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Properties of end-expiratory breath hold responses measured with near-infrared spectroscopy

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ABSTRACT

Near-infrared spectroscopy (NIRS) can be used to assess the cerebrovascular response to breath hold. We measured eight healthy subjects during voluntary end-expiratory breath hold to study inter- and intraindividual variability of the deoxy- (HbR) and oxyhemoglobin (HbO_2) response curves for the scalp and cerebral cortex. Although cortical [HbO_2] behaves qualitatively similarly in all subjects, there is large inter- and intraindividual variability, and in the case of [HbR] also qualitative variability. However, the linearity of [HbO_2] increase during the breath hold has encouraging measurement repeatability, and it may even indicate an individual's CO_2 tolerance. This result may help understand why breath hold duration varies between subjects more than the total [HbO_2] increase during breath hold.

Keywords: Near-infrared spectroscopy, breath hold response, cerebral blood volume, repeatability

1. INTRODUCTION

Near-infrared spectroscopy (NIRS) is a non-invasive technique for estimating hemodynamic changes in tissue based on their effects on light attenuation. Light in the 650-850 nm range is guided into tissue using, e.g., optical fibers, and light exiting the tissue is measured to determine physiological variables such as cortical concentration changes of oxy- ($\Delta[HbO_2]$), deoxy- (Δ[HbR]) and total ($\Delta[HbT] = \Delta[HbO_2] + \Delta$[HbR]) hemoglobin.[1] Compared to other functional brain imaging methods such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), NIRS combines the advantages of sub-second time resolution and robustness against the subject's motion, and does not expose the subject to ionizing radiation. NIRS instrumentation is also relatively inexpensive and portable. However, the attainable spatial resolution in NIRS is only moderate, approximately 1 cm in tomographic applications. In addition, systemic hemodynamic changes and especially in NIRS also surface tissue contribute to the recorded signal, which means that the NIRS signal reflects not only cortical hemodynamic responses but also pulse, blood pressure (BP) fluctuation, and hemodynamic changes in the scalp.[2]

Cerebral blood flow (CBF) is regulated by a complex physiological system that strives to maintain constant cerebral perfusion and adequate oxygenation. This cerebral autoregulation compensates for systemic factors such as BP and heart rate changes, local increases in oxygen consumption due to neuronal activity, and changes in blood O_2 and CO_2 content. Cerebral autoregulation is also known to be affected by factors such as smoking and migraine.[3,4] Particularly blood CO_2 content is an important determinant of CBF, so that an increase in CO_2 causes arteries to dilate to ensure adequate oxygenation, and a decrease in CO_2 causes a decrease in CBF. Since deoxygenated blood is drained from the brain relatively passively, changes in CBF typically result in parallel changes in total cerebral blood volume (CBV).[5] In NIRS, cortical Δ[HbT] is commonly used as an indicator of CBV changes.

Manipulation of blood CO_2 levels has often been used to evoke cerebral hemodynamic responses in order to evaluate the performance of NIRS devices and methods, and to examine how interventions and medical conditions affect cerebral autoregulation.[4,6-14] Blood CO_2 manipulation can be accomplished by breathing CO_2-enriched air, breath holding (BH), or hyperventilating. However, so far there have been no studies that examine the intra- and interindividual variability and repeatability of cerebral hemodynamic BH responses in NIRS, how long the hemodynamic changes persist after

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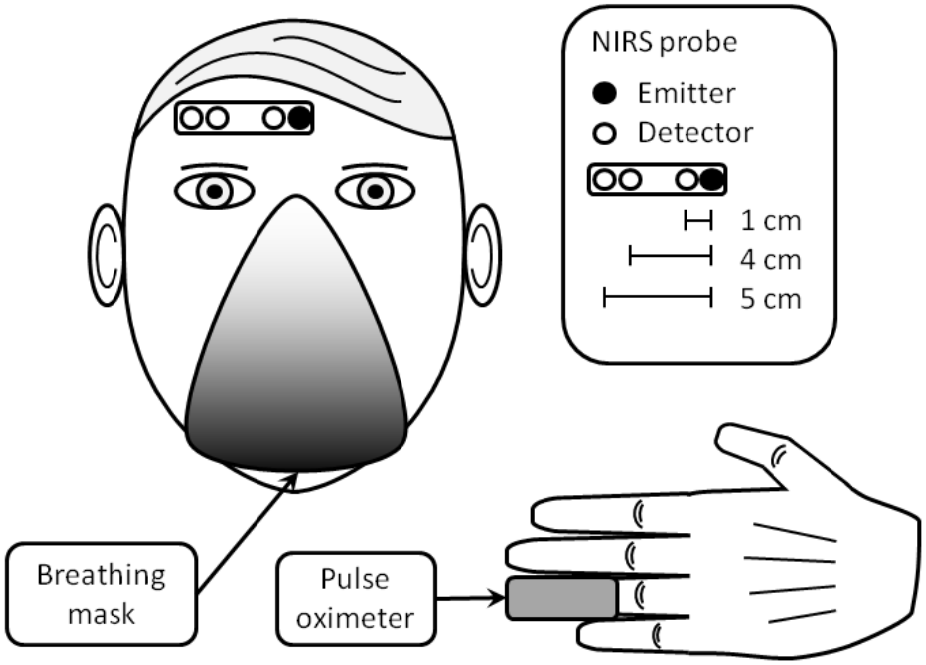

Figure 1. The measurement setup.

resumption of breathing, and how the cerebral and scalp responses differ from each other. The purpose of this study is to determine how cortical and scalp Δ[HbT], Δ[HbO_2], and Δ[HbR] behave during end-expiratory BH and the subsequent recovery phase, and to determine what BH response features are most reliable for evaluating the cerebral CO_2 response.

2. MATERIALS AND METHODS

2.1 The modified Beer-Lambert law

In NIRS, Δ[HbO_2], and Δ[HbR] can be estimated from light attenuation in tissue at two wavelengths (760 and 830 nm in this study) using the modified Beer-Lambert law.[1] If light scattering and background attenuation in tissue are assumed to be constant in time, the modified Beer-Lambert law can be written as

$$\begin{bmatrix} \Delta[\mathrm{HbO}_2] \\ \Delta[\mathrm{HbR}] \end{bmatrix} = \left(\alpha^{\mathrm{T}}\alpha\right)^{-1}\alpha^{\mathrm{T}}\begin{bmatrix} \Delta A_{685\,\mathrm{nm}} / d_{685\,\mathrm{nm}} \\ \Delta A_{830\,\mathrm{nm}} / d_{830\,\mathrm{nm}} \end{bmatrix}, \quad (1)$$

where α is a 2×2 matrix containing the specific extinction coefficients of HbO_2 and HbR at each wavelength, ΔA_i is the measured change in light attenuation at wavelength i, and d_i is the total light pathlength in tissue at wavelength i. In this study, literature values were used for α, and d_i was determined from NIRS data using the frequency domain (FD) technique.[15,16] Since the modified Beer-Lambert law only allows estimating concentration changes, not absolute levels, Δ[HbO_2], and Δ[HbR] are typically given relative to an arbitrary baseline level.

2.2 Experimental setup and instrumentation

The data were recorded from eight non-smoking subjects (S1-S8, seven males and one female, ages 20-29) in the BioMag Laboratory at Helsinki University Hospital. The study was approved by the local ethical committee. The measurement setup included a NIRS probe on the forehead, a breathing mask connected to a spirometry and gas analyzer unit to monitor respiratory air flow and end-tidal CO_2 concentration, and a fingertip pulse oximeter to measure heart rate and arterial blood oxygen saturation (Figure 1). A modified S/5 anesthesia monitor (GE Healthcare Finland Oy) was

used for the respiratory measurements and pulse oximetry. Heart rate was estimated from pulse oximeter raw data and resampled to 1-Hz sampling frequency. Breath hold duration was estimated from spirometry data.

After 3-4 minutes of relaxation in a dark room in supine position to establish a physiological baseline, each subject was instructed to hold their breath after normal expiration for as long as they felt comfortable, and then take a few breaths until they felt comfortable enough to repeat the BH. This was repeated for approximately 20 times for each subject. A researcher counted seconds aloud at 5-second intervals during the BH to allow the subject to produce BHs of relatively consistent duration. Since there was some variation in the duration of BHs, the BH responses were averaged for each subject in two ways. First, data from individual BHs were aligned at the beginning of BH, so that the onset of the BH response could be studied. Then, the BHs were aligned at the end of BH to study the recovery phase of the response. The beginning and end of BH were determined from the spirometry signal by choosing a threshold for airflow.

NIRS data were measured with an FD device developed at Helsinki University of Technology (now part of Aalto University).[16] The device allows measuring light attenuation in tissue using arbitrarily positioned light source fibers and detector fiber bundles. However, in practice the signal-to-noise ratio limits the maximum source-detector separation to approximately 5-6 cm. The depth of tissue probed by NIRS depends on the distance between the light source and detector, so that at source-detector separations of approximately 0-2 cm primarily extracerebral tissue is probed, and beyond approximately 2 cm the recorded signal contains both an extracerebral and a cortical component.[6,17] The effective sampling frequency for NIRS data was set at approximately 5 Hz to avoid aliasing of heartbeat, and the hemoglobin signals were low-pass filtered with a cutoff frequency of 0.5 Hz to remove the heartbeat rhythm.

The NIRS probe used in this study included one source and three detectors at distances of 1, 4, and 5 cm from the source. Only the 1- and 4-cm signals were used in data analysis since the 5-cm signal quality was poor for some subjects. The probe was attached on the right side of the forehead just below the hairline to avoid hair entering between tissue and the optode. $\Delta[HbO_2]$ and $\Delta[HbR]$ were estimated for each detector channel using the modified Beer-Lambert law (Eq. 1). We have previously used principal component analysis (PCA) for separating the cortical and extracerebral $\Delta[HbO_2]$ and $\Delta[HbR]$ components from each other, but in the present study preliminary trials showed that the cortical response was so strong that PCA did not improve signal quality appreciably.[17] Instead, we used the 1-cm measurement as an indicator of scalp blood flow and the 4-cm measurement as an indicator of cortical blood flow.

3. RESULTS

Figure 2 shows averaged data from S1, who produced one of the strongest and most repeatable BH responses. It is characterized by an initial delay of approximately 10 s after beginning of BH, then an increase in $[HbO_2]$, [HbR], and [HbT] in the scalp (1-cm signal), an increase of cortical $[HbO_2]$ and [HbT], and a decrease of cortical [HbR] (4-cm signal). After 20-30 s of BH concentrations start to plateau, and cortical [HbR] starts to increase approximately 10 s before termination of BH. Scalp concentrations return gradually to pre-BH levels, while cortical $[HbO_2]$ and [HbT] plateaus are maintained for approximately 10 s after BH termination, after which they rapidly return to pre-BH levels around 20 s after BH termination. Cortical [HbR] continues to increase for a few seconds after BH termination, then decreases, and finally increases back to the pre-BH level. The heart rate stays stable for the first 20 s of BH, then starts to increase until BH termination, after which it returns to the pre-BH level, oscillating with the breathing rhythm.

Figure 3 shows averaged data from S8, who displays similar cortical response to S1, while the scalp response during BH is negligible. However, after BH there is a prominent increase in scalp [HbR] and [HbT] and cortical $[HbO_2]$ and [HbT]. The differences in the responses of these two subjects may be explained by differences in heart rate – in S8, heart rate decreases during BH but returns to normal at BH termination.

Most of the BH response features observed in S1 are also visible when responses are averaged over the whole study group (Figure 4). However, a qualitative analysis of the BH responses reveals that the only features present in all subjects are the cortical $[HbO_2]$ and [HbT] changes (Table 1). For example, only two other subjects displayed a cortical [HbR] response similar to S1. Table 1 also shows that peripheral SpO_2 changes do not correlate well with BH duration, and that heart rate may either increase or decrease during BH.

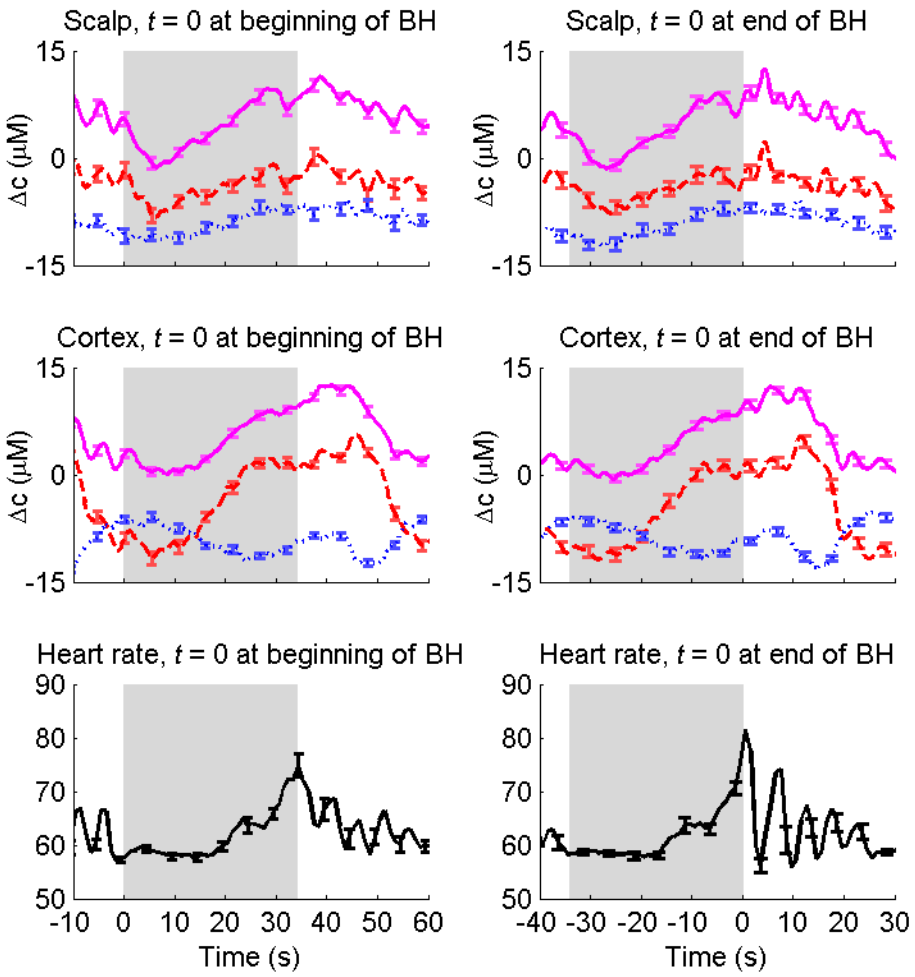

Figure 2. (Color online) Averaged hemodynamic and heart rate BH responses of S1. In the left column, responses were aligned at beginning of BH for averaging, and in the right column they were aligned at BH termination. Δ[HbT] is denoted with a solid magenta curve, Δ[HbO_2] with a dashed red curve, and Δ[HbR] with a dotted blue curve. Zero levels of the curves are arbitrarily chosen to separate them from each other. Error bars denote the standard error of the mean (SEM). The gray area shows the average BH duration.

Since the cortical HbO_2 response behaved similarly in all subjects, it was selected to form a quantitative measure for the effectiveness of a subject's cortical BH response. Prominent features of the response are onset time, direction of the response, total [HbO_2] increase, and time difference between onset and plateau phase. We decided to compare these features with BH duration, since the urge to breathe is linked to CO_2 tolerance through a complex set of neuronal mechanisms.[18,19] Preliminary analysis showed that the onset time of the response correlated poorly with BH duration and was difficult to determine accurately because of signal fluctuations, so it was excluded from the analysis. Similarly, the time difference between onset and plateau phase was excluded since only one subject reached the plateau phase.

Total [HbO_2] increase was determined as the difference between pre-BH [HbO_2] baseline and [HbO_2] level at BH termination. To account for the blood transport delay between lungs and the brain, the difference was determined between [HbO_2] means over the first five seconds of BH and first five seconds after BH termination. The shape of the [HbO_2] increase was roughly linear in all subjects, so we used least-squares linear regression to model the BH response:

$$\left[\mathrm{HbO}_2\right] = a_{\mathrm{HbO2}} t + b_{\mathrm{HbO2}}, \tag{2}$$

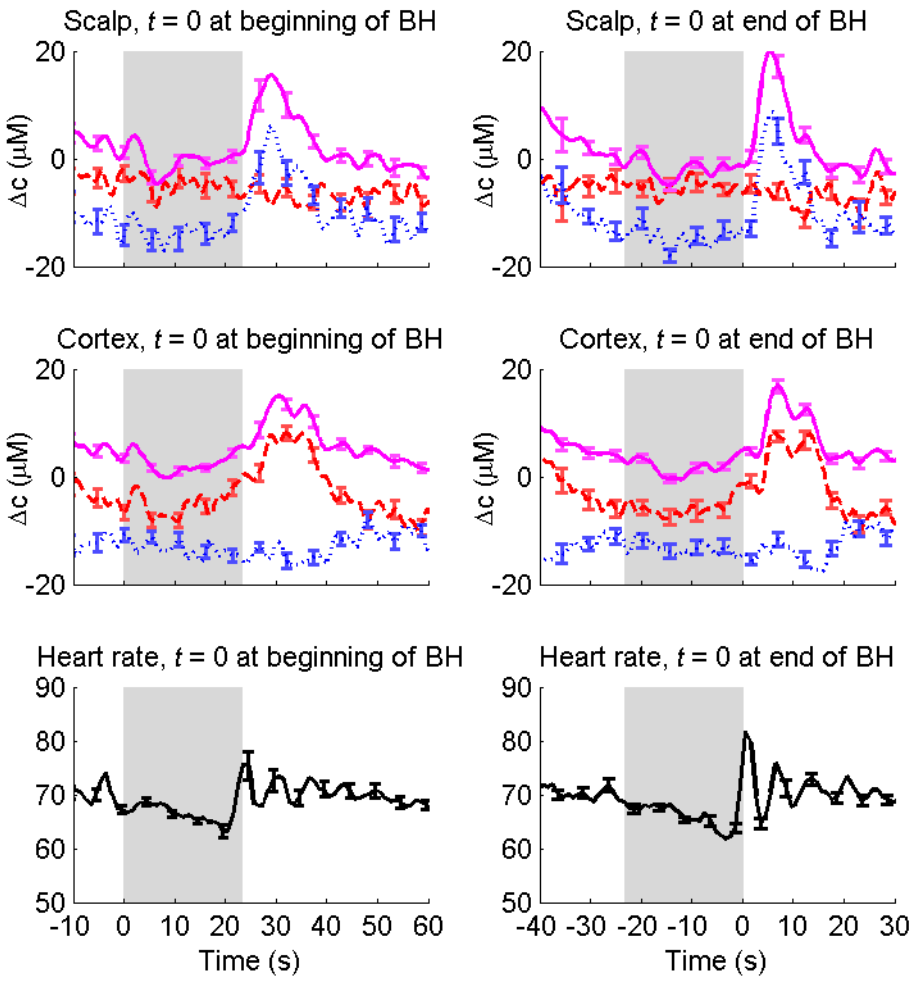

Figure 3. Averaged BH responses of S8. Notice the different concentration scale from Figure 1.

where t is time from onset of BH response to termination of BH, and a_{HbO2} and b_{HbO2} are the regression slope and intercept, respectively. The onset time of BH response could not be accurately determined for individual BHs due to signal fluctuations, so it was determined for each subject separately from averaged data. The coefficient of determination, R^2, was used to analyze the goodness of the regression fit – the closer R^2 is to 1, the better the fit. Table 2 shows the results of the quantitative analysis of the BH responses, including Pearson's correlation coefficients between the quantitative parameters and BH duration. S6 was excluded from the correlation calculation, since it was evident from the amplitude and light pathlength measurements that his cortical NIRS data had been corrupted by light leakage.[20]

We carried out a similar analysis on the BH recovery phase as the BH phase, but with data aligned at BH termination. Quantitatively, [HbO_2] features correlated more poorly with BH duration during the recovery phase than during BH. For example, the correlation coefficients of a_{HbO2} and R^2 during recovery with BH duration were 0.08 and 0.21, respectively. Because these correlations are much lower than during BH, no detailed results are given here.

Since the absence of BH response would indicate $\Delta[HbO_2] = a_{HbO2} = R^2 = 0$, the intraindividual SD of each measurand as a percentage of the mean allows quantifying the measurand's intraindividual repeatability. Also, it allows comparing the repeatability of the measurands with each other. We found the average intraindividual SD for $\Delta[HbO_2]$, a_{HbO2}, and R^2 to be, 59 %, 69 %, and 45 % of the mean, respectively. However, of these percentages only the difference between R^2 and a_{HbO2} is statistically significant at $p < 0.05$.

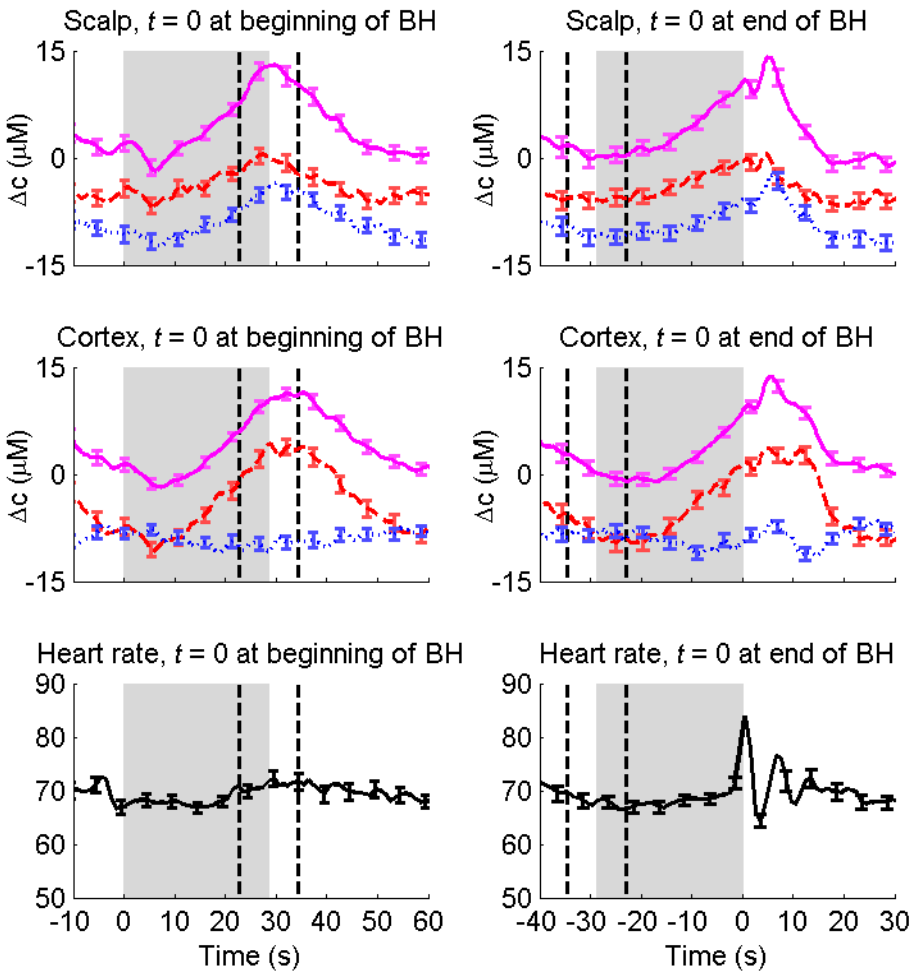

Figure 4. Averaged BH responses over all subjects. Vertical dashed lines show standard deviation (SD) of BH duration.

Table 1. Qualitative analysis of BH responses for different subjects, arranged by BH duration. If hemoglobin concentrations or heart rate increased, decreased, or remained relatively unchanged during BH, they are marked with +, -, or 0, respectively. This assessment was made subjectively based on the averaged BH response of each individual. BH duration is given as mean ± SEM. SpO_2 values give the average of post-BH SpO_2 minimum/maximum for each subject.

Subject (Sex, No. of BH)	BH duration (s)	Scalp HbO_2/HbR/HbT	Cortical HbO_2/HbR/HbT	Heart rate	SpO_2 min/max (%)
S5 (M, 21)	22.5 ± 0.3	0 / 0 / 0	+ / 0 / +	0	96.0 / 99.0
S8 (M, 18)	23.1 ± 0.7	0 / 0 / 0	+ / 0 / +	-	93.2 / 96.7
S4 (F, 20)	26.5 ± 0.7	+ / 0 / +	+ / - / +	0	94.9 / 97.6
S2 (M, 21)	27.0 ± 1.0	+ / + / +	+ / 0 / +	+	96.1 / 97.8
S7 (M, 19)	29.2 ± 0.7	0 / + / +	+ / - / +	+	92.8 / 97.7
S3 (M, 24)	29.6 ± 1.0	+ / + / +	+ / 0 / +	+	97.1 / 98.1
S1 (M, 20)	34.1 ± 0.4	+ / + / +	+ / - / +	+	97.5 / 99.6
S6 (M, 18)	37.8 ± 0.7	0 / + / +	+ / 0 / +	-	96.6 / 98.6

Table 2. Quantitative analysis of cortical HbO_2 response features. Data for different subjects are given as mean ± SEM. S6 is not quantitatively comparable with the others because of light leakage. On the last row, the correlation coefficient is calculated over 143 individual BHs from all subjects except S6. Correlations not statistically significant at the $p < 0.05$ level are in parentheses.

Subject (Sex, No. of BH)	BH duration (s)	$\Delta[HbO_2]$ during BH (μM)	a_{HbO2} (μM/s)	R^2
S5 (M, 21)	22.5 ± 0.3	9.7 ± 1.5	0.53 ± 0.09	0.30 ± 0.04
S8 (M, 18)	23.1 ± 0.7	8.6 ± 1.0	0.40 ± 0.16	0.26 ± 0.06
S4 (F, 20)	26.5 ± 0.7	21.0 ± 1.3	1.25 ± 0.09	0.75 ± 0.03
S2 (M, 21)	27.0 ± 1.0	7.6 ± 1.9	0.44 ± 0.07	0.61 ± 0.06
S7 (M, 19)	29.2 ± 0.7	9.9 ± 1.5	0.78 ± 0.10	0.48 ± 0.06
S3 (M, 24)	29.6 ± 1.0	13.9 ± 1.4	0.72 ± 0.06	0.72 ± 0.04
S1 (M, 20)	34.1 ± 0.4	11.3 ± 0.9	0.56 ± 0.04	0.70 ± 0.03
S6 (M, 18)	37.8 ± 0.7	(7.5 ± 2.4)	(0.31 ± 0.09)	(0.17 ± 0.04)
Correlation with BH duration (N = 143)	N/A	0.20	(0.02)	0.52

4. DISCUSSION AND CONCLUSIONS

Previous NIRS studies have documented the behavior of the cerebral BH response under various conditions. For example, migraine has been shown to diminish cerebral hemoglobin concentration changes during BH.[4,14] Other studies have used the BH response for examining the relationship between NIRS and fMRI signals,[7,13] or NIRS and blood flow measurements with transcranial Doppler.[10]

To our knowledge, there have been only a few quantitative studies on the properties of the NIRS BH response in healthy individuals. It has been shown that trained divers display larger changes in cerebral and brachial vascular resistance and cerebral oxygenation than non-divers during maximal BHs.[12] Also, cerebral CO_2 reactivity is known to be slightly impaired in the early morning,[11] and both the BH response and cerebral vasomotion have been shown to be diminished in older people.[9] Our own measurements were carried out at daytime on subjects of similar age to preclude these effects. However, none of the studies we reviewed had examined how the hemoglobin concentration signals varied between different subjects, between consecutive breath holds, or between scalp and cortical tissue. Consequently, they did not discuss in detail which response features would be ideal for determining the efficiency of the BH response in NIRS.

In this study, we have analyzed the cortical end-expiratory BH responses measured with NIRS in normal, healthy individuals. Instead of a fixed BH duration, the subjects were allowed to terminate BH when they started to feel uncomfortable to assess the relationship between measurable hemodynamic changes and subjective experience. End-expiratory BH was studied since it shortens the total measurement time compared to maximal BH, and the results can also be used as a reference in measurements on disabled and sick people who have trouble performing maximal inspiratory breath holds.

The only common hemodynamic feature to all subjects was the transient increase in cortical $[HbO_2]$ during BH. In some subjects the vasodilation reaction to CO_2 increase was so strong that [HbR] at first started to decrease due to the enhanced perfusion. An increase in heart rate always led to an increase in scalp blood volume, as indicated by [HbT] in the 1-cm measurement, but in some subjects heart rate remained stable or decreased during BH. In these cases, scalp blood volume either increased or stayed constant during BH. The blood volume increase was caused by $\Delta[HbO_2]$, Δ[HbR], or both, and typically resolved within 20 s from BH termination.

In general, the cortical BH response should be characterized by plateauing of [HbO_2] when the limits of the cerebral vasodilation capacity are met.[10] However, in our study, only one out of eight subjects reached the plateau phase. This indicates that end-expiratory BH cannot be reliably used to determine the maximal cerebral vasodilatory capacity, since the desire to start breathing will most likely become overwhelming before the plateau phase. In most individuals, cortical [HbR] started to increase around BH termination or immediately after it. This behavior appears to be caused by a gradual increase in arterial [HbR] due to oxygen consumption, and an increase in blood volume due to heart rate increase.

Recovery from BH required approximately 4-7 breaths, depending on the subject. The time from BH termination to the beginning of next BH ranged approximately from 20 to 30 s. Hemoglobin concentrations returned to pre-BH levels in approximately 20 s after BH termination. Although there was no extended period of rest between consecutive BHs, subjective willingness to perform another BH task and end-tidal CO_2 content reaching a normal level indicated that this was a sufficient time to reach a relatively stable base state. Also, there was no apparent decrease in mean BH duration towards the end of the measurement. Since hyperventilation in the resting state is known to cause cerebral vasoconstriction due to a decrease in blood CO_2,[5] we also considered whether heavy post-BH breathing might cause vasoconstrictory overcompensation and a CBF decrease below the resting state level. However, expiratory CO_2 concentrations indicated normocapnia, refuting this hypothesis.

In fMRI, the blood oxygen level dependent (BOLD) signal is based on changes in [HbO_2] and [HbR] relative to each other and thus is affected by BH. Although the BOLD BH response shape is not directly comparable to [HbO_2] and [HbR] changes measured with NIRS, it has been shown that there is an inflection point in the BOLD signal at approximately 10 s after beginning of BH.[21,22] The same studies indicate that the recovery time for the BOLD signal after BH termination to pre-BH level is approximately 20-30 s for BHs of 9-21 s, and no indication of the plateau phase is seen within the first 20 s of BH. These results support our own observations on the time course of the NIRS BH response.

While hemoglobin concentration changes and the [HbO_2] slope have been previously used as quantitative indicators of the BH response,[7,10] and they can be expected to indicate the extent of vasodilation and CBV increase, our results show that they correlate poorly with BH duration. Thus, they are not good indicators of subjective CO_2 tolerance. This has implications especially for studies aiming to better understand, study and quantify the functioning of the BH response, especially when examining the response before and after various interventions.

We found the strongest correlation between BH duration and quantitative data in R^2, the parameter describing the goodness of linear fit to the [HbO_2] response. This correlation was also statistically significant at $p < 0.05$. When calculated from the averaged data shown in Table 2, the correlation was even higher (0.73 instead of the 0.52 value given in Table 2), most likely due to noise reduction from averaging. However, because of the small sample size (seven subjects), the p-value for the correlation coefficient from averaged data was 0.06, slightly above the $p < 0.05$ significance level. Also intraindividual repeatability appeared to be better for R^2 than for total Δ[HbO_2] or a_{HbO2}, although the difference was statistically significant only between R^2 and a_{HbO2}.

Since the goodness of linear fit reflects the absence of fluctuations in the signal, it could be that in individuals who are able to hold their breath longer the vasodilatory response is better controlled. This could allow more stable blood flow through the brain, and consequently more stable gas transport within capillaries. It might also help explain why subjects displaying similar [HbO_2] and [HbT] increases can hold their breath for different times. However, the correlation between R^2 and BH duration could also reflect some common underlying factor instead of a direct causal relationship between response linearity and BH duration. Also, it is very difficult to quantify the level of discomfort that triggers breathing in individual subjects, so it might be that the subjects displaying the longest BHs were just more motivated, and the observed correlations result from coincidence.

Our study has some limitations that we hope to address in the future. First, since each subject was measured only once, we have yet to establish the intraindividual repeatability of the BH response over several days or months. Second, since the study group was somewhat limited in size and makeup, we have yet to establish the applicability of the results to a larger population including individuals of different ages, and normal and impaired cerebrovascular autoregulation.

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