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Translational Research

Brain Tissue Oxygen Monitoring in Intracerebral Hemorrhage

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Abstract

Introduction: Brain tissue oxygen ($P_{br}O_2$) monitoring is an emerging technique for detection of secondary brain injury in neurocritical care. Although it has been extensively reported in traumatic brain injury and aneurysmal subarachnoid hemorrhage, its use in nontraumatic intracerebral hemorrhage (ICH) has not been well described. We report complementary preliminary studies in a large animal model and in patients that demonstrate the feasibility of $P_{br}O_2$ monitoring after ICH.

Methods: To assess early events after ICH, Licox Clark-type oxygen probes were inserted in the bilateral frontal white matter of four anesthetized swine that subsequently underwent right parietal hematoma formation in an experimental model of ICH. Intracranial pressure (ICP) was monitored as well. Seven patients with acute ICH, who were undergoing ICP monitoring as part of standard neurocritical care, had placement of a frontal oxygen probe, with subsequent monitoring for up to 7 days.

Results: In the swine ICH model, a rise in ICP early after hematoma formation was accompanied by a decrease in ipsilateral and contralateral $P_{br}O_2$. Secondary increases in hematoma volume resulted in further decreases in $P_{br}O_2$ over the first hour after ICH. In patients undergoing oxygen monitoring, low $P_{br}O_2$ (<15 mmHg) was common. In these patients, changes in F_iO_2, mean arterial pressure, and cerebral perfusion pressure (but not ICP) predicted subsequent change in $P_{br}O_2$.

Conclusion: Brain tissue oxygen monitoring is feasible in ICH patients, as well as in a swine model of ICH. Translational research that emphasizes complementary information derived from human and animal studies may yield additional insights not available from either alone.

Key Words: Intracerebral hemorrhage; brain tissue oxygen tension; translational research; swine model.

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Introduction

Monitoring of brain tissue oxygen tension is an emerging tool for detection and treatment of secondary injury in neurocritical care. Its use has been extensively described in observational clinical research studies involving patients with traumatic brain injury (TBI), and to a lesser extent, aneurysmal subarachnoid hemorrhage (SAH) *(1–8)*. In these studies, a brain tissue oxygen tension below certain levels (usually around 15 mmHg) has been associated with a worsened outcome. That longer durations of low brain tissue oxygen tension ($P_{br}O_2$) seem to worsen outcome suggests a dose–response relationship *(9)* and has led some to begin to use brain tissue oxygen-guided treatment as a supplement to routine management *(1)* and

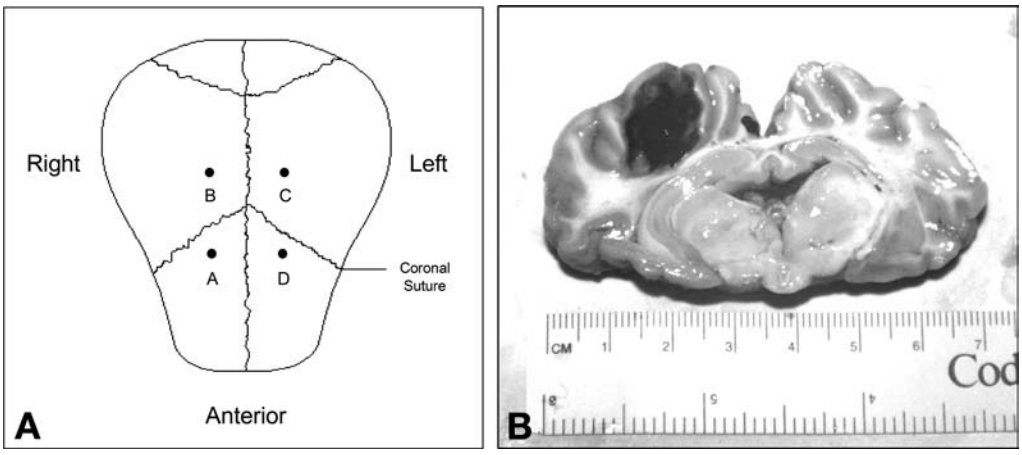

Fig. 1. Swine ICH model. **(A)** Diagram of the location of placement of the two brain tissue oxygen probes (A and D), the ICP monitor (C), and the spinal needle for ICH hematoma formation (B). **(B)** Coronal section through a swine brain demonstrating the right parietal hematoma. This hematoma would be analogous to a human lobar ICH with a volume of approximately 60 mL.

to propose prospective clinical trials of raising $P_{br}O_2$ in hopes of improving outcome after head trauma. These clinical studies of $P_{br}O_2$ monitoring, and a small number of animal studies *(10–12)*, also have provided new insight into injury mechanisms in these diseases. However, the usefulness of $P_{br}O_2$ monitoring in acute nontraumatic intracerebral hemorrhage (ICH) has not been reported.

ICH remains a challenging and difficult disease to treat. At present, there are no medical or surgical treatments of proven efficacy in reducing mortality or morbidity after ICH. In fact, the mechanisms of brain injury after ICH remain a point of debate. Previously, it was hypothesized that perihematoma ischemia was an important contributor (*13,14*). However, more recent animal studies and some small studies of physiological neuroimaging in humans have not supported this view *(15–18)*. New approaches that emphasize the importance of thrombin-related brain injury and early hematoma expansion seem to have merit *(19–22)*. It may be that advanced neuromonitoring of cerebral metabolism could provide new information on mechanisms of primary and secondary brain injury and potential treatment paradigms in ICH, just as it has begun to do in TBI and SAH. A translational research approach involving similar monitoring techniques in humans and in animal models could potentially help clarify this issue.

The purpose of this article is to describe our initial experience with $P_{br}O_2$ monitoring in patients with ICH as well as insight gained from pilot studies in a large animal swine ICH model. The swine model allows assessment of events early after ICH, whereas human studies allow for ongoing monitoring for several days in the neurocritical care unit. Thus, they provide complementary information that may lend new insight into ICH pathophysiology.

Methods

The animal experimental protocol was approved by the Committee on Animal Research at the University of California, San Francisco (UCSF). All experiments were performed in the UCSF Experimental Surgery Laboratory. Institutional review board approval was provided by the Committee on Human Research at the University of California, San Francisco, for the patient-based aspects of this study. Adults with nontraumatic intracerebral hemorrhage treated at San Francisco General Hospital who were undergoing intracranial pressure (ICP) monitoring as part of standard care were eligible for this study. Because all of the study patients were obtunded or comatose, informed consent was obtained for participation from a legally authorized surrogate in all cases.

Swine ICH Model

Four male Yorkshire swine weighing approximately 40 kg were studied. After intubation, anesthesia was maintained with a fentanyl infusion (1 µg/kg/hour) and inhaled isoflurane (1.0–1.5%). F_iO_2 was maintained constant at 0.3 or 0.4 throughout the experiment. The swine were paralyzed initially with 0.05 mg/kg pancuronium and received supplemental bolus injections as needed. Body temperature of 38.5 ± 1.0°C was maintained using a forced air warmer (BAIR Hugger, Augustine Medical, Eden Prairie, MN). Hemodynamic monitoring included heart rate and arterial blood pressure. Respiratory rate, tidal volume, end-tidal CO_2, end-tidal isoflurane, and F_iO_2 were monitored with a Capnomac II (Datex, Tewksbury, MA). Oxygen saturation was monitored with a pulse oximeter (Spacelabs Medical, Bellevue, WA). In all animals, four burr holes were made for the placement of a left parietal ICP monitor (Codman, Raynham, MA), two $P_{br}O_2$ monitors (one in each frontal region), and for ICH hematoma formation (right parietal) (Figure 1).

$P_{br}O_2$ was measured directly with the Licox Clark-type polarographic PO_2 probe (Integra Neurosciences, Plainsboro, NJ). Brain temperature was measured concurrently using a companion Licox temperature probe; $P_{br}O_2$ was then corrected for temperature by using the Licox computer. Probes were placed at a tip depth of approximately 10 mm below the dura to target frontal white matter. Initial PO_2 probe placement was undertaken at an F_iO_2 of 0.30; F_iO_2 was then raised to 1.0 and appropriate response confirmed the function of all probes used in this study.

After induction of anesthesia and monitor and probe placement, animals were allowed to stabilize for at least 1 hour before initiating any further experimental procedure. Baseline parameters were recorded, including mean arterial pressure, ICP, end-tidal carbon dioxide (ET-CO_2) concentration, and $P_{br}O_2$. Ventilation was adjusted for a target baseline ET-CO_2 of 40 mmHg. A right parietal ICH was then created using a modification of the method described by Qureshi *(15,23)*. A 22-gage spinal needle was introduced into the right parietal burr hole, angled 20° lateral to the vertical axis, and the tip advanced 2.0 cm to target deep white matter. Polyvinyl chloride tubing was attached to a stopcock at the distal end of the spinal needle and to the femoral artery. At the initiation of hematoma formation, autologous blood was introduced into the brain under arterial pressure via this tubing. To create different experimental paradigms of hematoma formation (timing and volumes), autologous blood also may have been injected via this system under manual pressure using a syringe attached to an intermediate stopcock. Physiological data were recorded at 1-minute intervals during the experiment via a custom-made data acquisition system.

ICH Patient Brain Tissue Oxygen Monitoring and Clinical Management

All patients underwent placement of a Licox Clarke-type oxygen electrode through a multilumen cranial bolt. The tip of the oxygen electrode was placed approximately 26 mm below the dura into the frontal white matter of the hemisphere ipsilateral to the intracerebral hemorrhage (five subjects), contralateral white matter (one subject), or right frontal white matter (one subject with a cerebellar ICH). A concurrent brain temperature probe was placed as well and $P_{br}O_2$ levels were automatically corrected for brain temperature by using the Licox computer. As part of standard care, a ventriculostomy, which was not part of the brain oxygen probe assembly, also was placed in each patient to monitor and treat ICP. Patients were managed with attention to established guidelines *(24)*, and all patients had previously been intubated as part of their regular ICH care. Only one subject (who had a cerebellar ICH) underwent surgical hematoma evacuation. In the intensive care unit, physiological information including $P_{br}O_2$, brain temperature, ICP, arterial blood pressure, heart rate, body temperature, respiratory rate, and F_iO_2 were recorded at 1-minute intervals via a custom made data acquisition system in six patients. In one patient, data were recorded at intermittent (usually hourly) intervals into the patient care record. Soon after oxygen probe placement, an oxygen challenge was performed by raising the F_iO_2 to 1.0 for approximately 20 minutes to determine probe responsiveness and viability. These oxygen challenges were repeated at least daily to assess oxygen probe function. All patients underwent noncontrast computed tomography (CT) scanning after oxygen probe placement to verify probe location. Brain oxygen monitors were removed after 7 days (five subjects), when the patient was extubated (one subject), or if the probe was deemed nonfunctional (one subject). No alterations in patient care were made directly based on $P_{br}O_2$ levels. Outcome was assessed as mortality during initial hospitalization and score on the modified Rankin Scale at 6-months post-ICH.

Data Analysis

Before analysis, recorded patient and swine data were cleaned by removing values if they represented extremes outside the range of physiological possibility (e.g., an ICP of 16777215, BP or T values of 0) because these represented artifact likely due to inadvertent monitor disconnection or monitor disconnection during patient transport. Additionally, because initial $P_{br}O_2$ values may be unstable immediately after probe placement, patient brain tissue oxygen data were discarded until the $P_{br}O_2$ equilibrated (usually 1 to 2 hours postinsertion). Otherwise, no systematic cleaning of data was performed. Patient data were then exported into a text file for import into a custom-written LabView-based software algorithm that determined the number of events, the cumulative duration of events, and the cumulative dose (defined as area under the curve below a threshold) for low brain tissue oxygen tension (<15 mmHg). For data collected every minute, this software algorithm used a filter that included only events that lasted at least 5 minutes to eliminate artifactual data, as has been described previously *(25,26)*. For noncontinuous data, the trapezoidal method of data interpolation was used.

For patient data, to assess how changes in physiological parameters influence $P_{br}O_2$, time-series multivariable linear regression was performed using a generalized least squares random effects model with a first-order autoregressive disturbance term. Lagged values of ICP, mean arterial pressure (MAP), and F_iO_2 for the preceding 10 minutes were entered into the model. In this manner, the independent impact of these parameters on subsequent changes in $P_{br}O_2$ could be determined. Because cerebral perfusion pressure (CPP) was collinear with ICP, the impact of changes in CPP on $P_{br}O_2$ was investigated alone in a similar model adjusting for F_iO_2. All statistical analyses were performed using Stata 8.0 (Stata, College Station, TX), and $p < 0.05$ was considered statistically significant.

Results

Brain tissue oxygen monitoring was successful in all four swine studied. Because this study represented an initial pilot study with the purpose of investigating the feasibility of assessing $P_{br}O_2$ early after ICH, four different experimental paradigms of ICH formation were undertaken. Figure 2 is a graphical representation of the time course of ICP as well as ipsilateral and contralateral (to the hematoma) $P_{br}O_2$ within the first minutes after ICH. The four different paradigms investigated included an initial large hematoma followed by several additional increases in hematoma volume (swine 1), single rapid monophasic hematoma formation (swine 2), an initial large hematoma followed by a smaller volume increase analogous to early rebleeding (swine 3), and a very large hematoma created over a lengthier time period (swine 4). For reference, a 6-mL hemorrhage in swine would be roughly analogous to a 60-mL hemorrhage in humans.

In all four swine, ICH creation resulted in an increase in ICP beginning about 2 to 3 minutes after initiation of hematoma formation. This increase was accompanied by a decline in both ipsilateral and contralateral $P_{br}O_2$ (Figure 2). In general, ipsilateral $P_{br}O_2$ declined more precipitously from its prehemorrhage baseline and remained lower for a longer duration

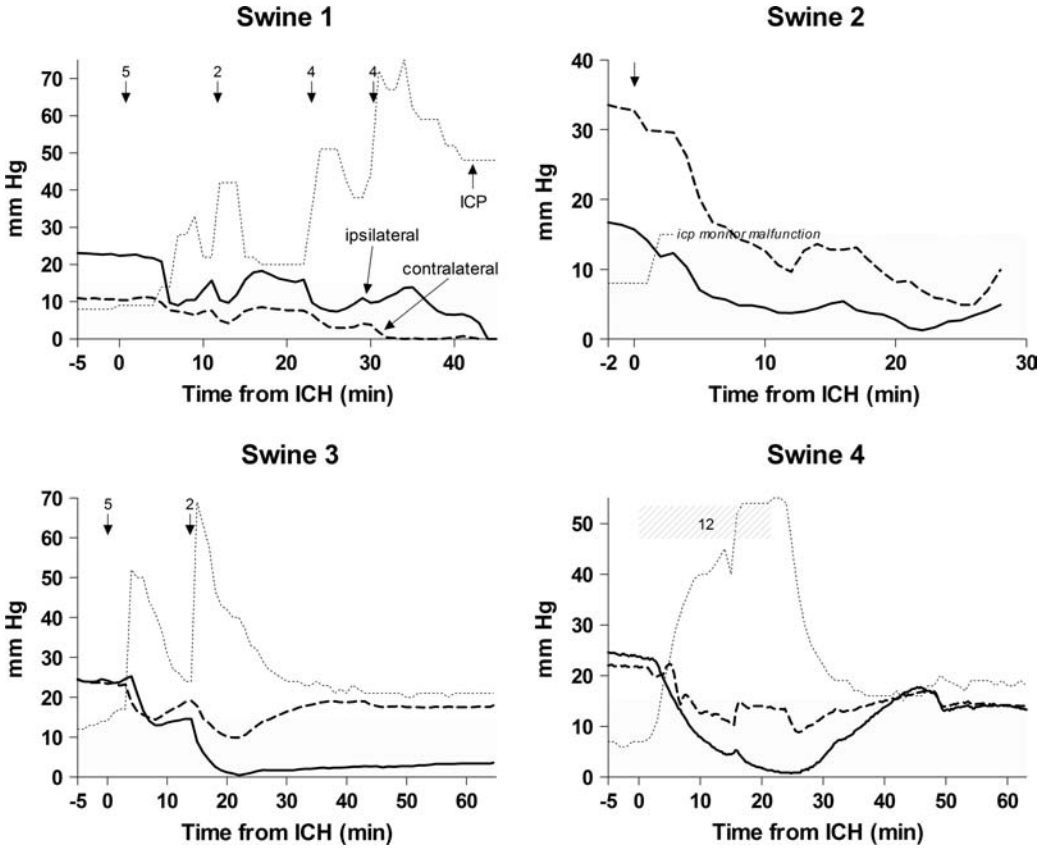

Fig. 2. Brain tissue oxygen tension and intracranial pressure profiles early after ICH in the swine model. Each graph demonstrates $P_{br}O_2$ from the probe ipsilateral to the ICH (solid line), $P_{br}O_2$ contralateral to the ICH (dashed line), and ICP (dotted line). In swine 1–3, the arrows indicate the point in time at which blood was injected (over approximately 2 minutes) to form the hematoma and the volume of blood injected in milliliters (when available). In swine 4, 12 mL was slowly infused over 23 minutes. Note that each swine represents a different potential pattern of ICH formation. The region below 15 mmHg is shaded because this region is often considered the threshold for low $P_{br}O_2$.

than contralateral $P_{br}O_2$. In all cases, both ipsilateral and contralateral $P_{br}O_2$ dropped below the 15 mmHg threshold for at least some time. In the two swine (1 and 3) that underwent multiple volume instillations, ICP peaked and $P_{br}O_2$ reached a nadir, and both began to improve before the next blood injection. This response presumably represents volume compensation after a dramatic volume-pressure response in the context of an acute intracranial mass lesion. Then, with additional increase in hematoma volume, ICP progressively increased and $P_{br}O_2$ decreased. Interestingly, different experimental paradigms had different relative effects on ipsilateral and contralateral $P_{br}O_2$. In swine 1 and 2, contralateral $P_{br}O_2$ was affected to a similar or somewhat greater degree than ipsilateral $P_{br}O_2$, whereas in swine 3 and 4, ipsilateral $P_{br}O_2$ recovered less quickly (swine 4) than contralateral $P_{br}O_2$ or not at all (swine 3). Throughout each experiment, F_iO_2 and $ETCO_2$ remained constant; in several instances, arterial blood pressure increased slightly with an increase in ICP (data not shown). Brain inspection after experiment conclusion did not demonstrate location of the oxygen probe tip within the hematoma, suggesting that low oxygen readings were reliable.

Seven patients (five men, two women) with acute ICH underwent brain tissue oxygen monitoring. Table 1 provides a summary of the characteristics of these patients as well as the $P_{br}O_2$ values during monitoring. Of the six patients with supratentorial location of their ICH, the oxygen probe was placed in the frontal white matter ipsilateral to the hemorrhage in all but one. One patient with a cerebellar hemorrhage had a right frontal oxygen probe placed at the time of surgical hematoma evacuation. The median time from ICH onset to oxygen probe placement was 15 hours (range 12–161), and the median time from emergency department arrival to oxygen probe placement was 14 hours (range 8–88). Mean ICH hematoma volume was 16.3 ± 12.7 mL. One patient sustained a 1-cm hematoma at the site of oxygen probe placement that was thought to be due to drill bit penetration noted at the time of placement. This hematoma was clinically asymptomatic, and no patient developed neurological worsening in the context of oxygen probe placement.

A common concern in brain tissue oxygen monitoring is the validity of early values after probe placement and the ability to ensure that the probe is functional. Figure 3 shows the $P_{br}O_2$ values for the first several hours after probe placement for the six patients in whom these data were acquired. A way to test probe reactivity after placement involves an "oxygen challenge" in which the ventilator F_iO_2 is increased to 1.0 for a short time, with the expectation that $P_{br}O_2$ values also should rise. In Figure 3, F_iO_2 is represented by the shaded area. In all

Table 1
Characteristics of Patients Undergoing Brain Tissue Oxygen Monitoring

							$P_{br}O_2$				
Patient	*Age/gender*	*GCS*	*ICH cause*	*6-Month Rankin*	*ICH location (side)*	*Side of $P_{br}O_2$ probe*	*Days monitored*	*Minimum (mmHg)*	*No. of events <15 mmHg*	*Duration (hours) <15 mmHg*	*Dose* <15 mmHg*
1	61/M	13	Hypertension	5	Thalamus (L)	Left	7.8	6.1	87	54.7	145.3
2	32/M	9	Tumor	3	Basal ganglia (L)	Left	6.7	2.2	10	17.3	142.7
3	48/M	4	Drugs (cocaine)	3	Thalamus (R)	Right	1.6	13.7	4	0.7	0.2
4	49/M	3	Hypertension	2	Cerebellum (L)	Right	8.8	9.3	4	10.2	33.2
5	46/F	3	Hypertension	2	Basal ganglia (R)	Right	7.7	15.9	0	0	0
6	48/F	11	Hypertension	6 (died)	Thalamus (R)	Right	6.8	10.3	2	6.4	14.0
7	48/M	7	Hypertension	3	Thalamus (L)	Right	1.5		Oxygen probe nonfunctional		

M, male; F, female; GCS, Glasgow Coma Scale score on emergency department discharge; $P_{br}O_2$, brain tissue oxygen tension, note:all probes were placed in frontal white matter; Rankin, modified Rankin Scale score; *, dose is determined as "area under the curve" below specified threshold; only $P_{br}O_2$ data from after probe equilibration is included.

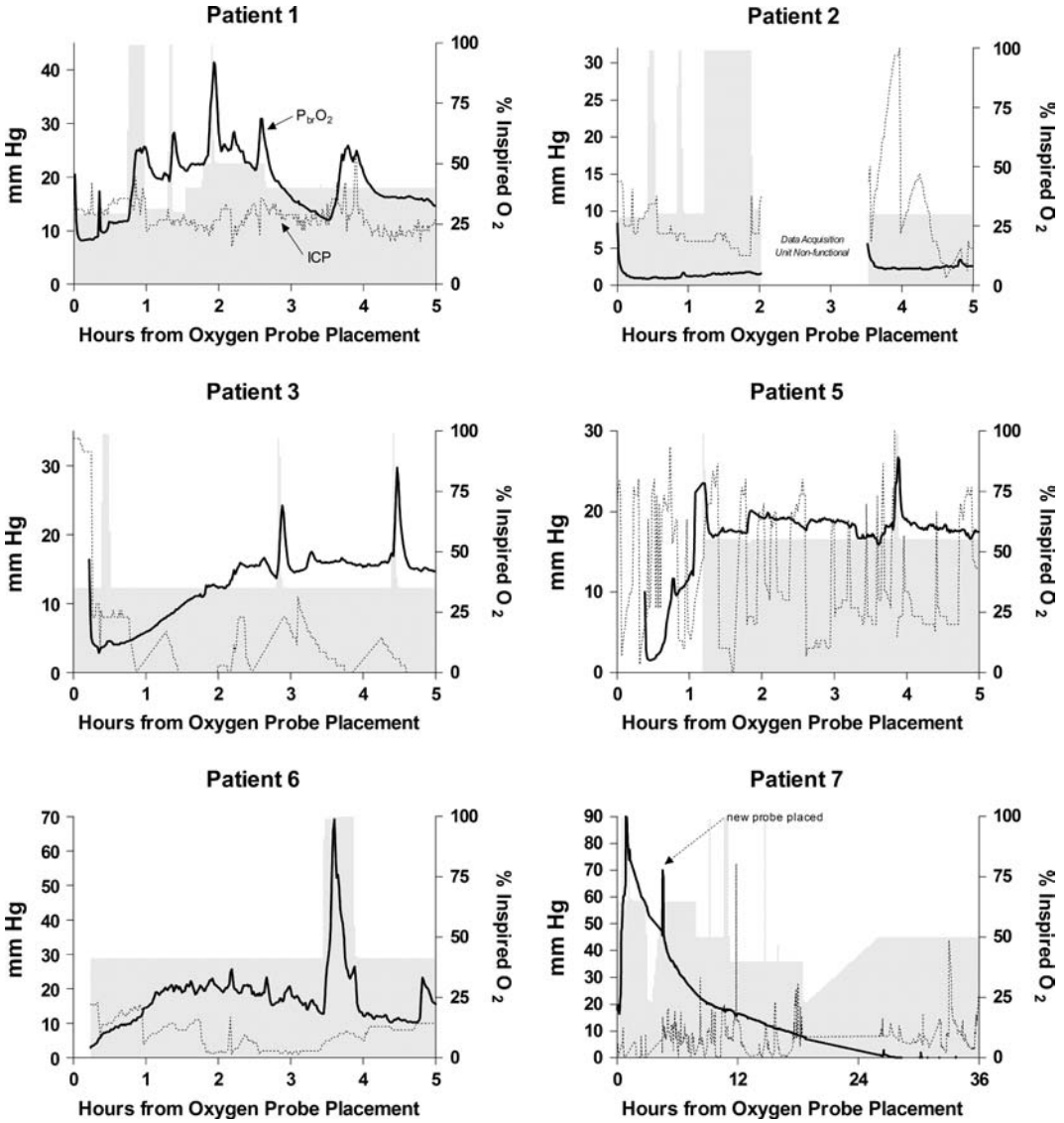

Fig. 3. Brain tissue oxygen tension and intracranial pressure profiles early after probe placement in patients. All PbrO2 values are shown (solid line), although values were not considered reliable until they initially stabilized (usually about 1 to 2 hours after placement). ICP (dotted line) and PbrO2 are referenced to the left axis. The shaded regions demonstrate FiO2 (right axis). During oxygen challenge (temporarily raising FiO2 to 1.0), PbrO2 usually increases, indicating a functional probe. In patient 7, the probe was never functional, and the tip was found on CT to be located in a small hematoma (*see* Figure 4). (Patient 4 is not shown as data was only collected hourly.)

patients except for patient 7, oxygen challenge was accompanied by some rise in $P_{br}O_2$ with return to baseline when F_iO_2 was subsequently decreased. In patient 7, the oxygen probe did not react as expected, and a new probe was placed that also did not react to oxygen challenge. Follow-up CT demonstrated that the probe tip was located in a small hematoma (Figure 4B). Figure 3 also demonstrates that initial $P_{br}O_2$ values are often very high or low and likely are not reliable. Visual inspection of each patient's data demonstrates that after 1 to 2 hours brain tissue oxygen values tend to equilibrate, and it is at this point that we consider the values reliable for use. In patient 7, $P_{br}O_2$ never equilibrated, instead moving steadily towards zero, at which time this nonfunctional probe was removed.

Low brain tissue oxygen tension (<15 mmHg) occurred in all but one of the six patients in whom monitoring was successful. The number of events of low $P_{br}O_2$, cumulative duration, and total dose of low $P_{br}O_2$ (as represented by the area of the $P_{br}O_2$ curve below the 15 mmHg threshold and above the $P_{br}O_2$ value) varied across patients. Of a total of 107 events of low $P_{br}O_2$ that occurred in these patients, 74 involved a $P_{br}O_2$ of 10–15 mmHg, 31 involved a $P_{br}O_2$ of 5–10 mmHg, and in only two episodes was the $P_{br}O_2$ <5 mmHg. Of the episodes of $P_{br}O_2$ from 10 to 15 mmHg, only 15 (20%) occurred in the context of low CPP (<70 mmHg), and in none of these events was ICP elevated (>20 mmHg). For the episodes of $P_{br}O_2$ ranging from 5 to 10 mmHg, 20 (65%) were associated with low CPP, and two of these episodes also had elevated ICP.

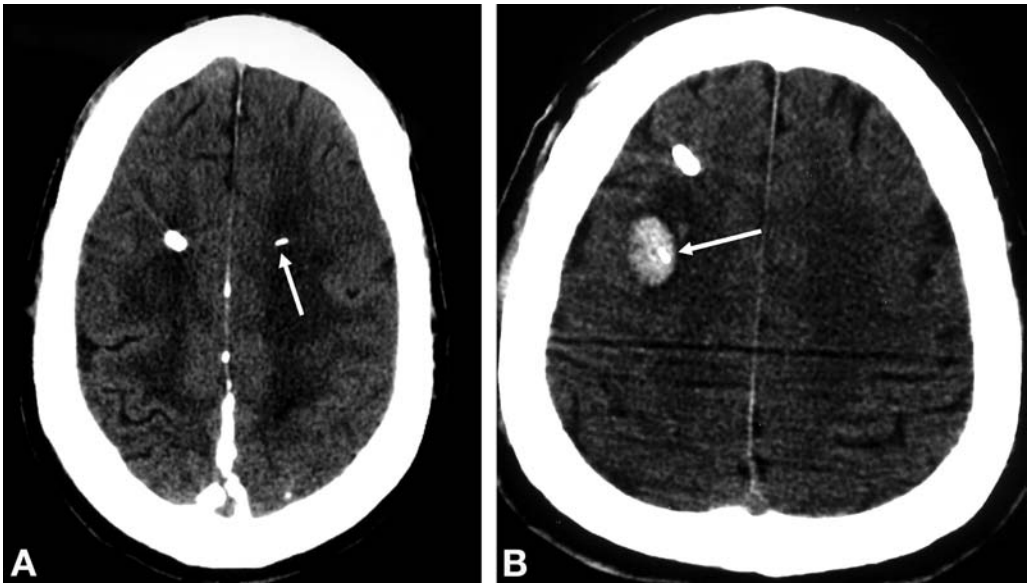

Fig. 4. Noncontrast CT scans demonstrating brain tissue oxygen probe tip location. Patient 1 **(A)** had a functional oxygen probe with the tip located in white matter ipsilateral to a thalamic hemorrhage. Patient 7 **(B)** had a nonfunctional oxygen probe because the tip was located in a hematoma that resulted from an insertion drill bit. The hematoma was clinically asymptomatic. The white arrows in A and B indicate the oxygen probe tips. The larger hyperdensities are ventriculostomy catheters.

Of the two episodes of extremely low $P_{br}O_2$, one of these occurred concurrently with low CPP (and nonelevated ICP). Thus, the majority of episodes of modestly low $P_{br}O_2$ occurred without concurrent systemic changes in CPP or ICP. However, most (but not all) episodes of significantly lower $P_{br}O_2$ (<10 mmHg) were associated with low CPP. Because of the small patient sample size, the relationship between $P_{br}O_2$ and outcome could not be reliably assessed.

To determine whether changes in systemic physiological parameters such as MAP, ICP, CPP, and F_iO_2 lead to changes in $P_{br}O_2$, multivariable time-series regression was undertaken using time-lagged variables. This regression allowed for the influence of parameters on the future values of $P_{br}O_2$ to be assessed. As demonstrated in Table 2, changes in F_iO_2 and MAP are independently predictive of a subsequent change in $P_{br}O_2$ several minutes later. The strongest effect of F_iO_2 on $P_{br}O_2$ occurs about 2 minutes after a change in F_iO_2 (largest coefficient) with the effect gradually diminishing over the next 9 minutes (gradual diminution in size of coefficient). The effect of MAP on $P_{br}O_2$ was less pronounced, but it was significant, with a change in MAP associated with a subsequent change in $P_{br}O_2$ 1 to 2 minutes later. In contrast, a change in ICP was not independently associated with a later change in $P_{br}O_2$ (as seen by very small coefficient values and nonsignificant or barely significant *p* values). The effect of a change in F_iO_2 was stronger than the effect of a change in MAP on $P_{br}O_2$, with a change of 0.1 in F_iO_2 overall associated with a maximal change in $P_{br}O_2$ of 1.52 mmHg, whereas a change in MAP of 10 mmHg was associated with a maximal change in $P_{br}O_2$ of 0.41 mmHg throughout the entire monitoring period. A separate model assessing CPP (adjusting for F_iO_2) found similar values as for MAP.

Discussion

This is the first report to detail brain tissue oxygen monitoring in a series of patients with nontraumatic intracerebral hemorrhage. It also is the first report, to our knowledge, to describe $P_{br}O_2$ monitoring using a parenchymal tissue oxygen probe in an animal ICH model. Given that brain tissue oxygen monitoring has been extensively described in other neurocritical care disorders such as traumatic brain injury, aneurysmal subarachnoid hemorrhage, and even ischemic stroke *(3,8,27–32)*, it seems reasonable that the feasibility and usefulness of this technique be investigated in ICH. Additionally, we suggest that a translational research approach that uses similar monitoring methods in patients and in clinically relevant animal models may provide important insights into disease pathophysiology and potential treatments that may not be apparent from either alone.

In our pilot swine model of ICH, brain tissue oxygen tension was affected by acute hematoma formation, declining in parallel with acute increases in ICP. However, in some instances, $P_{br}O_2$ remained low despite a return of ICP to near normal levels. This response suggests that $P_{br}O_2$ monitoring may potentially provide information about local events that are not reflected by global increases in ICP or systemic CPP. In patients, changes in F_iO_2, MAP, and CPP, but not ICP, were predictive of subsequent changes in brain tissue oxygen tension. However, no patient had a dramatic acute rise in ICP during the period of monitoring (suggestive of the formation of a new acute intracranial mass lesion as in the animal model). Even so, many events of low $P_{br}O_2$ in these patients were not accompanied by low CPP. Together, this suggests that during most periods of monitoring, systemic oxygen concentration (F_iO_2) and

Table 2
Multivariable Assessment of Influence of Physiological Changes on $P_{br}O_2$

Parameter	*Minutes after change in parameter*	*Coefficient*	*95% Confidence interval*			p
	Concurrent	– 0.12	– 0.22	to	– 0.02	0.02
	1	– 0.08	– 0.19	to	0.02	0.11
	2	– 0.02	– 0.12	to	0.09	0.75
	3	– 0.02	– 0.13	to	0.08	0.65
	4	– 0.12	– 0.22	to	– 0.01	0.03
ICP	5	– 0.11	– 0.21	to	0.00	0.04
	6	– 0.01	– 0.11	to	0.10	0.92
	7	– 0.01	– 0.11	to	0.10	0.92
	8	– 0.06	– 0.17	to	0.04	0.23
	9	– 0.04	– 0.15	to	0.06	0.41
	10	– 0.03	– 0.13	to	0.07	0.56
	Concurrent	0.05	0.01	to	0.09	0.02
	1	1.08	1.04	to	1.12	<0.001
	2	1.52	1.48	to	1.56	<0.001
	3	1.02	0.98	to	1.06	<0.001
	4	0.60	0.55	to	0.64	<0.001
F_iO_2	5	0.37	0.33	to	0.41	<0.001
	6	0.29	0.25	to	0.34	<0.001
	7	0.15	0.11	to	0.20	<0.001
	8	0.10	0.06	to	0.14	<0.001
	9	0.07	0.03	to	0.10	<0.001
	10	0.02	– 0.02	to	0.05	0.43
	Concurrent	0.15	0.11	to	0.19	<0.001
	1	0.47	0.43	to	0.51	<0.001
	2	0.31	0.27	to	0.36	<0.001
	3	0.13	0.09	to	0.17	<0.001
	4	0.02	– 0.02	to	0.07	0.27
MAP	5	0.03	– 0.02	to	0.07	0.21
	6	0.01	– 0.03	to	0.05	0.58
	7	0.05	0.00	to	0.09	0.03
	8	0.04	0.00	to	0.09	0.05
	9	0.04	0.00	to	0.09	0.05
	10	0.03	– 0.01	to	0.07	0.13

ICP and MAP are expressed per 10 mmHg; F_iO_2 is expressed per 0.1 change.

systemic perfusion (MAP), but not intracranial pressure, have important independent influences on $P_{br}O_2$, but acute dramatic rises in ICP (likely with diminished CPP) may markedly affect $P_{br}O_2$. Thus, although $P_{br}O_2$ may be altered by acute events that may be reflected in abnormalities in other physiological parameters such as blood pressure, systemic oxygenation, and ICP, it may be abnormal on its own as well. This situation lends credence to the idea that multimodal monitoring provides a more comprehensive picture of intracranial events in neurocritical care. This type of monitoring has certainly been an emerging emphasis in TBI and SAH *(28, 32–35)* and may have merit in ICH as well.

There are major limitations to both the swine and patient studies as presented here. Most importantly, these are pilot studies to assess the feasibility of brain tissue oxygen monitoring in these contexts. Thus, no major conclusions regarding the usefulness of $P_{br}O_2$ monitoring for detection of secondary brain injury or impact on outcome can be made. The swine model tested a different experimental paradigm in each animal. One of the most important issues in translational research is that animal models must represent clinically relevant models of human disease. ICH itself is a clinically heterogeneous disorder with epidemiological studies identifying several different factors, including hematoma location, size, Glasgow Coma Scale score, amount of intraventricular hemorrhage and old age, which are independently predictive of patient outcome *(36–41)*. Different prior ICH animal models have used rodents, larger animals (dogs, rabbits, or pigs) and primates, with some using mechanical external blood injections (such as ours) whereas others have used bacterial collagenase injection to create the hematoma *(13–15,42–45)*. Each of these models may have merit depending on the specific research question. However, we feel that large animal models (rather than rodents) are most relevant for studies related to hematoma mass effect, specifically because these animals have gyrencephalic brains analogous to humans, whereas rodents have lissencephalic brains. Unfortunately, large animal models are more unwieldy, expensive, and time-consuming; consequently they may be less attractive to research funding agencies despite their relevance. Although the rete mirabile

found in swine may restrict their usefulness for large vessel ischemic stroke models, it is likely that the study of the cerebral hemodynamics of intracranial mass lesions is not significantly affected *(12,46)*. Of the four models tested in this study, model 4 may be the most clinically relevant, although model 3 better represents the circumstance of early rehemorrhage, which may occur in up to one-third of ICH patients *(47,48)*. Additional information not undertaken in these animal pilot studies, such as continuous measurement of local cerebral blood flow and histological examination of mechanisms of cell injury and death, would be important in more definitive studies using these animal ICH models. Limitations specific to the patient studies include the fact that $P_{br}O_2$ values are not reliable for the 1 to 2 hours until probe equilibration; this lack of reliability may be the result of microscopic injury at the probe interface at the time of insertion *(49)*. Determining whether the distance between the hematoma and the tip of the oxygen probe (or perhaps even a more complex interaction between hematoma size and distance to probe) influences the detection of low $P_{br}O_2$ will require a much larger patient cohort. Also, although brain tissue oxygen monitoring has been shown to be very safe, it is invasive and the potential for complications germane to placement of any intracranial monitor (including ICP monitors) exists.

A lingering question about brain tissue oxygen monitoring is, What exactly does $P_{br}O_2$ represent? Although previous studies have suggested an "ischemic threshold" around 15 mmHg, this value was established based on patient outcomes, not an experimentally biologically determined level at which ischemia occurs *(9,50)*. Although perihematoma ischemia was a prior concern in ICH (*14*), more recent animal models and human imaging studies have suggested that ischemia is not a major cause of peri-hematoma injury *(16,17,51)*. However, studies have found depressed blood flow after ICH *(13,52)*. We have previously shown that $P_{br}O_2$ is strongly correlated with cerebral blood flow (CBF) in normal anesthetized swine (*12*). We also found that $P_{br}O_2$ is correlated with parameters from CT perfusion studies, specifically mean transit time *(53)*. Others also have found a relationship between $P_{br}O_2$ and CBF *(54–56)*. However, it is also clear from oxygen challenge tests in patients and swine that a change in F_iO_2 alters $P_{br}O_2$. It may be that brain tissue oxygen tension represents an interrelationship among several physiological processes, including perfusion, systemic oxygenation, and perhaps even local oxygen extraction fraction.

An additional challenge in patient studies is to establish that a monitoring technique or strategy leads to improved patient outcome. In actuality, this is a daunting task that would probably require a large randomized trial. It may be that this is not a necessary prerequisite for the use of advanced neuromonitors in neurocritical care. To date, there has not been a randomized clinical trial to verify the utility of ICP monitoring in improving outcome after head trauma, and many would consider performing such a trial as unethical. Yet, ICP monitoring is widely accepted as a useful and important tool. Likewise, $P_{br}O_2$ monitoring has been shown to be predictive of outcome, but randomized trials showing oxygen directed therapy as beneficial have not yet been performed. It seems more likely that the usefulness of advanced neuromonitoring with brain tissue oxygen probes, or other tools such as cerebral microdialysis or continuous quantitative CBF probes, is as part of a an overall milieu of multimodal monitoring that focuses attention on secondary brain injury after trauma and stroke.

Intracerebral hemorrhage remains a disease with high morbidity and mortality. Advanced neuromonitoring using tools such as brain tissue oxygen probes and cerebral microdialysis has emerged as an important direction in the study, and potentially the treatment, of other disorders in neurocritical care such as TBI, SAH, and ischemic stroke. ICH remains an understudied area. Whether $P_{br}O_2$ monitoring, cerebral microdialysis, or other advanced neuromonitoring techniques enhance the care of patients with ICH requires more study. Translational research is a two-way street; advances should proceed not only bench to bedside, but observations at the bedside should be used to improve the clinical relevance of basic research. Our preliminary studies of $P_{br}O_2$ in patients and swine can hopefully serve as an early point on this path to improving the neurocritical care of patients with ICH.

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