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Cerebrovascular dynamics in patients with migraine: Near-infrared spectroscopy study

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Abstract

Migraine is hypothesized to be a neurovascular coupling disorder where the cerebral vascular reactivity is malfunctioning and measuring hemodynamic changes during migraine without causing more disturbance has always been a challenge. Functional near infrared spectroscopy system (fNIRS) is being proposed as an inexpensive, rapid, safe and accurate alternative to fMRI, transcranial doppler sonography (TCD). We have developed NIROXCOPE 201, a novel device for fNIRS which offers 16 source-detector pairs distributed on a probe that is placed on the forehead. Measuring hemodynamic changes during migraine without causing more disturbance has always been a challenge. Using NIROXCOPE 201, we have attempted to investigate the cerebrovascular reactivity of migraine patients to a breath hold task which produces a metabolic perturbation. Six normals and six migraine patients performed four consecutive breath holding task. We calculated the peak and latencies of the initial dip and recovery phases for [Hb], [HbO_2], [tHb], and [OXY] signals. [Hb], [tHb], and [OXY] ID and R amplitudes of normals are approximately a magnitude higher than migraine patients ($P < 0.01$), while latencies showed no significant differences. Data suggests an altered neurovascular coupling in frontal cortex of migraine patients interictally. The application of NIROXCOPE 201 to patients suffering from other primary headache disorders will reveal diagnostic as well as therapeutic implications of the presented study.

Keywords: Migraine; Near-infrared spectroscopy; Cerebrovascular dynamics

Migraine is a complex neurovascular disorder, believed to affect nearly 12% of the world's population. Multifactorial etiology of migraine involve an abnormality in the cerebral vascular reactivity. It has been proposed that there is an uncoupling of the neuronal demand to hemodynamic activity termed as neurovascular coupling disorder in migraine patients [6,27]. Although the mechanisms leading to such an uncoupling still remains to be investigated, there are hypotheses suggesting that an increase of glutamate secretion in the presynaptic cleft due to a mutation of the P/Q type Ca^{++} channel or a Na-K ATPase mutation that affects the uptake of glutamate in the presynaptic astrocyte leads to a build of glutamate in the synaptic cleft in patients with familial hemiplegic migraine (FHM). These mutations are suggestive of the excessive excitability of the neurons of FHM patients resulting in cortical spreading depression (CSD). Moreover, as the Na/K ATPase is located in the metabolic pathway that adjusts the uptake of glucose uptake from the blood with respect to glutamate levels, it basically modulates the lactate production via anaerobic metabolism of glucose and allows neurons to use lactate as energy supply. Since this pathway does not require any oxygen, the neurovascular coupling is achieved only by an increase in the demand of glucose. Since the hemodynamic response is triggered by this demand, there will be an episode of excessive oxygenation within the vascular bed leading to the initial dip before the oxidative metabolism is fully initiated to account for ATP production. Although the genetic and molecular pathways are not identified for other migraine types including much more common form, migraine without aura (MO), we aimed to test whether patients with MO have a neurovascular coupling disorder that can be quantified by fNIRS system by using breath holding task as a challenge.

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Several methods have been used to investigate the cerebral hemodynamic response such as transcranial doppler sonography (TCD), PET, SPECT and fMRI. Although there are controversial conclusions on the etiology of migraine, still many have shown similar findings such as increased blood flow velocity in interictal period, increased blood flow during attacks as compared to normals. It has been suggested that elevated cerebral blood flow velocity in interictal periods possibly resulting from a reduced diameter of the measured artery leading to reduced delivery of blood (decreased regional cerebral blood flow, rCBF) or from alterations at the cerebral arteriole level [1,3,4,7,11,12,14,17,16,22,23,25,26,28,33,37].

To test the hypothesis that migraineurs have cerebrovascular deregulation, two sets of stimuli have been tried to elucidate the differences in cerebral vasoreactivity of normals versus migraineurs:

(1) Mechanical perturbation: This is performed by altering the systemic blood pressure (and, therewith, the cerebral perfusion pressure) for investigating cerebral autoregulatory responses [32].
(2) Metabolic perturbation: CO_2 inhalation, breath-holding, hyperventilation, and even cognitive stimuli evoke a hemodynamic response that is related to the altered metabolic situation of the brain parenchyma due to the stimulus (metabolic regulation) [32].

Recent interest in the fNIRS technology as a bedside system has directed researchers to study the feasibility of utilizing this technique in clinical studies. fNIRS has been used in several functional imaging studies of brain and muscle as well as breast cancer imaging [15,20,35]. The principle of the technique has been described in previous studies [9,29,39]. This technique basically uses transparency of biological tissue in near infrared spectrum where [Hb] and [HbO_2] absorption coefficients are higher than the other chromophores. It allows a high specificity of [Hb] and [HbO_2] along with a high temporal resolution. Summation of changes in [HbO_2] and [Hb] is shown to produce values of changes in total hemoglobin concentration ([tHb]) that are directly proportional to variations in regional cerebral blood volume.

Shinoura and Yamada [33] have investigated the cerebral vasoreactivity of migraineurs by a mechanical perturbation in which they showed that pressure-related vasoreactivity due to a head-down maneuver measured by fNIRS is suppressed in the right hemisphere of migraineurs during the interictal period. [tHb] calculated from fNIRS measurements in the head-down manoeuver produced a significantly smaller increase in right-sided [tHb] in migraineurs. So far, many studies have been attempted to test for response to a metabolic perturbation, in which CO_2 inhalation, breath holding or hyperventilation have been experimented. None of these studies have used fNIRS in their studies. Hence, our aim in this research is to investigate the cerebral vasoreactivity of migraineurs to consecutive breath holding protocol with the fNIRS device.

Six subjects diagnosed with migraine without aura (five females ages 29.2 ± 9.0, one male, age 39) according to IHS criteria and six healthy subjects (four females, two males, ages 26.3 ± 1.6) from the outpatient headache clinic, college students and hospital staff joined the study. Migraine subjects were not using any prophylactic medication or did not experience any attack three days prior to the day that they collaborated in the experiment. Although we had 10 normal subjects to start with (four female and six male subjects), we decided to use only two of the male subjects to minimize the affect of gender differences with the migraine group. The gender differences between normal subjects were not statistically significant[1]. Subjects were positioned in supine position, and asked to breath normally during rest periods. After an initial 60 s of rest, subjects were asked to exhale all the air and hold their breaths for a minimum of 20 s (usually 30 s). The procedure of holding the breath was repeated four times, with a 90 s of rest between each hold episode.

Commercially available continuous wave systems have limited number of source detector pairs and does not allow for re-engineering of the system to suit to different clinical applications. We have developed a fully re-configurable fNIRS system at the Biophotonics Laboratory[2] (NIROXCOPE 201) which is a modified version of the Cognoscope developed at Dr. Britton Chance's Laboratory in University of Pennsylvania. This system houses a probe that contains four LED light sources (Epitex L4X730/4X805/4X850-40Q96 multi-wavelength LED) each emitting at three near infrared wavelengths and 10 photodetectors (TI-Burr Brown, OPT101) that when time and wavelength-multiplexed end up with four non-overlapping quadruples of photodetectors.

The detectors are placed equidistantly at 2.5 cm away from the center of a source within each quadrant. The probe is positioned such that its base aligns with the eyebrows of the subject and the middle with the Fz location from EEG electrode placement. Taking into consideration Firbank et al.'s study [18], a pre-determined source detector separation of 2.5 cm accounts for an average adult cortex depth around 1.5 cm that allowed us to probe the first couple of millimeters of the gray matter [5,9,18].

The relative changes in [Hb] and [HbO_2] signals are calculated from the Beer-Lambert Law, explained in detail in other studies [8,10,21,39]. The sampling rate of the system is 1.7 Hz, hence the time gap between each sample point for [Hb] and [HbO_2] signals for each detector is 588 ms.

All data are preprocessed to eliminate for noise, unrelated physiological activity and baseline drifts by a program developed in MATLAB® environment (version 6.5). An outlier elimination algorithm based on Pearson's study ([30]) was employed to remove the spikes due to motion artifacts with a $K = 5$ and $TH = 0.3$. Outlier eliminated data were digitally low pass filtered with a fourth order butterworth filter with a cutoff frequency at 0.08 Hz to eliminate for Meyer's wave and any fluctuations due to breathing and arterial pulse [19,38,36]. The baseline drifts were removed by a moving average filter of length 60 points corresponding to high pass filtering at 0.03 Hz to remove

[1] Unpublished results.
[2] http://www.bme.boun.edu.tr/biophotonics

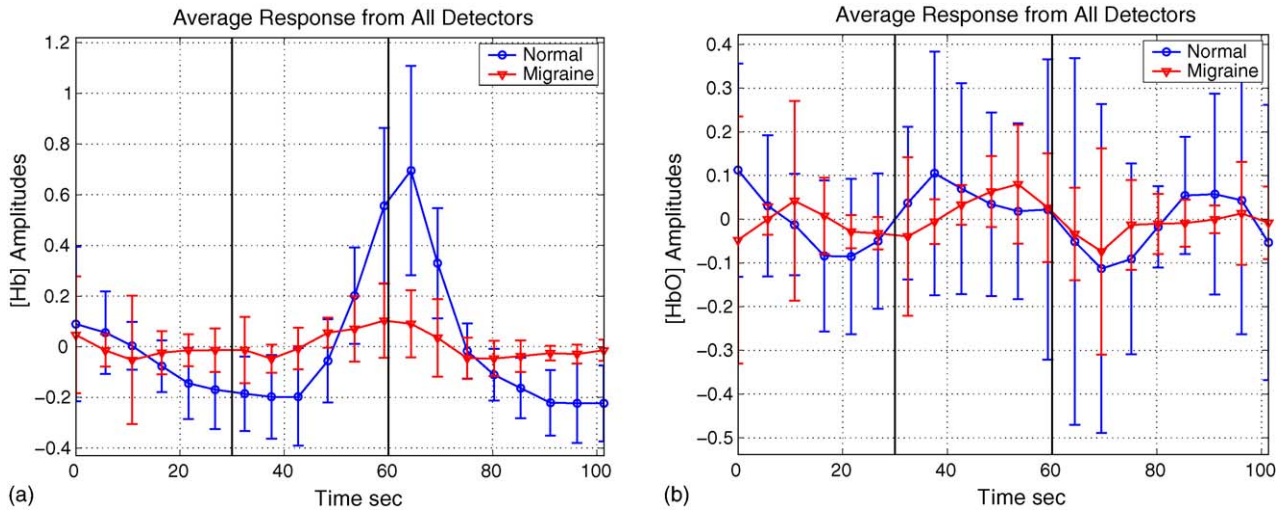

Fig. 1. Averaged (a) [Hb] and (b) [HbO_2] responses from all detectors of normal subjects vs. migraine patients to breath hold exercise. The lines at time instances 30 and 60 s correspond to the breath hold episodes.

the fluctuations due to heart rate [2,36,38]. The preprocessed data are then ensemble averaged on four breath hold episodes for each detector providing 16 of [Hb] and [HbO_2] signals per subject.

We have investigated the amplitude and latencies of significant points in the data. The data showed significant peaks and troughs which we named as the initial dip (ID), representing hyperaemic region as the first main valley at the beginning of the breath hold, and the recovery (R) peak, representing the hypoxic condition towards the end of the breath hold period.

Fig. 1a and b show the results of the ensemble averaged data over all normals and migraine patients over all detectors. The individual detector data show a temporal pattern with two significant phases: ID and R phases (see Fig. 2b and d). As a person holds the breath, metabolic activity of the neurons demand a steady oxygen income which is compensated by an increase in the arterial flow. The initial rise of [HbO_2] and an ID of [Hb] signal can be explained as the volumetric change in the ratio of the concentrations of these chromophores as the arterial inflow increases. As the arterial blood runs out of [HbO_2], a drop in the [HbO_2] signal is accompanied by a simultaneous rise in the [Hb] signal which lasts till the subject is asked to breath normally again. There is a delay of couple of seconds for [Hb] to return to baseline due to transition time of oxygen rich arterial blood to reach at the region of interest under the optodes. Importantly, the suppression of the waveform in [Hb] signals confirms the vasoconstrictive nature of cerebral veins in migraine patients.

We have tested the significance of the data by a one-way ANOVA analysis on a point by point basis. The purpose of this analysis was to pin point the time instances where the migraine data showed a significant difference from the normal data. The *P*-values calculated by ANOVA test over all detectors for [Hb]–[HbO_2] signals and [tHb]–[OXY] signals are presented in Fig. 2a and c, respectively.

The *P*-analysis on [Hb], [tHb] and [OXY] signals delineate the fact that any further parametric value extracted from these signals on the intervals with a *P*-value less than 0.05 can be a candidate for a diagnostic criteria. Exploiting the result of Fig. 2a and c, we can concentrate our parametric search in the intervals of 20–45 s, ID, and 55–75 s, R. Hence, we calculated the amplitude and latency of the ID and R phases on a subject basis. Fig. 2b and d display the ID and R points for a normal subject.

The ID for [Hb] ([tHb]) and [HbO_2] ([OXY]) signals are observed to be usually in reverse phase for most of the normal subjects. This confirms the explanation that arterial blood flow will increase to reduce hypercapnic effect till the middle of the hold episode. The drop in the second half of the hold episode may correspond to the time when the volume interrogated by the optodes is diminished from [HbO_2]; hence a decline of [HbO_2] is observed until the subject is asked to breath normally again (R phase). Note that right after the time instance (latency of ID) where [Hb] signal is minimum and [HbO_2] signal is maximum, [Hb] signal starts to increase in amplitude suggesting that the volume of interest is moving towards a hypoxic region. The R phase is quantified by (1) the amplitude of and (2) latency of the peak with respect to end of hold. Table 1 summarizes the findings of ID and R phases.

The ID and R amplitudes of [Hb] signals of migraine patients are found to be approximately 10 times smaller than that of the normals, a finding that is highly significant ($P < 0.01$). In contrast, [HbO_2] amplitude values in both phases are not significantly different. In terms of latency values (time to peak), values are observed to be comparable for all types of signals. Interestingly, low significance of [HbO_2] signals compared to high significance of [Hb] values is suggestive of a suppressed cerebral vasoreactivity of the venous side but not of the arterial side. Shinoura and Yamada [33] demonstrated a suppression of vasoreactivity in the right frontal lobe, however our results revealed no hemispheric difference. Overall, the method of picking up the peaks in the fNIRS signals during breath holding shows promise for differentiating among normals and migraine patients.

The amplitude values were computed for each breath hold task and then averaged for the initial, main and R responses.

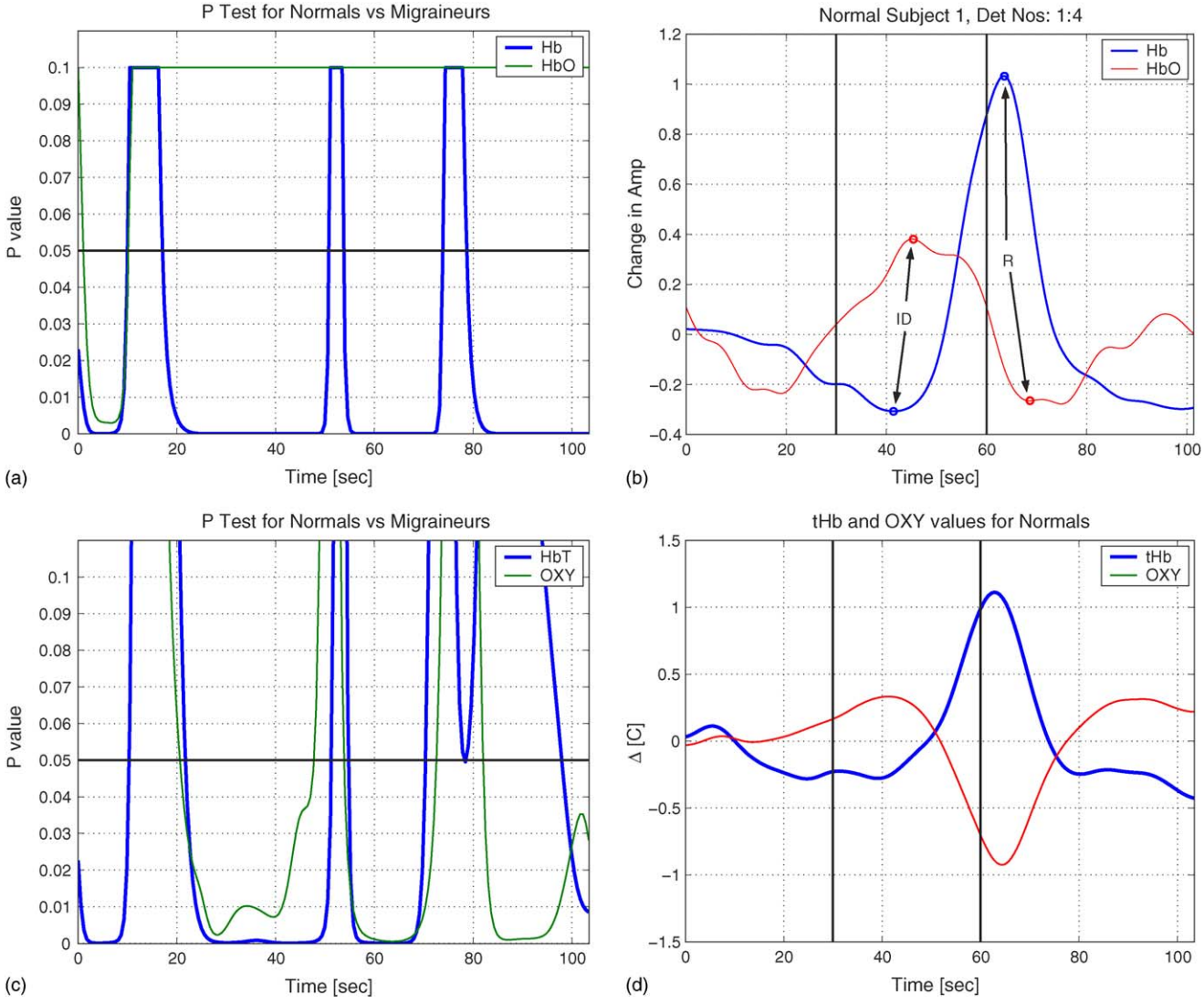

Fig. 2. (a) *P*-values for [Hb] and [HbO_2] signals and (c) [tHb] and [OXY] signals elucidating the statistical significance levels between normals and migraine patients on a point by point basis. The lines at time instances 30 and 60 s correspond to the breath hold episodes. Any *P*-value greater that 0.1 is clipped to 0.1. The thick line is the *P*-values for [Hb] ([tHb]) and the thin line is for [HbO_2] ([OXY]). [Hb], [tHb] and [OXY] signals are observed to show significant difference between normals and migraineurs. (b) and (d) ID and R points calculated from the averaged episodes averaged from detectors 1 through 4 for a normal subject.

Table 1
Amplitude (*A*) and latency (*T*) of ID and R values (mean ± S.D.)

Chromophore	ID			R		
	Normal	Migraine	*P*	Normal	Migraine	*P*
A [Hb] [a.u.]	−0.31 ± 0.14	0.002 ± 0.13	*	1.02 ± 0.45	0.10 ± 0.18	*
T [Hb] [s]	9.47 ± 3.92	10.61 ± 4.89	NS	3.22 ± 1.50	4.83 ± 5.61	NS
A [HbO_2] [a.u.]	0.078 ± 0.32	0.072 ± 0.097	NS	−0.11 ± 0.80	−0.085 ± 0.24	NS
T [HbO_2] [s]	10.08 ± 3.55	12.92 ± 5.91	**	6.01 ± 4.30	6.53 ± 4.37	NS
A [tHb] [a.u.]	−0.39 ± 0.34	−0.0023 ± 0.16	*	0.81 ± 0.94	0.12 ± 0.27	*
T [tHb] [s]	10.55 ± 5.24	11.25 ± 5.64	NS	5.58 ± 5.01	2.55 ± 4.67	NS
A [OXY] [a.u.]	0.29 ± 0.46	0.078 ± 0.063	0.056	−1.17 ± 1.16	−0.13 ± 0.23	*
T [OXY] [s]	9.86 ± 3.36	9.58 ± 5.26	NS	4.63 ± 2.49	4.85 ± 4.57	NS

NS: $P > 0.05$.
* $P < 0.01$.
** $P < 0.03$.

Once the parameters regarding the vascular dynamics are obtained, the first point to draw one's attention is the differences in the magnitude of the [Hb] amplitudes for migraine patients and normal subjects as seen in Table 1. These results may be attributed to the vasoconstrictive nature of the patients' cerebral vessels, which may be suppressing the response a healthy cerebrovascular system will generate. *P*-analysis test also proves that amplitude values, for all responses, are significantly different for the members of the two groups as seen in Table 1.

The amplitude differences emphasize the finding that there is an abnormality in the cerebral perfusion and cerebrovascular autoregulation of migraineurs as shown also by Calandre et al. [7] by a SPECT analysis obtained during a cognitive task. Lagreze et al.[25] have compared the cerebral perfusion of migraineurs and controls during normal breathing of 133 Xe inhalation technique for flow measurements, and concluded that there is an instability of rCBF control in patients with classic but not common migraine. In a similar SPECT study Mirza et al. [26] have claimed that an impaired regional cerebral vascular autoregulation may exist even during headache-free intervals in patients suffering from migraine. In a visual stimulation task Nedeltchev et al. [28] have shown that the cerebral blood flow velocity measured from middle cerebral artery of migraineurs increased more than the normals, suggesting a reduced adaptation to environmental stimuli. Since during a metabolic activity, vasodilation is expected to occur due to neurovascular coupling as shown in fMRI and SPECT studies and since vasodilatory processes are inhibited even in interictal periods of migraineurs, the only way to increase CBFV is to increase the pressure. This hypothesis can be supported by the well-known fluid dynamics approach stated by Bernouille stating that flowrate = velocity × area. Hence, as the area decreases (or increases) velocity must increase (or decrease) to sustain a constant flow rate. Fluid dynamics state that flow rate is directly proportional to the pressure difference across a tube (vein). Therefore, to maintain a comparable flow rate to the brain under the assumption that vasodilation is observed in lesser amounts in migraineurs, pressure must increase across the veins. This thought process can be further supported by our findings of decreased [Hb] and [HbO_2] response which lead us to the conclusion that there is a deregulation of vasodilation of the venous side in migraineurs. Table 1 shows that [tHb] and [OXY] changes of normal subjects is almost four to ten times larger than that of the migraineurs, consistent with the findings of [33].

Their explanation concluded that pressure-related vasoreactivity is suppressed in the right hemisphere of migraineurs during the interictal period. We have not found a significant difference. Furthermore, we believe that our findings can indicate a deregulation on capillary recruitment process since [tHb] of migraineurs which is an indicator of total blood volume inside a probed volume of interest has not increased as much as normals. NIROXCOPE 201 is believed to obtain data from the superficial layers of frontal cortex which has the highest synaptic activity along with superficial vasculature, though the exact distance for the penetration of light beams are not clear. Frontal and prefrontal cortical dysfunction has been demonstrated by various studies in affective disorders. Migraine disease is most frequently associated with mood and anxiety disorders. We assume, therefore, an abnormal cerebrovascular reactivity in prefrontal and (or) frontal cortex in our migraine patients could be related to the comorbidity of affective disorders and migraine, and even may suggest a common neurobiological background [13,24,31,34].

Healthy subjects have shorter time to peak values than migraineurs when [HbO_2] signal is concerned, while there is no significant difference in other signals. This may be attributed to the low sensitivity of our peak picking algorithm. Normally in a healthy person it is expected that [HbO_2] will increase due to the blood flow increase to reduce hypercapnic effect till the middle of the hold episode. In the mean time, [Hb] will start to climb to its peak value, while [HbO_2] starts to decrease from its maximum because of oxygen deficiency. On contrast, migraine patients might be experiencing a vasoconstriction in cerebral blood vessels when they hold their breath; hence, blood flow cannot increase as much as seen in healthy subjects. Blood flow increase will be slower due to vasoconstrictive nature of the vessels to account for a longer duration of oxygen use leading to a delayed peaking of [HbO_2] compared to healthy subjects, but the increase will reach a lower amplitude again because of vasoconstriction observed in migraineurs; just as observed in Table 1.

As a last word of discussion, we would like to note that this is a preliminary study that involved a relatively small number of individuals. Although the significance of the findings is high, we expect that a larger sampling of both healthy and migraine patients will strengthen our claims.

Migraine is hypothesized to be a neurovascular coupling disorder where the cerebral vascular reactivity is malfunctioning. Several studies of blood flow, cerebral glucose utilization and oxygenation studies have attempted to elucidate this fact. We have attempted to exploit the fNIRS technology in testing the neurovascular coupling disorder hypothesis of migraine patients. The breath hold task which produces a metabolic perturbation is a fairly simple and physiologically well investigated activation where the stimulation can be controlled easily. Since the subjects are usually at rest (cognitively), the only remaining variable becomes the increase of cerebral blood flow due to hypercapnic affect. Hence, this task is suitable for testing the coupling of neuronal demand to cerebral blood flow, a mechanism that is known to be deregulated for migraine patients. We have successfully collected fNIRS data from normals and migraine patients. The signals are ensemble averaged and analyzed for the peaks and troughs. The first half of the signals show an ID in the [Hb] amplitude which is in reverse phase with the [HbO_2] signals. Similarly, at the end of hold, the signals show a post overshoot for [Hb] and post undershoot for [HbO_2] signals. The amplitude and latency of these peaks are then compared with migraine patients. Our results show that amplitudes of the ID and R of [Hb], [tHb] and [OXY] signals are approximately 10 times higher than migraine patients. Our data implies a neurovascular coupling disorder in migraineurs and application of NIROXCOPE 201 to patients suffering from other primary headache disorders will reveal diagnostic as well as therapeutic implications of the presented study.

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