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The influence of hyperoxia on regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV) and cerebral blood flow velocity in the middle cerebral artery (CBFVMCA) in human volunteers

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Abstract

Conflicting results reported on the effects of hyperoxia on cerebral hemodynamics have been attributed mainly to methodical and species differences.

In the present study contrast-enhanced magnetic resonance imaging (MRI) perfusion measurement was used to analyze the influence of hyperoxia (fraction of inspired oxygen (FiO2) = 1.0) on regional cerebral blood flow (rCBF) and regional cerebral blood volume (rCBV) in awake, normoventilating volunteers (n = 19). Furthermore, the experiment was repeated in 20 volunteers for transcranial Doppler sonography (TCD) measurement of cerebral blood flow velocity in the middle cerebral artery ($CBFV_{MCA}$).

When compared to normoxia (FiO2 = 0.21), hyperoxia heterogeneously influenced rCBV (4.95 ± 0.02 to 12.87 ± 0.08 mL/100g (FiO2 = 0.21) *vs.* 4.50 ± 0.02 to 13.09 ± 0.09 mL/100g (FiO2 = 1.0). In contrast, hyperoxia diminished rCBF in all regions (68.08 ± 0.38 to 199.58 ± 1.58 mL/100g/min (FiO2 = 0.21) *vs.* 58.63 ± 0.32 to 175.16 ± 1.51 mL/100g/min (FiO2 = 1.0)) except in parietal and left frontal gray matter.

$CBFV_{MCA}$ remained unchanged regardless of the inspired oxygen fraction (62 ± 9 cm/s (FiO2 = 0.21) *vs.* 64 ± 8 cm/s (FiO2 = 1.0)).

Finding $CBFV_{MCA}$ unchanged during hyperoxia is consistent with the present study's unchanged rCBF in parietal and left frontal gray matter. In these fronto-parietal regions predominantly fed by the middle cerebral artery, the vasoconstrictor effect of oxygen was probably counteracted by increased perfusion of foci of neuronal activity controlling general behavior and arousal.

Keywords: Normoxia; Hyperoxia; Regional CBF; Regional CBV; Regional MTT; $CBFV_{MCA}$; Humans

1. Introduction

The effect of breathing 100% oxygen on cerebral blood flow (CBF) and cerebral blood volume (CBV) is of physiological but sometimes also of clinical interest (e.g., in patients ventilated with pure oxygen (FiO2 = 1.0) presenting for MRI perfusion measurements). Previous animal studies on the effects of hyperoxia on cerebral hemodynamics revealed conflicting results. Busija et al. found no change in CBF in ponies during normocapnic hyperoxia [1], whereas other authors reported an increase in CBF at high PaO2 levels in lambs [2] or a decrease in regional CBF in pigs [3].

In their classic study on the effects of altered arterial tensions of oxygen on cerebral blood flow Kety et al. found a decrease in CBF during hyperoxia in awake, normoven-

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tilating volunteers [4]. A more recent magnetic resonance imaging (MRI) phase-contrast angiography study reported a similar hyperoxic decrease in human global CBF [5].

These contradictory findings have been attributed to methodical, species [2] and age [6] differences, and thus conclusive results on the influence of hyperoxia on CBF and CBV have not been presented to date. We therefore *simultaneously* investigated regional CBF (rCBF) and regional CBV (rCBV) in awake, normoventilating voluteers during normoxia (FiO2 = 0.21) and hyperoxia (FiO2 = 1.0) by means of contrast-enhanced MRI perfusion measurement.

In many clinical settings, however, measurement of cerebral blood flow velocity in the middle cerebral artery (CBFVMCA) by use of transcranial Doppler sonography (TCD) provides an acknowledged monitoring of changes in CBF [7]. Therefore, we additionally measured CBFVMCA in human volunteers during normocapnic normoxia and hyperoxia.

2. Methods

Following approval by the local University Ethics Committee and written informed consent, forty, right-handed, non-smoking male volunteers (ASA physical status I) were enrolled in the study. The volunteers were randomly allocated to undergo either MRI contrast-enhanced cerebral perfusion measurement ($n = 20$) or TCD measurement of CBFV MCA ($n = 20$).

Wearing a closely fitting face mask in either group the volunteers normoventilated (end-tidal carbon dioxide concentration (EtCO2) = 40 mmHg) during control measurement (FiO2 = 0.21) and during inhalation of pure oxygen (FiO2 = 1.0). The order of the two measurements was randomized. A minimum of 10 to 15 min was allowed for stabilization at each level. During the measurements the volunteers were awake with eyes closed and sensory stimulation was kept to a minimum. The two MRI contrast-enhanced cerebral perfusion measurements were separated by 24 h. The volunteers had been trained both by verbal instruction and by watching the capnographic trace of the monitor on the day prior to the experiment. During the experiment, breathing at a constant EtCO2 (e.g., 40 mm Hg) was supported by voice command when necessary. The fraction of inspired and expired oxygen (FiO2, FeO2), EtCO2, respiration frequency (RF), non-invasive mean arterial blood pressure (MAP) and pulsoximetry hemoglobin saturation (SpO2) were monitored (S/5 MRI Monitor™, Datex-Ohmeda, Helsinki, Finland). QUICK CAL™ calibration gas (REF: 755582; Datex-Ohmeda, Helsinki, Finland) was used to calibrate the monitor.

2.1. TCD measurement (n = 20)

CBFVMCA was measured by TCD using a fixed 2-Mhz-pulsed TCD device (Multi-Dop-L, DWL, Sipplingen, Germany). The Doppler probe was placed on the right hemisphere above the zygomatic arch between the lateral margin of the orbit and the ear and directed toward the M1 segment of the middle cerebral artery (MCA) at a depth of 50–55 mm, depending on optimization and stability of the signal. All TCD measurements were taken by the same investigator.

2.2. MRI perfusion measurement (n = 20)

MRI measurements were performed on a 1.5-Tesla whole-body scanner (Magnetom VISION, Siemens, Germany) using a standard circular polarized head coil. Single-shot echo planar imaging (EPI) was performed with a repetition time (TR) of 2s and an echo time (TE) of 64 ms. An acquisition matrix of 64 × 128 (field of view (FOV) 22 × 22 cm, inplane resolution 1.7 × 3.4 mm) was used. The slice thickness was set to 5 mm (slice gap 1.25), and 15 slices were measured simultaneously. A paramagnetic contrast agent Gd-DTPA (0.1 mmol/kg) was injected into an antecubital vein at a rate of 9 mL/s using an MR-compatible power-injector (SPECTRIS, Medrad Inc., Pittsburgh, PA, USA). EPI scans ($n = 60$) were performed at 2s intervals to cover the entire passage of the contrast agent through the brain. Six scans (6/60 scans) taken preinjection were used as the baseline.

rCBV and rCBF were calculated by a blinded investigator in regions of interest (ROIs) outlined bilaterally in white and in (frontal, parietal, occipital, striatal and thalamic) gray matter (Figs. 1 and 2). Outlining ROIs on corresponding anatomic T2-weighted scans is not possible as EPI (echo planar imaging) T2*-weighted contrast-enhanced perfusion scans have a known geometric distortion. In order to check the ROIs for correct anatomic position, they were copied into the EPI T2*-weighted scans acquired before contrast media application. The definition of regions produced in this way is reliable and reproducible and is not biased to high signal areas on the CBV maps. Furthermore, varying partial volume effects from white and gray matter inclusion in regions accorded primarily to one category, which could account for some of the differences between the regions, were minimized. Corresponding ROIs contained comparable numbers of pixels.

The basic concept used to determine CBV and CBF was previously described by Ostergaard et al. [8,9,10]. An improved gamma variate fit was used to reduce underestimation of the arterial input function (AIF), which otherwise leads to overestimation of CBV and CBF values [11].

Following correction for the density of brain tissue [12] rCBF values are given in [mL/100g/min] and rCBV values in [mL/100g].

Mean Transit Time (MTT), which defines the average time that any particle of tracer, e.g., contrast media, remains within the region of interest [13], was calculated with the equation:

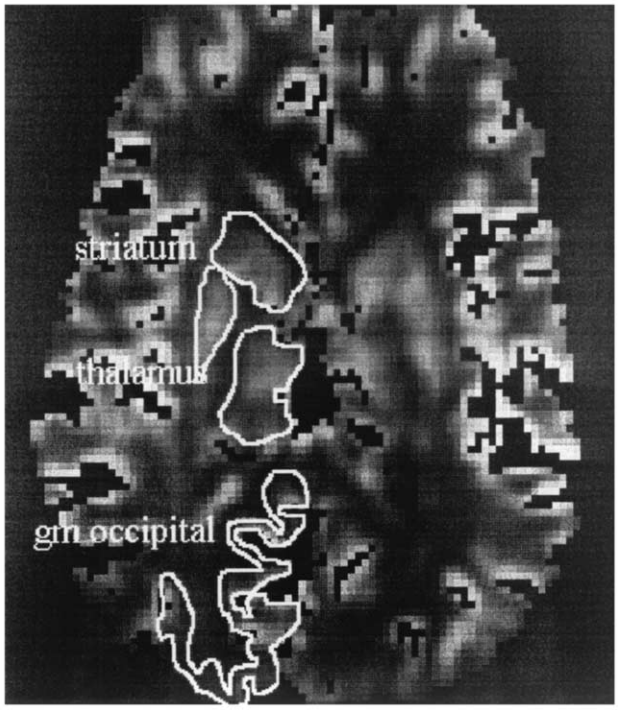

Fig. 1. Representative cerebral blood volume (CBV) map showing regions of interest (ROIs) for evaluation of right hemispheric thalamic (thalamus), striatal (striatum) and occipital (gm occipital) regional cerebral blood volume (rCBV).

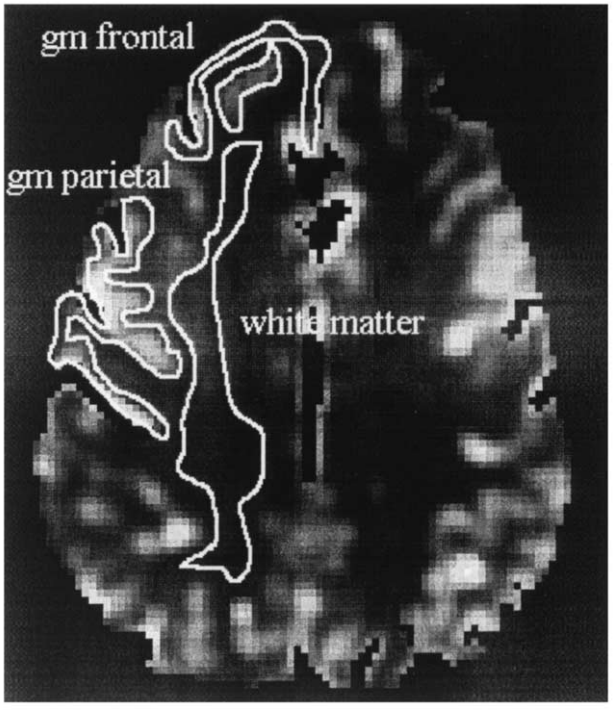

Fig. 2. Representative CBV map showing regions of interest (ROIs) for evaluation of right hemispheric white matter (white matter), parietal (gm parietal) and frontal (gm frontal) regional cerebral blood volume (rCBV).

$$\mathrm{rMTT} = \frac{rCBV}{rCBF} \cdot 60 \quad (1)$$

Regional MTT (rMTT) is given in [s].

3. Statistical analysis

Data are presented as mean ± SEM. Data were tested for normal distribution using the Kolmogorov-Smirnov Test. Since no normal distribution of data was available, between-group comparison was performed with a stable non-parametric test (e.g., Mann-Whitney *U* test), which also considered the comparable but not identical number of pixels in comparable regions (e.g., unpaired test). A $p \leq 0.05$ was considered statistically significant.

4. Results

All volunteers from the MRI group ($n = 20$; age: 26 ± 1 years; weight: 77 ± 1 kg; height: 179 ± 1 cm) and from the TCD group ($n = 20$; age: 33 ± 3 years; weight 75 ± 2 kg; 181 ± 2 cm) completed the study without complication. Due to motion artifacts volunteer No. 10 had to be excluded from the MRI group ($n = 19$). Moreover, MRI measurements were not obtainable during hyperoxia (FiO2 = 1.0) in volunteer No. 11 or during normoxia (FiO2 = 0.21) in volunteer No. 5.

In both groups verbal command was necessary once or maximum twice in each volunteer in order to maintain normocapnia. The TCD as well as the contrast-enhanced MRI perfusion measurement were commenced only after verbal command had produced stable normocapnia, so that no further verbal stimulation was needed during the measurement.

In the MRI group heart rate decreased and SpO2 increased significantly during hyperoxia. In all other cases hemodynamic (heart rate, MAP) and respiratory (SpO2, EtCO2, RF) parameters were influenced neither by hyperoxia nor by normoxia (Table 1).

4.1. TCD measurements

4.1.1. CBFV$_{MCA}$

Hyperoxia did not change CBFV$_{MCA}$ as compared to normoxia (Table 1).

4.2. Contrast-enhanced MRI perfusion measurements

4.2.1. Regional CBF (rCBF)

Hyperoxia diminished rCBF in all regions except in parietal and left hemispheric frontal gray matter (Table 2) (Figs. 3 and 4).

Table 1
Summarizes hemodynamic (heart rate (HR), mean arterial blood pressure (MAP)) and respiratory (pulsoximetry hemoglobin saturation (SpO2), end-tidal CO2 concentration (EtCO2)) parameters during cerebral blood flow velocity (CBFV) and contrast-enhanced MRI perfusion (MRI) measurements at normoxia (FiO2 = 0.21) and hyperoxia (FiO2 = 1.0) in spontaneously breathing humans.

FiO2 %	HR beats/minute	MAP mmHg	Sp02 %	EtCO2 mmHg	$CBFV_{MCA}$ cm/s
CBFV (n = 20)					
21	65 ± 8	88 ± 9	98 ± 2	40 ± 0.1	62 ± 9
100	66 ± 9	88 ± 9	100 ± 1	40 ± 0.1	64 ± 8
MRI (n = 19)					
21	70 (± 12)	90 (± 10)	97 (± 1)	40 (± 0.6)	
100	64 (± 11)*	89 (± 9)	99 (± 1)*	40 (± 0.5)	

*Significant to FiO2 = 0.21. ($p \leq 0.05$). Data are given as mean ± SD.

4.2.2. Regional CBV (rCBV)

Hyperoxia diminished rCBV in white matter and in right hemispheric striatal and thalamic gray matter. In contrast, in occipital gray matter hyperoxia increased rCBV. In all other regions hyperoxia did not change rCBV (Table 2) (Figs. 5 and 6).

4.2.3. Regional MTT (rMTT)

Hyperoxia increased rMTT in all regions and remained unchanged in parietal and left hemispheric frontal gray matter (Table 2).

5. Discussion

Already in 1921 Dautrebande et al. assumed the effect of high paO2 to be vasoconstriction [14]. Constriction of cerebral blood vessels during breathing of 100% oxygen was subsequently reported in cats [15], in monkeys [16] and in man [4,5,17]. However, methods based on analysis of blood concentrations of inert tracers during either saturation [18, 19] or desaturation [20] allow only assessment of global CBF. Moreover, the most important potential error factor involved in these techniques is the presence of slowly perfused tissue masses and contamination of venous blood sampled from extracerebral sources [21].

In the present study contrast-enhanced MRI perfusion measurement was used to assess regional CBF. In accordance with previous investigations reporting on global CBF [4,5] we found hyperoxia (FiO2 = 1.0) to decrease rCBF in all regions except parietal and left hemispheric frontal gray matter. Seeking an explanation for the hyperoxic reduction of CBF requires two major concepts [22]. One concept

Table 2
Shows regional cerebral blood flor (rCBF) [mL/100g/min], regional cerebral blood volume (rCBV) [mL/100g], and regional mean transit time (rMTT) [s] in white matter (WM) and in gray matter (striatum (GM_ST), thalamus (GM_TH), frontal (GM_FR), parietal (GM_PA), occipital (GM_OC)) during normoxia (FiO2 = 0.21) and during hyperoxia (FiO2 = 1.0). (n = 19). MRI measurements were not obtainable during hyperoxia (FiO2 = 1.0) in volunteer No. 11 or during normoxia (FiO2 = 0.21) in volunteer No. 5.

		Right Hemisphere					Left Hemisphere				
		100% Oxygen		21% Oxygen			100% Oxygen		21% Oxygen		
		Mean	SEM	Mean	SEM	p	Mean	SEM	Mean	SEM	p
WM	rCBF	60.03	0.33	70.54	0.39	*	58.63	0.32	68.08	0.38	*
	rCBV	4.60	0.02	5.06	0.02	*	4.50	0.02	4.95	0.02	*
	rMTT	5.09	0.02	4.87	0.02	*	5.10	0.02	4.94	0.03	*
GM_ST	rCBF	175.16	1.51	190.36	1.70	*	169.95	1.43	192.97	1.71	*
	rCBV	10.49	0.06	10.79	0.06	*	10.81	0.07	11.01	0.07	ns
	rMTT	4.03	0.03	3.85	0.03	*	4.24	0.03	3.80	0.02	*
GM_TH	rCBF	158.84	2.04	186.05	2.38	*	171.84	2.07	199.54	2.38	*
	rCBV	10.70	0.11	11.08	0.10	*	12.39	0.13	12.39	0.12	ns
	rMTT	4.56	0.04	4.08	0.04	*	4.78	0.05	4.18	0.04	*
GM_FR	rCBF	174.89	1.38	186.18	1.58	*	170.36	1.41	167.83	1.41	ns
	rCBV	12.04	0.07	12.23	0.08	ns	11.55	0.07	11.57	0.07	ns
	rMTT	4.61	0.03	4.39	0.03	*	4.58	0.03	4.60	0.03	ns
GM_PA	rCBF	192.58	1.47	199.58	1.58	ns	182.00	1.42	181.51	1.55	ns
	rCBV	12.73	0.07	12.87	0.08	ns	12.08	0.07	12.05	0.07	ns
	rMTT	4.42	0.03	4.29	0.02	*	4.42	0.02	4.44	0.03	ns
GM_OC	rCBF	168.67	1.64	185.76	1.70	*	171.93	1.57	187.08	1.71	*
	rCBV	13.09	0.09	12.63	0.08	*	12.84	0.09	12.61	0.08	*
	rMTT	5.23	0.04	4.64	0.03	*	5.02	0.03	4.59	0.03	*

*Significant ($p \leq 0.05$). Data are given as mean ± SEM.

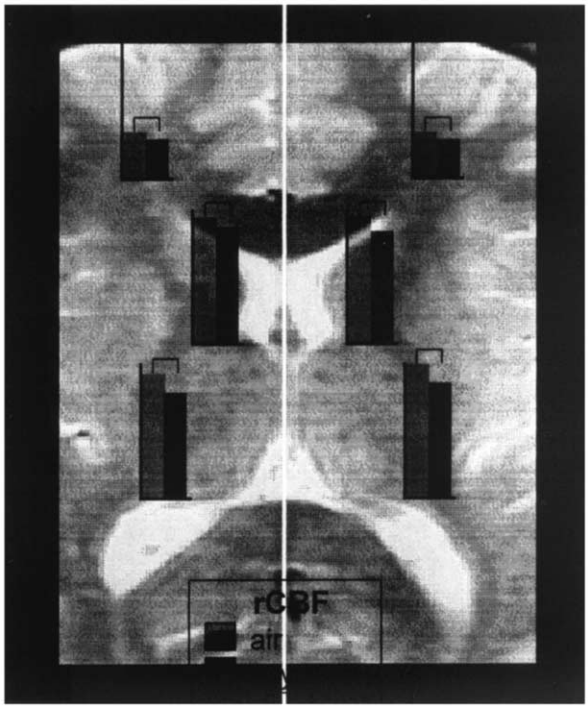

Fig. 3. Shows absolute changes in regional cerebral blood flow (rCBF) [mL/100g/min] in striatal and thalamic gray matter and in white matter during normoxia (FiO2 = 0.21) or hyperoxia (FiO2 = 1.0). left (left hemisphere), right (right hemisphere).

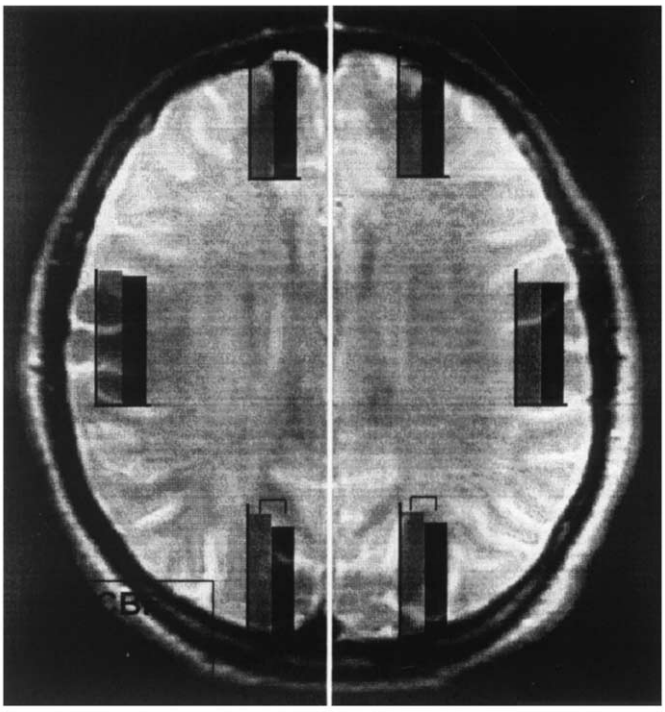

Fig. 4. Shows absolute changes in regional cerebral blood flow (rCBF) [mL/100g/min] in frontal, parietal and occipital gray matter during normoxia (FiO2 = 0.21) or hyperoxia (FiO2 = 1.0). left (left hemisphere), right (right hemisphere).

favors a direct vasoconstrictor action of oxygen, while the other favors primary hyperventilation and an associated drop in paCO2. The proposed cause of this primary hyperventilation is cerebral carbon dioxide accumulation as a consequence of a decreased carbon dioxide-carrying capacity of oxygenated hemoglobin (the Haldane effect) [22,23]. Supporting evidence for the latter concept is given by the observed hyperventilation during hyperoxia in animal [1] and human [5,24,25,26] studies.

In the present study, however, normocapnia was meticulously controlled by EtCO2, which correlates well with paCO2 [27,28,29]. Therefore, it is unlikely that paCO2-induced cerebral vasoconstriction influenced contrast-enhanced MRI perfusion measurements during hyperoxia in the present study.

Furthermore, in contrast to a simple vasoconstrictor like hypocapnia [30] there was a marked heterogeneity in rCBF during hyperoxia, as parietal and left hemispheric frontal gray matter rCBF were unaffected. Thus, the evidence available to us makes a direct vasoconstrictor action of oxygen more likely than an indirect paCO2-mediated one.

Changes in CBFVMCA as detected by transcranial Doppler sonography (TCD) of the middle cerebral artery reliably correlate with changes in CBF [31]. These changes in CBFVMCA are predominantly caused by vasomotion in arteriolar vessel areas. Changes in arteriolar vessel areas along with capillary and small venous vessel areas, however, are also responsible for hyperoxic changes in cerebral hemodynamics detected by contrast-enhanced MRI perfusion measurements. Thus, as the parietal cortex, in which hyperoxia left rCBF unchanged in this study, is predominantly supplied by the middle cerebral artery [32], it is of little surprise that CBFVMCA did not also change during hyperoxia.

Our data thus indicate that TCD measurements of cerebral blood flow velocity reliably detect the effects of hyperoxia on CBF in vessel areas fed predominantly by the middle cerebral artery. Performing the MRI and TCD studies in the same group of volunteers would certainly have increased the power of the present study, as a variation of cerebrovascular O2 reactivity in normal subjects is possible.

Cameron et al. reported in right-handed subjects right-hemispheric CBV to be higher than left-hemispheric [33]. Similarly, in the present study right supratentorial rCBV was found to be tendentially higher than left hemispheric at baseline. During hyperoxia rCBV in most of the regions either decreased or did not change at all. In occipital gray matter, however, rCBV increased. To further analyze the observed changes in rCBF and rCBV a detailed look at rMTT is essential. rMTT defines the average time needed by a tracer to transit the region of interest [13]. Because rMTT equals the ratio of rCBV to rCBF, the observed increase in rMTT in our volunteers reflects a relatively greater decrease in rCBF than in rCBV during hyperoxia. For changes in PaCO2 Grubb et al. reported in rhesus monkeys that CBV should increase as the 0.38 power of CBF [34]. The undis-

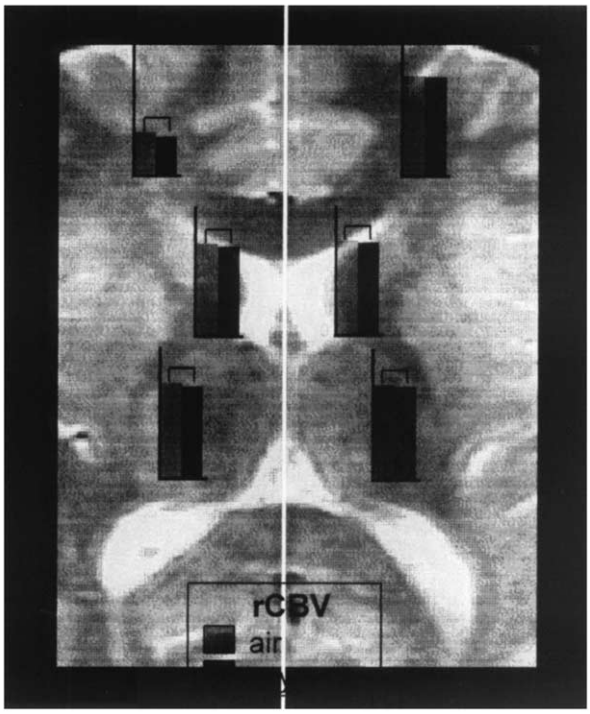

Fig. 5. Shows absolute changes in regional cerebral blood volume (rCBV) [mL/100g] in striatal and thalamic gray matter and in white matter during normoxia (FiO2 = 0.21) or hyperoxia (FiO2 = 1.0). left (left hemisphere), right (right hemisphere).

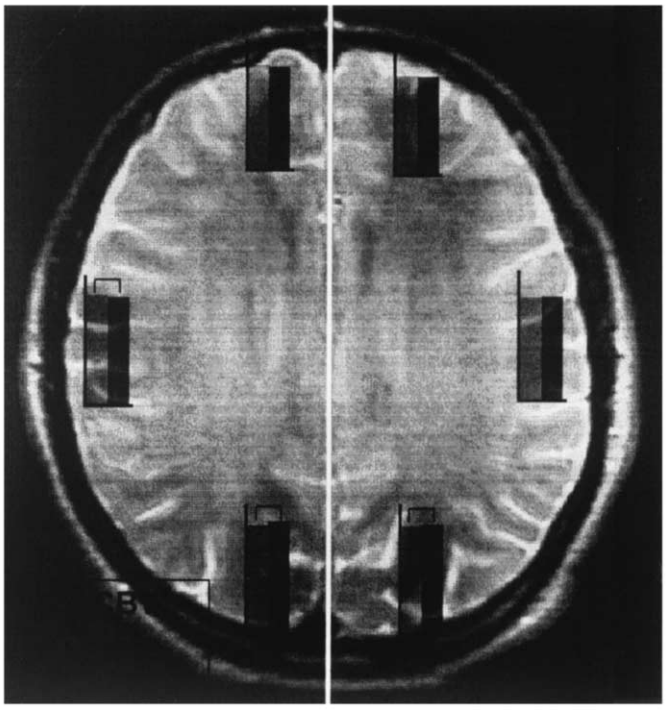

Fig. 6. Shows absolute changes in regional cerebral blood volume (rCBV) [mL/100g] in frontal, parietal and occipital gray matter during normoxia (FiO2 = 0.21) or hyperoxia (FiO2 = 1.0). left (left hemisphere), right (right hemisphere).

puted anatomic differences between the brain of rhesus monkey and man and the fact that in the present human study PaCO2 was meticulously kept at normocapnia during the entire experiment certainly preclude PaCO2-mediated changes in CBV and CBF and consequently rMTT.

In order to quantify absolute CBF and CBV values by using contrast-enhanced MRI perfusion measurement, the concentration of the paramagnetic contrast agent in an arterial vessel, the arterial input function (AIF), needs to be determined. Any underestimation of AIF leads to an overestimation of CBF and CBV values. As AIF is taken in the region of the middle cerebral artery, which is a rather small vessel, it can be underestimated due to partial volume. Moreover, the assumption of a linear [8,35] instead of a non-linear [36,37] relationship between blood concentration of paramagnetic contrast agent and the susceptibility contrast can cause the AIF to be underestimated. In the present study part of the underestimation of AIF and hence overestimation of CBV and CBF was compensated by using an improved AIF gamma variate fit [11].

Nevertheless, the present study's rCBF and rCBV values (see Table 2) are markedly higher than previously reported white and gray matter CBF and CBV [38] values, which deserves explanation. The present study used gradient-echo echo-planar (GE-EPI) imaging. In contrast to spin-echo echo-planar (SE-EPI) imaging GE-EPI imaging combines the advantages of better coverage of the brain, of being sensitive to the entire vascular bed and of a lower contrast dose [39]. Furthermore, in a very recent study Simsonsen-CZ et al. reported a conversion factor (0.43) relating GE-EPI CBF and CBV values to absolute CBF and CBV values obtained with positron emission tomography (PET) [39]. Applying this conversion factor (0.43) to the present study's rCBF and rCBV values (see Table 2) yields absolute CBF and CBV values similiar to those established in decades of literature. Furthermore, in the present study the ratios of CBF and CBV between gray matter and white matter were comparable to previously published gray: white matter ratios [9]. Hence, changes in rCBF and rCBV e.g., during hyperoxia (FiO2 = 1.0) should in any case be reliably detected.

In conclusion we here show that hyperoxia affected rCBV variably but relatively less than rCBF. During hyperoxia rCBF was decreased in all regions except parietal and left frontal gray matter, which well explains the unchanged $CBFV_{MCA}$ during hyperoxia in our volunteers. In these fronto-parietal regions, predominantly fed by the middle cerebral artery, the vasoconstrictor effect of oxygen was probably counteracted by increased perfusion of foci of neuronal activity controlling general behavior and arousal.

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