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Review

Functional near-infrared spectroscopy for the measurement of propofol effects in conscious sedation during outpatient elective colonoscopy

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ABSTRACT

Endoscopic procedures performed in the United States routinely involve the use of conscious sedation as standard of care. The use of sedation reduces patient discomfort and anxiety while improving the technical quality of the procedure, and as a result, over 98% of clinicians have adopted the practice. The tremendous benefits of sedation are offset by heightened costs, increased patient discharge time, and cardiopulmonary complication risks. The inherent liabilities of putting patients under sedation have necessitated a large number of physiological monitoring systems in order to ensure patient comfort and safety. Currently American Society of Anesthesiologist (ASA) guidelines recommend monitoring of pulse oximetry, blood pressure, heart rate, and end-tidal CO_2; although important safeguards, these physiological measurements do not allow for the reliable assessment of patient sedation. Proper monitoring of patient state ensures procedure quality and patient safety; however no "gold-standard" is available to determine the depth of sedation which is comparable to the anesthesiologist's professional judgment.

Developments in functional near-infrared spectroscopy (fNIRS) over the past two decades have introduced cost-effective, portable, and non-invasive neuroimaging tools which measure cortical hemodynamic activity as a correlate of neural functions. Anesthetic drugs, such as propofol, operate by suppressing cerebral metabolism. fNIRS imaging methods have the ability to detect these drug related effects as well as neuronal activity through the measurement of local cerebral hemodynamic changes.

In the present study, 41 patients were continuously monitored using fNIRS while undergoing outpatient elective colonoscopy with propofol sedation. The preliminary results indicated that oxygenated hemoglobin changes in the dorsolateral prefrontal cortex, as assessed by fNIRS were correlated with changes in response to bolus infusions of propofol, whereas other standard physiological measures were not significantly associated.

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Introduction

Endoscopic procedures, such as colonoscopies are commonly considered to be uncomfortable by a majority of the patient population. Sedation and analgesic methods have been shown to reduce patient discomfort and anxieties about the procedure and have also demonstrated improvements in the technical quality of gastrointestinal (GI) endoscopic procedures (Radaelli et al., 2008). As a result, sedation has become a routine practice with over 98% of endoscopists in the United States using intravenous methods for colonoscopies and esophagogastroduodenoscopy (EGD) (Cohen et al., 2006). Technological advances in endoscopy have also increased the complexity of procedures and commonly deep sedation is required. However, excessively deep sedation may also prolong recovery and discharge of the individual while placing the patient at risk for additional complications including the transition from deep sedation to general anesthesia (Schreiber et al., 2007). Patients being administered anesthetics are monitored with a variety of physiological measurements according to standards administered by the American Society of Anesthesiology. Proper monitoring of patient state ensures procedure quality and patient safety; however no "gold-standard" is available to determine the depth of sedation which is comparable to the anesthesiologist's professional judgment.

The need to develop more informative tools to assist clinicians during sedative practices has been a primary driving force for investigation into hypnotic state techniques. Currently available clinical methods rely on electroencephalographic (EEG) measures such as the Bispectral Index (BIS) and the Auditory Evoked Potential (AEP). These techniques, originally designed for use in the operating room, have been shown to correlate, but not discriminate between sedation states (von Delius et al., 2009). Advancements in functional near infrared spectroscopy (fNIRS) over the previous two decades have provided a safe, non-invasive, and cost-effective neuroimaging method for measuring hemodynamic changes in the cerebral cortex. fNIRS non-invasively detects changes in cortical blood content using near infrared light. These measures of deoxygenated (Hb) and oxygenated (HbO_2) hemoglobin concentrations have been shown to be correlates of neuronal activity through other neuroimaging modalities, such as fMRI (Steinbrink et al., 2006; Wolf et al., 2007). Neuronal activity and cerebral metabolism are inhibited under the influence of anesthetics such as propofol (Alkire et al., 1995), suggesting that fNIRS may provide an additional source of information regarding patient state.

Propofol sedation practice in lower gastrointestinal endoscopy

Propofol (2-6-di-isopropylphenol) is a fast-acting hypnotic agent with strong sedative and amnesic effects, but no analgesic properties. With a fast onset of 30–60 s, a half-life of 2–4 min, and high patient satisfaction, propofol has become the leading alternative to conventional sedation methods such as midazolam or benzodiazepine plus opioids with 25.7% of routine endoscopic procedures in the United States using the medication. As many as 68% of endoscopists using conventional sedation methods, have expressed interest in using propofol but, despite its advantages, had reservations about medicolegal issues or risk of cardiopulmonary complications (Cohen et al., 2006). Propofol has a narrow therapeutic window which can significantly increase the risk of cardiopulmonary complications in the absence of proper administration (Standards of Practice Committee of the American Society for Gastrointestinal et al., 2008) and for this reason, the current FDA-approved product label for propofol states that the emulsion "should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure" (AstraZeneca LP, 2007).

The American Society for Anesthesiologists (ASA) has described four classifications of sedation: minimal, moderate (frequently referred to as conscious sedation), deep and general anesthesia. Endoscopic procedures are typically performed under moderate sedation, but may involve periods of deep sedation. During moderate sedation, ventilation and cardiac function are maintained and the patient will purposefully respond to tactile or verbal stimulation. Under deep sedation conditions, the patient will respond only to repeated or painful stimulation and although cardiovascular function may be maintained, airway intervention may be required (Standards of Practice Committee of the American Society for Gastrointestinal et al., 2008). During the course of endoscopic procedures, identifying the ideal level of sedation is essential to guarantee both the quality of the procedure and the safety of the patient. Oversedation carries with it a significant risk of adverse events including peripheral oxygen desaturation, hypoxemia, hypotension and bradycardia (Department of Health and Services, 2010). Excessive use of sedation agents will transition a patient from deep sedation to general anesthesia, which corresponds with a loss of spontaneous respiration, loss of patient response to repeated painful stimulus, and may cause life-threatening impairments in cardiovascular functions. Even when not jeopardizing patient safety, overly deep sedation can prolong recovery and substantially delay patient discharge, adding to the cost of the procedure (Cohen et al., 2007). In order to minimize the risks presented by propofol sedation, 92.3% of endoscopic procedures using propofol sedation are overseen by either an anesthesiologist or a certified registered nurse anesthetist (CRNA) (Cohen et al., 2006).

Monitoring during moderate and deep sedation

Current standard of care, as recommended by the American Society for Gastrointestinal Endoscopy (ASGE), requires the monitoring of physiological parameters continuously, including pulse oximetry (SpO_2), electrocardiogram (ECG), as well as periodic measurement of noninvasive blood pressure (NIBP) (Standards of Practice Committee of the American Society for Gastrointestinal et al., 2008). These parameters are measured to detect clinically significant events before they occur. Additionally, modifications in 2011 to the ASA Standards for Basic Anesthetic Care Monitoring have recommended the inclusion of capnography to provide measurements of end-tidal carbon-dioxide ($Et\text{-}CO_2$) in the practice of moderate and deep sedation (American Society of Anesthesiology: Standards and Practice Parameters, 2011), although significant debate remains regarding the necessity of universal adoption (ASGE, 2011). These monitors, in conjunction with

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professional observation of the patient with particular emphasis on ensuring patient respiratory function, give the anesthesia provider tools to assess the state of anesthesia. However no physiological "gold-standard" is available to determine the depth of sedation in a patient which replaces the anesthesiologists' professional judgment.

During endoscopic procedures, the anesthesiologist is required to integrate all of the information provided by patient monitoring systems, while simultaneously making judgments about the patient's level of awareness. Anesthesiologist behavior in handling standard care as well as adverse events varies with the length of procedure, amount of and type of medication used, and most importantly the patient's condition. Because of the inherent risk to the patient, it is imperative that during deep sedation at least one individual has solitary responsibility of ensuring the patient's safety and is capable of applying positive-pressure ventilation, airway management, and cardiac support should the patient's systems be compromised.

Clinical use of functional near infrared spectroscopy

Functional near infrared spectroscopy (fNIRS) is an optical technique which exploits the general transparency of biological tissues to near infrared (NIR) light as well as the contrasting optical properties of deoxygenated (Hb) and oxygenated (HbO_2) hemoglobin, to allow the continuous and non-invasive measurement of tissue oxygenation. Typically NIR devices use two wavelengths, one above and one below the isosbestic point (805 nm), where the absorption spectra of HbO_2 and Hb are maximally separated (e.g., 730 nm and 850 nm). The technique was first described by Jöbsis using transmitted NIR directly through the skull (Jobsis, 1977), and has evolved into a versatile medical diagnostic modality and spurred advancements in investigatory tools for neuroscience. It was not until deeper investigation into light pulse propagation (Patterson et al., 1989) and optical path length (Delpy et al., 1988) in biological tissues furthered understanding about the nature of the method, that fNIRS devices became capable of accurately quantifying changes in hemodynamic state and activity. For a comprehensive review of fNIRS principles the reader is referred to Obrig and Villringer (2003). Commercialization and technological improvements have helped make these fNIRS devices accessible to physicians and help to both further the development of new translational technologies as well as the understanding of the brain activity under natural and clinical settings.

In 1993, INVOS 3100® by Somanetics Corporation, the first FDA approved commercial fNIRS device was released as a cerebral oximetry device, with several competing devices released shortly thereafter. Commercial systems are typically Continuous Wave (CW) devices which use relative measurements to provide estimated values of absolute changes and cerebral oxygen saturations (rSO_2) using calibrated estimations of chromophoric properties and photon path length found through the use of successive approximation techniques, computer simulation, and models (Murkin and Arango, 2009). Several newer systems have been introduced such as the NIRO300® of Hamamatsu Photonics, which use a spatially resolved spectroscopic (SRS) method to measure the absorption coefficient μ_a independent of the Beer–Lambert method (Delpy et al., 1988), allowing the calculation of an absolute tissue oxygen index (TOI) using measurements of linear intensity attenuation with respect to distance (Suzuki et al., 1999). Hybridization of these methods has additionally allowed for measurements of absolute concentrations of chromophores as well as cerebral blood volume with certain restrictions (Leung et al., 2006). Both of these techniques have been reported to correlate well with more technically complex methodologies such as Frequency Domain (FD) and Time Domain (TD), however lack of standardization between existing fNIRS devices has created issues in establishing physiological norms for clinical contexts (Dullenkopf et al., 2003).

Current clinical monitoring of cerebral oximetry has at its endpoint the safeguard of cerebral function. In many procedures, fNIRS has been praised for its ability to detect otherwise silent iatrogenic cerebral ischemia, such as that which can occur during carotid endarterectomy (Pennekamp et al., 2009), brain aneurism surgery (Bhatia et al., 2007), and circulatory arrest during aortic arch procedures (Harrer et al., 2010). High variability in baseline oxygen saturation has prevented absolute values from being useful in a clinical context and as a result fNIRS-interventions are most often based on relative deviations from baseline (Denault et al., 2007), although clear cut-off points have not been widely vetted. fNIRS-directed interventions attempt to prevent prolonged cerebral desaturation, an event associated with delayed hospital release, early cognitive decline (Slater et al., 2009), and perioperative stroke (Schön et al., 2009). The effectiveness of fNIRS to detect, localize, and monitor episodes of pathological cerebral ischemia such as stroke (Terborg et al., 2009) or traumatic brain injury (Dieters et al., 2011; Salonia et al., 2012), has proved promising and is currently an ongoing area of investigation.

fNIRS for anesthesia neuromonitoring

Dose-dependent propofol-induced suppression of cerebral metabolism as measured by glucose metabolic rate (GMR) and regional cerebral metabolic rate of oxygen ($rCMRO_2$) has been documented with positron emission tomography (PET) techniques (Alkire et al., 1995; Kaisti et al., 2003). The dose-dependent inhibition of neural function has also been tied to the progressive reduction in neural networks associated with auditory and memory tasks with particular sensitivity in the dorsolateral prefrontal cortex (DPFC) and other frontal association areas (Heinke et al., 2004; Veselis et al., 2002). Propofol-based reductions in $rCMRO_2$ are coupled with decreases in regional blood flow (rCBF) and associated vasoconstriction, suggesting that propofol preserves cerebral autoregulation of metabolism and oxygen demand/supply balances (Fiset et al., 1999; Oshima et al., 2002; Veselis et al., 2002). fNIRS technologies are capable of measuring changes related to these hemodynamic responses through Hb, HbO_2 and other derived metrics.

Investigation of the hemodynamic behavior of the prefrontal cortex during anesthesia has not been extensively studied with fNIRS. The ability of fNIRS to detect major events of cerebral ischemia is well established, but the relation to temporal dynamics of anesthesia and its applications have yet to be fully explored. During the induction of general anesthesia via propofol, a 10 μM mean increase of HbO_2 was shown 3 min after induction with no significant changes in Hb levels (Lovell et al., 1999). The same study found differing hemodynamic responses from etomidate and thiopental based anesthesia. Cerebral oxygen supply and demand balance as measured by rSO_2 has been shown to be stable during propofol anesthesia in normal conditions, and increased by the presence of administered oxygen (FiO_2 1) (Kim et al., 2009). However reductions of rSO_2 have been shown under a reduced oxygen administration (FiO_2 0.5) as well as in the Trendelenburg position, suggesting that oxygen saturation measurements are sensitive both to inspired oxygen and subject position (Kim et al., 2011). Other studies regarding positional changes have demonstrated sensitivity of hemodynamic variables to subject position (Ozgoren et al., 2012) as well as significant reductions in post positioning hemodynamic variability in anesthetized patients (Lovell et al., 2000). These changes may be related to alterations in the arterial–venous (A/V) contributions in the cortical capillary bed from which measurements are made as well as gravity related changes in regional CBV. Although differences in oxygen saturation did not reach statistical significance between supine and the left-lateral position in awake patients or patients anesthetized with sevoflurane, insufficient information is available to fully describe this effect (Fuchs et al., 2000). A 26 patient study conducted at the Drexel University College of Medicine that examined the ability of fNIRS to follow the emergence of patients from anesthesia after the use of the inhalant agents sevoflurane and desflurane, reported that gradual reductions in Hb approached baseline values as the subject began to awake (Izzetoglu, 2008). These findings for changes in total-Hb and Hb were

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explained by referring to findings that reported increased cerebral blood volume (CBV) and CBF with inhalation anesthetics (Bedforth et al., 2000). Differences between the influence of inhalation anesthetics and propofol on cerebral oxygenation measures have been the focus of a separate study (Kim et al., 2011). The combination of these results suggests that the use for fNIRS-based neurohemodynamic measurements under the context of anesthesia must be controlled for in both positional and drug-dependent manners in order to derive clinically relevant measurements.

The use of fNIRS in the context of gastrointestinal endoscopic procedures has not been extensively examined. Limited information is available about fNIRS responses during sedation that does not involve general anesthesia, and insufficient information is available regarding fNIRS neurohemodynamic changes while in the lateral decubitus (LD) position used during these procedures. fNIRS also has shown promise as a predictor for episodes of peripheral desaturation as has been reported in children (Tobias, 2008) and a predictor for maternal hypotension that can occur during caesarian section (Berlac and Rasmussen, 2005). Exploration of fNIRS ability to monitor drug-induced neurohemodynamic changes to prevent oversedation and potentially serve as a predictor for adverse events is a rich field of study. The current study attempts an initial evaluation into the benefits of using fNIRS during GI endoscopy with the ultimate goal of improving patient safety and satisfaction.

Methods

Participants

Study protocol, recruitment and informed consent statements were approved by the Human Subjects Institutional Review Board at Drexel University. A total of 42 patients undergoing elective outpatient colonoscopy at the Drexel Center for Digestive Health Ambulatory Endoscopy Center (AEC) were enrolled in the study, but 1 patient was discarded due to technical issues ($n = 41$). All patients treated at the outpatient clinic were ASA class I or II. Patients aged 18–80 were recruited prior to the endoscopic procedures and were subject to exclusion if they had a history of seizures, head injury, chronic headaches or neurological dysfunction. Patients signed informed consent statements and reported demographic information prior to participation in the study.

Study protocol

During the preoperative period, standard physiologic sensors were placed on the patients along with the fNIR100 system manufactured by fNIRS devices LLC. Prior to induction, LED current and detector gain were adjusted to appropriate levels to prevent signal saturation, a baseline measurement was established, and the fNIRS signal was recorded continuously at 2 Hz until the end of the procedure. Systemic physiologic variables were recorded from the PM-9000 patient monitoring system manufactured by Mindray Medical. ECG, side-stream $EtCO_2$, and SpO_2, were recorded non-invasively by the system at 1 Hz. NIBP was measured at 2–3 minute intervals depending on anesthesiologist's preference. fNIRS and PM-9000 system clocks were synced to ensure data alignment. Physiological data recorded from the patient monitoring system was transferred post-procedurally to a laptop and was extracted using custom written software. Throughout the procedure patients were provided with supplemental oxygen administered through nasal cannula at 2 L/min (Fi 0.28). Prior to drug induction, patients were rolled into the left lateral decubitus position (LDP). Premedication varied per patient, but typically included a combination of 60 mg lidocaine, 0.2 mg glycopyrrolate, 1–2.5 mg midazolam, or 50–100 μg remifentanil. Patients were then induced with bolus doses of propofol until the gastroenterologist (GI) was ready to begin the procedure. Anesthesiologists were instructed to report dosage and timing of delivered drugs.

Table 1
Ramsay sedation scale (Ramsay et al., 1974).

Ramsay sedation scale	
1	Patient anxious and agitated, or restless, or both
2	Patient co-operative, oriented, and tranquil
3	Patient responds to commands only
4	Brisk response to a light glabellar tap or auditory stimulus
5	Sluggish response to a light glabellar tap or auditory stimulus
6	No response to light glabellar tap or auditory stimulus

Sedation level was assessed according to the Ramsay sedation scale (Table 1) at thirty second intervals by an assisting GI resident who also recorded drug dosages and any intraprocedural events including anesthesiologist interventions and adverse events as defined in Table 2. Recording of physiologic variables, fNIRS, and sedation levels was discontinued after the conclusion of the procedure and immediately prior to subject transfer to the recovery room.

fNIRS data acquisition

The CW fNIRS system used in this study is based on a technique originally established by Chance et al. (1993) and further developed by the Optical Brain Imaging Lab at Drexel University (Bunce et al., 2006). The current generation system was commercialized by fNIRS devices LLC as the fNIRS 100. The sensor contains 4 tri-wavelength LED light sources and 10 photodetectors, with each photo-detector pair spaced 2.5 cm apart. fNIRS measurements are made sequentially with every LED forming optodes with each of 4 surrounding photo-detectors. Activated LEDs emitting peak wavelengths of 730 nm and 850 nm are measured at 2 Hz in addition to an ambient light measurement taken with no active LEDs.

Components are fixed on a flexible circuit board cased in medical grade silicone allowing the sensor to serve as a headband and comfortably conform to the subject's forehead (Fig. 1A). The sensor was placed flush with the skin and secured by an elastic headband to ensure optode contact. Once the sensor is placed, the emitter–detector array establishes a 16-channel map of hemodynamic activity (Fig. 1B), penetrating approximately 1.5 cm (Okada et al., 1997) beneath the scalp and into the dorsolateral pre-frontal cortex (DPFC). The sensor is connected to a data acquisition box which was connected in turn to a PC running the COBI studio recording software (Ayaz, 2005). Relevant events were recorded and time-stamped during the procedure by the experimenter.

fNIRS data was acquired for all 16 channels at 2 Hz. Raw light intensity data was filtered with a low pass FIR filter of length 200 and cutoff frequency 0.1 Hz. Saturated and undervalued intensities were rejected automatically. Light intensity was then compared using real-time correlation with a dark channel measurement to identify motion artifacts. Identified regions were then filtered using ICA and PCA methods (Izzetoglu, 2008) to minimize influence of artifacts. Hemodynamic variables of [Hb] and [HbO_2] terms were calculated using the modified Beer–Lambert Law (Delpy et al., 1988).

Values for extinction coefficients ϵ^{Hb}, and ϵ^{Hb} and mean photon path length d, are considered to be time-independent and spatially constant (Delpy et al., 1988), allowing the calculation of relative chromophore concentrations. An additional hemodynamic variable of [HbTotal] was calculated as the sum of [Hb] and [HbO_2]. This derived term is thought

Table 2
Clinically defined adverse events.

Adverse event	Definition
Hypoxia	Peripheral oxygen saturation (SpO_2) under 92% for >30 s
Hypotension	20% drop in MAP vs. baseline, or <90 mm Hg systolic blood pressure
Bradycardia	25% drop in pulse rate (PR) or <50 beats per minute
Altered respiration	50% decrease in $EtCO_2$ vs. baseline measurement

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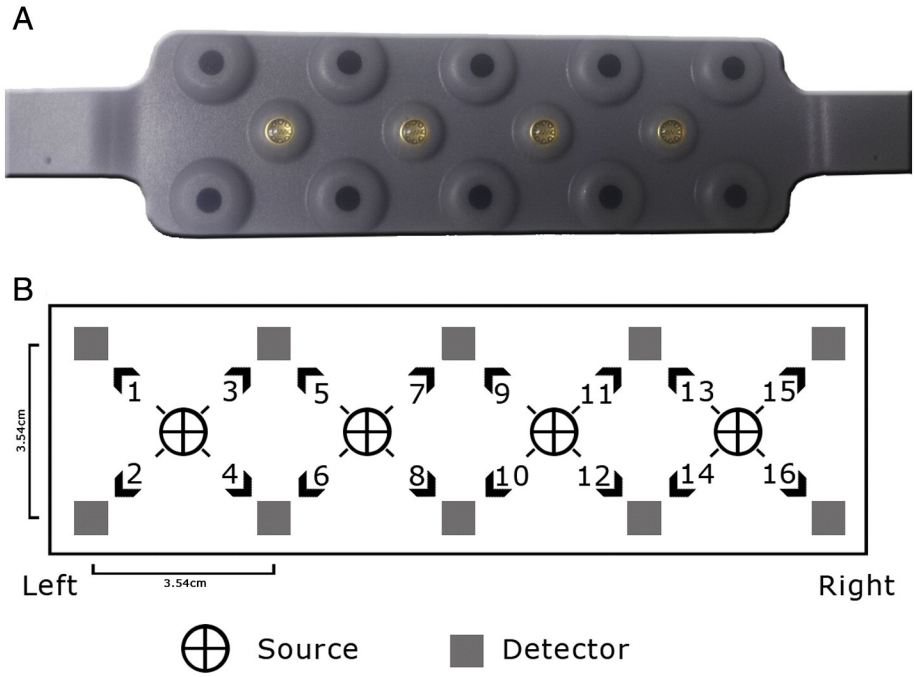

Fig. 1. fNIR100 NIRS probe (A) and source-detector schematic (B).

to be a good indicator of variations in regional cerebral blood volume (Tuchin, 2002).

Statistical analysis

Data analysis was conducted using SPSS version 20.0.0 (Statistical Package for the Social Sciences; SPSS Inc.). Descriptive demographic and procedural statistics are presented as mean ± standard deviation or as a percentage of cases. An alpha level of $\alpha = 0.05$ was used as the significant criteria for each test. To assess the normality assumption of the data, the Kolmogorov–Smirnov test was used for all continuous measures. Levene's test was used to examine the assumption that variables had homogenous variances. Variables were found to be non-normally distributed, therefore intergroup differences in nonparametric variables were identified by performing a one-way Kruskal–Wallis test. Post-hoc comparisons between identified groups were made using the Mann–Whitney *U*-test. The False Detection Rate (FDR) was applied to control for experiment-wise type I error (Benjamini et al., 2001). Correlations for continuous variables are reported using Spearman's rank correlation coefficients for identified groups as two-tailed test.

Results

Study description

A total of 42 subjects consented for the study, but one subject was discarded due to equipment issues (n = 41). Subject demographic information is presented in Table 3. Anesthesiologists were asked to perform a standardized anesthesia regimen using only propofol.

Clinical procedure data, as well as the occurrence of pre-defined adverse events are presented in Table 4. Adverse events were defined in Table 2 and are reported only once per subject regardless of how many times the specific event occurred during the course of the procedure. No subjects required aggressive interventions for any adverse event during the course of the study, and the colonoscopy procedure was never discontinued for anesthesia-related reasons.

Propofol bolus effects

Data from one subject was discarded from fNIRS study because the fNIRS data was mistakenly not recorded. Channels 12 and 14 corresponding with the right dorsolateral prefrontal cortex (right-DLPFC) have been associated with attention and were identified based on a previous channel selection study (Izzetoglu, 2008), so data from these channels were used as a region of interest for fNIRS data analysis. Channels 12 and 14 are positioned closely to Fp2 from the International 10–20 system (Jasper, 1958) with Channel 12 being medial to Channel 14.

Physiological data, including fNIRS features were calculated in 30 second blocks and matched with corresponding Ramsay and drug dose reports. The impact of bolus propofol infusions on hemodynamics was observed as a function of time and bolus dose. Because propofol doses and timing were not controlled during this study, the effects of drug doses were analyzed using a subset of drug doses. Propofol exhibits a short half-life of 2–4 min (Heuss et al., 2003), so sample selection criteria were established to assess the effects of individual bolus delivery and assure that dosages were independent from one another. Drug infusion samples were accepted if no additional samples occurred within 2 min prior to the initial dose. Drug doses were calculated as the total

Table 3
Demographic information for study.

Study demographics (N = 41)		
	Mean	Std.
Age	52.00	11.09
Weight (lbs.)	184.08	46.26
Height (in.)	65.99	5.28
BMI (kg/m^2)	29.28	6.72
Sex	17 male	24 female
Smoke	5 yes	36 no
Illegal drugs	0 yes	41 no
Handedness	35 right	6 left
Alcohol	0 heavy	26 light
	15 none	
Race	25 black	2 Hispanic
	11 white	2 Asian

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Table 4
Procedural statistics and adverse event frequencies reported as mean (S.D.) or % of total cases.

	Statistic
Procedural	
Duration (min)	23.05 (6.98)
Propofol (mg)	282.9 (107.2)
Midazolam	2 (4.9%)
Fentanyl	0 (0.0%)
$SpO_2 < 92\%$	1 (2.4%)
$\Delta MAP > 25\%$[a]	21 (51.2%)
MAP < 90 mm Hg	11 (26.8%)
$\Delta PR > 25\%$	8 (19.5%)
HR < 50 bpm	3 (7.3%)
$\Delta EtCO_2 > 50\%$	23 (56.1%)
Interventions	
Chin lift	10 (24.4%)
Tongue depression	0 (0.0%)
Ephedrine	2 (4.9%)
Other[b]	1 (2.4%)

[a] Due to lack of baseline BP measurement (N = 39).
[b] Includes Jaw thrust maneuver, increase in O_2, or intraprocedural glycopyrrolate.

amount of drug delivered within the 60 s after the initial bolus. In order to standardize drug doses to individuals, dose levels were divided by the subject's BMI. Differing drug bolus doses were placed into groups for statistical testing: 1 mg/BMI, 2 mg/BMI, 3 mg/BMI, and 3 + mg/BMI.

fNIRS results

Independent analysis of channels 12 and 14 revealed significant dose dependent changes for [HbO_2] which were clearly distinguished from baseline measurements after the three minute mark. Baseline measurements were taken as the average concentrations 30 s prior to drug delivery. Typical changes in oxygenated and deoxygenated hemoglobin content regionally associated with channel 14 during the receipt of a large propofol dose are shown in Fig. 2A, associated changes in physiological parameters are shown in the adjacent Fig. 2B. Because of the nature of the procedure, the largest bolus doses typically occurred during induction, but similar cerebral hemodynamic effects were observed during large mid-procedure doses while the patient was still sedated (Ramsey > 4.5) such as in Fig. 2C.

Smaller independent doses were typically administered mid-procedure and produced small changes that were not perceptibly different from normal variation Fig. 2E.

Propofol doses were placed in categories based on bolus size and subject BMI for significance testing. Each category was formed as the result of dividing the propofol dose in mg by the individual subject's BMI. Omnibus significance testing was conducted using the one-way Kruskal–Wallis analysis for each variable. To meet the assumptions for the Kruskal–Wallis test, doses were treated as independent samples. Post-hoc hypothesis testing was conducted with Mann–Whitney *U* tests using the False Detection Rate (FDR) to reduce type I error.

Significant main effects were associated with HbO_2 changes in channel 14 for 2 ($H = 13.04$, $p < 0.005$) and 3 ($H = 11.74$, $p < 0.008$) minutes following drug administration. Post-hoc tests showed that the largest doses were significantly different than doses less than 1 mg/BMI at 2 min ($U = 101$, $r = -0.41$) and 3 min ($U = 98$, $r = -0.42$) at $p < 0.01$ (Fig. 3C). No effects were detected for Hb on channel 14 (Fig. 3D).

Differences between the change in HbO_2 concentration at 3 min and 1 min were significant between doses ($H = 15.58$, $p = 0.001$). Post-hoc tests showed that dose categories 3 mg/BMI and 3 + mg/BMI were each statistically different from groups 2 mg/BMI ($p < 0.01$) and 1 mg/BMI ($p < 0.05$) (Fig. 4B). Changes in HbO_2 were significantly correlated with drug dosages at 2 ($r_s = 0.289$, $p = 0.002$) and 3 ($r_s = 0.257$, $p < 0.005$) minutes.

Significant main effects were found in HbO_2 changes in channel 12 for 2 ($H = 13.871$, $p = 0.003$) and 3 ($H = 18.955$, $p < 0.001$) minutes following drug receipt. Post-hoc tests showed that the doses larger than 3 mg/BMI doses were significantly different than doses less than 2 mg/BMI at 3 min ($U = 197$, $r = 2.65$, $p = 0.016$) and 3 mg/BMI doses showed significant differences from 1 mg/BMI at 2 ($U = 110$, $r = 0.391$, $p < 0.01$) and 3 ($U = 91$, $r = 0.460$, $p = 0.002$) (Fig. 3A). No effect was found for Hb in this channel when comparing changes from baseline (Fig. 3B).

Comparisons of minute 1 and minute 3 were significant under the Kruskal–Wallis test for both HbO_2 ($H = 14.72$, $p < 0.005$), and Hb ($H = 9.84$, $p < 0.05$) (Fig. 4A). Again dose categories 1 mg/BMI and 3 mg/BMI showed significant differences for HbO_2 ($U = 110$, $r = -0.39$, $p < 0.01$) as well as between 3 + mg/BMI and 2 mg/BMI ($U = 185$, $r = -0.329$, $p < 0.01$). Dose categories 1 mg/BMI and 3 mg/BMI also showed significant differences for Hb ($U = 103$, $r = -0.41$, $p = 0.005$).

Changes in HbO_2 were significantly correlated with drug dosages at 2 ($r_s = 0.356$, $p < 0.001$) and 3 ($r_s = 0.413$, $p < 0.001$) minutes.

Physiological results

Propofol dose effects were examined for two continuous physiologic parameters, pulse rate (PR) and end-tidal CO_2 (Et-CO_2). Physiological parameters were independently assessed, and samples were included irrespective of fNIRS quality. Main effects were significant for change in both pulse rate ($H = 8.018$, $p < 0.05$) and Et-CO_2 ($H = 8.21$, $p < 0.05$) for the first minute after propofol bolus delivery. Mann–Whitney post-hoc tests for pulse rate failed to show significant differences between variables after FDR significance correction (Fig. 3E). Et-CO_2 also failed to show significant differences between groups after FDR significance correction (Fig. 3F).

NIBP responses to propofol could not be analyzed in a similar manner due to lower sampling frequencies creating inconsistencies in timing with related propofol doses.

Correlation between fNIRS and pulse rate, $EtCO_2$

To evaluate the individual changes in Hb and HbO_2 associated with changes to the physiological parameters, PR and $EtCO_2$, correlations were assessed using Pearson's rho and Student's *t*-test was used to determine its significance. Independent of propofol bolus size, correlations found between the physiological parameters and the fNIRS measured hemodynamic variables, were not significant following the False Discovery Rate (FDR) test for type 2 error. However, $EtCO_2$ changes 2 min following bolus drug dose was significantly, but moderately correlated with pulse rate changes 2 ($p < 0.001$, $r = -.343$) and 3 ($p = 0.001$, $r = -.336$) minutes following delivery of the propofol bolus.

Discussion

Results of this study suggest that fNIRS can detect a dose-dependent response to the infusion of propofol. These findings are specific to the propofol sedation regimen. fNIRS measurements can be obtained continuously and non-invasively as an adjunct metric through which additional information about the patient's state can be assessed. Drug related effects on cerebral hemodynamic activity can be measured reliably through fNIRS techniques and show trends which indicate the

Fig. 2. (Panel A) Typical bolus drug response for induction dose (3 + mg/BMI) (channel 14) and (panel B) corresponding physiological response. Transition to Ramsay = 6 noted by vertical line. Patient was awake prior to drug delivery (Ramsay 2). 60 s [x] averages shown by dashed lines. (panel C) Typical bolus drug response for large dose (3 mg/BMI) (channel 14) and (panel D) corresponding physiological response. (Panel E) Typical bolus drug response for small dose (1 mg/BMI) (channel 14) and (panel F) corresponding physiological response. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ Kruskal Wallis test contrast with (1 mg/BMI) group.

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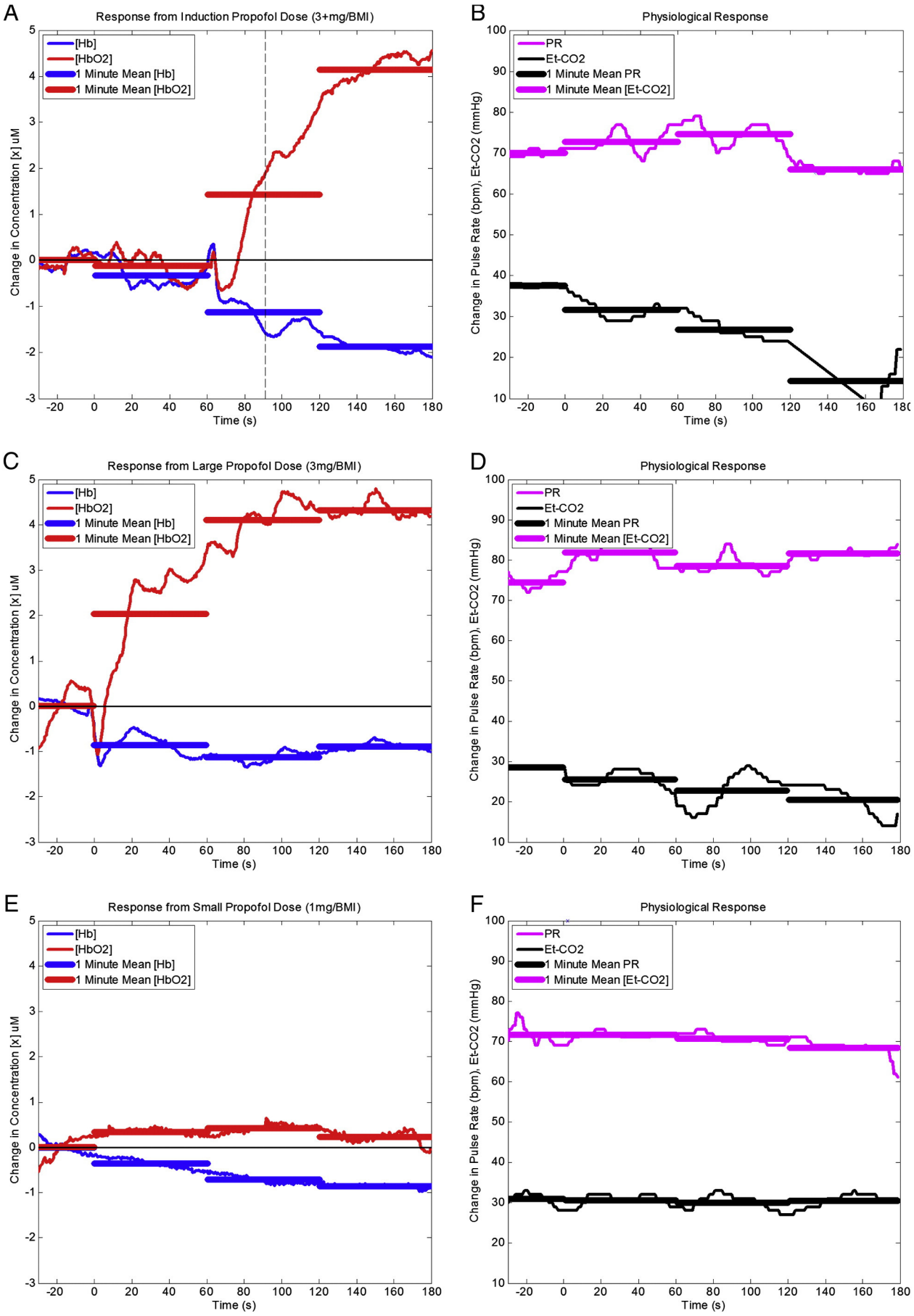

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existence of a neurohemodynamic signature of propofol which could be used to assess sedation regime quality with further investigation.

Propofol related effects were observed both during induction and maintenance of patient sedation. These effects support the claims of Lovell et al. (1999), who showed a significant increase in HbO_2 in response to propofol induction. The study conducted by Lovell differed from the presented work in that it featured a younger subject population (38 ± 13 yrs), focused only on induction, and involved a much larger propofol dose (average of 215 mg) approaching the total average dose delivered in the entire sedation period of the current study. The magnitude of propofol dose may explain why hemodynamic changes reported by Lovell were substantially larger than values reported in the current study, although the use of a different fNIRS system may be cause for additional variation.

The current study was designed as an observational study of cerebral hemodynamic activity with specific attention to responses during induction, maintenance, emergence, and pre-defined adverse events (Table 2). Adverse events could not be statistically analyzed with respect to continuous fNIRS measurements because the validity of long-term baseline comparisons was questioned due to frequent procedure-related patient repositioning. Peripheral desaturation (SpO_2 < 92%) only occurred as an isolated incident. The sensor used in this study was originally designed for the measurement of cognitive activity in the prefrontal cortex with patients in the upright positions. A sensor designed specifically for use in the clinical context would improve the reliability and utility of the device. Although anesthetic choice was more tightly controlled, working in the outpatient clinical setting with real patients prevented the details of drug administration from being controlled experimentally. Hence, in this observational study observed drug effects were recorded based on independent groups of drug doses categorized by dose/BMI.

fNIRS has previously been investigated for use in general anesthesia (Izzetoglu, 2008). The previous study focused primarily on emergence following uncontrolled anesthesia regimes that involved inhalation agents such as sevoflurane and desflurane. In the previous study, hemodynamic changes from the pre-induction base-line were compared with the four minute interval prior to wound closure and eye opening,

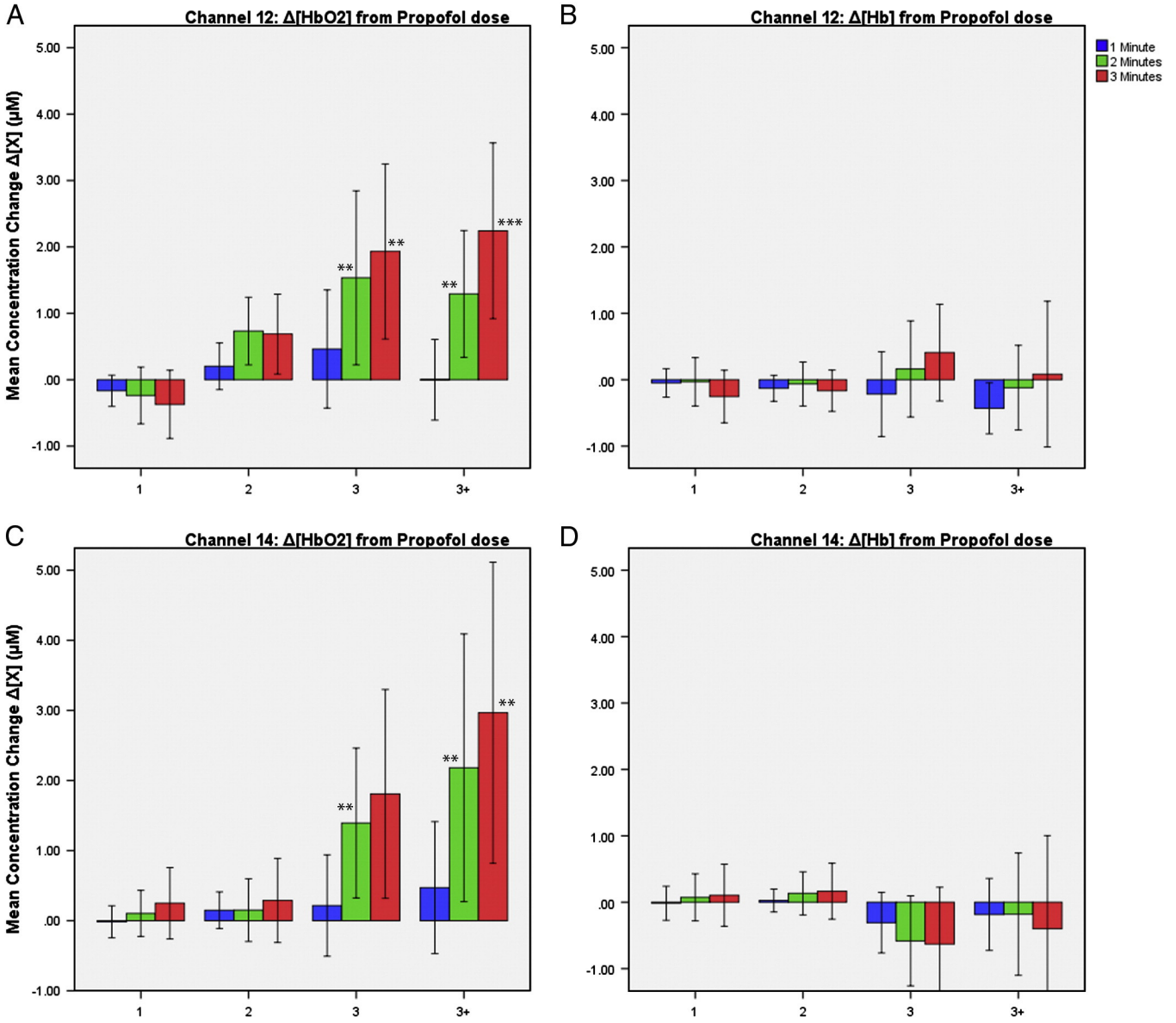

Fig. 3. Mean concentration changes for channels 12 and 14 on the right-dorsolateral prefrontal cortex (right-DLPFC). Panel A shows mean HbO_2 changes for channel 12. Panel B shows mean Hb changes for channel 12. Panel C shows mean HbO_2 changes for channel 14. Panel D shows mean Hb changes for channel 14. Measured changes in concentration are evaluated as average changes 1, 2, and 3 min following bolus delivery. Mean pulse rate (panel E) and Et-CO_2 (panel F) changes following bolus infusion. Measured change in pulse rate and Et-CO_2 is measured as the average change from the baseline value for 1, 2, and 3 min following bolus delivery.

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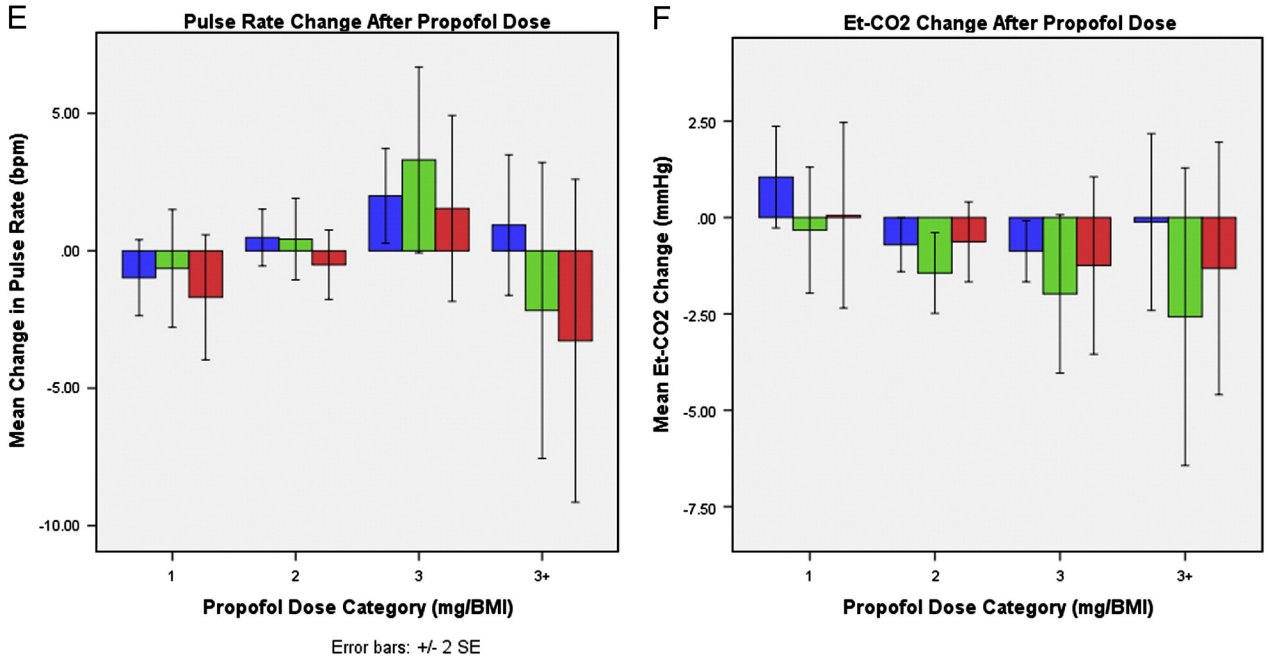

Fig. 3 (*continued*).

labeled 'Deep' and 'Light' anesthesia respectively. Hb was found to be the significant biomarker for classification between the two anesthetic states, whereas HbO_2 did not reach significance. However for channel 12, both HbO_2 and Hb were significantly different across the 'Deep' and 'Light' states. These hemodynamic trends in channel 12 showed large mean increases in Hb (~3.0 μM) and HbO_2 (~4.5 μM) concentrations for the 'Deep' stage (Izzetoglu, 2008) and reductions in hemodynamic changes as the subject approached emergence during the 'Light' stage. Increases in HbTotal were attributed to the cerebral vasodilatory effects of sevoflurane and desflurane (Kaisti et al., 2003) as well as decreased neuronal metabolic demand, an effect known as 'luxury perfusion' (Duffy and Matta, 2000). Sevoflurane and desflurane have different hemodynamic effects, with desflurane associated with increased HR, mean arterial pressure (MAP) and CBF as measured by transcranial Doppler, while sevoflurane is reported to preserve cerebral autoregulation and HR (Bedforth et al., 2000). Propofol is reported to decrease CBF as well as $CMRO_2$ (Oshima et al., 2002), while also causing systemic vasodilation, reducing systemic MAP and increasing blood flow to peripheral areas (Ebert, 2005). Reductions in MAP and HR as a result of propofol delivery were seen frequently in the presented study agreeing with published literature (Nissen et al., 2009; Oshima et al., 2002). Although CBF, and thus CBV, are expected to decrease under these conditions, frontal-lobe oxygen saturation is expected to be maintained or even increased (Nissen et al., 2009). These changes in cerebral hemodynamics caused by anesthetic agents have been reported to be spatially non-uniform in nature (Heinke and Koelsch,

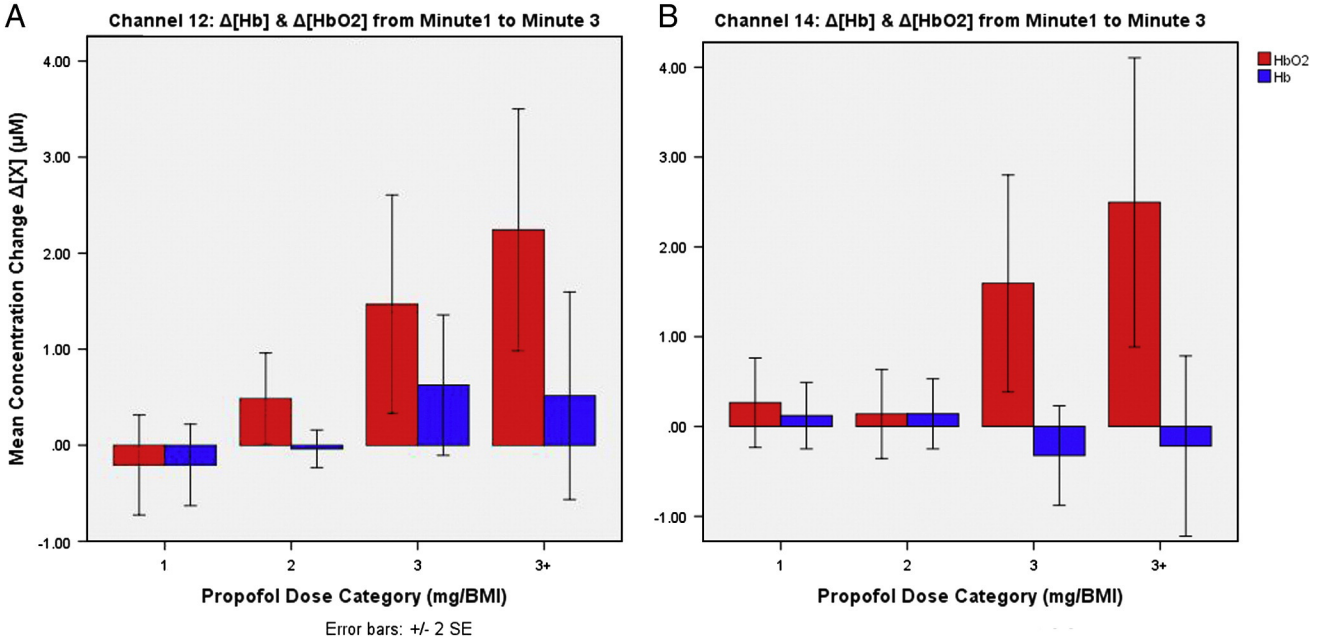

Fig. 4. Mean HbO_2 and Hb changes for channel 12 (panel A) and 14 (panel B). Measured changes in concentration are evaluated as the average change from 1 min following bolus infusion compared with the average change during minute 3.

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2005; Kaisti et al., 2002), and no studies have yet reported on the influence of subject position under sedation, particularly in left-lateral decubitus position. Drug induced changes in cerebral changes in regional cerebral blood flow in the frontal cortex have even been related back to the BIS index (Kaisti et al., 2002), suggesting that hemodynamic trends still reflect neurological activity instead of simply physiological changes.

From the results in previous studies (Izzetoglu, 2008; Lovell et al., 1999), together with the findings presented in this study, it is clear that fNIRS is capable of measuring changes in Hb and HbO_2 associated with different forms of anesthesia. However, interpretation of these changes and their use to monitor cerebral responses to anesthetic agents needs to be carefully considered and compared with data obtained using other techniques involving other physiologic measures and fNIRS measurements obtained over the full head to evaluate contribution of systemic, superficial, and other global effects in the fNIRS measurements. Currently the nature and the variability of the fNIRS response to propofol remain an area of investigation. Intra-subject variability with respect to propofol pharmacokinetics is high (Wachtel et al., 2011). In summary, further investigation and validity studies should be conducted with more patients in a controlled clinical setting.

Disclosure

fNIR Devices, LLC manufactures the optical brain imaging instrument and licensed IP and know-how from Drexel University. Drs. Banu Onaral, Meltem Izzetoglu and Kurtulus Izzetoglu were involved in the technology development and thus offered a minor share in the startup firm, fNIR Devices, LLC.

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References

Alkire, M.T., Haier, R.J., Barker, S.J., Shah, N.K., Wu, J.C., Kao, Y.J., 1995. Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. Anesthesiology 82, 393–403 (discussion 327A).

American Society of Anesthesiology: Standards and Practice Parameters, 2011. Standards for Basic Anesthetic Monitoring.

ASGE, A.I., ACG, 2011. Universal Adoption of Capnography for Moderate Sedation in Adults Undergoing Upper Endoscopy and Colonoscopy Has Not Been Shown to Improve Patient Safety or Clinical Outcomes and Significantly Increases Costs for Moderate Sedation.

AstraZeneca LP, 2007. Diprivan (propofol) injection, emulsion. DailyMed.National Medical Library, National Institute of Health, Caponago, Italy.

Ayaz, H., 2005. Analytical software and stimulus-presentation platform to utilize, visualize and analyze near-infrared spectroscopy measures. 206.

Bedforth, N.M., Hardman, J.G., Nathanson, M.H., 2000. Cerebral hemodynamic response to the introduction of desflurane: a comparison with sevoflurane. Anesth. Analg. 91, 152–155.

Benjamini, Y., Drai, D., Elmer, G., Kafkafi, N., Golani, I., 2001. Controlling the false discovery rate in behavior genetics research. Behav. Brain Res. 125, 279–284.

Berlac, P.A., Rasmussen, Y.H., 2005. Per-operative cerebral near-infrared spectroscopy (NIRS) predicts maternal hypotension during elective caesarean delivery in spinal anaesthesia. Int. J. Obstet. Anesth. 14, 26–31.

Bhatia, R., Hampton, T., Malde, S., Kandala, N.B., Muammar, M., Deasy, N., Strong, A., 2007. The application of near-infrared oximetry to cerebral monitoring during aneurysm embolization: a comparison with intraprocedural angiography. J. Neurosurg. Anesthesiol. 19, 97–104.

Bunce, S.C., Izzetoglu, M., Izzetoglu, K., Onaral, B., Pourrezaei, K., 2006. Functional near-infrared spectroscopy. IEEE Eng. Med. Biol. Mag. 25, 54–62.

Chance, B., Zhuang, Z., UnAh, C., Alter, C., Lipton, L., 1993. Cognition-activated low-frequency modulation of light absorption in human brain. Proc. Natl. Acad. Sci. U. S. A. 90, 3770–3774.

Cohen, L.B., Wecsler, J.S., Gaetano, J.N., Benson, A.A., Miller, K.M., Durkalski, V., Aisenberg, J., 2006. Endoscopic sedation in the United States: results from a nationwide survey. Am. J. Gastroenterol. 101, 967–974.

Cohen, L.B., Delegge, M.H., Aisenberg, J., Brill, J.V., Inadomi, J.M., Kochman, M.L., Piorkowski Jr., J.D., Institute, A.G.A., 2007. AGA Institute review of endoscopic sedation. Gastroenterology 133, 675–701.

Delpy, D.T., Cope, M., Vanderzee, P., Arridge, S., Wray, S., Wyatt, J., 1988. Estimation of optical pathlength through tissue from direct time of flight measurement. Phys. Med. Biol. 33, 1433–1442.

Denault, A., Deschamps, A., Murkin, J.M., 2007. A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy. Semin. Cardiothorac. Vasc. Anesth. 11, 274–281.

Department of Health, Services, Human, 2010. In: Woodcock, J. (Ed.), Petition denial for request for removal of warning of labeling for Diprivan (propofol).

Dieters, E., Hidding, S., Kalisvaart, M., Mik, E., 2011. Near infrared spectroscopy: an asset to the diagnosis and treatment of traumatic brain injury. Erasmus J. Med. 1, 23–26.

Duffy, C.M., Matta, B.F., 2000. Sevoflurane and anesthesia for neurosurgery: a review. J. Neurosurg. Anesthesiol. 12, 128–140.

Dullenkopf, A., Frey, B., Baenziger, O., Gerber, A., Weiss, M., 2003. Measurement of cerebral oxygenation state in anaesthetized children using the INVOS 5100 cerebral oximeter. Paediatr. Anaesth. 13, 384–391.

Ebert, T.J., 2005. Sympathetic and hemodynamic effects of moderate and deep sedation with propofol in humans. Anesthesiology 103, 20–24.

Fiset, P., Paus, T., Daloze, T., Plourde, G., Meuret, P., Bonhomme, V., Hajj-Ali, N., Backman, S.B., Evans, A.C., 1999. Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. J. Neurosci. 19, 5506–5513.

Fuchs, G., Schwarz, G., Kulier, A., Litscher, G., 2000. The influence of positioning on spectroscopic measurements of brain oxygenation. J. Neurosurg. Anesthesiol. 12, 75–80.

Harrer, M., Waldenberger, F.R., Weiss, G., Folkmann, S., Gorlitzer, M., Moidl, R., Grabenwoeger, M., 2010. Aortic arch surgery using bilateral antegrade selective cerebral perfusion in combination with near-infrared spectroscopy. Eur. J. Cardiothorac. Surg. 38, 561–567.

Heinke, W., Koelsch, S., 2005. The effects of anesthetics on brain activity and cognitive function. Curr. Opin. Anaesthesiol. 18, 625–631.

Heinke, W., Fiebach, C.J., Schwarzbauer, C., Meyer, M., Olthoff, D., Alter, K., 2004. Sequential effects of propofol on functional brain activation induced by auditory language processing: an event-related functional magnetic resonance imaging study. Br. J. Anaesth. 92, 641–650.

Heuss, L.T., Schnieper, P., Drewe, J., Pflimlin, E., Beglinger, C., 2003. Safety of propofol for conscious sedation during endoscopic procedures in high-risk patients—a prospective, controlled study. Am. J. Gastroenterol. 98, 1751–1757.

Izzetoglu, K., 2008. Neural Correlates of Cognitive Workload and Anesthetic Depth: fNIR Spectroscopy Investigation in Humans. Biomedical Engineering. Drexel University, Philadelphia, PA 72.

Jasper, H., 1958. Report of the committee on methods of clinical examination in electroencephalography. Electroencephalogr. Clin. Neurophysiol. 10, 370–375.

Jobsis, F.F., 1977. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 198, 1264–1267.

Kaisti, K.K., Metsahonkala, L., Teras, M., Oikonen, V., Aalto, S., Jaaskelainen, S., Hinkka, S., Scheinin, H., 2002. Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. Anesthesiology 96, 1358–1370.

Kaisti, K.K., Langsjo, J.W., Aalto, S., Oikonen, V., Sipila, H., Teras, M., Hinkka, S., Metsahonkala, L., Scheinin, H., 2003. Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiology 99, 603–613.

Kim, D.-H., Kwak, Y.L., Nam, S.H., Kim, M.-S., Kim, E.-M., Shim, J.-K., 2009. Assessment of cerebral oxygen supply–demand balance by near-infrared spectroscopy during induction of anesthesia in patients undergoing coronary artery bypass graft surgery: comparison of midazolam with propofol. Korean J. Anesthesiol. 57, 428–433.

Kim, S.J., Kwon, J.Y., Cho, A.R., Kim, H.K., Kim, T.K., 2011. The effects of sevoflurane and propofol anesthesia on cerebral oxygenation in gynecological laparoscopic surgery. Korean J. Anesthesiol. 61, 225–232.

Leung, T.S., Tachtsidis, I., Smith, M., Delpy, D.T., Elwell, C.E., 2006. Measurement of the absolute optical properties and cerebral blood volume of the adult human head with hybrid differential and spatially resolved spectroscopy. Phys. Med. Biol. 51, 703–717.

Lovell, A.T., Owen-Reece, H., Elwell, C.E., Smith, M., Goldstone, J.C., 1999. Continuous measurement of cerebral oxygenation by near infrared spectroscopy during induction of anesthesia. Anesth. Analg. 88, 554–558.

Lovell, A.T., Marshall, A.C., Elwell, C.E., Smith, M., Goldstone, J.C., 2000. Changes in cerebral blood volume with changes in position in awake and anesthetized subjects. Anesth. Analg. 90, 372–376.

Murkin, J.M., Arango, M., 2009. Near-infrared spectroscopy as an index of brain and tissue oxygenation. Br. J. Anaesth. 103, i3–i13.

Nissen, P., van Lieshout, J.J., Nielsen, H.B., Secher, N.H., 2009. Frontal lobe oxygenation is maintained during hypotension following propofol–fentanyl anesthesia. AANA J. 77, 271–276.

Obrig, H., Villringer, A., 2003. Beyond the visible—imaging the human brain with light. J. Cereb. Blood Flow Metab. 23, 1–18.

Okada, E., Firbank, M., Schweiger, M., Arridge, S.R., Cope, M., Delpy, D.T., 1997. Theoretical and experimental investigation of near-infrared light propagation in a model of the adult head. Appl. Opt. 36, 21–31.

Oshima, T., Karasawa, F., Satoh, T., 2002. Effects of propofol on cerebral blood flow and the metabolic rate of oxygen in humans. Acta Anaesthesiol. Scand. 46, 831–835.

Ozgoren, M., Tetik, M., Izzetoglu, K., Oniz, A., Onaral, B., 2012. Effect of Body Position on NIRS Based Hemodynamic Measures from Prefrontal Cortex Advances in Brain Inspired Cognitive Systems. In: Zhang, H., Hussain, A., Liu, D., Wang, Z. (Eds.), Lecture Notes in Computer Science (Vol. 7366, pp. 138–146). Springer Berlin / Heidelberg. http://dx.doi.org/10.1007/978-3-642-31561-9_15.

Patterson, M.S., Chance, B., Wilson, B.C., 1989. Time resolved reflectance and transmittance for the non-invasive measurement of tissue optical properties. Appl. Opt. 28, 2331–2336.

Pennekamp, C.W., Bots, M.L., Kappelle, L.J., Moll, F.L., de Borst, G.J., 2009. The value of near-infrared spectroscopy measured cerebral oximetry during carotid endarterectomy in perioperative stroke prevention. A review. Eur. J. Vasc. Endovasc. Surg. 38, 539–545.

Radaelli, F., Meucci, G., Sgroi, G., Minoli, G., Italian Association of Hospital, G., 2008. Technical performance of colonoscopy: the key role of sedation/analgesia and other quality indicators. Am J Gastroenterol 103, 1122–1130.

Ramsay, M.A., Savege, T.M., Simpson, B.R., Goodwin, R., 1974. Controlled sedation with alphaxalone-alphadolone. Br. Med. J. 2, 656–659 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/4835444.

Salonia, R., Bell, M.J., Kochanek, P.M., Berger, R.P., 2012. The utility of near infrared spectroscopy in detecting intracranial hemorrhage in children. J. Neurotrauma 29, 1047–1053.

Schön, J., Serien, V., Heinze, H., Hanke, T., Bechtel, M., Eleftheriadi, S., Groesdonk, H.-V., Dübener, L., Heringlake, M., 2009. Association between cerebral desaturation and an increased risk of stroke in patients undergoing deep hypothermic circulatory arrest for cardiothoracic surgery. Appl. Cardiopulm. Pathophysiol. 13, 201–207.

Schreiber, F., Working Group on Endoscopy, A.S.o.G., Hepatology, 2007. Austrian Society of Gastroenterology and Hepatology (OGGH)—guidelines on sedation and monitoring during gastrointestinal endoscopy. Endoscopy 39, 259–262.

Slater, J.P., Guarino, T., Stack, J., Vinod, K., Bustami, R.T., Brown III, J.M., Rodriguez, A.L., Magovern, C.J., Zaubler, T., Freundlich, K., Parr, G.V., 2009. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. Ann. Thorac. Surg. 87, 36–44 (discussion 44–35).

Standards of Practice Committee of the American Society for Gastrointestinal, Lichtenstein, D.R., Jagannath, S., Baron, T.H., Anderson, M.A., Banerjee, S., Dominitz, J.A., Fanelli, R.D., Gan, S.I., Harrison, M.E., Ikenberry, S.O., Shen, B., Stewart, L., Khan, K., Vargo, J.J., 2008. Sedation and anesthesia in GI endoscopy. Gastrointest Endosc 68, 815–826.

Steinbrink, J., Villringer, A., Kempf, F., Haux, D., Boden, S., Obrig, H., 2006. Illuminating the BOLD signal: combined fMRI–fNIRS studies. Magn. Reson. Imaging 24, 495–505.

Suzuki, Susumu, Takasaki, Sumio, Ozaki, Takeo, Kobayashi, Yukio, 1999. A tissue oxygenation monitor using NIR spatially resolved spectroscopy. Society of Photo-Optical Instrumentation Engineers, Bellingham, WA, ETATS-UNIS. 11.

Terborg, C., Groschel, K., Petrovitch, A., Ringer, T., Schnaudigel, S., Witte, O.W., Kastrup, A., 2009. Noninvasive assessment of cerebral perfusion and oxygenation in acute ischemic stroke by near-infrared spectroscopy. Eur. Neurol. 62, 338–343.

Tobias, J.D., 2008. Cerebral oximetry monitoring with near infrared spectroscopy detects alterations in oxygenation before pulse oximetry. J. Intensive Care Med. 23, 384–388.

Tuchin, V.V., 2002. Handbook of Optical Biomedical Diagnostics. SPIE Press Book.

Veselis, R.A., Reinsel, R.A., Feshchenko, V.A., Dnistrian, A.M., 2002. A neuroanatomical construct for the amnesic effects of propofol. Anesthesiology 97, 329–337.

von Delius, S., Thies, P., Rieder, T., Wagenpfeil, S., Herberich, E., Karagianni, A., Frimberger, E., Meining, A., Ludwig, L., Ebert, M.P., Schulte-Frohlinde, E., Neu, B., Prinz, C., Schmid, R.M., Huber, W., 2009. Auditory evoked potentials compared with bispectral index for monitoring of midazolam and propofol sedation during colonoscopy. Am. J. Gastroenterol. 104, 318–325.

Wachtel, R.E., Dexter, F., Epstein, R.H., Ledolter, J., 2011. Meta-analysis of desflurane and propofol average times and variability in times to extubation and following commands. Can. J. Anaesth. 58, 714–724.

Wolf, M., Ferrari, M., Quaresima, V., 2007. Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. J. Biomed. Opt. 12, 062104.

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