Assessment of Cortical Hemodynamics by Multichannel Near-Infrared Spectroscopy in Steno-Occlusive Disease of the Middle Cerebral Artery

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Background and Purpose—In a pilot study we evaluated near-infrared spectroscopy as to its potential benefit in monitoring patients with steno-occlusive disease of a major cerebral artery for alterations in cortical hemodynamics.

Methods—Cortical maps of time-to-peak (TTP) in 10 patients unilaterally affected by severe stenosis or occlusion of the middle cerebral artery were acquired by multichannel near-infrared spectroscopy after bolus application of indocyanine green. Hemodynamic manifestations were assessed by comparison between affected and unaffected hemisphere and evaluated for common constituents by principal component analysis. In one patient, TTP values were compared with those obtained by dynamic susceptibility contrast imaging.

Results—TTP was increased on the affected hemisphere in 9 patients. Mean difference in TTP between hemispheres was 0.44 second ($P<0.05$) as compared with a mean lateral difference of 0.12 second found in a control group of 10 individuals. In group analysis a significant rise in TTP was found in the distribution of the affected middle cerebral artery, whereas principal component analysis suggests augmentation of hemodynamic effects toward the border zones as a dominant pattern. A linear correlation of 0.61 between TTP values determined by dynamic susceptibility contrast MRI and near-infrared spectroscopy was found to be statistically significant ($P<0.001$).

Conclusion—Multichannel near-infrared spectroscopy might facilitate detection of disease-related hemodynamic changes as yet only accessible by tomographic imaging modalities. Being indicative for hypoperfusion and collateral flow increased values of TTP, as found to a varying extent in the present patient group, might be of clinical relevance. (Stroke. 2012;43:2980-2985.)

Key Words: cerebrovascular disease ■ hemodynamics ■ imaging ■ middle cerebral artery ■ near-infrared spectroscopy ■ steno-occlusive disease

Severe stenosis of large intracranial arteries, eminently the middle cerebral artery (MCA), is a potent cause of ischemic stroke and transient ischemic attack. Although the interaction between hemodynamic failure and embolism on the etiologic pathway from stenosis to stroke is still under debate, hypoperfusion is accepted to be an important consideration in cerebral border zone infarction rendering perfusion imaging an important diagnostic and monitoring tool in this disease.1-4 Here near-infrared spectroscopy (NIRS), owing to its wider applicability and increased time resolution, poses an attractive alternative to tomographic imaging modalities like CT, single photon emission CT, positron emission tomography, or MRI. Bolus application of an adequate chromophore like indocyanine green (ICG) allows for determination of perfusion-related parameters.5-8 Among these, time-to-peak (TTP) as a measure for delayed perfusion is sensitive to hypoperfusion and collateral flow as verified in previous studies.9 In the present study it was evaluated to which extent multichannel NIRS can detect spatial patterns of TTP characteristic for steno-occlusive disease of the MCA.

Methods

Patients

Ten patients from a group of 17 with severe unilateral stenosis or segmental occlusion of the MCA as confirmed by transcranial color-coded duplex sonography were enrolled into this study. Data obtained in the remaining 7 patients could not be included owing to insufficient NIRS signal quality as already assessed during data acquisition. Mean age of patients was 59.9±13.8 years. None of the patients had a major stroke or presented significant neurological signs at the time of investigation. One of 8 patients who underwent either clinical MRI or CT before this study showed signs of cerebral infarction in the posterior border zone of the MCA, a region not covered by our setting.
Figure 1. NIRS data acquisition and analysis. Optodes were arranged on the scalp according to the 10 to 20 EEG system (A). Red and blue spheres mark light sources and detectors, respectively. Numbers indicate the location of the corresponding channels each between a source–detector pair. Green circles denote the optodes aligned to F3 and C3 on the left hemisphere. Corresponding optodes on the right hemisphere were aligned to F4 and C4. For each channel, the time course of ICG concentration (gray line) was derived from the NIRS signal using the modified Lambert-Beer equation (B). For determination of TTP, a γ-variate function was fitted to the first bolus passage (red line). For visualization, TTP was mapped onto the enclosed plane by cubic interpolation (C). NIRS indicates near-infrared spectroscopy; EEG, electroencephalogram; ICG, indocyanine green; TTP, time-to-peak.

Control Cohort

Twelve volunteers with no history of neurological disorders were recruited as control subjects. Signal quality was found to be sufficient in 10 individuals who then had a standardized color-coded duplex sonography to exclude relevant steno-occlusion of the extra- and intracranial arteries. Mean age of the control group was 54.2±16.1 years. The local ethics committee approved the study protocol and informed consent was obtained from all patients and control subjects.

Duplex Sonography

Patients underwent a standardized color-coded duplex sonography of the extra- and intracranial arteries using an Apio XG US system (Toshiba, Tokyo, Japan). Severe MCA stenosis was confirmed by an intrastenotic peak systolic velocity >220 cm/second associated with a reduction of the arterial lumen diameter by more than 50% according to Baumgartner et al.10 Poststenotic mean flow velocity was measured under normal breathing and after carbon dioxide challenge to determine cerebrovascular reserve capacity. The latter was assumed exhausted at a flow velocity increase of <5% per volume percent increase of end-expiratory carbon dioxide.11

Near-Infrared Spectroscopy

NIRS examinations were conducted using a multichannel continuous wave device (ETG 4000; Hitachi) using 4×4 probe holders that allow for simultaneous measurement of up to 24 channels per hemisphere. To avoid signal contamination especially by the temporal muscle, the lowermost 7 channels on each hemisphere were not used.12 Optodes were arranged on the scalp following the 10 to 20 electroencephalographic system13 by an experienced medical technical assistant to ensure partial coverage of the cortical territory of the MCA and its border zone toward the anterior cerebral artery (Figure 1A). Selected optodes were aligned to F3/4 and C3/4 to further reduce interindividual variations in spatial probe configuration. The interoptode distance was 3 cm. Examinations took place in a dark and quiet environment with patients in a supine position.

Although the NIRS system used provides monochromatic light at 2 wavelengths (700 and 830 nm), only data for 830 nm were analyzed for assessment of ICG dynamics given that adjunction of albumin shifts the maximum of the ICG absorption spectrum toward 805 or 810 nm.14,15 Concentrations of other chromophores like deoxy- and oxyhemoglobin were assumed to be constant during data acquisition.

Bolus injection of ICG (ICG-Pulsion; Pulsion Medical Systems, Munich, Germany) into a peripheral vein of the right arm was carried out manually at a dose of 0.1 mg/kg body weight over a period of 1 second. Here 25 mg ICG was dissolved in 5 mL sterile water for injection. NIRS data acquisition was started approximately 60 seconds before ICG injection and continued for 120 seconds at a sampling rate of 10 Hz. Time series acquired this way were low pass-filtered offline at 0.8 Hz. For each channel, TTP was then determined as illustrated in Figure 1 using in-house software based on MATLAB (R2009b; The Mathworks Inc, Natick, MA). In the control group, ICG injection was repeated 5 minutes after the first data acquisition to assess reproducibility of TTP measurements. In 8 patients signal quality was sufficient in both measurements.

Before data acquisition, optode positions relative to 3 anatomic landmarks (nasion, right and left preauricular point) were determined using an electromagnetic digitizer system (Polhemus ISOTRAK II; Inition, London, UK).

Dynamic Susceptibility Contrast MRI

For validation of our approach, dynamic susceptibility contrast (DSC) MRI was performed in one patient on a 3-T Siemens Verio Scanner (Siemens, Erlangen, Germany) using a gradient-echo type echoplanar imaging sequence (echo time, 30 ms; repetition time, 1500 ms; flip angle, 90°; number of echoes, 1; slice thickness, 5 mm; planar image resolution, 1.6×1.6 mm2; interslice distance, 5.5 mm). Sixty scans were acquired over a period of 88 seconds. Intravenous administration of 0.1 mmol/L/kg body weight gadolinium–diethylenetriaminepenta-acetic acid was carried out after the seventh scan at a rate of 5 mL/second. A TTP map was derived from the resulting image series using native scanner software (Syngo MR B17; Siemens). Within the same session, a T1-weighted magnetization-prepared rapid acquisition with gradient-echo sequence (echo time, 4.37 ms; repetition time, 2500 ms; inversion time, 1.1 seconds; flip angle, 7°; number of echoes, 1; resolution, 1×1×1 mm3) was acquired to facilitate spatial correlation between MRI and NIRS TTP maps based on these anatomic landmarks.

After segmentation of the cortex in the magnetization-prepared rapid acquisition with gradient-echo images for each NIRS channel, a corresponding cortical area was defined as an intersection with the respective optical path volume here approximated by a half-sphere touching sending and receiving optode as diametrically opposite points. MRI TTP values averaged over these areas were then used to assess correlation with NIRS.
In group analysis, the difference in mean TTP between hemispheres was tested for statistical significance by Student paired t test (Here and throughout the text, mean TTP refers to the mean over all channels on one hemisphere.). To compare hemispheres on a per-channel basis over an entire population, a stepwise resampling approach was used to address the problem of multiple hypothesis testing.16 Linear correlation between parameters was assessed by Pearson correlation coefficient. For principal component analysis of hemodynamic alterations induced by stenosis or occlusion for TTP, the difference vector between affected and unaffected hemispheres was normalized to zero mean and unit SD to reduce interference of physiological parameters like cardiac output.

For all tests, a value of $P<0.05$ was assumed to indicate statistical significance. Parameter values are given as mean±SD. Statistical analysis was performed using MATLAB.

**Table. Patients’ Characteristics**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Site</th>
<th>IS Flow Velocity, cm/s</th>
<th>PS Flow Velocity, cm/s</th>
<th>Cerebrovascular Reserve Capacity, %</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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<td>F</td>
<td>R</td>
<td>259.7</td>
<td>163.4</td>
<td>54.9</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>F</td>
<td>L</td>
<td>247.5</td>
<td>73</td>
<td>25.8</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>M</td>
<td>L</td>
<td>…</td>
<td>63</td>
<td>22.3</td>
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<tr>
<td>4</td>
<td>71</td>
<td>M</td>
<td>L</td>
<td>…</td>
<td>49</td>
<td>…</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>M</td>
<td>R</td>
<td>…</td>
<td>14</td>
<td>&lt;0</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>F</td>
<td>L</td>
<td>278.2</td>
<td>105.5</td>
<td>30.5</td>
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<tr>
<td>7</td>
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<td>F</td>
<td>L</td>
<td>…</td>
<td>24</td>
<td>…</td>
</tr>
<tr>
<td>8</td>
<td>77</td>
<td>M</td>
<td>R</td>
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<td>129.5</td>
<td>37.3</td>
</tr>
<tr>
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<td>M</td>
<td>L</td>
<td>338.6</td>
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</tr>
<tr>
<td>10</td>
<td>57</td>
<td>M</td>
<td>L</td>
<td>…</td>
<td>56.8</td>
<td>…</td>
</tr>
</tbody>
</table>

IS indicates intrastenotic; PS, poststenotic; F, female; M, male; R, right; L, left.

*Systolic flow velocity and cerebrovascular reserve capacity were assessed in the M1 segment of the middle cerebral artery distal to the stenosis/occlusion.

**Statistical Analysis**

In group analysis, the difference in mean TTP between hemispheres was tested for statistical significance by Student paired t test (Here and throughout the text, mean TTP refers to the mean over all channels on one hemisphere.). To compare hemispheres on a per-channel basis over an entire population, a stepwise resampling approach was used to address the problem of multiple hypothesis testing.16 Linear correlation between parameters was assessed by Pearson correlation coefficient. For principal component analysis of hemodynamic alterations induced by stenosis or occlusion for TTP, the difference vector between affected and unaffected hemispheres was normalized to zero mean and unit SD to reduce interference of physiological parameters like cardiac output.

For all tests, a value of $P<0.05$ was assumed to indicate statistical significance. Parameter values are given as mean±SD. Statistical analysis was performed using MATLAB.

**Results**

In 7 patients, a high-grade stenosis or occlusion of the left MCA was found, whereas in 3 patients, the right MCA was affected (Table). Mean TTP was increased on the affected hemisphere in 9 patients. The increase varied from 0.09±0.82 to 1.5±1.5 seconds (Figure 2A). In one patient, mean TTP on the affected hemisphere was decreased by 0.7±1.2 seconds. For the entire patient population, mean TTP was significantly increased by 0.44±0.60 seconds on the affected hemisphere ($P<0.05$). Principal component analysis suggests 2 major components of induced hemodynamic alterations explaining 56.9% of variance observed in the entire patient population and indicates an augmentation of hemodynamic effects in the peripheral MCA distribution territory toward the distribution territory of either the anterior cerebral artery or posterior cerebral artery (Figure 3). Group analysis over the entire patient group showed a statistically significant increase in TTP for the affected hemisphere in 2 channels (9, 15; Figure 1A) in the peripheral MCA distribution territory adjacent to the anterior border zone. Differences were most pronounced for channel 15 showing an increase of 1.0±0.9 second in TTP. Between TTP maps determined by NIRS and DSC MRI in one patient (Figure 4), a statistically significant linear correlation of 0.61 was found ($P<0.001$).

In the control group, the difference in mean TTP between left and right hemispheres was −0.12±0.69 ranging from −1.4±1.1 to 1.2±1.2 seconds. In group analysis, not comparing left and right but delayed and contralateral hemispheres, no statistically significant difference could be established for any channel. Linear correlation between consecutively acquired TTP maps ranged from 0.75 to 0.96 and was statistically significant in all cases ($P<1.1\times10^{-7}$). The interhemispheric difference in mean TTP varied by 0.0±0.31 seconds for consecutive measurements.

**Discussion**

Evaluation of cerebral hemodynamics in steno-occlusive disease of a major cerebral artery focuses on cerebral blood flow, cerebrovascular reserve capacity, and direct visualization of collateral flow using a variety of approaches. Whereas procedures based on transcranial Doppler/duplex sonography do allow for appraisal of a respective distribution territory as a whole, only tomographic imaging modalities can provide information about specific hemodynamic risk zones. Use of the latter modalities, however, is often precluded by either mere inaccessibility or patient-specific restrictions. Especially measurement of cerebral blood flow by use of freely diffusible
tracers like $^{15}$O-labeled water in positron emission tomography, the criterion standard, is not ubiquitously available. More prevalent techniques based on bolus application of an intravascular contrast medium, however, are prone to inaccuracies in the determination of cerebral blood flow. As a consequence, perfusion-related parameters like TTP, which can be determined from bolus dynamics in a numerically robust way, are increasingly used to characterize cerebral hemodynamics, an approach that was adopted here for analysis of multichannel NIRS.

In previous studies, bolus delay has been used to characterize different stages of hemodynamic compromise. Sobesky et al tested different TTP thresholds for identification of hypoperfusion as established by $^{15}$O-water positron emission tomography in 11 patients with acute ischemic stroke. They report a threshold value of 4 seconds relative to the unaffected hemisphere to correctly identify 84% of the hypoperfused and 77% of the normal perfused tissue. Using DSC MRI in 29 patients with proximal MCA occlusion, Hermier et al found an increase in TTP to be a potential marker for leptomeningeal flow. Likewise, using arterial spin labeling MRI, Bokkers et al observed delayed arrival of labeled arterial blood in the anterior frontal region in patients with carotid artery occlusion if leptomeningeal collaterals were present. Acquiring TTP maps by DSC MRI in 10 patients with steno-occlusive disease of a major cerebral artery, Schubert et al established a significant negative correlation between TTP and cerebrovascular reserve capacity as determined by xenon...
contrast-enhanced CT. Introducing a standardized TTP in analyzing DSC MRIs of patients with stenotic or occlusive disease of the internal carotid artery Nasel et al.24 found a significant prolongation of peak times only in the anterior and posterior border zones but not in the central vascular regions of the affected hemisphere.

Comparable studies using NIRS have yet been conducted using a maximum of 4 channels per hemisphere.5,6,25-27 Using one channel per hemisphere in 13 patients with severe unilateral acute ischemic stroke, Terborg et al.25 found an average increase of 5.1 seconds in TTP on the affected hemisphere. In a second study using the same device in 11 patients with acute infarction in the territory of the MCA, they found a close correlation between interhemispherical differences of TTP values obtained by DSC MRI and NIRS (r=0.86).3 Using 4 channels per hemisphere, Steinkellner et al.6 reported a mean bolus delay of 1.5 seconds on the affected hemisphere in 10 patients with acute unilateral ischemic stroke.

Whereas most of these studies address hemodynamic changes like penumbral and collateral flow in acute stroke, the aim of the present study was to assess alterations in the chronically affected patient. Because all patients were clinically asymptomatic at the time of investigation, hemodynamic effects were expected to be less pronounced but present. In agreement with this assumption, we find a mean increase of 0.43±0.6 seconds for TTP on the affected hemisphere. Only in one patient was mean TTP significantly increased on the unaffected hemisphere. However, in this patient, too, increased values of TTP toward the anterior border zone could be observed ipsilateral to the affected artery.

In contrast to previous studies using ICG NIRS, here 17 channels per hemisphere were used to access spatial patterns of induced hemodynamic effects, yet given the interindividual variability in territorial distribution of the major cerebral arteries, an allocation of observed hemodynamic changes to distinct zones is possible only to a limited extent.38,29 Nevertheless, our results do suggest that most pronounced hemodynamic effects induced by stenosis or occlusion occur in the peripheral distribution territory of the affected artery, that is, toward the border zone regions. Especially an increase of TTP toward the distribution territory of the anterior cerebral artery due to collateral flow would comply with results obtained in a previous study by Choi et al.30 In reviewing the digital subtraction angiography of 60 patients with symptomatic severe MCA stenosis, they identified 2 abnormal angiographic patterns: a shift of the anterior cerebral artery/MCA border zone toward the MCA territory and a dilatation of the MCA branches. Whereas the first pattern would correspond to results shown for Patients 1 and 8 in Figure 5, dilatation of the MCA branches and concomitant slow blood flow could explain increased TTP values in the central vascular region of the MCA in Patient 5. The underlying assumptions are consistent with the exhausted reserve capacity observed in this patient as opposed to the normal values found in Patients 1 and 8. The increase of TTP in the core distribution of the affected MCA in Patient 5 is also consistent with the low poststenotic systolic flow velocity found in this patient (Table). Consistency between TTP values determined by DSC MRI and ICG NIRS in Patient 5 further corroborates the potential value of NIRS in assessment of cortical hemodynamics. The modest correlation of 0.61 between these 2 modalities might be owed to imprecise spatial correlation between MRI and NIRS due to head movements during localization of the optodes. The simplified model used to describe the optical pathway between sending and receiving optodes not taking into account the individual anatomy might have introduced further inaccuracies.31 Finally, signal contamination by extracerebral compartments might influence TTP values determined by NIRS. However, by performing numeric simulations taking into account the blood volumes of intra- and extracerebral tissues, Mudra et al.32 could show that during first passage of the ICG bolus contribution of the extracerebral tissue should not exceed 30% of the optical density signal. Given the delayed arrival of contrast medium in the extracerebral tissue time courses of the optical density signal during the first passage should therefore primarily reflect intracerebral bolus dynamics.27

In 9 of 10 patients, mean TTP was increased on the hemisphere affected by steno-occlusion of the MCA although absolute differences between hemispheres were in the magnitude of lateral differences seen in the control group. In contrast to the latter, however, changes induced by steno-occlusion were statistically significant for certain channels as well as for mean TTP in group analysis.
In conclusion, results of the present study suggest that NIRS is sensitive to alterations in cortical hemodynamics induced by severe stenosis or occlusion of the MCA and therefore might provide clinical benefit for affected patients. A quantitative measure for its sensitivity to these alterations cannot be inferred from this study because cerebral hemodynamics might not be affected in all patients. Whether spatial patterns or absolute quantification of changes in TTP are indeed of prognostic value in this disease will ultimately have to be evaluated in a prospective study encompassing a larger patient population. Independent of this, high reproducibility of TTP assessment by ICG NIRS suggests its use in monitoring the hemodynamic status of patients.

Other perfusion-related parameters like maximum ICG concentration and bolus rise time, the ratio of which has been suggested as an index for cerebral blood flow in previous studies, might allow for a more specific assessment of cortical hemodynamics. Here, use of these parameters was abandoned because they showed poor reproducibility in consecutive measurements. Improved correction of the optical density signal for baseline drifts, which NIRS is prone to, might, however, resolve this technical problem. Also, it should be assessed to which extend other NIRS-specific artifacts limit applicability given that in 9 of the 29 individuals considered for enrollment into this study, bolus dynamics could not be recovered for at least one channel. Despite its limitations, NIRS could provide further criteria in evaluation of steno-occlusive disease as to the need for clinical intervention.

Disclosures

None.

References

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