Influence of Chronic Hyperglycemia on Cerebral Microvascular Remodeling
An In Vivo Study Using Perfusion Computed Tomography in Acute Ischemic Stroke Patients

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Background and Purpose—To investigate the effect of chronic hyperglycemia on cerebral microvascular remodeling using perfusion computed tomography.

Methods—We retrospectively identified 26 patients from our registry of 2453 patients who underwent a perfusion computed tomographic study and had their hemoglobin A1c (HbA1c) measured. These 26 patients were divided into 2 groups: those with HbA1c>6.5% (n=15) and those with HbA1c≤6.5% (n=11). Perfusion computed tomographic studies were processed using a delay-corrected, deconvolution-based software. Perfusion computed tomographic values were compared between the 2 patient groups, including mean transit time, which relates to the cerebral capillary architecture and length.

Results—Mean transit time values in the nonischemic cerebral hemisphere were significantly longer in the patients with HbA1c>6.5% (P=0.033), especially in the white matter (P=0.005). Significant correlation (R=0.469; P=0.016) between mean transit time and HbA1c level was observed.

Conclusions—Our results from a small sample suggest that chronic hyperglycemia may be associated with cerebral microvascular remodeling in humans. Additional prospective studies with larger sample size are required to confirm this observation. (Stroke. 2013;44:3557-3560.)

Key Words: cerebrovascular disorders ■ diabetes mellitus ■ diabetic microangiopathy ■ perfusion imaging ■ stroke

Chronic hyperglycemia causes not only systemic macroangiopathy, but also microvascular remodeling. Microvascular remodeling encompasses increased thickness of the capillary basement membrane, hyperplasia of the smooth muscle cells, and altered capillary density. Cerebral microvascular remodeling in patients with diabetes mellitus has been linked to brain atrophy, cognition impairment, and ischemic events. The goal of our study was to use perfusion computed tomography (PCT) as a tool to investigate the effect of chronic hyperglycemia on cerebral microvascular remodeling. We hypothesized that PCT values would be significantly different in patients with and without chronic hyperglycemia.

Methods

Study Patients and Groups
The clinical and imaging data presented in this study belong to a systematic registry collected as part of the standard clinical stroke care from 2003 to 2011 at the University of Virginia, Charlottesville, VA, and at the Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland. This retrospective data analysis was approved by the institutional review boards of both the University of Virginia and the CHUV. Patients had to meet the following inclusion criteria to qualify for this study: (1) suspicion of acute stroke with completion of a stroke CT imaging work-up, including noncontrast head CT, PCT, and CT angiography, on admission; (2) blood draw and measurement of hemoglobin A1c (HbA1c) within 3 days of admission; (3) no evidence of chronic large-territory infarct; and (4) no significant (>70%) stenosis in the cervical or intracranial arteries contralateral to the acute ischemic stroke.

Clinical and Laboratory Variables
Clinical and laboratory variables listed in Table 1 were extracted from the patients’ medical records. Study patients were divided into 2 groups on the basis of whether their chronic glycemic control were satisfactory (HbA1c≤6.5%) or not (HbA1c>6.5%).

Image Processing and Interpretation
PCT studies were performed using a previously described protocol. PCT processing was automated to limit interobserver agreement.
issues. Parametric maps of cerebral blood volume, cerebral blood flow, and mean transit time (MTT) were generated, and values of these parameters were recorded in regions of interest drawn on slices running through the basal ganglia both on the ischemic and nonisch-
emic cerebral hemispheres. The volumes of infarct and at-risk isch-
emic tissues (penumbra) were semiautomatically calculated using previously reported thresholds.5 The volume of final infarction was measured. The image processing and interpretation were done in a blinded fashion with respect to the HbA1c values.

The degree of cervical internal carotid artery stenosis at the level
of the bulb was measured using the North American Symptomatic
Carotid Endarterectomy Trial investigator (NASCET) criterion both
on the ischemic side and on the contralateral side. Stenosis of the
intracranial arteries was evaluated using the methodology of the
Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) study.6
Chronic ischemic small vessel disease in white matter was graded
on the noncontrast head CT using the scales and methodology de-
scribed by van Swieten et al7 and Wahlund et al.8 The number of lacu-
nescles in the nonischemic hemisphere was counted.

Statistical Analysis

Descriptive statistics was used to assess differences in clinical
and imaging variables between the HbA1c ≤6.5% group and the
HbA1c >6.5% group. Mean±SD was used for continuous variables
with normal distribution, and Student t test was used to compare the
values of these variables between the 2 groups. Median, interquartile
range, and range were used for not normally distributed variables, and
Mann–Whitney U test was used to compare the values of these vari-
ables between the 2 groups. Pearson correlation analysis was applied
to assess the correlation between PCT values and HbA1c levels, and
Spearman rank-order correlation analysis was applied to assess the
correlation between PCT values and admission blood glucose data. A
P value <0.05 was considered as statistically significant.

Table 1. Clinical and Imaging Characteristics of Study Patients in the 2 Groups (HbA1c ≤6.5% and HbA1c >6.5%)

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=26)</th>
<th>HbA1c ≤6.5% Group (n=15)</th>
<th>HbA1c &gt;6.5% Group (n=11)</th>
<th>P Value (2-Tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.6±14.5</td>
<td>62.3±16.5</td>
<td>67.6±11.2</td>
<td>0.367</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>15/11</td>
<td>9/6</td>
<td>6/5</td>
<td>0.838</td>
</tr>
<tr>
<td>Admission NIHSS</td>
<td>Median, 1</td>
<td>Median, 11</td>
<td>Median, 17</td>
<td>0.077</td>
</tr>
<tr>
<td>IQR, 5–16</td>
<td></td>
<td>IQR, 9–20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, 3–25</td>
<td>Range, 8–21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7 mRS</td>
<td>Median, 1</td>
<td>Median, 4</td>
<td></td>
<td>0.018*</td>
</tr>
<tr>
<td>IQR, 1–4</td>
<td>IQR, 3–5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, 0–6</td>
<td>Range, 2–5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history (yes)</td>
<td>8/26 (31%)</td>
<td>4/15 (27%)</td>
<td>4/11 (36%)</td>
<td>0.683</td>
</tr>
<tr>
<td>Arterial hypertension history (yes)</td>
<td>18/26 (69%)</td>
<td>10/15 (67%)</td>
<td>8/11 (73%)</td>
<td>0.799</td>
</tr>
<tr>
<td>Diabetes mellitus history (yes)</td>
<td>9/26 (35%)</td>
<td>2/15 (13%)</td>
<td>7/11 (64%)</td>
<td>0.032*</td>
</tr>
<tr>
<td>Dyslipidemia history (yes)</td>
<td>18/26 (69%)</td>
<td>11/15 (73%)</td>
<td>7/11 (64%)</td>
<td>0.683</td>
</tr>
<tr>
<td>Atrial fibrillation (yes)</td>
<td>14/26 (54%)</td>
<td>6/15 (40%)</td>
<td>8/11 (73%)</td>
<td>0.164</td>
</tr>
<tr>
<td>Admission systolic blood pressure, mm Hg</td>
<td>172.2±33.4</td>
<td>162.9±27.1</td>
<td>187.3±37.3</td>
<td>0.065</td>
</tr>
<tr>
<td>Admission blood glucose, mmol/L</td>
<td>8.1±3.1</td>
<td>7.3±2.4</td>
<td>10.1±3.4</td>
<td>0.015*</td>
</tr>
<tr>
<td>Blood cholesterol, mg/dL</td>
<td>5.7±1.4</td>
<td>6.1±1.5</td>
<td>5.2±1.1</td>
<td>0.116</td>
</tr>
<tr>
<td>Blood creatinine, μmol/L</td>
<td>98.9±19.6</td>
<td>95.0±18.0</td>
<td>103.6±21.5</td>
<td>0.295</td>
</tr>
<tr>
<td>Admission hemocrit</td>
<td>0.41±0.04</td>
<td>0.42±0.04</td>
<td>0.41±0.04</td>
<td>0.793</td>
</tr>
<tr>
<td>HbA1c, mmol/mol</td>
<td>47.4±12.3</td>
<td>38.9±3.5</td>
<td>59.0±10.3</td>
<td>&lt;0.000*</td>
</tr>
<tr>
<td>Ipsilateral NASCET (&gt;70%) (yes)</td>
<td>7/26 (27%)</td>
<td>3/15 (20%)</td>
<td>4/11 (36%)</td>
<td>0.507</td>
</tr>
<tr>
<td>Contralateral NASCET (&gt;70%) (yes)</td>
<td>0/26 (0%)</td>
<td>0/15 (0%)</td>
<td>0/11 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Intracranial stenosis (&gt;70%) (yes)</td>
<td>0/26 (0%)</td>
<td>0/15 (0%)</td>
<td>0/11 (0%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

HbA1c indicates hemoglobin A1c; IQR, interquartile range; mRS, modified Rankin Scale; NA, nonavailable; NASCET, carotid artery stenosis at the level of the bulb measured with the North American Symptomatic Carotid Endarterectomy Trial investigator (NASCET) criterion; and NIHSS, National Institutes of Health Stroke Scale. *denotes statistically significant difference between the two study groups.

Study Population and Clinical Characteristics

Of 2453 patients in our registry from 2003 to 2011, 26 qualified for the current study (Figure). The median time from symptom onset to PCT imaging was 3.1 hours (interquartile range, 2–5.6) and was not significantly different between the 2 patient groups (P=0.081). The patients with HbA1c >6.5% had a lower modified Rankin Scale score at day 7 and tended to have a higher admission National Institutes of Health Stroke Scale score (Table 1). Patients with HbA1c >6.5% were more likely to have diabetes mellitus and had higher blood glucose levels on admission (Table 1).

Imaging Findings

In our study population, no patient in either group had a signif-
icant NASCET internal carotid stenosis on the contralateral, nonisch-
emic side. No patient had significant intracranial steno-
sis (Table 1). No significant difference was observed between the 2 patient groups in chronic ischemic lesions measured with the scales of van Swieten et al7 and Wahlund et al8 (both in the white matter and in the basal ganglia). No significant
difference in the number of chronic lacunes was seen between the 2 groups. The volume of ischemic core and penumbra on baseline PCT and the final infarct volume on follow-up images were not significantly different between the 2 patient groups.

The MTT values in the nonischemic contralateral hemisphere were significantly prolonged ($P=0.033$) in the HbA1c $>6.5\%$ group compared with the HbA1c $\leq6.5\%$ group, especially in the white matter ($P=0.005$; Table 2). No significant difference in cerebral blood volume and CBF was found between the 2 groups (Table 2). No significant difference in PCT values was observed between the 2 groups in the ischemic hemisphere.

A modest positive correlation between MTT values in the nonischemic contralateral hemisphere and HbA1c ($R=0.469$; $P=0.016$) was observed. No significant correlation was found between MTT values and admission blood glucose levels ($R=0.260$; $P=0.199$).

The mean MTT values in the nonischemic hemisphere were $5.5\pm0.8$ s and $5.2\pm0.8$ s in the patients with diabetes mellitus and without diabetes mellitus, respectively ($P=0.348$). The 2 patients with diabetes mellitus and HbA1c $\leq6.5\%$ had nonischemic hemispheric MTT values of 4.7 and 5.8 s. In the patients with diabetes mellitus and HbA1c $>6.5\%$, the mean MTT values in the nonischemic hemisphere were $5.5\pm0.9$ s.

### Discussion

The formation of HbA1c is a slow, irreversible, nonenzymatic process consisting of the glycation of valine and lysine residues of the hemoglobin A molecule on the membrane of red blood cells. Because the life span of circulating red cells is $\approx2$ to 3 months, the level of HbA1c, thus, reflects the integrated effect of ambient glucose levels during this time period. Therefore, HbA1c is a more accurate and reliable marker compared with fasting or postprandial blood glucose in accessing long-term glycemic control. Also, it has been demonstrated that the level of HbA1c is well associated with the microvascular complications of diabetes mellitus and with an increased risk of symptomatic hemorrhage after thrombolysis.

The increased MTT values observed on the nonischemic side in patients with poor glycemic control may reflect the increased number and the elongation of the capillaries observed as part of the microvascular remodeling.

Increased MTT may also reflect increased microvascular resistance, related to increased media/lumen ratio and stiffness of microvascular wall in animal models of diabetes mellitus and also demonstrated by myogenic tone and cerebral vascular pulsatility observations of intracranial arteries in subjects with diabetes mellitus. MTI is the PCT parameter that represents the residual time a bolus of contrast agent remains in the capillary bed, and therefore, it is an adequate surrogate for cerebral perfusion pressure and microvascular resistance.

The increased MTT values on the nonischemic hemisphere in the patients with poor chronic glycemic control were not associated with a larger ischemic core or ischemic penumbra, with abnormal PCT values on the ischemic side, or with conventional risk factors. The differences in MTT values were associated neither with an increased white matter disease burden nor with a difference in cervical or intracranial stenosis. The only statistically significant association we observed was between MTT values and an increased HbA1c related to chronic hyperglycemia. Of note, the relatively short time interval between symptom onset and baseline PCT imaging probably allows us to rule out inflammation triggered by stroke to be responsible for the increased MTT values observed because it takes at least 24 to 48 hours for significant cerebral inflammation to develop.

We acknowledge other limitations to our study, including the retrospective nature and small sample size of our study, leading to a potential bias in the selection of patients who matched all the inclusion criteria. Additional studies are needed to determine whether PCT MTT could be a long-term biomarker of chronic hyperglycemic exposure compared with

### Table 2. PCT Values in the Nonischemic Hemisphere

<table>
<thead>
<tr>
<th></th>
<th>HbA1c $\leq6.5%$ Group (n=15)</th>
<th>HbA1c $&gt;6.5%$ Group (n=11)</th>
<th>P Value (2-Tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTT, s</td>
<td>5.0±0.6</td>
<td>5.4±0.7</td>
<td>0.177</td>
</tr>
<tr>
<td>Cortical gray matter</td>
<td>3.8±1.1</td>
<td>3.9±0.9</td>
<td>0.642</td>
</tr>
<tr>
<td>White matter</td>
<td>2.0±1.1</td>
<td>2.1±0.2</td>
<td>0.680</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>3.5±1.1</td>
<td>3.4±1.1</td>
<td>0.551</td>
</tr>
<tr>
<td>Cerebral hemisphere</td>
<td>3.2±1.0</td>
<td>3.0±0.8</td>
<td>0.639</td>
</tr>
<tr>
<td>CBV, mL/100 g</td>
<td>44.5±10.7</td>
<td>45.3±11.2</td>
<td>0.854</td>
</tr>
<tr>
<td>Cortical gray matter</td>
<td>22.1±11.6</td>
<td>20.0±6.5</td>
<td>0.604</td>
</tr>
<tr>
<td>White matter</td>
<td>47.3±14.8</td>
<td>49.3±16.7</td>
<td>0.743</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>35.5±6.6</td>
<td>37.6±10.1</td>
<td>0.532</td>
</tr>
<tr>
<td>Cerebral hemisphere</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD. CBF indicates cerebral blood flow; CBV, cerebral blood volume; HbA1c, hemoglobin A1c; MTT, mean transit time; and PCT, perfusion computed tomography.
HbA1c, which reflects the average glucose level during the past 2 to 3 months only.

In conclusion, our study suggests that poor chronic glycemia control in patients presenting with ischemic stroke is associated with cerebral microvascular remodeling as measured by PCT MTT.

Disclosures
None.

References
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