Transcranial Doppler and Near-Infrared Spectroscopy Can Evaluate the Hemodynamic Effect of Carotid Artery Occlusion

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Background and Purpose—Cerebral hemodynamic and metabolic changes can compensate for the decrease in cerebral blood flow occurring in patients with carotid occlusive disease. At present, a complete assessment of the cerebral adaptive status is only possible with positron-emission tomography. Near-infrared spectroscopy (NIRS) is a noninvasive technique that, providing a real time assessment of fluctuations in cerebral hemoglobin, has been used to estimate the cerebral blood volume and to measure cerebral vasomotor reactivity (VMR). Moreover, NIRS technology, by allowing the absolute measurement of absorption and scattering coefficients of brain, can determine the oxyhemoglobin and deoxyhemoglobin concentrations in situ in the blood stream.

Methods—In order to evaluate different aspects of the cerebral hemodynamic status, 27 subjects with symptomatic and asymptomatic carotid artery occlusion and 30 healthy subjects underwent a simultaneous examination by means of transcranial Doppler (TCD), able to reliably detect collateral circulation and VMR, and NIRS at rest condition and during CO2 reactivity test.

Results—The main finding of this study was the demonstration of a difference between asymptomatic and symptomatic patients in terms of mean flow velocity increase (52.4% versus 21.0%; \( P < 0.001 \)) estimated by TCD and of hemoglobin saturation increase measured by NIRS (6.8% versus 3.8%; \( P = 0.015 \)).

Conclusions—The opportunity to perform NIRS and TCD simultaneously provides useful information about both hemodynamic and metabolic cerebral adaptive status in patients with occlusive disease in a simple, noninvasive, and reliable way. (Stroke. 2004;35:64-72.)

Key Words: carotid artery occlusion ■ hemodynamics ■ spectroscopy, near-infrared ■ stroke ■ ultrasonography, Doppler, transcranial

Several studies demonstrated that hemodynamic factors can be considered as independent risk factors for stroke occurrence in patients with carotid occlusive disease.1,2 There is also evidence that hypoperfusion and embolism often coexist in the pathogenesis of ischemic stroke.3

The combined hemodynamic and metabolic effect of an occlusion of the internal carotid artery (ICA) on distal circulation was previously categorized into 3 stages.4 A good collateral circulation can determine normal cerebral hemodynamics in patients with carotid occlusive disease (stage 0). When collaterals are not adequate, the perfusion pressure distal to the lesion begins to fall, producing reflex dilatation of arterioles in order to maintain normal blood flow (stage I). When this autoregulatory vasodilatation fails to occur, cerebral blood flow (CBF) begins to fall. In this situation, the brain can increase the amount of oxygen it extracts from the blood (oxygen extraction fraction [OEF]) to maintain normal cerebral oxygen metabolism. This stage II of hemodynamic compromise has been named misery perfusion and increased OEF, estimated by means of positron-emission tomography (PET) investigation, must be considered an independent predictor of stroke in patients with carotid occlusion.5 Recently, this sequence of hemodynamic and metabolic events was revised by the same authors after the demonstration that an increased OEF can occur even in the presence of normal cerebral blood volume (CBV), indicating the absence of an exhausted vasodilatation.6 Patients with this latter hemodynamic status had a better prognosis than those with an increased CBV that is associated with an arteriolo-capillary dilatation. These data suggest the importance of a complete evaluation of the cerebral adaptive processes in patients with...
carotid occlusion for a reliable definition of their prognosis. A full evaluation of the metabolic and hemodynamic changes occurring distally to a carotid occlusion can be obtained by means of PET investigation. Unfortunately, mainly due to its high costs, this technique is not so available to be recommended for a wide clinical employment.

Transcranial Doppler (TCD) follow-up studies showed the importance of both collaterals and cerebral vasomotor reactivity (VMR) on the outcome of patients with ICA occlusion. Information obtained with TCD is obviously limited to the hemodynamic aspects of the cerebral adaptive processes.

Near-infrared spectroscopy (NIRS) is a noninvasive technique deriving information about the concentrations and the oxygenation of hemoglobin (Hb) from the measurements of light backscattered from the brain. When using this technique, small changes in light intensity are almost proportional to the variations of total hemoglobin concentration. Changes in concentration of hemoglobin are directly proportional to the variation of regional blood volume. NIRS, providing a real-time assessment of fluctuations in cerebral hemoglobin, has been used to estimate the CBV and to measure the cerebral VMR. Moreover, NIRS technology, through the measurement of the concentrations of oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb), allows determination of the oxygen saturation of the blood in situ in a simple and noninvasive way.

Our aim in this study was to explore the possibility of obtaining a reliable and satisfactory evaluation of the adaptive processes occurring in patients with ICA occlusion by means of TCD and NIRS simultaneous examination.

Method

NIRS Measurements

NIRS measurements were carried out with an ISS Oximeter (Model 96208 Two-channel Non-Invasive Tissue Oximeter, ISS Inc). The ISS Oximeter allows the measurement of oxygenated and deoxygenated hemoglobin concentrations in tissue. The device works by injecting near-infrared light into tissue at 4 known distances (2, 2.5, 3, and 3.5 cm, respectively) from an optical fiber collecting the backscattered light. Light of 2 different wavelengths (750 and 825 nm), produced by solid-state lasers, is used. Light is modulated at a frequency of 110 MHz to allow the measurements of phase and modulation of the collected light. From these raw data the absorption and scattering coefficients of the medium are determined. Once the absorption and scattering are determined, the assumption that hemoglobin is the only significant absorber is applied and the oxygenated and deoxygenated hemoglobin concentrations are calculated.

The ISS Oximeter uses the theory of photon migration through highly scattering media. This method allows the absolute measurement of absorption and scattering in a highly scattering medium such as human tissue. Since the ISS Oximeter measures the absorption and scattering of tissues directly, it does not require any calibration, estimation, or assumption about scattering in order to make an accurate measurement of absorption and hence of the hemoglobin concentrations. Therefore, this technology provides a noninvasive system for the determination of the oxy-Hb and deoxy-Hb concentration in the analyzed volume.

From the concentration of the oxy and deoxy species, the hemoglobin saturation (oxygen%) and the total hemoglobin content (THC) can be obtained, respectively:

\[
\text{oxygen\%} = \frac{[\text{oxyHb}]}{[\text{oxyHb}]+[\text{deoxygenHb}]} \times 100
\]

\[
\text{THC} = [\text{oxyHb}]+[\text{deoxygenHb}]
\]

Oxygenated, deoxygenated, and total hemoglobin (THC) concentrations are expressed in micromoles.

Subjects and Methods

We enrolled in the present study 27 subjects (21 men and 6 women; mean age, 69.6±8.9 years) suffering from an occlusion of the ICA. Carotid artery disease was assessed and defined by color-coded duplex sonography (Aspen Acuson) in our neurosonology laboratory according to the standardized criteria. All patients underwent a careful neurological and cardiological examination, ECG, transthoracic or transesophageal echocardiography, and brain CT scan or MRI. Moreover, complete blood chemistries and a clinical history were obtained from each patient.

Out of the 27 patients, 13 were symptomatic in the vascular territory of the middle cerebral artery (MCA) ipsilateral to the carotid artery occlusion. Of these, 4 had suffered a transient ischemic attack (TIA) and 9 presented a functionally independent or minor stroke (Rankin scale score, 1 to 2). All these patients were selected from subjects coming to our department for a 6-month follow-up clinical and instrumental evaluation after a first stroke or TIA. In the same period, 14 subjects with asymptomatic carotid occlusion were also enrolled. These were undergoing ultrasonographic examination in our outpatient department and had been referred to us by their general practitioner for suspected carotid stenosis.

Exclusion criteria were a stenosis contralateral to ICA occlusion >50%, a significant alteration of the vertebral arteries, and cardiac failure or rhythm disturbances. The choice of these exclusion criteria was aimed to avoid interference with the hemodynamic effects of the carotid occlusion.

In order to identify “normal” TCD and, particularly, NIRS parameters with respect to “pathological” ones, a group of 30 healthy subjects was also enrolled (14 men and 16 women; mean age, 63.9±8.2 years). They were selected from asymptomatic subjects referred by their general practitioner for periodic clinical and instrumental evaluation as part of vascular primary prevention.

Ultrasonographic examinations of the cerebral vessels performed on these subjects in our outpatient department excluded any vascular stenosis.

Examination of vessels of the circle of Willis was performed by means of transcranial Doppler (MultiDop T TCD instrument, DWL Elektronische Systeme GmbH) as described by Aaslid et al. The patency of major collateral vessels—namely ophthalmic (OA), anterior (ACoA), and posterior (PCoA) communicating arteries—was also evaluated.

All subjects underwent a simultaneous examination by means of TCD and NIRS at rest condition and during cerebral VMR test. Cerebral VMR to hypercapnia was evaluated by means of CO reactivity test. During the experiments, end-tidal expiratory CO was measured by means of a capnometer (Drager Capnomid). Mean arterial blood pressure (mABP) was monitored by means of a blood pressure monitor (2300 Finapress, Ohmeda). The study was carried out in a quiet room, with patients lying in a comfortable supine position, without any visual or auditory stimulation. Two TCD dual 2-MHz transducers fitted on a headband and placed on the temporal bone windows were used so as to obtain a bilateral continuous measurement of mean flow velocity (MFV) in the MCAs sonicated at a depth of 50±4 mm. Once the signals recorded became stable, MFV and end-tidal CO at rest were obtained through the continuous recording of a 60-second period of normal room air breathing. Hypercapnia was induced by the inhalation of a mixture of 7% CO/air, and patients breathed through the mask until MCA velocity became stable. Once equilibrium was reached, a further 30-second recording was made at this stage (plateau period). The maximal vasodilatory range or reactivity to 7% CO was determined by the percentage increase in MCA velocity occurred during the administration of 7% CO.
The 2 near-infrared optodes, each consisting of 4 light-source fibers and 1 light-collecting fiber, were placed in 2 symmetrical points on the frontal region of the 2 hemispheres and fixed with the headband above.

Each experiment consisted of 3 consecutive periods, ie, a 60-second rest period, the 90-second CO2 inhalation period—always including for each patient the 30-second plateau period both for MFV and NIRS response—and, finally, the 90-second recovery period. Each experiment described above was repeated at least 3 times, at 10-minute intervals at least. The baseline value was taken as the average of the rest period (60 seconds). The CO2 value was the average of the plateau period of 30 seconds. Data from the 3 experiments were averaged for each patient.

CO2 reactivity values both for TCD and NIRS were obtained as described after 90 seconds of CO2 inhalation according to the following formula:

\[
VMR = \frac{\text{Value}_{\text{CO2}} - \text{Value}_{\text{Baseline}}}{\text{Value}_{\text{Baseline}}} \times 100
\]

For TCD recordings, VMR was considered as the relative change in values of MFV. For NIRS recordings, VMR was considered as the relative change in values of THC, oxygen%, oxy-Hb, and deoxy-Hb. When calculating VMR as the maximal vasodilatory response, the percentage increases are not divided by the changes in end-tidal CO2; however, in order to reduce the intersubject variance, we also normalized VMR values with respect to the changes in end-tidal CO2. Values of end-tidal CO2 were not different among the 3 groups considered [F(2,54)=1.33; P=0.272]; their percentage increases at the end of hypercapnia induced by the inhalation of the 7% CO2/air mixture were 38.8±8.0 in healthy subjects, 42.3±9.4 in asymptomatic patients, and 37.5±6.3 in symptomatic ones.

The study was approved by the local ethics committee. Each subject gave informed written consent.

**Statistical Analysis**

Comparisons among symptomatic patients, asymptomatic ones, and healthy subjects were evaluated by means of analysis of variance (ANOVA, followed by Tukey's post-hoc comparisons) and \(\chi^2\) test as appropriate. When the data distribution was not Gaussian-shaped and/or standard deviations were not homogeneous in the 3 groups (such as in the case of percent increases), ANOVA was applied also after appropriate mathematical transformation (ie, square root was applied to percentages), in order to verify the robustness of the findings. However, for the sake of clarity, means and standard deviations of untransformed data are reported in tables.

In order to verify the correlation between increments of blood flow velocity and total hemoglobin, Pearson’s \(r\) was used.

ANOVA for repeated measures with stimulus (within-subjects factor; before and after CO2 inhalation), side (within-subjects factor; occluded and contralateral), and group (between-subjects factor; healthy, symptomatic, and asymptomatic subjects) was applied to measure their effects on each considered parameter. Since no interhemispheric difference was found in healthy subjects, in order to perform balanced analysis, we arbitrarily aligned the left hemisphere data to the occluded side of patients and, consequently, the right hemisphere to the contralateral one. However, we also verified the robustness of our findings after the opposite alignment.

**Results**

As shown in Table 1, there was no statistically significant differences in baseline characteristics and risk factors between asymptomatic and symptomatic patients. The only exception was diabetes, since the only diabetic patients were in the symptomatic group; also hypertension was slightly different across patients’ groups. Thus, we verified each ANOVA model after adjusting for diabetes and hypertension. Since a strict overlap was found, we did not mention them any more. Neither the collaterals number nor the contralateral stenosis were different between groups.

Concerning TCD and NIRS parameters, descriptive statistics of healthy subjects and patients are reported in Table 2A (baseline) and in Table 2B (percentage increases). Significant differences were observed when comparing patients with the control group, the latter presenting higher MFV and THC with respect to the occluded side of both patients’ groups and higher THC with respect to the contralateral side of symptomatic patients. None of the parameters in rest condition resulted to be significantly different in the 2 groups of patients (Table 2A). Also, the oxy-Hb and deoxy-Hb were not significant (values not shown).

ANOVA for repeated measures allowed us to better understand the interactions between clinical condition and cerebral hemodynamic/metabolic parameters, evaluated by TCD and NIRS.

As a confirmation of previous studies,22 VMR increase estimated by TCD was larger in the asymptomatic than in the symptomatic group, while no differences were found between healthy and asymptomatic group [interaction stimulus×group: \(F(2,54)=26.035, P<0.001, \text{Table 2B} \) (Figure 1)]. Even when MFV% increase was normalized dividing by the percent changes in end-tidal CO2 the only significant differences were between symptomatic (0.56±0.35) and both healthy (1.29±0.37) and asymptomatic subjects (1.21±0.47).

Before submitting NIRS data to a similar ANOVA, we verified the relationship between blood flow velocity measured by TCD and total hemoglobin estimated by NIRS. Figure 2 represents the scatter plots between MFV and square root of THC increases in the occluded side of patients and in the left side of healthy subjects (very similar results was obtained when right side of controls was considered). Pearson’s \(r\) correlation coefficients resulted equal to 0.61 \((P=0.001)\) and 0.49 \((P=0.006)\), respectively. The slope of the 2 relationships were statistically parallel, according to the lack of interaction \(\text{MFV×group} \ [F(1,53)=0.078; P=0.781]\). In the whole sample, we obtained an \(R^2\) of approximately 0.34, indicating that the 34% of the variability of THC increase is accounted for by VMR (MFV increase). Therefore, the correlation between the 2 parameters, even though

**TABLE 1. Patients’ Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic (n=13)</th>
<th>Symptomatic (n=14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69.8 (8.7)</td>
<td>69.4 (9.5)</td>
<td>0.924</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11/2</td>
<td>10/4</td>
<td>0.410</td>
</tr>
<tr>
<td>Hypertension</td>
<td>54%</td>
<td>86%</td>
<td>0.070</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0%</td>
<td>29%</td>
<td>0.003</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>38%</td>
<td>21%</td>
<td>0.333</td>
</tr>
<tr>
<td>Smoking</td>
<td>69%</td>
<td>64%</td>
<td>0.785</td>
</tr>
<tr>
<td>Collaterals No.</td>
<td>1.7 (0.6)</td>
<td>1.4 (0.5)</td>
<td>0.136</td>
</tr>
<tr>
<td>Contralateral stenosis</td>
<td>0-6 (46.2%)</td>
<td>8 (57.1%)</td>
<td></td>
</tr>
<tr>
<td>≤30%</td>
<td>5 (38.5%)</td>
<td>5 (35.7%)</td>
<td></td>
</tr>
<tr>
<td>40%-50%</td>
<td>2 (15.4%)</td>
<td>1 (7.1%)</td>
<td>0.728</td>
</tr>
</tbody>
</table>
These considerations could justify the different findings obtained when ANOVA was applied on VMR and THC. In fact, when considering absolute values of THC, both in a rest condition and after stimulus, in the 3 groups the significant group×stimulus interaction \( [F(2, 54) = 3.756; P = 0.030] \) was due only to the control group, where higher THC increase

### TABLE 2. Baseline Values and Percentage Increases in Healthy Subjects, Asymptomatic Patients, and Symptomatic Patients

<table>
<thead>
<tr>
<th></th>
<th>H (n=30)</th>
<th>A (n=13)</th>
<th>S (n=14)</th>
<th>ANOVA (After Square Root Transformation)</th>
<th>Significant Tukey's Post-Hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Baseline</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MFV occluded side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>61.1</td>
<td>48.5</td>
<td>41.8</td>
<td>12.37</td>
<td>0.000 H-A, P=0.013</td>
</tr>
<tr>
<td>SD</td>
<td>14.0</td>
<td>13.6</td>
<td>10.1</td>
<td></td>
<td>H-S, P&lt;0.001</td>
</tr>
<tr>
<td>MFV contralateral side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>61.0</td>
<td>53.2</td>
<td>51.1</td>
<td>2.93</td>
<td>0.062</td>
</tr>
<tr>
<td>SD</td>
<td>13.6</td>
<td>20.1</td>
<td>12.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen% occluded side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>69.3</td>
<td>67.1</td>
<td>71.5</td>
<td>1.27</td>
<td>0.289</td>
</tr>
<tr>
<td>SD</td>
<td>6.8</td>
<td>6.5</td>
<td>8.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen% contralateral side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>68.9</td>
<td>64.2</td>
<td>70.2</td>
<td>2.91</td>
<td>0.063</td>
</tr>
<tr>
<td>SD</td>
<td>6.6</td>
<td>8.9</td>
<td>6.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC occluded side</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>46.2</td>
<td>35.5</td>
<td>36.1</td>
<td>7.64</td>
<td>0.001 H-A, P=0.006</td>
</tr>
<tr>
<td>SD</td>
<td>11.9</td>
<td>6.1</td>
<td>7.4</td>
<td></td>
<td>H-S, P=0.008</td>
</tr>
<tr>
<td>THC contralateral side</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>44.0</td>
<td>36.9</td>
<td>34.2</td>
<td>4.45</td>
<td>0.016 H-S, P=0.018</td>
</tr>
<tr>
<td>SD</td>
<td>12.9</td>
<td>6.7</td>
<td>9.6</td>
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</tr>
<tr>
<td><strong>B. Percentage increases</strong></td>
<td></td>
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<tr>
<td>MFV occluded side</td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>50.3</td>
<td>52.4</td>
<td>21.0</td>
<td>16.03</td>
<td>0.000 S-H, P&lt;0.001</td>
</tr>
<tr>
<td>SD</td>
<td>18.5</td>
<td>25.0</td>
<td>13.2</td>
<td></td>
<td>S-A, P&lt;0.001</td>
</tr>
<tr>
<td>MFV contralateral side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>51.3</td>
<td>56.5</td>
<td>40.9</td>
<td>2.30</td>
<td>0.110</td>
</tr>
<tr>
<td>SD</td>
<td>17.4</td>
<td>24.6</td>
<td>15.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen% occluded side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.6</td>
<td>6.8</td>
<td>3.8</td>
<td>5.47</td>
<td>0.007 S-H, P=0.008</td>
</tr>
<tr>
<td>SD</td>
<td>3.3</td>
<td>3.1</td>
<td>2.7</td>
<td></td>
<td>S-A, P=0.025</td>
</tr>
<tr>
<td>Oxygen% contralateral side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.4</td>
<td>10.3</td>
<td>5.7</td>
<td>3.59</td>
<td>0.034 S-A, P=0.026</td>
</tr>
<tr>
<td>SD</td>
<td>3.3</td>
<td>7.2</td>
<td>3.5</td>
<td></td>
<td></td>
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<tr>
<td>THC occluded side</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.0</td>
<td>2.6</td>
<td>2.1</td>
<td>3.01</td>
<td>0.058</td>
</tr>
<tr>
<td>SD</td>
<td>3.1</td>
<td>1.9</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC contralateral side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.1</td>
<td>4.2</td>
<td>3.1</td>
<td>1.17</td>
<td>0.318</td>
</tr>
<tr>
<td>SD</td>
<td>2.5</td>
<td>2.7</td>
<td>1.9</td>
<td></td>
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</tbody>
</table>

A: Baseline values of mean flow velocity (MFV) in the middle cerebral arteries, of oxygen%, and of total hemoglobin concentration (THC) in the left and right sides of healthy subjects (H) and in the ipsilateral and contralateral sides to the internal carotid occlusion of asymptomatic (A) and symptomatic patients (S).

B: Percentage increases of MFV, oxygen%, and THC from normocapnia to hypercapnic condition. MFV is expressed in centimeters per second and THC in micromoles. For healthy subjects, the occluded side corresponds to the left side and the contralateral to the right side.
was found. Indeed, when asymptomatic and symptomatic patients were compared, the only factor inducing a THC change resulted to be the CO2 inhalation [stimulus effect: $F(1,25) = 27.514; P = 0.001$]. Both group and group $\times$ stimulus terms did not reach the statistical significance. Considering the ratio [(MFV% increase)/(end-tidal CO2 % change)], similar findings were observed, with only a slight difference between healthy and symptomatic patients (Tukey’s $P = 0.060$).

Regarding the hemoglobin saturation (oxygen%) increase, a significant difference among increases in healthy, asymptomatic, and symptomatic subjects was found [group $\times$ stimulus effect; $F(2,54) = 4.55; P = 0.015$], with the oxygen% increase in symptomatic patients being significantly lower than in the other groups (Tukey’s $P = 0.019$ versus healthy, $P = 0.044$ versus asymptomatic patients) (see Figure 3). In addition (Table 2B), it should be noted that oxygen% increase in the occluded side was 1.8 higher in the asymptomatic patients than in the symptomatic ones (6.8% versus 3.8%). Even after dividing oxygen% increase by the percent changes in end-tidal CO2, similar findings were obtained, with the only significant differences between symptomatic (0.10 $\pm$ 0.06) and both healthy (0.17 $\pm$ 0.06) and asymptomatic subjects (0.16 $\pm$ 0.08).

As shown in Table 2B, parallel patterns of significant differences were found for MFV and oxygen% increases, and their correlation was verified. Pearson’s $r$ index resulted equal to 0.57 ($P < 0.001$), without differences among the 3 groups. The positive slope coefficient indicated that an increase in blood flow is associated with an increase in oxygen% (Figure 4). After taking into account CO2 increase, the Pearson’s correlation decreased but remained statistically significant ($r = 0.42; P = 0.001$).

**Discussion**

This study demonstrates that, thanks to the simultaneous performance of TCD and NIRS, it is possible to obtain useful information about both hemodynamic and metabolic cerebral adaptive status in the presence of carotid occlusive disease. In particular, TCD examination can reveal the anatomic supply from collateral vessels, and the 2 techniques together are able to support a complementary assessment of cerebral VMR. In fact, TCD is able to test CBF changes, while NIRS can estimate the total hemoglobin concentration as a measure of CBV. Moreover, by measuring oxy-Hb, deoxy-Hb, and, therefore, total Hb concentrations, NIRS technology allows quantifying the hemoglobin oxygen saturation (oxygen%)
changes in the CBV considered. The main finding of the present study is that NIRS parameter hemoglobin saturation, as well as VMR evaluated by TCD, is able to discriminate symptomatic from asymptomatic patients suffering from carotid occlusive disease, suggesting a major extent of both hemodynamic and metabolic compromise in patients with a previous cerebral ischemic event with respect to subjects with never symptomatic carotid occlusion. Moreover, the 2 parameters strongly correlate, indicating less increase in cerebral blood flow is associated with less increase in oxygen%.

The value of hemoglobin saturation at rest was slightly higher in the symptomatic than in both the asymptomatic and healthy groups. If further and larger studies confirm this finding, we will be able to consider it as a metabolic marker identifying symptomatic patients with carotid occlusive disease. However, at the moment the lower hemoglobin saturation value at rest in symptomatic patients could also be explained by a relatively increased extracerebral signal contribution through extracranial collaterals. So far, a persisting concern with NIRS is the extent to which light is attenuated by the extracerebral tissues as different studies showed controversial findings about this issue. However, it was demonstrated that the extracranial contamination does not appear to be significant during CO$_2$ reactivity test, since the recorded changes in the cutaneous blood flow are small.

The importance of hemodynamic factors in the pathogenesis of stroke has been repeatedly described. Positron emission tomography studies demonstrated that an increased OEF is associated with prior ischemic events, and it can be considered as an independent risk factor for stroke occurrence in patients with carotid occlusion. Recently, it was demonstrated that the simple measurement of OEF does not support complete information about the cerebral adaptive status, and it is not fully able to define the risk of subsequent stroke in the presence of carotid occlusion. As a matter of fact, patients with increased OEF can show a different prognosis according to the presence of normal or increased CBV. The highest risk is defined by the presence of an increased CBV, suggesting that pronounced vasodilation due to exhausted autoregulatory mechanism plays an important role in the pathophysiology of stroke occurrence. These data suggest the need for a global assessment of the cerebral hemodynamic and metabolic status for a complete and exhaustive evaluation of the risk in patients with carotid occlusive disease.

At present, such evaluations are only possible through PET. The most important problem for a widespread PET use in clinical practice is its being an invasive technique whose costs strongly reduce its availability outside a research context.

In the second half of the last decade, NIRS was introduced to evaluate the cerebral blood volume. In particular, Smielewski et al demonstrated that NIRS can be considered a reliable and alternative technique to investigate VMR in patients with carotid occlusive disease. Moreover, a study simultaneously performing NIRS and TCD on patients with carotid occlusion showed that the 2 techniques are able to provide complementary data on CBF and VMR at different depth in a completely noninvasive way, i.e., TCD by measuring flow velocity changes in the MCA, and NIRS by revealing cortical arterioles and capillaries CBV modifications.

In this study, NIRS was used to estimate the total hemoglobin concentration and, consequently, the hemoglobin saturation in the regional CBV in both rest and after hypercapnic challenge conditions in order to obtain a metabolic parameter able to differentiate patients with carotid artery occlusion. Our findings suggest that oxygen% increase, being strongly correlated to VMR in discriminating symptomatic from asymptomatic subjects, can represent a useful marker of cerebral metabolic supply to consider when evaluating stroke risk in patients with carotid disease.

The opportunity to perform NIRS and TCD together allowed us to have more complete information about the cerebral metabolic and hemodynamic status in patients with carotid occlusive disease. Of course, it is not possible at the moment to postulate our approach capability to replace PET, and in particular OEF parameter, in studying the cerebral hemodynamic and metabolic status. However, for clinical purposes the possibility of having at disposal simple, noninvasive, and not expensive methods to investigate different aspects—namely metabolic and hemodynamic, strongly correlated—of the cerebral adaptive changes could represent an important advantage.

On the basis of the encouraging results emerging from our preliminary investigation, we suggest the usefulness of prospective studies on a larger number of patients to assess whether the impairment in cerebral hemodynamic and metabolic parameters detected with TCD and NIRS in patients with symptomatic ICA occlusion can be identified as a prognostic risk factor for a subsequent stroke.

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Cerebral Near-Infrared Spectroscopy: How Far Away From a Routine Diagnostic Tool?

Pathophysiological events in cerebrovascular disorders are heterogeneous, e.g., the consequences of a carotid stenosis on cerebral circulation can differ considerably between patients and also the cerebral consequences of acute stroke are extremely heterogeneous, not only between different patients but also within one patient over time. Thus, there may not be the one optimal therapy for all patients, but rather the ideal therapeutic option should be tailored to the individual pathophysiological situation. Based on these considerations, a variety of methods have been developed to identify pathophysiological situations relevant for therapeutic decisions. One key issue when describing cerebral pathophysiology in the context of vascular disorders is the interplay between blood flow and oxygen consumption, and the most authoritative findings are still based on positron-emission tomography (PET) measurements. Cost, lack of general availability, poor temporal resolution, which prohibits any monitoring approach, and the exposure to radiation have motivated the search for alternatives. Beside MRI-based methods, near-infrared spectroscopy (NIRS) is a potential alternative allowing for an assessment of cerebral blood flow (CBF) and hemoglobin (Hb) oxygenation parameters of the human cerebral cortex noninvasively through skin and skull. NIRS has been termed a “promising method” for more than a quarter of a century now. The principle of a NIRS tool is based on a modified Beer-Lambert Law and is by far simpler than that of functional MRI or PET. Costs are low, commercial monitors are available at an expense of a head.
coil for an MRI scanner, and broader distribution may lower the costs even of the technically more advanced systems that allow 2-dimensional imaging and perspective also depth resolution. This, perhaps, is the most remarkable advantage when compared with the “alpha team” of functional imaging techniques: The method is applicable in almost any environment with a regular socket, and instead of the patient being transported to a distant (and sometimes difficult to monitor) environment, the system can be brought to the patient’s bedside and is easily combined with other bedside methods, eg, transcranial Doppler sonography (TCD). Numerous articles on NIRS have been written discussing functional brain imaging in adults and neonates, and it has been used for cerebral monitoring during heart surgery. In addition to assessment of hemoglobin oxygenation it has been established as a technique for measuring cerebral blood flow at the bedside. In this issue of Stroke, Vernieri et al present a study on the combination of TCD and NIRS in the evaluation of patients with carotid stenosis. The combination of both bedside tools allowed for the determination of a status-specific increase in arterial blood flow velocity and oxygen saturation during a vasomotor reactivity test.

So is NIRS ready for widespread diagnostic use? Our answer is “Yes, not today, but probably quite soon.” Subsequently, we will briefly touch on (1) some technical issues yet to be overcome, (2) research applications at hand, and (3) clinical applications on the horizon.

The main methodological issue regarding the validity of all NIRS parameters mentioned above is induced by the assumptions of the path of light through tissue, and the validity of chromophore concentration measurements based on a modified Beer-Lambert law. Of particular interest is the assessment of a baseline value of cerebral hemoglobin oxygenation, which is necessary for a measurement of hemoglobin saturation: [oxy-Hb]/([oxy-Hb]+[deoxy-Hb]). While it is clear that with a certain separation (>2 cm) of the sender/receiver pair brain tissue is part of the sample volume, the amount of extracerebral contamination is difficult to assign. This, however, is necessary to determine “brain-specific” concentration values of oxyhemoglobin and deoxyhemoglobin or an optical contrast agent. Furthermore, to enable precise concentration measurements, the usual implicit assumption of the head as a homogeneous semi-infinite structure obviously ignores anatomy and induces a number of errors, preventing a proper quantification. However, recently models respecting the human head’s layered structure (ideally determined individually with MRI) have been successful in showing that a differentiation of different layers is well possible. Such an approach will be able to address the issue of depth resolution as well as of quantification. This requires NIRS technology, more demanding than most of the standard continuous-wave systems, such as time- or frequency-resolved NIRS and/or multidistance approaches. While this refinement does not interfere with the simplicity and portability of the apparatus used, thus far it is not clear how far these methodological improvements will have to go in order to provide for an absolutely reliable cerebral measurement of absolute Hb concentrations and CBF. More precisely, are current implementations such as the one used in the article by Vernieri et al (and supported by the promising findings herein) explored enough or will time-resolved NIRS guided by individual MRI morphology be necessary? Two types of steps need to be taken: improved NIRS technology needs to be implemented, and the new systems have to be further validated in prospective clinical studies.

With these technical improvements implemented, the usefulness of NIRS as a research tool seems secured. Research applications include studies on neurovascular coupling and functional imaging in situations in babies and children and in situations in which functional MRI or PET is not feasible (walking, standing, etc), but also the elucidation of pathophysiological events, eg, the search for spreading ischemia in humans.

For clinical use, to monitor tissue at risk (perhaps after being defined by antecedent MRI) after ischemic stroke and (in combination with TCD) to assess the effect of thrombolysis—in particular, to determine the pathophysiologically relevant time-point of reperfusion—seem a likely perspective. In the preoperative assessment of patients with carotid stenosis, we envision NIRS data on CBF and Hb oxygenation, from which a clinically useful measure of the cerebral metabolic rate of oxygen can be derived. Time will tell whether these applications will “succeed” despite the one significant drawback of NIRS, which so far in adults can provide information only on the cerebral cortex and not on deeper structures. This drawback should not, however, significantly affect our “best bet” for a widespread clinical application. In our view it will be only a matter of time until incremental improvements of the NIRS method will help it surpass the “clinical usefulness threshold” of a rather old idea: the “cerebral oxygenation monitor” for the patient in coma (pharmacologically induced or due to brain damage) on the intensive care unit whose brain function is often being asked “why does she/he not wake up.”

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