Lacunar Infarcts and White Matter Attenuation

Ophthalmologic and Microcirculatory Aspects of the Pathophysiology

Rolf Schneider, Michael Rademacher, Sebastian Wolf

Background and Purpose: By means of neurological and ophthalmologic examinations we considered whether there is a microcirculatory disorder not related to hypertension and diabetes in patients with lacunar infarcts and whether there are microcirculatory differences in patients with lacunar infarcts compared with those with white matter attenuation.

Methods: Eighty neurological patients with a lacunar infarct underwent computed tomography and, based on the results, were prospectively assigned to subgroups as follows: (1) patients without changes; (2) patients with white matter attenuation but without lacunar infarcts; (3) patients with lacunar infarcts alone; and (4) patients with both lacunar infarcts and white matter attenuation. Clinical and ophthalmologic parameters were monitored. The retinal microcirculation was studied by videofluorescence angiography. These neurological patients were compared with control ophthalmologic patients matched for age, sex, hypertensive and diabetic ocular fundus changes, and smoking habits.

Results: On average, the 80 patients with lacunar infarcts had a significantly \( P=.0001 \) slower arteriovenous passage time (2.6±0.7 seconds) than the ophthalmologic control subjects (1.6±0.6 seconds). Arteriovenous dye passage time through the retinal microcirculation was nearly normal (2.2±0.8 seconds) in patients with white matter attenuation alone, but was significantly prolonged in patients with lacunar infarcts (2.9±0.8 seconds, \( P=.00085 \)) or both white matter attenuation and lacunar infarcts (2.8±0.4 seconds, \( P=.008 \)).

Conclusions: Patients with lacunar infarcts are characterized by an additional disorder of retinal microcirculation independent of arterial hypertension and diabetes. Our data suggested that white matter attenuation and lacunar infarcts may be phenomena with only weak interdependence. (Stroke. 1993;24:1874-1879.)

KEY WORDS • lacunar infarction • microcirculation • retina • white matter

The improved resolution of present generation computed tomography (CT), the introduction of magnetic resonance imaging technology, and the survival of increasing numbers of the population into old age have stimulated interest in lacunar infarcts, in white matter attenuation ("leukoaraiosis"), and inBinswanger's disease.1-3 Epidemiological and pathoanatomic investigations have identified age and hypertension as important risk factors for lacunar infarcts and white matter attenuation.1,2,4-9 However, the following questions are still debated: Is there a microcirculatory disorder exceeding the presence of hypertensive or diabetic small vessel disease in patients having lacunar infarcts? Is the white matter attenuation visible on CT related to a microcirculatory disorder? In response to these questions, this study was conducted to examine whether there is a microcirculatory disorder not related to hypertension and diabetes in patients with lacunar infarcts and whether there are microcirculatory differences in patients with lacunar infarcts compared with those with white matter attenuation.

Methods

Between March 1986 and March 1991, 208 patients with lacunar infarcts were admitted to the Neurological Department. The diagnostic criteria for a lacunar syndrome corresponded to those given by Fisher.1 All patients received clinical examination on admission and several times during hospital treatment. CT examination was done within 2 weeks after admission and was repeated 1 year later. Stenosis of the neck vessels was ruled out by Doppler sonography. In general, angiography was not performed, and patients displaying large vessel abnormalities on Doppler sonography were excluded. Patients displaying CT-identified lesions larger than 10 mm, patients with superficial infarcts, and patients with atrial fibrillation were excluded as well. Transthoracic and transesophageal echocardiography were performed when judged useful to exclude patients with possible embolic sources of lacunar infarcts.10 In addition, patients with concomitant diseases that might influence the microcirculation were excluded. Furthermore, in some patients videofluorescence angiography was not possible because of diseases involving the refracting media, and some people were unable to cooperate. Eighty participants remained in the study.
No patient was bedridden. The variables described below were recorded within 6 weeks after admission. The study was approved by the University Ethical Committee. Informed consent was obtained from each patient before he or she underwent any examination, according to the Declaration of Helsinki. Videofluorescence angiography (see below) was performed blindly to the clinical and radiological findings.

**Computed Tomography**

CT was performed with a Siemens Somatom DRH with infratentorial and supratentorial slice thicknesses of 4 mm and 8 mm, respectively. CT resolution allowed the detection of lesions as small as 2 mm. The diagnosis of a lacunar infarct was made if the lesion was round or ovaly shaped, did not exceed a diameter of 10 mm, and was situated in the lower corona radiata, the basal ganglia, the internal capsule, or the pons. White matter attenuation was defined as any bilateral patchy white matter attenuation not discernible as a clear-cut infarct. In view of the moderate interrater agreement for lacunar infarcts and white matter attenuation or leukoaraisis, classification of the CT scans into the different groups was based on the unanimous consensus judgment of three experienced raters. The categories slight, moderate, and severe white matter attenuation were used, and lacunar infarcts were counted. Four groups of patients were formed: group 1 (n=13), patients with a lacunar syndrome but normal CT; group 2 (n=26), patients with CT evidence of white matter attenuation but without lacunar infarcts; group 3 (n=19), patients with CT evidence of lacunar infarcts but without white matter attenuation; and group 4 (n=22), patients with CT evidence of both white matter attenuation and lacunar infarcts.

**Matching Process**

Patients matched for age, sex, hypertensive and diabetic fundus changes, and smoking were taken from a database of patients who underwent ophthalmologic examination in the Department of Ophthalmology. This data base contains more than 3000 subjects, and exact adjustment of individual matching partners was thus possible. The hypertensive changes on the ocular fundus were subclassified into four categories according to Neubauer’s classification system. Matching was extended to these categories (Table 1). These patients were screened using a questionnaire for the absence of signs or symptoms of stroke, and all except 15 patients with a normal fundus underwent examination in the Department of Ophthalmology for hypertensive or diabetic retinopathy. In all cases blood samples were taken and videofluorescence angiography was performed within 6 weeks after admission to the hospital.

**Neurological Findings**

Patient recruitment was based on the presence of a lacunar infarct. A record of clinical findings was kept as to whether purely motor deficits, purely sensory deficits, sensorimotor deficits, ataxic hemiparesis, or the clumsy-hand dysarthria syndrome were present.

**Risk Factors**

A patient was classified as hypertensive if systolic blood pressure was >160 mm Hg and/or diastolic blood

---

**TABLE 1. Matching Variables for Neurological and Ophthalmologic Patient Groups**

<table>
<thead>
<tr>
<th>Matching Variable</th>
<th>Patients With Lacunar Syndromes, n=80</th>
<th>Ophthalmologic Patients, n=80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.3±9.6</td>
<td>66.9±7.8</td>
</tr>
<tr>
<td></td>
<td>66 (38-81)</td>
<td>68 (50-83)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>53 (66%)</td>
<td>48 (60%)</td>
</tr>
<tr>
<td>F</td>
<td>27 (34%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>146±19</td>
<td>151±24</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>85±10</td>
<td>87±21</td>
</tr>
<tr>
<td>Hypertensive fundus, total*</td>
<td>63 (79%)</td>
<td>63 (79%)</td>
</tr>
<tr>
<td>Hypertensive fundus, 1*</td>
<td>25 (31%)</td>
<td>25 (31%)</td>
</tr>
<tr>
<td>Hypertensive fundus, 1-2*</td>
<td>6 (8%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Hypertensive fundus, 2*</td>
<td>30 (38%)</td>
<td>30 (38%)</td>
</tr>
<tr>
<td>Hypertensive fundus, 3*</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hypertensive fundus, 4*</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 (16%)</td>
<td>13 (16%)</td>
<td></td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>4 (5%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>20 (25%)</td>
<td>22 (28%)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. Values are expressed as mean±SD or median (range) where appropriate. Matching was extended to hypertensive and diabetic fundus changes and was perfect for almost all variables.

*Fundus grading is based on the classification system of Neubauer.12
pressure was >95 mm Hg. Patients were also classified as hypertensive if there was a known history of hypertension, including patients who were normotensive at the time of examination because of effective antihypertensive medication. In addition, left ventricular hypertrophy and hypertensive changes of the ocular fundus were considered to be indicative of arterial hypertension. Diabetes was diagnosed when patients required either oral antidiabetic drugs or were insulin dependent. Impaired lipid metabolism was diagnosed if cholesterol or triglyceride values exceeded 2.6 or 2.0 g/L, respectively. History taking included smoking, hyperuricemia, arterial occlusive disease, previous strokes, and positive family history of vascular disease.

**Ophthalmologic Examination**

The vessels of the ocular fundus were examined and assessed by direct ophthalmoscopy producing an upright image (Zeiss Cie), by indirect ophthalmoscopy (inverted image) using the Zeiss ophthalmoscope and examining lens, and, where necessary, by slit-lamp microscopy using a Goldmann triple-mirror contact lens. The retinal arteries and veins and their branches were assessed, the retinal parenchyma was described, and the optic nerve head was examined. The classic ocular fundus changes with hypertension (e.g., variations in vascular caliber, changes in vascular reflexes, hemorrhages, exudates, optic nerve head changes, and so forth) were recorded using Neubauer’s grading system of hypertension and were used for the assessment.

**Videofluorescence Angiography**

For videofluorescence angiography, 7 mg sodium fluorescein/kg body wt (5 mL, 10%) was given by IV injection. The videofluorescence angiogram was recorded using a Zeiss VK 50 fundus camera with an adapted video system. The videotapes were analyzed using an image analysis computer (Mikrovideomat 3, Zeiss Oberkochen). Density variations in the fluorescein angiograms were analyzed by means of a digital image-processing system. The angiograms were first corrected for eye movements based on a recursive estimation method. After correction, the digital image-processing system measured the entire angiogram sequence, recording the intensity of fluorescein at various locations. Four points (size, 3×3 pixel) were interactively selected for measurement. The computer then analyzed the entire angiogram frame by frame. Fifty frames per second were evaluated. For each image, the program recorded the mean intensity levels at each of the selected locations. Intensity curves were obtained by plotting the collected data against the time axis. The time of the first appearance of fluorescein was evaluated from the intensity curves. Two points were selected for measurement on the superotemporal and inferotemporal arteries 0.5-disk diameter from the disk margin. The time elapsed between injection of the dye into the antecubital vein and its appearance at these points provided the macular circulation arm-retina time (ART). The time elapsed between the appearance of dye at the reference point in the temporal arteries and an adjacent point in the corresponding vein was used to determine the arteriovenous passage time (AVP; Figure). The data obtained from the superior and inferior temporal quadrants were averaged for each patient to obtain representative values for the posterior pole, not only for one temporal quadrant. The intraindividual variation for the AVP is 15.6%. All angiograms were evaluated in masked fashion with no clinical data available.

**Statistics**

The Kruskal-Wallis rank test was used to establish whether significant mean differences could be identified for individual variables. Subsequent Mann-Whitney U tests were performed for all pairs of groups. The probability values of these comparisons were subjected to Holm’s sequentially rejective multiple test procedure at an overall type I error level of 0.05 per variable examined.

**Results**

**Clinical Findings**

The clinical results are shown in Table 2. Thirty patients were symptom-free on admission, and no post hoc classification was performed. Comparison of the original 208 patients with the remaining 80 disclosed no clinical differences.

**CT Classification**

Thirteen patients (16%) had a normal CT, 26 (32.5%) presented white matter attenuation, 19 (24%) had lacunar infarcts, and 22 (27.5%) had both lacunar infarcts and white matter attenuation. In 27 patients the lacune visible on CT was appropriate to symptoms. Nineteen patients had a single lacune, 4 patients had 2 lacunes, and 18 patients had 3 or more lacunes on CT. The CT subgroups were compared as to whether there were differences in risk factors, age, and sex. No differences were found except for age. Patients having white matter attenuation alone were significantly older than the patients of the other subgroups (67.4±6.6 years versus 59.4±5.3 years, P=.03 by Holm’s procedure).

**Ophthalmologic Results**

Of the 80 neurological patients, 63 displayed hypertensive changes of the ocular fundus. Detailed data are shown in Table 1. Since these hypertensive changes were part of the matching criteria, the same frequencies are found for the ophthalmologic subjects. Only four neurological patients had a diabetic retinopathy; they were matched with ophthalmologic patients with the same changes.

**AVP**

AVP in the neurological and the ophthalmologic groups differed considerably (P=.0001 by Mann-Whitney U test; Table 3). In the ophthalmologic patients the AVP was 1.61 seconds compared with 2.60 seconds in the patients with lacunar infarcts. No significant differences in ART were found. The same analysis was performed for each CT subgroup and the corresponding matching partners. Differences were most significant for patients having both lacunar infarcts and white matter attenuation (P=.0001), followed by patients with lacunar infarcts alone (P=.0002) and patients with white matter attenuation alone (P=.001). Differences were less pronounced but still significant for patients without CT changes (P=.007).
Significant group differences were found for the AVP ($P=.0133$ by Kruskal-Wallis test) in the CT subgroups. Patients having lacunar infarcts or both lacunar infarcts and white matter attenuation had delayed AVPs compared with those having white matter attenuation only (Table 4). AVP was significantly faster in patients with severe white matter attenuation ($n=8$) compared with patients with slight white matter attenuation ($n=14$; $P=.02$ by Holm’s procedure). Patients with moderate changes ($n=4$) were not numerous enough to undergo statistical evaluation.

### Discussion

Comparison of our clinical data with recent publications\textsuperscript{17-20} did not reveal any important differences. However, on admission 30 patients had already returned to a normal neurological status. For these patients we tried to reconstruct the initial lacunar syndrome. However, these patients were not classified into lacunar syndrome categories because the data from history taking, with a predictive value of 0.74,\textsuperscript{21} appeared too unreliable. In

### TABLE 2. Frequency of Lacunar Syndromes in 50 Patients From the Department of Neurology

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure motor hemiparesis</td>
<td>39</td>
<td>48.8</td>
</tr>
<tr>
<td>Pure sensory stroke</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>Ataxic hemiparesis</td>
<td>6</td>
<td>7.5</td>
</tr>
<tr>
<td>Clumsy-hand dysarthria</td>
<td>3</td>
<td>3.8</td>
</tr>
<tr>
<td>Symptomatic free on admission</td>
<td>30</td>
<td>37.5</td>
</tr>
</tbody>
</table>

No post hoc classification was attempted on the 30 symptom-free patients.
TABLE 3. AVP and ART in Patients With Lacunar Syndromes and Their Matching Partners

<table>
<thead>
<tr>
<th>Time</th>
<th>Neurological Patients, n=80</th>
<th>Ophthalmologic Patients, n=80</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVP, s</td>
<td>2.6±0.7</td>
<td>1.6±0.6</td>
<td>.001</td>
</tr>
<tr>
<td>ART, s</td>
<td>13.4±3.0</td>
<td>13.2±2.7</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(6.8-20.2)</td>
<td>(8.4-22.0)</td>
<td></td>
</tr>
</tbody>
</table>

AVP indicates arteriovenous passage time; ART, arm-retina time; NS, not significant. Ophthalmologic patients were the matched control subjects for the neurological patients with lacunar syndromes. All variables were complete (n=80). Data are expressed as mean±SD and median (range).

Those patients the diagnosis of a lacunar stroke was based on the presence of a lacunar infarct on CT, the absence of large vessel or cardiac disease, and good recovery. The remaining patients presented the most frequent lacunar syndromes (Table 2).

Acquisition and interpretation of our data depended on the ongoing development of CT technology. Because resolution was not as good as one CT generation ago, many patients who presented with the CT features of white matter attenuation and lacunar infarcts would earlier have been classified in the group with lacunar infarcts without white matter attenuation or normal. However, the resolution of the computer tomograph used in this study allowed the detection of lesions as small as 2 mm, and therefore the majority of lacunar infarcts was most probably documented. Furthermore, we used the most rigorous radiological definition of lacunar infarcts and of white matter attenuation described thus far. One could question whether patients without proven lacunar infarcts on CT were really lacunar. However, Boiten, in his study on 252 patients, reports a sensitivity of 95% and a specificity of 93% in diagnosing lacunar infarction if Bamford's operational definitions of lacunar syndromes are used.

Sixty-three (79%) patients had hypertensive signs on fundoscopy, suggesting hypertensive small vessel disease. Hypertension is well known to be the most important risk factor for lacunar infarcts. However, the predictive value of the variable hypertension for lacunar strokes is low. We thought it more accurate to choose hypertensive fundus vessel changes as a matching variable rather than blood pressure values. Two patients had hypertension but no hypertensive fundus changes. The same procedure was applied to diabetic fundus changes. Thirteen patients had diabetes, but only four presented a diabetic retinopathy.

We used retinal microcirculatory parameters assessed by videofluorescence angiography as an indicator for cerebral microcirculation. The correlation between retinal and cerebral circulation in patients suffering from extensive and hemodynamically effective occlusive disease of the extracranial arteries is well documented. It is also documented for small vessel disease by Lund, who performed correlative pathoanatomic examinations on 125 brains and eyes. In his study, cerebral vessel changes corresponded to retinal vessel changes in 109 of 125 cases. He specifies that there was severe hyalinosis of basal ganglia vessels in 21 patients, and all had the same changes in the retinal vessels. Additionally, he reports a high coincidence of vessel wall changes in patients with large artery disease and in normal patients. However, he does not provide information on the vessel size and the exact wall pathology. Therefore, retinal microcirculation possibly but not certainly reflects cerebral microcirculation, especially in patients with hypertensive vessel changes. Consequently, a long AVP might be indicative of a disturbed cerebral microcirculation and, therefore, may favor the occurrence of lacunar infarcts. To make sure that the AVP was not influenced by systemic hemodynamics or ipsilateral obstruction, we also measured the ART, which was normal in our patients.

Some authors have attributed white matter attenuation to small vessel disease or hypoperfusion and have, therefore, presumed a vascular etiology. However, the same phenomenon has also been observed in patients without vascular risk factors. In our study, patients with lacunar infarcts or both lacunar infarcts and white matter attenuation had a pronounced disturbance of the retinal microcirculation. As shown by the comparison with matched pairs, the disturbed retinal microcirculation occurred independently of hypertensive and diabetic vessel changes. Nothing is known about the nature of this additional microcirculatory disturbance. It is more likely that the microcirculatory disturbance is linked to the presence of lacunes and not to the white matter attenuation, because patients with white matter attenuation alone had only minor disturbances of the retinal microcirculation. Furthermore, the retinal AVP was faster and microcirculation therefore better in patients with severe white matter attenuation compared with patients with only mild white matter attenuation. One could speculate whether a normal AVP favors the occurrence of white matter attenuation or whether white matter attenuation is not a conse-

TABLE 4. AVPs for the Four Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal CT, n=13</th>
<th>White Matter Attenuation, n=26</th>
<th>Lacunar Infarcts, * n=19</th>
<th>Lacunar Infarcts and White Matter Attenuation, † n=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVP, s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.4 (0.5)</td>
<td>2.2 (0.8)</td>
<td>2.9 (0.8)</td>
<td>2.8 (0.4)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.5 (1.2-3.1)</td>
<td>2.1 (1.0-4.0)</td>
<td>2.8 (2.0-4.6)</td>
<td>2.7 (2.1-3.5)</td>
</tr>
</tbody>
</table>

AVP indicates arteriovenous passage time; CT, computed tomography.

*P = .0008 for white matter attenuation vs lacunar infarcts.

†P = .008 for white matter attenuation vs combined lacunar infaracts and white matter attenuation.
sequence of a microcirculatory disorder. The latter seems more reasonable to us.

Acknowledgments
This study was supported by a grant from Fresenius AG, Oberursel, FRG. We thank Dr Klaus Willmes for his statistical advice and Prof Armin Thron for his neuroradiological advice. Our technical assistant Simon Luerken and the following medical students were engaged in motivating and encouraging the patients: Ch. Ganzs, R. Kluge, B. Kahleri, F. Baltussen, E. Sibbel, J. Dorr, N. Braunen, Ch. Hoebkses, S. v. Landwuest, Ch. Hiemenz, H. Schepers, M. Schlichter, A. Wichert, and B. Ivanoff.

References
Lacunar infarcts and white matter attenuation. Ophthalmologic and microcirculatory aspects of the pathophysiology.

R Schneider, M Rademacher and Š Wolf

*Stroke*. 1993;24:1874-1879
doi: 10.1161/01.STR.24.12.1874

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/24/12/1874

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at: http://stroke.ahajournals.org//subscriptions/