Near-Infrared Spectra in Buccal Tissue as a Marker for Detection of Hypoxia

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INTRODUCTION: Hypoxia caused by high altitude exposure can impair cerebral and mental functions. Blood flow and oxygenation of the buccal tissue can be reliable markers to detect hypoxia. In this study, near infrared spectroscopy was used in combination with a novel optical probe to evaluate the applicability of the novel probe in measuring hypoxia markers in buccal tissue under a hypoxic condition.

METHODS: Six healthy participants were tested at altitudes from 2000 to 16,000 ft inside a hypobaric chamber. The buccal reference measurements of blood flow and oxygen saturation were synchronized with the spectral measurements of the novel near infrared probe and the relationship between the reference measurements and spectral data were evaluated by multivariate partial least square method. In addition, finger oxygen saturation was measured during the experiment and the recordings were compared with buccal oxygen saturation.

RESULTS: The spectral analysis illustrated that the spectral data from the near infrared probe correlated strongly with the absorption features of both buccal flow and oxygenation measured by the reflectance sensors (average $R^2 = 0.89$). The results showed probably overestimated values for buccal oxygen saturation recorded by the reference pulse oximeter in comparison with finger oxygen saturation, with the mean difference increasing from 1.8% at 2000 ft to 11.4% at 16,000 ft.

CONCLUSION: The novel near infrared probe showed promising results for simultaneous measurement of blood flow and oxygen saturation in the buccal tissue. The suggested method can be used as a new technique for early indication of hypoxia in future clinical applications.

KEYWORDS: hypobaric chamber, near infrared spectroscopy, synchronization, multivariate calibration.

Amini M, Hisdal J, Gjøvaag T, Kapetanovic N, Strand T-E, Owe JO, Hørthe JR, Mirtaheri P. *Near-infrared spectra in buccal tissue as a marker for detection of hypoxia.* Aerosp Med Hum Perform. 2016; 87(5):498–504.

Oxygen saturation (S_pO_2), as a marker for hypoxia, can be noninvasively measured using a pulse oximeter with sensors that can be mounted on the finger, ear, or head. However, motion artifacts and other physiological considerations make pulse oximetry problematic in aviation.[21] In addition, delays and errant readings occur in finger-based pulse oximetry under conditions of peripheral vasoconstriction.[16] Exposure to G forces is also known to give false low S_pO_2 readings at the fingertip, probably due to venous pooling in the fingers.[8] The more central placement of pulse oximeter sensors, for example, over the temporal artery or on the forehead, provides more accurate response, less influenced by vasoconstriction despite the extreme motion encountered in the tactical aviation environment.[21]

Near-infrared spectroscopy (NIRS) can also be used for detection of hypoxia by continuous and noninvasive monitoring of tissue oxygenation as well as hemodynamics in all vascular compartments of the tissue in the near-infrared region (600-950 nm) and with a greater tissue penetration than pulse oximetry.[20] The possibility of having a more central positioning of NIRS sensors, i.e., on the forehead, allows measurement of cerebral oxygenation, which is highly sensitive to acute changes in air oxygen content and is faster in reaching oxygen saturation benchmarks compared to a finger pulse oximeter.[10,18] The NIRS

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This manuscript was received for review in October 2015. It was accepted for publication in December 2015.

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DOI: 10.3357/AMHP.4510.2016

technique reduces placement constraints and affords greater subject mobility than finger pulse oximeters and does not appear to be significantly affected by motion artifacts.[18] Though one of the limitations of NIRS forehead sensors is the extracranial contamination,[3] which is the contamination of the intracranial oxygen saturation signal by the less oxygenated blood from the external carotid artery in the scalp. In addition, similar to pulse oximetry, NIRS is sensitive to G-force induced drops in S_pO_2, which may make it difficult to determine whether a desaturation event is the product of stagnant or hypoxic hypoxia[9].

Recent studies have suggested buccal tissue as the monitoring site for detection of hypoxia[19] and monitoring of oxygen saturation.[7] Since buccal tissue is supplied by arteries from a branch of the external carotid artery, this tissue is highly vulnerable to decreases in perfusion and oxygenation.[19] The aim of this study was, therefore, to test the applicability of a newly designed NIRS probe[1] in detection of hypoxia in the buccal tissue. We hypothesized that the spectra from our novel NIRS probe would contain information about both oxygen saturation and flow as reliable markers for detection of hypoxia.

METHODS

Subjects

Six healthy male adults with an average age of 31 ± 7 yr, height 186 ± 4.4 cm, and weight 83.9 ± 10.4 kg volunteered as test participants and signed an informed consent form in accordance with the Helsinki declaration. The experiments were performed in the hypobaric chamber at the Institute of Aviation Medicine, Norwegian Armed Forces Medical Services, Norway. The study protocol was approved by the Regional Committee for Research Ethics.

Equipment and Procedure

In the pretest preparation stage, the participants underwent a general medical screening, including blood pressure measurements and pulmonary function testing. A preliminary familiarization test was then performed in the hypobaric chamber with a simulated altitude of 8200 ft (2499 m) to test the pressure equalization of the ears and sinuses.

The altitude changes during the main experiment, comprised of seven levels, starting with a climb from ground level to 2000 ft (609 m), which was selected as ground level pressure to stay clear of atmospheric changes in daily pressures. From 2000 ft to 6000 (1829 m), 8000 (2438 m), 10,000 (3048 m), 12,000 (3658 m), 14,000 (4267 m), and 16,000 ft (4877 m), the rate of change was 4000 ft · min^{-1} (1219 m · min^{-1}). The participants spent 10 min at each level. During each altitude stop, the chamber was ventilated to keep the CO_2 level below 0.15% and oxygen concentration at 20.9% in the air inside the chamber. To obtain the desired hypoxic condition, the air pressure inside the chamber was reduced to its corresponding altitude and measured with calibrated pressure sensors (Honeywell Sensing & Control, Golden Valley, MN). The temperature inside the chamber for all the six experiments and during the whole run was regulated around 25 ± 1°C.

The following probes were placed inside the subject's mouth (**Fig. 1**): 1) the laser Doppler flowmeter (LDF) probe, consisting of a titanium low-profile disc probe (VP8c, Moor Instruments, Devon, UK) with a fiber separation of 0.5 mm. The 785-nm laser diode light with a power of 2.5 mW was delivered via a central window and at a right angle to the cable. 2) The reflectance pulse oximeter sensor (PRO2, ConMed, Utica, NY), with a light source placed at the center of the sensor, consisted of three chips of three wavelengths (one red: 660 nm, and two infrared: 850 and 940 nm). Two detecting areas on the sensor were arranged concentrically around the light sources at two different diameters.[11] 3) The specially designed NIRS probe by Amini et al.[1] consists of two light guides with the diameter of 1 mm for sending and detecting the reflected light from the tissue with the separation width of 1 mm. Two optical fibers were used to connect the light guides of the probe to a halogen light source and a spectrometer. A lens with the radius of 2 mm focused the light in to the depth of 670 μm, which is below the epithelium of the buccal tissue. The probes were immobilized by a silicone-based impression material (Affinis Putty Soft 6530, Coltene, Switzerland) toward the buccal tissue for each individual. Participants were instructed to breathe through their nose to minimize noise in the probe measurements.

The measurement set-up for the NIRS system consisted of a 30-W halogen light source (Avalight-Hal-S 10-W Tungsten Halogen Lamp, Avantes, Netherlands) with an external glass filter to cut off the visual light (GL600, Avantes) and a spectrometer (AvaSpec-2048 × 14 Fiber Optic Spectrometer, slit 50 μm, Avantes). Relevant software (Avasoft Application Software, Aventes) was used to process the reflected light from the tissue. The three measuring devices were connected to a USB-6211 DAQ digital input/output (I/O) device (National Instruments, Austin, TX) to be synchronized with beat to beat peaks of blood pressure using a custom made LabVIEW software (LabVIEW version 11.0, National Instruments) (**Fig. 2**).

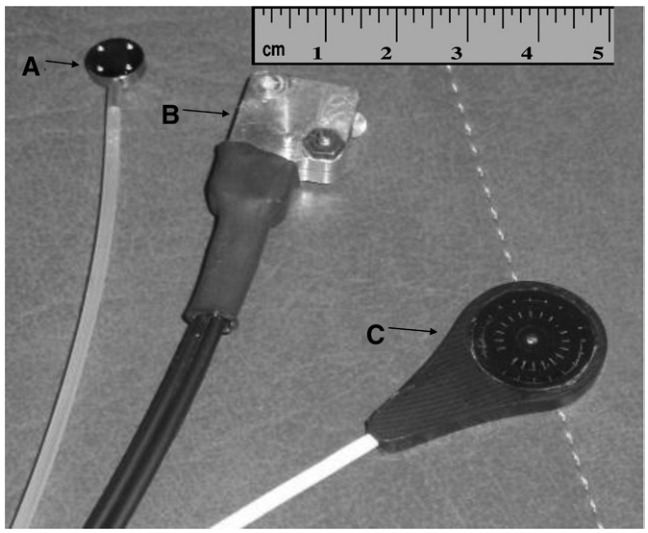

Fig. 1. The probes applied inside the mouth including: A) laser Doppler flowmeter, B) near infrared spectroscopy probe, and C) reflectance pulse oximeter.

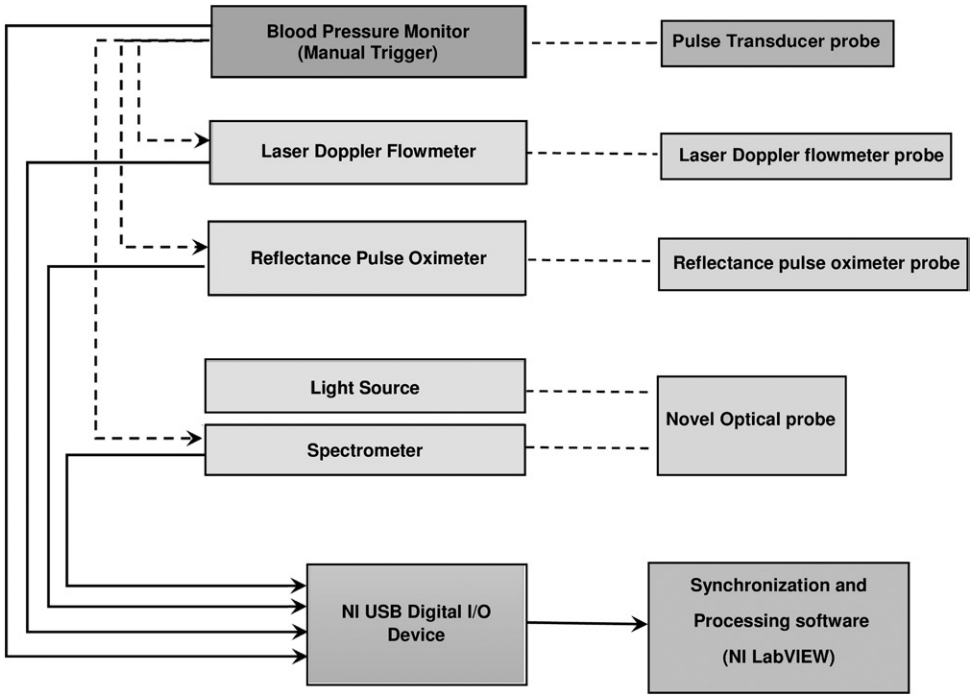

Fig. 2. Schematic overview of the measurement set-up with a software controlled synchronization.

Data from the reflectance pulse oximeter was a digitized number collected from the RS232 port, while the data from the laser Doppler flowmeter was achieved by the "Data Acquisition 8-channel Module" (VMS-DAQ, Moor Instruments). For the spectrometer, the DLL NI interface package was used to log the data through the USB port. A manual trigger started the measurements. The blood pressure peak signals were measured by a piezoelectric pulse transducer (Model 1010, UFI, Morro Bay, CA) attached to the finger of the participants. The signal could trigger instruments to start measurement as soon as the peak of the pulse wave was reached. Due to the high variations of the flow signal, the sampling rate was set to 1 Hz for all the devices. The synchronized data was collected and saved in seven altitude levels or stages. Each stage was a combination of wait, synchronization, and measurement sections and only the data from the measurement section, which was about 300 s, was logged and saved in computer. The data recorded from the above synchronized devices were then compared with the recordings of a Lifepak monitor /defibrillator (Lifepak 15, Physio-Control, Redmond, WA) during the same experiment, including S_pO_2 from a finger pulse oximeter (LNCS reusable sensor, Masimo Corporation, Irvine, CA) and heart rate from a 12-lead electrocardiogram.

Statistical Analysis

The blood flow f in the measured tissue is defined by the volume V (m^3) of the blood divided by time t (s) as indicated in Eq. 1, and the concentration of blood cells (c) is defined as the number of blood cells (n) divided by the same given volume (V in m^3) (Eq. 2)[2]:

$$f = v/t \qquad \text{Eq. 1}$$

$$[c] = n/v \qquad \text{Eq. 2}$$

One would expect from Eqs. 1 and 2 that the relationship of $(\text{flow*time})^{-1}$ would be positively correlated to the concentration of the blood, which is reflected by the absorbance measurements from the spectra. Therefore, in our analysis, we applied the calculated parameter $(\text{flow*time})^{-1}$ against our spectra during the validation of our explanatory models.

S_pO_2 and blood flow measurements were preprocessed (smoothed) by calculating the moving average of 50 points for all the samples of each subject. A partial least square (PLS) calibration method (PLS Toolbox version 10.2, Unscrambler, CAMO, Oslo, Norway) was used to study the correlation between the smoothed values of S_pO_2 and calibrated flow measured by the reference probes from the buccal tissue and the spectra obtained from the buccal tissue by the novel optical probe in the wavelength range of 600-950 nm. In our calibration data set, the measured variables consisted of the intensity values for 1370 different wavelengths for 306 different measurements, while the reference variables consisted of the smoothed S_pO_2 and $(\text{flow*time})^{-1}$ values for all the 306 different measurements. Considering the strength of S_pO_2 and flow effects in the different wavelengths of the achieved spectra, the spectra was divided into three segments of 620-750, 770-830, and 840-950 nm. In order to decrease the spectral noise, the spectra were then preprocessed by the following methods:

- Smoothing transformation: moving average which finds a data value by averaging the values within a segment of 51 data points.
- Spectroscopic transformation: transforms reflectance data into Kubelka-Munk units to compensate for scatter in diffuse reflectance measurements.

To confirm the selectivity of the spectra and reference probe measurements, a two-sample t-test was run for each segment assuming equal variances of the R^2 values of S_pO_2 and $(\text{flow*time})^{-1}$.

RESULTS

Recordings of buccal and finger S_pO_2 measured by pulse oximeters, buccal flow measured by the laser Doppler flowmeter, and heart rate, as well as the partial pressure of oxygen in the chamber (PO_2), for one representative test participant at seven

different levels of altitude are shown in **Fig. 3**. The plots show that the S_pO_2 recordings by the buccal pulse oximeter are higher than finger S_pO_2 values at all altitude levels.

The preprocessed NIR spectra achieved from the NIRS probe in the range of 600 to 950 nm with 306 measurements for each of the six participants at the sampling rate of 1 Hz is illustrated in **Fig. 4**, where the variations due to the absorption are clearly shown in the spectra as tops and valleys. The seven layers of spectra seen in Fig. 4 are the results of seven levels of pressure applied during the experiment. The thickness of the layer indicates more variations in intensity values in the bottom layer in comparison to the other six layers of the spectra.

The PLS regression method for two variables of buccal S_pO_2 and $(\text{flow*time})^{-1}$ was run separately for all three segments (620-750, 770-830, and 840-950 nm) and outliers were removed from the data set. Model quality was evaluated by calculating the coefficient of determination (R^2) as an indicator of the degree of correlation between the measured and reference values, as well as the root-mean-square error of prediction (RMSEP) as a measure of prediction accuracy. The correlation results between the spectral data and the buccal flow and S_pO_2 values for all the six participants are shown in **Table I**.

The results for all participants confirmed an average correlation of $R^2 = 0.889$ between the measured oxygen saturation and spectral output for the ranges of 620-750 and 840-950 nm, while the average correlation of flow and measured spectra was $R^2 = 0.888$ for the range of 770-830 nm. Model validation indicated low prediction errors (RMSEP) of 0.003 for blood flow, and higher average RMSEP of 0.266 for buccal S_pO_2 (Table I), which is most probably due to the variations of the buccal S_pO_2 in comparison to buccal blood flow.

The two-tailed *t*-test was performed for R^2 values of buccal S_pO_2 and $(\text{flow*time})^{-1}$ in each segment, and the results showed $t(10) = 3.2$, $P = 0.0088$; $t(10) = 2.26$, $P = 0.0474$; and $t(10) = 5.132$, $P = 0.0004$ for the first, second, and the third segments of the NIR spectra, respectively. These results demonstrate a significant difference between the measurements of buccal S_pO_2 and blood flow within the selected regions.

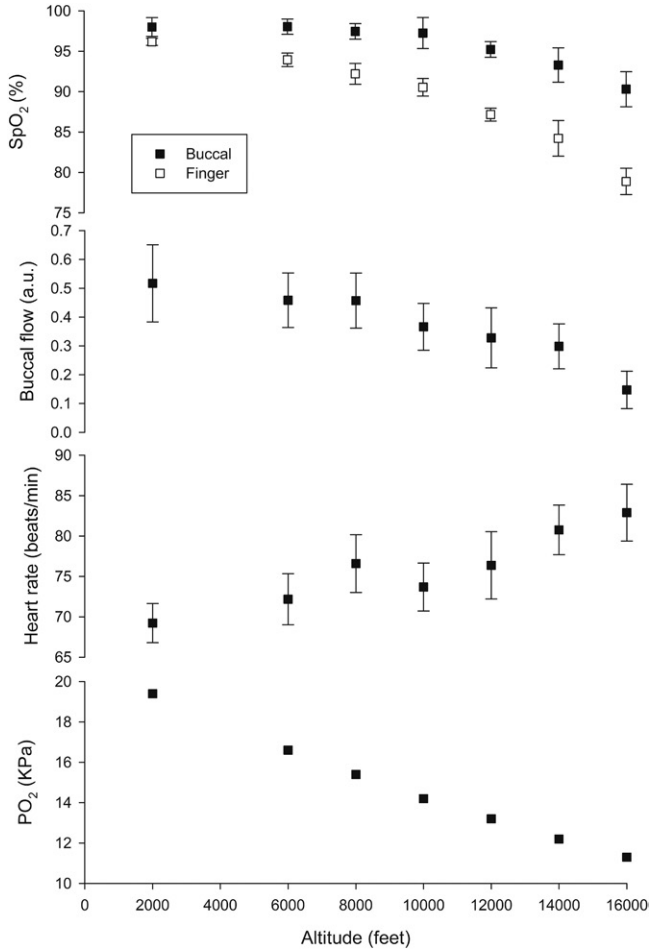

Fig. 3. Recordings for one representative test participant (No. 1) during altitude rise from 2000 to 16,000 ft (609 to 4877 m), including, from top to bottom: 1) buccal S_pO_2 recorded by the ConMed reflectance pulse oximeter and 2) finger S_pO_2 recorded by the Masimo pulse oximeter; 3) buccal flow recorded by the Moor laser Doppler flowmeter; 4) heart rate recorded by the Lifepak monitor; and 5) partial pressure of oxygen in the chamber (P_{O_2}). The values are presented as the average values and their standard deviation for the last 300 s of each altitude level.

DISCUSSION

The main finding in the present study is that NIRS spectra monitored from the buccal tissue by our new NIRS probe contained information on both oxygen saturation and blood flow in the tissue and, therefore, these measurements can be used as an indicator of hypoxia. The raw NIRS spectra and the buccal reference measurements all needed data preprocessing due to the noise in the recordings. Movement of the probes could have been the source of the measurement errors as most of the optical probes are sensitive to movement.[1] The small variations in the amplitude of individual specters are due to the small slit (50 μm) on the spectrometer, which provides a high resolution spectra (FWMH resolution of 1.2 nm), but transmits less light to the detector and may result in a lower signal to noise ratio. Choosing a larger slit to measure low light intensities from the tissue with less noise is possible, but this would lead to a lower resolution spectra. Moreover, the effect of light scattering in the tissue is another source of error for all the sensors used in this study. Martens et al. suggested that correcting the scattering can be done using implicit and explicit scatter correction methods.[14] Explicit scatter correction can be done through appropriate data pretreatment, while the implicit method is addressed by using multivariate calibration (PLS).

The process of developing a PLS model involves determining the minimum number of calibration factors that produce the smallest error in estimating buccal S_pO_2 and flow from the calibration data set. For blood flow, the best calibration model was established with two factors and the spectral range of 770-830 nm, while three factors and the spectral ranges of 620-750 and 840-950 nm were best for buccal S_pO_2. Model performance was enhanced by limiting the PLS analysis to spectral regions where buccal S_pO_2 or flow signal-to-noise ratio is highest. Using

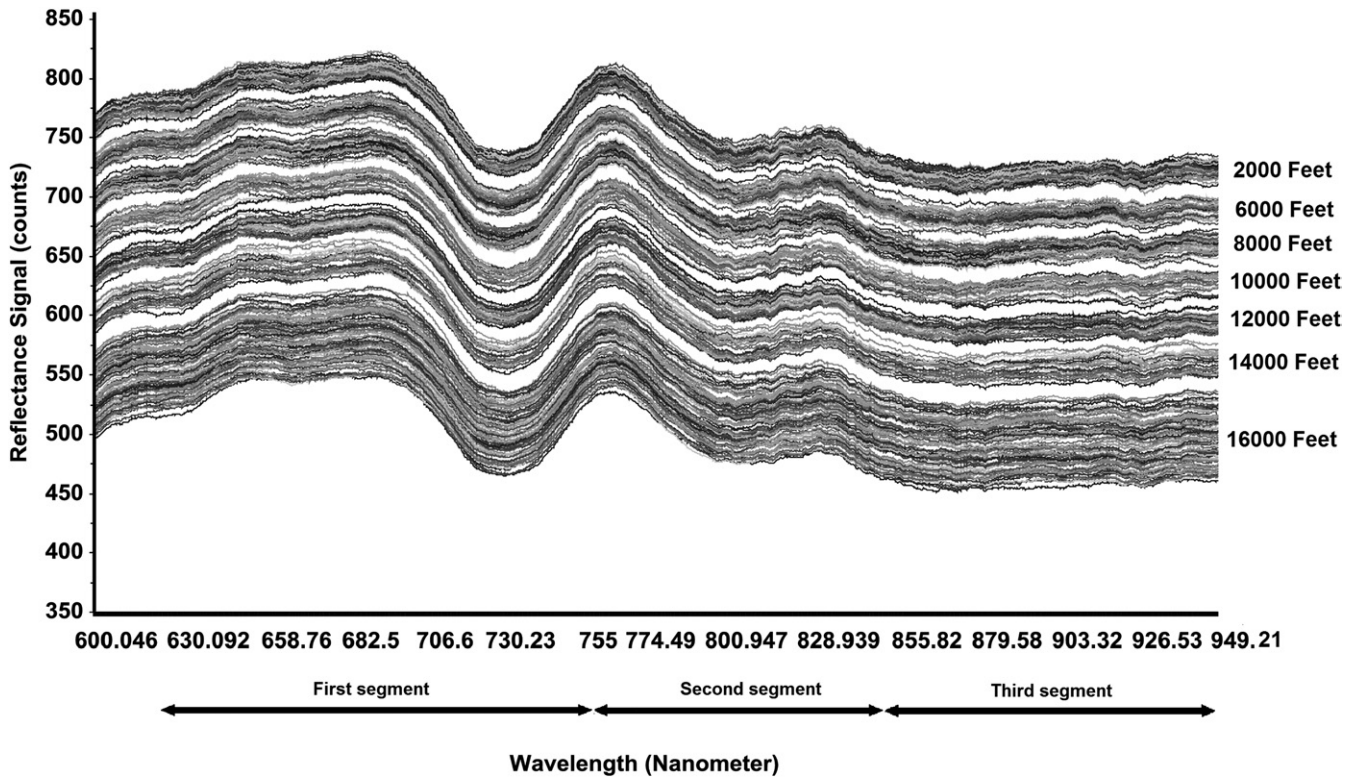

Fig. 4. Spectra achieved by the novel near infrared spectroscopy probe for one representative test participant (No. 1) after preprocessing in the wavelength range of 600-950 nm, which is divided in three segments of: first (620-750 nm), second (770-830 nm), and third (840-950 nm). The seven layers of spectra seen in the picture are the result of seven levels of pressure applied during the experiment (2000-16,000 ft/609 to 4877 m).

these particular spectral ranges (620-750, 770-830, and 840-950 nm) effectively reduces the impact of other ranges in describing buccal S_pO_2 versus flow. As depicted in Table I, the influence of buccal S_pO_2 can be seen more in the first and the third segment of the spectra, while flow has a higher influence in the middle segment, which is also where we have the isobestic region, where the absorbance spectra of oxygenated and deoxygenated hemoglobin intersect. The above argument can be logical as the buccal S_pO_2 probe is measuring at three wavelengths of 660, 850, and 940 nm while the laser Doppler flowmeter is measuring flow at the wavelength of 785 nm. Overall, spectral analysis illustrated how the spectral information used in the PLS regression correlated strongly with the absorption features of both buccal flow and S_pO_2 (average R^2 of 0.89).

As illustrated in the plots of Fig. 3, heart rate increased by 10-15 bpm as a response to the decrease in the ambient pressure.[15] On the other hand, buccal flow measured by laser Doppler technique decreased with the increase in altitude (Fig. 3). Perfusion changes in the buccal tissue may, therefore, serve as an indicator and marker of hypoxia. In addition, the plots of Fig. 3 demonstrate a decrease in oxygen saturation levels measured with pulse oximetry both at the finger and in the buccal tissue as the result of the decrease in the ambient pressure. According to previous studies, buccal pulse oximetry correlates better with intra-arterial measurements, although it shows higher values than finger pulse oximetry.[17] Our results also show higher S_pO_2 in buccal tissue at all altitude levels compared to finger S_pO_2, while the means difference seems to increase

Table I. Results from Partial Least Square Calibration of the Spectral Data Measured from the Buccal Tissue by the Novel NIRS Probe vs. Oxygen Saturation from the Buccal Pulse Oximeter and the Calculated (Flow*Time)$^{-1}$ from the Buccal Laser Doppler Flowmeter.

SPECTRAL RANGE (nm)	NUMBER OF TEST PARTICIPANTS	NUMBER OF CALIBRATION FACTORS* FOR S_pO_2	AVERAGE R^{2**} FOR S_pO_2	AVERAGE RMSEP*** FOR S_pO_2	NUMBER OF CALIBRATION FACTORS FOR FLOW	AVERAGE R^2 FOR FLOW	AVERAGE RMSEP FOR FLOW
620-750 nm	6	3	0.864	0.258	2	0.695	0.009
770-830 nm	6	3	0.727	0.470	2	0.888	0.003
840-950 nm	6	3	0.914	0.274	2	0.679	0.012

* Calibration factor is the minimum number of factors that produce the smallest error in estimating buccal S_pO_2 and flow from the calibration data set.
** R^2 or the coefficient of determination is an indicator of the degree of correlation between the predicted values (from the NIRS probe) and actual values (oxygen saturation and flow from the reference pulse oximeter and laser Doppler flowmeter probes).
*** RMSEP or the root-mean-square error of prediction is a measure of prediction accuracy.

from 1.8% at 2000 ft (609 m) to 11.4% at 16,000 ft (4877 m) with the increase of the level of hypoxia. This is in agreement with the previous findings, which have shown that buccal pulse oximetry tends to overestimate oxygen saturation in proportion to the degree of hypoxia.[5] The reasons for the increasing divergence between the oxygen saturation measurements in buccal tissue and the finger is not completely resolved, but it is reasonable to assume that at high altitudes the values are overestimated in buccal tissue and, at the same time, they may be underestimated in the finger. A possible explanation for the underestimation in the finger is the peripheral vasoconstriction in the extremities during hypoxia, resulting in a reduction in the pulse wave signal and the portion of the signal used to measure hemoglobin saturation by pulse oximeters.[6,13] One could argue that the larger change shown by finger S_pO_2 compared to buccal S_pO_2 is indicating a better sensitivity of the measurements as a hypoxic marker; however, there are three problems with such a statement. Firstly, finger S_pO_2 can indicate a hypoxic condition while the metabolism might still be aerobic and, in this way, finger SpO_2 values will be misleading as a hypoxic marker. Secondly, all S_pO_2 devices have a dynamic measuring range (saturation accuracy of 70–100% for the Masimo finger pulse oximeter used) and measurements beyond those values will result in unreliable measurements. Thirdly, fingers as the monitoring site for pulse oximetry would be more prone to errors due to movement and temperature changes. Therefore, choosing extremities as a site for detection of hypoxia can result in false conclusions regarding the degree of hypoxia.

There are a few studies which have applied the NIRS technique to measure regional blood flow and oxygen consumption simultaneously[2,4,22] while comparing the NIRS method with other conventional methods in quantifying blood flow and oxygenation at the same time.[4,22] These studies, though, have used only a few wavelengths in the near infrared range to study blood flow and oxygenation of peripheral tissues under stagnant hypoxia caused by venous and arterial occlusion. In another recent study,[12] although combining oxygenation and flow measurements, the measurements were restricted to the skin due to the limited measurement depth of the white-light reflectance spectroscopy technique used.

To the best of our knowledge, there are no studies on NIRS spectra in the whole range of NIR wavelengths with the purpose of monitoring oxygen saturation and blood flow changes simultaneously. This approach, with the use of an optical probe which focuses the light into a defined depth of the buccal tissue, makes it possible to study perfusion changes closely and in more detail. Hence, early indication of tissue hypoxia and prevention of harmful effects of hypoxia and exposure to high G forces can be obtained.

A limitation of our current study is that for ethical reasons, arterial oxygen saturation from blood samples, which is considered the gold standard for oxygen saturation measurements, was not measured. These measurements can provide us with a reliable reference for the oxygen saturation recordings from the buccal tissue. The complementary phase to our preliminary study would be developing algorithms to calculate concrete values of oxygen saturation and blood flow from the NIR spectra monitored by the buccal NIR probe. Thus, measurement of arterial oxygen saturation is definitely recommended in our future studies for developing our new NIR technique and probe. In addition, a more stable fixation method for the buccal probe in order to reduce motion artifacts and saliva accumulation, and to reduce its interference with user activities is also required for future studies.

ACKNOWLEDGMENTS

The authors are indebted to Prof. Knut Lehre Seip and also the staff of the Institute of Aviation Medicine for their close collaboration and providing the possibility of using their facilities in performing this experiment. This project was supported by funding from the Oslo and Akershus University College of Applied Sciences and the Norwegian Research Council.

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