UC Irvine
UC Irvine Previously Published Works

Title

Non-invasive in vivo diffuse optical spectroscopy monitoring of cyanide poisoning in a rabbit model**Presented in part in Chest 128 (4) 301S (October 2005) and Journal of Investigative Medicine 53 (1) S113 (January 2005) as abstracts.

Permalink

https://escholarship.org/uc/item/9dx6z0zn

Journal

Physiological Measurement, 28(9)

ISSN

Authors

Lee, Jangwoen
Armstrong, Jennifer
Kreuter, Kelly
et al.

Publication Date

2007-09-01

DOI

Copyright Information

Peer reviewed

Non-invasive *in vivo* diffuse optical spectroscopy monitoring of cyanide poisoning in a rabbit model[*]

Jangwoen Lee[1]**, Jennifer Armstrong**[1]**, Kelly Kreuter**[1]**, Bruce J Tromberg**[1]
and Matthew Brenner[1,2]

[1] Laser Microbeam and Medical Program, Beckman Laser Institute, University of California, Irvine, CA 92612-1475, USA
[2] Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California, Irvine, CA 92868, USA

E-mail: jangwl@uci.edu

Abstract

The objective of this study is to establish a cyanide toxicity animal model and to investigate the ability of broadband diffuse optical spectroscopy (DOS) to non-invasively monitor physiological changes that occur during the development of cyanide toxicity in a rabbit model. Broadband DOS combines multi-frequency frequency-domain photon migration (FDPM) with time-independent near-infrared spectroscopy (NIRS) to quantitatively measure bulk tissue absorption and scattering spectra between 600 nm and 1000 nm. Serum cyanide concentration and arterial and venous blood gas analysis at pre- and post-cyanide infusion were presented. To investigate the ability of DOS to non-invasively monitor physiologic changes occurring during development of CN toxicity, tissue concentrations of deoxyhemoglobin [Hb-R], oxyhemoglobin [Hb-O$_2$], cytochrome c oxidase oxidized state [CcO_Ox] and reduced state [CcO_Re] were determined from absorption spectra acquired in 'real time' during cyanide infusions (NaCN 6 mg/60 ml normal saline) in six pathogen-free New Zealand white rabbits. During cyanide infusion, *in vivo* tissue oxygen saturation increased ($\sim$10%). In addition, broadband DOS was able to detect a concurrent increase in [CcO_Re] and decrease in [CcO_Ox]. Changes in tissue scattering properties in all six animals were detected during these events, confirming the need for DOS-based methods over traditional NIR spectroscopy to obtain accurate results.

Keywords: diffuse optical spectroscopy, cyanide, non-invasive

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

Abbreviations

DOS	diffuse optical spectroscopy
FD	frequency domain
SS	steady state
CcO_Ox	cytochrome c oxidase, oxidized state
CcO_Re	cytochrome c oxidase, reduced state
NIR	near infrared
sCN	serum cyanide concentration

1. Introduction

Cyanide- (CN) based derivatives have been sought out as poisons and chemical weapons (Bokan 2003). CN still constitutes a potential chemical threat to civilians and military personnel. There are numerous sources of potential chemical cyanide exposure (Hall and Rumack 1986). In addition, carbon monoxide, aldehydes and soot are components of traditional fires and plastics such as acrylics and acrylonitriles are the sources of cyanide combustion in modern residential and commercial fires. Tissue hypoxia from cyanide is a major cause of combustion-related fatalities. Studies of victims of residential fires have found higher blood CN concentrations in the deceased than in the survivors, suggesting CN toxicity may predominate over carbon monoxide poisoning (Barillo *et al* 1994, Baud *et al* 1991, Riddle 2004, Strickland *et al* 1992). CN impairs the tissue's ability to utilize oxygen. Cyanide has a high binding affinity for the active site on cytochrome c oxidase. When bound, the electron transport chain is arrested in its reduced form, preventing the donation of an electron. Progressive cytotoxic tissue hypoxia develops. Non-specific symptoms such as pulmonary edema and lactic acidosis are resultant (Graham *et al* 1977, Way *et al* 1988). Currently there is no rapid method to measure blood cyanide levels; the only available method to detect cyanide exposure is through blood CN level tests (Clark *et al* 1981). However, interpretation of blood cyanide levels is difficult due to potential degradation in the blood sample, and the time of sampling and the conditions of blood storage are critical to accurate cyanide concentration levels (Brierley *et al* 1976, Groff *et al* 1985).

The need for rapid identification and ability to continuously monitor patients exposed to cyanide, in a hospital or on the battlefield, is critical. This need is heightened by the potentially large number of people with significant chance of severe injury in catastrophic exposure events and the requirement for a method for effective triage. To address these needs, tissue oxygen hemoglobin saturation (Beilman *et al* 1999, Chaisson *et al* 2003, Crookes *et al* 2004, Boushel and Piantadosi 2000) and cytochrome oxidation monitoring with near-infrared spectroscopy (NIRS) has long been proposed as a possible alternative to invasive monitoring (Noriuki *et al* 1997, Piantadosi *et al* 1983). The optical extinction coefficients of Hb-R, Hb-O$_2$, CcO_Ox and CcO_Re have unique properties that can be used to distinguish amongst them in the NIR region between 600 and 1000 nm (figure 1). NIRS devices exploit light absorption properties of tissue chromophores at characteristic wavelengths in an attempt to detect changes in tissue concentrations and oxidation states. However, previously reported studies have been limited by the ability to measure only light absorption and have not simultaneously accounted for the light scatter that occurs in the tissue (Matcher *et al* 1994). Since blood is a substantial scatterer, changes in tissue perfusion are associated with major changes in both scattering and absorption during cyanide toxicity as well with other changes in hemodynamic state. This inability to measure and account for scattering results in significant limitations on accurately
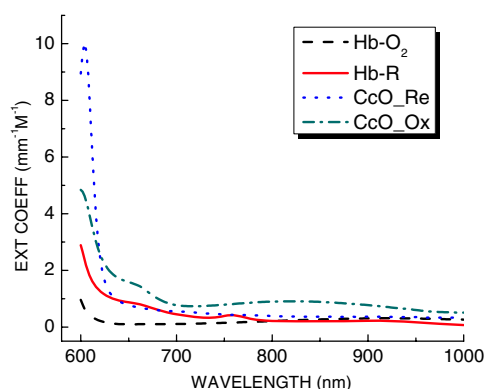
Figure 1. Molar extinction coefficient spectra of deoxyhemoglobin (Hb-R), oxyhemoglobin (Hb-O$_2$), cytochrome c oxidase reduced state (CcO_Re) and oxidized state (CcO_Ox).

measuring oxygenated tissue hemoglobin (Hb-O$_2$), deoxygenated tissue hemoglobin (Hb-R) and total tissue hemoglobin (THC, [Hb-O$_2$] + [Hb-R]). The ability to obtain accurate tissue hemoglobin and perfusion state information, as well as cytochrome redox states would be of great value in detection and monitoring of cyanide toxicity. Since broadband DOS can accurately determine scattering and therefore, absorption, these spectral features of oxidized and reduced states of cytochrome c oxidase together with quantification of endogenous tissue chromophores, including Hb-R and Hb-O$_2$ can be used to optically monitor the progression of cyanide toxicity.

In this study we evaluate the potential for DOS technology to non-invasively monitor and identify cyanide-induced changes and concurrent physiological effects in a rabbit model. The preliminary results to demonstrate the feasibility of DOS technology to non-invasively detect and monitor the physiologic changes associated with CN toxicity.

2. Material and methods

Six pathogen-free New Zealand white rabbits (Western Oregon Rabbit Company, Philomath, OR), weighing 4.17 ± 0.21 kg, were used. Animals were housed in an animal facility and were given a commercial basal diet and water *ad libitum*. The study was approved by the Institutional Laboratory Animal Care and Use Committee, University of California, Irvine (ARC protocol No. 2000-2218).

2.1. Broadband diffuse optical spectroscopy

A prototype multi-wavelength, frequency-domain instrument (FDPM) that we designed and constructed in our laboratory was combined with a steady-state near-infrared (NIR) spectrometer to create the broadband DOS device for the non-invasive *in vivo* assessment of tissue chromophore content (Bevilacqua *et al* 2000, Tromberg *et al* 2000). The broadband DOS system employs six laser diodes (661, 681, 783, 810, 823 and 850 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 300 MHz after propagation through the tissue. The absorption and reduced scattering coefficients (μ_a and μ'_s, respectively) are measured directly at each of the six

laser diode wavelengths using the frequency-dependent phase and amplitude data (Bevilacqua *et al* 2000, Tromberg *et al* 2000, Pham *et al* 2000). μ_s' describes the diffusion of photons in a random walk of step size of $1/\mu_s'$ (cm) where each step involves isotropic scattering. The reduced scattering coefficient is calculated as a function of wavelength throughout the NIR by fitting a power law to these six reduced scattering coefficients ($\mu_s'(\lambda) = $ constant $\times \lambda^{SP}$, where SP is the scattering power) (Graaff *et al* 1992, Mourant *et al* 1997, Schmitt and Kumar 1998). The steady-state acquisition is a broadband reflectance measurement from 600 nm to 1000 nm using a tungsten–halogen light source (Ocean Optics HL-2000) and a spectrometer (Oriel MS127i, InstraSpec IV CCD) after the FD measurements are completed. The intensity of the steady-state (SS) reflectance measurements are calibrated to the FD values of absorption and scattering to establish the *absolute* reflectance intensity. Finally, the tissue concentrations of Hb-O$_2$, Hb-R, H$_2$O and cytochrome c oxidase reduced and oxidized states are calculated by a linear least squares fit of the wavelength-dependent extinction coefficient spectra of each chromophore. We used Hb-O$_2$, and Hb-R absorption spectra reported by Zijlstra *et al* (2000) and CcO_Ox and CcO_Re absorption spectra reported by Moody *et al* (Rich and Moody 1996) for the subsequent fitting and analysis (figure 1).

2.2. Experimental procedures

The animals were initially sedated by an intramuscular injection of a mixture of ketamine HCl (100 mg ml^{-1}, Ketaject, Phoenix Pharmaceutical Inc., St Joseph, MI) and xylazine (20 mg ml^{-1}, Anased, Lloyd Laboratories, Shenandoah, IA) at a dose of 0.75 cc kg^{-1}. The animal's body weight and temperature were assessed after sedation. A 22-gauge catheter was secured in the animal's marginal ear vein for subsequent intravenous anesthesia injections. The maintenance anesthetic was dosed at 0.3 cc of a 1:1 mixture of ketamine:zylazine (ketamine 100 mg ml^{-1} : xylazine 20 mg ml^{-1}) and administered accordingly. The animals were incubated with a 3.0 cuffed endotracheal tube and placed on mechanical ventilation (dual phase control respirator, model 32A4BEPM-5R, Harvard Apparatus, Chicago, IL) with the following settings: tidal volume, 50 cc, respiratory rate 25 breaths min^{-1}, and 100% oxygen. Blunt dissection was performed to isolate the femoral artery and vein on the left thigh slightly distal to the inguinal ligament and 20-gauge catheters were secured within the femoral artery and vein for the systemic blood pressure measurements, and arterial and venous blood gas sampling. Blood pressure measurements were obtained with a calibrated pressure transducer (TSD104A Transducer and MP100 WSW System, Biopac Systems, Inc., Santa Barbara, CA, USA). A plastic probe containing the source and detector optical fibers (separation distance of 10 mm) was placed on the medial surface of the right thigh anteriorly for the broadband DOS measurements.

Cyanide dosage was determined based upon previous literatures (NaCN 6 mg/60 ml normal saline) to provide non-lethal cyanide toxicity (Vick *et al* 2000, Rumack 1983) and NaCN solution was infused at a rate of 1 ml min^{-1}. Blood was drawn twice, prior the cyanide infusion and immediately after the completion of cyanide infusion. Blood samples were obtained from the femoral artery and vein and were analyzed for pH, pO$_2$, pCO$_2$ and% O$_2$ saturation (IRMA series 2000 Blood Analysis System, Diametrics Medical Inc.). Animals that developed distress during the study and all surviving animals were euthanized by standard procedures (Eutha-6, intravenous injection).

2.3. Statistical analysis

For the statistical analysis, Wilcoxon matched-pairs signed rank sum test was used to evaluate significant changes in blood gas and broadband DOS parameters between pre- and post-

Table 1. Serum cyanide concentration (sCN), mean arterial pressure (mAP) and arterial and venous blood gas measurements (PCO_2, partial pressure of CO_2; PO_2, partial pressure of O_2; BE, base excess; SO_2, oxygen saturation in blood) at baseline and immediately after the completion of CN infusion. The subscripts, a and v, designate arterial and venous values, respectively. Data are presented as mean ± SEM. (bpm) indicates beats per minute of the heart rate.

	Baseline	Post CN injection	*p*-value
sCN (μg dl^{-1})	<5	111.3 ± 12.2	0.028[a]
mAP (mmHg)	58.0 ± 4.0	35.6 ± 2.3	0.066
Heart rate (bpm)	160.0 ± 3.9	171.0 ± 4.1	0.068
pH_a	7.48 ± 0.01	7.43 ± 0.04	0.5
P_aCO_2 (mmHg)	46.5 ± 3.4	39.3 ± 3.5	0.116
P_aO_2 (mmHg)	493.4 ± 14.8	597.22 ± 23.2	0.028[a]
BE_a (mM)	9.47 ± 1.15	2.08 ± 1.68	0.028[a]
S_aO_2 (%)	99.9 ± 0.00	99.9 ± 0.00	
pH_v	7.42 ± 0.01	7.29 ±0.04	0.027[a]
P_vCO_2 (mmHg)	56.3 ± 3.3	58.8 ± 3.9	0.5
P_vO_2 (mmHg)	39.2 ± 3.0	48.2 ± 1.6	0.028[a]
BE_v (mM)	10.07 ± 1.33	0.60 ± 1.93	0.043[a]
S_vO_2 (%)	70.0 ± 2.2	77.7 ± 1.7	0.043[a]

[a] Statistical significance with $P < 0.05$.

cyanide infusion. Two-sided *p*-values using normal approximation were reported. All data are shown as means ± standard error of mean (SEM) and a difference $p < 0.05$ was considered significant. The statistical analysis was carried out using the interactive website (http://www.fon.hum.uva.nl/Service/Statistics/Signed_Rank_Test.html).

3. Results

Table 1 summarizes the results of arterial and venous blood gas analysis and serum cyanide (sCN) concentrations from the toxicology laboratory. After 6 mg of CN infusion (in 60 ml normal saline, NS), the sCN levels rose to $111.3 \pm 12.2 \, \mu$g dl^{-1}. From blood gas analysis data, notable changes are observed after CN infusion in mean arterial and venous partial pressure of oxygen (PO_2), arterial and venous base excess values (BE), venous pH and venous oxygen saturation (S_vO_2). Mean arterial pressure (mAP) decreased post-CN infusion even though the change was not statistically significant ($p = 0.066$). The changes in these parameters are indicative of cyanide toxic effects. Despite an increase in post-CN venous PO_2 (22%), concurrent increases in arterial PO_2 during cyanide toxicity led to variable degrees of change in arterial–venous oxygen difference in this animal model. However, an overall decrease in arteriovenous oxygen saturation difference was observed due to the increase in the venous oxygen saturation values. The decreases found in both arterial and venous base excess (BE) were expected as a result of increased anaerobic metabolism due to tissue hypoxia from mitochondrial dysfunction in the setting of cyanide poisoning.

Figures 2(a) and (b) show the changes in absorption and scattering spectra at the baseline and post-cyanide injection in a single rabbit to illustrate the importance of the need to separate tissue scattering and absorption components in the reflectance signal. The infusion of cyanide and resultant physiologic responses to cyanide toxicity led to changes in tissue μ_s' and resulting scattering power (SP). Figure 2(b) demonstrates the ability of DOS to measure *in vivo* tissue absorption spectra in order to quantify the tissue concentrations of Hb-O_2, Hb-R and cytochrome c oxidase redox states. Without separating scattering and absorption
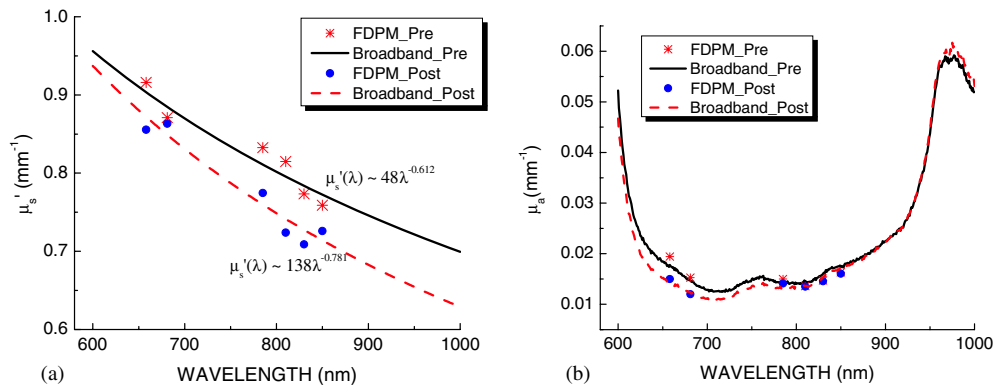
Figure 2. (a) Changes in the reduced scattering coefficient (μ_s') from frequency-domain measurements at discrete wavelengths (FDPM) and broadband μ_s' spectra (Broadband) between baseline (_pre) and the end of CN infusion (_post). Formulae inside the figure represent the power-law fit of μ_s' at six discrete FDPM wavelengths ($\mu_s'(\lambda) = $ constant $\times \lambda^{SP}$, where SP is the scattering power). Data are from a single animal. (b) Changes in the absorption coefficient (μ_a) from frequency-domain measurements at discrete wavelengths (FDPM) and broadband μ_a spectra (broadband) between baseline (-pre) and the end of CN infusion (-post). Data are from a single animal.

Table 2. Tissue hemoglobin concentrations (THC), tissue oxygen saturation (S_TO_2), scattering power (SP), and the changes in cytochrome c oxidase redox states (ΔCcO_Ox and ΔCcO_Re) measured by broadband DOS at baseline and post-CN injection. Data are presented as mean $\pm$ SEM.

	Baseline	Post CN injection	*p*-values
Hb-R (μM)	10.55 ± 1.47	6.51 ± 1.03	0.0313^a
Hb-O$_2$ (μM)	38.60 ± 5.94	38.55 ± 3.69	0.687
THC (μM)	49.15 ± 6.62	45.42 ± 4.21	0.313
S$_T$O$_2$ (%)	78.00 ± 2.93	85.46 ± 2.24	0.0313^a
SP	-0.77 ± 0.07	-1.00 ± 0.07	0.0313^a
ΔCcO_Ox (μM)	0	-1.10 ± 0.43	$<0.001^a$
ΔCcO_Re (μM)	0	0.82 ± 0.35	$<0.001^a$

[a] Statistical significance with $P < 0.05$.

signal from the reflectance measurement as in conventional NIRS measurements, this kind of quantification of tissue chromophore concentrations would not be possible. For instance, overall decrease in tissue absorption spectrum was observed post-cyanide and changes in hemoglobin and cytochrome c oxidase redox state concentrations were quantified as a result.

Figures 3(a) and (b) illustrate the changes in [Hb-O$_2$], [Hb-R] (figure 3(a)) and corresponding changes in tissue oxygen saturation (S$_T$O$_2$ = [Hb-O$_2$]/THC $\times$ 100%), [CcO_Ox], and [CcO_Re] (figure 3(b)) during cyanide infusion (6 mg total) in a single rabbit. It shows the increase in [Hb-O$_2$] and decrease in [Hb-R] resulting in the increase in S$_T$O$_2$. Table 2 summarizes tissue hemoglobin concentrations, S$_T$O$_2$, and scattering power measured by broadband DOS at baseline and post-CN injection. In all six animals, we observed a slight decrease in THC ($\sim -8\%$), which was confirmed by total hemoglobin concentration measured with cooximetry from blood sample (-6.8%). [Hb-R] decreased by 38% while
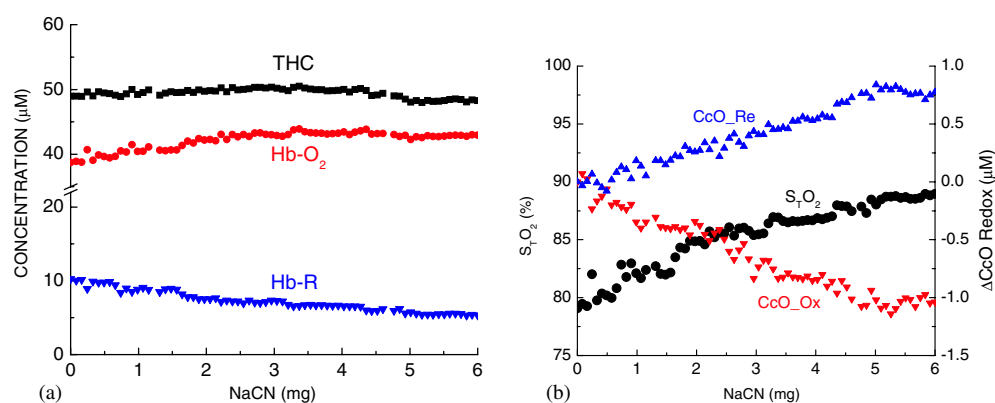
Figure 3. (a) Progression of total tissue hemoglobin concentration (THC) and oxy- and deoxyhemoglobin concentrations ([Hb-O$_2$] and [Hb-R], respectively) during the cyanide infusion (6 mg total) in a single rabbit. (b) Progression of tissue oxygen saturation (S$_T$O$_2$) and oxidized and reduced states of cytochrome c oxidase ([CcO_Ox] and [CcO_Re], respectively) during the cyanide infusion (6 mg total) in the same rabbit.

[Hb-O$_2$] remained nearly constant. The decrease in the [Hb-R] is expected because oxygen consumption at the cellular level is inhibited, and the tissues cannot extract oxygen from the blood. Similar to the S$_v$O$_2$ results from the venous blood gas analysis (+6.7%), the venous oxygen saturation values from the cooximetry increased from a baseline of 70% to post-CN levels of 77%, while the arterial oxygen saturation remained at 99% due to maintenance of the animals on 100% oxygen throughout the studies. This increase in the venous oxygen saturation accounts for the increase in S$_T$O$_2$ values, which were measured using broadband DOS shown in table 2. Figure 3(b) also shows the changes in cytochrome c oxidase redox states with increasing cyanide toxicity. In six animals, the changes in [CcO_Ox] and [CcO_Re] were -1.10 ± 0.43 and 0.82 ± 0.35 μM, respectively.

4. Discussion

We developed a reliable rabbit model to investigate the feasibility of broadband DOS for non-invasive *in vivo* cyanide toxicity monitoring. The development of a rabbit model was chosen due to its economy, availability and the relative ease of handling versus larger animals with comparable physiologic responses of a human. We were not able to find a reliable rabbit CN toxicity model described in the recent literature. Attempts at bolus injections of cyanide during our early animal model development investigations induced seizures and fatal cardiovascular collapse. Subsequently, we utilized a continuous infusion of cyanide in place of the bolus injection with improved stability and reproducibility. The level of [sCN] was significant enough to induce clinical physiologic changes, without resulting in coma or death. Our results were consistent with reported relevant laboratory findings during cyanide toxicity, including an early decreased arteriovenous difference in the partial pressure of oxygen (PO$_2$) with increased venous PO$_2$ and an increase in base deficit (Rumack 1983). In addition, this animal model allowed continuous quantification of the dose response of broadband DOS measurements of *in vivo* [HbO$_2$], [Hb-R], S$_T$O$_2$, [CcO_Ox] and [CcO_Re].

We have demonstrated that broadband DOS can be used to dynamically monitor *in vivo* concentrations of multiple chromophores in tissue non-invasively. Particular emphasis is placed on DOS sensitivity to concurrent physiologic changes due to cyanide toxicity. Near-

infrared spectroscopy has been widely employed for this purpose. However, conventional methods generally do not separate light absorption from scattering, and as a result, do not report absolute biochemical concentrations in tissue. Advances in time- and frequency-domain NIR measurements have resulted in the development of quantitative approaches. However, these methods typically rely on a limited number of optical wavelengths and therefore have reduced sensitivity to multiple analytes over a broad range of concentrations. Broadband DOS is an ideal diagnostic platform for cyanide toxicity determination because it quantifies tissue hemoglobin concentrations and cytochrome c oxidase redox states non-invasively in real time. Because cyanide binds directly to cytochrome c oxidase and induces progressive tissue hypoxia, the evaluation of hemoglobin concentrations and the oxygen saturation at the tissue level would be indicative of the toxic effects of cyanide. In addition, we demonstrate that broadband DOS-detected respective changes in [CcO_Ox] and [CcO_Re] due to the inhibition of the electron transfer chain in mitochondria, findings consistent with reports from previous researchers (Noriuki *et al* 1997, Piantadosi *et al* 1983).

While these findings are encouraging, the definitive analysis of cytochrome c oxidase and proper interpretation of the optical signal originating from the redox changes have been difficult, especially due to the effects of tissue scattering, other potentially interfering chromophores and influence of hematocrit (Sakamoto *et al* 2001). Broadband DOS overcomes some of these problems by directly measuring the scattering properties of tissue. As a result, the changes in optical path length during measurements are taken into account. Also, the combined broadband measurement component of the DOS methodology provides significantly more wavelengths than major chromophores and allows us to more fully utilize the characteristic spectral features of individual chromophores. In theory, concentrations of virtually any NIR absorbing chromophore could be included in the analytical approach. However, there are a number of limitations to this initial study. Our study was limited to an isolated cyanide toxicity, in order to establish the animal model for the cyanide toxicity and demonstrate the feasibility of non-invasive DOS measurements. The cyanide poisonings with co-exposure such as methemoglobin and carbon monoxide were not discussed in this study. However, the feasibility of non-invasive *in vivo* DOS monitoring of methemoglobin has been demonstrated (Lee *et al* 2006) and future studies include the treatment of cyanide toxicity with the therapeutically induced methemoglobinemia and hydroxocobalamin and the study on DOS monitoring of the smoke inhalation.

5. Conclusion

The findings of this study illustrate the feasibility and potential value of broadband DOS as a non-invasive platform for *in vivo* monitoring of cyanide toxicity in an animal model. Future investigations will be needed to validate such potential applications. Ultimately this approach could be used in the clinical setting to gain insight on therapeutic efficacy, particularly in the cases of cyanide toxicity treatment. Additionally, broadband DOS has the theoretical capability for detecting and monitoring a range of processes associated with NIR absorbing solutes *in vivo*.

Acknowledgments

References

Barillo D J, Goode R and Esch V 1994 Cyanide poisoning in victims of fire: analysis of 364 cases and review of the literature *J. Burn Care Rehabil.* **15** 46–57

Baud F J, Barriot P, Toffis V, Riou B, Vicaut E, Lecarpentier Y, Bourdon R, Astier A and Bismuth C 1991 Elevated blood cyanide concentrations in victims of smoke inhalation *N. Engl. J. Med.* **325** 1761–6

Beilman G J, Groehler K E, Lazaron 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

Bokan S 2003 Biological and toxin terrorism weapons *Arh. Hig. Rada Toksikol.* **54** 29–43

Boushel R and Piantadosi C A 2000 Near-infrared spectroscopy for monitoring muscle oxygenation *Acta Physiol. Scand.* **168** 615–22

Brierley J B, Brown A W and Calverley J 1976 Cyanide intoxication in the rat: physiological and neuropathological aspects *J. Neurol. Neurosurg. Psychiatry* **39** 129–40

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

Clark C J, Campbell D and Reid W H 1981 Blood carboxyhaemoglobin and cyanide levels in fire survivors *Lancet* **1** 1332–5

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

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

Graham D L, Laman D, Theodore J and Robin E D 1977 Acute cyanide poisoning complicated by lactic acidosis and pulmonary edema *Arch. Int. Med.* **137** 1051–5

Groff W A Sr S F, Kaminskis A, Froehlich H l and Johnson R P 1985 Plasma free cyanide and blood total cyanide: A rapid completely automated microdistillation assay *Clin. Toxicol.* **23** 133–63

Hall A H and Rumack B H 1986 Clinical toxicology of cyanide *Ann. Emerg. Med.* **15** 1067–74

Lee J, El-Abaddi N, Duke A, Cerussi A E, Brenner M and Tromberg B J 2006 Noninvasive *in vivo* monitoring of methemoglobin formation and reduction with broadband diffuse optical spectroscopy *J. Appl. Physiol.* **100** 615–22

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

Noriuki T, Ohdan H, Yoshioka S, Miyata Y, Asahara T and Dohi K 1997 Near-infrared spectroscopic method for assessing the tissue oxygenation state of living lung *Am. J. Respir. Crit. Care Med.* **156** 1656–61

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

Piantadosi C A, Sylvia A L and Jobsis F F 1983 Cyanide-induced cytochrome a,a$_3$ oxidation reduction responses in rat brain in vivo *J. Clin. Invest.* **72** 1224–33

Rich P R and Moody A J 1996 Cytochrome c Oxidase *Treatise on Bioelectrochemistry (Bioenergetics* vol 3*)* ed G Milazzo and P Graber (Basel: Birkhauser) chapter 10

Riddle K 2004 Hydrogen cyanide: fire smoke's silent killer *J. Emerg. Med. Serv. JEMS* suppl 5 **29** 2

Rumack B H 1983 Cyanide poisoning *Proc. Symp. on Respiratory Care of Chemical Casualties* ed H H Newball (Fort Detrick, Frederick, MD: US Army Medical Research and Development Command)

Sakamoto T, Jonas R A, Stock U A, Hatsuoka S, Cope M, Springett R J and Nollert G 2001 Utility and limitation of near-infrared spectroscopy during cardiopulmonary bypass in a piglet model *Pediatr. Res.* **49** 770–6

Schmitt J M and Kumar G 1998 Optical scattering properties of soft tissue: a discrete particle model *Appl. Opt.* **37** 2788–97

Strickland A, Wang R Y, Hoffman R S and Goldfrank L R 1992 Blood cyanide concentrations after smoke inhalation *N. Engl. J. Med.* **326** 1362

Tromberg B J, Shah N, Lanning R, Cerussi A, Espinoza J, Pham T, Svaasand L and Butler J 2000 Non-invasive *in vivo* characterization of breast tumors using photon migration spectroscopy *Neoplasia* **2** 26–40

Vick J, Marino M T, von Bredow J D, Kaminskis A and Brewer T A 2000 Reproducible nonlethal animal model for studying cyanide poisoning *Mil. Med.* **165** 967–72

Way J L, Leung P, Cannon E, Morgan R, Tamulinas C, Leong-Way J, Baxter L, Nagi A and Chui C 1988 The mechanism of cyanide intoxication and its antagonism *Ciba Found. Symp.* **140** 232–43

Zijlstra W G, Buursma A and Assendelft O W 2000 *Visible and Near-infrared Absorption Spectra of Human and Animal Hemoglobin* (AH Zeist, The Netherlands: VSP BV)