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Journal

Physiological Measurement, 27(8)

ISSN

0967-3334

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Publication Date

2006-08-01

DOI

10.1088/0967-3334/27/8/009

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Peer reviewed

Broadband diffuse optical spectroscopy measurement of hemoglobin concentration during hypovolemia in rabbits

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Received 13 March 2006, accepted for publication 18 May 2006

Published 13 June 2006

Online at stacks.iop.org/PM/27/757

Abstract

Serial blood draws for the assessment of trauma patients' hemoglobin (sHgb) and hematocrit (sHct) is standard practice. A device that would allow for continuous real-time, non-invasive monitoring of hemoglobin and tissue perfusion would potentially improve recognition, monitoring and resuscitation of blood loss. We developed a device utilizing diffuse optical spectroscopy (DOS) technology that simultaneously measures tissue scattering and near-infrared (NIR) absorption to obtain non-invasive measurements of oxy-hemoglobin (Hb-O₂), deoxyhemoglobin (Hb-R) concentrations and tissue hemoglobin concentration (THC) in an animal model of hypovolemic shock induced by successive blood withdrawals. Intubated New Zealand White rabbits ($N = 16$) were hemorrhaged via a femoral arterial line every 20 min until a 20% blood loss ($10\text{--}15\text{ cc kg}^{-1}$) was achieved to attain hypovolemia. A broadband DOS probe placed on the inner thigh was used to measure muscle concentrations of Hb-O₂ and Hb-R, during blood withdrawal. THC and tissue hemoglobin saturation ($S_T\text{O}_2$) were calculated from DOS [Hb-O₂] and [Hb-R]. Broadband DOS-measured values were compared against traditional invasive measurements: systemic sHgb, arterial oxygen saturation ($S_a\text{O}_2$) and venous oxygen saturation ($S_v\text{O}_2$) drawn from arterial and central venous blood. DOS and traditional invasive measurements versus blood loss were closely correlated ($r^2 = 0.96$) showing a decline with removal of blood. $S_T\text{O}_2$ and [Hb-O₂] followed similar trends with hemorrhage, while [Hb-R] remained relatively constant. These measurements may be limited to some extent by the inability to distinguish between hemoglobin and myoglobin contributions to DOS signals in tissue at this time. Broadband DOS provides a potential platform for reliable non-invasive measurements of tissue oxygenated and deoxygenated hemoglobin and

may accurately reflect the degree of systemic hypovolemia and compromised tissue perfusion.

Keywords: near-infrared, optical properties, light absorption, tissue scattering, photon migration, tissue perfusion

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Hemorrhage remains a leading cause of death in civilian and military trauma (Dubick and Atkins 2003). In multiple traumas, rapid assessment of victims that are critically volume depleted is necessary to gauge resuscitation efforts, thereby reducing the morbidity and mortality associated with hypoperfusion. Assessment is generally achieved by obtaining vital signs and by determination of systemic hematocrit (sHct) and hemoglobin (sHgb). During acute hemorrhage, however, sHct and sHgb may be normal or even increased due to the inherent lag time in body fluid shifts (Guyton and Hall 1997) and may result in a delayed recognition and initiation of volume replacement.

Because of this, observations in tissue peripheral perfusion may be a more representative indicator of volume status during acute hemorrhage. A means for rapid and portable non-invasive assessment of tissue hemoglobin concentration (THC) and tissue perfusion may increase efficiency in diagnosing patients in greatest need of volume replacement and aid in the assessment of those patients undergoing resuscitation.

In the hospital setting, evaluation of critically ill patients often includes systemic hemodynamic monitoring by invasive central venous access along with serial blood drawing. The ability to assess tissue hemoglobin and perfusion variables non-invasively in real time may improve recognition as well as reduce the cost and complications associated with invasive monitoring techniques.

To address these issues, tissue hemoglobin monitoring with near-infrared spectroscopy (NIRS) has been proposed as a possible alternative to invasive monitoring (Beilman *et al* 1999, Boushel and Piantadosi 2000, Buchner *et al* 2000, Chaisson *et al* 2003, Crookes *et al* 2004, Lovell *et al* 1999, Puyana *et al* 1999, Shadid *et al* 1999, Soller *et al* 2003, Torella *et al* 2002). In the near-infrared wavelength region, especially between 600 nm and 1000 nm, light can penetrate relatively deeply due to weak absorption, where optical signal loss is predominantly due to scattering by tissue. Generally, optical properties of tissue can be characterized by the absorption (μ_a) and reduced scattering coefficients (μ'_s). μ_a and μ'_s are defined as the inverse of the average photon path length before absorption and the inverse of the average distance over which the direction of propagation of a photon is randomized, respectively. In addition, oxy- and deoxyhemoglobin have distinct absorption spectra in this wavelength region. NIRS devices exploit blood chromophore properties of light absorption at characteristic wavelengths, and accordingly, the amount of light absorbed is directly proportional to the chromophore concentration. However, these are limited by their ability to measure only light absorption and do not account for light scatter that occurs in complex tissues (Matcher and Cooper 1994, Matcher *et al* 1994). While NIRS devices are able to monitor relative changes in tissue chromophore concentration, this results in significant limitations, with the inability to accurately differentiate absolute concentration of oxygenated

tissue hemoglobin (Hb-O₂) from deoxygenated tissue hemoglobin (Hb-R) (Boas *et al* 2001, Matcher and Cooper 1994, Strangman *et al* 2003). In addition, there may exist rapid changes in scattering properties during hemorrhage that may also confound chromophore concentration calculations if scattering properties of tissue are assumed to be constant.

Broadband diffuse optical spectroscopy (DOS) is a novel technique that is able to simultaneously measure both light absorption and light scattering in turbid media and tissue (Bevilacqua *et al* 2000, Jakubowski 2002, Pham *et al* 2000, Tromberg *et al* 2000). Instrumentation based on this theory is not limited by the restrictions seen in conventional NIRS, and as a result, DOS has the potential to accurately measure absolute tissue chromophore amounts, especially those of considerable clinical importance in hemorrhage: Hb-O₂ and Hb-R. In previous studies using a prototype instrument developed in our laboratory, we were able to demonstrate that DOS-derived physiologic hemoglobin properties correlated with invasive measurements of cardiac output (CO), mean pulmonary artery pressure (mPAP), mean systemic arterial pressure (mAP) and arterial oxygen saturation (S_aO₂) (Pham *et al* 2002).

In this study, we address changes of peripheral tissue perfusion during blood volume depletion, by comparing systemic variables (sHgb, CO, mAP, S_aO₂ and venous oxygen saturation (S_vO₂)) to non-invasive measurements obtained by DOS. We hypothesized that tissue hemoglobin concentration (THC), where $THC = [Hb-O_2] + [Hb-R]$ and tissue oxygenation ($S_T O_2 = [Hb-O_2]/THC \times 100\%$), would correlate with both invasive physiologic and systemic hemoglobin measurements.

2. Material and methods

The study was approved by the Institutional Laboratory Animal Care and Use Committee, University of California, Irvine (ARC protocol no 2000-2218).

2.1. Anesthesia and intubation

Male New Zealand White rabbits ($N = 16$) (Myrtle's Rabbitry Inc., Thompson Station, TN) weighing 4.0 ± 0.4 kg were anesthetized with 2:1 ratio of ketamine HCl (100 mg ml^{-1}) (Ketaject, Phoenix Pharmaceutical Inc., St Hoeseph, MI):xylazine (20 mg ml^{-1}) (Anased, Lloyed Laboratories, Shenandoa, IA) at a dose of 0.75 ml kg^{-1} IM. After the IM injection, a 22–24 gauge, 1 inch catheter was placed in the animal's marginal ear vein to administer IV anesthesia and secured with 1 inch standard porous adhesive tape. Maintenance anesthetic was dosed at 0.3 ml of 1:1 mixture of ketamine:xylazine IV (ketamine 100 mg ml^{-1} :xylazine 20 mg ml^{-1}) as needed. Depth of anesthesia was monitored according to established guidelines. Animals were intubated with a 3.0 endotracheal tube and mechanically ventilated (Harvard apparatus dual phase control respirator, South Natick, MA) at a respiration rate of 32 min^{-1} and a tidal volume of 50 cc and FiO₂ of 100%. Pulse oximetry was accomplished with a probe placed on the tongue to measure S_aO₂ (Biox 3700 Pulse Oximeter, Ohmeda, Boulder, CO) and compared to arterial blood gas measurements.

2.2. Cardiac output and blood pressure

After adequate anesthesia, a median sternotomy was performed to expose the heart. A calibrated flow transducer (T106 small animal flow meter, Transonic System Inc., Ithaca, NY) was placed around the ascending aorta to determine cardiac output (CO). The mean CO was determined from a 10 s sample. Pulmonary artery pressures were obtained by placement of an

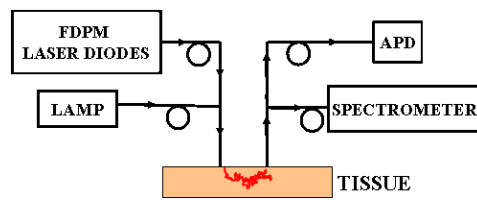


Figure 1. Schematic diagram of broadband diffuse optical spectroscopy (DOS). Broadband DOS combines frequency domain photon migration (FDPM) measurements obtained from intensity-modulated laser diodes and an avalanche photodiode (APD) with a steady-state near-infrared (NIR) spectroscopy obtained from the broadband source (lamp) and the spectrometer for the quantitative measurement of the absolute tissue chromophore concentrations.

18-gauge catheter in the pulmonary artery and connected to a calibrated pressure transducer (TSD104A transducer and MP100 WSW System, Biopac Systems Inc., Santa Barbara) and collected digitally. Mean, systolic and diastolic pressures were determined from 5–10 s tracings.

2.3. Blood gas analysis and complete blood count

A right femoral arterial line was placed for arterial blood draws and systemic pressures. After each blood draw, lines were flushed with less than 0.5 cc of heparin (Elkins-Sinn Inc., Cherry Hill, NJ) to prevent line thrombus occlusion. Arterial blood samples were measured with a blood gas analyzer (IRMA Series 2000 Blood Analysis System, Diametrics Medical Inc., St Paul, MN). Mixed venous blood samples were drawn from the pulmonary artery. Complete blood counts (CBC) were obtained from collected samples of venous blood and sent to an outside facility (Antech Diagnostics, Irvine, CA) for measurements.

2.4. Non-invasive measurements (broadband diffuse optical spectroscopy)

Detailed analysis of broadband DOS and the prototype system we constructed in our laboratory has been described previously (Bevilacqua *et al* 2000, Jakubowski 2002, Pham *et al* 2000, Tromberg *et al* 2000). Briefly, a multi-wavelength, frequency domain photon migration (FDPM) instrument (Fantini *et al* 1995, Pogue and Patterson 1994) was combined with a steady-state near-infrared (NIR) spectrometer for the non-invasive *in vivo* measurement of tissue chromophore concentration (figure 1). A plastic probe containing the source and detector fibers was placed on the anterior medial surface of the right hind thigh for broadband DOS measurement. The source and detector separation of 10 mm is used for both FD and steady-state (SS) acquisitions. The broadband DOS prototype we used employs six laser diodes (661, 681, 783, 823, 850 and 910 nm) and a fiber-coupled avalanche photodiode (APD) detector (Hamamatsu high-speed APD module C5658). The APD detects the intensity-modulated diffuse reflectance signal at modulation frequencies between 50 and 550 MHz after propagating through the tissue. The absorption and reduced scattering coefficients are measured directly at each of the six laser diode wavelengths using the frequency-dependent phase and amplitude data. The reduced scattering coefficient is calculated throughout the NIR by fitting a power law to these six reduced scattering coefficients ($\mu'_s = a\lambda^{SP}$, where λ is the wavelength, a is the prefactor and SP is the scattering power) (Graaff *et al* 1992, Mourant *et al* 1997, Schmitt and Kumar 1998). The acquired reduced scattering spectrum characterizes the scattering properties of tissue throughout NIR. The steady-state acquisition is a broadband NIR

reflectance measurement from 650 nm to 1000 nm that follows the FD measurements using a tungsten–halogen light source (FiberLite lamp) and a miniature spectrometer (Ocean Optics USB2000). It takes ~ 30 s to make a single broadband DOS measurement. The intensity of the steady-state (SS) reflectance measurements is calibrated to the FD values of absorption and scattering to establish the absolute reflectance intensity. The absolute steady-state reflectance spectra are then analyzed to calculate tissue absorption coefficient (μ_a) spectra. Finally, the tissue concentrations of Hb-O₂, Hb-R and H₂O are calculated by a linear least-squares fit of the wavelength-dependent extinction coefficient spectra of each chromophore. The concentration calculation was conducted after each experiment using real-time data acquired during the study.

2.5. Experimental procedures

After completion of the sternotomy, baseline measurements of the above-mentioned variables were obtained and non-invasive assessment of Hb-O₂ and Hb-R was completed. The first hemorrhage was accomplished by withdrawing blood via a femoral arterial line over 30–60 s. The blood drawing and measurement process was repeated every 20 min until a 20% blood loss (10–15 cc kg⁻¹) was achieved to attain hypovolemia. Measurements took about 10 min. An individual animal experiment lasted for approximately 60 min. At completion of the experiment, each animal was euthanized with an intravenous injection of Eutha-6 (1.0–2.0 ml) through the marginal ear vein catheter according to animal laboratory guidelines (Institutional Laboratory Animal Care and Use Committee, University of California, Irvine, ARC protocol no 2000-2218).

2.6. Statistical analysis

Pairwise related changes for data points over more than two time points were assessed by a paired nonparametric test (Wilcoxon rank sum test). Statistical significance was assumed for $p < 0.05$. Error bars in figures indicate standard error.

3. Results

3.1. Control experiment

Non-hemorrhage control experiments were conducted with three animals to determine any changes in physiological and broadband DOS measurements. Hb-O₂, Hb-R, THC concentrations and S_TO₂ were within 5% of baseline values at the end of hemorrhage. Likewise, sHgb, S_aO₂, S_vO₂, CO and mAP all remained within 6% of baseline values at the end of hemorrhage. These changes may be attributed to exposure to anesthesia effects and blood withdrawals for blood gas and sHgb analysis.

3.2. Broadband DOS tissue hemoglobin concentrations versus conventional physiological variables

Figure 2(a) demonstrates the changes in absolute concentrations of THC, Hb-O₂ and Hb-R with each successive blood draw. Prior to the blood draw, the baseline [Hb-O₂], [Hb-R] and THC from the broadband DOS were 38.3 ± 3.1 , 20.7 ± 3.2 and 59.6 ± 3.3 μM , respectively. With increasing hemorrhage blood volume, THC and [Hb-O₂] showed a decrease of 27% and 41% from the baseline concentrations, respectively, at the end of hemorrhage, while [Hb-R] remained nearly constant during blood draw. Also, when examining the ratio of the

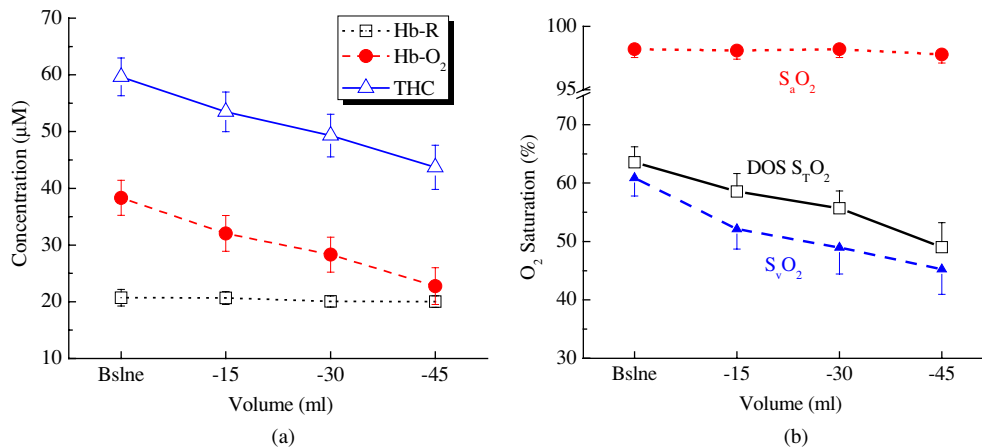


Figure 2. (a) Total tissue hemoglobin concentration (THC), [Hb-O₂] and [Hb-R] versus volume loss (ml of blood removed) during hemorrhage. (b) Arterial blood (S_aO₂), venous blood (S_vO₂) and DOS tissue oxygen (S_TO₂) saturation versus hemorrhage. Data are presented as mean ± standard error.

absolute concentration of Hb-O₂ and Hb-R, a decline of about 38% from baseline was noted. In figure 2(b), arterial oxygen saturation (S_aO₂) from the blood was maintained above 97% throughout the experiment. Systemic venous oxygen saturation (S_vO₂) from the blood, however, decreased during blood volume withdrawal. Similarly, a decline of about 14% in broadband DOS S_TO₂ was observed. Changes in S_TO₂ were similar to those of S_vO₂ measured directly (figure 2(b)). The decrease in THC is due to blood loss. However, the decrease in THC due to blood loss results in decrease in tissue perfusion, with a resultant increased tissue extraction of oxygen. This increased oxygen extraction then leads to the decrease in [Hb-O₂] and the overall average oxygen saturation in tissue and decreased [Hb-O₂]/[Hb-R].

Broadband DOS measurements of tissue oxygen saturation S_TO₂ and THC demonstrated similar trends with systemic arterial pressure and cardiac output (figures 2(b) and 3). All variables displayed a decreasing trend with successive blood withdrawal. Also, both measurements of broadband DOS THC and systemic hemoglobin (sHgb) displayed a downward trend with blood volume withdraw (figure 3). DOS demonstrated a greater percent change when compared to systemic values. Significant differences compared to baseline ($p < 0.05$) were noted in DOS THC and not sHgb following the initial blood draw. As can be seen in figure 3, the initial measurement of DOS THC decrease from baseline following blood removal is greater than the initial drop in measured sHgb. This is an example where some divergence between DOS THC measurements and standard sHgb would be expected since the initial response to early hemorrhage is predominately vasoconstriction in decreased cardiac output, while serum hemoglobin concentrations are not expected to change so quickly. Overall, however, broadband DOS THC and sHgb versus blood loss were closely correlated ($r^2 = 0.96$).

3.3. Broadband DOS tissue hemoglobin concentrations versus NIRS

The conventional NIRS calculation methods assume that tissue scattering properties do not change in a given tissue region, even during acute hemorrhage. As a result, the differential path length factors (the ratio of the mean optical path length and the physical light

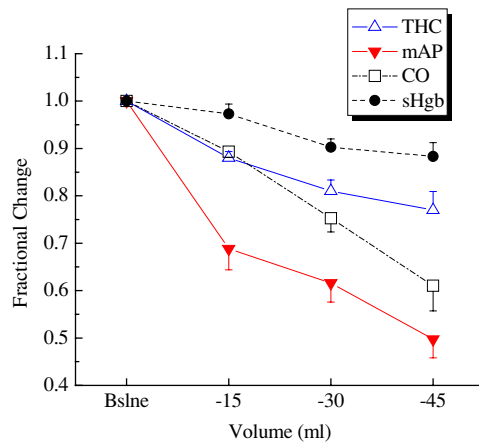


Figure 3. Total tissue hemoglobin concentration (THC) and systemic variables versus volume loss (ml of blood removed) during hemorrhage. THC, cardiac output (CO), mean arterial pressure (mAP) and systemic hemoglobin (sHgb) declined with hemorrhage when compared to baseline measurements. A significant ($p < 0.05$) reduction in THC during the initial blood draw was observed when compared to baseline measurements. This was not apparent with sHgb initially, although by the second blood draw both had significantly decreased. Data are presented as mean \pm standard error.

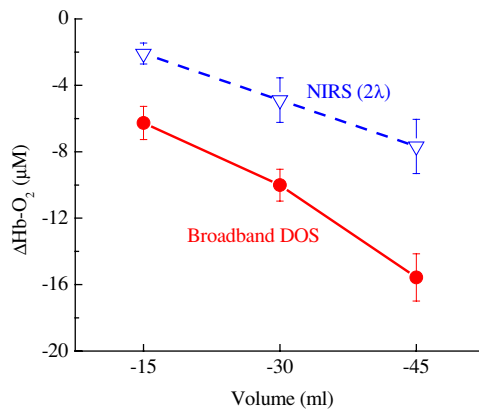


Figure 4. Comparison of $[\text{Hb-O}_2]$ between broadband DOS and two wavelength NIRS calculations. Wavelengths of 685 and 850 nm were used for NIRS analysis. Data are presented as mean \pm standard error.

source–detector separation at each wavelength) are assigned fixed values at the baseline measurement. Figure 4 demonstrates the sensitivity of broadband DOS over the conventional NIRS during hemorrhage. For this purpose, the changes in NIRS $[\text{Hb-O}_2]$ and $[\text{Hb-R}]$ were calculated with two wavelengths (685 and 850 nm) with fixed differential path length factors and compared with broadband values. While both $[\text{Hb-R}]$ remained nearly constant at the respective baseline values, broadband DOS $[\text{Hb-O}_2]$ showed about two-fold greater decline than NIRS values with each blood withdrawal. Also, from broadband DOS measurements, we observed significant changes ($p = 0.043$) in tissue scattering properties from the scattering power ($\text{SP}, \mu'_s = a\lambda^{\text{SP}}$) between the baseline and the post-hemorrhage values (+23%).

4. Discussion

The results of these studies demonstrate that broadband DOS can non-invasively quantify *in vivo* Hb-O₂ and Hb-R in tissue during hemorrhage. Broadband DOS measured decreases in THC, which paralleled sHgb, during hemorrhage. The greater sensitivity of broadband DOS is realized by greater percent changes in broadband DOS-measured tissue hemoglobin concentration compared to changes in systemic invasively measured hemoglobin concentrations (which may take time to equilibrate). The decrease in THC was mainly due to decrease in [Hb-O₂], while [Hb-R] was maintained nearly constant in tissue. [Hb-O₂] drops because of decreases in tissue blood volume, and increased extraction of oxygen from the blood by the tissues. [Hb-R] stays relatively constant because the decrease in blood volume and sHgb are countered by the greater conversion of Hb-O₂ to Hb-R in the tissues from the increased oxygen extraction during hemorrhage. Whether [Hb-R] increases or decreases is dependent on whether increased Hb-R fraction is outweighed by the loss in total hemoglobin from hemorrhage or vasoconstriction.

Previous NIRS studies have been applied in the use of monitoring tissue oxygen saturation status (Beilman *et al* 1999, Buchner *et al* 2000, Chaisson *et al* 2003, Crookes *et al* 2004, Torella *et al* 2002). These devices, however, are limited because tissue optical properties (particularly NIR scattering) change under varying degrees of hypovolemia, and as a result, confound determinations. While standard NIRS devices can measure relative changes in tissue hemoglobin concentrations and estimate tissue oxygen saturation changes, many lack the ability to measure absolute concentrations of oxygenated and deoxygenated hemoglobin in tissue and do not account for scattering changes. This limitation that arises from an inability to measure tissue light scattering is a major limitation because scattering is the dominant effect in NIR light transport and scattering changes are substantial during hemorrhage (Wilson *et al* 1992). To compensate for this, standard NIRS approaches often use calibration curves or average path length calculations empirically derived from healthy subjects. These corrections can provide reliable measurements for hemodynamically stable patients. However, as stated above, since both tissue scattering and absorption are changing during volume depletion, results become unreliable when these acute systemic changes occur. In addition, photon path lengths display a high degree of intra-subject variation, which complicates absolute comparisons in both individuals and across populations (Quaresima *et al* 1998). Broadband DOS overcomes these limitations by simultaneously measuring both tissue absorption and scattering properties directly and can therefore measure absolute tissue deoxygenated and oxygenated hemoglobin concentrations without the above assumptions or the need to generate a calibration curve for each series of observations.

Because the correlation between broadband DOS-measured THC and systemic variables is seen, this added functionality may serve well in assessing acute hemorrhage. Often systemic hemoglobin measurements do not reflect volume loss until compensation by the intracellular and interstitial fluid compartment occurs (Guyton and Hall 1997). Furthermore, vasoconstriction mechanisms by skin and muscle microvasculature compensate for hypovolemia by shunting blood centrally, and as a result, further decrease peripheral tissue hemoglobin. Broadband DOS may provide a unique advantage by detecting these decreases in tissue hemoglobin at more 'volume-sensitive' regional sites sooner than that which would be observed by systemic hemoglobin measurements. Therefore, broadband DOS may detect these peripheral changes initiated by hypovolemia before systemic signs are present and may provide further insight in regard to the patient's perfusion state.

A critical advantage broadband DOS has over previously described NIRS devices is the ability to measure absolute concentrations of tissue Hb-O₂ and Hb-R. Out in the field, the

initial assessment of a trauma victim is limited to available monitoring devices. As a result, it is difficult to assess the degree of hypovolemia, or more importantly, hypoperfusion. NIRS devices are limited in these situations because of the need to start with a baseline measurement and compare future measurements with these over a given time period or perturb tissue. Although these devices may be useful in the assessment of the resuscitation period, they lack the ability to assess the patient's initial perfusion state. Broadband DOS measurements provide the potential capability of giving an initial assessment to the perfusion state of the patient, by providing tissue Hb-O₂ and Hb-R that is derived from the absolute hemoglobin concentrations. For example, decreased ratios of Hb-O₂ to Hb-R suggest oxygen debt whereas increasing ratios are more suggestive of an oxygen reserve. We speculate that by applying these data with the vital signs and clinical observation one may be able to provide a more rapid assessment of the patient's perfusion state, and depending on the available resources, initiate the resuscitation effort, or as in the case of multiple traumas rapidly move to assess the next injured party. Future clinical studies will be needed to assess this potential.

There are a number of limitations to this initial study. Our study was limited to a single perturbation, hemorrhage, in order to minimize confounding variables. However, we cannot account for possible contributions from peripheral vascular changes that may occur from concomitant events other than hemorrhage. In addition, anesthesia may alter some of the physiologic compensatory mechanisms reflected in the broadband DOS measurements. To address these concerns, further studies delineating the influence of vasopressors and vasodilators on broadband DOS measurements are under investigation. Trauma involving burns, serious infections resulting in sepsis, hyperthermia and hypothermia may also influence broadband DOS observations, which is another limitation to our current model. One could envision that monitoring multiple sites may be more representative of the systemic condition of the subject; however, our studies include only single-site measurements. Since the absolute tissue Hgb levels will change with variations in tissue composition, multiple-site measurements may normalize these tissue differences. In addition, a two-layer diffuse model of the layered structure of tissue would potentially reduce the variation in absolute quantification of tissue hemoglobin concentrations (Kienle *et al* 1998). Another limitation of broadband DOS and NIRS in general is the inability to distinguish between hemoglobin and myoglobin contributions. However, the concentration of oxy- and deoxymyoglobin shows little detectable variation in the clinically relevant ranges of tissue pO₂; hence, the absorbance due to this chromophore is essentially constant (Richards-Kortum and Sevick-Muraca 1996).

5. Conclusion

A significant amount of resources are needed for assessment of volume depletion in the critically ill patient, often consisting of surveillance serial blood drawing. This is not only time consuming with a substantial cost, but, as mentioned previously, has a time delay in physiologic response. A non-invasive, continuous real-time assessment would be an advance for monitoring signs of hypovolemia and of possible hypoperfusion. Broadband DOS has the potential to offer these assessment capabilities at the initial patient examination and over a continuous time period.

Acknowledgments

The authors would like to thank Terry Waite-Kennedy, Tanya Burney, David Mukai, Hamza Beydoun, Jennifer Armstrong, Kelly Kreuter, Erin Matheny, Reza Mina, Andrew Duke and

Blanding Jones for their assistance with these experiments. This work was supported by Air Force (AF49620-00-10371) and Laser Microbeam and Medical Program, Beckman Laser Institute, University of California, Irvine (grant no 445574-30133).

References

- Beilman G J, Groehler K E, Lazon V and Ortner J P 1999 Near-infrared spectroscopy measurement of regional tissue oxyhemoglobin saturation during hemorrhagic shock *Shock* **12** 196–200
- Bevilacqua F, Berger A J, Cerussi A E, Jakubowski D and Tromberg B J 2000 Broadband absorption spectroscopy in turbid media by combined frequency-domain and steady-state methods *Appl. Opt.* **39** 6498–507
- Boas D A, Gaudette T, Strangman G, Cheng X, Marota J J and Mandeville J B 2001 The accuracy of near infrared spectroscopy and imaging during focal changes in cerebral hemodynamics *Neuroimage* **13** 76–90
- Boushel R and Piantadosi C A 2000 Near-infrared spectroscopy for monitoring muscle oxygenation *Acta Physiol. Scand.* **168** 615–22
- Buchner K, Meixensberger J, Dings J and Roosen K 2000 Near-infrared spectroscopy—not useful to monitor cerebral oxygenation after severe brain injury *Zentralbl. Neurochir.* **61** 69–73
- Chaisson N F, Kirschner R A, Deyo D J, Lopez J A, Prough D S and Kramer G C 2003 Near-infrared spectroscopy-guided closed-loop resuscitation of hemorrhage *J. Trauma* **54** S183–92
- Crookes B A, Cohn S M, Burton E A, Nelson J and Proctor K G 2004 Noninvasive muscle oxygenation to guide fluid resuscitation after traumatic shock *Surgery* **135** 662–70
- Dubick M A and Atkins J L 2003 Small-volume fluid resuscitation for the far-forward combat environment: current concepts *J. Trauma* **54** S43–5
- Fantini S, Franceschini M, Maier J S, Walker S A, Barbieri B and Gratton E 1995 Frequency-domain multichannel optical detector for noninvasive tissue spectroscopy and oximetry *Opt. Eng.* **34** 32–42
- Graaff R, Aarnoose J G, Zijp J R, Sloot P M A, de Mul F F M, Greve J and Koelink M H 1992 Reduced light-scattering properties for mixtures of spherical particles: a simple approximation derived from Mie calculation *Appl. Opt.* **31** 1370–6
- Guyton A and Hall J 1997 *Human Physiology and Mechanisms of Disease* 6th edn (Philadelphia, PA: Saunders)
- Jakubowski D J 2002 Development of broadband quantitative tissue optical spectroscopy for the non-invasive characterization of breast disease *PhD Thesis* Beckman Laser Institute, University of California, Irvine
- Kienle A, Patterson M S, Dgnitz N, Bays R, Wagnires G and van den Bergh H 1998 Noninvasive determination of the optical properties of two-layered turbid media *Appl. Opt.* **37** 779–91
- Lovell A T, Owen-Reece H, Elwell C E, Smith M and Goldstone J C 1999 Continuous measurement of cerebral oxygenation by near infrared spectroscopy during induction of anesthesia *Anesth. Analg.* **88** 554–8
- Matcher S J and Cooper C E 1994 Absolute quantification of deoxyhaemoglobin concentration in tissue near infrared spectroscopy *Phys. Med. Biol.* **39** 1295–312
- Matcher S J, Cope M and Delpy D T 1994 Use of the water absorption spectrum to quantify tissue chromophore concentration changes in near-infrared spectroscopy *Phys. Med. Biol.* **39** 177–96
- Mourant J R, Fuselier T, Boyer J, Johnson T and Bigio I J 1997 Predictions and measurements of scattering and absorption over broad wavelength ranges in tissue phantoms *Appl. Opt.* **36** 949–57
- Pham T H, Coquoz O, Fishikin J B, Anderson E and Tromberg B J 2000 Broad bandwidth frequency domain instrument for quantitative tissue optical spectroscopy *Rev. Sci. Instrum.* **71** 2500–13
- Pham T H, Hornung R, Ha H P, Burney T, Serna D, Powell L, Brenner M and Tromberg B J 2002 Noninvasive monitoring of hemodynamic stress using quantitative near-infrared frequency-domain photon migration spectroscopy *J. Biomed. Opt.* **7** 34–44
- Pogue B W and Patterson M S 1994 Frequency-domain optical absorption spectroscopy of finite tissue volumes using diffusion theory *Phys. Med. Biol.* **39** 1157–80
- Puyana J C, Soller B R, Zhang S and Heard S O 1999 Continuous measurement of gut pH with near-infrared spectroscopy during hemorrhagic shock *J. Trauma* **46** 9–15
- Quaresima V, Matcher S J and Ferrari M 1998 Identification and quantification of intrinsic optical contrast for near-infrared mammography *Photochem. Photobiol.* **67** 4–14
- Richards-Kortum R and Sevick-Muraca E 1996 Quantitative optical spectroscopy for tissue diagnosis *Annu. Rev. Phys. Chem.* **47** 555–606
- Schmitt J M and Kumar G 1998 Optical scattering properties of soft tissue: a discrete particle model *Appl. Opt.* **37** 2788–97
- Shadid M, Hiltermann L, Monteiro L, Fontijn J and Van Bel F 1999 Near infrared spectroscopy-measured changes in cerebral blood volume and cytochrome aa3 in newborn lambs exposed to hypoxia and hypercapnia,

- and ischemia: a comparison with changes in brain perfusion and O₂ metabolism *Early Hum. Dev.* **55** 169–82
- Soller B R, Idwasi P O, Balaguer J, Levin S, Simsir S A, Vander Salm T J, Collette H and Heard S O 2003 Noninvasive, near infrared spectroscopic-measured muscle pH and PO₂ indicate tissue perfusion for cardiac surgical patients undergoing cardiopulmonary bypass *Crit. Care Med.* **31** 2324–31
- Strangman G, Franceschini M A and Boas D A 2003 Factors affecting the accuracy of near-infrared spectroscopy concentration calculations for focal changes in oxygenation parameters *Neuroimage* **18** 865–79
- Torella F, Cowley R, Thorniley M S and McCollum C N 2002 Monitoring blood loss with near infrared spectroscopy *Comp. Biochem. Physiol. A: Mol. Integr. Physiol.* **132** 199–203
- Tromberg B J, Shah N, Lanning R, Cerussi A, Espinoza J, Pham T, Svaasnad L and Butler J 2000 Non-invasive *in vivo* characterization of breast tumors using photon migration spectroscopy *Neoplasia* **2** 26–40
- Wilson B C, Sevick E M, Patterson M S and Chance B 1992 Time-dependent optical spectroscopy and imaging for biomedical applications *Proc. IEEE* **80** 918–30