Regional response of cerebral blood volume to graded hypoxic hypoxia in rat brain

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Background. The response of cerebral blood flow to hypoxic hypoxia is usually effected by dilation of cerebral arterioles. However, the resulting changes in cerebral blood volume (CBV) have received little attention. We have determined, using susceptibility contrast magnetic resonance imaging (MRI), changes in regional CBV induced by graded hypoxic hypoxia.

Methods. Six anaesthetized rats were subjected to incremental reduction in the fraction of inspired oxygen: 0.35, 0.25, 0.15, and 0.12. At each episode, CBV was determined in five regions of each hemisphere after injection of a contrast agent: superficial and deep neocortex, striatum, corpus callosum and cerebellum. A control group (n=6 rats) was studied with the same protocol without contrast agent, to determine blood oxygenation level dependent (BOLD) contribution to the MRI changes.

Results. Each brain region exhibited a significant graded increase in CBV during the two hypoxic episodes: 10–27% of control values at 70% SaO₂, and 26–38% at 55% SaO₂. There was no difference between regions in their response to hypoxia. The mean CBV of all regions increased from 3.6 (SD 0.6) to 4.1 (0.6) ml (100 g)⁻¹ and to 4.7 (0.7) ml (100 g)⁻¹ during the two hypoxic episodes, respectively (Scheffé F-test; P<0.01). Over this range, CBV was inversely proportional to SaO₂ (r²=0.80). In the absence of the contrast agent, changes due to the BOLD effect were negligible.

Conclusions. These findings imply that hypoxic hypoxia significantly raises CBV in different brain areas, in proportion to the severity of the insult. These results support the notion that the vasodilatory effect of hypoxia is deleterious in patients with reduced intracranial compliance.

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It is established that hypoxic hypoxia is accompanied by an increase in cerebral blood flow (CBF) so that delivery of oxygen tends to be maintained.¹,² This increase is due to the dilation of cerebral arterioles.³ As a result, cerebral blood volume (CBV) rises. However, the change in CBV cannot be inferred from that in CBF because there is no clear relationship between the two.⁴,⁵ There have been few studies of changes in CBV induced by hypoxia: reports describe either only small effects on CBV⁶,⁷ or marked increases.⁸,⁹ By measuring regional CBV response to hypoxic hypoxia in anaesthetized, mechanically ventilated rats, our goal was to determine: (i) the relationship between the degree of the hypoxic insult and CBV changes; and (ii) possible differences in responsiveness to hypoxia between brain areas. We used susceptibility contrast magnetic resonance imaging (MRI) to measure CBV in dorsoparietal neocortex, striatum, corpus callosum and cerebellum during incremental reduction in the fraction of inspired oxygen (FIO₂): 0.35, 0.25, 0.15 and 0.12.

Materials and methods
Two groups of fed Wistar female rats (200–220 g) were studied sequentially. Group 1 (n=6 rats) was used for the
determination of regional CBV using susceptibility contrast MRI. Susceptibility contrast MRI exploits the increase in the magnetic susceptibility difference ($\Delta \chi$) between the vascular and the extravascular compartments induced by the presence of a long-lived contrast agent confined in the vascular bed. This increase in $\Delta \chi$ results in an increase $\Delta R^2$ of the decay rate ($R^2 = 1/T^2$) of the NMR signal from water protons, which is proportional to regional CBV, as previously shown.\textsuperscript{10,11}

\begin{equation}
\hat{r}_{CBV} = \frac{3}{4\pi} \frac{\Delta R^2_{CBV}}{\gamma \Delta \chi B_0}
\end{equation}

where $\gamma$ is the gyromagnetic ratio, and $B_0$ is the magnetic field in the absence of sample.

It has been shown that deoxygenated haemoglobin acts as a natural intravascular contrast agent, which is the basis for the BOLD image contrast.\textsuperscript{12} This may interfere with the accuracy of CBV measurements during hypoxia.\textsuperscript{13} Therefore, a second group of rats (Group 2, $n=6$ rats) was studied during the same protocol without the contrast agent, to delineate the influence of the BOLD effect on the images obtained with contrast agent.

**Animal preparation**

Preparation of animals was similar in the two groups and conformed to the guidelines of the French Government (decree N° 87-848 of October 19, 1987, licenses 006683 and A38071). Anaesthesia was induced with 4% halothane and then maintained with an intraperitoneal injection of thiopental (40 mg kg$^{-1}$). One percent lidocaine was injected subcutaneously for local anaesthesia at all surgical sites. After tracheostomy, rat lungs were mechanically ventilated with 65% nitrous oxide, 35% oxygen using a rodent ventilator (Model 683, Harvard Apparatus Inc., South Natick, MA, USA). Ventilation was adjusted to maintain $P_{aCO_2}$ at =35 mm Hg. $F_{IO_2}$ was continuously monitored (MiniOX I analyzer, Catalyst Research Corporation, Owings Mills, MD, USA). A 0.7 mm indwelling catheter was inserted into the left femoral artery to monitor mean arterial blood pressure (MABP) via a chart recorder (8000S, Gould Electronic, Ballainvilliers, France). Blood gases ($P_{aO_2}$ and $P_{aCO_2}$), arterial saturation of haemoglobin in oxygen ($S_{aO_2}$), arterial pH and haemoglobin content (Hb) were analysed in arterial blood samples of less than 0.1 ml (ABL 510, Radiometer, Copenhagen, Denmark). Another 0.7 mm indwelling catheter was inserted into the left femoral vein to continuously infuse normal saline containing epinephrine (1.5 $\mu$g ml$^{-1}$) and sodium bicarbonate (0.025 mmol ml$^{-1}$) at a rate of 2 ml h$^{-1}$ throughout the study. Epinephrine was prevented to prevent the adverse effects of combined anaesthesia and hypoxic hypoxia on the cardiovascular system. Sodium bicarbonate was used to prevent arterial acidosis. Cannulation of the femoral vein was also required for the injection of the contrast agent (Group 1). Rectal temperature was maintained at 37.5 (0.5)°C by using a heating pad placed under the abdomen. Blood gases and arterial pH were corrected for rectal temperature.

**Experimental protocol**

Animals were subjected to a stepwise lowering of $F_{IO_2}$: 0.35, 0.25, 0.15 and 0.12. The basic cycle was started after more than 30 min of equilibration at $F_{IO_2}$ of 0.35 (control). The initial criteria for exclusion from the study were: MABP <100 mm Hg, arterial pH <7.30, $P_{aO_2}$ <100 mm Hg, arterial haemoglobin content <10 g dl$^{-1}$. Subsequent episodes were then first induced by lowering the inhaled oxygen for $F_{IO_2}$=0.25, then by replacing the oxygen by air ($F_{IO_2}$ of 0.15 and 0.12). During these four episodes, fractions of inspired nitrous oxide were 0.65, 0.75, 0.25 and 0.40, respectively. Each episode lasted 10 min: a 5 min equilibration period followed by NMR acquisition and determination of MABP and arterial blood sampling. Preliminary studies showed that $P_{aO_2}$ reached a steady value within 5 min. When the cycle of measurements ended the rat was killed by administration of an overdose of thiopental (50 mg kg$^{-1}$).

**MRI measurement**

MRI was performed with a SMIS console (SMIS Ltd, Guildford, UK) equipped with a 2.35 T, 40 cm diameter horizontal bore magnet (Bruker Spectrospin, Wissembourg, France) and a 20 cm diameter actively shielded gradient coil (Magnex Scientific Ltd., Yarnton, Oxford, UK). The rat was prone, its head secured via ear bars, and a 30 mm diameter surface coil was located directly above the brain. After radiofrequency coil matching and tuning, the magnetic field homogeneity was adjusted to obtain a linewidth for water less than 0.5 parts per million (ppm) in the brain. Six adjacent horizontal slices (from 2 mm below bregma) were chosen from a $T_1$ transverse scout image. A series of images for each slice at different echo times was acquired using a multi gradient-echo sequence with an interecho interval of 4.2 ms (repetition time $T_E=2$ s; first echo time $T_E=7.6$ ms; number of slices=6; field of view=35×35 mm; slice thickness=1 mm; 64×32 image matrix; number of averages=2). Acquisition of all images of the six slices took about 3 min.

In Group 1 (measurement of CBV), superparamagnetic iron oxide particles (200 µmol iron kg$^{-1}$ body mass of AMI 227, Sinerem\textsuperscript{®}; Guerbet, Aulnay-sous-Bois, France) were injected intravenously 30 min after the start of the experiment ($F_{IO_2}$ of 0.35). Images were acquired before ($n=24$ echoes, pre-contrast image) and 3 min after injection ($n=12$ echoes, post-contrast image). Acquisition of post-contrast images was then repeated at the end of each subsequent $P_{aO_2}$ episode ($F_{IO_2}$ of 0.25, 0.15 and 0.12).
Data analysis

Image processing and determination of regional CBV were performed using an Ultrasparc workstation (Sun Microsystems, Pasadena, CA, USA). In Group 1, for each \( PaO_2 \) episode, \( T_2^* \) images were calculated by a least squares monoexponential fit of the signal intensity vs the echo time on a pixel by pixel basis. Differences in relaxation rates in each pixel were then calculated according to the formula:

\[
\Delta R_2^* = \frac{1}{T_{2\text{post}}} - \frac{1}{T_{2\text{pre}}}
\]

with \( T_{2\text{pre}} \) and \( T_{2\text{post}} \) being the decay time constants before and after administration of the contrast agent (Group 1), respectively. The \( \Delta R_2^* \) values were obtained from the \( T_2^* \) post-contrast values during the four successive episodes. Five regions of interest (ROI) were defined in the two hemispheres: superficial and deep neocortex, corpus callosum, striatum and cerebellum. Selection of regions was made on slice 1 for superficial neocortex, on slice 2 for deep neocortex, on slice 3 for corpus callosum, and on slice 5 for striatum and cerebellum, by comparing the images to an anatomical atlas. Large \( \Delta R_2^* \) values (>200 s\(^{-1}\)) assigned to large vessels were discarded. A correction for clearance of the contrast agent from the plasma (elimination half-time =4.5 h) was applied since the post-contrast experiments lasted =60 min. This correction is described elsewhere.

In Group 2, \( \Delta R_2^* \) BOLD was calculated using equation (2), where \( T_{2\text{pre}} \) and \( T_{2\text{post}} \) are the decay time constants during control and subsequent episodes, respectively. Assuming a similar BOLD effect within the selected brain regions for each episode, a mean value of \( T_{2\text{post}} \) was then determined from \( T_2^* \) values obtained in the five brain regions. \( \Delta R_2^* \) BOLD has been used to correct the \( \Delta R_2^* \) values measured in Group 1 for the changes in deoxygenated haemoglobin concentration during hypoxia.

\[
\Delta R_{2\text{COR}} = \Delta R_2^* - \Delta R_2^* \text{BOLD}
\]

Regional CBV, expressed as the percentage of blood volume in each voxel, or ml (100 g\(^{-1}\)) tissue, was then determined according to equation (1). For an injection of AMI-227 of 200 \( \mu \)mol of iron kg\(^{-1}\) of body mass, \( \Delta X = 0.571 \) ppm at 2.35T in large vessels. We assumed that the average haematocrit in the brain microcirculation was 0.83 of that in large vessels, resulting in a \( \Delta X \) value of 0.688. Finally, we assumed that the brain haematocrit remains constant during hypoxic hypoxia, as previously shown in most brain areas.

Statistical analysis

Data were expressed as mean (SD). Analysis for statistical significance of changes during the successive episodes was performed using one-way analysis of variance (ANOVA) for repeated measurements (StatView SE program, SAS Institute Inc., Cary, NC, USA). Each value at a given episode was compared to that obtained at another episode using the Scheffé F-test post-hoc test. To look for a regional difference in the responsiveness to hypoxia, interaction between brain regions and episodes was assessed using a two-way ANOVA (brain region × episode) for repeated measurements. Differences between the two hemispheres was tested using a non-parametric Wilcoxon signed rank test. If no significant difference was found between the two hemispheres, pooled data were subjected to the analysis. A stepwise regression analysis was used to estimate the respective influence of \( SaO_2 \) and of other factors (MABP, \( PaCO_2 \)) on the CBV changes for each episode. Statistical significance was set at \( P < 0.05 \).

Results

Physiological data are shown in Table 1. Hypoxic hypoxia caused a significant decrease in MABP at \( FIO_2 \) of 0.15 and 0.12. There was also significant hypocapnia at \( FIO_2 \) of 0.12.

Typical \( T_2^* \) images of different coronal sections before and after the injection of the contrast agent and during the successive episodes of hypoxic hypoxia are shown in Figure 1. Administration of the contrast agent results in a decrease in \( T_2^* \) values, allowing determination of CBV in cerebral regions during the control period (\( FIO_2 \) of 0.35). As \( FIO_2 \) decreased, the brightness of \( T_2^* \) images was reduced, reflecting an increase in CBV. Table 2 shows CBV values in the selected brain regions. No significant difference in CBV was found between the two hemispheres. Each brain region exhibited a significant graded increase in CBV during the two hypoxic episodes, with the greatest degree of hypoxia (\( FIO_2 \) of 0.12) yielding the largest regional CBV changes (Table 2). Percentage change in regional CBV was 10–27% of control values at \( FIO_2 \) of 0.15, and 26–38% at \( FIO_2 \) of 0.12. There was no significant interaction between brain regions and episodes (\( F_{test} = 1.3; P = 0.22 \)), meaning that no evidence of regional difference was found in the responsiveness to hypoxia.

Mean CBV of the five brain regions for each animal (mCBV) was also calculated. Hypoxic hypoxia significantly raised mean CBV from 3.6 (SD 0.6) (\( FIO_2 \) of 0.35) to 4.1 (0.6) ml (100 g\(^{-1}\)) to 4.7 (0.7) ml (100 g\(^{-1}\)) at \( SaO_2 \) 70% (\( FIO_2 \) of 0.15) and 55% (\( FIO_2 \) of 0.12), respectively (\( P < 0.01 \)). Since \( SaO_2 \) and \( PaCO_2 \) are two parameters independently measured by the blood gas analyser, we plotted experimental \( SaO_2 \) and \( PaCO_2 \) values against mCBV (Fig. 2A and B). No relationship between mCBV changes and MABP or \( PaCO_2 \) was found. In contrast, there was a negative linear relationship between \( SaO_2 \) and mCBV changes, with an \( r^2 \) value of 0.80 (\( P < 0.01 \)).

\[
mCBV (\% of control) = 165.5 – 0.65 \times SaO_2
\]

To quantify the error due to the BOLD effect in these changes, \( \Delta R_2^* \) BOLD values were measured in Group 2 (no
contrast agent). In this group, $\Delta R_2^*$ Bold values were $+0.48$ (2.04), $+1.02$ (2.37), and $+2.36$ (2.66) s$^{-1}$, at $F_{IO2}$ of 0.25, 0.15 and 0.12, respectively. These values corresponded respectively to 0.7%, 1.3% and 2.8% of those observed in Group 1. The increase in $R_2^*$ Bold was significant at $F_{IO2}$ of 0.12 only ($P<0.05$).

**Discussion**

The present study indicates that a direct relationship exists between CBV and hypoxic hypoxia. To our knowledge, this is the first in vivo study measuring regional CBV in a model of graded hypoxia. CBV increased in proportion to the severity of the hypoxic insult, suggesting that vasodilatory capacity is not limited to this range of hypoxia. In addition, the changes were not significantly different between the various brain regions investigated.

**Methodological critique**

The use of exogenous contrast agent allowed us to monitor regional CBV changes during graded hypoxic hypoxia. Such techniques have been successfully used to investigate cerebrovascular changes in the brain during challenges such as hypercapnia, ischaemia or functional stimulation.\textsuperscript{15} 18 19 Equation (1), used to determine absolute CBV, is based on a highly simplified model of the brain vessel architecture.\textsuperscript{10} Despite this approximation, control values of regional CBV (2.8–4.3 ml (100 g)$^{-1}$) obtained are in reasonable agreement with other studies in rats using different techniques\textsuperscript{5} 9 or bolus tracking MRI.\textsuperscript{20}

Deoxygenated haemoglobin, acting as an endogenous paramagnetic contrast agent, contributes to the difference in magnetic susceptibility between blood vessels and surrounding tissue.\textsuperscript{12} During hypoxic hypoxia, the increase in deoxygenated haemoglobin affects in a linear manner the changes in $R_2^*$ with respect to the control state.\textsuperscript{13} 21 We found a 2–3 s$^{-1}$ increase in $R_2^*$ when $Sao_2$ fell to 55%, in close agreement with those studies. Because of the large doses of contrast agent used in the present study, $R_2^*$ changes due to those in deoxyhaemoglobin concentration accounted for less than 5% of the CBV changes.

Despite epinephrine, the greatest level of hypoxic hypoxia used in this study ($F_{IO2}$ of 0.12) was associated with hypocapnia and a decrease in MABP, which might have interfered with CBV changes. For example, using a similar MRI procedure, we found that marked hypocapnia ($P_aCO_2$ 25 mm Hg) resulted in a decrease in regional CBV of 12–17% in normoxic rats.\textsuperscript{22} However, the present change in $P_aCO_2$ was of smaller magnitude. In a recent study using

**Table 1** Physiological and biochemical data in Group 1 (with contrast agent) during successive episodes of reduced $F_{IO2}$. Values are mean (sd). *$P<0.05$ vs $F_{IO2}$ 0.35 (Scheffe F-test)

<table>
<thead>
<tr>
<th>$F_{IO2}$</th>
<th>0.35</th>
<th>0.25</th>
<th>0.15</th>
<th>0.12</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP (mm Hg)</td>
<td>131 (10)</td>
<td>134 (10)</td>
<td>111 (15)*</td>
<td>92 (16)*</td>
</tr>
<tr>
<td>$P_aCO_2$ (mm Hg)</td>
<td>142.3 (16.9)</td>
<td>97.3 (9.3)*</td>
<td>55.0 (9.6)*</td>
<td>41.5 (3.5)*</td>
</tr>
<tr>
<td>$Sao_2$ (%)</td>
<td>100</td>
<td>95.6 (1.8)</td>
<td>70.7 (7.3)*</td>
<td>53.2 (5.3)*</td>
</tr>
<tr>
<td>$P_aCO_2$ (mm Hg)</td>
<td>37.1 (2.7)</td>
<td>36.0 (4.8)</td>
<td>31.7 (2.8)</td>
<td>30.0 (2.7)*</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.32 (0.01)</td>
<td>7.32 (0.01)</td>
<td>7.36 (0.03)</td>
<td>7.36 (0.04)</td>
</tr>
<tr>
<td>Haemoglobin (g dl$^{-1}$)</td>
<td>13.0 (1.1)</td>
<td>12.5 (0.9)</td>
<td>12.0 (0.7)</td>
<td>11.9 (1.1)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.5 (0.3)</td>
<td>37.6 (0.3)</td>
<td>37.4 (0.1)</td>
<td>37.5 (0.2)</td>
</tr>
</tbody>
</table>
MRI contrast imaging, an increase of only 10% in regional CBV was reported during progressive haemorrhagic hypotension in rats (MABP between 40 and 10 mm Hg). The lack of a significant influence of MABP and $P_{aCO_2}$ on the CBV (see stepwise regression analysis) indicates that both parameters probably have only minor effects on the present CBV changes.

Another potential confounding factor in the CBV changes was the associated change in inspired concentration of nitrous oxide ($F_{N_2O}$) during the successive episodes. Since nitrous oxide is a potent cerebrovasodilator, any change in its concentration might have interfered with our results. However, significant increase in CBV was found during the two hypoxic episodes in which the fraction of inspired nitrous oxide was lowered ($F_{N_2O}$ of 0.25 and 0.40). Consequently, it is possible that the CBV changes would have been larger if the nitrous oxide fraction had been maintained constant.

**CBV response to hypoxic hypoxia**

The present study shows that CBV is significantly increased by $\approx15\%$ at $S_{aO_2}$ 70% ($P_{aO_2}$ 55 mm Hg) and this rise reaches $\approx30\%$ at $S_{aO_2}$ 55% ($P_{aO_2}$ 40 mm Hg). These findings are in accordance with other studies which reported a gradual change in CBF during graded hypoxic hypoxia. A gradual change in cerebral haemodynamics is seen as the oxygen content is lowered; this tends to maintain a constant oxygen supply to brain.

We found that a stepwise reduction of the $F_{O_2}$ raised regional CBV by 26–38% in all brain areas at $S_{aO_2}$ of 55%. It is recognized that the CBV values in normoxia differ among brain regions. In the present study, similar regional CBV responses to hypoxia were found in all regions, in agreement with studies measuring the CBF response to hypoxia. This suggests that the hypoxic stimulus may affect the various brain regions in a comparable manner regardless of their baseline blood flow or blood volume. Recently, D’Arceuil and co-workers reported a 40–50% increase in cortical CBV at $S_{aO_2}$ of 40% in neonatal rabbits. In addition, under moderate hypoxia and hypercapnia, a 50% increase in CBV was found in the cortex of newborn piglets. In moderately hypoxic rats, a 30% increase in cortical CBV was reported by Shockley and LaManna. Although these results were obtained with various techniques (MRI, autoradiography, or optical methods), they are in agreement with our measurements of the changes in CBV found in both superficial and deep neocortical regions at comparable levels of hypoxia.

However, other studies have reported smaller CBV changes during hypoxia. Berezki and co-workers found that moderate hypoxia ($P_{aO_2}$ 40 mm Hg) increased microvascular volume by $<20\%$ in most areas of rat brain. However, in that study results were obtained in parenchyma-

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**Fig 2** Relationship between mCBV changes (% value in control) and $S_{aO_2}$ (A) and $P_{aO_2}$ (B) at differing $F_{O_2}$ (0.35, 0.25, 0.15, and 0.12). *$P<0.05$ vs $F_{O_2}$ 0.35.

**Table 2** CBV values (ml/100 g) in different brain regions at differing $F_{O_2}$: control ($F_{O_2}$ 0.35). Values are mean (sd). *$P<0.05$ vs $F_{O_2}$ 0.35; †$P<0.05$ vs $F_{O_2}$ 0.25; ‡$P<0.05$ vs $F_{O_2}$ 0.15 (Scheffe $F$-test).

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>$F_{O_2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>Superficial cortex</td>
<td>4.28 (0.97)</td>
</tr>
<tr>
<td>Deep cortex</td>
<td>3.26 (1.02)</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>2.84 (0.47)</td>
</tr>
<tr>
<td>Striatum</td>
<td>3.13 (0.72)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>4.28 (1.38)</td>
</tr>
</tbody>
</table>
nal microvessels with diameter <50 μm, still having small baseline regional CBV values (0.4–2.2 ml (100 g)⁻¹). CBV measured with the gradient-echo pulse sequence, used here, is less sensitive to vessel size, and reflects total CBV after the injection of a large dose of contrast agent.¹¹¹⁹ Considering that large vessels, with estimated diameter >200 μm, were excluded (see Materials and methods), the present changes in CBV should include pial arterioles, parenchymal arterioles, and venules. Therefore, if most of the CBV changes during hypoxia do indeed occur in these vessels, it is not surprising that methods detecting microvascular changes are associated with smaller changes.

In contrast, it has been reported that hypoxic hypoxia (S\textsubscript{aO\textsubscript{2}} 70–75%) increased CBV by only 5–8% in human studies,⁷⁻²⁸ instead of the 15% we found in rats. These differences may result from differences in the status (awake vs anaesthetized), species, or methods used for measuring CBV. There is no evidence that cerebrovascular responses to hypoxia should have been increased by the use of thiopental in rats. The well-known depressive effect of thiopental on brain metabolism would reduce baseline CBV, but the per cent response to hypoxia is not different from awake animals.²⁹ Similarly, there is no reason to suspect a greater sensitivity to hypoxia in rats in comparison with humans. Therefore, differences between methods in their ability to detect CBV changes might be possible. For example, Fortune and co-workers⁷ used single-photon emission computed tomography (SPECT) with ⁹⁹ᵐ-Tc-labelled erythrocytes. In addition to its limited spatial resolution (4 cm in that study), the unavoidable problem with SPECT is extracranial contamination by labelled cells, possibly resulting in a large attenuation of CBV changes during respiratory challenges. The study by Hampson and colleagues²⁸ used near-infrared spectroscopy (NIRS), whose reliability for determining CBV changes during hypoxia has not been established. It is thus possible that the changes in human CBV in response to hypoxia may have been underestimated.

Clinical implications

Identifying a relationship between the severity of a hypoxic insult and the range of CBV changes is of particular clinical relevance in patients with compromised intracranial compliance (i.e. head-injured patients). Any vasodilatory stimulus, for example hypoxic hypoxia, can aggravate intracranial hypertension and reduce cerebral perfusion pressure in such patients.³⁰ In addition, the most severe degree of hypoxia led to the largest increase in CBV, showing no limit in cerebrovascular capacity for vasodilation within this range of hypoxia. If these experimental data are applicable in humans, our results indicate that a fall of S\textsubscript{aO\textsubscript{2}} to 70% progressively increases the CBV by 15%. This is considerably more than the 7% blood volume change required to raise ICP to the threshold of 20 mm Hg in head-injured patients.³¹ Our results therefore underline the deleterious consequences of transient episodes of hypoxic hypoxia on cerebral haemodynamics in such patients.

In summary, the present study shows that graded hypoxic hypoxia results in significant increase in CBV in proportion to the severity of the insult. CBV changes were not significantly different between the various brain regions investigated. We conclude that hypoxic hypoxia can significantly contribute to increased intracranial pressure in subjects with reduced intracranial compliance.

Acknowledgements

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References

9 Shockley RP, LaManna JC. Determination of rat cerebral cortical blood volume changes by capillary mean transit time analysis during hypoxia, hypercapnia and hyperventilation. Brain Res 1988; 454: 170–8
13 Lin W, Paczynski RP, Celik A, Kuppusamy K, Hsu CY, Powers WJ. Experimental hypoxemic hypoxia: changes in R² of brain...
24 Archer DP, Lebrecque P, Tyler JL, Meyer E, Trop D. Cerebral blood volume is increased in dogs during administration of nitrous oxide or isoflurane. Anesthesiology 1987; 67: 642–8

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