Noninvasive Assessment of Cerebral Perfusion and Oxygenation in Acute Ischemic Stroke by Near-Infrared Spectroscopy

Christoph Terborg¹, c Klaus Gröschel¹, d Alexander Petrovitchb
Thomas Ringer¹ Sonja Schnaudigel¹, d Otto W. Witte¹ Andreas Kastrup¹, d

¹Department of Neurology, and b Institute of Diagnostic and Interventional Radiology, Friedrich Schiller University Jena, Jena, c Department of Neurology, Asklepios Klinik St. Georg, Hamburg, and d Department of Neurology, Georg August University of Göttingen, Göttingen, Germany

Abstract

Background: In acute stroke patients, there is a need for noninvasive measurement to monitor blood flow-based therapies. We investigated the utility of near-infrared spectroscopy (NIRS) to determine cerebral perfusion in these patients.

Methods: Eleven patients were investigated within 1.4 ± 2.2 days after onset of an ischemic middle cerebral artery infarction by monitoring the kinetics of an intravenous bolus of indocyanine green (ICG). For ICG kinetics, bolus peak time, time to peak (TTP = time between 0 and 100% ICG maximum), maximum ICG concentration, rise time (time between 10 and 90% ICG maximum), slope (maximum ICG/TTP), and blood flow index (BFI = maximum ICG/rise time) were obtained. Perfusion-weighted MRI (PWI) and NIRS measurements were performed within 24 h, and the interhemispherical differences of TTP values were compared.

Results: Stroke patients showed an increased bolus peak time (p < 0.02), TTP (p < 0.01), and rise time (p < 0.01), whereas slope (p < 0.01) and BFI (p < 0.01) were diminished at the site of infarction as compared to the unaffected hemisphere. The interhemispherical differences of TTP as measured by PWI and NIRS were closely correlated (r = 0.86). Conclusions: Noninvasive measurements of cerebral ICG kinetics by NIRS provide a useful means of detecting cerebral perfusion deficits in patients with acute stroke, which correlate well with those obtained by PWI.

Key Words
Near-infrared spectroscopy · Acute ischemic stroke · Cerebral perfusion · Perfusion-weighted imaging · Indocyanine green · Regional blood flow

Introduction

In the past few years, evidence has accumulated that the early restoration of cerebral blood flow (CBF) is a prerequisite for a favorable outcome in acute ischemic stroke [1–3]. Therapeutic reopening of an occluded cerebral vessel might prevent the progression of an ischemic infarction into the surrounding tissue at risk of infarction, the so-called penumbra. However, the time window for thrombolytic therapy is narrow and requires rapid logistics and decision making. The NINDS rtPA trial, for instance, used a 3-hour time window for thrombolytic therapy [4] and the recently published ECASS III trial shows a beneficial outcome within up to 4.5 h [5]. Thus,

C. Terborg and K. Gröschel contributed equally to this work.
only a minority of acute stroke patients are currently treated with rtPA. In addition to intra-arterial or intravenous rtPA, general supportive care including management of respiration, cardiac rhythm, arterial blood pressure, body temperature and glucose metabolism has therefore received increased attention and shown to prevent worsening of the neurological injury \[6–8\]. In particular, the elevation of blood pressure in acute ischemic stroke could achieve major importance in terms of increasing the penumbral CBF and improving the functional outcome as shown in small, uncontrolled studies \[9, 10\]. Until the completion of randomized trials a close monitoring of potential side effects on brain function and perfusion as well as of benefits from blood pressure-related therapies has recently been postulated \[11\].

However, CBF measurements with MRI or PET are time consuming and expensive and might therefore not be suitable for monitoring of acute stroke patients. In this scenario, near-infrared spectroscopy (NIRS) is an encouraging, noninvasive tool to study cerebral oxygenation and hemodynamics at the bedside. Animal studies measuring CBF with an intravenous bolus of indocyanine green (ICG) and NIRS have shown a high correlation between absolute blood flow measurements obtained with the radioactive microsphere technique and CBF values obtained noninvasively with ICG NIRS \[12\]. In a pilot study, we could recently demonstrate a reduced cerebral perfusion at the site of infarction in patients with acute ischemic stroke \[13\]. In addition to ICG NIRS, the advent of spatially resolved spectroscopy has provided a means to continuously measure cerebral blood oxygenation noninvasively with a good correlation to standardized methods \[14\]. Therefore, NIRS seems to be an ideal bedside tool to monitor cerebral oxygenation, as well as CBF in critically ill patients.

The aims of our study were to assess cerebral perfusion and tissue oxygenation in middle cerebral artery (MCA) infarction by NIRS and to compare these CBF values with perfusion-weighted MRI (PWI) data.

**Patients and Methods**

We noninvasively measured CBF and tissue oxygenation in both hemispheres of 11 patients (6 male, 5 female; mean age, 65.8 ± 12.4 years) with an acute infarction in the territory of the MCA by means of NIRS (NIRO 300, Hamamatsu Photonics KK, Japan). All patients were evaluated according to the National Institutes of Health Stroke Scale score at the time of the measurement, or, in ventilated patients, at the time before intubation. The site and extent of infarction was confirmed either by CT or MRI. In every patient, both the kinetics of an intravenous bolus of ICG (ICG-Pulsion, Pulsion Medical Systems, Munich, Germany) and tissue oxygenation were assessed by NIRS 1.4 ± 2.2 days after symptom onset.

The NIRS optodes were placed bilaterally on the scalp above the territory of the MCA using the 10-20 EEG system \[15\]. These locations corresponded to F3-F4. The interoptode distance was 4 or 5 cm depending on the individual light absorption. The NIRS device emits light at 4 distinct wavelengths (775, 810, 853, and 913 nm), and the photodetector collects the scattered light with a sample rate of 6 Hz. The study was performed in a quiet environment, and patients were in a supine position. ICG was injected rapidly into the antecubital vein through an 18-gauge catheter or into a central venous line with a mean dosage of 0.1 mg/kg body weight. A differential path length factor of 6 was adopted, and absolute
concentration changes of ICG from light attenuation were calculated according to a modified Beer-Lambert law with a commercial software (Hamamatsu Photonics KK, Japan) [12]. For off-line analysis, the bolus peak time, the time to peak (TTP, defined as time between 0 and 100% of the maximum ICG concentration), the rise time (defined as time between 10 and 90% of the maximum ICG concentration), the maximum ICG concentration (μmol/l), the slope (maximum ICG/TTP), and the blood flow index (BFI = ΔICG/rise time) were calculated for both hemispheres. Figure 1 shows a typical measurement.

Before each ICG measurement, mean values of the cerebral tissue oxygenation index (TOI) of each hemisphere provided by the NIRS device were obtained during an observation period of 1 min. PWI (1.5 T, MR-Vision and Sonata, Siemens, Erlangen, Germany) was performed within 24 h of the NIRS measurements using dynamic contrast-enhanced MRI with the following parameters: TR/TE = 1,440/43, flip angle = 90°, FOV = 230, matrix = 128 × 128, slice thickness = 5 mm, intersection gap = 2 mm. A bolus of 0.1 mmol/kg Gd-DTPA was injected followed by 20 ml normal saline during acquisition of 600 images. The perfusion images were processed to obtain TTP values from an elliptic region of interest below F3-F4 of the 10-20 system using the middle frontal gyrus as anatomical landmark with a diameter of 4 or 5 cm according to the distance of the NIRS interoptodes [15]. The interhemispherical differences of TTP assessed from both methods were compared.

All stroke patients who received a PWI protocol were consecutively and prospectively enrolled in this study. The protocol was approved by our Institutional Ethics Review Board, and informed consent was obtained from each patient or their relatives prior to the procedure.

Statistics
All values are given as means ± standard deviation. The differences of TOI and ICG kinetics between both hemispheres were calculated by a nonparametric, matched-pairs Wilcoxon test. The correlation between the interhemispherical differences of TTP assessed from ICG kinetics (NIRS) and from PWI was calculated by Pearson’s or Spearman’s formula. A value of p < 0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed with SPSS (version 12, SPSS Inc.).

Results
Clinical Characteristics
Seven patients had an infarction in the territory of the left MCA, and in 4 cases the right MCA was affected. In 3 patients, the anterior cerebral artery was additionally involved. The mean National Institutes of Health Stroke Scale score was 14.1 ± 4.7 (range, 7–21), and stroke volumes ranged between 30 and 100% of the territory of the MCA. The ipsilateral internal carotid artery was occluded in 3 cases, in 1 patient due to a nontraumatic arterial dissection. Significant carotid artery disease of the unaffected side was excluded by duplex sonography.

Cerebral Perfusion and Tissue Oxygenation Measurements
The values of the ICG kinetics are summarized in table 1. Most parameters of the cerebral ICG kinetics differed significantly between the site of infarction and the unaffected hemisphere. On the affected side, the TOI was lower than on the unaffected side; however, the difference was not statistically significant (table 1).

Correlation between ICG Kinetics and PWI
We found a close correlation between the interhemispherical TTP difference obtained with ICG NIRS and PWI measurements (r = 0.857; p = 0.001; fig. 2).

Discussion
Monitoring cerebral hemodynamics and oxygenation in patients with acute ischemic stroke might be crucial to prevent secondary ischemic damage in the peri-infarct tissue and subsequent clinical deterioration. In this sce-

Table 1. Comparison of cerebral ICG kinetics (means with standard deviations in parentheses) between the affected and unaffected hemisphere (matched-pairs Wilcoxon test)

<table>
<thead>
<tr>
<th>Variable</th>
<th>MCA infarction</th>
<th>Unaffected hemisphere</th>
<th>Wilcoxon p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus peak time, s</td>
<td>26.1 (8.9)</td>
<td>21.8 (6.8)</td>
<td>0.012</td>
</tr>
<tr>
<td>TTP, s</td>
<td>14.49 (5.6)</td>
<td>10.90 (4.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>Rise time, s</td>
<td>9.2 (3.7)</td>
<td>6.3 (2.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>ICG peak, μmol/l</td>
<td>0.056 (0.054)</td>
<td>0.063 (0.022)</td>
<td>0.084</td>
</tr>
<tr>
<td>Slope, μmol/l/s</td>
<td>0.0052 (0.0054)</td>
<td>0.0071 (0.0060)</td>
<td>0.004</td>
</tr>
<tr>
<td>BFI, μmol/l/s</td>
<td>0.0087 (0.0095)</td>
<td>0.0125 (0.0108)</td>
<td>0.003</td>
</tr>
<tr>
<td>TOI, %</td>
<td>58.5 (8.6)</td>
<td>61.0 (10.1)</td>
<td>0.374</td>
</tr>
</tbody>
</table>
nario, a simple test for this purpose is of major interest. Our study shows that the perfusion deficit in patients with acute MCA infarction can be measured noninvasively with NIRS. The interhemispherical TTP differences assessed with NIRS correlated well with those obtained by PWI.

Physiological variables of our patients were assumed constant during our measurements; however, as we focused our study on interhemispherical differences of perfusion and oxygenation, a major influence e.g. from differences in FiO2 seems negligible, as it would affect both hemispheres.

It has recently been proven that the semi-quantitative assessment of CBF by PWI correlates well with absolute regional blood flow measurements by PET, if a TTP threshold of 4–6 s as compared to the unaffected hemisphere is adopted [16, 17]. The clinical importance of the parameter TTP measured by PWI has recently been shown: TTP was the best predictor of both infarct growth and successful recanalization in thrombolytic therapy [18, 19]. In our study, we calculated cerebral ICG kinetics, e.g. TTP values from light attenuation of an intravenous bolus of the dye ICG by NIRS in patients with ischemic stroke and found a good correlation with corresponding indices of PWI. Whether TTP measurements by NIRS provide similar clinical information in patients with acute cerebral infarctions has still to be evaluated. Using a double indicator dilution technique from the jugular bulb with ICG and NIRS a reduced CBF was found in patients with acute hemispheric stroke with poor outcome, but this requires catheterization of the internal jugular vein and the spatial resolution is inferior to our technique [20].

In acute ischemic stroke, a reduction in CBF goes along with a local hemoglobin deoxygenation due to an increased oxygen extraction fraction, which characterizes the penumbral zone [17]. Recently, in hyperacute ischemic stroke an increased deoxymyoglobin level as well as an abnormal visualization of leptomeningeal veins were seen by T2*-based blood oxygen level-dependent MRI; these data may indicate an increased oxygen extraction fraction in the affected tissue characterizing the ischemic penumbra [21–23]. However, this encouraging metabolic MRI technique cannot be applied for continuous monitoring. Within our study, we did not find significant differences in cerebral tissue oxygenation in the affected hemisphere. This might be due to the limited sample size, the well-known influence from extracerebral tissue, and from a reopening of the occluded vessels over time. Furthermore, not all of our NIRS measurements were performed at the day of symptom onset, so that the results might underestimate the local decrease in tissue oxygenation as well as the perfusion deficit at the site of infarction. Further studies should consider the rapid time course of ischemic stroke.

There are several general limitations concerning the NIRS technique, as well as specific limitations to our study. First, the spatial resolution of conventional NIRS devices is poor, so that simultaneous measurements are restricted to a few positions. This means that we probably measured the hypoperfusion and tissue oxygenation of the infarct core as well as the penumbral zone. Second, skin blood flow has been shown to influence NIRS measurements, especially if the optodes are placed in the temporal region [24, 25]. This could explain the lack of correlation between ICG kinetics and rCBF measurements by the Xenon-133 clearance technique in neurosurgical patients [26]. On the other hand, animal studies comparing CBF measurements by ICG and NIRS with established methods showed a high correlation of the parameter BFI with those assessed by the radioactive microsphere technique, and CBF measurements by ICG kinetics in volunteers agreed with those assessed by PWI [12, 27]. Our result of a close correlation of ICG kinetics, e.g. the parameter TTP with corresponding PWI values, underlines these observations. Third, the penetration depth of NIRS in the reflection mode is only about 1 cm beneath the brain surface, so that oxygenation of deeper tissue, e.g. subcortical infarctions, cannot be assessed.

Fig. 2. Correlation between intraindividual TTP differences (seconds) from frontotemporal regions of interest in patients undergoing PWI and ICG NIRS (n = 11).
A good reproducibility of the parameter BFI as a relative measure of rCBF has been shown in healthy as well as in pediatric patients [29, 30] although an increased accuracy of CBF measurements by NIRS has recently been shown using a two-detector partial path length algorithm which reduces the influence of extracerebral contributions to the ICG kinetics [31]. In principal, time-resolved NIRS approaches could become useful to separate cerebral from extracerebral contributions to the ICG kinetics [32]. With this technique a significant delay in cerebral transit time has recently been found in patients with acute and chronic vessel occlusion but not in volunteers [33].

In conclusion, our study shows that in patients with ischemic stroke the perfusion deficit can be assessed by NIRS. This technique is easy to apply at the bedside, repeatable, reproducible, without toxic effects, and might be used to guide therapy in the early stages after symptom onset [30, 34]. Although transcranial Doppler and duplex sonography could theoretically also be used for this purpose, modern NIRS devices can assess cerebral perfusion (and tissue oxygenation) as the main target for therapeutic strategies in cerebrovascular diseases. Whether NIRS measurements in ischemic stroke might predict outcome and if NIRS monitoring can be used to guide therapy has to be shown in prospective studies.


