Reduced Vasomotor Reactivity in Cerebral Microangiopathy
A Study With Near-Infrared Spectroscopy and Transcranial Doppler Sonography

Christoph Terborg, MD; Felix Gora, MS; Cornelius Weiller, MD; Joachim Röther, MD

Background and Purpose—Reduction of cerebral blood flow and vasomotor reactivity (VMR) are thought to play an important role in the pathogenesis of cerebral microangiopathy. The aim of our study was to determine whether near-infrared spectroscopy (NIRS) can detect a reduced VMR in patients with microangiopathy, whether NIRS reactivities correlate with VMR assessed by transcranial Doppler sonography (TCD), and whether the differing extents of patients’ microangiopathy demonstrated on MRI or CT can be distinguished by both noninvasive techniques.

Methods—We compared the VMR of 46 patients with cerebral microangiopathy with 13 age-matched control subjects. Patients were classified with the Erkinjuntti scale. We monitored cerebral blood flow velocity (CBFV) in both middle cerebral arteries by TCD, changes in concentration of oxyhemoglobin (HbO₂), deoxyhemoglobin (Hb) and blood volume (HbT) by NIRS, mean arterial blood pressure, and end-tidal CO₂ (Et CO₂ ) during normocapnia and hypocapnia. VMRs were calculated as percent change of CBFV (NCR) and as absolute change in concentration of HbO₂, Hb, and HbT per 1% increase in EtCO₂ (CR-HbO₂, CR-Hb, CR-HbT).

Results—NCR and NIRS reactivities were significantly reduced in patients with cerebral microangiopathy. CR-HbO₂ and CR-Hb showed a close correlation with NCR, and NCR and NIRS reactivities were related to the severity of cerebral microangiopathy according to the Erkinjuntti scale. Validity of NCR and NIRS reactivities were similar.

Conclusions—VMR is reduced in patients with cerebral microangiopathy and can be noninvasively assessed in basal arteries (with TCD) and brain parenchyma (with NIRS). Reduction of CO₂-induced VMR, as measured by NIRS and TCD, may indicate the severity of microangiopathy. (Stroke. 2000;31:924-929.)

Key Words: cerebral blood flow • microangiopathy • spectroscopy, near-infrared • ultrasonography, Doppler, transcranial • vasomotor reactivity

Cerebral microangiopathy is associated with age, arterial hypertension, and other vascular risk factors, and coincides with lacunar infarction and demyelination of the deep white matter.¹–⁶ Cerebral microangiopathy is characterized anatomically by lipohyalinosis of cerebral arteries and arterioles and hemodynamically by decreased cerebral blood flow and loss of autoregulation.⁷–¹⁰ Impaired VMR is thought to cause further ischemic infarctions and progression ofBinswanger’s disease.⁵,¹¹

NIRS measures changes in concentration of the chromophores HbO₂ and Hb, and enables the assessment of cerebral hemodynamics noninvasively (see References 12 through 14). NIRS has been applied to test CO₂-induced VMR, and correlations with cerebral blood flow and cerebral blood volume measurements were found in preterm neonates¹⁵ and newborn infants.¹⁶ In adults with various neurological diseases, CO₂ reactivity measured by NIRS was similar to changes in jugular venous oxygen saturation.¹⁷

Simultaneous assessment of CO₂-induced VMR by TCD and NIRS revealed correlating results in adult volunteers and patients with different degrees of carotid artery stenosis.¹⁸,¹⁹

TCD measurements of VMR reflect autoregulatory changes of the whole downstream microcirculatory bed. In contrast to TCD, NIRS semiquantitatively measures changes of the regional cerebral blood volume (rCBV) in cerebral tissue and therefore assesses VMR from a different location.

The aim of our study was therefore to evaluate whether cerebral microangiopathy is associated with a reduced CO₂-induced VMR, whether VMR measured by NIRS correlates with NCR, and whether there is a correlation between impairment of autoregulation and the pattern and extent of white matter changes on CT or MRI.

Subjects and Methods
We compared CO₂-induced VMR in 46 patients with cerebral microangiopathy who were treated in our Department of Neurology (38 male, 8 female; mean age 68.8 years, SD 9.6 years) with a group...
of 13 age-matched volunteers from our staff or our department
without previous or present diseases of the central nervous system (9
male, 4 female; mean age 66.8 years, SD 7.6 years). Patients fulfilled
the following criteria:

1. ischemic events consistent with transient
ischemic attack or lacunar infarction (n = 33),
2. dementia (n = 13), or
3. both (n = 3), and white matter changes on CT or MRI in concordance
with cerebral microangiopathy. Patients or volunteers with insuffi-
cient temporal bone window, significant carotid artery stenosis, or
territorial brain infarction were excluded. All gave informed consent
prior to the reactivity test.

Patients were classified in a blinded manner according to their
MRI scans with the Erkinjuntti scale20 by one of the authors as
follows. For periventricular hyperintensities: 0 indicates lesions
absent; 1, caps; 2, pencil-thin lining; 3, smooth halo; and 4, irregular
hyperintensities extending to the deep white matter. For other white
matter hyperintensities: 0 indicates absent; 1, 5 small focal and/or
2 large focal lesions; 2, 5 to 12 small and/or 2 to 4 large focal
lesions; 3, 12 small focal and/or >4 large focal or some confluent
lesions; and 4, predominantly confluent lesions.

The above groups and all patients were divided into mild and
severe white matter changes. In 14 patients with a CT scan only, the
Erkinjuntti scale was applied in an analogous manner.

Recordings
We recorded simultaneously the CBFV in both middle cerebral
arteries by transcranial Doppler sonography (X4, DWL), changes in
concentration of HbO2, Hb, and HbT by near-infrared spectroscopy
(NIRO 500, Hamamatsu Photonics), and end-tidal CO2 (Kapno-
graph, Datex-Engström) during nororcapania and hypercapnia. Mean
arterial blood pressure was measured continuously by a noninvasive,
beat-to-beat finger blood-pressure monitor (Portapres, TNO Biomed-
ical Instrumentation). The transmitting probe of the NIRS was placed
on the left side of the forehead 2 cm beside the midline and 3 to 4 cm
above the supraorbital ridge, and the receiving probe (photomulti-
plier) was fixed laterally at a distance of 5 cm with an
elastic bandage.

Reactivity Test
For baseline conditions, subjects lay in a supine position, breathing
room air through a breathing mask. After registration of a stable
signal for at least 5 minutes, a CO2 test was performed by their
breathing carbogene gas (5% CO2 and 95% O2), until a 1% increase
in EtCO2 was achieved. Figure 1 shows a typical recording.

Data Collection and Processing
For offline analysis, data were collected and digitized with use of an
AD converter with a sampling rate of 50 Hz, averaged, and stored on
a laptop personal computer by means of a data collecting software
(Dasylab, Synotech). CO2-induced VMRs were calculated as per-
centage change of the CBFV in TCD (NCR) and as absolute change
in concentrations of oxyhemoglobin and deoxyhem-
globin (Δ HbO2, Δ Hb).

TABLE 1. Classification of Patients According to the
Erkinjuntti Scale

<table>
<thead>
<tr>
<th>Mild (0–2), n</th>
<th>Severe (3–4), n</th>
<th>Sum, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>DWMMH</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>PH and DWMMH</td>
<td>Mild (1–4)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Severe (5–8)</td>
<td></td>
</tr>
</tbody>
</table>

PH indicates periventricular hyperintensities; DWMMH, deep white matter
hyperintensities.

TABLE 2. Vasomotor Reactivities of Patients and
Control Subjects (Mean/SD)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>66.8/7.6</td>
<td>68.8/9.6</td>
<td>0.2374</td>
</tr>
<tr>
<td>NCR left</td>
<td>27.6/14.0</td>
<td>19.0/9.1</td>
<td>0.0215</td>
</tr>
<tr>
<td>NCR right</td>
<td>27.3/10.6</td>
<td>19.6/9.2</td>
<td>0.0090</td>
</tr>
<tr>
<td>CR-HbO2</td>
<td>2.60/93</td>
<td>1.54/56</td>
<td>0.0001</td>
</tr>
<tr>
<td>CR-Hb</td>
<td>−2.25/80</td>
<td>−1.47/61</td>
<td>0.0012</td>
</tr>
<tr>
<td>CR-HBT</td>
<td>0.63/81</td>
<td>−0.14/25</td>
<td>0.0275</td>
</tr>
<tr>
<td>CR-Hbdiff</td>
<td>4.72/1.65</td>
<td>2.94/1.15</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Figure 1. CO2 reactivity test in a healthy volunteer. Monitoring comprises cerebral blood flow velocities in both middle cerebral arteries assessed by TCD (MCA right and left), capnograph (EtCO2), mean arterial blood pressure (MAP), and changes in concentrations of oxyhemoglobin and deoxyhemoglobin (Δ HbO2, Δ Hb).
between HbO₂ and Hb, and CR-Hbdiff as an additional reactivity index.

Vasomotor Reactivities

$$\text{VAS} = \frac{(\text{HbO}_2 \text{max} - \text{HbO}_2 \text{normo})}{\Delta \text{CO}_2}$$

analogous calculations for CR-Hb, CR-HbT, and CR-Hbdiff

$$\text{NCR} = \frac{100 \times (\text{CBFVmax} - \text{CBFVnormo})}{\text{CBFVnormo} \times \Delta \text{CO}_2}$$

where CR-HbO₂ is the CO₂ reactivity of HbO₂, NCR is normalized CO₂ reactivity, and CBFVmax and CBFVnormo are cerebral blood flow velocity during hypercapnia and normocapnia, respectively.

Statistical Analysis

For statistical analysis we used the nonparametric Mann-Whitney U test, because most values did not show normality. Differences in VMR between control subjects and patients with mild and severe white matter hyperintensities according to the Erkinjuntti scale were tested by a Kruskal-Wallis 1-way ANOVA. Post hoc tests (2x2) were performed by the use of the Scheffe test.

The correlation coefficients between reactivity indices and between VMRs and the extent of microangiopathy according to the Erkinjuntti scale were tested with the nonparametric Pearson and Spearman formulas. The validity of all reactivity indices was assessed by sensitivity, specificity, and receiver operating characteristic (ROC) analysis.

Results

The classification of the patients according to the Erkinjuntti scale is summarized in Table 1. Patients with cerebral microangiopathy had a significantly reduced CO₂-induced VMR demonstrated on TCD and NIRS: NCR, CR-HbO₂, CR-Hb, CR-HbT, and CR-Hbdiff were diminished compared with values from the age-matched control group (Table 2). NIRS reactivities showed a higher level of significance compared with NCR, in particular CR-HbO₂ and CR-Hbdiff (NCR left, P = 0.0215; CR-HbO₂, P = 0.0001; CR-Hbdiff, P = 0.0006).

NIRS reactivities showed a significant correlation with the NCR (Spearman and Pearson correlation coefficients; P < 0.05) except for the parameter CR-HbT (Table 3, Figure 2).

Blood pressure usually rose during CO₂ tests (mean 6.8 mm Hg, SD 7.1 mm Hg). Changes in blood pressure during reactivity tests did not correlate with NCR but did correlate with CR-HbO₂, CR-Hb, and CR-Hbdiff (P < 0.05).

The reduction of CO₂-induced VMR was highest in patients with white matter changes qualified as “severe” (Erkinjuntti scale 5 to 8) and less in patients with “mild” abnormalities (Erkinjuntti scale 1 to 4) compared with the controls. The global difference between the groups was significant (NCR, P < 0.05; CR-HbO₂, P = 0.0001; CR-Hb, P < 0.003; CR-Hbdiff, P < 0.002; Figures 3 through 7). A 2x2 post hoc test (Scheffé) showed a difference between controls and patients with white matter changes qualified as “severe” (Erkinjuntti scale 5 to 8) and less in patients with “mild” abnormalities (Erkinjuntti scale 1 to 4) compared with the controls.
with severe microangiopathy for NCR right ($P<0.05$) and a trend toward a reduced NCR left ($P=0.055$). Concerning the NIRS reactivities, differences between controls and patients with mild microangiopathy and between controls and patients with severe microangiopathy were significant for the parameters CR-HbO$_2$ ($P=0.001$ and $P=0.000$, respectively), CR-Hb ($P=0.017$ and $P=0.001$, respectively), and CR-Hbdiff ($P=0.003$ and $P=0.000$, respectively). The homogeneity of variances of these parameters could be verified. We did not find significant differences between patients with mild and those with severe microangiopathy (Scheffé test) in either TCD or NIRS.

Furthermore, we found a negative correlation between VMR and the extent of microangiopathy according to the Erkinjuntti scale (NCR, $P=0.024$; CR-HbO$_2$, $P=0.000$; CR-Hb, $P=0.000$; CR-Hbdiff, $P=0.000$; and CR-HbT, $P=0.008$).

Sensitivity and specificity of NCR left were 72.7% and 64.4% ($P=0.021$); NCR right, 69.2% and 60.0% ($P=0.009$); CR-HbO$_2$, 92.3% and 65.2% ($P=0.000$); and CR-Hbdiff, 76.9% and 63% ($P=0.001$; Table 4). ROC analysis of all reactivity indices showed the largest areas under the curve for the indices CR-HbO$_2$, CR-Hb, and CR-Hbdiff (Table 4, Figures 8 through 10).

**Discussion**

Several studies indicate hemodynamic alterations in cerebral microangiopathy.$^{6,8,9,21}$ Impaired cerebral autoregulation and altered pulsatility characteristics measured by TCD were found in patients with vascular dementia and lacunes$^{22–25}$; however, most of these studies did not distinguish between cerebral microangiopathy and lacunar and territorial brain infarction.

In our patients with cerebral microangiopathy (defined as focal neurological signs and/or dementia in the presence of white matter abnormalities on CT or MRI), we found a significantly reduced CO$_2$ reactivity in both noninvasive techniques, TCD and NIRS. Compared with the control subjects, VMR was more reduced in patients with severe than with mild microangiopathy (Figures 3 through 7), and differences (global comparison) between the 3 groups were significant. The reduction of NCR and NIRS reactivities correlated with the extent of periventricular and deep white matter hyperintensities on the Erkinjuntti scale.

Our results are in line with recent hemodynamic studies: reduction of rCBF and rCBF change to acetazolamide measured by xenon-enhanced CT was described in the cerebral white matter and cortex of patients with single and multiple lacunes. Patients with multiple lacunar infarctions showed a significantly lower VMR in the cerebral cortex than did

![Figure 5. Box plots showing differences of CR-Hb ($\mu$mol/L) between controls, patients with mild, and patients with severe white matter changes on the Erkinjuntti scale.](image1)

![Figure 6. Box plots showing differences of CR-HbT ($\mu$mol/L) between controls, patients with mild, and patients with severe white matter changes on the Erkinjuntti scale.](image2)

![Figure 7. Box plots showing differences of CR-Hbdiff ($\mu$mol/L) between controls, patients with mild, and patients with severe white matter changes on the Erkinjuntti scale.](image3)

**TABLE 4. Sensitivity, Specificity, and ROC Analysis of NCR and NIRS Reactivities**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Threshold Value</th>
<th>Area Under Curve</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCR left</td>
<td>72.7</td>
<td>64.4</td>
<td>19.6%</td>
<td>.725</td>
<td>0.021</td>
</tr>
<tr>
<td>NCR right</td>
<td>69.2</td>
<td>60.0</td>
<td>20.6%</td>
<td>.739</td>
<td>0.009</td>
</tr>
<tr>
<td>CR-HbO$_2$</td>
<td>92.3</td>
<td>65.2</td>
<td>1.69 $\mu$mol/L</td>
<td>.863</td>
<td>0.000</td>
</tr>
<tr>
<td>CR-Hb</td>
<td>84.6</td>
<td>58.7</td>
<td>$-1.53$ $\mu$mol/L</td>
<td>.797</td>
<td>0.001</td>
</tr>
<tr>
<td>CR-HbT</td>
<td>69.2</td>
<td>56.5</td>
<td>.18 mmol/L</td>
<td>.702</td>
<td>0.028</td>
</tr>
<tr>
<td>CR-Hbdiff</td>
<td>76.9</td>
<td>63.0</td>
<td>3.35 $\mu$mol/L</td>
<td>.814</td>
<td>0.001</td>
</tr>
</tbody>
</table>
patients with single lacunes. In patients with leukoaraiosis and lacunar infarctions, Oishi et al found a more reduced rCBF and acetazolamide reactivity than in patients with leukoaraiosis alone. A negative correlation between vasodilatory capacity to acetazolamide in the cortex and the severity of periventricular hyperintensities on MRI of the brain was also shown in asymptomatic subjects with periventricular hyperintensities (xenon clearance). In patients with vascular dementia of the Binswanger type, a decreased CO2 reactivity was demonstrated in cerebral cortex and in the deep white matter (by PET), and in lacunar dementia De Reuck et al found a decreased blood flow to oxygen metabolism with increased oxygen extraction rate. These studies indicate that cerebral microangiopathy goes along with a reduction of rCBF and, as noninvasively shown in our study, an impaired cerebral autoregulation.

Findings of impaired VMR fit into the concept that the disturbed autoregulation in cerebral microangiopathy results in temporary critical hypoperfusion during episodes of hypotension. Recurrent decreases in cerebral perfusion (eg, during blood pressure dysregulation or cardiac arrhythmia) may lead to ischemia in the deep white matter.

Functional studies with NIRS and PET have shown that the sample volume of NIRS is located in the superficial part of the brain. We have hypothesized that measurements with NIRS might therefore be more sensitive and reliable than those with TCD, because NIRS measures the hemodynamic response to hypercapnia closer to the presumed site of the disturbed autoregulation. In our study, sensitivity and specificity of the reactivity indices CR-HbO2 and CR-Hbdiff were higher compared with NCR, and ROC analysis revealed the largest areas under the curve for CR-HbO2, CR-Hb, and CR-Hbdiff (Table 4, Figures 8 through 10). Validity of VMR measured by NIRS might therefore be similar (or even better) compared with TCD in patients with cerebral microangiopathy.

Interestingly, Sabri et al found that in microangiopathy dementia and neuropsychological impairment correlate with the reduction of regional cerebral blood flow and glucose utilization and not with MRI changes. Whether a normal neurological and neuropsychological status correlates with a preserved autoregulation in patients with cerebral microangiopathy has yet to be determined.

Acknowledgments
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References


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