Brain tissue oxygen tension and its response to physiological manipulations: influence of distance from injury site in a swine model of traumatic brain injury

Gregory W. J. Hawryluk, MD, PhD, FRCSC; Nicolas Phan, MD, FRCSC; Adam R. Ferguson, PhD; Diane Morabito, RN, MPH; Nikita Derugin, MS; Campbell L. Stewart, MD; M. Margaret Knudson, MD; Geoffrey Manley, MD, PhD; and Guy Rosenthal, MD

OBJECTIVE The optimal site for placement of tissue oxygen probes following traumatic brain injury (TBI) remains unresolved. The authors used a previously described swine model of focal TBI and studied brain tissue oxygen tension (PbtO2) at the sites of contusion, proximal and distal to contusion, and in the contralateral hemisphere to determine the effect of probe location on PbtO2 and to assess the effects of physiological interventions on PbtO2 at these different sites.

METHODS A controlled cortical impact device was used to generate a focal lesion in the right frontal lobe in 12 anesthetized swine. PbtO2 was measured using Licox brain tissue oxygen probes placed at the site of contusion, pericontusional tissue (proximal probe), in the right parietal region (distal probe), and in the contralateral hemisphere. PbtO2 was measured during normoxia, hyperoxia, hypoventilation, and hyperventilation.

RESULTS Physiological interventions led to expected changes, including a large increase in partial pressure of oxygen in arterial blood with hyperoxia, increased intracranial pressure (ICP) with hypoventilation, and decreased ICP with hyperventilation. Importantly, PbtO2 decreased substantially with proximity to the focal injury (contusion and proximal probes), and this difference was maintained at different levels of fraction of inspired oxygen and partial pressure of carbon dioxide in arterial blood. In the distal and contralateral probes, hypoventilation and hyperventilation were associated with expected increased and decreased PbtO2 values, respectively. However, in the contusion and proximal probes, these effects were diminished, consistent with loss of cerebrovascular CO2 reactivity at and near the injury site. Similarly, hyperoxia led to the expected rise in PbtO2 only in the distal and contralateral probes, with little or no effect in the proximal and contusion probes, respectively.

CONCLUSIONS PbtO2 measurements are strongly influenced by the distance from the site of focal injury. Physiological alterations, including hyperoxia, hyperventilation, and hypoventilation substantially affect PbtO2 values distal to the site of injury but have little effect in and around the site of contusion. Clinical interpretations of brain tissue oxygen measurements should take into account the spatial relation of probe position to the site of injury. The decision of where to place a brain tissue oxygen probe in TBI patients should also take these factors into consideration.

http://thejns.org/doi/abs/10.3171/2015.7.JNS15809

KEY WORDS traumatic brain injury; oxygen monitor; optimal location; licox; in vivo
While tissues such as muscle can tolerate ischemia for hours, cells of the brain die after only minutes of anoxia.\textsuperscript{3,12} Cerebral ischemic injury is a significant problem after traumatic brain injury (TBI).\textsuperscript{24} ischemic changes are seen in 80% of brains of patients who die following TBI.\textsuperscript{19} Given the limited regenerative capacity of the CNS, as well as evidence that brain tissue hypoxia after TBI is predictive of poor outcome,\textsuperscript{3,4,16,23,26,32,35,48,49} efforts to minimize brain tissue hypoxia following TBI are warranted.

To reliably prevent brain tissue hypoxia, it is important to be able to continuously measure cerebral oxygenation, either directly or indirectly.\textsuperscript{31} For over 2 decades brain tissue oxygen probes have been available, allowing practitioners of neurocritical care to continuously monitor brain tissue oxygen tension ($P_{btO2}$) directly.\textsuperscript{11} Importantly, these invasive brain tissue oxygen probes provide focal measurements reflecting oxygen tension within a small volume of brain near the sensor. The limited knowledge regarding optimal probe placement in the injured brain remains a major limitation when brain tissue oxygen probes are used to monitor TBI patients.

Several studies have investigated the relevance of brain tissue oxygen probe location in human patients; however, these investigations have studied data from different patients, each with a single probe located at different distances from a focal brain lesion. In these studies, the distance of the probe from focal injury was not planned, since the probes are placed in standard locations in the frontal lobes and the distance from focal injury varies.\textsuperscript{9,14,20,35} Therefore, it is difficult to draw definitive conclusions regarding optimal probe location based on these clinical studies. A laboratory study performed under controlled conditions to continuously monitor brain tissue oxygen tension ($P_{btO2}$) directly.\textsuperscript{11} Importantly, these invasive brain tissue oxygen probes provide focal measurements reflecting oxygen tension within a small volume of brain near the sensor. The limited knowledge regarding optimal probe placement in the injured brain remains a major limitation when brain tissue oxygen probes are used to monitor TBI patients.

Several studies have investigated the relevance of brain tissue oxygen probe location in human patients; however, these investigations have studied data from different patients, each with a single probe located at different distances from a focal brain lesion. In these studies, the distance of the probe from focal injury was not planned, since the probes are placed in standard locations in the frontal lobes and the distance from focal injury varies.\textsuperscript{9,14,20,35} Therefore, it is difficult to draw definitive conclusions regarding optimal probe location based on these clinical studies. A laboratory study performed under controlled conditions that involves placement of multiple concurrent probes may be better able to provide data concerning the relative advantages of different probe locations. Our study used a previously characterized porcine model of controlled cortical impact (CCI),\textsuperscript{24} which generates a focal contusion injury to determine how measurements of $P_{btO2}$ are affected by distance from a focal injury in the gyrencephalic brain. We also sought to determine how concurrent readings at distinct sites responded to physiological alterations including hypoxemia, hyperventilation, and hypoventilation in a controlled fashion that could not be easily achieved in humans.\textsuperscript{20}

Methods

This experiment employed our previously described CCI model in swine that mimics the gross anatomical and histological features of human focal brain injury.\textsuperscript{24} The experimental protocol was approved by the Committee on Animal Research at the University of California, San Francisco.

Animal Preparation

We used male Yorkshire swine weighing from 35 to 45 kg. Surgeries and perioperative intensive care were performed in the large animal facility at the University of California, San Francisco.\textsuperscript{24} As previously described,\textsuperscript{24} animals were premedicated with ketamine (20 mg/kg) and xylazine (2 mg/kg). They were paralyzed with 0.05 mg/kg of pancuronium and were mechanically ventilated following intubation (Narkovet 2; Drager). Anesthesia consisted of a fentanyl infusion (1 $\mu$g/kg/hr) and inhaled isoflurane (0.5%–2%). Inspired oxygen concentration and end-tidal $CO_2$ were monitored continuously. An arterial line facilitated arterial blood gas (ABG) analysis. A Swan-Ganz catheter was employed to monitor cardiac indices. Body temperature (38.5°C ± 1.0°C) was maintained with the use of a forced air warmer (BAIR Hugger; Augustine Medical). Animals were additionally monitored by electrocardiography, pulse oximetry, and placement of a urinary catheter to measure urine output.

Controlled Cortical Impact

To secure the heads of the swine, a modified animal head frame was applied (David Kopf Instruments). The surgical sites were then cleansed, sterilized, and draped. A scalp incision was made to facilitate placement of a 15-mm bur hole 7 mm anterior to the coronal suture and 3 mm to the right side of the midline.\textsuperscript{24} The right frontal dura was exposed but kept intact. The head was then placed in the CCI device\textsuperscript{24} (Bioengineering Department, Medical College of Virginia). CCI was performed using the following parameters: velocity 3.5 m/sec, dwell time 400 msec, and depth of depression 11 mm. These parameters lead to a well-characterized focal contusion associated with subarachnoid hemorrhage.\textsuperscript{24}

Brain Tissue Oxygen Monitor Placement

Four Licox brain tissue oxygen probes (Integra Lifesciences) were placed in each animal (Fig. 1) in the same fashion and locations previously employed by our group.\textsuperscript{41} Before placement, all probes were tested to ensure proper functioning. Distal and contralateral probes were placed prior to the CCI while the probes placed in the contusion and the penumbra were placed through the right frontal bur hole subsequent to the CCI at that site. Probes were inserted to a depth of 12 mm using a stereotactic device (David Kopf Instruments) and micromanipulators. The distal probe was placed through a separate bur hole 3.5 mm posterior to the posterior edge of the bur hole at the right frontal impact site and 7 mm to the right side of midline. The contralateral probe was placed 3.5 mm posterior to the posterior edge of the bur hole at the right frontal impact site and 7 mm to the left of midline. Following CCI, the contusion probe was inserted through the center of the bur hole used for the impact injury. The proximal probe was placed at the posterior margin of the impact injury bur hole. All bur holes were then sealed with dental impression material (CutterSil; Heraeus Kulzer GmbH) to reduce leakage of CSF and to secure the brain tissue probes in place.

Data Collection

Physiological data were collected continuously throughout the experiment using a computerized data acquisition system designed by Aristein Bioinformatics LLC. Data were collected at 1-min intervals. Measured parameters included heart rate; systolic, diastolic, and mean arterial
blood pressure (MAP); systolic, diastolic, and mean pulmonary artery pressures; intracranial pressure (ICP); and cerebral perfusion pressure (CPP). Respiratory rate, fraction of inspired oxygen (F\textsubscript{i}O\textsubscript{2}), end-tidal CO\textsubscript{2}, and oxygen saturation were also recorded once per minute. In addition, P\textsubscript{bt}O\textsubscript{2} and brain temperature measurements were recorded from each of the 4 probes. Mean values at each physiological intervention were calculated as described below. ABG measurements including pH, partial pressure of carbon dioxide in arterial blood (P\textsubscript{a}CO\textsubscript{2}), partial pressure of oxygen in arterial blood (P\textsubscript{a}O\textsubscript{2}), and base excess and bicarbonate were performed to verify anticipated physiological responses to changes in ventilation or F\textsubscript{i}O\textsubscript{2}.

**Physiological Interventions**

Following CCI and insertion of all P\textsubscript{bt}O\textsubscript{2} monitors, animals were exposed to a total of 6 physiological states. These included baseline, hyperventilation, and hypventilation under conditions of normoxia (F\textsubscript{i}O\textsubscript{2} = 0.21) and hyperoxia (F\textsubscript{i}O\textsubscript{2} = 1.00). After baseline was established at normoxia, animals were exposed to the remainder of the conditions (Fig. 2). A stratified randomization was performed whereby animals were first randomized to normoxic or hyperoxic conditions. In the second stage animals were randomized to the 3 respiratory rates, which they completed before the F\textsubscript{i}O\textsubscript{2} was changed. After the F\textsubscript{i}O\textsubscript{2} change, the 3 different respiratory rates were repeated in random order. At baseline, the respiratory rate was 10/min, during hyperventilation it was 22/min, and during hypoventilation it was 5/min. Vital signs and brain P\textsubscript{a}O\textsubscript{2} measures had to reach a steady state for a minimum of a 5-minute period before physiological conditions were altered. At each of the 6 physiological conditions (normoxic normocarbia, normoxic hypocarbia, normoxic hypercarbia, hyperoxic normocarbia, hyperoxic hypocarbia, hyperoxic hypercarbia) parameters including MAP, ICP, CPP, heart rate, and brain tissue oxygen were recorded. Mean values for each physiological parameter were calculated for each physiological state as follows: the time point at which P\textsubscript{bt}O\textsubscript{2} values at the distal or contralateral probes first reached 90% of the maximal change induced by each particular physiological intervention were identified. Five
measures of MAP, ICP, CPP, heart rate, and $P_aO_2$ (mean minute values) extending from 2 minutes before to 2 minutes after this point were averaged to calculate the mean values at that physiological state. The same number of measurements of MAP, ICP, CPP, heart rate, and $P_aO_2$ were made at each condition and for each experimental animal. In addition, in the first 3 experimental animals an ABG was drawn at baseline and with each physiological intervention to verify the anticipated changes in $P_aO_2$ and $P_aCO_2$.

**Postoperative Care**

At the completion of the experimentation animals were killed while under anesthesia. All probes were removed and a return to previously measured atmospheric oxygen values was verified.

**Imaging**

During model optimization prior to the experimentation described here, a Philips Intera I/T 1.5-T whole-body MR imager (Philips Medical Systems) was used to characterize the tissue injury associated with the employed CCI model in a fashion previously described by our group. An anesthetized, ventilated pig subjected to the same injury parameters employed in the experimental animals underwent T2-weighted MR imaging 8 hours after CCI, generating the image shown in Fig. 3 right. While in the MRI suite, the swine received maintenance intravenous fluids and analgesics. Oxygen saturation and heart rate were continuously monitored using an MRI-compatible pulse oximeter (In Vivo Research, Inc.).

**Statistical Analysis**

SPSS version 21.0.0.1 was employed for statistical analysis. GraphPad Prism version 6.03 was used to generate graphs. ANOVA was performed with a 3-way repeated-measures general linear model (GLM) to assess effects complying with the sphericity assumption. In cases in which the Mauchly test revealed a violation of sphericity, linear mixed model (LMM) regression was applied using restricted maximum likelihood modeling (REML). Significant main effects and interactions were followed up with Tukey and Bonferroni post hoc testing (for GLM procedures) and with fixed-effect tests REML procedures. In all cases a p value < 0.05 was employed as the threshold for statistical significance. Error bars in graphs (Figs. 4 and 5) represent the standard error in all cases.

**Results**

We studied 12 swine, all of which survived to comple-
tation of the protocol. Typical gross pathology that demonstrates the extent of focal injury is shown in Fig. 3 left. Figure 3 right demonstrates a T2-weighted MR image of the swine brain with a focal contusion and surrounding edema.

On average, the time spent from anesthesia induction to CCI was 322.1 ± 59.2 minutes (Fig. 2, Segment a) and the time from CCI to normoxic baseline was 124.8 ± 83.5 minutes (Fig. 2, Segment b). For normoxic hyperventilation, it took a mean of 27.4 ± 21.9 minutes to reach 90% FiO2.

**FIG. 4.** Box plots showing that ICP is associated with P_aCO2 change. ICP at baseline as well as changes related to hypoventilation and hyperventilation are presented at normoxia (FiO2 = 0.21 [left]) and hyperoxia (FiO2 = 1.00 [right]). A 3-way within-subject GLM revealed a significant effect of ventilation on ICP (p < 0.0001) but no significant main effect of FiO2 or higher-order interactions. An LMM confirmed this result. Post hoc fixed-effects testing indicated hypoventilation increased ICP relative to baseline (p < 0.0001). Mean ICP values during hypoventilation were substantially greater than those measured at baseline and during hyperventilation (p < 0.001 on Bonferroni post hoc comparisons); however, baseline values were not significantly different from those measured during hyperventilation (p = 0.508 on Bonferroni post hoc comparison). The same results were observed at normoxia (FiO2 of 0.21 [left]) and hyperoxia (FiO2 of 1.0 [right]). In each of the 12 swine, mean ICP values were calculated at each of the 6 physiological states. **Boxes** indicate interquartile range, **horizontal rules** indicate the median, and **whiskers** demonstrate the maximum and minimum values.

**FIG. 5.** Graphs showing P_btO2 measurements with different P_aCO2 values. P_btO2 values measured in 4 probes located in different positions relative to cerebral contusion are compared at baseline and during hypoventilation and hyperventilation. Hypoventilation and hyperventilation were associated with hypercarbia and hypocarbia, respectively. This physiological manipulation was performed under conditions of normoxia (FiO2 = 0.21 [left]) and hyperoxia (FiO2 = 1.00 [right]). LMM analysis revealed significant main effects of probe location, ventilation, and FiO2 on P_btO2 (all p < 0.001). In addition there was a probe-ventilation interaction, (p < 0.001). Post hoc fixed-effects testing by probe location revealed that the contusion and proximal probes were unresponsive to the ventilation condition (both p > 0.05), whereas the distal and contralateral probes were highly responsive to the ventilation condition and FiO2 (both p < 0.001). Fixed-effects testing of the main effects also revealed that the contusion probe registered P_BT2 values significantly lower than the proximal probe (p < 0.05). The distal and contralateral probes both had significantly higher P_BT2 than the proximal probe (p < 0.001) but did not differ from each other (p > 0.05). In each of the 12 swine, mean P_BT2 values were calculated at each of the 6 physiological states. **Error bars** represent standard error.
of the maximal change (Fig. 2, Segment c); animals remained in this condition for a mean of 10.1 ± 6.7 additional minutes before changing conditions. For normoxic hypoventilation, it took a mean of 22.2 ± 9.4 minutes to reach 90% of maximal change (Fig. 2, Segment e); animals remained in this condition for a mean of 17.2 ± 21.1 additional minutes before changing conditions. The mean time for physiological normalization between normoxic and hyperoxic conditions was 28.9 ± 13.1 minutes (Fig. 2, Segment d). The mean time for physiological normalization between normoxic and hyperoxic conditions was 62.5 ± 35.4 minutes (Fig. 2, Segment f). From normoxia to hyperoxic baseline, the mean time to reach 90% of maximal change was 21.3 ± 8.9 minutes (Fig. 2, Segment g), with a mean of 22.9 ± 27.5 additional minutes in the condition prior to change. For hyperoxic hyperventilation, it took a mean of 18.9 ± 7.6 minutes to reach 90% of maximal change (Fig. 2, Segment h), with 16.0 ± 12.2 additional minutes before change in conditions. It took a mean of 22.5 ± 7.3 minutes to reach 90% of maximal change for hyperoxic hyperventilation (Fig. 2, Segment j), and 11.1 ± 6.9 additional minutes were spent in the condition prior to change. A mean of 37.4 ± 15.6 minutes were spent to reach physiological normalization between hyperoxic conditions (Fig. 2, Segment i).

Total mean time for completion of the experimental protocol was 15.2 hours.

Mean values for heart rate, MAP, ICP, CPP, P\textsubscript{aO2}, and P\textsubscript{aCO2} during each of the 6 physiological states are presented in Table 1. These data demonstrate significant differences between physiological states with respect to MAP, ICP, P\textsubscript{aO2}, and P\textsubscript{aCO2} values. Hyperoxia led to the expected marked increase in P\textsubscript{aO2}; hyperventilation was associated with expected hypocarbia and higher ICP values. In contrast, hyperventilation was associated with expected hypocarbia and lower ICP values.

ICP values for each of the 6 physiological states are presented in Fig. 4. A 3-way within-subject GLM revealed a significant effect of ventilation on ICP (p < 0.0001) but no significant main effect of F\textsubscript{O2} or higher-order interactions. The same effect was independently confirmed by LMM.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Hypoventilation</th>
<th>Hyperventilation</th>
<th>Hypoventilation</th>
<th>Hyperventilation</th>
<th>ANOVA p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>106.2 ± 27.2</td>
<td>131.2 ± 35.3</td>
<td>106.2 ± 19.9</td>
<td>104.8 ± 23.7</td>
<td>120.2 ± 34.8</td>
<td>103.9 ± 21.2</td>
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<td>MAP</td>
<td>92.0 ± 12.0</td>
<td>82.4 ± 18.3</td>
<td>71.9 ± 15.7</td>
<td>(p = 0.031)</td>
<td>88.4 ± 11.7</td>
<td>92.6 ± 17.6</td>
</tr>
<tr>
<td>ICP</td>
<td>11.5 ± 2.9</td>
<td>16.6 ± 3.8</td>
<td>(p = 0.002)</td>
<td>8.3 ± 1.8</td>
<td>11.1 ± 2.5</td>
<td>17.2 ± 4.6</td>
</tr>
<tr>
<td>CPP</td>
<td>78.3 ± 14.6</td>
<td>64.4 ± 19.6</td>
<td>63.1 ± 15.6</td>
<td>75.4 ± 13.1</td>
<td>73.1 ± 17.3</td>
<td>71.1 ± 11.8</td>
</tr>
<tr>
<td>P\textsubscript{aO2}</td>
<td>125.7 ± 26.6</td>
<td>85.0 ± 39.6</td>
<td>151.5 ± 36.1</td>
<td>555.0 ± 36.4</td>
<td>(p &lt; 0.0001)</td>
<td>506.0 ± 51.6</td>
</tr>
<tr>
<td>P\textsubscript{aCO2}</td>
<td>40.0 ± 3.5</td>
<td>51.0 ± 1.4</td>
<td>34.5 ± 7.8</td>
<td>37.7 ± 2.5</td>
<td>60.0 ± 7.0</td>
<td>29.7 ± 1.5</td>
</tr>
</tbody>
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HR = heart rate.

* Values are mean mm Hg ± SD unless otherwise indicated. Values typifying the physiological state in question were selected for analysis when P\textsubscript{aO2} measures at the distal or contralateral probes first reached 90% of the maximal change. Boldface indicates values that significantly differ from baseline values on Bonferroni post hoc testing.

† ANOVA reflects statistical comparison between all 6 physiological states.
contrast, the lack of response of $P_{btO_2}$ to a rise in $P_{aO_2}$ is clearly evident for the proximal and contusion probes (Fig. 6C and D), indicating that the relationship between arterial and brain tissue oxygen tension is lost at the site of injury (contusion probe), and nearly lost in its close vicinity (proximal probe). These data were analyzed with a GLM as well as an LMM, which demonstrated a significant 2-way interaction of probe location and $P_{aO_2}$ level ($p < 0.001$). This effect was observed whether $P_{aO_2}$ was dichotomized into normoxia and hyperoxia or treated as a continuous covariate (all $p < 0.001$). Post hoc 1-way ANOVA on dichotomized $P_{aO_2}$ and Bonferroni tests revealed that $P_{aO_2}$ influenced $P_{btO_2}$ readouts at the contralateral (A) and distal (B) probes ($p < 0.001$) but not the proximal (C) and contusion (D) probes ($p > 0.05$).

**Discussion**

Currently, a major limitation of brain tissue oxygen monitoring is a lack of clear data about how probe location relative to a focal lesion affects measured values, and how these values respond differently to physiological events such as decreased MAP, impaired systemic oxygenation, or alterations in ventilation based on their distance from a focal injury. How the response of brain tissue oxygenation to treatment interventions may differ due to distance of the probe from injury site is also uncertain.

Several clinical reports have studied the effect of probe location on brain tissue oxygen values. Previous studies have documented different brain tissue oxygen values within white matter, gray matter, and the ventricular system.22 Dings et al. found that $P_{btO_2}$ values decreased as probe depth increased.9 Longhi et al. found that $P_{btO_2}$ values were lower in pericontusional tissue than in apparently normal brain and that episodes of hypoxia were of longer duration in pericontusional tissue.20 Similarly, Ponce et al. found that $P_{btO_2}$ values were lower near focal traumatic lesions than in apparently normal brain.35 $P_{btO_2}$ measures in pericontusional tissue were predictive of outcome while those in normal brain were not. Hlatky et al. found that $P_{btO_2}$ values change minimally in response to systemic hyperoxia in areas of low regional cerebral blood flow as...
determined by xenon CT. However, these data have not settled debate among clinicians regarding the optimal location for probe placement, because multiple probes were not studied concurrently in individual patients. To our knowledge, only 2 human studies have investigated concurrent placement of 2 P O 2 probes. Sarrafzadeh et al., using Licox and Paratrend monitors concurrently, found that P O 2 values were lower near the contusion and recommended that P O 2 monitor placement be remote from focal injuries. Kiening et al. employed only Licox probes and reported similar findings in a sample of only 7 patients.

Several human studies have associated low P O 2 values with poor outcome following TBI. Maloney-Wilensky et al. performed a systematic review of such studies in 2009; 3 of their criteria. In these studies, an association between low P O 2 and poor outcome was demonstrated, and it was concluded that P O 2 values below 10 mm Hg may portend a worse prognosis. The same group published a similar systematic review of the literature in 2012, this time pooling available evidence on whether P O 2 -guided therapy improves outcome. They identified 7 relevant studies and on a pooled analysis of 4 studies that they felt could be combined, they concluded that P O 2 -guided therapy was associated with improved outcomes from severe TBI.

An ongoing multicenter randomized clinical trial is comparing treatment directed by ICP values alone versus treatment directed by ICP and P O 2 values (BOOST 2, NCT00974259). It is possible that it will be easier to interpret the results of therapeutic trials if the influence of probe location is better understood. Of interest, the P O 2 monitors in the BOOST 2 study are being placed in the more normal frontal lobe.

Our results indicate that probe location in relation to a focal injury is an important determinant of brain tissue oxygen tension. Basic physiological parameters including arterial oxygen tension, hypocarbia, and hypercarbia influence P O 2 in a fashion that is dependent on the distance of the probe from the injury site. This finding has important clinical implications. The 2007 edition of the Brain Trauma Foundation's Guidelines for the Management of Severe Traumatic Brain Injury recommends a P O 2 treatment threshold of 15 mm Hg. This recommendation is made without reference to probe location, however. Indeed, the guidelines recognize this limitation of the present literature and recommend studying the site of probe location in relation to focal injury as a "key issue for further investigation."

Both in this experimental study and in the clinical setting, we prefer to place brain tissue oxygen probes within the white matter. Placement of probes within gray matter is technically challenging, making proper positioning difficult both to achieve and to verify. In addition, cerebral blood flow, which strongly influences brain tissue oxygen tension, varies over a greater range in gray matter than in white matter and is also influenced by the functional activation of specific brain regions, making interpretation of measured values more difficult. Placement of probes within the ventricular system also does not appear to be very clinically useful since it is most strongly influenced by arterial partial pressure of oxygen and is less dependent on cerebral physiological parameters. Placement of brain tissue oxygen probes within the white matter has advantages including technical feasibility, relatively low variability in readings compared with other sites, and responsiveness to changes in both systemic oxygenation (P O 2) and cerebral physiological parameters such as cerebral blood flow. However, our study indicates that varying location within the white matter itself in relation to the site of injury strongly influences brain tissue oxygen tension measurements, making the decision of where to place the probe clinically important.

Not surprisingly, in this experimental model, the closer the probe was to the site of focal contusion, the lower the P O 2 measurements and the less responsive measures were to actions that augment P O 2 in other brain regions. Several pathophysiological phenomena may account for this observation. First, an anatomically disturbed vascular tree at the site of focal contusion may impair blood flow and, thus, oxygen delivery at the site of focal brain injury. Second, since P O 2 measurements are strongly influenced by oxygen diffusion rather than total oxygen delivery, the edema around focal injury may impair oxygen diffusion into the injured region, thereby decreasing measured tissue oxygen tension. In this regard, it is important to note that the brain tissue oxygen monitor is not truly an "ischemia monitor," since it directly measures cerebral tissue oxygen tension and not the balance between oxygen delivery and metabolism. Even so, measuring brain tissue oxygen tension can still be very clinically useful since low values will reflect either poor systemic oxygenation or low cerebral blood flow and can assist in the early detection of both issues. Our study implies that local changes around a site of cerebral injury strongly impact brain tissue oxygen measurements and, therefore, need to be taken into account when interpreting P O 2 values.

An important goal of management in the neurointensive care unit is to control intracranial pressure while maintaining adequate cerebral blood flow and oxygenation. Physiological manipulations such as adjusting fraction of inspired oxygenation and moderate hyperventilation to lower elevated ICP are routinely used in patients with severe TBI. Advanced cerebral monitors are often used to monitor the effect of these manipulations and one of the goals of monitoring brain tissue oxygen tension after TBI is to assess the effect of interventions on P O 2 . Our data indicate that brain tissue oxygenation is affected in a markedly different fashion depending on the distance of the probe from the site of a cerebral contusion. Brain tissue oxygen increases more than 2-fold during hyperoxia when the probe is distant to the injury site or in the contralateral hemisphere (Fig. 6A and B) but only negligibly when the probe is located at the site of contusion or near it (Fig. 6C and D). This has important clinical implications since adjusting F O 2 to optimize cerebral tissue oxygenation may be less efficacious in the areas around cerebral contusions. Similarly, changes in ventilation that alter cerebral blood flow influence P O 2 in a manner that is strongly dependent on the location of the probe in relation to injury (Fig. 5). Hyperventilation increases P O 2 at sites distal to the contusion and in the contralateral hemisphere but not at the site.
of injury or near it. Conversely, hyperventilation decreases \( P_{btO_2} \) distal to a contusion and in the contralateral hemisphere but not within or near a contusion. These results imply that cerebral \( CO_2 \) vasoreactivity is impaired in and around contused cerebral tissue, hindering or making less effective the alterations in ventilation that influence perfusion or lower ICP in and around the site of the focal contusion.

Our results are in general agreement with those of McLaughlin and Marion who demonstrated, using xenon CT, low cerebral blood flow and variable cerebral vasoreactivity in pericontusional tissue in patients with severe TBI.\(^\text{27}\) Our findings are also similar to those previously described in work by Hlatky et al.\(^\text{14}\) In general, our results indicate that \( P_{btO_2} \) measurements will be less sensitive to physiological alterations when placed in or near a contusion, limiting the ability of the brain tissue oxygen monitor to guide therapeutic interventions. It is interesting that in some instances hyperoxia did not increase \( P_{btO_2} \), even in the distal and contralateral probes (Fig. 6). This may relate to focal brain injury induced during placement of some of the probes and is consistent with variability noted in humans.\(^\text{14}\)

Our findings are relevant to the important question of where to place the probe in patients with severe TBI. However, the answer to this simple question is not necessarily clear-cut. The advantages and disadvantages of different placement strategies need to be carefully weighed. One school of thought advocates placement of \( P_{btO_2} \) probes in pericontusional tissue to help save cerebral “tissue at risk.”\(^\text{35}\) In the aforementioned paper by Ponce and colleagues, a multivariate analysis found that probe location was an important factor when looking at the relationship between mean \( P_{btO_2} \) and patient outcome in severe TBI.\(^\text{35}\) When the probe was placed in “vulnerable” or abnormal brain tissue defined on postinjury CT as being within a contusion, near a contusion, or under a surgically evacuated hematoma, mean \( P_{btO_2} \) values were substantially higher in patients with a favorable outcome (28.8 ± 12.0 mm Hg) compared with those with a poor outcome (19.5 ± 13.7 mm Hg, \( p = 0.01 \)). Conversely, when the probe was placed in normal-appearing brain, \( P_{btO_2} \) was not related to outcome in the multivariate model. On the one hand, our data could be viewed as supporting placement of brain tissue oxygen monitors in pericontusional tissue since values will be lowest in and around focal injuries. Therapy would then be geared to maximizing values in this “tissue at risk.” However, the \( P_{btO_2} \) threshold to maintain tissue viability is not known, either clinically or in controlled experimental models. In this regard, it is important to remember that the brain tissue oxygen monitor does not convey information about oxygen utilization or metabolism.\(^\text{38,41}\) In addition, it is well known that mitochondrial dysfunction can lead to cellular energy failure, even when sufficient oxygen is provided to tissue.\(^\text{7,45}\) Nevertheless, an argument can be made that maintaining \( P_{btO_2} \) as high as possible around focal injury may be advantageous. In our view, the data more strongly support the placement of brain tissue oxygen probes distal to the site of focal injury or in the contralateral hemisphere since cerebral tissue in these regions behaves in a more “physiological” way and therefore can be used to assess the effect of interventions such as changing \( F\text{O}_2 \), changing ventilation, or altering CPP. Such use of the brain tissue oxygen monitor allows the clinician to “fine tune” systemic and cerebral physiological parameters to optimize cerebral tissue oxygenation.

It is important to consider that an additional probe site between our proximal and distal probes might better characterize lesion penumbra and exhibit greater responsiveness. Such a probe site could have optimal intermediate properties. We strongly discourage readers from abandoning efforts to characterize or study penumbral \( P_{btO_2} \) on the basis of these results, especially because our proximal probes are likely located nearer the focal lesion than pericontusional probes investigated in other studies.

In clinical practice, considerations other than purely physiological ones often affect the decision on where to place monitors. If a brain tissue oxygen monitor is placed via a bolt, it can only be inserted where the cranium is intact. Therefore, patients undergoing decompressive hemicraniectomy must have bolts placed on the side contralateral to decompression, which is usually the least-injured hemisphere. In addition, bolt placement is generally limited to the anterior frontal lobes to achieve safe localization within the large white matter tracts without injury to descending motor fibers. Given these practical considerations, placement of probes in truly pericontusional cerebral tissue is often difficult without imaging-based stereotactic guidance. Placement in the contralateral frontal lobe may thus be the best option until more precise placement of brain tissue oxygen probes becomes possible in human patients.\(^\text{15}\) In interpreting the results of our study it is important to consider that the precise location of proximal probes in relation to injury was not determined by anatomical imaging studies. Previous work by our group in a swine model of CCI used MRI loaded to a Stealth neuronavigation station to precisely determine the site of proximal probes in relation to the injury site.\(^\text{41}\) In that study, we found that proximal probes were actually located within the contusion 20% of the time, indicating the difficulty of precise probe placement even under controlled experimental conditions. This difficulty is likely to apply to the clinical setting as well, making the placement of probes in precise pericontusional regions that reflect “tissue at risk” or penumbral tissue challenging. The values measured by the proximal probe likely reflect some bias introduced by proximal probe location within contusional tissue, and for this reason, the proximal probe should not be viewed as providing information about penumbral tissue and should not discourage future efforts to study probes located in a formally defined penumbra. Despite this limitation, we found a subtle but statistically significant difference in the physiological responses between proximal and contusion probes. Our data would likely reflect the clinical reality of imprecise placement in any attempt to place probes near a site of focal injury.

**Limitations**

Our study has several limitations. First, it analyzed the characteristics of \( P_{btO_2} \) measurements in relation to the distance of a brain tissue oxygen monitor from a focal contusion, but it did not aim to define a treatment threshold that
would preserve tissue viability. Neither does it provide information on histological or functional outcomes that could be used for this purpose. Defining the threshold and duration of low brain tissue oxygen values that lead to irreversible cellular damage is an important goal for future studies. However, it does demonstrate that probe location should be a key consideration when such studies are performed and whenever probe readings are interpreted. A second limitation of our model is that the experiment was performed in the period immediately following injury, extending to a mean of 15.2 hours postinjury. Since many physiological alterations, including increased brain edema, alterations in cerebral blood flow, and autoregulation, can occur days after injury, caution must be used in extrapolating our results to a period of days after injury. Our study design may not exactly duplicate the clinical situation during the period of maximal brain swelling. Both ethical concerns regarding the humane treatment of the experimental animals and practical issues of resource availability prevented us from extending the experiment to several days postinjury to more closely parallel the typical clinical scenario. Lastly, we did not verify probe location in this study by imaging studies. We, therefore, cannot be certain whether the proximal probe sensors were located in penumbra. A previous study by our group did image the swine brain with MRI following CCI and probe placement, demonstrating the capabilities and limitations of probe placement in the swine CCI model. Our goal in the present study was to assess the impact of distance from a focal injury and not presence within tissue formally defined as penumbra. Because of this, our findings related to the proximal probe should not discourage needed research into PbtO2 monitoring in the injury penumbra nor should it prompt cessation of clinical efforts to monitor the penumbra. We did not endeavor to define the location of the proximal probe employed in our study relative to penumbra, as penumbra is not routinely characterized in the course of TBI patient care, and brain oxygen probes cannot currently be placed into such a region with stereotactic precision.

Conclusions

Brain tissue oxygen measurements are strongly influenced by the distance from focal brain injury. Physiologic alterations including hypoxemia, hyperventilation, and hypoventilation more readily affect PbtO2 values distal to the site of injury but have little effect on measures near the contusion. Clinical interpretations of brain tissue oxygen measurements should take into account the spatial relation of probe position to sites of focal brain injury. Likewise, decisions regarding optimal placement of brain tissue oxygen probes in patients with severe TBI should take these factors into consideration.

Acknowledgments

We would like to thank Larry Carbone, DVM, PhD, and Ron Bairuther for their assistance with the large-animal studies. Kotaro Oshio MD, PhD, and Ken Monson, PhD, also made important contributions to the technical aspects of this study. This work was supported by CDC grant R49, CCR903697, and ONR grant N00014002-1-0203.

References


Brain tissue oxygen probe location


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Correspondence
Geoffrey Manley, Department of Neurological Surgery, University of California San Francisco, 1001 Potrero Ave., Rm. 101, San Francisco, CA 94110. email: manleyg@neurosurg.ucsf.edu.