Title: Correlating brain tissue oxygen tension ($PbrO_2$) and regional cerebral oximetry (rSO_2) in normal human brain under the conditions of changing ventilation strategy

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ACRC Proposal

Correlating brain tissue oxygen tension ($PbrO_2$) and regional cerebral oximetry (rSO_2) in normal human brain under the conditions of changing ventilation strategy

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Hypothesis: We will test the hypothesis that there is a positive correlation between brain tissue oxygen ($PbrO_2$) and regional cerebral oximetry (rSO_2). Confirmation of this hypothesis would provide evidence that rSO_2 is a clinically useful surrogate marker of brain tissue oxygen.

Study type: Prospective cohort study.

Study population: Adult patients attending the University of Michigan Neurosurgical Unit for elective excision of secondary cerebral metastases.

Outcome measures: The change in brain tissue and regional cerebral oxygenation (dependent variables) resultant upon changes in inspired oxygen fraction and the partial pressure of carbon dioxide in arterial blood (independent variables).

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Introduction

Controversy surrounds the use of regional cerebral oximetry (rSO_2) as a measure of true cerebral oxygenation because extracranial contamination has been demonstrated for cerebral oximeters from several manufacturers.[1] An additional major concern is the unmeasured confounding effect of cerebral a:v ratio[2] which is assumed fixed within mathematical algorithms used in device software. Yet, cerebral oximetry has been employed in multiple clinical settings[3-5] and decreases below an absolute measure of 50% or relative decreases of 20% appear to correlate to cerebral ischemia.[2] Furthermore, low baseline values are associated with poor outcome.[6]

The measurement of brain tissue oxygen ($PbrO_2$) has been used in routine neurosurgery[7] and has been shown to reliably demonstrate cerebral hypoxia following severe head injury.[8] It is the most direct measure of cerebral oxygenation but probe insertion is highly invasive and hence precludes use outside of the neurosurgical or neurocritical care setting. Correlation between rSO_2 and jugular bulb monitoring has been demonstrated under conditions of varying inspired oxygen fraction (FIO_2) in both uninjured[9] and injured human brain[10] but no study has been specifically designed to compare $PbrO_2$ (the most reliable) and rSO_2 (the least invasive) as measures of cerebral oxygenation. Here, we test the hypothesis that there is a correlation between $PbrO_2$ and rSO_2 under conditions of varying inspired oxygen fraction and the varying partial pressure of carbon dioxide in arterial blood in uninjured, normal human brain. This study has the potential for a positive impact because confirmation of the hypothesis would validate cerebral oximetry as a surrogate of cerebral oxygenation.

Methods/Design

The primary aim of this prospective cohort study is to evaluate for correlation between $PbrO_2$ and rSO_2. The secondary aim is to investigate the relationship between combined changes in FIO_2 and the partial pressure of carbon dioxide in arterial blood (PaCO2) with both $PbrO_2$ and rSO_2 in un-injured human brain during general anesthesia.

Patients who are scheduled for elective removal of secondary cerebral metastases under general anesthesia will be recruited following written informed consent obtained by a study team member during their preoperative evaluation. This evaluation typically takes place at the surgeon's office or at a separate pre-operative clinic within 30 days of the scheduled surgical procedure. Patients will be excluded if they refuse to give consent, have evidence of elevated intracranial pressure on preoperative CT scan, have coagulopathy, are taking therapeutic agents known to increase bleeding risk, have a history of cardiovascular disease, cerebrovascular disease, suffer from respiratory failure, are scheduled for surgery in the prone position, or are not fluent English speakers. Since skin pigmentation may impact rSO_2 values[11] and the study is small, recruitment will be limited to Caucasian patients. All patients will undergo the same 2 step variation in ventilation strategy designed to maximize the potential changes in brain oxygenation.

Following pre-oxygenation, anesthesia will be induced using fentanyl (1-2mcg/kg) and propofol (0.5-2mg/kg). Muscle relaxation will be initiated and maintained with an appropriate combination of succinylcholine and non-depolarizing muscle relaxants as deemed necessary by their anesthesiologist and as dictated by the requirements of the particular surgical procedure.

The patient's trachea will be intubated and their lungs will be ventilated to achieve an FIO_2 and $PaCO_2$ determined by the study protocol. General anesthesia will be maintained by total intravenous anesthesia (TIVA) with a combination of propofol (80-150 mcg/kg/min) and remifentanil (0.05-0.1 mcg/kg/min) targeted to a Bispectral Index range 40-60 (BIS; Covidien, Boulder, CO).

Routine perioperative monitoring and invasive blood pressure monitoring will be used for all patients. rSO_2 will be measured using the INVOS 5100B monitor (Somanetics Corporation, Troy, MI) and PbO_2 using the LICOX brain tissue oxygen monitoring system (Integra LifeSciences Corporation, Plainsboro, NJ). BIS and rSO_2 optodes will be applied, before induction of anesthesia, by a single researcher on both sides of the patient's forehead, as recommended by the manufacturer. Baseline readings will be recorded in the pre-operative holding room with the patient sitting and breathing room air.

Following craniotomy, the LICOX probe will be placed under direct vision into an area of normal brain within the tumor excision canal by the attending neurosurgeon. The probe will secured in place and allowed to equilibrate as directed by the manufacturer. The starting tidal volume will be set at 6-8 mls/kg and adjustments will be made by changing respiratory rate rather than manipulating tidal volume further. During a pause in surgery FIO_2 and minute ventilation will be sequentially adjusted to achieve the following pairs of ventilation set points:

1) FIO_2 0.3 and paCO2 30mmHg

2) FIO_2 1.0 and paCO2 40mmHg

Changes in rSO_2 are complete and stable within 5 minutes following a change in inspired gas composition;[4] LICOX responds more rapidly. Thus, after ≥5 minutes at each set point FIO_2, PaCO2, rSO_2 and $PbrO_2$ will be recorded as a "snap-shot". Blood pressure, heart rate, hematocrit, BIS value and propofol and remifentanil infusion rates will also be recorded at each set point. The anesthesiologist caring for the patient will be blinded to the measures of cerebral oxygenation. N_2O, a possible confounding factor, will be avoided. Bolus dose phenylephrine is associated with a 2.8% reduction in rSO_2 of approximately 8 minutes duration[1121] and if required, the recording of results will be delayed in order to minimize this potential confounding effect. A total of two blood samples (2 teaspoons each) will be collected during the surgery through the arterial line, which is already in place for surgery. This will allow us to measure arterial blood gas and hematocrit levels. Demographic and intra-operative data will be retrieved from the patient's electronic anesthetic and medical records. The preliminary de-identified electronic data captured in this study will be retained for future use in a larger-scale study. No specimens will be retained for any reason as part of the research study.

Statistical analysis

A sample size of 15 achieves an 80% power with a one-sided type I error of 5% to detect a positive correlation of 0.6 (from the null hypothesis of no correlation) between changes in $PbrO_2$ and changes in rSO_2 subsequent on alterations made in ventilation strategy. Correlation will be measured using Pearson's Correlation. P values < 0.05 will be considered statistically significant.

Licox probe insertion and risk

PbrO2 monitoring is most typically utilized to guide blood pressure, oxygenation and intracranial pressure (ICP) management in patients with severe head injury; probes are inserted into the least injured cerebral hemisphere.[8,10] Device placement in head injured patients requires bolt placement through the skull. The Licox probe penetrates the dura, via the bolt and is held 1-2cm within brain parenchyma. Even with this highly invasive approach the technique is reported to be safe,[13] the main complication being hematoma which occurs in < 2% patients.[14] We anticipate that the risk of placing the probes under direct vision, following the craniotomy portion of surgery, into brain tissue that will ultimately be excised would be extremely low. In fact, despite extensive use within the operating room environment[7,15,16] complications have not been reported.

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