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Use of diffusion tensor imaging to assess the impact of normobaric hyperoxia within at-risk pericontusional tissue after traumatic brain injury

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INTRODUCTION

Cerebral ischemia and metabolic dysfunction remain important causes of neuronal loss after head injury. We have previously used [¹⁸F]fluorodeoxyglucose positron emission tomography to show that normobaric hyperoxia increases oxygen utilization in ‘at-risk’ regions of metabolically compromised tissue, typically in pericontusional regions and white matter. Such improvements in oxidative metabolism may result through the alleviation of physiologic and metabolic compromise linked to a range of pathophysiological processes. These include classic ischemia, increased diffusion barriers to oxygen delivery associated with microvascular ischemia, and mitochondrial dysfunction. However, while previous studies demonstrate a consistent effect of hyperoxia in increasing brain tissue oxygen levels, reports of the impact on brain metabolism have been inconsistent, regionally variant, and dependent on the underlying metabolic state of the tissue concerned. Additional concerns have been raised regarding the potential deleterious effects on pulmonary function and worsening of neuronal injury because of oxidative stress. Studies within other pathologies such as stroke and myocardial infarction have also shown conflicting evidence of benefit and harm. Given this background, it is clear that further study of the regional effects of normobaric hyperoxia is warranted before definitive clinical trials of the intervention after TBI.

Diffusion tensor imaging has shown benefit in a variety of neurologic disease states in predicting both local tissue and functional outcome. Studies after TBI have demonstrated evidence of traumatic axonal injury that is not evident using conventional imaging techniques. Diffusion tensor imaging (DTI) images dynamic metabolic processes, including cytotoxic edema associated with cellular metabolic failure, and experience in stroke shows that these imaging changes are dynamic and reversible, suggesting that they may be able to image acute treatment effects. We have therefore used DTI to assess the impact of normobaric hyperoxia in this context, and provide data for the planning and design of future therapeutic trials of hyperoxia therapy for patients with head injury.

MATERIALS AND METHODS

Ethical approval was obtained from the Cambridgeshire Research Ethics Committee (reference numbers 97/290 and 02/293), and written informed consent, or consultee agreement from next-of-kin where appropriate, were obtained in all cases in accordance with the Declaration of Helsinki.

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imaging was obtained at each level after an equilibration period of 15 mins.

Diffusion tensor (21%, 60%, and 100% inspired oxygen) delivered via a venturi mask.

Controls:

Seven controls (four females and three males) with a mean age of 31 (22 to 42) years were exposed to graded oxygen therapy (21%, 60%, and 100% inspired oxygen) delivered via a ventilated mask (Flexicare Medical Limited, Mid Glamorgan, Wales, UK). Diffusion tensor imaging was obtained at each level after an equilibration period of 15 mins.

After acquisition of baseline diffusion tensor imaging (DTI) at a partial pressure of oxygen (PaO₂) of approximately 75 to 90 mmHg (10 to 12 kPa), the fraction of inspired oxygen (FiO₂) was increased to a maximum of 0.8 to achieve a PaO₂ of approximately 225 to 260 mmHg (30 to 35 kPa). After a 60-min period to allow impact of higher PaO₂ (and by inference, brain pO₂) levels on cerebral metabolism, repeat DTI was obtained within the same imaging session without moving the patient.

Controls:

Seven controls (four females and three males) with a mean age of 31 (22 to 42) years were exposed to graded oxygen therapy (21%, 60%, and 100% inspired oxygen) delivered via a ventilated mask (Flexicare Medical Limited, Mid Glamorgan, Wales, UK). Diffusion tensor imaging was obtained at each level after an equilibration period of 15 mins to assess the impact of oxygen therapy on normal brain.

Image processing:

Diffusion tensor imaging (DTI) maps were created using the Oxford Centre for functional magnetic resonance imaging of the brain FSL Diffusion Toolbox. To aid coregistration, the skull and extracranial soft tissue were stripped from the T1-weighted images using the Brain Extraction Tool (BET). Diffusion-weighted data were normalized using a two-step approach. First, T1-weighted images were coregistered to the Montreal Neurological Institute 152 (MNI152) template using the vtcCSG normalized mutual information algorithm. The b = 0 image was subsequently coregistered to the subject's own T1-weighted image. The transformation matrix normalizing the magnetization prepared rapid gradient echo was then applied to the b = 0 image. All coregistered and normalized images were visually checked to ensure that they were aligned.

Table 1. Patient characteristics

| Subject | Age | Sex | Mechanism | Injury | GCS | Marshall score | APACHE II | ISS | Neurosurgery | Second-tier therapies | Days to MRI | GOS |
|---------|-----|-----|-----------|--------|-----|----------------|-----------|-----|--------------|---------------------|-------------|-----|
| 1       | 53  | M   | RTA       | Multiple contusions and DAI | 4   | NEML           | 17        | 34  | —            | —                   | 4           | MD  |
| 2       | 34  | M   | RTA       | tSAH, SDH and IVH          | 4   | EML            | 21        | 20  | EVD          | —                   | 3           | VS  |
| 3       | 34  | M   | Assault   | Multiple contusions        | 8   | EML            | 25        | 16  | DC           | —                   | 3           | SD  |
| 4       | 21  | M   | RTA       | Multiple contusions        | 10  | NEML           | 21        | 50  | —            | Hypothermia        | 2           | MD  |
| 5       | 31  | M   | RTA       | Multiple SDH              | 6   | EML            | 17        | 29  | DC           | —                   | 1           | MD  |
| 6       | 29  | M   | Assault   | Multiple contusions        | 10  | EML            | 17        | 16  | DC, EVD      | Hypothermia        | 2           | GR  |
| 7       | 58  | M   | Fall      | Multiple contusions        | 10  | NEML           | 20        | 34  | —            | —                   | 4           | GR  |
| 8       | 26  | M   | RTA       | SDH and Multiple contusions | 3   | NEML           | 17        | 75  | —            | —                   | 3           | MD  |
| 9       | 28  | M   | Assault   | SDH and EDH               | 12  | EML            | 24        | 36  | DC           | —                   | 3           | GR  |
| 10      | 61  | M   | Fall      | Multiple contusions        | 5   | NEML           | 22        | 75  | —            | —                   | 9           | Not available |
| 11      | 60  | M   | Fall      | Multiple contusions        | 14  | NEML           | 8         | 34  | —            | Hypothermia        | 3           | MD  |
| 12      | 31  | F   | Fall      | Multiple contusions        | 3   | EML            | 25        | 75  | DC           | —                   | 4           | VS  |
| 13      | 70  | F   | RTA       | Multiple contusions        | 3   | NEML           | 21        | 34  | —            | —                   | 1           | GR  |
| 14      | 27  | M   | RTA       | Multiple contusions        | 7   | NEML           | 16        | 25  | —            | —                   | 4           | GR  |

Table 1: Patient characteristics

DTL, diffuse axonal injury; DC, decompressive cranioectomcy; EDH, extradural hemorrhage; EML, evacuated mass lesion; EVD external ventricular drain; F, female; GCS, Glasgow coma score; GOS, Glasgow outcome score; GR, good recovery; IVH, intraventricular hemorrhage; M, male; MD, moderate disability; MRI, magnetic resonance imaging; NEML, non evacuated mass lesion; RTA, road traffic accident; SD, severe disability; SDH, subdural hemorrhage; tSAH, traumatic subarachnoid hemorrhage; VS, vegetative state.

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Lesion core was identified as a region of mixed signal intensity consistent with hemorrhage and necrotic tissue, contusion as an area of high signal on FLAIR, and pericontusional as a 1-cm border zone of tissue surrounding the contusion (Figure 1). Where visible, we also defined a rim of cytotoxic edema ('traumatic penumbra') on ADC images that we have previously reported around contusions using DTI (Figure 2).9 The ROIs were drawn using Analyze 8.5 (Analyze Direct, Lenexa, KS, USA). FLAIR images were coregistered to T1 space using SPM8, and the coregistration matrix subsequently applied to the individual lesion ROIs. For comparison, a comparable region of brain composed of mixed gray and white matter was defined in controls.14

RESULTS

Impact of Oxygen Therapy on Diffusion Tensor Imaging in Healthy Volunteers

There was no significant ADC change using the standard template ROI for an increase in the inspired fraction of oxygen (FiO₂) (P > 0.99, analysis of variance). The mean (s.d.) ADC was 8.98 × 10⁻⁴ (1.37 × 10⁻⁴), 9.21 × 10⁻⁴ (1.37 × 10⁻⁴) and 9.20 × 10⁻⁴ (1.35 × 10⁻⁴) mm/second for an FiO₂ of 0.21, 0.6, and 1.0, respectively.

Injured brain regions. The mean (s.d.) ADC in contusional and pericontusional ROIs was 1.11 × 10⁻³ (1.41 × 10⁻³) and 1.08 × 10⁻³ (1.79 × 10⁻³), respectively, and was significantly higher than controls (9.21 × 10⁻⁴ (2.78 × 10⁻⁵), P < 0.01, analysis of variance with Bonferroni correction)). There was no significant change in ADC after hyperoxia within contusional ROIs (P = 0.16, paired t-test), but an increase within pericontusional ROIs (P = 0.02, paired t-test). One subject with low pericontusional ADC showed an increase to within the normal range. The data are displayed compared with the mixed gray and white matter region from controls (Figure 3).

There was a rim of low ADC around brain contusions consistent with cytotoxic edema in 13 subjects with a mean (range) volume of 8 (1 to 20) ml (Figure 2). There was a significant increase in ADC towards the normal range (7.04 × 10⁻⁴ versus 8.28 × 10⁻⁴ P = 0.02, paired t-test). The data are displayed compared with a mixed gray and white matter region from controls, and shows that while all subjects demonstrate an increase this is to within or more than the normal range in four subjects (Figure 4).

DISCUSSION

In this study we used DTI to examine whether an increase in the fraction of inspired oxygen had any beneficial effects within the injured brain. We found no significant change in healthy volunteers and no evidence of benefit within lesion brain identified on structural imaging. The rim of cytotoxic edema that we have previously defined as a region of ‘traumatic penumbra’ around brain contusions9 demonstrated a significant increase in ADC values towards normal. While an increase in the fraction of inspired oxygen has been reported to increase brain tissue partial pressure of oxygen, reduce microdialysis lactate and lactate pyruvate ratio,2,15,16 and improve brain metabolism17,18; we show evidence of benefit within ‘at-risk’ traumatic penumbra regions of the injured brain. While these data are provisional, they provide a
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Figure 3. Lesion-based analysis. Apparent diffusion coefficient (ADC) within brain tissue identified as contusion (A) and pericontusion (B) at baseline and after normobaric hyperoxia. The shaded gray box represents the 99% confidence interval for healthy controls from a region of mixed gray and white matter.

Figure 4. Impact of hyperoxia within traumatic penumbra. Changes in apparent diffusion coefficient (ADC) for the rim of cytotoxic edema surrounding visible brain lesions in 13 subjects. The shaded gray box represents the 99% confidence interval for healthy controls from a region of mixed gray and white matter.

The effects that result from an improvement in tissue oxygenation are clearly dependent on oxygen delivery and (probably) diffusion gradients in the injured brain. Pathophysiological derangements within the injured brain are spatially variant and are not limited to regions that appear structurally injured. Therefore, adequate definition of the effects of hyperoxia across the injured brain demands measurement of regional and global cerebral metabolism using a physiologic imaging technique such as $^{15}$O positron emission tomography. An $^{15}$O positron emission tomography study showed that ventilation with 100% oxygen in a group of five patients within 24 hours of severe head injury resulted in no change in hemispheric cerebral blood flow or oxygen metabolism (CMRO$_2$). These results are in contrast to a further study that demonstrated that a brief intervention (~1 hour) of normobaric hyperoxia resulted in an increase of CMRO$_2$ within brain regions at the greatest risk of infarction. This analysis included perilesional and white matter regions of the injured brain. While these data suggest that the impact of hyperoxia may be dependent on the underlying physiologic characteristics of different regions of the injured brain, another study using near-infrared spectroscopy has suggested that short-term therapy with hyperoxia can improve oxygen metabolism within a frontal brain region.

An explanation for these findings comes from postmortem studies showing widespread microvascular occlusion and perivascular edema after TBI, associated with selective neuronal loss. The relevance of these findings to clinical ischemia is explained by $^{15}$O positron emission tomography and brain tissue oximetry studies, which show increased vascular to tissue gradients for oxygen tension in the injured brain. We have previously used DTI to demonstrate contusion expansion, and that a rim of low ADC consistent with cytotoxic edema is often found surrounding a region of high ADC (vasogenic edema). This rim of hypodensity may characterize a region of microvascular failure resulting in cytotoxic edema, and represent a ‘traumatic penumbra’ that may be rescued by effective therapy or be subsumed as the contusion enlarges. Higher brain oxygen levels may overcome diffusion barriers to oxygen delivery, or compensate for mitochondrial dysfunction. Indeed, in regions of low oxygen tension, nitric oxide can competitively inhibit cytochrome oxidase and thereby render mitochondrial respiration dependent on the level of cellular oxygen. $^{15}$O positron emission tomography and brain tissue oximetry studies, which show increased vascular to tissue gradients for oxygen tension in the injured brain, have previously used DTI to demonstrate contusion expansion, and that a rim of low ADC consistent with cytotoxic edema is often found surrounding a region of high ADC (vasogenic edema). This rim of hypodensity may characterize a region of microvascular failure resulting in cytotoxic edema, and represent a ‘traumatic penumbra’ that may be rescued by effective therapy or be subsumed as the contusion enlarges. Higher brain oxygen levels may overcome diffusion barriers to oxygen delivery, or compensate for mitochondrial dysfunction. Indeed, in regions of low oxygen tension, nitric oxide can competitively inhibit cytochrome oxidase and thereby render mitochondrial respiration dependent on the level of cellular oxygen. Ex vivo studies in clinical and experimental head injury show impaired function in mitochondria (typically <4 hours of injury). Experimental data also show that mitochondrial ATP production is preserved, and that this is associated with improved cognitive recovery and reduced neuronal cell loss in the hippocampus after injury and treatment with hyperbaric and
normoxic hyperoxia. Experimental data also report that hyperoxia has neuroprotective and antiinflammatory effects within the injured and ischemic brain. Our clinical data are suggestive of a normalization of ADC values in such regions after a brief period of hyperoxia. However, we have no data on whether such an increase is beneficial in terms of preventing lesion expansion and improving functional outcome. Indeed, in two subjects the increase in ADC was greater than the 95% confidence interval for controls and could reflect tissue injury.

Although the use of high partial pressures of oxygen may be beneficial in a variety of disease states and after brain injury, there may be a relatively narrow margin of safety because of the known toxic effects. The maximum FiO2 in this interventional study was limited to 0.8 to reduce potential side effects including alveolar atelectasis and pulmonary injury. However, clinical studies in TBI have used short exposures of normobaric and hyperbaric hyperoxia and failed to demonstrate increased oxidative stress. While these clinical studies suggest that the use of high concentrations of inspired oxygen in this context may be safe, further studies are required to calculate the risk benefit ratio of hyperoxia and failed to demonstrate increased oxidative stress. The maximum FiO2 in this interventional study was limited to 0.8 to reduce potential side effects including alveolar atelectasis and pulmonary injury. However, clinical studies in TBI have used short exposures of normobaric and hyperbaric hyperoxia and failed to demonstrate increased oxidative stress.

While evidence of significant changes in brain oxygenation and metabolism and suggestions that improved outcome may be associated with targeted therapy are encouraging, a firm recommendation for clinical use of the intervention requires a clinical trial. Previous studies have suggested that hyperoxia therapy in TBI can improve mortality, but not favorable outcome. A recently published phase II study from Rockswold et al provided valuable evidence of the risks and benefits of hyperoxia therapy over several days. This study compared 60 minutes of hyperbaric hyperoxia (1.5 atmospheres) with 3 hours of 100% oxygen and standard care in a group of 69 patients with severe head injury. Patients received therapy on three consecutive days starting within 24 hours of injury and demonstrated some evidence of an improvement in cerebral physiology that lasted until the next treatment period. Importantly, there were no signs of pulmonary or cerebral toxicity. A more recent publication from the same group suggests that a combination of daily hyperbaric (60 minutes at 1.5 atmospheres) followed by 3 hours of normobaric hyperoxia (FiO2 1.0) can result in an increase in favorable outcome.

Despite the promising findings, the studies by Rockswold et al do not provide definitive evidence of an improvement in clinical outcome. Evidence of a change in tissue fate may come from DTI but evidence of improved outcome will require a large clinical trial. Previous studies have shown serial DTI changes in gray and white matter after head injury that represent microstructural injury. Our study addressed this within the time frame of metabolic changes that we have previously demonstrated with short-term hyperoxia, but was only able to show improvement in DTI parameters within a rim of potentially vulnerable tissue around brain contusions. However, we can use the data from this study to design the required Rockswold studies to refine the design of a future therapeutic trial of hyperoxia therapy after clinical head injury. In the studies published by Rockswold et al, subjects received daily exposure to hyperoxia within the first 4 days after injury, and we have shown that evolution of DTI signal changes within pericontusional tissue is maximal within the first 2 hours. In our study, 9 of 14 subjects underwent intervention within 72 hours of injury and only two subjects were studied within 24 hours of injury. Previous studies have clearly demonstrated that evidence of ischemia is more evident at earlier time points after injury. However, derangements in brain metabolism continue for many days after injury, and may be particularly prominent in white matter regions, and have shown evidence of improvement after hyperoxia therapy.

CONCLUSIONS

Previous studies have suggested that cerebral metabolism can be improved through an increase in the fraction of inspired oxygen. Using DTI we demonstrate that a short interval of normobaric hyperoxia may result in benefit within the rim of cytotoxic edema around brain contusions. Future longitudinal studies should address whether a longer period of hyperoxia therapy during the time that patients require critical care management of raised ICP has a favorable impact on the evolution of tissue injury. Such data would help inform the design of future clinical trials of targeted oxygen therapy for patients with head injury.

DISCLOSURE/CONFLICT OF INTEREST

The funders had no role in study design, data collection and analyses, decision to publish, or preparation of the manuscript.

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