

Spontaneous Low Frequency Oscillations in Acute Ischemic Stroke – A Near Infrared Spectroscopy (NIRS) Study

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Abstract

Background and purpose: Continuous wave near infrared spectroscopy (NIRS) is a non-invasive bed-side optical method to detect changes in oxygenated (oxyHb) and deoxygenated hemoglobin (deoxyHb) in the outermost layers of the cerebral cortex. Cortical oxyHb low frequency oscillations (LFOs) in the 0.09-0.11 Hz range are affected by changes in cerebral autoregulation (CA), which is altered following stroke. We examined oxyHb LFOs at bed-side as a marker of CA in the subacute phase in stroke patients with or without recombinant tissue plasminogen activator thrombolytic therapy.

Methods: We recruited 29 patients admitted to the stroke unit with symptoms of ischemic stroke. 11/29 patients received thrombolytic therapy. NIRS examination was conducted 2 days (median time) from stroke onset. NIRS optodes were placed on each side of the head with a 3 cm source-detector distance. Using transfer function analysis, inter-hemispheric phase shift and amplitude ratio of the oxyHb oscillations in the 0.09-0.11 Hz range were assessed.

Results: The correlation between NIHSS scores at admission and oxyHb parameters revealed a significant positive correlation between stroke severity at admission and inter-hemispheric phase shift ($P=0.028$). The oxyHb absolute inter-hemispheric phase shift was significantly less in patients receiving thrombolytic therapy compared to non-thrombolytic therapy patients (3° vs. 23° , $P=0.005$).

Conclusions: Stroke severity correlates with the degree of impaired cortical CA and stroke patients receiving thrombolytic therapy might have less severely impaired CA. NIRS detects alteration in cortical oxyHb LFOs between hemispheres in stroke patients in the subacute phase and may be a feasible method to explore changes at bed-side in a stroke unit.

Keywords: Cerebral autoregulation; Low frequency oscillations; Stroke; Near infrared spectroscopy; Thrombolytic treatment; rtPA thrombolytic therapy; Transfer function analysis

Introduction

Low frequency oscillations (LFOs), known as Mayer waves [1], at 0.1 Hz of systemic and cerebral vessels are affected by neuronal [2], metabolic [3] and myogenic [4] stimuli. Spontaneous LFOs are relatively easy to investigate under clinical conditions, as they only require the patient to lie still and breathe normally during examination [5,6]. In cerebral vessels, LFOs are affected by changes in cerebral autoregulation (CA) [6] and have primarily been investigated by detecting the relationship between the systemic arterial blood pressure (ABP) and flow velocity changes in the middle cerebral artery (Vmca) using transcranial Doppler (TCD) [7,8].

In ischemic stroke cortical vessels may be affected, and it is therefore of interest to directly measure local changes in cortical resistance vessels. Studies of LFOs using TCD have shown changes in CA following ischemic stroke, which are dependent on the time

interval after ictus [9,10] and infarct location [11]. Changes in CA are associated with the clinical outcome following ischemic stroke [10,12].

Near infrared spectroscopy (NIRS) is a non-invasive optical bed-side method to investigate regional changes in oxygenated (oxyHb) and deoxygenated haemoglobin (deoxyHb) in the outermost layers of the cerebral cortex [13]. Specific cortical oxyHb LFOs can be altered by brain activity [14-16], metabolic [5] and sympathetic changes [17]. Furthermore, phase shift and gain between ABP and oxyHb LFOs may correlate to Vmca changes in carotid artery disease [18]. Subject variation in anatomy [19] may challenge inter-subject comparisons using NIRS. By measuring oxyHb inter-hemispheric phase shift, amplitude ratio and inter-hemispheric cross correlation (IHCC) [19,20], these issues are minimized, as each subject serves as their own control. Thus, NIRS may be an ideal tool to investigate subacute cortical changes in CA in stroke patients at bedside.

In the present study we aimed to explore changes in spontaneous cortical oxyHb LFOs measured with NIRS following ischemic stroke. We hypothesized that oxyHb LFOs would reveal differences between the symptomatic and contralateral side for ABP-oxyHb phase shift and gain as well as oxyHb amplitude. We expected NIH stroke scale

(NIHSS) scores at admission and 24 h after to be correlated with ABP-oxyHb and oxyHb parameters. Furthermore, we examined ABP-oxyHb phase shift and gain, oxyHb amplitude as well as inter-hemispheric oxyHb parameters for differences between thrombolytic and non-thrombolytic therapy patients.

Material and Methods

We recruited 29 patient (15 male, mean age 67, range 39-91) admitted to the Stroke Unit, Glostrup Hospital in Denmark from

September 2009 to September 2011 with symptoms of stroke in the territory of the internal carotid artery (Table 1). 11 out of 29 patients received rtPA thrombolytic therapy before participating in the study. The median time of examination was day 2 (range 1-5) after infarct onset. The Biomedical Research Ethics committee in the Capital Region of Denmark approved the study (H-B-2008-088). All subjects gave informed consent to participate in the study, which was undertaken in accordance with the Helsinki Declaration of 1964, as revised in Edinburgh in 2000.

	Thrombolytic therapy (n=11)	No thrombolytic therapy (n=18)	P value
Age	65 ± 16	68 ± 12	0.653
Male	8	7	0.648
Hypertension	7	10	0.180
Diabetes	1	0	
Previous stroke	3	3	0.227
Hypercholesterolemia	5	4	0.754
NIHSS at admission	5 (2-11)	2.5 (0-14)	0.025
Time of recording	1 (0-2)	2 (0-4)	0.06
Hemisphere affected, left	7	9	0.481
Remission after 24 H	4	5	0.774
Systolic blood pressure mmHg	122 ± 18	144 ± 29	0.031
Diastolic blood pressure mmHg	77 ± 13	82 ± 12	0.290
Smoking:			
Yes	3	4	
No	5	10	
Previous	3	4	

Table 1: Baseline clinical characteristics of patients

Near infrared spectroscopy

We used continuous wave NIRS (NIRS2; TechEn Inc, Milford, MA, USA) at a sampling rate of 200 Hz. The NIRS optodes were placed with 1 source and 1 detector on each side of the head with a distance of 3 cm between source and detector, each light source emitting two different wavelengths (690 nm and 830 nm). On each hemisphere the source was placed on the forehead, carefully avoiding the midline sinus, and with the detector placed laterally.

Arterial blood pressure

Continuous non-invasive ABP recording was collected via a finger plethysmograph (CNAP500, CNSystems, Graz, Austria) using the left hand, positioned at heart level. Data from the finger plethysmograph was stored with the NIRS data for subsequent off-line analysis.

Procedures

Before the experiments, each participant underwent a general physical and neurological examination. All experiments were performed with the patients placed in a supine position in a silent room with constant temperature and the light dimmed. After 15 min of rest in the supine position, data acquisition was started, with a 10 min trial of spontaneous breathing.

Data analysis

To remove motion artefact, we used spline interpolation as previous described [21]. In short, periods of motion artefacts are defined, and each period is modulated using spline interpolation. The modelled data is then subtracted from that period of original data.

All signals were analysed in successive 50% overlapping time segments of 100 seconds. The NIRS light intensities at 690 nm and 830

nm were first converted to time series of variations in oxyHb concentrations using the modified Beer-Lambert law.

On each time segment, we then computed the power spectra of all signals (ABP, oxyHb), the coherence spectra for ABP-oxyHb and the complex transfer function for ABP-oxyHb (The Math Works, Inc, Natick, MA, USA). The phase shift and gain between ABP oscillations and oxyHb were obtained as the phase and absolute value of the complex transfer function respectively. The LFO frequency was selected as the frequency with maximal ABP oscillation power in the 0.09-0.11 Hz range. In this manner, for each run we obtained 11 (10 min run) overlapping segments each characterized by a coherence value, a phase shift, and a gain for ABP-oxyHb. We selected the segments for which the coherence was above an arbitrary threshold of 0.7, and averaged the gain (linear average) and the phase shift (circular average) over these selected segments. If the total number of segments with coherence above 0.7 was less than 3 for a specific run, we discarded that run. The oxyHb inter-hemispheric phase shift was defined as the phase shift between the stroke side and contralateral sides. Thus, a positive phase shift implied that the stroke side was ahead in time compared to the contralateral side. The oxyHb inter-hemispheric amplitude ratio was defined as the amplitude ratio of contralateral/stroke sides. Thus, an amplitude ratio above 1 implied that the amplitude was lower on the stroke side compared to the contralateral side. Inter-hemispheric cross correlation (IHCC) was defined as the cross correlation of changes in the optical density at 830 nm. An IHCC of 1 indicates that the hemispheres are in phase (phase delay 0), and an IHCC of -1 indicates a 180° phase delay.

We also analysed the absolute values of oxyHb inter-hemispheric phase shift, and the oxyHb amplitude ratio of the hemisphere with higher amplitude over that of lower amplitude (ratio above 1, referred to below as the “absolute oxyHb amplitude ratio”) This allows us to investigate the inter-hemispheric synchronicity and amplitude difference independently of whether the infarct side is systematically behind or ahead in time, or whether it presents larger or smaller amplitude of oscillations than the contralateral side.

All NIRS data was assessed blindly in respect to symptomatic and non-symptomatic side.

Statistics

Data are presented as mean values and standard deviation (± SD).

The primary endpoint was: 1) To compare the infarct versus the non-infarct side for ABP-OxyHb phase and gain as well as OxyHb amplitude.

The secondary end points were: 1) The correlation between NIHSS score at admission to ABP-oxyHb phase shift, gain and oxyHb amplitude on the symptomatic side, and oxyHb inter-hemispheric phase shift, amplitude ratio and IHCC.

2) To compare thrombolytic therapy patients vs. non-thrombolytic therapy patients on the symptomatic side for ABP-oxyHb phase shift and gain as well as oxyHb amplitude, and oxyHb inter-hemispheric phase shift, amplitude ratio and IHCC.

3) The correlation between NIHSS score changes from admission to 2 h and 24 h to ABP-oxyHb phase shift and gain and oxyHb amplitude on the symptomatic side, and oxyHb inter-hemispheric phase shift, amplitude ratio and IHCC.

In the group of patients not receiving thrombolytic treatment we made a post hoc analysis comparing patients with manifest infarction versus transient ischemic attack (TIA) patients for ABP-oxyHb phase shift and gain as well as oxyHb amplitude on the symptomatic side, and oxyHb inter-hemispheric phase shift, amplitude ratio and IHCC.

To test the differences between the infarct and non-infarct hemisphere for amplitude, we used Wilcoxon’s Signed Ranks test. Differences between thrombolytic therapy patients and non-thrombolytic therapy patients were tested using Mann-Whitney test and McNemar test for dichotomic data. The relationship between NIHSS score and NIRS variables were tested by Spearman’s correlation, as well as the relationship between changes in NIHSS and NIRS parameters. All analyses were performed with IBM SPSS (20.0). We made no adjustment for multiple analyses. Thus, the level of significance at 0.05 was accepted for each comparison.

Results

All 29 patients completed the study and clinical characteristics of the patients are shown in Table 1. 4/11 subjects in the thrombolytic group and 6/18 in the non-thrombolytic group received inhibitors of platelet aggregation prior to the admission. The coherence in ABP-oxyHb phase shift and gain was too low, and was therefore not analysed further. For oxyHb inter-hemispheric amplitude ratio and phase shift we excluded 10 % of the runs due to low coherence.

The oxyHb oscillation amplitude on the infarct side was not different compared to the contralateral side (0.014 ± 0.030 vs. 0.017 ± 0.032, P = 0.758). The oxyHb absolute inter-hemispheric phase shift was significantly smaller in patients receiving thrombolytic therapy compared to non-thrombolytic therapy patients (3° vs. 23°, P = 0.005). For the other oxyHb variables we found no differences between patient groups (Table 2).

	Thrombolytic therapy (n=11)	No thrombolytic therapy (n=18)	P-value
Amplitude on stroke side	0.029 (± 0.046)	0.005 (± 0.005)	0.170
Inter-hemispheric phase shift	-1° (± 5°)	-13° (± 48°)	0.550
Absolute inter-hemispheric phase shift	3° (± 3°)	23° (± 44°)	0.005
Inter-hemispheric amplitude ratio	0.990 (± 0.312)	1.519 (± 1.161)	0.186
Absolute inter-hemispheric amplitude ratio	1.304 (± 0.313)	1.773 (± 1.038)	0.073
Inter-hemispheric cross correlation	0.6 (± 0.2°)	0.5 (± 0.3)	0.500

Table 2: Differences in low frequency oscillation variables between patients with or without thrombolytic therapy

The correlation between NIHSS scores at admission and oxyHb parameters revealed a significant positive correlation between stroke severity at admission and inter-hemispheric phase shift (r 0.430, P=0.028, Figure 1). For the other oxyHb variables no correlations were found (Table 3). Post hoc analysis revealed no correlation between systolic ABP and absolute inter-hemispheric phase (p=0.755) or NIHSS at admission (p=0.452).

	Correlation coefficient Spearman's rho	P-value
Amplitude on stroke side	0.154	0.426
Inter-hemispheric phase shift	0.430	0.028
Absolute inter-hemispheric phase shift	-0.099	0.631
Inter-hemispheric amplitude ratio	0.062	0.762
Absolute inter-hemispheric amplitude ratio	-0.017	0.933
Inter-hemispheric cross correlation	-0.165	0.393

Table 3: Correlation between NIH stroke scale (NIHSS) values at admission and low frequency oscillation variables. P values: Spearman's correlation.

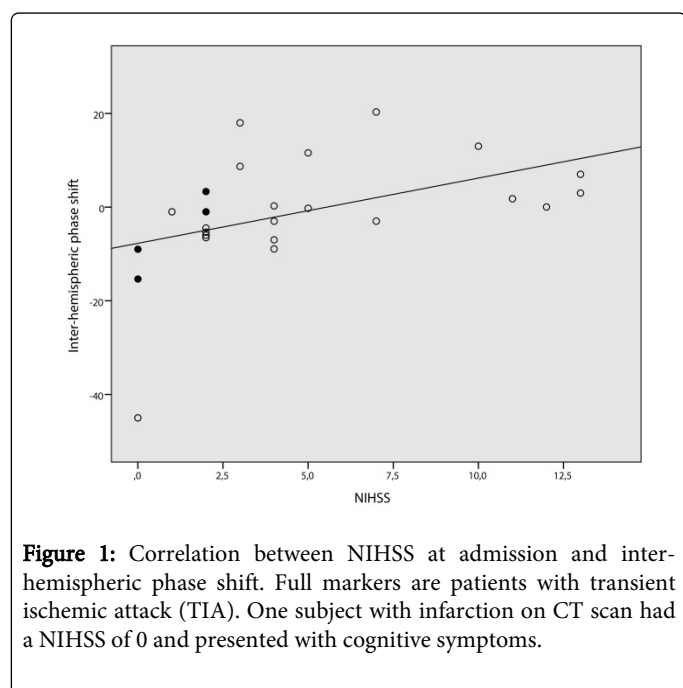


Figure 1: Correlation between NIHSS at admission and inter-hemispheric phase shift. Full markers are patients with transient ischemic attack (TIA). One subject with infarction on CT scan had a NIHSS of 0 and presented with cognitive symptoms.

In patients receiving thrombolytic treatment, the changes in NIHSS between admission and 2 and 24 h revealed no correlation for any oxyHb variables.

Post hoc analysis of the 13 patients with manifest infarction versus 5 patients with TIA revealed no statistical differences (Table 4).

Channel	Stroke (n=13)	TIA (n=5)	P-values
Amplitude	0.006 (± 0.006)	0.004 (± 0.003)	0.843
Inter-hemispheric phase shift	-15° (± 57°)	-8° (± 6°)	0.267
Absolute inter-hemispheric phase shift	28° (± 51°)	8° (± 6°)	0.327
Inter-hemispheric amplitude ratio	1.597 (± 1.331)	1.303 (± 0.549)	1.000

Absolute inter-hemispheric amplitude ratio	1.891 (± 1.184)	1.448 (± 0.401)	0.602
Inter-hemispheric cross correlation	0.5 (± 0.3)	0.7 (± 0.2)	0.218

Table 4: Differences in low frequency oscillation variables for non-thrombolytic patients with transient ischemic attack (TIA) versus manifest infarction. P-values: Mann-Whitney test.

Discussion

The major outcome of this study was a positive correlation between NIHSS scores at admission and the oxyHb inter-hemispheric phase shift. Furthermore, we showed that oxyHb absolute inter-hemispheric phase shift was significantly smaller in ischemic stroke patients receiving thrombolytic therapy compared to non-thrombolytic therapy patients. For the remaining oxyHb variables no differences were found between hemispheres, therapy groups and NIHSS score.

Recently, Obrig [22] suggested stroke and cerebrovascular disease as a promising area for NIRS in clinical neurology and that subacute stroke might be the most relevant field that NIRS could reach the clinical neurologist. The present study is, to our knowledge, the first to analyse LFOs with NIRS following ischemic stroke in the subacute phase. To date, no studies are available to directly compare our results to, and no gold standard is provided on how to investigate stroke patients with NIRS. We used a variety of measures to investigate possible changes in CA and found that ABP-oxyHb had too low coherence to obtain valid data. Whether this finding is due to motion artefacts or pathological loss of coherence is unknown. Furthermore, we found no differences in oxyHb amplitudes, which might be due to arterioles distal to the infarct area dilated compensatively to ensure oxygen delivery. However, this effect might have been attenuated due to LFOs decreasing with age [23] and cerebral microangiopathy [24]. Of the 29 patients recruited, only 7 patients had clear involvement of cerebral cortex based upon symptoms and imaging at admission, and two of these were without any neurological signs after 24 h (both received thrombolytic therapy). The lack of difference between hemispheres may be due to impaired CA in both hemispheres, which has previously been shown in patients with lacunar strokes assessed by ABP-Vmca LFOs [11].

Using NIRS, a previous pilot study (20) examined 9 patients with ischemic stroke and analysed IHCC within cardiac (0.7–3 Hz) and respiratory (0.15–0.7 Hz) frequency spectrums. This study showed a smaller IHCC in stroke compared to healthy controls. This suggests a de-synchronization between hemispheres following ischemic stroke, but the change may also be caused by 44% of the patients in the study having a high-degree ipsilateral carotid disease. In the present study, we found a significantly smaller oxyHb absolute inter-hemispheric phase shift in patients treated with thrombolytic therapy compared to patients not receiving thrombolytic therapy. This reflects de-synchronization in the non-thrombolytic group and possible a decline in CA. The patients undergoing thrombolytic therapy were examined after administration of thrombolytic treatment and they had in general a good outcome (full remission in 36% vs. 28%) (Table 1). It is therefore possible, that the treatment had an effect on the variability and CA as well as on the NIHSS. In support, a previous study has measured LFOs ABP-Vmca correlation coefficient and phase in patients undergoing successful or unsuccessful rtPA thrombolytic therapy [10]. The study showed that CA was increasingly impaired, mainly on the affected side, over the first 5 days of major ischemic

stroke after unsuccessful rtPA thrombolysis, but was bilaterally preserved in minor stroke after successful rtPA thrombolysis, indicating no separate detrimental effect of rtPA on the cerebral autoregulatory mechanism. Collectively, these studies suggest that disturbance in CA following ischemic stroke is not caused by the rtPA thrombolytic therapy, but by the degree of stroke severity.

There are some limitations in the present study. We did not examine healthy controls and it is possible that the inter-hemispheric variables would be different between patients and controls. The patients undergoing thrombolytic treatment were investigated earlier than the rest, and it is possible that CA alterations changes over time, which may blur the results. Furthermore, the patients present a mixture of lacunar and cortical infarction, with 13 patients without clear evidence of infarct localization and only 7 patients had clear involvement of cerebral cortex based upon imaging and symptoms. This may lead to false negative results. In addition, we did not correct for the contribution of skin vasculature, which may bias our results. This is a small explorative study with a low number of subjects, and we did not adjust for multiple comparisons in statistical testing. Therefore the results need to be handled with caution and further investigations are needed.

In conclusion, our results suggest that NIRS may detect asymmetry in cortical LFOs between hemispheres in stroke patients in the subacute phase. The study shows that NIHSS score at admission is correlated to the LFOs oxyHb inter-hemispheric phase shift. Patients receiving thrombolytic therapy seem to have less impaired CA, which can be measured using the absolute inter-hemispheric phase shift. Thus, NIRS may be a feasible method to explore changes in ischemic stroke patients using inter-hemispheric phase shift analysis. Further studies are needed to prospectively investigate changes in cortical LFOs using NIRS in cerebrovascular disease.

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