Retinal Microvascular Signs May Provide Clues to the Underlying Vasculopathy in Patients With Deep Intracerebral Hemorrhage

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**Background and Purpose**—Deep intracerebral hemorrhage (ICH) and lacunar infarcts are the result of small vessel disease, whereas nonlacunar infarcts are often caused by large artery atherosclerosis or cardiac embolism. We hypothesized that patients with deep ICH and lacunar infarcts have similar retinal microvascular signs and that these differ from those seen in patients with nonlacunar infarcts.

**Methods**—We studied patients with acute stroke and classified their stroke as deep ICH, lacunar infarction, or nonlacunar infarction. In a masked fashion we assessed retinal photographs for quantitative and qualitative evidence of microvascular damage.

**Results**—We recruited 630 patients (51 had deep ICH, 93 had lacunar infarction, and 486 had nonlacunar infarction). Patients with deep ICH were more likely than those with nonlacunar infarcts to have severe focal narrowing of the retinal arterioles (OR, 3.7), severe arteriovenous nicking (OR, 2.6), and quantitatively narrower retinal arterioles and wider retinal venules. Retinal microvascular signs were similar in patients with deep ICH and lacunar infarction.

**Conclusions**—Patients with deep ICH and lacunar infarcts are more likely than patients with nonlacunar infarcts to have signs indicating hypertensive damage in the retinal arteriolar wall. (*Stroke*. 2010;41:618-623.)

**Key Words:** deep intracerebral hemorrhage • lacunar infarction • retinal microvascular signs

Deep intracerebral hemorrhage (ICH) in the territory of the small perforating arteries of the basal ganglia, thalamus, pons, and cerebellum is classically taught to be caused by hypertensive small vessel disease; however, other vasculopathies cannot be excluded. Similarly, lacunar infarction is a disease of the small perforating arteries in the brain, but the precise etiology is uncertain, with treatment largely based on an assumption of underlying thrombotic small vessel disease. Recent studies, however, have challenged this assumption and suggested an alternative hypothesis that lacunar infarction is related to nonatherothrombotic small vessel pathology. We recently reported that among 1321 patients with acute ischemic stroke, those with lacunar infarction were more likely to have focal retinal arteriolar narrowing, enhanced arteriolar light reflex, arteriovenous nicking, and widening of retinal venules than patients with nonlacunar infarction, and that both lacunar and nonlacunar infarction had similar proportions with hypertension, diabetes, or hypercholesterolemia. Because deep ICH and lacunar infarcts occur within the same vascular structural level (ie, small vessel disease), we hypothesized they may share similar retinal microvascular signs with those seen in lacunar infarction, but that this pattern would differ from the retinal microvascular signs seen in patients with nonlacunar infarction (eg, resulting from atherothromboembolism and cardiac embolism). To test this hypothesis, we examined patterns of retinal microvascular signs associated with deep ICH compared to those of patients with both lacunar and nonlacunar infarction, separately.

**Materials and Methods**

**Study Population**

The study sample for this report consisted of patients from the Multi-Center Retina and Stroke Study, a hospital-based study of acute stroke patients. Detailed methodology has been described elsewhere. In brief, acute stroke patients (n=842) from 2 Australian centers (Melbourne and Sydney) were recruited from 2004 to 2007. Written informed consent was obtained from patients or their next of kin. The study was approved by the Human Research Ethics Committee, University of Melbourne.

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committees of the respective hospitals. All patients underwent an interview with standardized questionnaires, neurological examination brain imaging and an extensive assessment of atherosclerotic diseases and their risk factors, as well as retinal photography. In the present study, we included 630 patients after excluding 43 cases classified as stroke mimics, 93 as transient ischemic attacks, 57 with lobar or secondary ICH, and 19 with ungradable retinal images.

Assessment of Acute Stroke
The diagnosis of ICH or cerebral infarction was determined by a consensus panel of stroke experts with access to the clinical information and neuroimaging. All patients had a CT brain scan, and a subset of stroke patients (43%) had MRI scanning. The finding of a hyperdense lesion on CT (and not determined to be calcium) led to a diagnosis of ICH; hemorrhagic transformation of an infarct was coded as a cerebral infarct, and ICH attributable to secondary causes, such as neoplasm or arteriovenous malformation, was excluded. Cerebral infarction subtypes were classified as large vessel atherosclerotic, small vessel (lacunar), cardioembolic infarction, and others with undetermined etiology. Details of the definitions for other acute stroke subtypes are reported elsewhere.

Retinal Photography and Grading
Retinal photography procedures are described elsewhere. Briefly, all study participants had up to 6 retinal photographic fields taken of each eye, mimicking fields 1 to 6 of the Diabetic Retinopathy Study, using a non-mydriatic digital camera (Canon D60; Canon), and after pharmacological pupil dilation for the majority of patients. All retinal photographs were taken at least 24 hours after deep ICH was diagnosed. De-identified images were graded centrally at the 2 study sites using an established and reliable grading system. Qualitative retinal signs, including retinal arteriolar wall signs, were graded as absent, mild, or severe for focal arteriolar narrowing, arteriovenous nicking, and enhanced arteriolar light reflex (Figure). Isolated retinopathy lesions (microaneurysms, cotton wool spots, retinal hemorrhages, and hard exudates) were graded as either present or absent. The grading was performed by comparison with a standard set of images at the Centre for Vision Research, University of Sydney. All lesions detected were adjudicated by 2 senior researchers (J.J.W., P.M.). Quantitative retinal vessel signs, graded at the Centre for Eye Research Australia, University of Melbourne, included estimates of retinal arteriolar and venular caliber obtained using a semiautomated computer assisted method. The Parr-Hubbard-Knudtson formula was used to summarize the average caliber of retinal arterioles and venules and is represented as the central retinal arteriolar equivalent and central retinal venular equivalent. Graders were masked to clinical diagnoses. Kappa values for the intragrader and intergrader reproducibility were very high, with 0.97 to 0.98 for arteriolar caliber and 0.94 to 0.98 for venular caliber.

Vascular Risk Factors
Patients underwent an extensive assessment of atherosclerotic diseases and their risk factors during their admission. Hypertension was diagnosed as a self-reported history of hypertension, which included the use of antihypertensive medications. Diabetes was diagnosed as a fasting glucose ≥7.0 mmol/L or a self-reported history of diabetes, which included use of oral hypoglycemic agents or insulin. Coronary heart disease and myocardial infarction were ascertained by an adjudication process involving medical history, physical examination, and laboratory criteria, including an ECG.

Statistical Methods
We constructed logistic regression models to assess the associations of deep ICH with various retinal vascular signs compared with
There were 630 patients (75% of 842 patients recruited from the Melbourne and Sydney centers); 51 had deep ICH, 93 had lacunar infarction, and 486 had nonlacunar cerebral infarction. A comparison of baseline characteristics and cardiovascular risk factors of patients is shown in Table 1. Patients with deep ICH had substantially higher mean admission systolic and diastolic blood pressures than patients with either lacunar or nonlacunar infarction. Compared to patients with lacunar infarction, those with deep ICH were more likely to have atrial fibrillation (12.2% vs 2.3%) but were less likely to be using an antiplatelet agent (24.0% vs 42.9%) or to have hypercholesterolemia (25.5% vs 44.1%). Compared to patients with nonlacunar infarction, those with deep ICH tended to be younger (64.9 vs 69.3 years), were less likely to be white (76.5% vs 88.8%), or were less likely to have a history of cardiovascular disease (3.9% vs 16.1%).

Severe focal arteriolar narrowing, severe arteriovenous nicking, enhanced arteriolar light reflex, and retinopathy were most frequently present in patients with deep ICH (31.9%, 40.4%, 31.9%, and 42.0%) compared to patients with lacunar (19.8%, 22.5%, 24.7%, and 35.5%) or nonlacunar infarction (13.2%, 21.2%, 19.9%, and 31.9%). After adjusting for age, gender, cigarette smoking, hypercholesterolemia, hypertension, and diabetes, compared to nonlacunar infarction deep ICH was significantly associated with severe focal arteriolar narrowing and severe arteriovenous nicking (Table 2). These associations persisted in patients without diabetes mellitus (data not shown). After stratifying by presence of hypertension, in those without hypertension, deep ICH was significantly associated with all qualitative retinal arteriolar wall signs but not with retinopathy lesions (data not shown). None of these associations was present in people with hypertension or diabetes (data not shown). Deep ICH was not significantly different from lacunar infarction in the associations with qualitative retinal microvascular signs (Table 3).

Table 4 shows the association of mean retinal vessel caliber with deep ICH, compared to nonlacunar infarction, stratified by hypertension. After multivariable adjustment, patients with deep ICH had significantly narrower mean retinal arteriolar caliber (131.9 μm vs 138.7 μm; P=0.0004) and wider mean retinal venular caliber (212.5 μm vs 205.9 μm; P=0.03). In subgroup analyses, however, these differences persisted only in those without hypertension. In patients without diabetes, deep ICH was associated with narrower mean retinal arteriolar caliber but not wider venular caliber (data not shown). None of these associations was present in patients with hypertension or diabetes. The mean retinal arteriolar and venular caliber did not differ significantly from those with lacunar or nonlacunar infarction in separate models. Models adjusted for age, gender, hypertension, hypercholesterolemia, diabetes, and cigarette smoking status. Multiple linear models were used to assess the associations of deep ICH with central retinal arteriolar equivalent and central retinal venular equivalent separately, after adjusting for the fellow vessel caliber (ie, arteriolar caliber adjusted for venular caliber to account for the correlation between the 2 measures). Odds ratios and 95% confidence intervals are reported.

Table 2. Association Between Deep ICH With Qualitative Microvascular Signs Compared to Nonlacunar Cerebral Infarction

<table>
<thead>
<tr>
<th></th>
<th>Focal Arteriolar Narrowing</th>
<th>Arteriovenous Nicking</th>
<th>Enhanced Arteriolar Light Reflex</th>
<th>Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td>OR* (95% CI)</td>
<td>% (n)</td>
<td>OR* (95% CI)</td>
</tr>
<tr>
<td>Nonlacunar cerebral infarction</td>
<td>13.2 (69)</td>
<td>1.0 (ref)</td>
<td>21.2 (94)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Deep ICH</td>
<td>31.9 (15)</td>
<td>3.7 (1.8–7.6)</td>
<td>40.4 (19)</td>
<td>2.6 (1.4–5.1)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, cigarette smoking, hypercholesterolemia, hypertension, and diabetes.
significantly between patients with deep ICH and those with lacunar infarction.

**Discussion**

In this report, retinal arteriolar wall signs were defined as focal arteriolar narrowing, arteriovenous nicking, and enhancement of the arteriolar light reflex. The combination of these retinal vessel signs with generalized arteriolar narrowing, in the absence of retinopathy, has been classified as representing mild hypertensive retinopathy. Focal arteriolar narrowing is an indicator of localized arteriolar damage, whereas arteriovenous nicking (“nipping”) occurs when the sclerotic arteriolar wall, at points where the arteriole crossing the venule shares a common adventitia, compresses the venular column and the venules develop a “nicked” appearance. Enhancement of the arteriolar light reflex could reflect either arteriolar wall thickening or changes in blood flow velocity.

There are no other relevant studies for comparison with our study. Findings from this study demonstrate patients with deep ICH were more likely to have qualitative and quantitative retinal arteriolar wall signs, consistent with hypertensive damage to small vessels, but not retinopathy lesions, compared to patients with nonlacunar infarction. Our study may provide evidence supporting a microvascular link with deep ICH. Specifically, it supports current knowledge that hypertension is a major risk factor for deep ICH. Second, it shows that patients with deep ICH are more likely to have similar retinal microvascular signs to those with lacunar infarction when compared to those with nonlacunar cerebral infarction. Third, retinal microvascular signs may be a surrogate for cerebral small vessel disease.

In subgroup analyses, we found significant associations of deep ICH with retinal vessel signs only in patients without a diagnosed history of hypertension. It is possible that some of these patients may have had undetected hypertension, because this is the main risk factor for deep ICH. We did not find similar associations separately in persons with hypertension or diabetes, which could have resulted from the relatively small numbers in these subgroups. Hypertension is traditionally diagnosed using arbitrary cut-off levels for both systolic and diastolic blood pressures, which may not be universally appropriate for all individuals. Our finding that patients with deep ICH but without a history of hypertension were more likely to present with hypertensive retinal vessel wall signs may also suggest that in these individuals traditionally “normal” blood pressure levels could already represent relatively “hypertensive” levels.

Retinal microvascular signs are thought to be part of a spectrum of pathological processes in response to hypertension. Some of these signs may represent transient alterations of retinal arterioles in response to acute elevations of blood pressure, whereas others represent irreversible structural damage resulting from chronic hypertension. Many studies

<table>
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<tr>
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<th>Enhanced Arteriolar Light Reflex</th>
<th>Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (n) OR (95% CI)</td>
<td>% (n) OR (95% CI)</td>
<td>% (n) OR (95% CI)</td>
<td>% (n) OR (95% CI)</td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.8 (18) 1.0 (ref)</td>
<td>22.5 (20) 1.0 (ref)</td>
<td>24.7 (22) 1.0 (ref)</td>
<td>35.5 (33) 1.0 (ref)</td>
</tr>
<tr>
<td>Deep ICH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.9 (15) 1.9 (0.8–4.6)</td>
<td>40.4 (19) 2.1 (0.9–5.0)</td>
<td>31.9 (15) 1.4 (0.5–3.1)</td>
<td>42.0 (21) 1.7 (0.8–3.7)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, cigarette smoking, hypercholesterolemia, hypertension, diabetes, and the fellow vessel caliber.

**Table 4. Mean Retinal Vascular Caliber of Patients With Deep ICH Compared to Lacunar and Nonlacunar Infarction Unstratified and Stratified by Hypertension Status**

<table>
<thead>
<tr>
<th>Retinal Arteriolar Caliber, μm</th>
<th>Retinal Venular Caliber, μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>Adjusted*</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>All persons</strong></td>
<td></td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td>136.6 (P=0.18)</td>
</tr>
<tr>
<td>Nonlacunar cerebral infarction</td>
<td>138.3 (P=0.07)</td>
</tr>
<tr>
<td>Deep ICH</td>
<td>132.4</td>
</tr>
<tr>
<td><strong>Without hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td>133.1</td>
</tr>
<tr>
<td>Nonlacunar cerebral infarction</td>
<td>140.3</td>
</tr>
<tr>
<td>Deep ICH</td>
<td>131.3</td>
</tr>
<tr>
<td><strong>With hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td>138.4</td>
</tr>
<tr>
<td>Nonlacunar cerebral infarction</td>
<td>137.2</td>
</tr>
<tr>
<td>Deep ICH</td>
<td>133.1</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, cigarette smoking, hypercholesterolemia, hypertension, diabetes, and the fellow vessel caliber.
have confirmed the association of hypertension, particularly chronic hypertension, with retinal arteriolar wall signs, including arteriovenous nicking, generalized arteriolar narrowing, and an enhanced retinal arteriolar light reflex.\textsuperscript{10,17–19} Recently, a number of population-based studies\textsuperscript{20–22} reported that arteriovenous nicking and generalized arteriolar narrowing were associated with both current and past elevated diastolic and systolic blood pressure levels, and that the past blood pressure levels were documented 6 to 8 years before the retinal vessel wall signs were assessed. The hypothesis that arteriovenous nicking is a sclerotic change associated with chronic rather than acute hypertension is supported by evidence from a histopathologic study.\textsuperscript{23}

In contrast, focal arteriolar narrowing and retinopathy were found to be associated with acute hypertension\textsuperscript{24–26} and current, but not past, levels of elevated blood pressure.\textsuperscript{22} Focal arteriolar narrowing is proposed to occur when the blood pressure increases above the upper limit of autoregulation, with arteriolar pressures ranging from 130 mm Hg to 160 mm Hg\textsuperscript{27} causing structural damage to the intima layer of the arteriolar wall. If blood pressure further increases, then fibrinoid necrosis of the muscle cells in the arteriolar wall can occur at localized vulnerable points, possibly through the breakdown of the blood–retina barrier, allowing insudation of plasma into the vessel wall and deposition of fibrin.\textsuperscript{26} Therefore, an alternative interpretation of our findings may be that some of the arteriolar wall signs, such as focal arteriolar narrowing, could be secondary to acute blood pressure elevation or to a more recent, further elevation of blood pressure in patients with ICH. Patients with deep ICH had significantly higher admission blood pressure levels than patients with nonlacunar stroke subtypes (Table 1). Thus, retinal microvascular signs may be subclinical markers of either acute or chronic microvascular structural damage, which carries cerebral vascular risk information independent of traditional cerebrovascular risk factors.

Retinopathy in persons without diabetes is considered a sign suggesting retinal ischemia and breakdown of the blood–retinal barrier. In epidemiological studies of older populations, retinopathy in persons with or without diabetes has been found to be associated with clinical stroke,\textsuperscript{28} subclinical cerebral infarction,\textsuperscript{29} white matter lesions,\textsuperscript{30} cerebral atrophy,\textsuperscript{31} cognitive decline,\textsuperscript{32,33} and mortality.\textsuperscript{34–36} However, we did not find an association of deep ICH with retinopathy, which either could be attributable to small numbers or could suggest a difference in pathophysiology between cerebral infarction (or retinopathy) and deep ICH. The latter could explain why traditional cerebrovascular risk factors for cerebral infarction, such as cigarette smoking, hypercholesterolemia, and diabetes, are not obvious risk factors for deep ICH.

The significance of our finding of wider mean retinal venular caliber in deep ICH is unclear, but it is consistent with previous associations of wider mean retinal venular caliber with an increased risk of stroke,\textsuperscript{37,38} cerebral white matter lesions,\textsuperscript{39,40} cerebral hypoxia, reduced small vessel arteriolar compliance, endothelial dysfunction, hyperglycemia, and inflammation.\textsuperscript{41}

Strengths of our study include its prospective collection of a relatively large sample of patients inclusive of all ages (19–94 years) and stroke severity, standardized central evaluation of retinal photographs masked to participant characteristics and stroke subtype, and the use of validated diagnostic criteria for stroke subtypes by stroke physicians. Important limitations of this study should also be mentioned. First, the small sample of patients recruited with deep ICH (n=51) has led to some limitation in study power to detect significant associations in subgroup analyses. Further, in these subgroup analyses there is a possibility of misdiagnosis of cardiovascular risk factors because hypertension was abstracted from the admission, highest and lowest blood pressure readings performed for each participant rather than from continuous 24-hour monitoring of the blood pressure. We acknowledge that in future studies 24-hour monitoring of blood pressure (and 24-hour ECG monitoring) should be considered. Second, there is a possibility of misclassification of stroke subtypes because CT was performed for every participant and MRI of the brain imaging was only performed in a subset (43%) of acute stroke cases. CT has been the gold standard for identifying acute ICH and remains the most commonly used brain imaging modality for acute stroke. However, a higher proportion of patients undergoing MRI would have allowed for a more accurate classification of stroke subtypes.\textsuperscript{42} Third, the clinical assessment of patients between the 2 centers was not centralized. However, we attempted to minimize this potential bias by using standardized assessment questionnaires and held regular consensus meetings to diagnose stroke subtypes masked to retinal imaging findings. Finally, because this study was cross-sectional, we could not elucidate if the retinal arteriolar wall signs occurred simultaneously or before the stroke event. Longitudinal data to confirm the link between retinal microvascular signs and deep ICH would be valuable.

From a clinical perspective, determining the extent to which the retinal microvasculature is a surrogate for microvascular beds in the brain will greatly strengthen the rationale for the use of retinal microvascular signs to probe the pathophysiology of cerebrovascular disease.\textsuperscript{28} Future studies of acute stroke patients with optical coherence tomography, in addition to genetic studies,\textsuperscript{43} could noninvasively evaluate the vascular structure of the retina and choroid\textsuperscript{44} to further complement our knowledge of the pathogenesis of deep ICH.

**Summary**

In this study, patients presenting with deep ICH were found to have retinal microvascular signs consistent with hypertensive damage to arteriolar wall structure as opposed to those presenting with nonlacunar infarction. These findings support our hypothesis of concomitant changes occurring in small vessels of the brain (deep ICH) and the retina. In addition, in patients with deep ICH, the finding of retinal microvascular signs similar to the signs observed in patients with lacunar infarction\textsuperscript{3,4} support our hypothesis that deep ICH and lacunar infarction likely share similar underlying pathophysiology.

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Disclosures

None.

References

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