images, but was not found in the scans presented here. Cerebral atrophy and ventricular dilatation have been reported by quantitative analyses of CT scans in healthy elderly subjects (Schwartz *et al.*, 1985). The degree and the age at onset of cerebral atrophy are variable. Correction for atrophy of the functional values obtained by PET scans has been suggested (Herscovitch *et al.*, 1986; Chawluk *et al.*, 1987). However, De Leon *et al.* (1984) found significant age-related atrophy

on CT scans, particularly in the cerebral cortex, without changes in brain glucose metabolic rate measured with PET. This suggests that the normal ageing brain undergoes structural atrophic changes which are not necessarily reflected in regional functional activity. The same group (De Leon *et al.*, 1987) replicated these results using carbon-11 labelled glucose and a different tomograph. Although, after controlling for ventricular size, no age effect was found for the absolute values of glucose utilization, a relative hypofrontality was apparent in elderly subjects. Also, Yoshii *et al.* (1988) found that atrophy contributed only a small amount to the variance of cerebral glucose utilization in normal subjects. Equally, McGeer *et al.* (1986) did not find a correlation between brain atrophy and regional glucose metabolic rate in patients with Alzheimer's disease. However, CT measurements, particularly of cortical atrophy, may not be reliable enough to demonstrate a correlation with regional functional activity. The newer methods employing MRI scans promise to yield better comparisons. On the other hand, the noncorrespondence of CT-defined atrophy and PET measurements might be due to the fact that values in a ROI of a PET image are heavily influenced by tissue outside the delineated ROI. Only special regional corrections for atrophy of the PET values may provide valid comparisons. This issue was reviewed by Videen *et al.* (1988).

Energy requirements of the brain are determined in large part by processes such as membrane depolarization. These in turn are a function of cell membrane surface-to-volume ratio of the tissue (Mata *et al.*, 1980). Brain regions with high densities of nerve endings and dendrites will have high energy requirements and thus high $CMRO_2$ and CBF. Chugani *et al.* (1987) measured regional brain glucose utilization with PET in 19 children in several stages of development and found an anatomical and temporal pattern of glucose utilization paralleling neuronal and synaptic density. In human cortex neuronal cell losses and cell shrinkage with age have been reported by several authors (Henderson *et al.*, 1980; DeKosky and Bass, 1982; Anderson *et al.*, 1983). More recently, Terry *et al.* (1987) showed significant age-related decrements in large cortical neurons and a reduction of cortical thickness. However, the total number of neurons was unchanged because of an increase in the numbers of small neurons. Hence neuronal density remained constant. These authors suggested that shrinkage of neuronal cell bodies is a prominent finding in the ageing neocortex. A minor degree of neuronal loss was also detected when the cerebrum was considered as a whole. The changing nature of the neurons composing the cortex with age may be at the basis of the functional alterations assessed in vivo in this and other studies.

If for whatever reason loss of neurons within a sample volume (ROI) occurs, it will result in decreased energy metabolism within that ROI. If such a cell loss is accompanied by tissue shrinkage and the morphological phenomenon 'atrophy', then changes in $CMRO_2$ could parallel atrophy. We have shown a decline of $CMRO_2$ within an ROI with age and are not in a position to say whether the loss of 'functional activity' was accompanied by atrophy. If in atrophied brain tissue the remainder of the tissue has an unaltered neuronal density and composition, then $CMRO_2$ per gram tissue should be unchanged. If only selective cell loss or shrinkage occurs without atrophy, $CMRO_2$ will be decreased both in the ROI and per gram tissue. The newer dynamic PET tracer

models for determination of rCBF are expected to provide in addition a measure of the regional volume of distribution of water. This should make it possible to approach the issue of atrophy and function direct.

There is clear evidence for age-related effects on brain neurochemistry, particularly in the dopaminergic and cholinergic neurotransmitter systems (McGeer and McGeer 1976; Allen *et al.*, 1983; DeKosky *et al.*, 1985). Effects of age on dopamine and serotonin receptors have been investigated by PET techniques in human living brain (Wong *et al.*, 1984). Receptor density in striatum and frontal cerebral cortex declined with age. These changes of neurotransmitter systems might equally be related to changes of the neuronal composition of cortex with age. Alternatively, these changes might be an expression of decreased activation by subcortical brain systems (DeKosky *et al.*, 1985). This may in turn result in decreased cortical energy requirement. Deactivation of the frontal cortex resulting in decreased energy metabolism demonstrated by PET has been suggested in the Steele-Richardson-Olszewski syndrome (D'Antona *et al.*, 1985; Leenders *et al.*, 1988). Our results as such cannot make a distinction between deafferentation or local cell loss as possible explanations for the decreased energy metabolism with age, but we favour the first mechanism.

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