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Effects of acute hypobaric hypoxia on regional cerebral blood flow distribution: a Single Photon Emission Computed Tomography study in humans

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ABSTRACT

Single Photon Emission Computed Tomography (SPECT) and radiopharmaceutical stabilizing agents allowed us to investigate regional cerebral blood flow (CBF) distribution in six resting healthy subjects during acute laboratory hypobaric hypoxic conditions. In the hypobaric experiment stabilized ^{99m}Tc-D,L-hexamethyl-propylene amine oxime was injected 40 min after reaching hypoxic conditions corresponding to an altitude of 5500 m above sea level. Arterial blood sample was taken after five additional minutes. Mean arterial oxygen pressure and haemoglobin saturation were 28 mmHg and 56%, respectively. The control experiment was performed similarly, apart from barometric pressure and blood gas analysis. We analysed CBF distribution in 12 regions of functional interest bilaterally in frontal, parietal, temporal, occipital cortex, in the hippocampus, in the basal ganglia and other central structures of brain. No overall effect of hypoxia on normalized regional CBF distribution in the considered regions was found. Motor cortex (Brodmann 4) and basal ganglia were the only regions in which hypobaric hypoxia significantly increased relative distribution of the radiopharmaceutical [$F(1,5) = 18.30$; $P < 0.008$ and $F(1,5) = 10.85$; $P < 0.022$, respectively]. Despite severe hypoxia, we did not observe any major regional CBF redistribution. We found a small relative increase in blood flow to the motor cortex and the basal ganglia, at rest after 40 min of hypobaric hypoxia, suggesting a preferential compensatory mechanism of these functional regions of brain.

Keywords basal ganglia, hypobaric hypoxia, motor cortex, regional cerebral blood flow, Single Photon Emission Computed Tomography.

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Acute hypobaric hypoxia is faced by people ascending rapidly by car or cable car to high mountains or when flying without a pressurized cabin.

Acute hypoxia elicits several biochemical and cerebrovascular responses in both humans and animals (Siesjö 1992, Haddad & Jiang 1993). Global cerebral blood flow (CBF) increases (Borgström *et al.* 1975), both due to a direct vascular effect of hypoxia on the endothelium and to hypoxic cerebral vasodilatation mediated by vasodilator metabolites, i.e. potassium, prostaglandin and adenosine (Pearce 1995). A larger heart stroke volume and an increased blood pressure, as well as redistribution of aortic blood flow (Kuwahira *et al.* 1993), contribute to the rise of global CBF under normobaric (hypoxic gas mixture) hypoxia. Hypoxia induces hyperventilation, resulting in a hypocapnic vasoconstrictive reflex, but it seems like oxygen lack is a more effective vascular stimulus (Holmstrom 1971).

Several human and animal studies (Severinghaus *et al.* 1966, Shapiro *et al.* 1970, Jensen *et al.* 1996, Buck *et al.* 1998) have been performed in order to analyse

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regional CBF (rCBF) changes following either acute or chronic exposure to hypoxia. Studies of CBF in laboratory hypobaric hypoxia do not permit use of advanced technology, such as Positron Emission Tomography (PET) or Magnetic Resonance Imaging (MRI), on-line in hypobaric environment. These techniques are limited by the need to manipulate inhaled gas mixture to simulate environmental changes. Breathing hypoxic gas mixtures does not fully mimic hypobaric conditions, with physiologic influences from barometric pressure and gas density as well.

High altitude hypoxia (Regard *et al.* 1989, Nelson *et al.* 1990, Kramer *et al.* 1993), as well as experimentally induced hypoxia (Kennedy *et al.* 1989, Crowley *et al.* 1992, Fowler & Prlic 1995), has been reported to affect specific brain functions and cognitive performances in various ways. These studies support the hypothesis that some brain structures are more affected than others by acute hypoxia.

In this investigation a hypobaric chamber and Single Photon Emission Computed Tomography (SPECT) were used to study rCBF. The hypobaric chamber permitted simulation of barometric conditions faced by humans acutely exposed to high altitude. The controlled experimental procedure with minimal mental stress was performed to minimize individual physiological variability. Injection of stabilized SPECT tracer ^{99m}Tc-D,L-hexamethyl-propylene amine oxime (^{99m}Tc-HMPAO) during hypoxia postpones time of registration with respect to stimulus. This tracer is distributed in a slightly non-linear proportion to regional flow of the brain. By means of a lipophilic–hydrophilic conversion, it remains trapped in brain cells, with only a few percentage loss, for more than 24 h. As physical half-life of ^{99m}Tc-HMPAO is 6 h, SPECT imaging can be performed up to several hours after injection. This makes SPECT unique compared with PET or MRI techniques. Unfortunately the method does not admit evaluation of absolute changes in CBF.

The aim of this study was to investigate relative rCBF distribution during acute exposure to hypobaric hypoxia under controlled resting conditions.

MATERIALS AND METHODS

Subjects

Six healthy right-handed volunteers, four males and two females, mean age 33 years, range 24–43, were studied. All of them had a normal MR image of brain. Both Ethical and Isotope Committees of Karolinska Hospital approved the study. The experiments were performed with the informed consent of each subject.

Materials

All experiments were performed in a hypobaric chamber (Kockums, Sweden 1965). Monitoring of EKG, peripheral haemoglobin saturation and non-invasive blood pressure (NIBP) were performed by Propaq 106 EL (Protocol Systems, Oregon, USA). A polyethylene catheter was initially inserted into the right cubital vein and blood sample for haemoglobin and haematocrit was obtained before experiment. The same iv line was used for administration of radiopharmaceutical. The subjects were breathing from a mask in a low resistance gas delivery system and connected to a set of headphones delivering soft music. They were lying supine on a couch in the chamber in complete relaxation for 15 min. During each experiment one physician was attending inside the chamber and visually recording respiratory rates, while two more physicians were assisting outside the chamber.

Radiopharmaceutical

Pertechnetate eluation was made just before reconstitution of the freeze-dried kit (Ceretec, Amersham International plc, Amersham, Buckinghamshire, UK) which was made according to the manufacturer's instructions. To allow administration up to 4 h after preparation, ^{99m}Tc-HMPAO was stabilized with methylene blue according to manufacturer instruction. In all cases, administration of radiopharmaceutical was made between 33 and 236 min after its preparation.

SPECT

SPECT brain imaging was performed using a three-headed gamma camera (TRIAD XLT 20, Trionix, Twinsburg, OH, USA) equipped with low-energy ultra high-resolution (LEUR) parallel-hole collimators. The reconstructed in-plane spatial resolution, as measured in water with a line source on central axis, was 11 mm, expressed as full width at half maximum. The reconstructed spatial resolution in axial direction was about the same.

In-chamber protocol

The subjects were investigated in normobaric normoxia (control, 760 mmHg) and in hypobaric hypoxia (hypoxia, 380 mmHg) on two separate occasions. At these ambient conditions inspiratory partial pressure of oxygen corresponded to 160 and 80 mmHg for control and hypoxia, respectively. For each subject, sequence of experiments was randomly assigned and time interval between experiments varied between 2 and 20 days.

The chamber hatch was closed after a 15-min resting period. To reach desired hypoxia, pressure was reduced at a rate of 45–50 mmHg min^{-1} to a simulated altitude of 5500 m a.s.l. (380 mmHg), which was obtained in 8 min. During normoxia, the chamber was at normal pressure and subjects were breathing normal air through a mask.

After reaching desired hypobaric condition, the subjects carried on resting with closed eyes. After 40 min 330 MBq of ^{99m}Tc-HMPAO was injected followed by 10 mL saline to flush the catheter. As for normoxic control, injection was made 48 min after closing the chamber hatch, in order to compensate for the eight additional minutes spent to reach simulated altitude in hypoxia. To avoid disturbances in radiopharmaceutical distribution, NIBP measurements were suspended for 5 min upon injection.

In the hypoxic experiment, a blood sample was obtained by fine-needle puncture of radial artery 5 min after tracer injection. Blood gas analysis was made for oxygen (P_aO_2) and carbon dioxide (P_aCO_2) partial pressures, oxygen haemoglobin saturation ($SatO_2$) and pH to assess the degree of expected hypoxia and hypocapnia. Owing to invasiveness of the technique and to ethical considerations, arterial puncture was not performed in the control experiment. With the strict protocol used, long resting period and no signs of mental stress, we assumed normoxia and normocapnia in the healthy subjects during control condition. After return to sea level pressure, monitoring of all parameters continued for 15–20 min, with chamber hatch closed and subjects still resting.

SPECT examination

Directly after finishing each experiment, subjects walked to the gamma camera in the same building. Data were acquired for 30 s per projection at 90 equal angles of a complete 360° revolution. The SPECT images were reconstructed by filtered back projection using a Ramp filter with a cut-off frequency of 0.6 cycles cm^{-1}. Before reconstruction, data were smoothed using a Hamming filter with a cut-off frequency of 2.25 cycles cm^{-1}. The Chang uniform attenuation correction was performed. Data were back projected into 128×128 pixel matrix with a pixel size of 2.2×2.2 mm^2.

Computerized brain atlas

The 3D data sets of reconstructed rCBF values were transferred to a computerized brain atlas (CBA) program for evaluation. CBA is a software tool used to facilitate interpretation of neuroimaging data (Thurfjell *et al.* 1995). It uses a detailed 3D atlas derived from a cryosectioned brain (Greitz *et al.* 1991). CBA can be transformed to fit PET, SPECT, MRI or CT images of a any brain using a combination of automatic and manual tools including translations, rotations and linear scalings as well as second order, non-linear deformations. Each brain is standardized into a common space allowing intra- and inter-individual voxel by voxel operations. The standardized volume contained 48 slices, with a slice thickness and pixel size of 2.8 mm. In this study, a fully automatic fitting method (Andersson & Thurfjell 1997) was systematically implemented.

Selected brain regions for flow-analysis

Within this reformatted data set, 56 volumes of interest (VOIs), automatically recognized by CBA, identifying Brodmann areas (B) and anatomical structures, were lumped together in 12 functional regions. These regions corresponded to prefrontal (B: 8, 9, 10, 44, 45, 46), premotor (B6), motor (B4), somatosensory (SE), parietal (B: 5, 7, 39, 40), lateral temporal (B: 21, 37, 38), auditory (B: 22, 41, 42, 52) and occipital (B: 17, 18, 19) cortex as well as hippocampus, basal ganglia (putamen, and nc. caudatus), thalamus, hypothalamus, on both sides. The uptake values of each functional region defined above were averaged in all six subjects, and statistical analysis was performed.

The numerical evaluation of flow data was made after normalizing brain uptake data to average value of those 13% of all voxels in the complete 3-D set of data containing the largest number of registered events. This routine is default in the automatic atlas adaptation. It is considered to represent average grey matter uptake values and is set to 50 in arbitrary units.

For group comparisons, uptake in the standardized volume of six subjects of each group was averaged pixel by pixel. On this basis, average images of controls and hypoxia were subtracted from each other to highlight possible differences. In these images the black and white scale represented arbitrary units giving a qualitative representation of rCBF changes.

Statistical evaluation

Analysis of variance (Three-way ANOVA for repeated measure) was made to analyse rCBF distribution across 12 functional regions, hemispheric laterality (left and right), and experimental condition (control and hypoxia).

RESULTS

Except slight signs of dizziness, no adverse effects were seen during hypoxia. Subject characteristics, data on arterial blood gases, pH and cardiovascular responses

Table 1 Subject characteristics, arterial blood gas analysis, pH and cardiorespiratory responses to acute hypobaric hypoxia

	Subject no. (sex)						
	1 (F)	2 (F)	3 (M)	4 (M)	5 (M)	6 (M)	Mean
Age	24	29	30	38	42	43	34 ± 7.8
Haemoglobin in blood (g L^{-1})	143	131	159	134	143	138	141 ± 11
Haematocrit (%)	42	37	45	44	42	40	42 ± 2.9
P_aO_2 (mmHg) [normal ref. 75–100]	34	25	27	31	26	24	28 ± 3.9
P_aCO_2 (mmHg) [normal ref. 35–45]	29	36	33	29	38	41	34 ± 4.9
Arterial $Sato_2$ (%) [normal ref. 96–99]	71	49	56	68	50	43	56 ± 11
Arterial pH [normal ref. 7.3–7.5]	7.49	7.47	7.48	7.54	7.45	7.43	7.48 ± 0.04
Base excess (mmol L^{-1}) [normal ref. –3 to +3]	−0.1	3.1	2.0	3.2	3.0	2.7	2.3 ± 1.3
Respiratory rate (min^{-1})	11	7	6	6.3	8	7.5	7.6 ± 1.8
[normoxic control]	16	16	20	13	8	10	13.8 ± 4.4
Heart rate (min^{-1})	92	119	91	83	62	71	86 ± 20
[normoxic control]	75	85	60	61	48	49	63 ± 15
NIBP (mmHg, mean)	81	87	89	81	72	75	81 ± 6.6
[normoxic control]	82	86	82	93	81	73	83 ± 6.6

Normoxic control is reported for respiratory rate, heart rate and NIBP (non-invasive blood pressure).

during hypoxia are summarized in Table 1. Blood gases partial pressures varied much between individuals. P_aO_2 ranged between 24 and 34 mmHg and P_aCO_2 between 29 and 41 mmHg. The same variability was found for $Sato_2$. None of these parameters were correlated to rCBF distribution in any of the considered functional regions.

The three-way ANOVA for repeated measures applied to rCBF data did not show any significant overall effect of conditions. However, this analysis revealed two significant interactions: (1) Region × Hemispheres [$F(11,55) = 4.23$, $P = 000$] and (2) Region × Condition × Hemispheres [$F(11,55) = 2.15$, $P < 0.032$]. Separate analyses (two-way, repeated measures) were then carried out for each region.

During both control and hypoxia premotor cortex [$F(1,5) = 18.86$; $P < 0.007$], temporal lobe [$F(1,5) = 50.14$; $P < 0.001$] and auditory cortex [$F(1,5) = 13.47$; $P < 0.014$] showed a significant side difference (Table 2). As for region × condition interaction, normalized uptake values were significantly increased during hypoxia in motor cortex [$F(1,5) = 18.30$; $P < 0.008$] and basal ganglia [$F(1,5) = 10.85$; $P < 0.022$] (Table 2).

The change in motor cortex rCBF distribution under hypoxia was small but was present in all six subjects.

Table 2 Averaged right and left mean ^{99m}Tc-HMPAO uptake values in functional regions and relative standard deviations (SD) under normoxia (Norm) and hypoxia (Hypo)

Functional regions	VOIs (Brodmann)	Norm (mean rCBF ± SD)	Hypo (mean rCBF ± SD)	Hypo > Norm (no. of subjects)	R Hem (mean rCBF ± SD)	L Hem (mean rCBF ± SD)
Prefrontal Cortex	8,9,10, 44,45,46	43.2 ± 0.8	43.3 ± 0.4	4	46.3 ± 0.4	42.9 ± 0.9
Premotor Cortex	6	46.8 ± 1.5	46.8 ± 1.3	4	45.9 ± 1.1	47.7 ± 1.6
Motor Cortex	4	43.0 ± 1.4	43.7 ± 1.6	6	43.1 ± 1.4	43.6 ± 1.8
Somatosensory Cortex	1,2,3	40.9 ± 1.0	41.1 ± 1.1	2	40.9 ± 0.8	41.1 ± 1.4
Parietal Cortex	5,7,39,40	43.7 ± 1.1	43.3 ± 1.2	2	43.5 ± 1.0	43.5 ± 1.4
Temporal Cortex	21,37,38	38.8 ± 1.4	39.3 ± 1.2	3	40.0 ± 1.0	38.7 ± 1.1
Auditory Cortex	22,41,42,52	44.1 ± 1.3	44.0 ± 1.1	3	45.0 ± 0.9	43.1 ± 1.6
Visual Cortex	17,18,19	41.8 ± 1.6	41.6 ± 0.8	2	41.6 ± 0.5	41.8 ± 1.5
Hippocampus		40.9 ± 2.6	41.6 ± 1.8	4	41.1 ± 2.1	41.4 ± 2.1
Basal Ganglia (Caudatus, Putamen)		43.5 ± 1.7	45.0 ± 1.0	5	43.9 ± 1.0	44.6 ± 1.6
Thalamus		47.3 ± 0.9	47.8 ± 1.4	2	47.5 ± 1.3	47.7 ± 1.0
Hypothalamus		44.6 ± 3.2	44.2 ± 1.7	4	44.2 ± 2.0	44.8 ± 2.1

Mean values on the right (R Hem) and left (L Hem) hemisphere are averaged between hypoxia and normoxia. VOIs = volumes of interest; rCBF = regional cerebral blood flow.

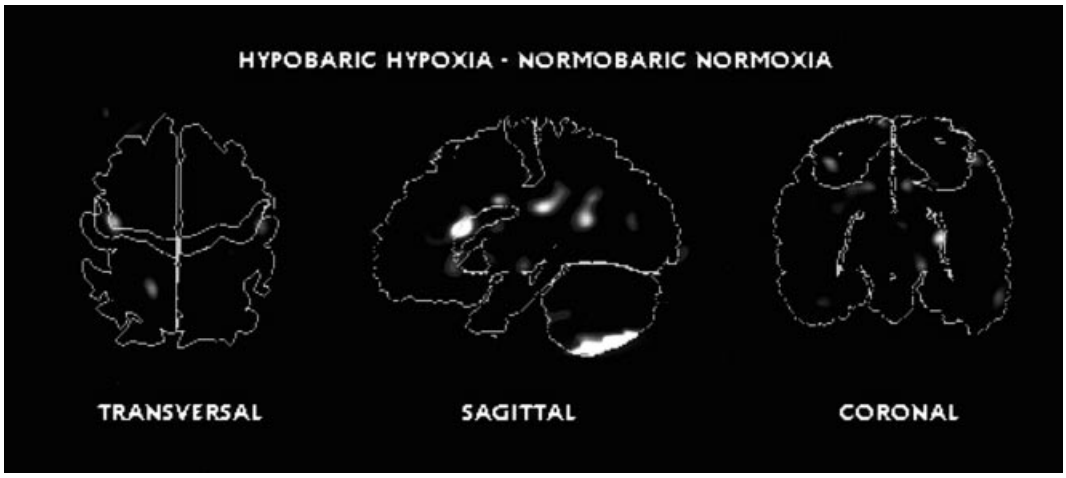

Figure 1 Subtraction image highlighting cerebral areas with increased ^{99m}Tc-HMPAO uptake distribution under hypoxia. Images are obtained by subtracting voxel by voxel the average normoxia from the average hypoxia data sets ($n = 6$). Motor cortex and basal ganglia are automatically outlined by CBA in transversal, sagittal and coronal projections. The black and white scale is in arbitrary units.

Five out of six subjects showed increased flow distribution in basal ganglia.

Mean differences in rCBF distribution between normoxia and hypoxia were generally small in all regions, ranging, in arbitrary units, from –0.4 in parietal cortex to +1.5 in basal ganglia.

When flow data at normoxia were subtracted from those obtained under hypoxia, parts of motor cortex, basal ganglia and some regions belonging to cingulate cortex were highlighted in image (Fig. 1). The opposite subtraction did not enhance any particular region.

The high activity appearing in ventral part of cerebellum (Fig. 1) is due to a methodological error given by a discrepancy between abnormal shape of cerebellum in CBA (Greitz *et al.* 1991) and truncation of reconstructed field of view in some of the subjects in normoxia.

DISCUSSION

The aim of this study was to investigate rCBF in healthy humans, during acute hypobaric exposure and under minimal physical and mental stress. Despite a rigorous experimental protocol and a relatively long exposure, we found a considerable interindividual variability in P_aO_2, P_aCO_2 and $SatO_2$, most probably related to different individual hypoxic ventilatory responses.

Despite quite severe hypoxia, we did not find any major rCBF redistribution. However, a small but significant increase of relative rCBF in motor cortex and in basal ganglia was found. The close functional and anatomical relationship between these two regions suggests a specific response of motor–basal ganglia–thalamic–motor loop to hypoxia. Haghighi *et al.* (1993) showed that transient hypoxia affected evoked potential of motor cortex in rats. Motor cortex and basal ganglia seem to be particularly sensitive to hypoxia (Inoue *et al.* 1992, Burke *et al.* 1994, Azzarelli *et al.* 1996, Jansen *et al.* 1997). The strong neuroanatomical connection between the motor cortex and the basal ganglia has previously been described at neuronal level (Selemon & Goldman-Rakic 1985). Fibres from the motor cortex selectively end in the putamen remaining separate during their path to more central structures. Hence, a primary change in blood flow in either the motor cortex or the basal ganglia could cause a concomitant change in structures belonging to same functional loop. The increase of rCBF found in these two structures may be due to a specifically high sensitivity to hypobaric hypoxia leading to a compensatory rCBF increase.

The lack of statistical significance in the thalamus, as part of loop, may be explained by partial involvement of its nuclei. Only the ventral lateral, ventral anterior and centromedian nuclei are part of motor loop pathway.

Another factor that may have accounted for motor cortex rCBF increase is activation of primary motor and premotor cortex induced by hypocapnia during hyperventilation, as previously reported by Ishii *et al.* (1998). However, not all subjects hyperventilated in our experiment. A reduction in P_aCO_2 has a strong vasoconstrictor effect on cerebral blood vessels while a decrease in P_aO_2 greatly increases rCBF. In our study, when present, the decrease in P_aCO_2 was minimal and it is not clear in human studies which is the magnitude of absolute change of rCBF due to both the opposing effects of hypoxemia and hypocapnia.

The rCBF redistribution obtained in this investigation differs from that of Buck *et al.* (1998) using PET and $H_2^{15}O$. They observed a larger increase in hypothalamic flow compared with the rest of brain following

a 20-min period of normobaric hypoxia. Oxygen partial pressure corresponded to that at 4500 m a.s.l., which in that study gave a global CBF increase of about 36%. In our study, we did not find any significant change in relative hypothalamic flow. One explanation could be that our subjects were exposed to more severe hypoxia, for a time more than twice as long as compared with that of Buck *et al.* (1998) The hypobaric condition per se could also have affected physiology in a different manner. Another explanation may be better spatial resolution of PET, giving a less pronounced partial volume effect, as compared with SPECT. However, in a recent comparison of SPECT and PET rCBF (Jonsson *et al.* 1998) we found that for the thalamus, a structure comparable for size and location to the hypothalamus, the difference between the two methodologies was only about 13%. Other factors that may contribute to observed differences are difficulties in outlining hypothalamus – in both studies – as well as non-linear uptake of ^{99m}Tc-HMPAO at increasing flow (Lassen *et al.* 1987).

Another finding of our study – an inter-hemispheric difference of rCBF in premotor, lateral temporal and auditory cortex – may be due to physiological as well as anatomical reasons, e.g. larger size of right temporal lobe as compared with the left one and confirms studies reported previously (Jack *et al.* 1988, Greitz *et al.* 1991).

The choice of 3-D VOIs instead of 2-D regions of interest renders analysis more sensitive to changes in perfusion and less dependent on errors in outlining positioning (Tikofski & Hellman 1991, Pagani *et al.* 1998). It also has the advantage of a lower variance due to better counting statistic since the number of voxels in functional regions is larger than the number of pixels in a ROI. Moreover, this particular 3-D analysis represents flow in functional regions rather than in a selected section of a functional area, and may therefore be more representative and sensitive to neuropsychological changes in defined functional regions of the brain.

In conclusion, this study showed no major changes in rCBF distribution during acute hypobaric hypoxia at rest. The increase in rCBF in the motor cortex and the basal ganglia, even if relatively small, suggests a possible preferential compensatory mechanism for these brain functional regions. Further studies with specific brain activation tasks, are needed to clarify possible rCBF changes under hypobaric hypoxia in other functional regions of the human brain.

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