The Journal of Maternal-Fetal Medicine 9:142–149 (2000)

NEW TECHNOLOGY

Role of Frequency Domain Optical Spectroscopy in the Detection of Neonatal Brain Hemorrhage — A Newborn Piglet Study

Miljan R. Stankovic,[1,2,3*] Dev Maulik,[3] Warren Rosenfeld,[3] Phillip G. Stubblefield,[2] Alexander D. Kofinas,[1] Enrico Gratton,[4] Maria Angela Franceschini,[4] Sergio Fantini,[4] and Dennis M. Hueber[5]

[1]*Department of Obstetrics and Gynecology, Brooklyn Hospital Center, Cornell University School of Medicine, Brooklyn, New York*
[2]*Department of Obstetrics and Gynecology, Boston University School of Medicine, Boston, Massachusetts*
[3]*Departments of Obstetrics and Gynecology and Pediatrics, Winthrop University Hospital, State University of New York at Stony Brook, Mineola, New York*
[4]*Laboratory for Fluorescence Dynamics, Department of Physics, University of Illinois at Urbana–Champaign, Urbana, Illinois*
[5]*ISS Inc., Champaign, Illinois*

Objective: Inability of continuous wave (CW) optical spectroscopy to measure changes in scattering, and the use of an arbitrary rather than an actual baseline, makes the CW method highly susceptible to errors that can lead to a false-positive or false-negative diagnosis. Our objective was to assess whether, and to what extent, the use of quantitative frequency domain spectroscopy would improve our ability to detect and monitor the development of brain hemorrhage.

Methods: A dual-channel frequency-domain tissue spectrometer (Model 96208, ISS, Inc., Champaign, IL) was used to monitor the development of experimental subcortical and periventricular–intraventricular hemorrhage (IVH) in 10 newborn piglets (blood injection model). The multidistance approach was employed to calculate the absorption and reduced scattering coefficients and hemoglobin changes from the ac, dc, and phase values acquired at four different source-detector distances and at 752 nm and 830 nm.

Results: There were significant absorption and scattering changes in the subcortical hematoma (n = 5) and the IVH groups (n = 5). The smallest detectable amount of blood in the brain was 0.04 ml. Changes associated with subcortical hematoma were several times higher than those associated with IVH, and correlated better with the estimated cross-sectional area of the hematoma than with the volume of the injected blood. As opposed to IVH, there was a significant absorption difference between the injured (subcortical hematoma) and normal side of the brain, probably because in case of IVH a significant volume of the injected blood had accumulated/spread beyond the reach of the probe.

Conclusion: Clearly, frequency-domain spectroscopy cannot increase our ability to quantify the volume (size) or the oxygenation of the injected blood, especially in the case of IVH. However, the ability to quantify the baseline tissue absorption and scattering would significantly improve diagnostic performance, and may allow for early identification and treatment of neonatal brain hemorrhage. *J. Matern.-Fetal Med. 2000;9:142–149.*

Key words: optical spectroscopy; frequency-domain; brain hemorrhage; newborn piglet

Abbreviations: NIRS, near-infrared spectroscopy; CW, continuous wave; HbT, total hemoglobin concentration; HbO, oxyhemoglobin concentration; Hb, deoxyhemoglobin concentration; IVH, intraventricular hemorrhage; CT, computer tomography.

Contract grant sponsor: US National Institutes of Health (NIH); Contract grant number: CA57032; Contract grant sponsor: Whitaker-NIH; Contract grant number: RR10966.

*Correspondence to: Miljan R. Stankovic, Department of Obstetrics and Gynecology, The Brooklyn Hospital Center, 121 Dekalb Avenue, Brooklyn NY 11201. E-mail: MILJANRS@AOL.COM

Received 25 June 1999; revised 1 November 1999; accepted 4 November 1999

INTRODUCTION

Germinal matrix – intraventricular hemorrhage (IVH) is a major source of neurological morbidity associated with prematurity [1]. Early detection of IVH, as well as the preceding and/or accompanying disturbances in cerebral hemodynamics and oxygenation, would be an important step in the prevention and treatment of this type of brain injury [1]. IVH in neonates is currently diagnosed by cranial ultrasound [2]. Additional diagnostic evaluation and follow-up is commonly hampered by the difficulties related to transport of the smallest and sickest infants dependent on vital monitoring or life support, the inability to perform continuous or repeated studies, low availability, and the high cost of the available diagnostic techniques, namely, MRI and CT [3]. It has been proposed that a noninvasive bedside technique capable of detecting ischemic and/or hemorrhagic brain injury, and continuously monitoring changes in cerebral perfusion and oxygenation, might significantly improve the ability to identify and treat neonates that suffered, or are at risk for developing brain injury [1]. Optical (near infrared) spectroscopy has been identified as a diagnostic/monitoring technique that has the potential to achieve this goal [4].

Optical spectroscopy is based on the relative optical transparency of tissues in the red and near infrared light region (ranging from ~670 to ~1,000 nm) and the distinct absorption properties of oxy- and deoxyhemoglobin [3]. Optical spectroscopy is capable of detecting brain ischemia [5,6] and hemorrhage [7–11], and monitoring cerebral perfusion and oxygenation in a continuous, noninvasive, and real-time manner [12,13]. Continuous wave (CW) spectroscopy is able to detect intracranial hemorrhage prior to an increase in intracranial pressure, a change in the neurological examination, or a change on CT scan [7,8]. Finally, CW imaging is capable of detecting and monitoring the development of experimental subcortical and periventricular–intraventricular hemorrhage in newborn piglets [10,14].

Without a priori knowledge of either the initial absorption and/or the scattering coefficient, CW spectroscopy can only measure changes in tissue absorption from (an arbitrarily set) baseline, without providing any information on whether the baseline was normal, high, or low [3,15]. The development of frequency-domain [16,17] and time-domain [18] spectroscopy has enabled quantitative measurements of tissue absorption and scattering and hemoglobin concentrations, thus providing us with the ability to tell the difference between normal and abnormal tissue [15,17–19]. However, it is not clear whether, and to what extent, our ability to quantify brain absorption and scattering would improve our ability to detect and monitor the development of brain hemorrhage. In order to address this important question, we developed a newborn piglet model of brain hemorrhage to asses the ability of frequency-domain spectroscopy to 1) detect brain hemorrhage, and 2) quantify changes in brain absorption and scattering associated with the development of a) subcortical and b) periventricular–intraventricular brain hemorrhage.

METHOD

Optical Spectroscopy

The basic principles of optical spectroscopy have been extensively described in the literature [3,15,17,19–21]. Briefly, optical spectroscopy uses near infrared light ranging from ~670 to ~1,000 nm to investigate optical properties of deep tissues. The total attenuation of light that traversed tissue is a function of tissue absorption and scattering. Absorption is a function of concentrations of fixed (e.g., skin pigment and lipids) and mobile chromophores (e.g., oxy- and deoxyhemoglobin) [22,23]. In a nonscattering medium, the total light absorption is a linear sum of that due to each chromophore [22]. For our study, we used a dual-channel frequency-domain tissue spectrometer (Model 96208, ISS, Inc., Champaign, IL). Each of the channels has four pairs of light sources (laser diodes: four at 752 nm and four at 830 nm) and one optical detector (photomultiplier tube) (Fig. 1). The data acquisition time was 1.5 sec per data point. The ISS Oximeter measures the scattering coefficient directly and is thus able to determine hemoglobin concentrations in any highly scattering medium. In order to quantify brain absorption and reduced scattering coefficient, ac, dc, and phase values have to be acquired at four different source-detector distances and at each of the two wavelengths (the multidistance approach) [21]. Knowledge of phase enables direct conversion of an attenuation change into a change in chromophore concentration [15,17,22]. In order to satisfy these requirements, optical fibers were coupled with the help of a custom-built optical probe at four different source-detector distances ranging from 1.48 to 2.98 cm (Figs. 1, 2) [19]. The estimated sampling volume of this probe falls between the minimum of 1.5 cc (1.5 cm length, 1 cm depth, 1 cm width) and the maximum of 12 cc (3 cm length, 2 cm depth, 2 cm width). A medium value of 5 cc (2.5 cm length, 1 cm depth, 2 cm width) would be the most realistic sampling volume of the probe.

By assuming that hemoglobin and water are the dominant brain absorbers in the near-infrared range, the absorption coefficients at 752 and 830 nm were used to determine absolute values of oxyhemoglobin (HbO), deoxyhemoglobin (Hb), total hemoglobin concentrations (HbT), and brain tissue saturation (HbO / HbO + Hb) [24]. Absolute hemoglobin concentration measurements depend on the volume of tissue interrogated (sampling volume) and tissue geometry. Both sampling volume and tissue geometry can be described (although not fully) using diffusion theory or other methods, such as Monte-Carlo modeling [22]. Diffusion theory assumes that tissues are homogeneous and scatter isotropically on a microscopic scale. Although this is

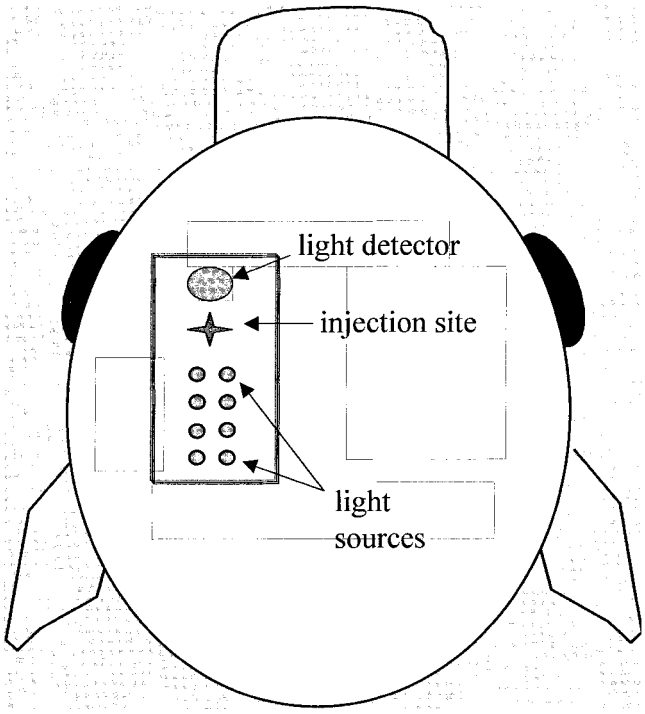

Fig. 1. Optical probe: geometrical arrangement of the fibers.

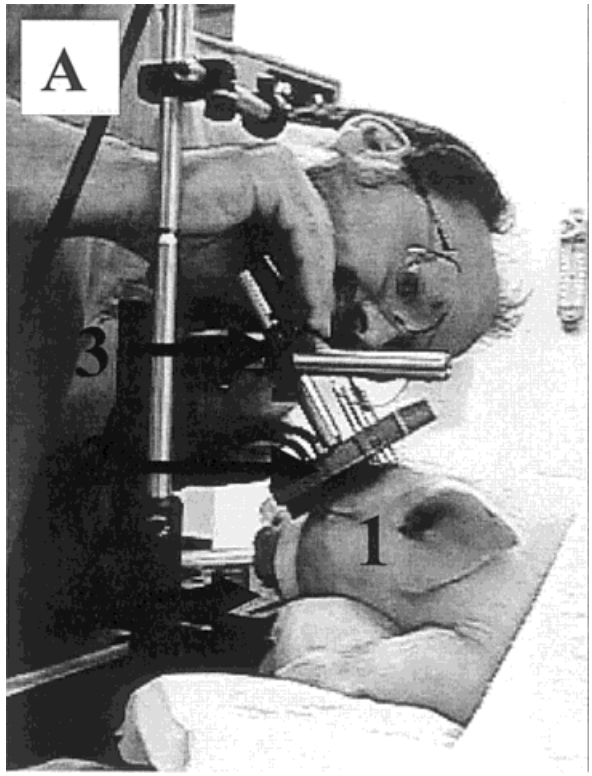

Fig. 2. Experimental setup. **A**: Photograph shows the pig's head (#1) with the optical probe (#2) attached to the manipulator arm (#3) of the stereotaxic frame (#4). **B**: Diagrammatic summary of the development of subcortical. **C**: Periventricular–intraventricular hemorrhage.

obviously not true for heterogeneous tissues like a head (containing a clear, nonscattering layer of cerebrospinal fluid), diffusion theory has been remarkably successful in describing the experimentally observed light distributions across many centimeters of tissue [22]. The multidistance approach that we used minimizes the contribution of the scalp and skull to the absorption and scattering of the brain [19].

The sensitivity of our instrument to detect blood inside the brain was defined as a volume of injected blood causing a change in measured intensity greater than 3 times the standard deviation of the baseline intensity [6]. The readings were "zeroed" in order to highlight the changes induced by the experiments.

Animal Model

The study was approved by the Institutional Review Board at Winthrop University Hospital, Long Island, New York, and was conducted according to the guidelines for the care and use of animals for scientific purposes. This animal model has been used previously for magnetic resonance [25] and optical imaging studies [10,19,26]. Briefly, a total of 10 12.3 ± 1.3-day-old newborn piglets, of either sex, weighing 3.8 ± 0.2 kg, were sedated with ketamine 20 mg/kg mixed with xylazine 4 mg/kg, IM. The animals were intubated and ventilated with an infant ventilator (Bear Medical Systems, Riverside, CA) to achieve normal blood gas values. General anesthesia was maintained by a continuous infusion of propofol mixed in D5W at a concentration of 0.8 mg/ml at 4–8 mg/kg/h. The core temperature was maintained at 37°C with the use of a heating blanket and continuously monitored by a rectal thermometer. Femoral artery and vein were catheterized to monitor the mean arterial pressure (Hewlett Packard 78353B, Corvallis, OR), arterial blood gasses (Ciba Corning 238 pH Blood Gas Analyzer, Medfield, MA), and to continuously infuse the propofol and D5W, respectively. Heart rate and arterial oxygen saturation were monitored by pulse oximetry (Nellcor, Hayward, CA) with the probe attached to the pig's tail. To achieve a motion-artifact-free optical environment and reproducible brain hematomas, the preshaved animal's head was secured within a custom-built stereotaxic frame (ISS) that allowed placement of holes in the skull in precise stereotaxic coordinates, three-dimensional positioning of the optical probe, and optimal, motionless probe-to-scalp contact (Fig. 2A). Using the precise stereotaxic coordinates, a 0.25-mm hole was placed in the left frontal region of the pig's skull, and a $25\frac{3}{4}$ G needle was inserted into the brain and secured within the optical probe (Fig. 2B,C). Using a manually controlled syringe, a total of 2 cc of autologous arterial blood was injected in small increments over a period of approximately 20 min. It was verified that the arterial blood retained an oxygen saturation of over 90% for the entire injection period. Subcortical hematoma was induced in 5 piglets by injecting 2 cc of blood into the

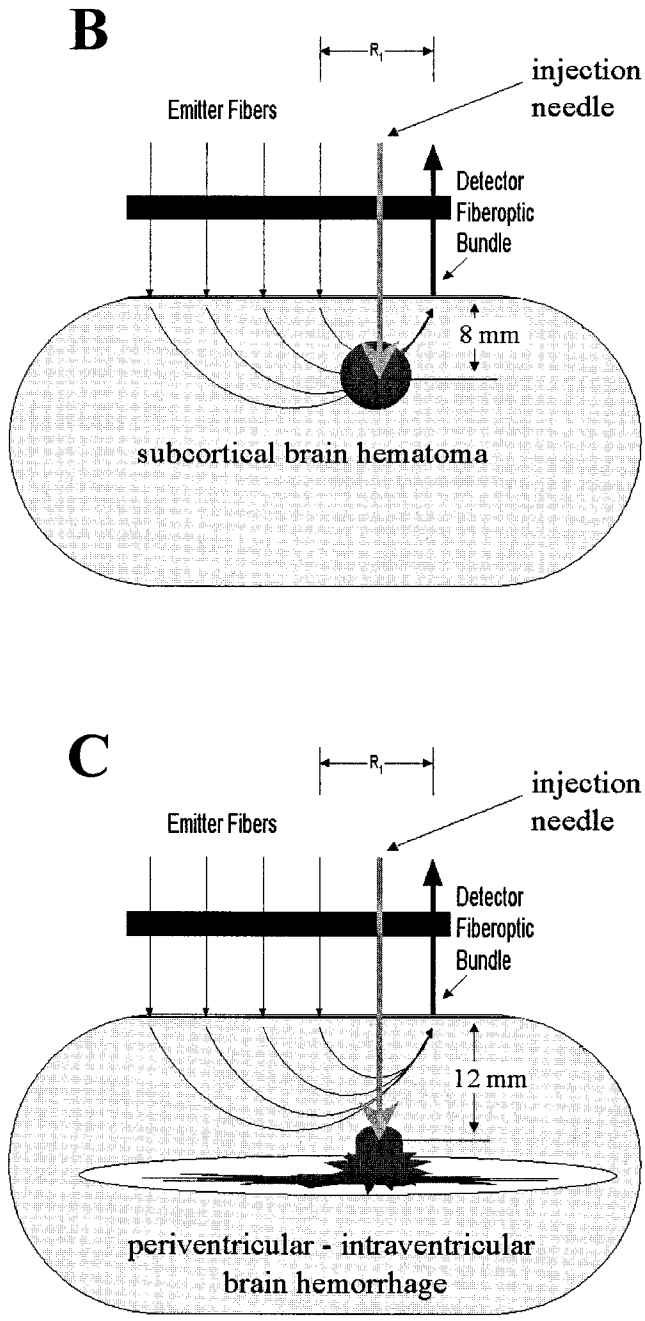

Figure 2. (Continued.)

left frontal subcortical white matter (8 mm from the skin surface, 4 mm below the surface of the brain) (Fig. 2B). Periventricular IVH was induced in 5 piglets by injecting 2 cc of blood into the white matter in the proximity of the left lateral ventricle (12 mm from the skin surface, 8 mm below the surface of the brain) (Fig. 2C). The blood injected into the periventricular region invariably expanded into the left lateral ventricle causing IVH (Fig. 2C). Optical data was recorded from the ipsilateral side of the brain (right above the injection site) in a continuous manner throughout the duration of the injection. All animals survived the experiments and no resuscitation was required thereafter. After termination of the experiment, the piglets were sacrificed with an overdose of pentobarbital sodium (500 mg IV). An autopsy was performed in order to determine the type, size, and location of the hemorrhage and to validate optical data.

RESULTS

The baseline brain tissue saturation was 46.5 ± 6.9% (n = 10). Blood injections rendered a total of five subcortical hematomas and five IVH, as confirmed ex-vivo by pathology. The smallest detectable amount of blood in the brain was 0.04 ml. Blood injections caused significant absorption and scattering changes in the subcortical hematoma (section 2) and the IVH groups (section 6) (Fig. 3). Absorption and scattering changes associated with subcortical hematoma were several times higher (Fig. 3, section 2) than those associated with IVH (Fig. 3, section 6). Blood injections caused significant, incremental HbT and Hb changes in the subcortical hematoma (section 2) and the IVH groups (section 6) (Fig. 4). Changes in HbT associated with subcortical hematoma, however, were significantly larger than those associated with IVH (e.g., 12.5 ± 0.7 μMol/L vs. 5.3 ± 0.3 μMol/L) (Fig. 4). Tissue saturation remained constant in the subcortical hematoma (Fig. 4, section 2) and the IVH groups (Figure 4, section 6), despite the fact that the fully saturated arterial blood was injected.

In order to compare optical properties of the injured (ipsilateral) and the normal (contralateral) brain hemispheres, the probe was transferred from the ipsilateral to the contralateral side of the head (Figs. 3, 4, section 3) as soon as the injection was completed. After a period of 5–10 min, the probe was returned to the ipsilateral side (Figs. 3, 4, section 4). A significant increase in HbT and Hb values (section 4), compared to those from section 2, indicates the presence of hyperemia of the surrounding uninjured brain tissue. In order to investigate the variability of the measurements associated with the repositioning of the probe, the probe was removed and reapplied several times in approximately the same position (note a tooth-like pattern presented in sections 3 and 4) (Figs. 3, 4). Figure 5 further highlights this tooth-like variability of HbT measurements due to the repositioning of the probe, as well as the right-to-left differences, typical for subcortical hematoma (5A) and IVH (5B). Changes in HbT associated with subcortical hematoma correlated better with the estimated cross-sectional area of the hematoma (Fig. 6A) than with the volume of the injected blood (Fig. 6B).

DISCUSSION

This study reports a successful application of frequency-domain optical spectroscopy in the detection of experimental brain hemorrhage in neonatal piglets. We successfully detected minute amounts of blood in the brain (Figs. 2, 3,

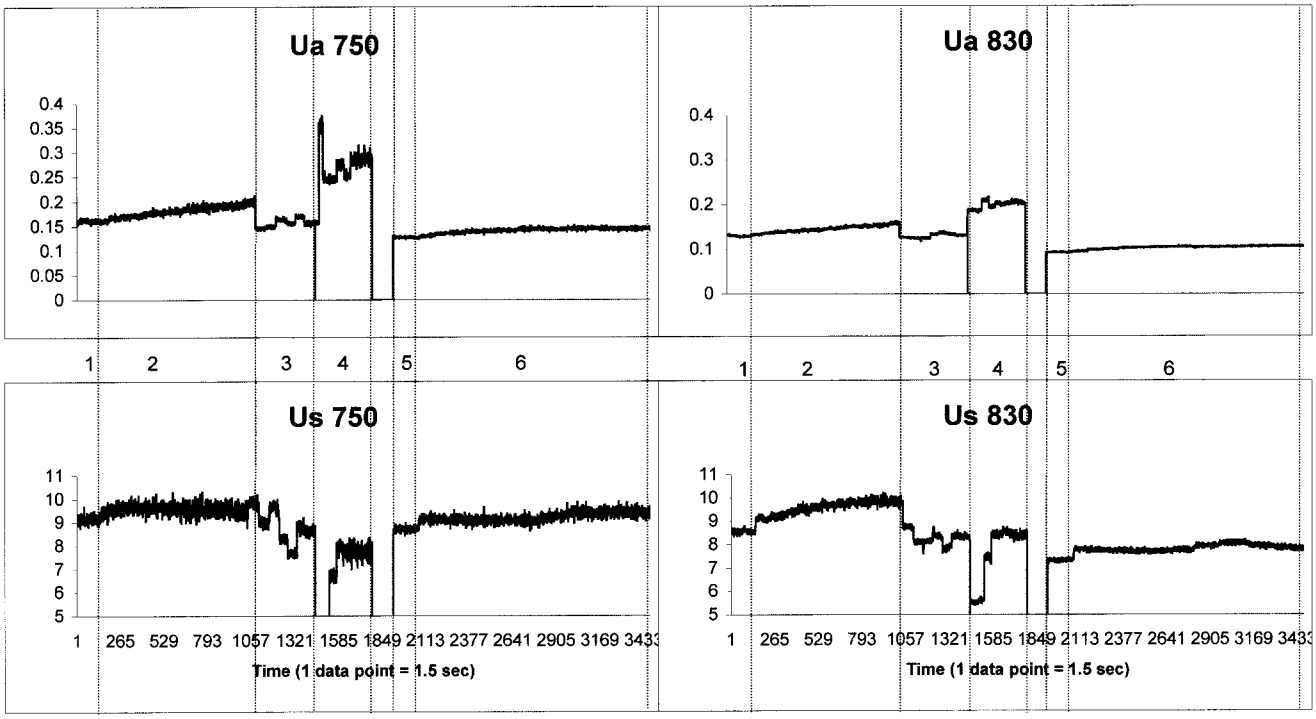

Fig. 3. Typical changes in brain absorption and scattering associated with subcortical and periventricular–intraventricular hemorrhage. Subcortical brain hematoma: Section 1: The probe was placed on the left frontal–parietal side of the head and the baseline was recorded. Section 2: A total of 2 cc of blood was injected into the left frontal subcortical white matter directly underneath the optical probe. Section 3: The optical probe was moved to the contralateral side of the head in order to collect the data from the normal (right) brain hemisphere. The probe was then repositioned several times, i.e., removed and repositioned in approximately the same position. Section 4: The probe was moved back to the ipsilateral (blood injection) side of the head in order to collect the data from the injured (left) brain hemisphere. The probe was repositioned several times, i.e., removed and repositioned in approximately the same position. Periventricular–intraventricular hemorrhage: Section 5: The probe was placed on the left frontal–parietal side of the head and the baseline was recorded. Section 6: A total of 2 cc of blood was injected into the left periventricular white matter right underneath the optical probe.

sections 2, 6) and distinguished normal and abnormal brain tissue (Figs. 2, 3, 5), but we were not able to quantify the volume of the injected blood (Fig. 6). The goal of quantification is not only to measure the magnitude of changes, but also to determine the baseline from which the changes are occurring [22]. Over the past two decades, near-infrared scientists have focused on solving the problem of data quantification. In continuous wave spectroscopy, it is assumed that tissue scattering and optical pathlength are constant, and that small changes in absorption are linearly related to the measured change in light attenuation [22]. In biological tissues, quantification is a function of wavelength-dependent absorption and scattering, scattering phase function, tissue and measurement geometry [22], and changes attributed to tissue physiology/pathophysiology [15].

The animal injection model described in this study provides an elegant testing ground for the comparison of different optical techniques (e.g., CW and frequency-domain spectroscopy and imaging) and for assessing which of them are best suited for given clinical conditions (e.g., subarachnoid, subcortical, intraventricular hemorrhage, etc.) [9,10,19,26]. The injected volume of 2 cc of autologous blood over 20 min are small enough to ensure survival of the animal, but large enough to be detected by the oximeter [9,10,19,26]. The slow blood injection allows the brain to adjust to the increase in intracranial pressure. It is generally associated with much smaller acute changes in brain hemodynamics (ischemia and reperfusion), compared to those noticed during fast (<1 min) injection [9,10,19,26]. Blood injected into the subcortical white matter easily dissects between the myelinated fibers, forming a reproducible subcortical hematoma with minimal or no subarachnoid bleeding (Fig. 2B) [9,10,19,26,27]. Blood injected deeper into the periventricular region, on the other hand, forms a small periventricular hematoma that eventually expands into the nearby lateral ventricle, forming an IVH (Fig. 2C).

In the first successful application of optical spectroscopy in detection of brain hemorrhage in humans, Gopinath and Robertson [7,8] described a dual wavelength continuous wave spectrometer developed by Chance et al. [15] (RunMan; NIM, Philadelphia, PA). The instrument was used to quantify hemispheric differences in light absorption (expressed as delta optical density, ΔOD). The measurements were performed on the patients with moderate and severe head injury in the emergency room at the time of the

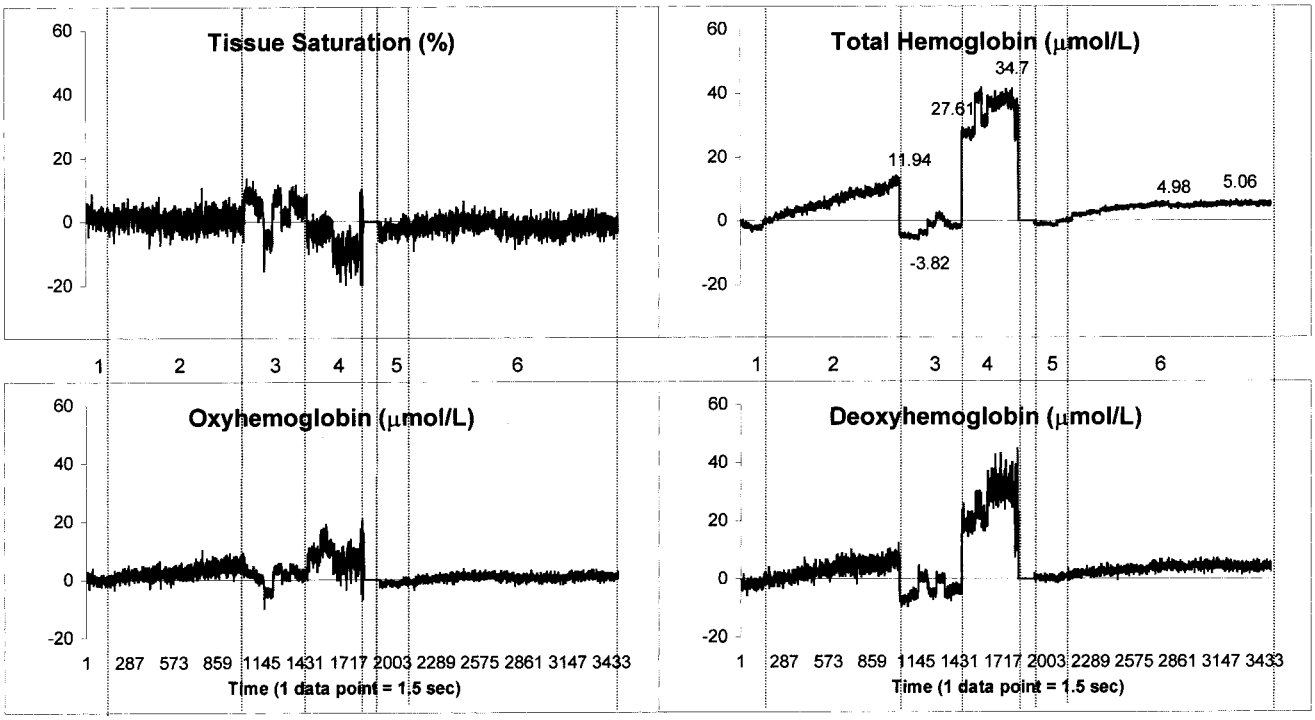

Fig. 4. Typical changes in tissue saturation (%), total hemoglobin, oxyhemoglobin, and deoxyhemoglobin associated with subcortical and periventricular–intraventricular hemorrhage. Subcortical brain hematoma: Section 1: The probe was placed on the left frontal–parietal side of the head and the baseline was recorded. Section 2: A total of 2 cc of blood was injected into the left frontal subcortical white matter right underneath the optical probe. Section 3: The optical probe was moved to the contralateral side of the head in order to collect the data from the normal (right) brain hemisphere. The probe was then repositioned several times, i.e., removed and repositioned in approximately the same position. Section 4: The probe was moved back to the ipsilateral (blood injection) side of the head in order to collect the data from the injured (left) brain hemisphere. The probe was repositioned several times, i.e., removed and repositioned in approximately the same position. Periventricular–intraventricular hemorrhage: Section 5: The probe was placed on the left frontal–parietal side of the head and the baseline was recorded. Section 6: A total of 2 cc of blood was injected into the left periventricular white matter directly underneath the optical probe.

admission CT scan, followed by serial measurements during the hospital course. Their oximeter was able to detect intracranial hemorrhage prior to an increase in intracranial pressure, a change in the neurological examination, or a change on CT scan [7,8]. The absorption difference in the patients with all types of hematomas (n = 118) was significantly greater than in the patients with diffuse brain injury. In the patients with subdural or epidural (superficial) hematomas, the absorption difference was significantly greater than in those with intracerebral (deep) hematomas. This is in agreement with the results of our study, i.e., that the absorption and scattering changes associated with the superficial blood collections (subcortical hematoma: Fig. 3, section 2) were several times higher than the changes associated with the deep ones (IVH: Fig. 3, section 6).

It is generally accepted that optical spectroscopy is extremely sensitive to changes that occur in small blood vessels because the photons that enter large blood vessels (or blood collections) will be readily absorbed [15,28]. This may explain why the changes in HbT associated with subcortical hematoma correlate better with the estimated cross-sectional area of the hematoma (Fig. 6A) than with the volume of the injected blood (Fig. 6B). In addition, this can explain our inability to measure the saturation of injected, fully saturated blood (Fig. 4, sections 2, 6). Similarly, Gopinath and Robertson [7] found a significant correlation between the thickness of the hematoma and the absorption difference in the patients with epidural (n = 35) and subdural hematomas (n = 62). The absorption difference positively correlated with the size of the hematoma up to a thickness of approximately 1.5 cm, as measured by CT, and then plateaued [7]. We believe that, with the possible exception of subarachnoid hemorrhage, optical spectroscopy cannot measure the thickness of the hematoma, as all the photons that enter the hematoma will be absorbed [19]. However, optical spectroscopy can be used to outline the hemodynamically active, noninjured brain tissue from the abnormal one, providing, in a sense, indirect information on the size the hematoma.

Gopinath and Robertson [7] found that in patients with intracerebral hematoma (n = 15), the absorption difference was not related to the size of the intracerebral hematoma, perhaps because a significant volume of the hematoma was deeper than the 2-cm light penetration afforded by the design of the optical probe used for their study. Their probe source-detector separation of 4 cm allowed measure-

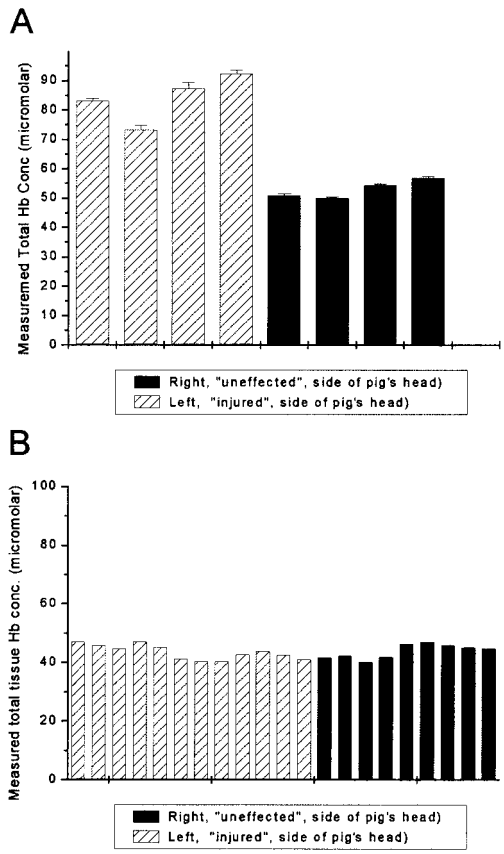

Fig. 5. Figure shows the variability of the repeated spectroscopic measurements of the total brain hemoglobin concentration obtained from the left (injured) and right (normal) brain hemisphere in the pigs that developed subcortical hematoma (**A**) and periventricular–intraventricular hemorrhage (**B**).

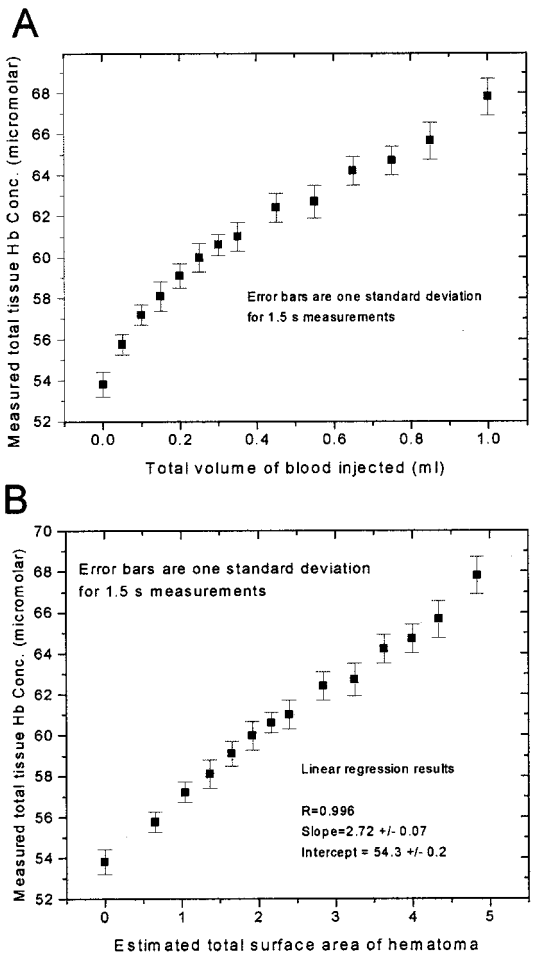

Fig. 6. Subcortical brain hematoma: the correlation between total hemoglobin concentration and the volume of the injected blood (**A**), and total hemoglobin concentration and the estimated cross-sectional surface of the hematoma (**B**).

ments of near-infrared absorption in a volume of tissue approximately 2 cm wide, and 2–3 cm deep [7,8]. In our study, the difference between the changes in absorption and scattering associated with subcortical hematoma (Figs. 2, 3, section 6) and IVH (Figs. 2, 3, section 6) are likely due to the limited sampling volume and the penetration depth of our optical probe. In other words, subcortical blood injections remained within the reach of the probe (i.e., between 1 and 2 cm penetration depth) (Fig. 2B), whereas periventricular blood injections "escaped" into the brain's ventricular system, beyond the reach of the probe (Fig. 2C).

The major problem with optical data quantification arises from the fact that light attenuation in tissue comes not only from absorption changes, but also from light scattering. CW spectroscopy is based on the assumption that tissue scattering does not change during the acquisition period [3,15]. In reality, changes in tissue hemodynamics and oxygenation cause changes in tissue scattering [19]. Therefore, in order to make accurate determinations of absorption coefficient, we must account for tissue scattering. Inability to measure changes in scattering, and the use of an arbitrary rather than an actual baseline, makes the CW method highly susceptible to errors that can lead to a false-positive or false-negative diagnosis [7,22]. However, CW absolute concentration measurements can be made using the "dc slope" approach [10,19].

This study shows that frequency-domain spectroscopy cannot increase our ability to quantify the volume (size) or the oxygenation of the injected blood, especially in the case of IVH. However, the ability to quantify the baseline tissue absorption and scattering would significantly improve our diagnostic performance, and may allow for early identification and treatment of neonatal brain hemorrhage [15,17,19].

ACKNOWLEDGMENTS

We thank Jean Handel, Darrin Chester, Pauline Bitteto, and Patricia Johnson for technical assistance.

REFERENCES

1. Volpe JJ. Neurology of the newborn, 3rd ed. Philadelphia: WB Saunders; 1995. p 297–298.

2. Vohr B, M LR. Intraventricular hemorrhage in the preterm infant. Early Hum Dev 1996;44:1–16.
3. Wahr JA, et al. Near-infrared spectroscopy: theory and applications. J Cardiothorac Vasc Anesth 1996;3:406–418.
4. Hirtz DG. Report of the National Institute of Neurological Disorders and Stroke workshop on near infrared spectroscopy. Pediatrics 1993; 91:414–417.
5. Tsuji M, et al. Near infrared spectroscopy detects cerebral ischemia during hypotension. Pediatr Res 1998;44:591–595.
6. Stankovic MR, et al. Optical monitoring of cerebral hemodynamics and oxygenation in the neonatal piglet. J Matern Fetal Invest 1998; 8:71–78.
7. Gopinath SP, et al. Early detection of delayed traumatic intracranial hematomas using near-infrared spectroscopy. J Neurosurg 1995;83: 438–444.
8. Robertson CS, Gopinath SP, C B. A new application for near-infrared spectroscopy: detection of delayed intracranial hematomas after head injury. J Neurotrauma 1995;12:591–600.
9. Stankovic MR, Maulik D, Rosenfeld W, Stubblefield PG, Kofinas AD, Drexler S, Nair R, Franceschini MA, Hueber D., Gratton E, Fantini S. Real-time optical imaging of experimental brain ischemia and hemorrhage in neonatal piglets. J Perinat Med 1999;27(4):1–8.
10. Stankovic MR, et al. Real-time optical imaging of experimental brain ischemia and hemorrhage in neonatal piglets. J Perinatol 1999;27: 1–8.
11. Hintz SR, et al. Bedside imaging of intracranial hemorrhage in the neonate using light: comparison with ultrasound, computed tomography, and magnetic resonance imaging. Pediatr Res 1999;45:54–59.
12. Wyatt JS, et al. Quantification of cerebral blood volume in newborn infants by near infrared spectroscopy. J Appl Physiol 1990;68:1086–1091.
13. Brazy JE. Cerebral oxygen monitoring with near infrared spectroscopy: clinical application to neonates. J Clin Monit 1991;7:325–334.
14. Fantini S, et al. Non-invasive optical mapping of the piglet brain in real time. Optics Express 1999;4:308–314.
15. Chance B, et al. Optical investigations of physiology: a study of intrinsic and extrinsic biomedical contrast. Philos Trans R Soc Lond B Biol Sci 1997;352:707–716.
16. Chance B, et al. Phase measurement of light absorption and scatter in human tissue. Rev Sci Instrum 1998;69:3457–3481.
17. Gratton E, et al. Measurements of scattering and absorption changes in muscle and brain. Philos Trans R Soc Lond B Biol Sci 1997;352:727–735.
18. Benaron DA, et al. Noninvasive methods for estimating in vivo oxygenation. Clin Pediatr 1992;31:258–273.
19. Fantini S, et al. Non-invasive optical monitoring of the newborn piglet brain using continuous wave and frequency domain spectroscopy. Phys Med Biol 1999;44:1543–1563.
20. Benaron DA, Cheong WF, S DK. Tissue optics. Science 1997;276: 2002–2003.
21. Fantini S, Franceschini MA, G E. Semi-infinite-geometry boundary problem for light migration in highly scattering media: a frequency-domain study in the diffusion approximation. J Opt Soc Am 1994; B11:2128–2138.
22. Delpy DT, CM. Quantification in tissue near-infrared spectroscopy. Philos Trans R Soc Lond B Biol Sci 1997;352:649–659.
23. Wyatt JS. Cerebral oxygenation and haemodynamics in the foetus and newborn infant. Philos Trans R Soc Lond B Biol Sci 1997;352:697–700.
24. Sevick EM, et al. Quantitation of time- and frequency-resolved optical spectra for the determination of tissue oxygenation. Anal Biochem 1991;195:330–351.
25. Thulborn KR, et al. The role of ferritin and hemosiderin in the MR appearance of cerebral hemorrhage: a histopathologic biochemical study in rats. AJR Am J Roentgenol 1990;154:1053–1059.
26. Stankovic MR, et al. Optical brain monitoring and imaging in the fetus and neonate. J Fertil Reprod 1998;2:18.
27. Wagner KR, et al. Lobar intracerebral hemorrhage model in pigs: rapid edema development in perihematomal white matter. Stroke 1996;27:490–497.
28. Kurth CD, et al. Near-infrared monitoring of cerebral circulation. J Clin Monit 1993;9:163–170.