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Transcranial diffuse optical monitoring of microvascular cerebral hemodynamics after thrombolysis in ischemic stroke

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Abstract. The ultimate goal of therapeutic strategies for ischemic stroke is to reestablish the blood flow to the ischemic region of the brain. However, currently, the local cerebral hemodynamics (microvascular) is almost entirely inaccessible for stroke clinicians at the patient bed-side, and the recanalization of the major cerebral arteries (macrovascular) is the only available measure to evaluate the therapy, which does not always reflect the local conditions. Here we report the case of an ischemic stroke patient whose microvascular cerebral blood flow and oxygenation were monitored by a compact hybrid diffuse optical monitor during thrombolytic therapy. This monitor combined diffuse correlation spectroscopy and near-infrared spectroscopy. The reperfusion assessed by hybrid diffuse optics temporally correlated with the recanalization of the middle cerebral artery (assessed by transcranial-Doppler) and was in agreement with the patient outcome. This study suggests that upon further investigation, diffuse optics might have a potential for bed-side acute stroke monitoring and therapy guidance by providing hemodynamics information at the microvascular level. © The Authors. Published by SPIE under a Creative Commons Attribution 3.0 Unported License. Distribution or reproduction of this work in whole or in part requires full attribution of the original publication, including its DOI. [DOI: [10.1117/1.JBO.19.1.018002](https://doi.org/10.1117/1.JBO.19.1.018002)]

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1 Introduction

Intensive monitoring of physiological variables during the early hours after ischemic stroke onset reduces death, dependency, and the need for institutional care.¹ While most interventions following ischemic stroke aim to restore the blood supply to the ischemic tissue, in practice, the local (microvascular) oxygenation, perfusion, and the metabolic status of brain is almost entirely inaccessible. The continuous brain monitoring in the framework of stroke units could potentially identify biomarkers, allowing the early detection of the tissue deterioration prior to irreversible damage and serve as a tool to individualize the clinical management.² However, currently, the real-time monitoring, even in specialized ischemic stroke units, is mostly limited to systemic physiology.

In this study, we present a case report from a patient with an acute ischemic stroke who underwent thrombolysis therapy with recombinant tissue plasminogen activator (rtPA). The patient was monitored by a hybrid diffuse optical monitor that we have developed. The hybrid diffuse optical monitor simultaneously and transcranially followed the local cerebral blood flow (CBF) and the blood oxygenation (via the oxy- and deoxy-hemoglobin concentrations) in real time and at the patient bed-side. Our method combined continuous-wave (CW) near-infrared or diffuse optical spectroscopy (NIRS-DOS) to measure the oxy- and deoxy-hemoglobin concentrations³ alongside diffuse correlation spectroscopy (DCS).³⁻⁵ DCS is a relatively new method for direct measurement of CBF with no need for

exogenous markers. It has been extensively validated *in vivo* against other standard clinical modalities for CBF assessment^{3,6} and has not previously been adapted to the emergency settings of the hyperacute stroke management.

This case study reports the first application of the hybrid diffuse optics to real-time and continuous monitoring of cerebral hemodynamics assessment of a patient with ischemic stroke due to acute thromboembolism of the middle cerebral artery (MCA), at admission and during thrombolysis therapy with rtPA up to the recanalization time point. Our aim was to demonstrate the feasibility of bed-side monitoring of microvascular hemodynamics of the ischemic brain by hybrid diffuse optics at hectic clinical settings and its sensitivity to the hemodynamic changes of the ischemic brain.

2 Methods

The CBF was measured by DCS, which consisted of a mode-hop free long coherence length laser at 785 nm and eight avalanche photo diodes for detection as further explained in Ref. 3 and was used in prior ischemic stroke studies.⁷ In a fashion similar to Refs. 8 and 9, two extra diode lasers were added at 690 and 830 nm with the same avalanche photo diodes utilized for light detection in order to measure the tissue absorption changes at these wavelengths. Optical switches were used to switch the measurement wavelength as well as the measurements from the left/right cerebral hemispheres. This has allowed us to use CW NIRS-DOS to evaluate the changes in oxy- and deoxy-hemoglobin concentrations alongside microvascular CBF. The selection of CW mode of NIRS-DOS was a compromise compared to

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earlier works⁵ in terms of the accuracy and the comprehensiveness of the NIRS-DOS results, but it was an important requirement for the intensive care settings. The optical probes were made of custom-built 90-deg bent fibers and had a source and a detector for each hemisphere (right and left hemispheres) with a 2.5 cm source-detector separation as shown in Fig. 1.

For the DCS analysis, the reduced scattering coefficient of the tissue at 785 nm was assumed to be constant ($\mu'_s = 8.5 \text{ cm}^{-1}$), taken from Ref. 10. We have measured the changes of the absorption coefficient (μ_a) at 785 nm from their baseline value ($\mu_a = 0.14 \text{ cm}^{-1}$), used from Ref. 10, by NIRS-DOS. These μ_a changes at 785 nm were then utilized in DCS analysis to improve accuracy of the CBF measures.⁵

In addition, in order to obtain more precise measures of the microvascular oxygenation changes, we have corrected our (NIRS-DOS) data for pathlength and partial volume effects as explained in Refs. 11 and 12. These measures were then used to derive the changes of oxy- and deoxy-hemoglobin concentrations and CBF from their baseline values, ΔHbO_2 , ΔHb , and $\Delta r\text{CBF} = [(CBF/CBF_{\text{baseline}}) - 1] \times 100$, respectively. The baseline values for CBF (CBF_{baseline}), HbO_2 , and Hb were obtained by averaging the first 5 min of DCS and NIRS-DOS measurements. The changes in total hemoglobin concentration (THC; $\Delta\text{THC} = \Delta\text{HbO}_2 + \Delta\text{Hb}$) and $r\text{CBF}$ were reported from the frontal poles of peri-infarct and contra-infarct hemispheres. Details of the analysis as well as the correction methods were discussed previously in Refs. 7 and 8.

On admission, the patient underwent a head computed tomography (CT) scan before rtPA treatment, which was repeated at 24 h. The MCA patency was evaluated using angio-CT and transcranial-Doppler (TCD). Recanalization by TCD was confirmed by thrombolysis in brain ischemia (TIBI) flow grade criteria.¹³ The clinical status of the patient was reported using National Institutes of Health Stroke Scale (NIHSS) at baseline and 6, 24, and 48 h after the stroke onset. Long-term (three-month) patient outcome was evaluated by the modified Rankin scale (mRS).¹⁴

The study was approved by the institutional ethics committee at the Hospital Santa Creu i Sant Pau and informed consent was obtained from the relatives.

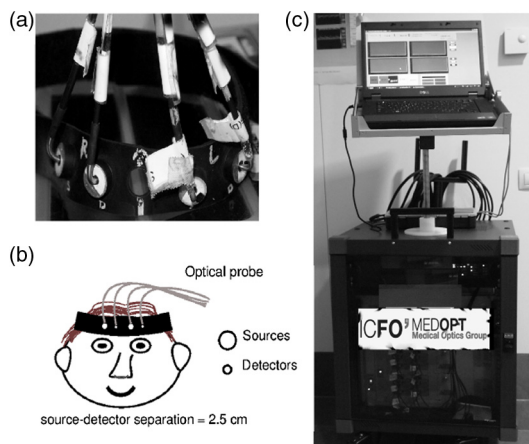


Fig. 1 Front view of the optical probe showing: (a) 90 deg bent optical fibers, and button like fiber holders; (b) placement and the design of the optical probe on the forehead; (c) hybrid diffuse optics monitor used for the measurements.

3 Case Study

We report the case of a 92-year-old woman who was admitted to the stroke unit of the hospital Santa Creu i Sant Pau ~40 min after developing left-side hemiplegia and dysarthria of acute onset. She had no previous history of stroke. On the first physical exam, there was clinical evidence of the involvement of the complete right MCA territory, including the frontal lobe, i.e., forced right eye deviation and left hemiplegia with an NIHSS score of 19.

The CT scan on admission revealed a hyperdense right MCA sign and early signs of temporal ischemia. Proximal occlusion of the right MCA was demonstrated by angio-CT and confirmed by TCD. TIBI was 1 measured at 50 mm depth at baseline for TCD measurement.

At ~80 min after the stroke onset, we started to acquire bilateral optical data. About 5 min after the start of the optical data acquisition, intravenous rtPA was administered (0.9 mg/kg as a 10% bolus and 90% continuous infusion over 60 min). During treatment, TCD showed an improvement of TIBI flow grade to 4 at 30 min after rtPA bolus and 5 at the end of infusion, indicating a complete recanalization of the right MCA, which happened ~2 h after ischemia onset.

The continuous optical measurements continued up to 10 min after this recanalization time point. Clinically, the patient improved, presenting an NIHSS score reduction to 7 at 6 h from admission and further to 1 at 24 h and until discharge. Follow-up CT at 24 h after the stroke onset revealed a temporal and deep MCA ischemic lesion. Functional outcome at three months follow-up was excellent as revealed by mRS score of 1, i.e., no significant disability.

Figure 2 shows the changes of the microvascular CBF and THC starting from ~5 min before rtPA infusion until 10 min after the recanalization confirmation by TCD (marked with vertical solid line). $\Delta r\text{CBF}$ and ΔTHC were averaged from 3 min before recanalization time point (confirmed with TCD) up to 3 min after recanalization time point and reported as changes of CBF and THC upon complete recanalization. The averaging

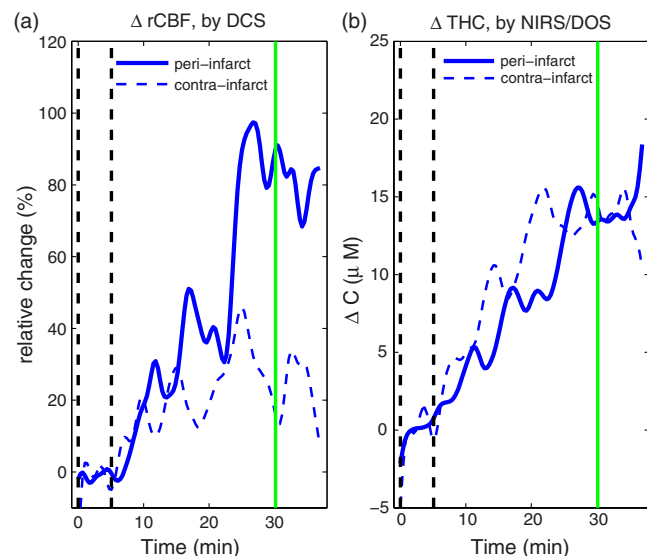


Fig. 2 (a) Cerebral blood flow changes. (b) Total hemoglobin concentration changes for peri-infarct and contra-infarct hemispheres. Dashed vertical lines show the first 5 min of the measurement (baseline period), and vertical solid line shows the complete recanalization time point observed by transcranial-Doppler.

over 6 min about the recanalization time point was performed to account for possible differences between reperfusion (microvascular) and recanalization (macrovascular) time points. Finally, in the peri-infarct hemisphere, an $84.8 (\%) \pm 22$ (mean \pm standard deviation) CBF increase and a $14.2 (\mu\text{M}) \pm 1.4$ THC increase were obtained. Similarly, a $23.2 (\%) \pm 18.8$ CBF increase and a $14.5 (\mu\text{M}) \pm 2.1$ THC increase were measured on the contra-infarct hemisphere.

No significant changes on systemic blood pressure and oxygen saturation occurred during monitoring. The systolic blood pressure (BP_{sys}), diastolic blood pressure (BP_{dias}), and oxygen saturation (StO_2) were 128 mmHg, 60 mmHg, and 91% at the measurement start and 140 mmHg, 61 mmHg, and 93% during the recanalization, respectively.

4 Discussion and Conclusions

In this case report, we demonstrated that the home-made hybrid diffuse optical system could be utilized in the hyperacute stroke settings for real-time monitoring of the ischemic brain. We presented the case of a stroke patient in which hybrid diffuse optics revealed the reperfusion of the ischemic region of the brain (frontal) after successful recanalization of the MCA with rtPA treatment. This concurrent recanalization and reperfusion correlated with the clinical recovery of the patient. To the best of our knowledge, this is the first study that reports the observation of microvascular reperfusion upon successful recanalization of the ischemic brain at the patient's bed-side using hybrid diffuse optics.

It is interesting to note (see Fig. 2) that the microvascular hemodynamic parameters changed at both the peri-infarct and contra-infarct hemispheres. The changes of the microvascular flow of the peri-infarct hemisphere was more pronounced than that of the contra-infarct hemisphere as expected, whereas the microvascular THC changes were similar for both peri- and contra-infarct hemispheres. This finding seems to be in contrast to the expected relation between CBF and THC first discussed by Grubb et al.¹⁵ However, it should be noted that the first empirical formulation¹⁵ or its modified forms (e.g., Ref. 16) relate the absolute measures of CBF and THC, while here we compare the changes of CBF with the changes in THC. This needs to be further explored since relative changes could be biased in case of vastly different baseline values.

Similar to our findings in this study (DCS results), the reperfusion of hypoperfused tissue upon successful thrombolysis at microvascular level was very recently reported in a study using arterial spin labeled perfusion magnetic resonance imaging (Ref. 17) in which the increases in the regional CBF upon successful recanalization in concurrence with the patient clinical improvement were observed. NIRS-DOS usage was previously reported in one case study to assess the changes of microvascular oxygenation during thrombolysis.¹⁸ Although, the authors have reported changes of oxygen saturation, which is not directly comparable with our ΔTHC results, the direction of the changes (increasing trend of oxygenation) of the peri-infarct side after complete recanalization is in qualitative agreement with our results.

It should be noted that our flow measures were limited to a small area of the frontal cortex and reflect an undetermined mix of the affected and unaffected tissues. As a result, the location and the intensity of the occlusion as well as the speed and degree of recanalization are expected to affect the diffuse optical measures. Future probe designs by implementing larger number of

sources and detectors could lead to monitoring larger region of the brain and consequently increasing the information content of diffuse optics measures.

This case study suggests that the diffuse optical technique may be sensitive to the microvascular effects of the ischemia and thrombolysis. If this is confirmed by future studies and ultimately clinical trials, the application of bed-side hybrid diffuse optical monitors in stroke clinics may fill the current gap for bed-side monitoring of the ischemic stroke at the microvascular level and possibly help optimizing the therapeutic strategies for individuals. The microvascular flow measures could then be used to evaluate the patency of the microvasculature or the collateral circulation, which has been shown to be a better predictor of patient outcome than the large artery recanalization alone.¹⁹ Currently, we are recruiting more patients to study the effect of the infarct location and intensity, and the speed and the degree of recanalization on our diffuse optical measures as well as the correlation of these diffuse optical measures with the patient short- and long-term outcomes. Furthermore, absolute values of oxygenation and flow parameters may be assessed in the near future for DCS and NIRS-DOS in a similar fashion to Refs. 20 and 21). These would provide more precise and robust measures of microvascular hemodynamics and oxygen metabolism characterization.

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Biographies of the authors are not available.