Tissue Oxygen Index
Thresholds for Cerebral Ischemia Using Near-Infrared Spectroscopy
Pippa G. Al-Rawi, BSc; Peter J. Kirkpatrick, FRCS (SN)

Background and Purpose—To date, the clinical application of near infrared spectroscopy in the adult brain has been limited. The NIRO 300 (Hamamatsu Photonics) provides a continuous measurement of tissue oxygen index (TOI) using spatially resolved spectroscopy. Although TOI reflects cerebral oxygenation to a high degree of sensitivity and specificity, to become a useful clinical tool, thresholds for cerebral ischemia need to be defined. This study has attempted to identify a quantifiable TOI threshold for ischemia in the adult brain.

Methods—One hundred sixty-seven patients undergoing carotid endarterectomy were studied. The NIRO 300 was incorporated into an established multimodal monitoring system enabling observations of cerebral hemodynamic changes under highly controlled conditions. Changes in TOI (% ΔTOI) on clamping the internal carotid artery were compared with intracranial blood flow (middle cerebral artery flow velocity) and cerebral function monitoring to identify and quantify periods of cerebral ischemia.

Results—Significant correlation was seen between changes in middle cerebral artery flow velocity and ΔTOI on clamping (r = 0.74, P < 0.0001). Thirty-one patients showed cerebral ischemia on internal carotid artery clamping as defined by a sustained fall in cerebral function monitoring. A threshold for % ΔTOI of −13 was identified, above which no patients showed any evidence of ischemia on clamping. This threshold provided 100% sensitivity and 93.2% specificity for patients satisfying the preset criteria for cerebral ischemia.

Conclusions—These data demonstrate the potential to identify TOI-quantified thresholds for cerebral ischemia in the adult brain and thus improve the clinical use of near infrared spectroscopy. Our observations have defined a drop in TOI (13%) that can be adopted as a threshold for severe cerebral ischemia with high sensitivity and specificity. (Stroke. 2006;37:2720-2725.)

Key Words: carotid endarterectomy ■ cerebral ischemia ■ near infrared spectroscopy ■ spatially resolved spectroscopy ■ tissue oxygen index

Optical methods based on near-infrared spectroscopy (NIRS) can be used to monitor hemodynamic variables in the clinical setting.1 Applications include monitors of fetal physiology,2–4 during cardiac surgery,5,6 muscle function,7–10 and neonatal,11 pediatric,12 and adult brain.13–19 A number of NIRS instruments are now available that detect changes in optical attenuation from several wavelengths of light, and although a variety of algorithms have been applied to attempt quantification, accuracy of these instruments remains a concern.

The NIRO 300 (Hamamatsu Photonics) provides a continuous online measurement of tissue oxygen index (TOI) using spatially resolved spectroscopy.20,21 We have previously determined that TOI reflects cerebral oxygenation to a high degree of sensitivity and specificity during carotid surgery,20 an indication that NIRS can show clinically relevant estimations of cerebral hemodynamic and oxygen changes in the adult head (Figure 1). However, there are no data currently available to correlate TOI change with absolute measures of cerebral blood flow and/or cerebral oxygenation; hence, quantification is difficult.

Defining thresholds for cerebral ischemia may be more fruitful. In this article, we have compared TOI with changes in signals from a cerebral function monitor (CFM) and transcranial Doppler ultrasonography during carotid artery crossclamping in an attempt to identify a threshold for ischemia in the adult brain.

Materials and Methods
Near-Infrared Spectroscopy
The principle for NIRS is that near infrared light (delivered through optodes placed on the skin) penetrates the scalp and brain tissue whereby scatter and absorption occurs within the various tissues layers. The concentration changes of the chromophores oxy-, deoxy-, and total hemoglobin are measured by a modified Beer-Lambert method. Calculation of the TOI depends on spatially resolved spectroscopy; TOI is defined as the ratio of oxygenated to total tissue hemoglobin.21,22
Method
The NIRO 300 was incorporated into an established multimodal monitoring system for patients undergoing carotid endarterectomy enabling observations of cerebral hemodynamic change under highly controlled conditions. During surgery, brief and variable degrees of cerebral ischemia occur during crossclamping of the internal carotid artery. Routine intraoperative monitoring of mean ipsilateral middle cerebral artery flow velocity (FV; SciMed), laser Doppler flowmetry (Moor Instruments Ltd), bilateral CFM (LectroMed UK Ltd), and mean arterial blood pressure has helped to characterize these changes.

The NIRO 300 probes were placed high on the ipsilateral forehead to avoid the temporalis muscle and sufficiently lateral from the midline to avoid the superior sagittal sinus. NIRS optodes were kept at a constant distance of 5 cm in a specialized rubber holder and secured to the skin with an adhesive sheet. In addition, the optode holder was secured still further by a crepe bandage around the head. The sampling time was set at 5 seconds. Sequential clamping of the external (ECA) and internal carotid arteries (ICA) was performed intraoperatively as previously described allowing a sufficient time interval (approximately 2 minutes) for stabilization of signals after each clamp application. Severe cerebral ischemia was defined as a persistent fall in CFM and a drop in mean flow velocity to <40% of baseline. Selective shunting was performed in the presence of either of these criteria.

Patients
After Local Research Ethics Committee approval and with informed consent, 167 patients (121 male and 46 female) undergoing elective carotid endarterectomy were studied. The mean age was 69 years (range, 44 to 86 years). Monitoring was applied after induction of anesthesia, when the patient entered the operating room. All patients underwent direct microscopic closure of the endarterectomized vessel with the exception of those patients who had very tortuous or small arteries when a selective patch repair was undertaken. Anesthesia was standardized and patients were maintained physiologically stable throughout the procedure.

Data Processing and Analysis
Data signals from all the monitored parameters were digitized and collected using specialized multimodality software. Maximum physiological stability is generally observed at the time of application of clamps rather than removal; therefore, data from this period were used for analysis. Values of mean arterial pressure, laser Doppler flowmetry, FV and TOI were averaged at baseline (before clamping but after completion of dissection) and over a 2-minute period immediately after ECA and ICA clamping. Changes in TOI (ΔTOI) on clamping the ICA were compared with intracranial blood flow (middle cerebral artery flow velocity [MCA FV]) and CFM to identify and quantify periods of cerebral ischemia. Data are given as mean±SD.

Figure 1. Graphic display of data obtained from a patient during elective carotid endarterectomy. The vertical lines demonstrate time of application of vascular clamps. ABP indicates mean arterial blood pressure; LDF, frontal cutaneous laser Doppler flow.
Results
Looking at the pooled data for all patients, the values obtained before and after clamping of the internal carotid artery are shown in Table 1. The mean baseline flow velocity (MCA FV) was 37.8 cm/second and the mean TOI was 68%. There was no significant change in mean arterial blood pressure seen with clamping. The mean percentage change in TOI from baseline to after ICA clamping (%ΔTOI) was −8.2 (±9.0).

Significant correlation was seen between changes in MCA FV and ΔTOI on clamping ($r = 0.74, P = 0.0001$).

Of the 167 patients, 31 (19%) showed severe cerebral ischemia on ICA clamping as defined by a sustained fall in ipsilateral cerebral function monitoring (Figure 2) and underwent selective shunting. We defined a %ΔTOI threshold of −13%, above which no patients showed any evidence of ischemia.

Below the threshold of −13%, 10 false-positive cases occurred. Six showed a fall in both flow velocity and TOI on clamping the ECA with a further drop on clamping the ICA (mean arterial blood pressure remaining stable). In one case, review of the data showed that the ECA clamp time was too brief to assess the extracranial contribution to the signal. In a further case, the calculated value of %ΔTOI (−13.6%) was very close to the defined threshold value of −13%. Finally, in the remaining 2 patients, a significant increase in FV occurred shortly after clamping the ICA, one being associated with a significant increase in blood pressure at the time of ICA clamping.

The threshold for %ΔTOI of −13 provided 100% sensitivity and 93.2% specificity for patients satisfying the preset criteria for cerebral ischemia (Table 2).

Discussion
Many established forms of neuromonitoring require technical expertise and experience in interpreting the results.30 Cerebral oximetry is an attractive alternative as a continuous, noninvasive measurement that is both safe and simple to apply. This study has addressed the issue of determining a threshold for ischemia when using NIRS for monitoring the adult brain. Our approach has been to sequentially clamp the ECA and ICA during carotid endarterectomy, allowing the opportunity to separate the intracranial and extracranial signal contribu-

Table 1. Summary of Baseline and Percent Change (%Δ) in Mean Flow Velocity (mFV; cm/sec), Mean Arterial Blood Pressure (mABP; mm Hg), and TOI (%) During Sequential Clamping

<table>
<thead>
<tr>
<th></th>
<th>Baseline (mean ± SD)</th>
<th>Post ICA Clamping (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOI (%)</td>
<td>68±8.96 (range, 46–93.6)</td>
<td>64.1±10.3 (range, 40.6–93)</td>
</tr>
<tr>
<td>FV (cm/sec)</td>
<td>37.8±13.18 (range, 17.2–76)</td>
<td>28.8±13.7 (range, 4.54–92.4)</td>
</tr>
<tr>
<td>mABP (mm Hg)</td>
<td>89.1±14.3 (range, 60.9–121)</td>
<td>89.3±17.2 (range, 53.4–114)</td>
</tr>
</tbody>
</table>

Figure 2. Scatterplot comparing percentage change in MCA flow velocity (%ΔFV) with percentage change in tissue oxygen index (%ΔTOI) from baseline to postapplication of ICA clamp for all 167 patients. Patients exhibiting a sustained fall in ipsilateral CFM marked as unfilled symbols.
Mean %ΔTOI (including those patients where TOI increased on clamping), was −8.2 and changes were closely correlated with ΔFV. In all patients who showed severe cerebral ischemia (n=31), ΔTOI fell by ≥13%. The sensitivity of %ΔTOI threshold of −13 was 100% (Table 2). However some cases (n=10) showed a fall in TOI in the absence of satisfying the criteria for severe critical ischemia, leading to a lower specificity of 93.2%. These findings were on a background of a stable blood pressure; hence, the divergences between ΔTOI and ischemic criteria require more complicated anatomic and physiological considerations.

Sensitivity to superficial tissue layers is a common limitation of noninvasive NIRS measurement. Intrapatient variability in head geometry accounts for many model-related systematic errors in the absolute measurements. However, by focusing on relative hemodynamic and oxygenation changes, we believe that such systematic errors are largely canceled out.

Sensitivity to superficial tissue layers is a common limitation of noninvasive NIRS for the adult brain. However, we have previously shown that the NIRO 300 TOI measurement reflects adult intracranial brain tissue oxygenation to a high degree of sensitivity and specificity. When a fall in both FV and TOI was seen on clamping the ECA, this probably reflects reverse flow from ECA to ICA through extracranial to intracranial collaterals. Thus, clamping the ECA will affect both cranial and intracranial blood compartments, augmenting ΔTOI. When there is a lack of correlation between TOI and FV, which cannot be explained by the presence of simple EC-IC collaterals, or by arterial blood pressure instability, complex vascular anatomy may be accountable. A more robust anterior hemispheric contribution from the anterior cerebral artery with crossflow through the anterior communicating artery has already been shown to influence the chances of severe cerebral ischemia during carotid clamping and serves to contaminate the relationship between ΔTOI and ΔFV, the latter being a pure MCA derivative.

Cerebral oxygenation measured by NIRS may be influenced by changes in cerebral blood flow, cerebral metabolism, arterial saturation, and hematocrit. However, arterial saturation was over 99% in each case and because there was no blood loss, it is unlikely that hematocrit changed during the surgery up until the point of crossclamping. Likewise, patients were maintained under stable anesthesia so we consider changes in cerebral metabolic rate unlikely to influence the observations.

The difficulty in defining the “normal range” of cerebral oxygenation remains. In adults, normal TOI values have been reported to range from 65% to 85%. Although a number of authors have compared NIRS with other techniques such as jugular bulb oxygen saturation (SjO2), transcranial Doppler ultrasonography and somatosensory-evoked potential or with neurologic events, few have attempted to define an absolute threshold for ischemia. Most studies of this type using NIRS make no attempt to correct for extracranial contributions to signal changes. Of those who have tried to identify a threshold, the results show a low sensitivity and specificity. Furthermore, given the low incidence of clamp-related ischemia in carotid surgery, a large number of patients need to be studied to obtain sufficient power. Very few studies have achieved this.

In a study of 317 patients undergoing carotid endarterectomy, Beeke et al compared somatosensory-evoked potential with regional oxygen saturation (rSO2; INVOS 3100A) to detect severe cerebral ischemia requiring shunt placement. A significant decrease in rSO2 was seen in patients both with and without loss of cortical somatosensory-evoked potential. Although the difference between the decreases seen in the 2 groups was highly significant; they were unable to determine a threshold resulting from individual variability of both the rSO2 and the derived changes.

A more recent study of 594 patients undergoing carotid endarterectomy aimed to determine whether NIRS could be used to determine the need for shunt placement. Using the INVOS 3100-A and INVOS 4100-SSA, a drop of ≥20%ΔrSO2 was defined as clinically relevant. The sensitivity and specificity for this threshold was 30% and 98%, respectively. In both these studies, however, no attempt was made to determine the ECA contribution to the signal.

In conclusion, the NIRO 300 provides a measure of cerebral oxygenation that can be monitored during carotid surgery. Relative changes in TOI correlated well with FV. Our observations have defined a drop in TOI (13%) that can be adopted as a threshold for severe cerebral ischemia with high sensitivity and specificity. Confirmation that these findings apply in different clinical scenarios is needed, however, especially those where scalp swelling (eg, trauma, postcraniotomy) is present.

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Disclosures
None.

References

TABLE 2. Contingency Table of Sustained Fall in CFM by Change in ΔTOI >−13% on ICA Clamping*

<table>
<thead>
<tr>
<th>ΔTOI</th>
<th>Fall in CFM</th>
<th>No Fall in CFM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤−13%</td>
<td>31</td>
<td>10</td>
<td>41</td>
</tr>
<tr>
<td>&gt;−13%</td>
<td>0</td>
<td>126</td>
<td>126</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>136</td>
<td>167</td>
</tr>
</tbody>
</table>

*Sensitivity of ΔTOI to detect cerebral ischemia (at threshold of %ΔTOI ≤−13%)=100% and specificity=93.2%.


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