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Cerebral blood flow changes in the primary motor and premotor cortices during hyperventilation

Kazunari ISHII, Masahiro SASAKI, Shigeru YAMAJI, Setsu SAKAMOTO and Kiyoshi MAEDA

Division of Neuroimaging Research and Radiology Service, Hyogo Institute for Aging Brain and Cognitive Disorders (HI-ABCD)

The aim of this study was to clarify the regional differences in cerebral blood flow (CBF) change during hyperventilation by using $H_2{}^{15}O$ and positron emission tomography (PET). Eight healthy volunteers (age: 63.0 ± 8.9 yr.) were studied. Regional CBF was measured by the $H_2{}^{15}O$ autoradiographic method and PET. Statistical parametric maps (SPM) and conventional regions of interest (ROI) analysis were used for estimating regional CBF differences in the normocapnic state with normal breathing and the hypocapnic state induced by hyperventilation. Total CBF decreased during the hypocapnic state. The SPM revealed that primary motor and premotor cortices were significantly activated by hyperventilation. In these areas absolute CBF values were significantly higher than those in the temporal, occipital and parietal lobes in the hypocapnic state, but there were no significant regional differences in the normocapnic state. In the hypocapnic state induced by hyperventilation, the primary motor and premotor CBF shows combined changes with vasoreaction to hypocapnia and increase in activation due to hyperventilation.

Key words: PET, ^{15}O labeled water, hyperventilation, cerebral blood flow

INTRODUCTION

THE FACT that an evident decrease in cerebral blood flow (CBF) is acutely induced by hyperventilation is well known. Kety and Schmidt first reported this phenomenon by developing the nitrous oxide washout technique for estimating CBF.[1] The mechanism of this effect is caused by vasoconstriction secondary to a respiratory alkalosis, with an increase in pH.[2,3] In the past 20 years, regional CBF responses to hypocapnia in patients with cerebral infarction have been widely studied as well as the hypercapnic state in single photon emission computed tomography (SPECT) and positron emission tomography (PET).[4–6] Nevertheless, the regional differences in CBF change during hyperventilation in the normal brain tissue in relative and absolute values have not been studied in normal aged subjects. The purpose of this study was to estimate the regional differences in CBF change during hyperventilation in relative and absolute values especially in the primary motor and premotor areas, measuring regional CBF by the $H_2{}^{15}O$ autoradiographic method and PET.

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For reprint contact: Kazunari Ishii, Hyogo Institute for Aging Brain and Cognitive Disorders, 520 Saisho-Ko, Himeji, Hyogo 670–0981, JAPAN.

E-mail: ishii@hiabcd.go.jp

METHODS

Subject Selection

Eight healthy female volunteers (mean ± SD age 63.0 ± 8.9 yr.) were studied. They had no neurological signs or significant medical antecedents and no abnormal magnetic resonance (MR) findings except for age-related hyperintensities on T2-weighted images. Written informed consent was obtained from all the subjects. The PET procedure was approved by our institution's Ethical Committee.

Before PET scans, all subjects received MR imaging for anatomical reference, and for PET positioning. Detailed MR procedures have been reported elsewhere.[7] Immedi-

ately before the PET examination, sagittal gradient-echo images were obtained to determine the coordinates for positioning of the head on the PET table.

PET Procedure

A Headtome IV (Shimadzu Corp., Kyoto, Japan) PET scanner, which had four rings located 13 mm apart and yielded a transverse resolution of 4.5 mm full-width-half-maximum (FWHM)[8] was used in this study. The scanner slice thickness was 11 mm and the slice interval was 6.5 mm when the z-motion mode was used. On the table of the PET scanner, the subject's head was placed horizontally, and the gantry and the table of the PET scanner were adjusted according to the coordinates determined by MR imaging, so that the scans were taken parallel to the AC-PC plane.[9,10] A transmission scan was performed with a $^{68}Ga/^{68}Ge$ pin source for absorption correction after each subject was positioned. PET studies were performed in the supine position with eyes closed and ears unplugged.

The CBF was calculated by an autoradiographic technique with a table look up procedure over a 90 sec accumulation after the intravenous injection of $H_2{}^{15}O$.[11] The usual amount of the tracer was 5 m*l* and the dose of radioactivity of $H_2{}^{15}O$ was 740–1110 MBq. Details of the procedure are reported elsewhere.[12,13]

Two trials of regional CBF were examined for each subject with normal breathing (normocapnia) and voluntary hyperventilation (hypocapnia). Voluntary hyperventilation by deep breathing was started 60 sec before $H_2{}^{15}O$ injection and ended after arterial blood sampling. The $PaCO_2$ level was measured 30 sec before $H_2{}^{15}O$ injection and immediately after the end of the scan, and the two measures were averaged.

Data Analysis

PET and MR image data sets were directly transmitted to a workstation (Indigo^2, SGI, Mountain View, CA, USA) from the PET and MR imaging units, and image analysis was performed on the workstation.

For the relative regional CBF change analysis, statistical processing was performed with SPM 95 software (MRC Cyclotron Unit, London, United Kingdom). Calculations and image matrix manipulations were performed in MATLAB (Mathworks Inc., MA, USA). The original 14 contiguous, 6.5-mm scan slices were interpolated to 43 planes with approximately cubic voxels. The data were then transformed into a standard stereotactic space[14,15] and the images were smoothed with an isotropic Gaussian filter to compensate for intersubject gyral variability and to reduce high frequency noise. The stereotactically normalized regional CBF images were then adjusted for individual differences in global blood flow using an analysis of covariance (ANCOVA).[16] This algorithm scales all images to a global mean regional CBF of 50 m*l*/100 m*l*/min. Finally between the two conditions comparisons were performed on a pixel-by-pixel basis for all voxels common to all subjects. The subset of voxels exceeding a threshold of $p < 0.001$ in omnibus comparisons and remaining significant after correction for multiple comparisons ($p < 0.05$) was displayed as a volume image rendered in three orthogonal projections.

Table 1 Mean blood gas data and cerebral blood flow

	normocapnia	hypocapnia
pH	7.42 ± 0.02	7.52 ± 0.05*
PaO_2	87.3 ± 7.9	113.8 ± 16.6*
$PaCO_2$	40.0 ± 2.6	28.5 ± 4.7*
CBF		
temporal	53.1 ± 5.8	38.0 ± 4.6*
occipital	53.2 ± 7.7	38.6 ± 3.8*
parietal	51.7 ± 6.3	37.5 ± 4.0*
primary motor and premotor	53.9 ± 7.0	41.9 ± 5.6*,†

Values are expressed as mean ± one standard deviation
Units: PaO_2 and $PaCO_2$: mmHg, CBF: m*l*/100 m*l*/min
*: Significantly different compared with normocapnia ($p < 0.001$), †: Significantly higher compared with other regional CBF in hypocapnia ($p < 0.05$)

Quantitative analyses were performed with conventional region of interest (ROI) settings and image analysis software Dr. View (Asahi Kasei Joho System, Tokyo, Japan) referencing the results of the SPM analysis. We determined two or three circular ROIs (10 mm diameter) on the cortical ribbon of the temporal lobe, occipital lobe, parietal lobe and primary motor and premotor cortices on the co-registered MR images. The same ROIs were transferred to the CBF images of the normocapnia and hypocapnia. These values were shown as the average of the right and left regional values. For regional differences, one-way analysis of variance (ANOVA) was used and Scheffé's test was used for multiple post hoc comparisons. Differences were considered significant when the p-value was less than 0.05.

RESULTS

Table 1 summarizes the averaged pH, $PaCO_2$, PaO_2 and CBF of each regional cortex in both normal breathing and hyperventilation condition groups. There was a significant difference between the two states in each parameter ($p < 0.001$). Averaged differences between the normocapnia and hypocapnia in $PaCO_2$, PaO_2, pH and whole CBF were 11.6 ± 3.9 mmHg, 26.5 ± 11.8 mmHg, 0.11 ± 0.04 and 14.9 ± 5.1 m*l*/100 m*l*/min, respectively.

In the SPM study, significant focal relative increases in regional CBF due to hyperventilation are shown in Fig. 1 and Table 2. Bilateral primary motor and premotor areas were included in the activated areas. In addition to the cortical areas shown above, an extracerebral region near the sphenoid sinus was shown as a significantly activated area.

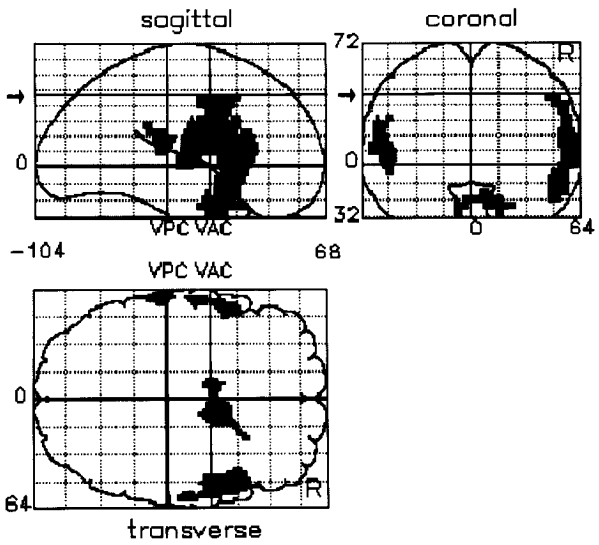

Fig. 1 Statistical parametric mapping projections of the comparison of hyperventilation and normal breathing. Relative blood flow increase due to hyperventilation were demonstrated in bilateral middle frontal to superior temporal region and in the extracerebral region ($p < 0.05$ corrected for multiple comparisons). The arrow indicates the superior limit of the field of view.

Table 2 Areas activated in hyperventilation analyzed statistical parametric map with a significance of $p = 0.05$ corrected for multiple comparisons

Brain region	x	y	z	Z score
Rt. middle frontal gy.	48	6	40	4.84
Rt. superior temporal gy.	52	6	−12	4.39
Lt. superior temporal gy.	−56	−30	16	4.39
Lt. precentral gy.	−54	10	8	4.45

Rt. = right, Lt. = left, gy. = gyrus
Coordinates are in millimeters, relative to the anterior commissure, corresponding to the atlas of Talairach and Tournoux (1988). x: distance (mm) to right (+) or left (−) of the midsagittal line; y: distance anterior (+) or posterior (−) to vertical plane through the anterior commissure; z: distance above (+) or below (−) the intercommissureral line. The Z score is a measure of the degree of significance of the difference and is the number of standard deviations from the mean *t* value in the (*t*) statistical map of the *t* value for the most significant pixel in the plane.

In the absolute CBF value, there was no significant difference among the temporal lobe, occipital lobe, parietal lobe and primary motor and premotor cortices in normocapnia, ($F = 0.636$, $p = 0.600$), but in hypocapnia there was a significant regional CBF difference ($F = 4.549$, $p = 0.013$) and the CBF in the primary motor and premotor areas was significantly higher than that in other regions ($p < 0.05$).

DISCUSSION

The present study revealed that in the areas which were activated by hyperventilation there existed a different regional CBF change in hypocapnia. This CBF change should be combined with vasoreaction and neural activation induced by hyperventilation.

Bednarczyk et al.[17] reported the effects of hypocapnia in ten normal volunteers by using $H_2{}^{15}O$ and PET before and after five minutes of hyperventilation and found that CBF decreased by a mean of 49.5%. They showed a significant change over the baseline in $PaCO_2$ and CBF, in the hyperventilated state. Our study also demonstrated similar results, although the magnitude of $PaCO_2$ and CBF changes in ours was smaller than that in their results. This would be due to the duration of the hyperventilation task; that is the hyperventilation time in our study was 2.5 min and theirs was 5 min. Because our subjects were elderly females, age and gender differences also would have affected the magnitude of activation.

On the other hand concerning relative CBF change, Ramsay et al.[18] reported identified areas of neural activation associated with volitional inspiration and with volitional expiration in five normal male subjects promoting their previous report.[19] They performed PET scans on each subject under conditions of volitional inspiration with passive expiration, passive inspiration with volitional expiration and passive inspiration with passive expiration. Regional CBF increases during the volitional and passive ventilation phases, due to increased neural activity associated with either active inspiration or active expiration, were analyzed by SPM. During active inspiration significant increases in regional CBF were found bilaterally in the primary motor cortex, in the supplementary motor area (SMA), in the right lateral premotor cortex and in the left ventrolateral thalamus. In active expiration, significant increases in regional CBF were found in the right and left primary motor cortices, the SMA, the right lateral premotor cortex, the ventrolateral thalamus bilaterally, and the cerebellum. For volitional expiration the areas activated were more extensive, but overlapped with those involved in volitional inspiration. Compared with Ramsay's study, our study demonstrated almost the same activated regions in primary motor and premotor cortices. In our study, some of the superior temporal gyri were also activated. In Ramsay et al.'s study, absolute blood flow values were not measured. On the other hand, in our study we could not demonstrate an activated area in the SMA, which was demonstrated as an activated area by Ramsay et al. in their study, because of the limited total axial field of view of our PET scanner (91 mm). The SMA was outside the field of view of the scanner. We suspect that in our study the SMA concerning respiration would also have been activated as in other studies.[17,18]

Shimosegawa et al.[20] demonstrated that the absolute CBF increase induced by visual stimulation was affected by the $PaCO_2$ level, whereas the fractional CBF increase remained unchanged at different baseline CBF levels, which meant that the CBF increase induced by neural

activation changes proportionally with the changes in baseline CBF. Ishii et al.[6] reported that the alteration in absolute cerebellar blood flow change to $PaCO_2$ changes was proportional to the level of $PaCO_2$ on the affected and unaffected sides with crossed cerebellar diaschisis (CCD) in 27 cerebrovascular patients and indicated that the rate of change in percent cerebellar blood flow per millimeters of mercury $PaCO_2$ change was uniform across affected and unaffected cerebellar hemispheres with CCD. But these two reports were concerned with not regional cerebral blood changes but only the occipital region, whole brain or cerebellar hemisphere blood flow. Our results indicated that in primary motor and premotor areas the magnitude of CBF decreases, which was a vasoreaction to hypocapnia, was small because those areas were activated by hyperventilation. Therefore, in estimating global CBF reactivity to hypocapnia induced by hyperventilation, we must be careful to set a ROI. Setting ROIs on the primary motor and premotor areas may lead to an error that shows an underestimated vasoreaction to hypocapnia.

In the SPM study, ANCOVA removes variance due to differences in global flow, but there may be a problem because the relationship between the global CBF and regional CBF is additive or proportional. Ramsay et al.[21] suggested that it is additive and Shimosegawa et al. suggested that it is proportional. In our relative CBF study, we used SPM with ANCOVA to survey the regional CBF changes. Under a condition of dynamic global CBF change such as hypocapnia, there may be a difference in the ability to detect an activated area. To solve these problems, additional research is required.

SPM demonstrated activated areas in the extracerebral region near the sphenoid sinus. The finding of a relative increase in sphenoid sinus perfusion due to hyperventilation cannot be explained. We suppose this was caused by an artifact preventing SPM from correctly standardizing extracerebral structures.

CONCLUSION

There were different regional CBF changes in hypocapnia induced by hyperventilation. In analyzing vasoreaction by means of the voluntary hyperventilation technique, the primary motor and premotor areas which are activated by hyperventilation should be considered as different areas, where the CBF reductions are smaller than in other non-activated areas. These CBF changes are combined with vasoreaction and neural activation.

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