Cerebral Hemodynamic Changes in Stroke During Sleep-Disordered Breathing

Fabio Pizza, MD, PhD; Martin Biallas, Dipl Ing; Ulf Kallweit, MD; Martin Wolf, DrScTech*; Claudio L. Bassetti, MD*

**Background and Purpose**—Sleep-disordered breathing (SDB) negatively impacts stroke outcome. Near-infrared spectroscopy showed the acute cerebral hemodynamic effects of SDB.

**Methods**—Eleven patients (7 men, age 61 ± 13 years) with acute/subacute middle cerebral artery stroke (National Institutes of Health Stroke Scale score 10 ± 7) and SDB (apnea–hypopnea index 32 ± 28/hour) were assessed with nocturnal polysomnography and bilateral near-infrared spectroscopy recording. Cerebral oxygenation and hemoglobin concentration changes during obstructive and central apneas were analyzed.

**Results**—During SDB, near-infrared spectroscopy showed asymmetrical patterns of cerebral oxygenation and hemoglobin concentrations with changes significantly larger on the unaffected compared with the affected hemisphere. Brain tissue hypoxia was more severe during obstructive compared with central apneas.

**Conclusions**—Profound cerebral deoxygenation effects of SDB occurred in acute/subacute stroke. These changes may contribute to poor outcome, arising in the possibility of a potential benefit of SDB treatment in stroke management. (Stroke. 2012;43:1951-1953.)

**Key Words:** acute stroke ■ cerebral hemodynamics ■ microcirculation ■ near-infrared spectroscopy ■ sleep apnea

Sleep-disordered breathing (SDB) independently increases the risk of cardiovascular events, stroke, and death. SDB is associated with worse clinical outcome in stroke, but the acute impact of repetitive brain hypoxia has never been documented.1 Cerebral near-infrared spectroscopy (NIRS) provides a noninvasive, bedside assessment of oxygen saturation and oxygenated, deoxygenated, and total hemoglobin concentrations at the cortical level.2 Cerebral NIRS coupled with transcranial Doppler (TCD) during the breath-holding test in patients with carotid occlusion distinguished symptomatic patients for their insufficient cerebrovascular autoregulation.3 NIRS also proved the inability of cerebral autoregulation to prevent hypoxia in patients with severe obstructive SDB.4

**Methods**

Nocturnal polysomnography was coupled with bilateral cerebral NIRS performed with OxiplexTS. The study was approved by local ethic committee. All patients signed a written informed consent.

Patients were consecutively recruited (University Hospital of Zürich) over a period of 6 months with the following inclusion criteria: (1) first-ever ischemic stroke with unilateral involvement of areas supplied by middle cerebral artery (MCA); (2) stable clinical condition; and (3) TCD and neuroimaging studies performed after stroke treatment.

**NIRS Recording and Signal Analysis**

Our 2-wavelength system, based on a frequency-domain technology, provides absolute values of oxygen saturation, oxygenated hemoglobin, deoxygenated hemoglobin, and total hemoglobin. The multidistance approach subtracts superficial layers, thus yielding values of a cortical brain volume of a few cube centimeters.5 Two probes were calibrated, attached to corresponding frontal areas through a medical adhesive, and shielded from external light.

NIRS data underwent the signal analyses described before.4 NIRS and peripheral oxygen saturation (SpO2) data associated with obstructive and central apneas occurring in different sleep stages of each patient were averaged for each of the 2 hemispheres (Figure). Respiratory event duration was defined from the first SpO2 decrease to its return to baseline and SpO2 signal was integrated. Averaged NIRS parameters were plotted together for each hemisphere to detect the first hemodynamic change occurring close to time 0 second. Synchronous integrals were calculated from the start of the cerebral event and for the duration defined on the SpO2 average. Integrals results were adjusted for duration of the respiratory event, leading to relative changes per second.

NIRS parameters changes occurring on the 2 hemispheres were compared using Wilcoxon test on the whole data set and independently for obstructive and central apneas. NIRS parameter (and SpO2) changes of different event types were compared using the Mann–Whitney test.

**Results**

**Patients**

Fifteen patients were consecutively enrolled. Three patients lacking unilateral MCA involvement (one bilateral, one posterior, and one lacunar) and one because of a technical NIRS failure were excluded. Eleven patients (7 men, mean...
age 61±13 years) with unilateral MCA stroke and TCD evidence of stenosis/occlusion of intracranial arteries (n=5) or symmetrical MCA blood flow velocities (n=6), respectively, were analyzed. Their mean National Institutes of Health Stroke Scale score was 10±7 at admission, and their mean Rankin Scale score was 2±1 at discharge.

Nocturnal polysomnography, performed 7±5 days after symptom onset, showed a mean apnea–hypopnea index of 32±28/hour (range, 5–94/hour) with a predominant central and obstructive SDB in 5 and 3 patients, respectively and an apnea–hypopnea index >30/hour in 3.

Bilateral Hemodynamic Patterns
Averaged NIRS parameters occurring during respiratory events revealed an asymmetrical pattern of cerebral hemodynamics over the 2 hemispheres (Figure): a trend of decrease of oxygenated hemoglobin and an increase of deoxygenated hemoglobin, apparently of higher amplitude on the unaffected hemisphere followed by return to baseline values. Reduced oscillations of cerebral oxygen saturation on the affected side were the result of the 3 dynamic hemoglobins’ concentration changes over the 2 hemispheres.

Hemisphere and Event-Type Comparison
Relative changes of NIRS parameters showed a larger decrease of oxygen saturation, oxygenated hemoglobin, and, to a lesser extent, of total hemoglobin, associated with an increase of deoxygenated hemoglobin on the normal compared with the affected hemisphere (Table).

The comparison between different event types showed that obstructive events induced larger hemodynamic changes than central ones with statistical significance for oxygen saturation of the unaffected hemisphere (P=0.010), oxygenated hemoglobin of the affected hemisphere (P=0.027), and for Spo2 (P=0.004) on the Mann–Whitney test.

The larger amplitude of the hemodynamic changes occurring on the unaffected versus affected hemisphere was confirmed for all NIRS parameters during obstructive apneas, but only for oxygen saturation and deoxygenated hemoglobin during central apneas (Table).

Discussion
We firstly explored the SDB effect on cerebral hemodynamics in acute/subacute stroke using bilateral NIRS. We improved the signal-to-noise ratio (averaging) and included the temporal dimension in NIRS measurements (integrals adjusted for duration). We disclosed that SDB acutely induces larger hemodynamic changes in the unaffected hemisphere than in the affected one and that obstructive apneas more profoundly impacted on cerebral hemodynamics than central apneas.

NIRS changes during SDB reflect the cortical balance between blood supply and metabolism. Positron emission tomography during cerebral ischemia revealed a complex interaction between cerebral perfusion and metabolic oxygen consumption that defines the dynamic evolution of an ischemic “core.” Once brain damage has occurred, cerebrovascular autoregulation fails, even if cerebral perfusion returns to normal.

The “paradoxical” observation of lower hemodynamic changes on the affected hemisphere induced by SDB cannot be explained by diminished blood perfusion, because additional analyses of 6 patients with normal or increased MCA blood flow velocities in the affected side yielded comparable results (data not shown). TCD studies during obstructive apneas showed repetitive, transient increases of MCA blood
Table. Mean (and SEM) Relative Changes of Peripheral Oxygen Saturation and Cerebral NIRS Parameters of the 2 Hemispheres With Side Comparison Significance on Wilcoxon Test

<table>
<thead>
<tr>
<th></th>
<th>Unaffected</th>
<th>Affected</th>
<th>Side Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
</tr>
<tr>
<td>All apneas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO2, %*s⁻¹</td>
<td>-3.24</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>StO2, %*s⁻¹</td>
<td>-0.76</td>
<td>0.08</td>
<td>-0.19</td>
</tr>
<tr>
<td>thb, μmol<em>L⁻¹</em>s⁻¹</td>
<td>-0.13</td>
<td>0.03</td>
<td>-0.03</td>
</tr>
<tr>
<td>O₂Hb, μmol<em>L⁻¹</em>s⁻¹</td>
<td>-0.33</td>
<td>0.03</td>
<td>-0.09</td>
</tr>
<tr>
<td>HHb, μmol<em>L⁻¹</em>s⁻¹</td>
<td>0.20</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>Central apneas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO2, %*s⁻¹</td>
<td>-2.67</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>StO2, %*s⁻¹</td>
<td>-0.60</td>
<td>0.07</td>
<td>-0.26</td>
</tr>
<tr>
<td>thb, μmol<em>L⁻¹</em>s⁻¹</td>
<td>-0.12</td>
<td>0.04</td>
<td>-0.14</td>
</tr>
<tr>
<td>O₂Hb, μmol<em>L⁻¹</em>s⁻¹</td>
<td>-0.28</td>
<td>0.03</td>
<td>-0.21</td>
</tr>
<tr>
<td>HHb, μmol<em>L⁻¹</em>s⁻¹</td>
<td>0.17</td>
<td>0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>Obstructive apneas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO2, %*s⁻¹</td>
<td>-4.12</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>StO2, %*s⁻¹</td>
<td>-1.02</td>
<td>0.15</td>
<td>-0.08</td>
</tr>
<tr>
<td>thb, μmol<em>L⁻¹</em>s⁻¹</td>
<td>-0.15</td>
<td>0.07</td>
<td>0.15</td>
</tr>
<tr>
<td>O₂Hb, μmol<em>L⁻¹</em>s⁻¹</td>
<td>-0.40</td>
<td>0.07</td>
<td>0.08</td>
</tr>
<tr>
<td>HHb, μmol<em>L⁻¹</em>s⁻¹</td>
<td>0.24</td>
<td>0.04</td>
<td>0.06</td>
</tr>
</tbody>
</table>

NIRS indicates near-infrared spectroscopy; StO2, cerebral oxygen saturation; tHb, peripheral total hemoglobin; O₂Hb, oxygenated hemoglobin; HHb, deoxygenated hemoglobin; NS, nonsignificant.

flow velocity. Moreover, cerebral vasoregulation assessed by TCD, or by NIRS, is impaired in acute stroke with consequent dependence of brain perfusion of the affected hemisphere from arterial blood pressure. Therefore, blood pressure increases at each obstructive apnea termination probably induce transient cerebral blood flow velocity increases in the affected hemisphere of patients with stroke. Alternative explanations for our findings could be: reduced cerebral metabolism; alteration of the “neurovascular unit,” including posts ischemic vasoparalysis with maximal vasodilation; and impaired cerebral vasomotor reactivity to hypercapnia with intracerebral blood steal to the unaffected hemisphere. Minor hemodynamic changes of the affected hemisphere could therefore reflect its diminished cerebral metabolism, or a detrimental vascular “storm” induced by SDB.

The more profound hemodynamic impact of obstructive versus central apneas during the acute stroke phase parallels the negative effect of obstructive SDB on stroke outcome. NIRS has a poor spatial resolution. We therefore standardized stroke topography and NIRS positioning. Moreover, positron emission tomography studies on acute stroke evolution in humans, and in animals, revealed reduced metabolic activity in cerebral sites distant from the ischemic core (diaschisis) during infarction evolution with a protective role for cerebral plasticity.

Summary
We documented asymmetrical nocturnal cerebral hemodynamic changes induced by SDB during the acute/subacute phase of stroke. Lower hemodynamic fluctuations occurred over the affected hemisphere, and the oxygen desaturations on the unaffected side were more profound during obstructive SDB. Studies coupling different techniques (TCD and positron emission tomography) to NIRS in a larger sample of patients with and without stroke and different SDB severity will confirm our findings and their clinical relevance for stroke pathophysiology and recovery.

Sources of Funding
Supported by the Swiss National Science Foundation, Grant 320030_125069, K-23KO_120727, and 315200–112677.

Disclosures
None.

References
Stroke 2012; 43: 1951-1953