ACTA PHYSIOLOGICA

Acta Physiol 2013

# Neurobiological insight into hyperbaric hyperoxia

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Received 14 March 2013, revision requested 2 May 2013, revision received 8 May 2013, accepted 15 May 2013

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**Abstract**

**Aim:** Hyperbaric hyperoxia (HBO) is known to modulate aerobic metabolism, vasoreactivity and blood flow in the brain. Nevertheless, mechanisms underlying its therapeutic effects, especially in traumatic brain injury (TBI) and stroke patients, are debated. The present study aimed at investigating regional cerebral blood flow (rCBF) distribution during acute HBO exposure.

**Methods:** Regional cerebral blood flow response was investigated in seven healthy subjects exposed to either normobaric normoxia or HBO with ambient pressure/inspired oxygen pressure of 101/21 and 250/250 kPa respectively. After 40 min at the desired pressure, they were injected a perfusion tracer and subsequently underwent brain single photon emission computed tomography. rCBF distribution changes in the whole brain were assessed by Statistical Parametric Mapping.

**Results:** During HBO, an increased relative rCBF distribution was found in sensory-motor, premotor, visual and posterior cingulate cortices as well as in superior frontal gyrus, middle/inferior temporal and angular gyrus and cerebellum, mainly in the dominant hemisphere. During normobaric normoxia, a higher $^{99m}$Tc-HMPAO distribution in the right insula and subcortical structures as well as in bilateral hippocampi and anterior cingulated cortex was found.

**Conclusions:** The present study firstly confirmed the rCBF distribution increase during HBO in sensory-motor and visual cortices, and it showed for the first time a higher perfusion tracer distribution in areas encompassed in dorsal attention system and in default mode network. These findings unfold both the externally directed cognition performance improvement related to the HBO and the internally directed cognition states during resting-state conditions, suggesting possible beneficial effects in TBI and stroke patients.

*Keywords* attention system, hyperbaric hyperoxia, posterior cingulated cortex, rCBF, SPECT.

Hyperoxia can be achieved under normobaric (NBO) or hyperbaric (HBO) conditions. Upon NBO, oxygen transport is limited by the binding capacity of haemoglobin, almost saturated at atmospheric pressure, and the increase in the amount of plasma-dissolved oxygen ranges approx. between 0.5 and 1%. Conversely, during HBO, oxygen carried by plasma is significantly increased, and the amount of plasma dissolved oxygen increases up to 6% (Liu *et al.* 2011). Although some studies tried to explain, since the half of the past century (Ingvar *et al.* 1960), the mechanisms underlying its therapeutic effects, they remain quite complex. It

 doi: 10.1111/apha.12116 

was suggested that hyperoxia may modulate aerobic metabolism, vasoreactivity and blood flow in humans and animals (Melsom *et al.* 1999, Rousseau *et al.* 2005). Indeed, the marked increase in oxygen tension gradient from the capillary blood to tissue cells is a key mechanism by which hyperoxygenation of arterial blood can improve effective cellular oxygenation, even at a low rate of tissue perfusion (Belda *et al.* 2005, Mathieu & Wattel 2006).

Over a normal physiological range of partial pressure of oxygen ($PaO_2$), regional cerebral blood flow (rCBF) may change (Liu *et al.* 2011). In fact, Kety & Schmidt (1948) originally described a reduction of 13% in CBF and a moderate increase in the cerebrovascular resistance of young male volunteers inhaling 85–100% oxygen under NBO conditions. Later, Omae *et al.* (1998) confirmed that increases in $PaO_2$ led to a significant reduction in the flow velocity within the middle cerebral artery in NBO as well as in HBO conditions.

Additionally, the increase in the mean partial pressure of oxygen in the tissues caused by hyperoxia possibly results in redistribution of blood flow, with vasoconstriction in some areas and shunting in others (Liu *et al.* 2011). Indeed, non-invasive evaluations of the cerebral circulation in humans, showed that CBF tends to decrease in absolute values, in parallel with oxygen percentage increase in the air and/or its pressure, and this phenomenon could be caused by the constriction of the superficial cortical arterioles due to an higher arterial oxygen tension (Bergofsky & Bertun 1966, Regli *et al.* 1970, Omae *et al.* 1998). Unlike most drugs, oxygen is simple to administer, easily diffuses to target tissues, is well tolerated, can be delivered for short time at 100% concentrations without any significant side effects and may theoretically be merged with other treatments. Thus, in the field of brain physiopathology, interest in HBO increased mainly in the field of stroke and traumatic brain injury (TBI) management (Liu *et al.* 2011).

In the former condition, three randomized clinical trials using HBO therapy have been published (Anderson *et al.* 1991, Nighoghossian *et al.* 1995, Rusyniak *et al.* 2003). With the exception of improvements in the Trouillas and the Orgogozo scale scores found by Nighoghossian *et al.* after 1 year of HBO treatment, all other studies have reported mainly negative results. Similarly, many studies have demonstrated that HBO treatment increases Glasgow Coma Scale and Glasgow Outcome Scale scores (Ren *et al.* 2001, Xie *et al.* 2007, Lin *et al.* 2008) in TBI patients. However, the existing data do not justify the use of HBO therapy in neither condition due to the lack of significant effects possibly related to the small number of patients, to delays in initiating HBO therapy and to absence of successful blinding among the main literature (Liu *et al.* 2011).

In the last years, many techniques were used in order to investigate CBF changes during hyperoxic conditions, but some limitation were found in the level of inspired oxygen achievable and in the ability to determine changes in global and regional CBF (rCBF) (Johnston *et al.* 2003, Macey *et al.* 2007).

The majority of the neuroimaging studies investigating cerebral changes during various hyperoxic models have been performed in NBO (Ishii *et al.* 1996, 1998, Boakye *et al.* 2002, Kolbitsch *et al.* 2002, Johnston *et al.* 2003, Chung *et al.* 2004, 2006, Bulte *et al.* 2007, Choi *et al.* 2010). On the other hand, brain changes during NBO have been investigated by techniques in which the inhalation phase was simultaneous to image acquisition (i.e. fMRI or PET) possibly causing bias due to unintended visual, auditory and olfactory stimulation through the scanning time.

To the best of our knowledge, the only resting-state study on rCBF distribution during acute HBO exposure was performed by using Single Photon Emission Computed Tomography (SPECT) by Di Piero *et al.* (2002). In this study, the authors investigated by $^{99m}$Tc-HMPAO both controls and professional divers in NBO but only in the latter group, SPECT was repeated under HBO. Hence, rCBF distribution changes in normal subjects during HBO remained unrevealed. Moreover by regional and ANOVA analyses, no significant global CBF differences between controls and professional divers during both NBO and HBO were found.

In previous studies (Pagani *et al.* 2000, 2011), we investigated, under controlled baric conditions, hypoxia-related rCBF distribution changes by using a stabilized SPECT perfusion tracer allowing us to inject the radiotracer in the baric chamber during exposition to altered ambient conditions.

Due to the limited number of functional neuroimaging investigations upon hyperbaric hyperoxia, the aim of the present study was to contribute by means of SPECT to investigate relative rCBF distribution changes during acute exposure to HBO at 2.5 ATM in a hyperbaric chamber mimicking a possible therapeutic condition (Liu *et al.* 2011).

## Materials and methods

### *Experimental procedure*

Regional CBF response to hyperbaric oxygenation was investigated in seven non-smoker and right-handed healthy subjects (four males and three females, mean age 33 ± 8) with normal brain at magnetic resonance imaging (MRI) exposed to either normobaric normoxia

  doi: 10.1111/apha.12116

or 100% oxygen breathing at 2.5 bar ambient pressure (HBO) with ambient pressure/inspired oxygen pressure of 101/21 and 250/250 kPa respectively. All experiments were performed in a hyperbaric chamber (Kockums, Sweden) upon informed consent of each subject, and both Ethical and Isotope Committees of Karolinska Hospital approved the study.

### *Spect*

A dose of 330 MBq of $^{99m}$Tc-d,l-hexamethylpropylene amine oxime ($^{99m}$Tc-HMPAO, CERETEC®, Amersham International plc, Little Chalfont, UK) was injected after 40 min at the desired hyperoxic level. Because the experiment was performed within a hyperbaric chamber with an experimental protocol relatively long in time, $^{99m}$Tc-HMPAO was stabilized with methylene blue to allow administration up to 4 h after preparation, according to the manufacturer's instructions (Pagani *et al.* 2000). In all cases, administration of radiopharmaceutical was made between 33 and 236 min after its preparation. By means of a lipophilic–hydrophilic conversion, HMPAO remains trapped in brain cells for more than 24 h. As physical half-life of $^{99m}$Tc-HMPAO is 6 h, SPECT imaging can be then performed up to several hours after injection. At the end of the experiment, the subjects returned to normobaric room air and SPECT was performed in a next-door laboratory at the Karolinska University hospital within 30 min.

Brain imaging using SPECT was performed using a three-headed Gamma Camera (TRIAD XLT 20; Trionix Research Laboratory, Twinsburg, OH, USA) equipped with low-energy ultrahigh-resolution collimators. The intrinsic spatial resolution of the camera was 8 mm at full width half mMaximum (FWHM). The projection data were acquired for 15 s per projection at 90 equal angles of a complete revolution (0–360°). Before reconstruction, the projection data were pre-processed using a 2D Hamming filter with a cut-off frequency of 2.25 cycles cm$^{-1}$. Sectional images were reconstructed by filtered back projection using a Ramp filter with a cut-off frequency of 0.6 cycles cm$^{-1}$. During pre-processing, correction for attenuation was made. No scatter correction was applied. Both acquisition and reconstruction were performed in 128 × 128 matrices with a pixel size of 2.22 × 2.22 mm resulting in an isotropic voxel size of 2.2 mm$^3$.

### *SPM analysis*

Voxel-based analysis was performed using the 2000 version of SPM (SPM2; Wellcome Department of Cognitive Neurology, London, UK). Images of relative tracer distribution were spatially normalized to a predefined Montreal Neurological Institute (MNI) space (voxel size 2 × 2 × 2 mm) using a 16-parameter affine (non-linear) transformation. Correction of SPM coordinates to match the Talairach coordinates was achieved by the subroutine implemented by Brett *et al.* (2001).

Brodmann areas (BAs) were then identified at a range of 0–2 mm from the corrected Talairach coordinates of the SPM output isocentres by Talairach client (http://www.talairach.org/index.html).

After global normalization, images were smoothed with a Gaussian filter (10 mm) to account for individual gyral differences and brain anatomy, also taking into consideration the spatial resolution of the SPECT camera. Images were globally normalized using proportional scaling to remove confounding effects due to global CBF changes, with a threshold masking of 0.8.

The voxel-based analyses were performed using a 'two conditions: one scan/condition, paired *t*-test' design model, and significances were sought for the contrasts between normoxic and hyperoxic conditions. Significant differences between the two conditions were set at $P < 0.001$ both at cluster and voxel level. Only clusters containing more than 400 voxels were considered to be significant. This was based on the calculation of the partial volume effect resulting from the spatial resolution.

## Results

As compared to the normoxic condition, HBO showed mainly on the left hemisphere significant relative higher rCBF distribution in primary motor, premotor and somatosensory association cortex, superior frontal gyrus, middle and inferior temporal gyri, as well as posterior cingulate cortex, primary and associative visual cortex, angular gyrus and cerebellum (Table 1; Fig. 1).

The opposite comparison showed a higher $^{99m}$Tc-HMPAO distribution in right insula and subcortical structures (thalamus, nucleus caudatus, putamen and globus pallidus) as well as in bilateral hippocampi and anterior cingulated cortex, (Table 2, Fig. 2).

## Discussion

The first overt result of the study was a relative rCBF distribution change upon hyperbaric hyperoxia in large cortical and subcortical regions indicating a clear neurobiological effect of such condition. Unlike the only previous SPECT investigation during HBO (Di Piero *et al.* 2002), we did not investigate experimental subjects used to hyperbaric conditions, but individuals comparable to patients undergoing HBO

 

**Table 1** Numerical results of SPM comparisons between cerebral blood flow (CBF) distribution in hyperbaric ($n = 7$) and normobaric ($n = 7$) condition

| | Cluster level | | | Voxel level | | | |
|---|---|---|---|---|---|---|---|
| Comparison | Cluster extent | Corrected *P*-value | Cortical region | *Z*-score of maximum | Talairach coordinates | Cortical region | BA |
| Hyperbaric – Normobaric | 4931 | 0.000 | R | 4.04 | 8, 55, 23 | Posterior cingulate | 31 |
| | | | L | 3.96 | −18, −93, 0 | Cuneus | 17 |
| | | | L | 3.71 | 0, −79, 22 | Cuneus | 18 |
| | | | L | 3.64 | −18, −86, −6 | Lingual gyrus | 18 |
| | | | L | 3.56 | −4, −29, 36 | Posterior cingulate | 31 |
| | | | L | 3.55 | 0, −14, 71 | Medial frontal gyrus | 6 |
| | | | R | 3.52 | 20, −59, 31 | Precuneus | 7 |
| | | | R | 3.04 | 8, −8, 70 | Superior frontal gyrus | 6 |
| | | | R | 2.69 | 12, −64, 7 | Lingual gyrus | 18 |
| | | | R | 2.62 | 30, −74, 28 | Cuneus | 19 |
| | 3016 | 0.001 | L | 4.01 | −53, −37, 7 | Middle temporal gyrus | 22 |
| | | | L | 3.90 | −42, −13, 41 | Precentral gyrus | 4 |
| | | | L | 3.56 | −46, 20, 21 | Middle frontal gyrus | 46 |
| | | | L | 3.48 | −59, −9, −25 | Fusiform gyrus | 20 |
| | | | L | 3.05 | −32, 17, 34 | Middle frontal gyrus | 9 |
| | | | L | 2.60 | −-51, 5, 15 | Inferior frontal gyrus | 44 |
| | | | L | 2.45 | −59, −51, −9 | Inferior temporal gyrus | 37 |
| | | | L | 2.43 | −50, −44, 25 | Culmen of cerebellum | |

A value of $P \leq 0.001$, corrected for multiple comparison at cluster level, was accepted as statistically significant. In the 'cluster level' section on left, the number of voxels, the corrected *P*-value of significance and the cortical region where the voxel is found, are all reported for each significant cluster. In the 'voxel level' section, all of the coordinates of the correlation sites (with the *Z*-score of the maximum correlation point), the corresponding cortical region and BA are reported for each significant cluster. L, left; R, right; BA, Brodmann's area. In the case that the maximum correlation is achieved outside the grey matter, the nearest grey matter (within a range of 3 mm) is indicated with the corresponding BA.

treatment. This resulted in findings applicable to everyday clinical routine and not only in decompression sickness. Furthermore, voxel-based analysis implemented in our study is more sensitive in detecting significant differences especially when cluster of voxels are not strictly confined within predetermined boundaries as in regional analysis.

The results of the present study confirm the previously reported hyperperfusion and neural activation induced by hyperoxia in motor and premotor cortices as well as in cerebellum (Ramsay *et al.* 1993, Ishii *et al.* 1998). Furthermore, they back up what found by some authors in a recent $H_2{}^{15}O$ Positron Emission Tomography study, in which, under hypocapnia induced by hyperventilation, a significant relative hyperperfusion in the precentral gyrus, the prefrontal cortex and part of the cerebellum was found, probably due to vascular responsiveness (Ito *et al.* 2000). Cerebral hemispheres rCBF distribution increase was described during a HBO in fifty patients (25 adult and 25 children) affected by chronic neurological disorders that underwent SPECT at pre- (B), middle- (M) and post-HBO treatment (P) administered at 1.25–2.5 atmospheres in a range from twice to 12 times a week (Golden *et al.* 2002). An overall increase in CBF distribution between SPECT-B and SPECT-P in right and left hemispheres was found. However, scans were performed after HBO outside the hyperbaric chamber, hence investigating the post-acute effects of hyperoxia.

In this respect, an important issue when investigating subjects upon HBO is to reproduce the conditions faced by patients during HBO therapy and contribute to the knowledge of physiological changes occurring during such peculiar therapeutic condition. Moreover, the HBO SPECT model proposed in our investigation provides the opportunity to perform the study in an ecologic environment, avoiding possible biases resulting from physical and psychological discomfort due to an unfriendly examination environment (Mazard *et al.* 2002).

Sensory-motor cortex involvement under hyperoxia (Boakye *et al.* 2002) was found to be heterogeneous across studies, possibly due to different recording techniques and experimental models. We found in this area a higher rCBF distribution in hyperoxia as compared to normoxia. Some studies suggest that, during resting state, the oxygen extraction fraction and rCBF in the somatosensory cortex are lower than in other

 

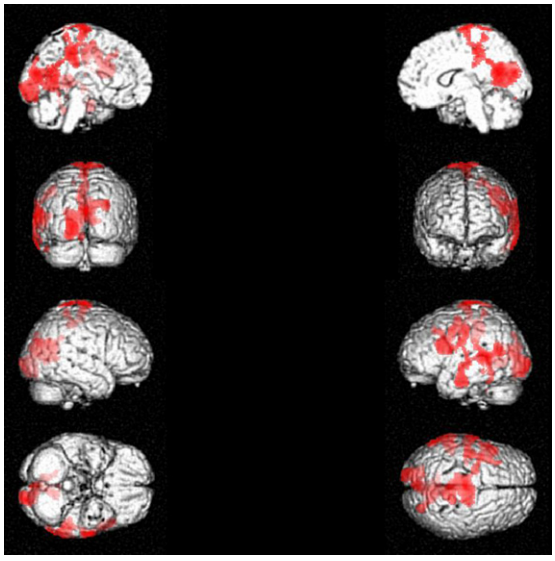

**Figure 1** 3D rendering showing those regions in which relative cerebral blood flow distribution was significantly higher in hyperbaric hyperoxia as compared with normobaric normoxia. The first row represents the medial aspect of left (on the left) and right (on the right) hemispheres; the second row represents the anterior (on the left) and posterior (on the right) aspect on the brain; the third row represents the lateral aspect of the right (on the left) and of the left (on the right) hemispheres; the fourth row represents the inferior (on the left) and the superior (on the right) aspects of the brain.

cortices, for example, in visual one, (Ishii *et al.* 1996) but its strong physiological response under hyperoxic conditions appears confirmed by other studies (Kanno *et al.* 1996, Kashikura *et al.* 2000, 2001).

Our results are also in accordance with previously reported hypoperfusion in cingulate, hippocampal, temporal and insular cortex as well as in subcortical regions, that is, basal ganglia, mainly in the right hemisphere (Kolbitsch *et al.* 2002). We could hypothesize that the low rCBF distribution detected in these areas, mainly in the non-dominant hemisphere, may be associated with the hyperoxia-related relative hyperperfusion detected at cortical level in the left hemisphere. This inter-regional activation/deactivation pattern fits well with the basic architectural and functional organization of the brain connections, especially with the marked vascular responsiveness of right subcortical regions, such as the basal ganglia (Ito *et al.* 2000).

Furthermore, a HBO-related increased rCBF distribution in the superior frontal, ventral premotor, parietal and middle temporal cortex mainly on the left hemisphere was found. Notably, these areas are also labelled together as the principal components of the dorsal attention system (DAS) (Vincent *et al.* 2008) which is associated with externally directed cognition including covert and overt shifts of spatial attention, eye movements and hand–eye coordination (Corbetta & Shulman 2002).

**Table 2** Numerical results of SPM comparisons between CBF distribution in normobaric ($n$ = 7) and hyperbaric ($n$ = 7) condition

| | Cluster level | | | Voxel level | | | |
|---|---|---|---|---|---|---|---|
| Comparison | Cluster extent | Corrected *P*-value | Cortical region | *Z*-score of maximum | Talairach coordinates | Cortical region | BA |
| Normobaric -Hyperbaric | 2607 | 0.000 | R | 3.88 | 18, −15, 4 | Thalamus | |
| | | | R | 3.83 | 20, −2, 30 | Caudate body | |
| | | | R | 3.61 | 40, −34, 20 | Insula | 13 |
| | | | L | 3.44 | −16, −2, 41 | Cingulate gyrus | 24 |
| | | | R | 2.91 | 26, −2, 7 | Putamen | |
| | | | R | 2.57 | 30, −35, 5 | Caudate tail | |
| | | | R | 2.56 | 40, −10, −8 | Sub-Gyral | 21 |
| | 1542 | 0.000 | L | 3.37 | −8, −5, −17 | Parahippocampal gyrus | 34 |
| | | | R | 3.05 | 4, 4, −4 | Anterior cingulate | 25 |
| | | | L | 2.96 | −22, −11, −23 | Parahippocampal gyrus | 35 |
| | | | | 2.89 | 2, 1, −14 | Hypothalamus | |
| | | | R | 2.76 | 22, −13, −21 | Parahippocampal gyrus | 28 |

A value of $P \leq 0.001$, corrected for multiple comparison at cluster level, was accepted as statistically significant. In the 'cluster level' section on left, the number of voxels, the corrected *P*-value of significance and the cortical region where the voxel is found, are all reported for each significant cluster. In the 'voxel level' section, all of the coordinates of the correlation sites (with the *Z*-score of the maximum correlation point), the corresponding cortical region and BA are reported for each significant cluster. L, left; R, right; BA, Brodmann's area. In the case that the maximum correlation is achieved outside the grey matter, the nearest grey matter (within a range of 3 mm) is indicated with the corresponding BA.

 

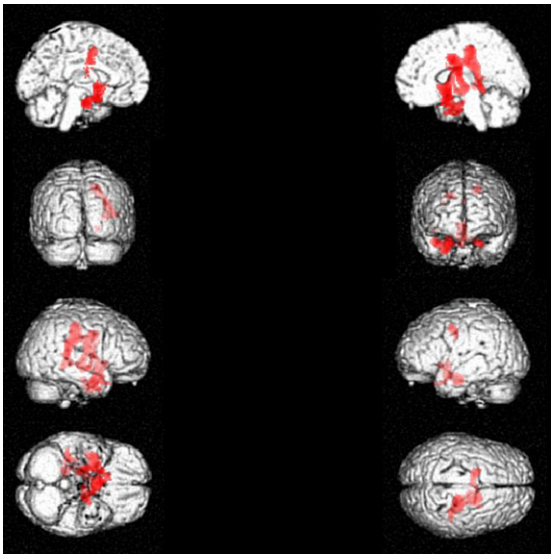

**Figure 2** 3D rendering showing those regions in which relative cerebral blood flow distribution was significantly higher in normobaric normoxia as compared with hyperbaric hyperoxia. The first row represents the medial aspect of left (on the left) and right (on the right) hemispheres; the second row represents the anterior (on the left) and posterior (on the right) aspect on the brain; the third row represents the lateral aspect of the right (on the left) and of the left (on the right) hemispheres; the fourth row represents the inferior (on the left) and the superior (on the right) aspects of the brain.

Recent reports have largely demonstrated that HBO and NBO have positive influences on cognitive abilities, such as memory, visuospatial and verbal abilities, addition (related to working memory function) and n-back tasks (Chung *et al.* 2009, Choi *et al.* 2010, Schellart *et al.* 2011). Our findings suggest that these reported neuro-psychological improvements might be associated during HBO exposure to rCBF distribution changes found in the regions encompassed in the DAS.

Moreover, in the present study, we detected a rCBF distribution increase in the regions of prefrontal cortex, posterior cingulate cortex and middle temporal lobe during HBO. These areas are recognized to encompass together in a second attention system also labelled default mode network (DMN) (Vincent *et al.* 2008). DMN is a hippocampal-cortical memory system that is active during passive mental states linked to internally directed cognition including recollection of the past and thinking about the future, as it happens in neuropsychiatric studies not employing specific brain activations (Raichle *et al.* 2001, Buckner *et al.* 2008, Vincent *et al.* 2008, Papo 2013).

The CBF at rest reflects the baseline state of the brain, always active even during repose periods. During the 'resting state' in clinical and experimental studies, each individual is actually processing information and elaborating on concepts and sensations (Pagani *et al.* 2012). The unique experimental conditions in the hyperbaric chamber may also have caused hypersensitivity to the external environment. Because the DMN is peculiar of such physiological state, its relative hyperperfusion in hyperoxia can be interpreted as a direct effect of this condition on the neuropsychological circuits implicated in insight, attention and autobiographical memory.

Some recent MRI studies in TBI (Zhou *et al.* 2012) demonstrated a decreased functional connectivity within the DMN, including the cuneus, left calcarine cortex and PCC. These components of the DMN (i.e. the PCC) have been reported to be vulnerable to injury after TBI; in fact, some authors (Yount *et al.* 2002, Levine *et al.* 2008) found a decreased volume as well as grey matter atrophy predominantly involving the PCC after TBI. Moreover, recent findings (Vanhaudenhuyse *et al.* 2010) have implicated DMN connectivity as being reflective of level of consciousness in patients with brain damage. This holds true also in stroke after acute phase in which a natural post-damage reactivation of functionally suppressed areas remote from, but connected to, the area of primary injury takes place (Corbetta 2012). The rCBF distribution increase found in the present study in regions belonging to the DAS as well as to the DMN encompassed mainly regions in the dominant hemisphere. This peculiar pattern, possibly related to the cerebral neurovascular behaviour (Kashikura *et al.* 2000, 2001, Kolbitsch *et al.* 2002), would suggest a beneficial effect of HBO on neural networks in TBI patients as well as in re-focusing to the pre-injury topography correlates in stroke patients encouraging clinical trials investigating patients outcomes using HBO therapy.

The main limitation of the study is the relatively low number of patients, often a necessity in complex neuroimaging studies, such as the present one. However, the within-subjects experimental design reinforces the performed statistics and the very large clusters of voxels found to show significant differences make results reliable (Chumbley & Friston 2009).

In addition, the strict protocol implemented in the hyperbaric chamber assures the quality of the measurements.

## Conclusions

In the present study, we found, when comparing HBO to resting-state condition, an increased brain perfusion distribution mainly in the left hemisphere with a relative CBF increase in the neural networks involving dorsal as well ventral attention pathways. These findings suggest a possible beneficial effect of HBO on both externally directed cognition performance and

 

internally directed resting condition cognition states. On the other hand, a strong deactivation pattern, in the opposite comparison, was found mainly in right subcortical regions, possibly due to adaptive neurovascular responses.

These findings encourage further studies in hyperoxic environment as well as clinical trials to explore possible HBO applications in TBI and stroke patients.

## Conflict of interest

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

The authors wish to thank Mr. Giorgio Giorgi for technical assistance and Doctors Ralph Ansjön, Folke Lind, Gamze Sumen and Johan Uusijärvi for their contribution to the study ideation and collection of data.

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  doi: 10.1111/apha.12116