Tommi Noponen, Kalle Kotilahti, Jussi Toppila, Ilkka Nissilä, Tapani Salmi, Timo Kajava, and Toivo Katila. 2003. Near-infrared measurements of hemodynamic and oxygenation changes on the frontal cortex during breath holding, hyperventilation, and natural sleep. In: Britton Chance, Robert R. Alfano, Bruce J. Tromberg, Mamoru Tamura, and Eva M. Sevick-Muraca (editors). Optical Tomography and Spectroscopy of Tissue V. Proceedings of SPIE, volume 4955, pages 124-133.

Near-infrared measurements of hemodynamic and oxygenation changes on the frontal cortex during breath holding, hyperventilation, and natural sleep

Tommi Noponen[a], Kalle Kotilahti[a], Jussi Toppila[b], Ilkka Nissilä[a], Tapani Salmi[b], Timo Kajava[a], and Toivo Katila[a]

[a]Laboratory of Biomedical Engineering, Helsinki University of Technology, Finland
[b]Department of Clinical Neurophysiology, Helsinki University Central Hospital, Finland

ABSTRACT

We have developed a frequency-domain near-infrared device suitable for physiological studies in human. In this work, a four-channel configuration of the instrument is applied to monitor hemodynamic and oxygenation changes in the frontal cortex of volunteers during different ventilation tasks. We use four different source-receiver separations (2, 3, 4, and 5 cm) and three wavelengths (760, 808, and 830 nm) to test the sensitivity of these parameters to cardiovascular and metabolic changes. Low-frequency oscillations ($\sim$ 0.02 Hz) and variations in heart rate during different ventilation tasks are investigated as well. We also study physiological changes during natural sleep using the frequency-domain instrument simultaneously with a polysomnography system containing a pulse oximeter. Our results indicate that hemodynamic and oxygenation changes in the frontal cortex during natural sleep can be detected using near-infrared measurements.

Keywords: Hemodynamic and oxygenation changes, frequency-domain instrumentation, ventilation and sleep measurements

1. INTRODUCTION

In tissue, there is a so-called window of transparency at the wavelength region between 650 and 950 nm. This makes it possible to detect diffuse near-infrared light through several centimeters of tissue and to obtain information from the changes of its optical properties. If at least two wavelengths are used, it is also possible to estimate the changes in [HbO_2] and [Hb]. These parameters are related to physiological processes such as blood-flow and volume changes in the underlying tissue.

In the frequency-domain technique, tissue is illuminated with radio-frequency (RF) modulated light and the modulation amplitude, the phase shift with respect to the incident light, and sometimes also the average intensity are measured. The phase-shift measurement makes it possible to estimate the pathlength that the photons have traveled. The phase information provides a measure of background scattering and it can be used, e.g., to more accurately estimate the changes in [HbO_2] and [Hb] in tissue.

The changes in optical fiber coupling, movement artifacts and especially noise and interference from physiological processes in the underlying tissue may limit the contrast-to-noise ratio (CNR) of measurements. In some cases, also instrumental noise may overwhelm the signal. Different source-detector separations affect the spatial sensitivity and contrast of the measurement. With near-infrared measurements, it is possible to monitor changes in blood flow and volume as well as in oxygen saturation and consumption. A careful choice of wavelengths and source-detector separations used in the measurements may enable the detection of these physiological processes even from noisy data.

Sleep disorders (e.g., sleep apnea) form a major health care problem. Insufficient blood circulation during sleep may have life-threatening consequences (such as an infarct). Polysomnography is a method to monitor disorders during sleep. It does not include, however, a method to monitor directly local hemodynamic changes and tissue oxygenation in the brain. Near-infrared measurements, however, may provide such information.

Further author information: (Send correspondence to T.N.)
E-mail: Tommi.Noponen@hut.fi, Telephone: +358 9 451 5838

Optical Tomography and Spectroscopy of Tissue V, Britton Chance, Robert R. Alfano, Bruce J. Tromberg, Mamoru Tamura, Eva Marie Sevick-Muraca, Editors, Proceedings of SPIE Vol. 4955 (2003)

In this work, we investigate the feasibility of our frequency-domain near-infrared instrument to detect different physiological changes. A hyperventilation and breath-holding protocol is used to study the sensitivity of the measurements. By using different source-detector separations and NIR wavelengths, we demonstrate that the measurement can be made sensitive to different physiological processes. Also, the frequency content of the optical signals is studied, which reveals, e.g., low-frequency oscillations and variations in the heart rate. Finally, the frequency-domain instrument is applied to measure natural sleep simultaneously with polysomnography.

2. MATERIALS AND METHODS

A brief overview of the operation principle of our frequency-domain instrument is presented. We also describe the measurement methods and instrumentation applied to the hyperventilation and breath-holding and natural-sleep studies.

2.1. Multi-channel frequency-domain instrument

We have developed an accurate frequency-domain imaging instrument suitable for physiological studies. Currently, the instrument has 16 time-multiplexed source fibers and four parallel detection channels. During the measurements in this work, just a single source fiber is used.

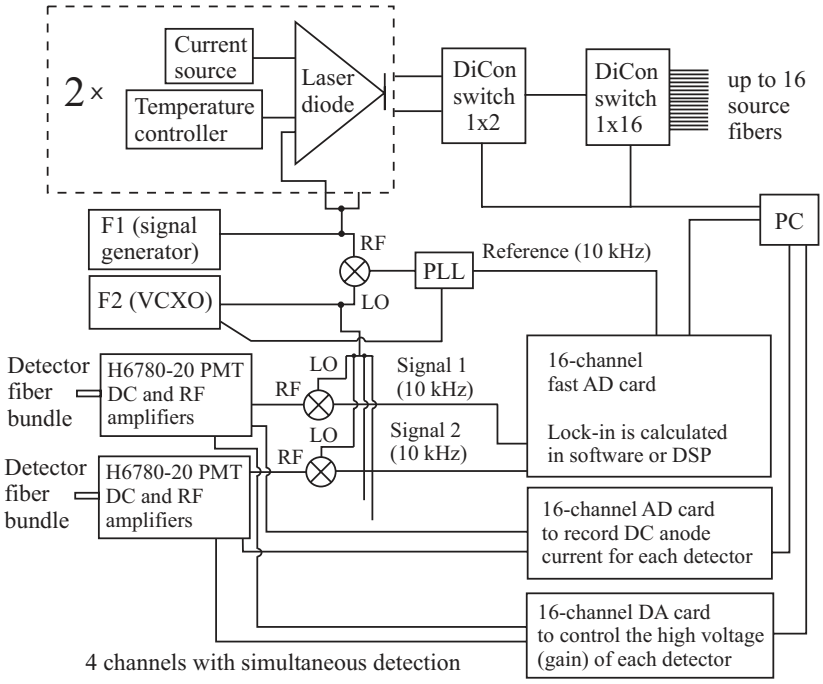

Figure 1. Block diagram of the frequency-domain imaging system.

A signal generator and voltage-controlled crystal oscillator (VCXO) are used as RF-signal sources. The output of the signal generator (100 MHz) is split and guided into two laser diodes (760-830 nm). The measurement wavelength and the active source channel is selected using a 1×2 prism switch and a 1×16 fiberoptic switch, which are connected in sequence. The wavelength switch, however, was integrated into the system during the work reported in this paper so that some of the results were measured using a single wavelength only. The laser intensity of $\sim$ 4 mW was used in all the measurements presented in this paper.

Photo-multiplier tubes (PMT) are used for light detection and their outputs are mixed with the output of the VCXO. The phase and amplitude of the intermediate-frequency signal (10 kHz) are measured using a digital lock-in amplifier and the measured data is post processed in a PC. A phase-locked loop (PLL) improves the phase-measurement accuracy. Also, the mean anode current from the PMT output is measured.[1, 2]

2.2. Methods for hyperventilation and breath holding studies

Hyperventilation and breath holding can be used to artificially generate hemodynamic and oxygenation changes in the cortex of the brain. During hyperventilation, the partial pressure of CO_2 decreases in the lungs and blood which causes hypocapnia. This in turn affects the cerebral circulation leading to vasoconstriction since CO_2 is an important regulator of cerebral blood flow (CBF). The result of hyperventilation is a decrease in both CBF and oxygen delivery to the cortex generating cerebral hypoxia.

During breath holding, the partial pressure of CO_2 increases in the blood and lungs, causing hypercapnia. This generates vasodilation in the cortex, increasing cerebral blood volume (CBV). During breath holding, oxygen reserves are reduced, decreasing oxygen saturation in arteries. This results in cerebral hypoxia, during which the blood and tissue oxygenation decreases in the cortex.

Hyperventilation and breath holding are suitable tests of the sensitivity of near-infrared measurements to two different kinds of hemodynamic and oxygenation changes in the frontal cortex. In our measurements, a sequence containing a period of rest, hyperventilation, rest, breath holding, and rest was repeated twice. Each period was approximately 2 minutes long except the last rest period which took approximately 4 minutes. The total measurement time was 22 minutes (Fig. 2a).

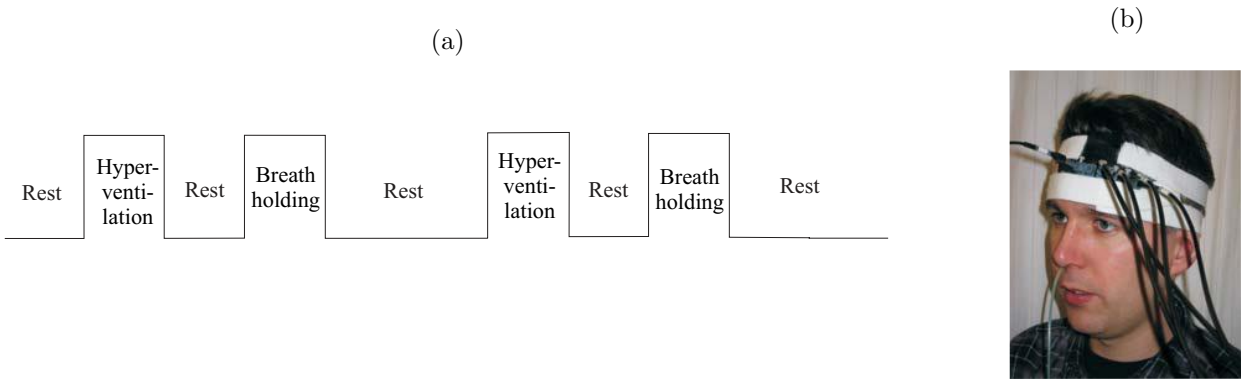

Figure 2. a) The measurement protocol and b) the placement of optical fibers and capnography tube used in the hyperventilation and breath-holding studies.

A single source fiber and four receiving bundles were attached to the forehead of the subject using a thermoplastic fiber holder as shown in Fig. 2b. The fiber holder was individually shaped for each person. The signals from the four different source-detector separations (2, 3, 4, and 5 cm) were detected in parallel. The carbon-dioxide content of expiratory air was simultaneously monitored using capnography.

We studied two volunteers. The frequency-domain instrument was operating at a single wavelength and the laser source was manually replaced between the measurements to test the sensitivity of wavelength to different physiological changes. We carried out three measurements at 760 nm and at 808 nm, and two measurements at 830 nm.

2.3. Setup for measurements of natural sleep

A decrease in cerebral blood flow (CBF) takes place during natural sleep. This phenomenon is related especially to the transition to deep sleep (sleep stages III and IV). The cerebral-oxygen metabolic rate ($CMRO_2$) reduces during this transition as well, but it should be smaller than the change in the CBF. This explains the reduction in cerebral oxygenation.

The setup used in our natural-sleep measurements is illustrated in Figs. 3a and b. A single source fiber and four detector bundles were attached on the left side of forehead of volunteer using a similar fiber holder with the same source-detector separations as in the hyperventilation and breath-holding studies. Simultaneously, a polysomnogram was recorded to verify the sleep stage and to compare the results to the optical signals. The

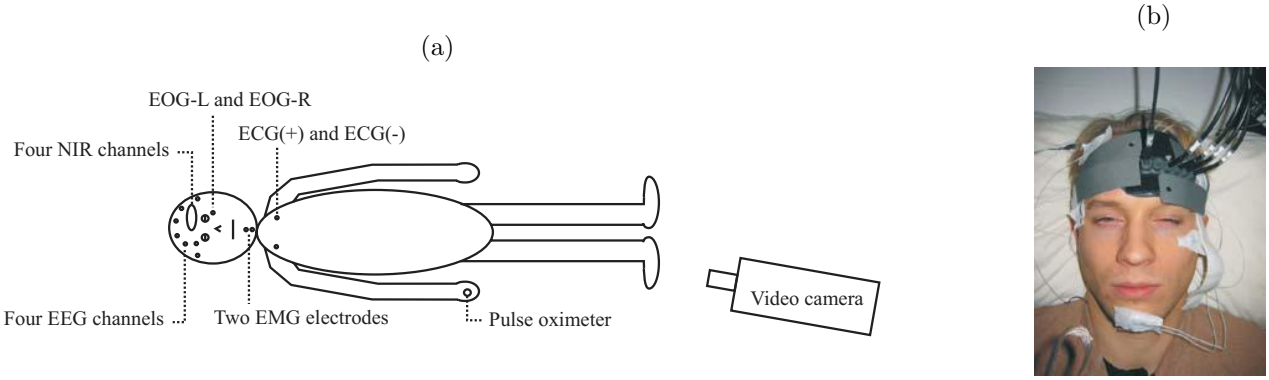

Figure 3. a) The schematic diagram of measurement setup during natural sleep studies. b) Attachment of optical fibers and polysomnography electrodes.

polysomnogram was recorded and stored using an ambulatory sleep-recording device (Embla, Flaga hf. Medical Devices) and analyzed using a polygraphic workstation (Somnologica, Flaga hf. Medical Devices). The device includes four EEG channels (C4-A1, O2-A1, C3-A2, and O1-A2), two EOG electrodes close to the eyes, two EMG electrodes on the chin, and two ECG electrodes close to the shoulders (Fig. 3). A pulse-oximeter sensor was attached to the index finger of the subject. The polysomnogram was used to classify the sleep stages to the six different categories: sleep I, II, III, IV, and REM (rapid eye movements) and awake. The measurement was video recorded to visually observe movement artifacts. The studies were carried out at the Helsinki University Central Hospital and were granted a permission by the hospital ethical commission.

During measurements the volunteer lay supine on bed. The measurement time varied from approximately 1.5 to 2.5 hours. The subject was asked to stay awake for a couple of hours during the preceding night to make it easier for him/her to fall asleep during the measurement. At the end of the measurement, the subject was woken up.

From the measurements at two wavelengths, the changes in [Hb] and [HbO_2] were estimated using the modified Beer-Lambert law.[3] The attenuation due to scattering and background absorption was assumed constant. Using the specific extinction coefficient, the concentration changes of a chromophore can then be estimated from attenuation changes. When a medium contains N chromophores of interest and the number of measurement wavelengths is M ($N \leq M$), the changes of concentrations are given by

$$\Delta \mathbf{c} = (\alpha^T \alpha)^{-1} \alpha^T \frac{\Delta \mathbf{A}}{d \cdot DPF}, \tag{1}$$

where d is the geometrical distance between the source and detector, $\Delta \mathbf{c}$ is a N×1 vector and $\Delta \mathbf{A}$ is a M×1 vector containing the changes in attenuation. The matrix α (M×N) contains the specific extinction coefficients for each chromophore at each wavelength.

We used wavelengths of 760 and 808 nm. The values of DPF (5.93 at 760 nm and 6.26 at 808 nm) and α were taken from the literature.[4–6] The DPF was not calculated from the phase data, since the frequency-domain instrument was not calibrated for these test measurements.

3. RESULTS

3.1. Contrast and sensitivity studies

The changes in the amplitude signal as a function of source-detector separation are shown in Fig 4. This particular example is one of the hyperventilation and breath-holding measurements at 760 nm. The same features can be seen in measurements at the other wavelengths as well. The data was sampled at a frequency of 45 Hz using an effective bandwidth of 25 Hz for the lowpass filter of the lock-in amplifier. The mean values of amplitude signals were normalized to unity.

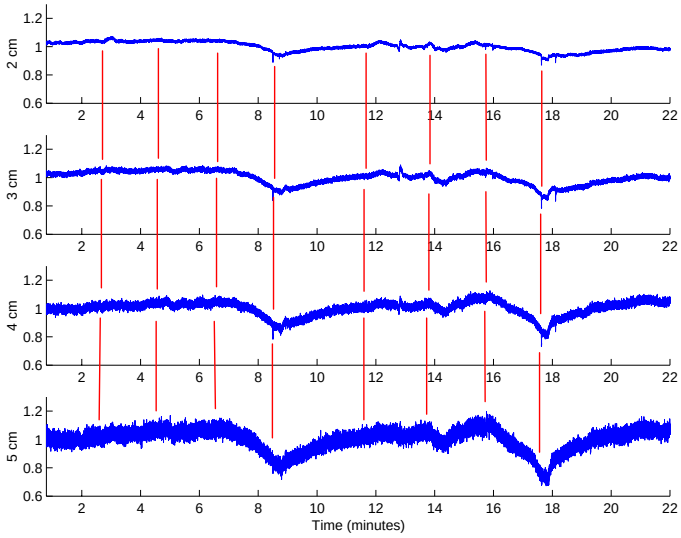

Figure 4. Amplitude signals from hyperventilation and breath-holding studies for four different source-detector separations. The vertical markers separate the hyperventilation and breath-holding periods. These markers were placed with a help of the capnography signal. The measurement wavelength is 760 nm.

The data shows how the contrast and noise in the amplitude signal increase as the source-detector separation changes from 2 to 5 cm. This behavior is mostly due to the change in the measured tissue volume. At 2-cm separation, a significant part of the signal comes from surface tissues whereas at longer distances, a larger portion of signal arises from the brain tissue. In Fig. 5, the phase signals of the same measurement are shown. The signal CNR is clearly lower than that of amplitude signal. For this reason, we use amplitude signals to reveal physiological changes in this paper. The anode current (the DC intensity) is not shown here, but it has a contrast similar to that of the amplitude signal.

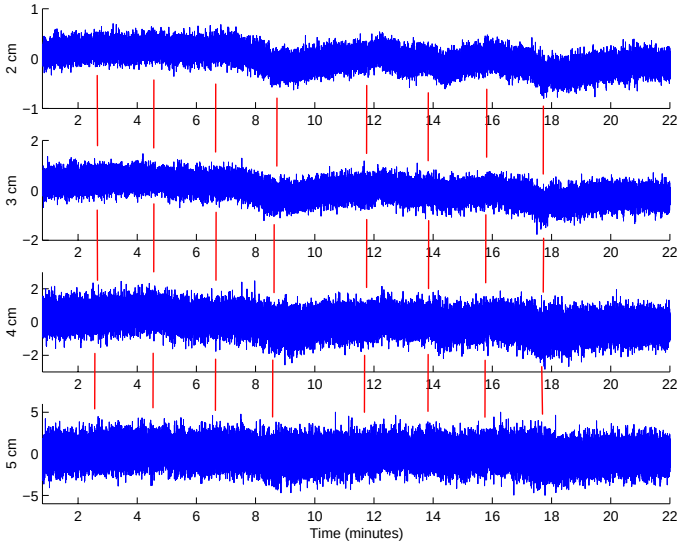

Figure 5. The phase signals corresponding to the measurements of Fig. 4.

The sensitivity of a measurement for different physiological phenomena depends on wavelength. Using the Hb-sensitive wavelength of 760 nm, the largest contrast is obtained during breath holding whereas the hyperventilation period is hardly visible. CBV is increased slightly and the oxygen saturation in tissue decreases during breath holding. These changes raise [Hb], which shows as a clear decrease in the amplitude signal.

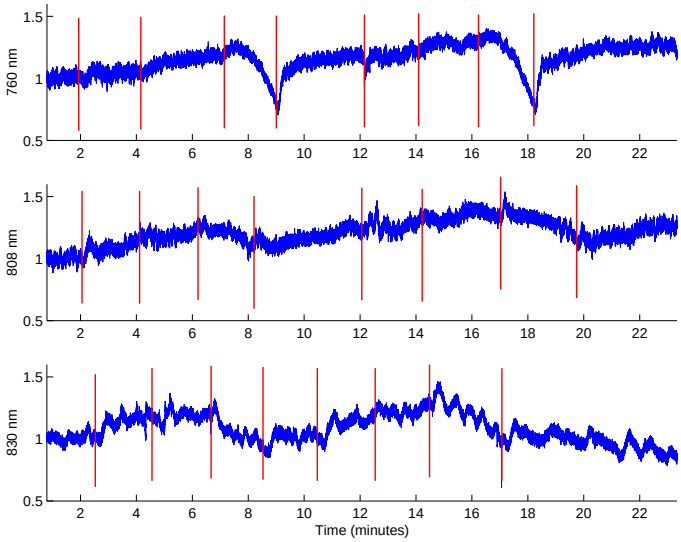

Figure 6. Amplitude signals measured at different wavelengths are sensitive to different physiological changes.

The measurement sensitivity of this test protocol is lowest at 808 nm. The amplitude signal at this wavelength indicates changes in CBV which, however, are relatively small during this protocol. A small increase in signal can be observed during hyperventilation due to the decrease of CBV, and, correspondingly, the signal decreases during breath holding.

The highest sensitivity to hyperventilation is obtained at the HbO_2-sensitive wavelength of 830 nm. The decrease in CBF reduces the [HbO_2] in the cortex which is clearly visible at this wavelength. During breath holding, the decrease in [HbO_2] is compensated by a much larger increase in [Hb] which results in a decrease in the amplitude signal.

3.2. Frequency content of the signals

The frequency content of the hyperventilation and breath-holding amplitude signals was investigated. Different frequency components were studied using the power spectral density (PSD) and the temporal variations in different components were illustrated with spectrograms. The PSD was calculated using Welch's method with a Hanning window (width $\sim$ 730 s) so that subsequent windows had an overlap of $\sim$ 365 s. For the spectrogram, a Hanning window width of $\sim$ 11.4 s was used so that the overlap was $\sim$ 5.7 s and the frequency spectrum was calculated at $\sim$ 161-ms intervals.

Two relatively strong frequency components were found in each measurement. The frequency component around 1 Hz corresponds to arterial blood pulsations. The frequency of this component changes during the test protocol (Fig. 7). At the beginning of hyperventilation, the heart rate increases but stays relatively constant during the whole period. After hyperventilation, the heart rate returns back to its rest level. During breath holding, the rate increases gradually returning back to its rest level at the end of the period.

Another relatively strong component was found at very-low frequencies. The data was filtered using a sharp bandpass filter (passband from 0.01 to 0.25 Hz). The stopband attenuation was -50 dB. Also, similar filters with narrower bandwidths (e.g., from 0.01 to 0.02 Hz) were designed to extract only the very-low frequencies from the signal. In Fig. 8, the PSD of the bandpass-filtered signal (0.01-0.25 Hz) is illustrated. This data represents well the general features of all PSDs calculated from the hyperventilation and breath-holding data. In each case,

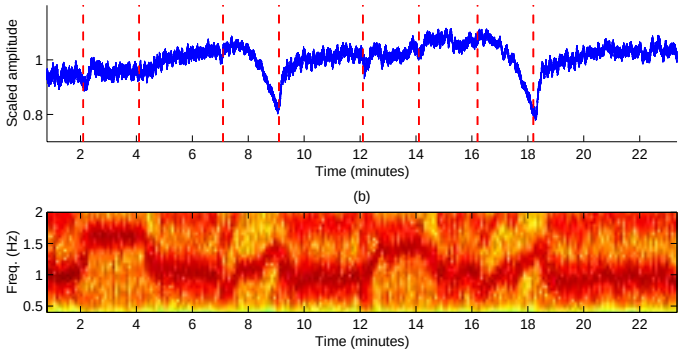

Figure 7. On the top row, an amplitude signal measured at 760 nm and with a source-detector separation of 2 cm. On the bottom, a spectrogram calculated from a bandpass filtered amplitude signal (passband 0.6 − 2.0 Hz). Dark colors represent strong frequency components.

strong frequency components were found around 0.01−0.03 Hz while there was practically no signal at higher frequencies (> 0.05 Hz). An example of this relatively strong very-low frequency oscillation is illustrated on the second row of Fig. 8. These oscillations were more pronounced at HbO_2-sensitive measurements.

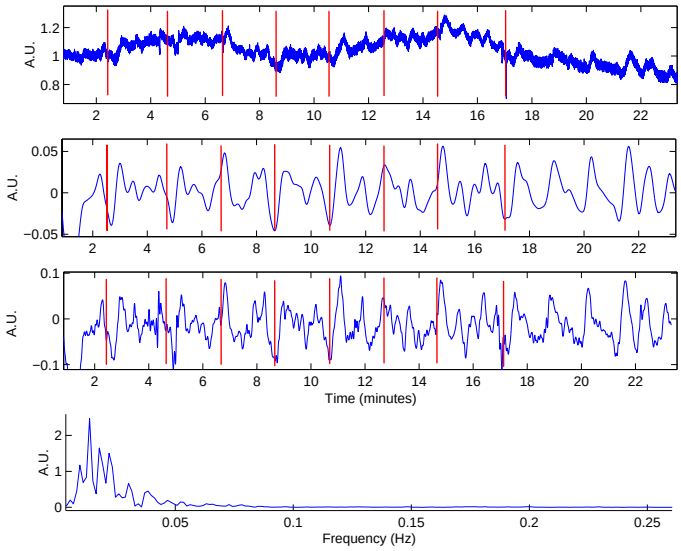

Figure 8. Top row: an amplitude signal measured at 830 nm. Second row: a filtered signal (passband from 0.01 to 0.02 Hz). Third row: a filtered signal (passband from 0.01 to 0.25 Hz). Fourth row: the PSD calculated from the signal shown on the third row.

3.3. The measurements of natural sleep

Preliminary natural-sleep measurements were carried out by studying two volunteers. In the first measurement, a single wavelength (808 nm) was used and in the five following studies, two wavelengths (760 and 808 nm) were applied. Optical fibers were adjusted to gently touch the subject's skin during the first two measurements whereas the fibers were ~ 1.2 mm apart from the skin in the other studies.

In Fig. 9, a single-wavelength measurement during natural sleep is shown. During the transition from the awake stage to a deep sleep (around 16:08:00), a gradual decrease in the heart rate and a slight decrease in the arterial oxygen saturation (SaO_2) can be detected. These changes correlate well with the increase in the

amplitude signals. At the end of sleep period (around 16:38:00), the amplitude signals return back to the baseline and correlate well with the increase in heart rate and SaO_2. Also a shorter sleep period at the beginning of the measurement (around 15:55:00) can be observed as a slight increase in the amplitude signal, especially in the data with 2-cm separation. The amplitude signal of the 3-cm measurement resembles the signal of the 2-cm measurement, whereas the signal of the 5-cm measurement is similar to the signal of the 4-cm measurement.

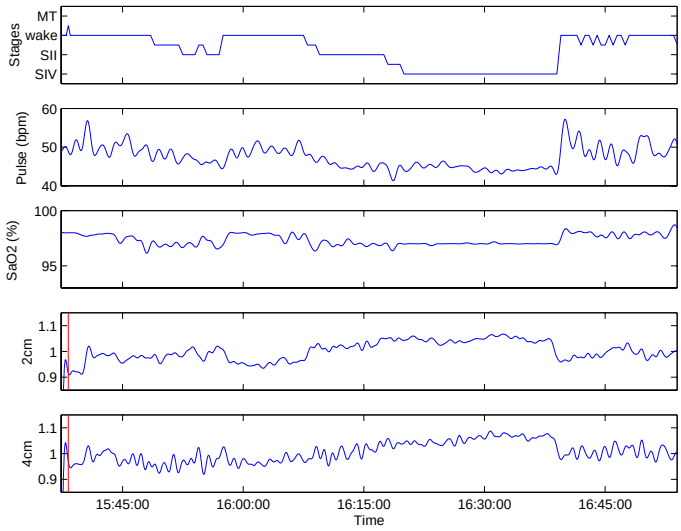

Figure 9. A measurement during natural sleep. In addition to the sleep-stage classifications, the heart rate and SaO_2 signals are shown, which are both measured using a pulse oximeter. The amplitude signals are measured with source-detector separations of 2 and 4 cm. These signals are filtered using a 15-s time constant and the signals are decimated to a sampling frequency of 1 Hz to emphasize their low frequency changes. The vertical lines of the amplitude plots depict the beginning of the measurement.

For the dual-wavelength measurements, the wavelength was switched at a rate of $\sim$ 1 Hz. The first $\sim$ 200 ms of the data was discarded at the beginning of each block due to the settling time of the PMT high-voltage suppliers. The data was averaged over the $\sim$ 800 ms window at each wavelength so that the sampling frequency of data became $\sim$ 0.5 Hz. Before calculating the $[HbO_2]$ and [Hb], the amplitude data was interpolated to $\sim$ 1 Hz and the amplitude values measured at the other wavelength were shifted by a single sampling interval to align the data points with each other.

In Fig. 10, the changes in $[HbO_2]$ and [Hb] in μmolar are shown. In this measurement, the $[HbO_2]$ seems to increase during the transition from sleep to wake and the [Hb] seems to decrease (e.g., around 16:58:00 and 17:08:00 and at the end of measurement). The decrease in [Hb] is smaller than the increase in $[HbO_2]$ indicating a larger change in the CBF than in the $CMRO_2$. At the beginning of this measurement, there was a slight instrumental drift because of an insufficient warm-up time of the optical device. The gradual increase in $[HbO_2]$ around 16:45:00 is possibly caused by this effect.

4. DISCUSSION AND CONCLUSIONS

We demonstrated that the source-detector separation and measurement wavelength significantly affect the sensitivity and contrast of the optical measurements. In some cases, a short source-detector separation gives a more meaningful signal because of lower noise, e.g., during the natural-sleep measurements presented in this paper. Small hemodynamic and oxygenation changes may be easier to detect using short source-detector separations.

The selection of the measurement wavelengths depends on the physiological phenomena to be studied. In most cases, however, various kinds of hemodynamic and oxygenation changes are of interest. Multi-wavelength systems should contain both HbO_2- and Hb-sensitive wavelengths. In addition to the sensitivity of the wavelength

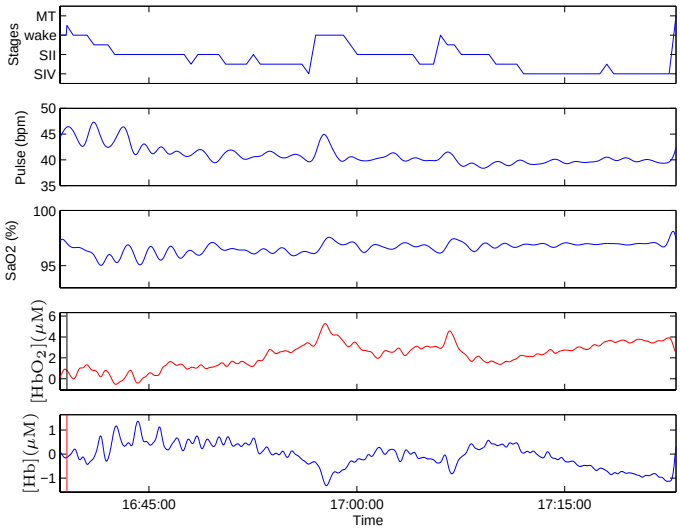

Figure 10. Changes in [HbO_2] and [Hb] during natural sleep. The optical data was measured with a 3-cm source-detector separation. The signals were filtered using a time constant of 15 s to emphasize the slow changes in the signal.

to different chromophores in tissue, also the window of transparency and the sensitivity of the applied photo detectors should be considered. Especially in fast photon-counting systems, the sensitivity of currently available detectors decreases with increasing wavelength. In general, the wavelengths and source-detector separations should be individually considered for each measurement.

The very-low frequency oscillations recorded in our hyperventilation and breath-holding studies have been previously reported by other groups as well.[7] However, we report here slightly slower rhythms (~ 0.02 Hz). The physiological origin of these oscillations is not completely understood, but one possible explanation is the slow periodic movement of arterioles (vasomotion). Our measurements support this theory because the oscillations were more pronounced at a HbO_2-sensitive wavelength.

Whether the oscillations have a global or local nature is an important question for their understanding. If the fluctuations show globally in the circulation, it might be possible to model their behavior using some other physiological parameters such as the heart rate. A successful modeling of these oscillations could facilitate many applications in optical imaging. The oscillations may overwhelm, e.g., small hemodynamic changes and they may limit the contrast of various measurements. Also, the inclusion of these dynamic changes in an advanced model may improve image reconstruction.[8]

We reported hemodynamic and oxygenation changes in the frontal cortex during natural sleep measured with our frequency-domain instrument. There are only a few similar studies carried out previously.[9–13] Our measured changes in [HbO_2] and [Hb] agree with the results in Ref. 9 measured using the continuous-wave technique. The physiologically meaningful results of our preliminary measurements encourage us to carry out a larger measurement series. In these measurements, we will more thoroughly study the influence of different instrumental and measurement parameters. We will also carry out a proper calibration of the frequency-domain instrument to enable measurement of the mean pathlength. A very important further research topic is the possibility to optically detect local hemodynamic and oxygenation changes in the frontal lobe, which is not directly possible using current polysomnography. These changes may be related to the physiology of sleep so that the optical measurement would provide also clinically interesting information on natural sleep.

ACKNOWLEDGMENTS

This work is financially supported by the National Technology Agency (Tekes), the Academy of Finland, the Jenny and Antti Wihuri Foundation, the Foundation of Technology (TES), and the Finnish Cultural Foundation. The authors would also like to acknowledge the staff of the BioMag Laboratory of the Helsinki University Central Hospital and especially Ms. Suvi Heikkilä for her help to start the natural-sleep measurements.

REFERENCES

1. I. Nissilä, K. Kotilahti, K. Fallström, and T. Katila, "Instrumentation for the accurate measurement of phase and amplitude in optical tomography," *Rev. Sci. Instrum.*, **73**, pp. 3306-3312, 2002.
2. I. Nissilä, K. Kotilahti, T. Noponen, and T. Katila, "A method for the accurate measurement of phase in intensity modulated optical imaging," in *OSA Biomedical Topical Meetings and Exhibit: Advances in Optical Imaging and Photon Migration (AOIPM)*, pp. 683-685, Miami Beach, Florida, USA, 2002.
3. D.T. Delpy, M. Cope, P. van der Zee, S. Arridge, S. Wray, and J. Wyatt, "Estimation of optical pathlength through tissue from direct time of flight measurement," *Phys. Med. Biol.*, **33**, pp. 1433-1442, 1988.
4. M. Cope, *The development of a near infrared spectoscopy system and its application for non-invasive monitoring of cerebral blood and tissue oxygenation in the newborn infant,* Ph.D., University of London, 1991.
5. A. Duncan, J.H. Meek, M. Clemence, C.E. Elwell, L. Tyszchuk, M. Cope, and D.T. Delpy, "Optical pathlength measurements on adult head, calf, and forearm and the head of the newborn infant using phase resolved optical spectroscopy," *Phys. Med. Biol.*, **40**, pp. 295-304, 1995.
6. P. van der Zee, M. Cope, S.R. Arridge, M. Essenpreis, L.A. Potter, and A.D. Edwards, "Experimentally measured optical pathlengths for the adult head, calf and forearm and the head of the newborn infant as a function of interoptode spacing," *Adv. Exp. Med. & Biol.*, **316**, pp. 143-153, 1992.
7. H. Obrig, M. Neufang, R. Wenzel, M. Kohl, J. Steinbrink, K.M. Einhäupl, and A. Villringer, "Spontaneous low frequency oscillations of cerebral hemodynamics and metabolism in human adults," *NeuroImage*, **12**, pp. 623-639, 2000.
8. R. L. Barbour, H. L. Graber, Y. Pei, S. Zhong, and C. H. Schmitz, "Optical tomographic imaging of dynamic features of dense-scattering media," *J. Optical Society of America A*, **18**, pp. 3018-3036, 2001.
9. Y. Hoshi, S. Mizukami, and M. Tamura, "Dynamic features of hemodynamic and metabolic changes in the human brain during all-night sleep as revealed by near-infrared spectroscopy," *Brain Research*, **652**, pp. 257-262, 1994.
10. T. Hayakawa, M. Terahima, Y. Kayukawa, T. Ohta, and T. Okada, "Changes in cerebral oxygenation and hemodynamics during obstructive sleep apneas," *Chest*, **109**, pp. 916-921, 1996.
11. A. Spielman, G. Zhang, C.M. Yang, P. D'Ambrosio, S. Serizawa, M. Nagata, H. von Gizycki, and R. Alfano, "Intracerebral hemodynamics probed by near infrared spectroscopy in the transition between wakefulness and sleep," *Brain Research*, **866**, pp. 313-325, 2000.
12. P. Aggarwal, K. Chen, M.A. Franceschini, B.L. Ehrenberg, and S. Fantini, "Concurrent cerebral near-infrared spectroscopy and electroencephalography during all-night sleep," in *OSA Biomedical Topical Meetings and Exhibit: Advances in Optical Imaging and Photon Migration (AOIPM)*, pp. 297-299, Miami Beach, Florida, USA, 2002.
13. L.P. Safonova, A. Michalos, U. Wolf, M. Wolf, W.W. Mantulin, D.M. Hueber, and E. Gratton, "Diminished cerebral circulatory autoregulation in obstructive sleep apnea investigated by near-infrared spectroscopy," (submitted to Sleep Research on-line), 2002.