The Correlation Between Brain Near-Infrared Spectroscopy and Cerebral Blood Flow in Piglets with Intracranial Hypertension

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Running title: NIRS and CBF in increased intracranial pressure
Abstract

Cerebral perfusion pressure (CPP) is used as a surrogate for measurement of cerebral blood flow (CBF) but its determination requires that intracranial pressure be directly measured. Near-infrared spectroscopy (NIRS) can non-invasively measure tissue oxygenation. We hypothesized that NIRS would correlate well with CBF, with cerebral metabolism of oxygen (CMRO$_2$) and glucose and with lactate production as CPP was reduced. Seven anesthetized piglets were subjected to reductions in CPP to 60, 50, 40, 30 and 20 mmHg by infusing an artificial cerebral spinal fluid into the lateral ventricle of the brain. After a period of equilibration, NIRS over the left temporal cortex and regional CBF (microspheres) were measured at each CPP level as well as arterial and internal jugular PaO$_2$, glucose and lactate. CMRO$_2$ and glucose consumption and lactate production were calculated by standard formulae. NIRS correlated very well (p<0.05) with CBF in the left temporal cortex (mean r[95% CI] =0.95[0.91-0.99]) and with left hemispheric CMRO$_2$ (0.94[0.90-0.98]), glucose consumption (0.87[0.76-0.97]) and lactate production (0.89[0.81-0.97]). The correlation of NIRS with CBF was slightly better (p<0.05) than that of CPP with CBF (0.89[0.84-0.94]). In this model of global cerebral hypertension, NIRS correlated well with CBF and measures of cerebral metabolism and might be useful as a surrogate for CPP. Further studies are warranted to determine if NIRS is associated with these variables in focal cerebral injury.

Keywords: NIRS, near-infrared spectroscopy, ICP, cerebral hypertension, brain
Near-infrared spectroscopy (NIRS) can non-invasively measure tissue oxygenation but its usefulness in global cerebral ischemia has not been evaluated. By reducing cerebral perfusion pressure stepwise in an animal model, we found a strong correlation between NIRS and cerebral blood flow. This correlation was better than that between NIRS and cerebral perfusion pressure. Cerebral NIRS has great potential as a bedside monitor of brain blood flow in global cerebral hypertension.
Introduction

Neuronal viability is dependent upon an adequate amount of cerebral blood flow (CBF) to deliver oxygen, but in cerebral hypertension, increased intracranial pressure (ICP) may impede this. Since there is no simple bedside test to continuously monitor CBF, cerebral perfusion pressure (CPP) has been used as a surrogate in the management of patients with elevated ICP. However, CPP may not correlate well with measures of cerebral oxygen delivery and utilization and there is a need for alternative methods to guide treatment.

Near infrared spectroscopy (NIRS) is a non-invasive technique that can be used to monitor tissue oxygenation (9,12). The technology is based on the transmission and absorption of near-infrared light (700-1000 nm) at multiple wavelengths as it passes through tissue. NIRS allows monitoring of cerebral cortex using reflectance spectroscopy via optodes (light transmitting and detecting devices) placed on the scalp. Oxygenated and deoxygenated hemoglobin have different absorption spectra and cerebral oxygenation can be determined by their relative absorption of near infrared light. Thus, NIRS provides a continuous clinical measure of the balance between cerebral oxygen delivery and utilization. Although the saturation includes that from extracerebral tissue, it is thought that about 85% is derived from brain tissue (9).

Clinically, brain NIRS has been used as a marker for cerebral oxygenation during the intraoperative management of cardiopulmonary bypass and carotid endarterectomy (8,10,11,18). It has also been investigated for use in the management of adult and neonatal ischemic brain injury (1,3,6,14) and traumatic brain injury (22). However, the utility of NIRS in assisting in the management of cerebral hypertension has not been well assessed. No investigation has attempted to correlate brain NIRS values with CBF, cerebral metabolism of oxygen (CMRO$_2$) and glucose (CMR$_{glu}$) or cerebral lactate production in global cerebral hypertension.

In this investigation, we evaluated the use of NIRS for assessing brain oxygenation in piglets subjected to incremental decreases in CPP. We hypothesized that brain NIRS is an effective
tool to monitor CBF, CMRO$_2$, CMR$_{glu}$ and lactate production in global cerebral hypertension. We examined the correlation between brain NIRS values with CBF as CPP is reduced as well as the association of NIRS with CMRO$_2$, CMR$_{glu}$ and lactate production.
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Methods

Surgical Preparation

The study was approved by the Institutional Animal Use and Care Committee at Los Angeles BioMedical Research Institute. Immature Yucatan minipigs of either sex weighing 3.8 - 5.8 kilograms were induced with 7% sevoflurane and the animal was endotracheally intubated and mechanically ventilated (goal pCO$_2$ 45-55 torr). An esophageal temperature probe was inserted and then bilateral femoral arterial and venous catheters were placed by cutdown. The right side of the neck was bluntly dissected and after tying off the facial branch of the internal jugular vein, a catheter was placed retrograde into the right internal jugular catheter under direct vision to obtain cerebral venous blood samples. Subsequently, a median sternotomy was performed and the animal’s heart was exposed. A PE-10 polyethylene catheter (Clay Adams, Parsippany, NJ) was inserted into the left ventricle, secured in place and the sternum closed. This catheter was used to inject colored microspheres for the measurement of CBF.

The piglet was then placed prone in a stereotaxic frame, the scalp retracted and an infant OxyAlert NIRSensor (INVOS, Troy MI) was glued to the hemicranium over the left temporal area. A Camino ICP probe (Integra Life Sciences, Plainsboro, NJ) was inserted in the right parietal region 1 cm lateral to the sagittal suture and 1 cm posterior to the coronal suture and then a small thermocouple was placed in the cerebral cortex to measure brain temperature. Next, a 20-gauge spinal needle was inserted into the cerebral right lateral ventricle through a burr hole drilled 1 cm lateral to the sagittal suture and 1 cm anterior to the coronal suture at a 30 degree angle to the skull (7). Placement was confirmed by aspirating cerebral spinal fluid and identifying intracranial pressure waves.

Throughout the preparation, anesthesia was maintained with sevoflurane at 1-2% and a fentanyl infusion of 1 to 4 mcg/kg/hr. Prior to the median sternotomy, muscle relaxation with
vecuronium at 0.1-0.4 mg/kg/hr was initiated and continued throughout the study. At the end of
the protocol, the animal was sacrificed with Euthasol. Then, the brain was removed and stored
at 4°C until dissection the following day. A sample of kidney tissue was also collected.

Experimental protocol

After stabilization, 30 ml of blood was removed from the piglet into syringes filled with
150 units of heparin as 30 mL of Ringer’s lactate was administered intravenously. Baseline
measurements of MAP, ICP, NIRS and brain and esophageal temperatures were obtained and
arterial and cerebral venous samples were acquired to measure blood gases, hemoglobin,
glucose and lactate levels (i-STAT Abbott Point of Care Inc, NJ). Baseline CBF was measured
and then 6 ml of the stored blood was returned to the animal.

ICP was increased by infusing a mock CSF into the lateral ventricle thereby reducing
CPP. After 20 minutes of stabilization at a CPP of 60 mmHg, another set of arterial and cerebral
venous blood gases were obtained, CBF was measured and then 6 ml of the stored blood was
given to the animal. For each piglet, this procedure was repeated at CPPs of 50, 40, 30 and 20
mmHg. MAP, ICP, NIRS and brain and esophageal temperatures were continuously monitored
and recorded throughout the experiment. As necessary, MAP was supported with fluid boluses
and/or an epinephrine infusion.

To evaluate the effect of multiple microsphere injections on NIRS and regional CBF, two
animals underwent the experimental preparation without elevation of ICP. NIRS and CBF were
measured using the same timeline as if the animal was subjected to injury.

Measurement of Regional CBF
Regional CBF and renal blood flow were measured using the established colored microspheres technique (20). Dye-Trak VII+ microspheres (4.5-5.4 × 10^6 microspheres, Triton Technologies Inc, San Diego, CA) were sonicated for 1 minute and then injected into the left ventricle over 30-45 seconds. Starting just prior to the injection, arterial blood was drawn for reference at a rate of 3.0 mL per min for 120 seconds.

Tissue processing was performed as described by the manufacturer (19). Briefly, the brain was dissected into regions, the tissue placed into pre weighed centrifuge tubes and the net weight of the sample calculated. Samples typically ranged from 2 to 5 grams. As recommended, blue process control was utilized to account for loss of microspheres during processing. Alkaline digestion reagent was added to each of the tissue and reference blood samples and placed in an oven at 50°C for overnight digestion. Samples were then filtered using a 10 μm polyester filter membrane (Triton Technology, Inc., San Diego) and rinsed first with water and then ethyl alcohol. Once dry, the filter was carefully placed into a 15mL polypropylene centrifuge tube and acidified cellosolve acetate solution was added to each tube and the tube vortexed. After standing for one hour at room temperature, the filter was removed and the tubes centrifuged for 10 minutes at 1,500 X g at 25°C. Subsequently, the samples were analyzed spectrophotometrically at 670, 590, 545, 495, 440, and 390 nm. If absorbance was greater than 1.8, the sample was diluted with acidified cellosolve acetate and reread. Data were entered into a spreadsheet provided by the manufacturer that calculates blood flow and corrects the results for loss of spheres and, as recommended, it was verified that all regions contained a minimum of 400 spheres.

Data analysis
Physiologic variables MAP, ICP, brain and esophageal temperatures and NIRS were recorded every minute. Values were then averaged over the period of time from when the targeted CPP was achieved until the CBF measurement was completed. CPP was determined as the difference between MAP and ICP. Left hemispheric CMRO\textsubscript{2} was calculated by equation 1:

\begin{equation}
\text{CMRO}_2 = \text{left hemispheric CBF} \times (C_{aO_2} - C_{cvO_2})
\end{equation}

where \(C_{aO_2} = 1.34 \times \text{hemoglobin} \times \text{arterial O}_2 \text{Saturation} + 0.003 \ P_{aO_2}\)

and

\(C_{cvO_2} = 1.34 \text{hemoglobin} \times \text{cerebral venous O}_2 \text{saturation} + 0.003 \ P_{cvO_2}\)

To determine left hemispheric CBF, CBF from the left cerebrum, including the left frontal, temporal and occipital regions, caudate, hippocampus and thalamus were averaged. CMR\textsubscript{glu} was determined by multiplying the difference between the arterial and cerebral venous glucose levels by the left hemispheric CBF. Cerebral lactate production was calculated by subtracting the arterial lactate level from that in the cerebral venous blood and multiplying this by left hemispheric CBF.

Physiologic variables, blood gases, glucose and lactate and CBF were compared over the various CPPs using a repeated-measures ANOVA. Post-hoc testing utilized Fischer’s LSD. The correlation of brain NIRS or CPP with CBF, CMRO\textsubscript{2}, CMR\textsubscript{glu} and cerebral lactate production was determined using simple regression. After evaluating several models, the optimal one was determined to be power regression \((y = b + x^a)\). The correlation of CBF with brain NIRS and with CPP was compared using a paired t-test. NIRS measurements are reported as the actual percent saturation displayed on the instrument. A \(p<0.05\) was considered significant. Data are mean ± SD except correlation is reported as mean[95% confidence interval].
Results

In both sham-operated control piglets, NIRS was stable throughout the time course of the protocol (67.3% at baseline and 67.4% after the final CBF measurement in one animal, 73.9% and 76.4% in the other, respectively). In addition, CBF was not significantly altered by the multiple microsphere injections. In the left temporal region, the six CBFs (ml/min/100 grams) were 124.6, 87.2, 81.9, 78.9, 76.7, 103.7 and 82.8, 88.9, 82.0, 104.4, 94.4, 95.5 in the two piglets, respectively. The other regions in each animal showed similar results.

Seven piglets were subjected to the experimental procedure. As shown in Table 1, MAP did not differ (p >0.5) over the range of CPPs. As expected, the increase in ICP resulted in a decrease (p<0.05) in CPP and the measured CPPs were very close to the target. Brain temperature was stable throughout the experiment procedure, although it was slightly lower (p<0.05) at a CPP of 20, likely reflecting the severe decrease in CBF. In spite of the amount of blood withdrawn to measure CBF, hemoglobin did not change (p>0.05) throughout the study. pCO₂, and arterial and cerebral venous glucose and lactate were all elevated (p<0.05) at CPP 20 and greater than that at baseline. NIRS values were similar (p<0.05) at baseline, CPP 60 and CPP 50. However, at CPP 40 and lower, values were different from the other points (p<0.05).

Data for CBF in the various brain regions are presented in Table 2. In all regions, CBF did not differ (p>0.05) between baseline (mean CPP 86 ±12 mm Hg) and CPP 60. CBF declined as CPP decreased. In all regions, NIRS correlated well with CBF with mean r ranging from 0.88 to 0.97. Blood flow to the kidney was not different (p> 0.05) over time, consistent with the manipulation of only CPP and, as would be expected, NIRS correlated poorly with renal blood flow (r=0.60).
Figure 1 illustrates the relationship between NIRS and CBF in the left temporal region for each individual piglet. There was a strong association between the two variables with r ranging from 0.87 to 0.9 in the 7 animals. The average correlation coefficient for this region was 0.95 [0.91-0.99], significantly different (p<0.05) from r=0.

Data for CMRO\textsubscript{2}, CMR\textsubscript{glu} and cerebral lactate production in the left hemisphere at each CPP are shown in table 3. Below CPP 50, cerebral oxygen consumption and lactate production decreased (p<0.05) as CPP was reduced. Although brain glucose consumption declined as CPP decreased, these differences were not statistically significant (p>0.05). CMRO\textsubscript{2}, CMR\textsubscript{glu} and cerebral lactate production all correlated well with NIRS (p<0.05), although the correlation was highest with CMRO\textsubscript{2}.

Figure 2 displays the comparison of NIRS and CPP as CBF changes in the left temporal region. As CBF decreases, there are similar reductions in NIRS and CPP. Although CPP correlated well (p<0.05) with CBF (0.89 [0.84-0.94]), the correlation of NIRS with CBF was better (p<0.05) with a large effect size (Cohen’s d of 1.12).
Discussion

This is the first study to compare brain NIRS with CBF and measures of cerebral metabolism while the brain is subjected to incremental decreases in CPP. We found that brain NIRS is correlated with CBF, CMRO₂, CMR_{glu} and lactate production. In addition, the correlation between NIRS and CBF was better than that between CPP and CBF.

We used a model of global cerebral hypertension to allow for consistent measurement of CBF, CMRO₂ and CMR_{glu} and lactate production. We attempted to maintain the same level of anesthesia during the protocol so as to minimize the cerebral vasodilatory effects of the anesthetics. The actual CPP measurements were close to those that were targeted and MAP did not differ throughout the experiment. Brain temperature was stable at all CPPs except at 20 mm HG in which there was a slight decrease, likely reflecting the severe decrease in CBF at this CPP. The partial pressure of CO₂ was maintained at the normal levels of 45-55 for piglets (21), although it was slightly elevated at a CPP of 20 mm HG. By removing blood at the start of the protocol and then reinfusing after each microsphere injection, hemoglobin was unchanged and did not influence oxygen delivery. At the end of each experiment, correct placement of the internal jugular venous catheter was verified.

CBF was measured with colored microspheres, a method that has been previously validated in piglets. Walter et. al. (20) compared blood flow measured by colored microspheres with that determined using radioactive microspheres in uninjured piglets and noted an excellent correlation. Our values for CBF are comparable to those reported by others (16) as are our measurements of CMRO₂ (2,17). In addition, as shown in the sham-operated control animals, multiple injections of the microspheres did not alter the NIRS measurements or reduce CBF.

We found that the NIRS was highly correlated with CBF. Although the NIRS optode was placed over the left temporal region and measured tissue oxygen saturation in this area, there was a strong association between decreases in CBF with NIRS in all other regions of the brain. Only one previous investigation has evaluated the use of NIRS in intracranial hypertension.
Using a model similar to the one we used, Soul et al. (13) examined the relationship between cerebral oxygenation and CBF in piglets subjected to incremental increases in ICP by infusing a mock CSF into the lateral ventricle. These investigators calculated the difference (HbD) between oxygenated and deoxygenated blood in the brain as measured by the NIRS. They found that while there was a linear relationship between the changes in HbD with CPP, this was best described by a nonlinear sigmoidal curve. However, changes in HbD were directly associated with changes in CBF as was observed in our investigation. There was no attempt to correlate NIRS with CMRO$_2$.

NIRS has also been used to measure cerebral oxygenation in hypoxic-ischemic brain injury. Tichauer et al. (15) used NIRS to calculate CMRO$_2$ in piglets exposed to 30 minutes of hypoxemia-ischemia induced by bilateral carotid artery occlusion and breathing 8% oxygen. Similarly, Brown et al. (2) utilized the NIRS to evaluate the effects of indomethacin on CMRO$_2$ in piglets. As opposed to these studies, we calculated CMRO$_2$ independently of the NIRS. Nonetheless, we found a strong correlation between NIRS and CMRO$_2$ indicating that the NIRS can indeed be used as indirect measure of hemispheric CMRO$_2$.

Lactate production decreased, rather than increased, as CPP was reduced, an unanticipated finding. We expected that the amount of lactate measured in the internal jugular vein would increase as CBF was reduced, reflecting a shift to anaerobic metabolism. The measured lactate is dependent upon the amount generated and the amount utilized. Perhaps there was an increase in lactate utilization and less production. Dienel (4) proposed that lactate is an opportunistic glucose-sparing substrate in the brain. This investigator argued that when the brain is under stress, it can utilize lactate as a source of pyruvate. Consequently, the decreasing amount of lactate associated with the reduction in CBF could be attributed to increased utilization and less release of lactate by the brain. However, this point is controversial. In addition, Fillenz et al (5) showed that neuronal activation leads to a delayed rise in lactate followed by a slow decay. Perhaps with a longer period of observation, we would have found an
increase in venous lactate. However, this would not explain our observed decrease in brain lactate production.

In addition to NIRS, CPP was also strongly correlated with CBF. Although this association was not as strong as with NIRS and CBF, it is not clear that the difference is clinically important. If the two modalities have similar utility, what is the usefulness of NIRS? Measuring NIRS is noninvasive and the sensors are easy to place so it could be used earlier in the course of the illness before an ICP monitor can be inserted and CPP determined. Additionally, based on the information obtained from the NIRS, ICP monitoring may be deemed unnecessary. Furthermore, when a ventriculostomy is left open to drain, ICP cannot be measured and CPP is unknown. Consequently, the NIRS monitor could alert the clinician that the CPP is reduced.

There are several limitations to this investigation. While we found an excellent correlation between the NIRS with CBF, CMRO$_2$, CMR$_{glu}$ and cerebral lactate production, this was in a model of global cerebral hypertension. As a result, our data are only applicable to patients with conditions such as brain edema observed with diabetic ketoacidosis, meningitis/encephalitis or other cases of global cerebral ischemia. The applicability of these data to focal cerebral pathologies, such as traumatic brain injury and cerebral tumors, is unknown. We used only one NIRS optode and positioned it over the left temporal region but the instrument can utilize two optodes. This would allow placement over both sides of the cerebral cortex. To obtain hemispheric CBF, we used an average of those brain regions providing the majority of blood flow through the internal jugular vein assuming each provided an equal contribution. Although this may have introduced some error, this average is likely a reasonable approximation and our values for CMRO$_2$ are similar to those reported by others (2,17). Nonetheless, the measurements of CMRO$_2$, CMR$_{glu}$, and lactate production were global and it is possible that there were regional differences that were not detected. In addition, our measurements of arterial and venous oxygen saturations were calculated rather than directly
measured by oximetry but this likely introduced minimal error. One other limitation in this experiment was the time spent at each CPP level. While we believed that twenty minutes was adequate for stabilization, it might have been too short to observe changes in glucose metabolism. We conclude that cerebral NIRS has great potential as a bedside monitor of CBF in global cerebral hypertension. Further studies are needed to evaluate the utility of this instrument in focal brain injury.
Acknowledgement

We thank Covidien for loaning the INVOS® monitor and for providing the NIRS sensors.


Table 1: Physiologic parameters, blood gas values, glucose, lactate and hemoglobin at each CPP (mean ± SD).

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>CPP 60</th>
<th>CPP 50</th>
<th>CPP 40</th>
<th>CPP 30</th>
<th>CPP 20</th>
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<tr>
<td>Mean Arterial Pressure (mm Hg)</td>
<td>95 ± 10</td>
<td>92 ± 5</td>
<td>91 ± 6</td>
<td>89 ± 9</td>
<td>100 ± 27</td>
<td>100 ± 4</td>
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<td>Intracranial Pressure (mm Hg)</td>
<td>8 ± 3b-f</td>
<td>33 ± 5a,df</td>
<td>41 ± 2a,ef</td>
<td>49 ± 9ab,ef</td>
<td>70 ± 26ad</td>
<td>81 ± 4ad</td>
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<tr>
<td>Cerebral Perfusion Pressure (mm Hg)</td>
<td>86 ± 12b,f</td>
<td>59 ± 1ac,f</td>
<td>50 ± 1ab,df</td>
<td>40 ± 1ac,ef</td>
<td>30 ± 1ad, f</td>
<td>18 ± 5ae</td>
</tr>
<tr>
<td>Esophageal Temperature (°C)</td>
<td>38.4 ± 0.9</td>
<td>38.5 ± 0.8</td>
<td>38.6 ± 0.7</td>
<td>38.5 ± 0.8</td>
<td>38.5 ± 0.8</td>
<td>38.7 ± 0.9</td>
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<tr>
<td>Brain Temperature (°C)</td>
<td>38.3 ± 0.5f</td>
<td>38.5 ± 0.3f</td>
<td>38.4 ± 0.7f</td>
<td>38.2 ± 0.4f</td>
<td>38.2 ± 0.4f</td>
<td>37.7 ± 0.7ae</td>
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<td>NIRS (%)</td>
<td>60 ± 10d,f</td>
<td>59 ± 8d,f</td>
<td>56 ± 9d,f</td>
<td>47 ± 9ae, ef</td>
<td>30 ± 8ae, f</td>
<td>18 ± 5ae</td>
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<td>pH</td>
<td>7.43 ± 0.06e,f</td>
<td>7.42 ± 0.06e,f</td>
<td>7.43 ± 0.04e,f</td>
<td>7.40 ± 0.06f</td>
<td>7.37±0.03ae, f</td>
<td>7.28±0.07ae,e</td>
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<td>pCO2 (torr)</td>
<td>41 ± 4f</td>
<td>43 ± 5f</td>
<td>41 ± 3f</td>
<td>43 ± 3f</td>
<td>46 ± 4f</td>
<td>57 ± 12ae</td>
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<td>pO2 (torr)</td>
<td>107 ± 18</td>
<td>102 ± 23</td>
<td>103 ± 13</td>
<td>94 ± 14</td>
<td>89 ± 14</td>
<td>105 ± 57</td>
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<td>Arterial Hemoglobin (%)</td>
<td>9 ± 2</td>
<td>10 ± 2</td>
<td>10 ± 2</td>
<td>9 ± 1</td>
<td>10 ± 2</td>
<td>10 ± 1</td>
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<tr>
<td>Arterial Glucose (mg/dL)</td>
<td>81 ± 25c-f</td>
<td>92 ± 23f</td>
<td>96 ± 31ah, f</td>
<td>100 ± 33ah, f</td>
<td>107 ± 32a</td>
<td>117 ± 26ad</td>
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<tr>
<td>Arterial Saturation (%)</td>
<td>98 ± 1</td>
<td>97 ± 3</td>
<td>98 ± 1</td>
<td>97 ± 2</td>
<td>96 ± 2</td>
<td>95 ± 3</td>
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<tr>
<td>Arterial Lactate (mg/dL)</td>
<td>1.20 ± 0.91f</td>
<td>1.02 ± 0.70ef</td>
<td>0.88 ± 0.71ef</td>
<td>0.95 ± 0.63ef</td>
<td>1.46±0.60bd, f</td>
<td>2.60±0.92ae</td>
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<td>IJ-Glucose (mg/dL)</td>
<td>72 ± 21c-f</td>
<td>83 ± 27f</td>
<td>87 ± 32ah,f</td>
<td>90 ± 35ah,f</td>
<td>90 ± 23ah,f</td>
<td>108 ± 25bf</td>
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<tr>
<td>IJ Saturation (%)</td>
<td>80 ± 13</td>
<td>79 ± 10</td>
<td>82 ± 10</td>
<td>82 ± 9</td>
<td>82 ± 16</td>
<td>84 ± 7</td>
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<tr>
<td>IJ-Lactate (mg/dL)</td>
<td>1.63 ± 0.97f</td>
<td>1.37 ± 0.81f</td>
<td>1.33 ± 0.72ef</td>
<td>1.44 ± 0.60f</td>
<td>1.70 ± 0.58cf</td>
<td>2.63±0.82ae</td>
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CPP = cerebral perfusion pressure; IJ = internal jugular

- a = p<0.05 from baseline
- b = p<0.05 from CPP 60
- c = p<0.05 from CPP 50
- d = p<0.05 from CPP 40
- e = p<0.05 from CPP 30
- f = p<0.05 from CPP 20
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<tr>
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<th>Correlation with NIRS</th>
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<tbody>
<tr>
<td>Right Frontal Cortex</td>
<td>86 ± 40c-f</td>
<td>94 ± 6c-f</td>
<td>47 ± 9ab,b,e-f</td>
<td>35 ± 9ab</td>
<td>12 ± 13abc</td>
<td>3 ± 2abc</td>
<td>0.88[0.72-1.00]</td>
</tr>
<tr>
<td>Left Frontal Cortex</td>
<td>96 ± 41c-f</td>
<td>99 ± 50c-f</td>
<td>54 ± 10ab,b,e-f</td>
<td>44 ± 9ab,b,f</td>
<td>16 ± 12abc</td>
<td>4 ± 4abd</td>
<td>0.97[0.95-0.98]</td>
</tr>
<tr>
<td>Right Caudate</td>
<td>100 ± 44c-f</td>
<td>120 ± 81c-f</td>
<td>53 ± 10ab,b,f</td>
<td>50 ± 14ab,b,f</td>
<td>16 ± 13abc</td>
<td>2 ± 6abd</td>
<td>0.92[0.89-0.95]</td>
</tr>
<tr>
<td>Left Caudate</td>
<td>112 ± 45c-f</td>
<td>112 ± 59c-f</td>
<td>56 ± 14ab,b,e-f</td>
<td>52 ± 15ab,b,e-f</td>
<td>16 ± 13abd</td>
<td>3 ± 6abd</td>
<td>0.95[0.91-0.97]</td>
</tr>
<tr>
<td>Right Temporal Cortex</td>
<td>83 ± 36c-f</td>
<td>90 ± 57c-f</td>
<td>44 ± 10ab,b,e-f</td>
<td>35 ± 10ab,b,f</td>
<td>13 ± 12abc</td>
<td>2 ± 3abd</td>
<td>0.96[0.93-0.98]</td>
</tr>
<tr>
<td>Left Temporal Cortex</td>
<td>100 ± 42c-f</td>
<td>109 ± 66c-f</td>
<td>56 ± 13ab,b,f</td>
<td>44 ± 12abc</td>
<td>14 ± 13abd</td>
<td>2 ± 2abd</td>
<td>0.95[0.91-0.99]</td>
</tr>
<tr>
<td>Right Occipital Cortex</td>
<td>89 ± 53c-f</td>
<td>99 ± 61c-f</td>
<td>51 ± 6ab,b,e-f</td>
<td>40 ± 10ab,b,f</td>
<td>13 ± 11abc</td>
<td>2 ± 3abd</td>
<td>0.92[0.87-0.97]</td>
</tr>
<tr>
<td>Left Occipital Cortex</td>
<td>102 ± 42c-f</td>
<td>106 ± 62c-f</td>
<td>52 ± 9ab,b,e-f</td>
<td>42 ± 11ab,b,f</td>
<td>13 ± 12abc</td>
<td>3 ± 2abd</td>
<td>0.95[0.91-0.98]</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>82 ± 42c-f</td>
<td>92 ± 72c-f</td>
<td>39 ± 6ab,b,f</td>
<td>37 ± 7ab,b,f</td>
<td>12 ± 10ab,b</td>
<td>1 ± 1abd</td>
<td>0.93[0.89-0.97]</td>
</tr>
<tr>
<td>Thalamus</td>
<td>115 ± 63d-f</td>
<td>140 ± 107c-f</td>
<td>63 ± 10b,f</td>
<td>57 ± 12ab,b,f</td>
<td>21 ± 15ab,b</td>
<td>3 ± 3abd</td>
<td>0.92[0.88-0.97]</td>
</tr>
<tr>
<td>Right Cerebellum</td>
<td>128 ± 58c-f</td>
<td>146 ± 89c-f</td>
<td>66 ± 18ab,b,e-f</td>
<td>48 ± 8ab,b</td>
<td>15 ± 13abc</td>
<td>2 ± 3abc</td>
<td>0.90[0.78-1.00]</td>
</tr>
<tr>
<td>Left Cerebellum</td>
<td>127 ± 59c-f</td>
<td>133 ± 81c-f</td>
<td>63 ± 17ab,b,e-f</td>
<td>47 ± 13ab,b</td>
<td>14 ± 12abc</td>
<td>3 ± 4abc</td>
<td>0.91[0.77-1.00]</td>
</tr>
<tr>
<td>Kidney</td>
<td>367 ± 271</td>
<td>419 ± 308</td>
<td>277 ± 95</td>
<td>270 ± 69</td>
<td>224 ± 72</td>
<td>232 ± 95</td>
<td>0.60[0.34-0.86]</td>
</tr>
</tbody>
</table>

a = p<0.05 from baseline; b = p<0.05 from CPP 60; c = p<0.05 from CPP 50; d = p<0.05 from CPP 40; e = p<0.05 from CPP 30; f = p<0.05 from CPP 20
Table 3: CMRO$_2$ (ml O$_2$/min/100 gm tissue), CMR$_{\text{glu}}$ (mg glucose/min/100 gm tissue) and cerebral lactate production (mg lactate/min/100 gm tissue) at each CPP (mean ± SD) and correlation with NIRS (mean r[95% CI]) in the left hemisphere.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>CPP 60</th>
<th>CPP 50</th>
<th>CPP 40</th>
<th>CPP 30</th>
<th>CPP 20</th>
<th>Correlation with NIRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMRO$_2$</td>
<td>1.96 ± 1.15$^a$</td>
<td>2.19 ± 0.77$^a$</td>
<td>1.27 ± 0.99$^b$</td>
<td>1.06 ± 0.95$^b$</td>
<td>0.42 ± 0.78$^c$</td>
<td>0.04 ± 0.06$^c$</td>
<td>0.94[0.90-0.98]</td>
</tr>
<tr>
<td>CMR$_{\text{glu}}$</td>
<td>16.6 ± 19.2</td>
<td>21.6 ± 44.9</td>
<td>14.9 ± 24.9</td>
<td>14.2 ± 24.2</td>
<td>7.7 ± 14.7</td>
<td>0.7 ± 1.0</td>
<td>0.87[0.76-0.97]</td>
</tr>
<tr>
<td>Cerebral Lactate Production</td>
<td>0.34 ± 0.18$^a$</td>
<td>0.33 ± 0.12$^a$</td>
<td>0.17 ± 0.10$^b$</td>
<td>0.14 ± 0.06$^d$</td>
<td>0.05 ± 0.06$^e$</td>
<td>0.00 ± 0.01$^c$</td>
<td>0.89[0.81-0.97]</td>
</tr>
</tbody>
</table>

$^a$= p<0.05 from CPP 50, 40, 30 and 20; $^b$= p<0.05 from baseline, CPP 60, 30 and 20; $^c$= p<0.05 from baseline, CPP 60 and 20; $^d$= p<0.05 from baseline, CPP 60 and 20; $^e$= p<0.05 from baseline, CPP 60 and 50.
Figure Legends

Figure 1. Graphs show the correlation (r) between brain NIRS and CBF in the left temporal region for each of the seven piglets.

Figure 2. Graph shows the comparison between the correlation of NIRS with CBF (circles, left axis) and the correlation of CPP with CBF (triangles, right axis) in the left temporal region. Mean±SD.
The diagrams show the relationship between CBF (ml/min/100gm) and NIRS (%). The correlation coefficients (r) for each graph are as follows:

- Upper left: r = 0.99
- Upper right: r = 0.95
- Lower left: r = 0.87
- Lower right: r = 0.97
- Lower middle: r = 0.92