Retinal Vascular Caliber and Extracranial Carotid Disease in Patients With Acute Ischemic Stroke
The Multi-Centre Retinal Stroke (MCRS) Study

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Background and Purpose—Previous studies show that both retinal vascular caliber and carotid disease predict incident stroke in the general population, but the exact relationship between these 2 microvascular and macrovascular structural risk factors is unclear. We studied the relationship between retinal vascular caliber and carotid disease in patients presenting with acute ischemic stroke.

Methods—We conducted a cross-sectional study of patients with acute ischemic stroke recruited from 3 centers (Melbourne, Sydney, Singapore). The caliber of retinal arterioles and venules was measured from digital retinal photographs. Severe extracranial carotid disease was defined as stenosis ≥75% or occlusion determined by carotid Doppler using North American Symptomatic Carotid Endarterectomy Trial-based criteria.

Results—Among the 1029 patients with acute stroke studied, 7% of the population had severe extracranial carotid disease. Retinal venular caliber was associated with ipsilateral severe carotid disease (P<0.001 in multivariate models). Patients with wider retinal venular caliber were more likely to have severe ipsilateral carotid disease (multivariable-adjusted OR, 3.81; 95% CI, 1.80 to 8.07, comparing the largest and smallest venular caliber quartiles). The retinal venular caliber–carotid disease association remained significant in patients with large artery stroke.

Conclusions—In patients with acute stroke, retinal venular widening was strongly associated with ipsilateral severe extracranial carotid disease. Our findings suggest concomitant retinal and cerebral microvascular disease may be present in patients with carotid stenosis or occlusion disease. The pathogenesis of stroke due to carotid disease may thus be partially mediated by microvascular disease. (Stroke. 2009;40:3695-3699.)

Key Words: carotid disease ■ ischemic stroke ■ retinal vessel caliber

Extracranial carotid disease is a known risk factor for stroke.1,2 Recent studies show that retinal vascular caliber, which can be objectively measured from retinal images and provides a noninvasive means of examining the cerebral microcirculation,3,4 also predicts clinical and subclinical stroke plus other cerebrovascular diseases.5–9 In the Rotterdam Study, wider retinal venular caliber was associated with a higher risk of lacunar infarct and progression of white matter disease.8 In the Cardiovascular Health Study, wider retinal venular caliber tripled the risk of stroke, comparing the widest with the narrowest quartiles.5 However, the relationship between these 2 markers of macrovascular and microvascular disease is unclear.

The few studies to examine the relationship between retinal vascular caliber and carotid artery disease have been conducted in the general population and have not reported consistent findings.10,11 In the Rotterdam Study, retinal arteriolar narrowing was associated with increased carotid intima media thickness and retinal venular widening with higher carotid plaque score,11 and similar results were reported from the Hoorn study.12 Other studies have reported no association of retinal vascular caliber with carotid intima media thickness.13 These dissimilar findings may reflect differing methods of assessing carotid disease and the general good health of populations sampled in whom severe carotid disease was rare. Any association between carotid disease and retinal
vascular caliber would clearly be most clinically relevant in a population with, or at high risk of, stroke. Furthermore, to the best of our knowledge, no studies have explored the laterality of the association between carotid artery disease and retinal vessel caliber. We therefore studied the association of retinal vascular caliber with extracranial carotid stenosis in a prospectively recruited cohort of patients presenting with acute ischemic stroke.

Materials and Methods

Study Population
The Multi-Centre Retinal Stroke (MCRS) study is a cross-sectional observational study of patients with acute stroke, described in detail elsewhere. In brief, we recruited patients with first-ever or recurrent acute stroke within 7 days of onset from 3 major centers (Singapore General Hospital, Singapore; Royal Melbourne Hospital, Melbourne, Australia; Westmead Hospital, Sydney, Australia) between 2005 and 2007. Ethics approval was obtained from each hospital’s Institutional Review Board and informed consent was obtained from each patient or his or her surrogate. For the purpose of these analyses, the inclusion criteria were ischemic etiology of stroke and adequate tolerance for retinal photography and carotid ultrasound. Stroke was subtyped using a pragmatic modification of the Trial of Org 10172 in Acute Stroke Treatment classification used in the Greater Metropolitan Clinical Taskforce for Stroke in New South Wales, Australia. Stroke subtypes were defined as large vessel atherosclerotic stroke, small vessel lacunar stroke, cardioembolic stroke, stroke of other etiology, and stroke of undetermined etiology.

Retinal Photography
Retinal photographs were taken of each eye using a high-resolution digital camera according to a standardized protocol and assessed masked to clinical data. The caliber of retinal arterioles and venules passing through a well-defined region 0.5- to 1.0-disc diameter from the optic disc was measured using a well-reported validated computer-assisted method, which was then summarized using the Parr-Hubbard formula modified by Knudtson to compute the optic disc was measured using a well-reported validated computer-assisted method, which was then summarized using the Parr-Hubbard formula modified by Knudtson

Carotid Assessment
The degree of carotid stenosis was determined using carotid Doppler and was defined by the ratio of the linear luminal diameter of the narrowest segment of the stenosed portion of the artery to the diameter beyond any poststenotic dilatation, similar to the calculation used in the North American Symptomatic Carotid Endarterectomy Trial. Patients were considered to have severe extracranial carotid disease if there was stenosis ≥75% or complete occlusion.

Definitions of Other Variables
Hypertension, diabetes, and hypercholesterolemia diagnosed before or during the admission for stroke were defined as a physician-confirmed diagnosis or from documentation in medical records. Atrial fibrillation was defined from electrocardiographs during admission and from medical records. Current smoking (within the last year) was defined from the history.

Statistical Analysis
Differences between patients with and without severe carotid disease were analyzed using the Independent-samples t test for continuous variables and the Pearson χ² test for categorical variables. Patients with missing data were excluded from analysis for that particular variable. Logistic regression was performed to determine the relationship of retinal vascular caliber and carotid disease with age- and gender-adjusted as well as multivariable-adjusted (age, gender, ethnicity, stroke subtype, smoking, and study site) models. We used the generalized estimating equation method of logistic regression using an exchangeable correlation matrix to investigate the ipsilateral relationship between carotid disease and retinal changes. Subgroup analysis for patients with large artery stroke was performed because this stroke subtype is symptomatic of extracranial carotid disease. ORs and 95% CIs are reported.

Results
There were 1321 patients with acute ischemic stroke recruited into the MCRS study. Among the 1135 (86% of 1321) patients with carotid assessment, 1029 (91% of 1135) had adequate retinal vessel measurement. As compared with those excluded (n=292), the 1029 patients included in the analysis were younger (mean age, 65 versus 70 years), more likely to be Chinese (50% versus 31%), smokers (28% versus 19%), and to have small artery stroke (35% versus 18%). Included patients were less likely to have cardioembolic stroke (16% versus 22%) or atrial fibrillation (11% versus 16%). Severe carotid disease was present in 75 patients (7% of 1029): 30 with right involvement alone, 38 with left involvement alone, and 7 with bilateral disease. There were no significant differences in age and ethnic distribution between patients with and without severe carotid disease (Table 1). There was

| Table 1. Associations of Severe Carotid Disease With Vascular Risk Factors |
|-------------------------------|-------------------------------|----------------|
| Severe Carotid Disease        | Absent (n=954) | Present (n=75) | P     |
| Mean age, years (95% CI)      | 65 (41–89)    | 68 (46–89)    | 0.090 |
| Male gender, n (%)            | 586 (61)      | 55 (73)       | 0.040 |
| Ethnicity, n (%)              | 479 (50)      | 30 (40)       | 0.158 |
| Chinese                       | 316 (33)      | 38 (51)       |       |
| White                         | 66 (7)        | 3 (4)         |       |
| Malay                         | 51 (5)        | 2 (3)         |       |
| Indian                        | 39 (4)        | 2 (3)         |       |
| Other ethnicity               | 414 (43)      | 35 (47)       | 0.588 |
| Hypertension, n (%)           | 648 (68)      | 53 (71)       | 0.633 |
| Diabetes, n (%)               | 327 (34)      | 21 (28)       | 0.269 |
| Hyperlipidemia, n (%)         | 414 (43)      | 35 (47)       | 0.588 |
| Current smoker, n (%)         | 246 (26)      | 34 (46)       | <0.001|
| Atrial fibrillation, n (%)    | 103 (11)      | 8 (11)        | 0.972 |
| Study site, n (%)             | 586 (61)      | 34 (45)       | 0.005 |
| Singapore                     | 233 (24)      | 31 (41)       |       |
| Melbourne                     | 135 (14)      | 10 (13)       | 0.001 |

TOAST indicates Trial of Org 10172 in Acute Stroke Treatment.
a higher male preponderance and larger proportion with large vessel stroke among those with severe carotid disease. There was no difference in risk factor distribution, except that patients with severe carotid disease were more likely to be current smokers. A lower proportion of patients with severe carotid disease were recruited from the Singapore site.

Mean CRVE of the right eye was wider among patients with severe right carotid disease (231 ± 31 mm, \( P < 0.001 \)). Similarly, mean CRVE of the left eye was wider among patients with severe left carotid disease (221 ± 31 mm, \( P = 0.013 \)). There was no significant association between mean central retinal artery equivalent of the right eye with severe right carotid disease (137 ± 16 mm, \( P = 0.219 \)) nor between mean central retinal artery equivalent of the left eye and severe left carotid disease (138 ± 15 mm, \( P = 0.098 \)). Using generalized estimating equation logistic regression, CRVE was associated with severe ipsilateral carotid disease. Compared with patients with CRVE in the lowest quartile, those with CRVE in the highest quartile were more likely to have severe ipsilateral carotid disease (OR, 3.81; CI, 1.80 to 8.07 in multivariable-adjusted models; Table 2).

There was no statistical difference in mean CRVE of the right eye between patients with and without severe left carotid disease (215 ± 27 versus 211 ± 24 mm, \( P = 0.316 \)). The mean CRVE of the left eye was wider in patients with severe right carotid disease than those without (222 ± 25 versus 213 ± 24 mm, \( P = 0.037 \)). With exclusion of severe bilateral carotid disease, which may be a confounder, logistic regression showed that CRVE of the right eye was significantly associated with severe right carotid disease (OR, 2.31; CI, 1.52 to 3.53 in the multivariate model) and there was a strong trend for association between CRVE of the left eye and severe left carotid disease (OR, 1.44; CI, 1.00 to 2.07 in the multivariate model; Table 3). However, there was no significant association between CRVE of the right (\( P = 0.875 \)) or CRVE (\( P = 0.136 \)) of the left eye and severe contralateral carotid disease. Among patients with large artery stroke, wider CRVE remained significantly associated with severe ipsilateral carotid disease (Table 4).

**Discussion**

In this study, we demonstrated that wider retinal venular caliber was significantly associated with the presence of severe ipsilateral carotid disease among patients with acute ischemic stroke. Patients with retinal venules in the widest quartile were 5 times more likely to have severe carotid stenosis than patients with venules in the narrowest quartile after adjusting for stroke risk factors. Because carotid disease is associated with stroke incidence, our findings offer potential explanations as to why retinal venular widening has been documented as a risk marker for incident stroke and cerebrovascular disease in previous population-based studies.

Prior studies had conflicting results with regard to the association between retinal venular caliber and carotid disease. These previous studies used assessments for subclinical disease (carotid intima media thickness) and the number of locations with plaque (carotid plaque score). Our study is the first to investigate the association of retinal vessel caliber with severe carotid disease by degree of stenosis and laterality of association, in an acute stroke population, in which the impact and clinical relevance of a possible association is most relevant. Our data provide confirmatory evidence that retinal venular widening is associated with carotid disease. Furthermore, we present novel findings that retinal venular widening is associated with ipsilateral carotid disease but not contralateral disease. Defining the association of retinal venular caliber and carotid disease in a clinically relevant context of patients with ischemic stroke as well as highlighting its ipsilateral nature provides insights into the basis of the association.

<table>
<thead>
<tr>
<th>Retinal Venular Caliber</th>
<th>No. at Risk</th>
<th>n (%)</th>
<th>Age–Gender OR (95% CI)</th>
<th>( P )</th>
<th>Multivariate* OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>First quartile</td>
<td>473</td>
<td>12 (2.5)</td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second quartile</td>
<td>472</td>
<td>7 (1.5)</td>
<td>0.67 (0.25–1.72)</td>
<td>0.391</td>
<td>0.62 (0.23–1.68)</td>
<td>0.352</td>
</tr>
<tr>
<td>Third quartile</td>
<td>473</td>
<td>21 (4.4)</td>
<td>2.24 (1.08–4.67)</td>
<td>0.031</td>
<td>2.02 (0.95–4.32)</td>
<td>0.070</td>
</tr>
<tr>
<td>Fourth quartile</td>
<td>472</td>
<td>33 (7.0)</td>
<td>3.66 (1.78–7.52)</td>
<td>&lt;0.001</td>
<td>3.81 (1.80–8.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Per SD increase</td>
<td>1890</td>
<td>73 (3.9)</td>
<td>1.88 (1.41–2.50)</td>
<td>&lt;0.001</td>
<td>1.89 (1.40–2.55)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Multivariate adjustment for age, gender, ethnicity, stroke subtype, smoking, and study site.

<table>
<thead>
<tr>
<th>Per SD Increase of</th>
<th>Multivariate* OR (95% CI) for Severe Right Carotid Disease</th>
<th>( P )</th>
<th>Multivariate* OR (95% CI) for Severe Left Carotid Disease</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal venular caliber of the right eye</td>
<td>2.31 (1.52–3.53)</td>
<td>&lt;0.001</td>
<td>1.03 (0.71–1.51)</td>
<td>0.875</td>
</tr>
<tr>
<td>Retinal venular caliber of the left eye</td>
<td>1.36 (0.91–2.02)</td>
<td>0.136</td>
<td>1.44 (1.00–2.07)</td>
<td>0.048</td>
</tr>
<tr>
<td>Retinal arteriolar caliber of the right eye</td>
<td>1.41 (0.88–2.26)</td>
<td>0.148</td>
<td>0.95 (0.62–1.46)</td>
<td>0.823</td>
</tr>
<tr>
<td>Retinal arteriolar caliber of the left eye</td>
<td>1.07 (0.68–1.68)</td>
<td>0.764</td>
<td>1.04 (0.69–1.55)</td>
<td>0.863</td>
</tr>
</tbody>
</table>

*Multivariate adjustment for age, gender, ethnicity, stroke subtype, smoking, and study site.
In view of the laterality of the retinal venular widening—carotid disease association, a plausible reasoning is that severe carotid disease adversely affects the ipsilateral retinal and, based on our assumptions, cerebral microvasculature. Severe carotid disease can result in mral hypoxia or ischemia in retinal veins, thereby causing retinal venular widening.23 This possibility is supported by work showing retinal venular widening is associated with cerebral hypoxia, particularly in the presence of reduced cerebral blood flow.24 Our findings indicate pathological changes in the cerebral microcirculation may parallel changes in the macrovascular circulation. This suggests that carotid disease may contribute to increased stroke risk through adverse effects on the microcirculation in addition to a thromboembolic predisposition. Because this study is cross-sectional, causality cannot be confirmed and future longitudinal studies of these associations will be needed to test our hypotheses.

As this association was also found in patients with larger artery stroke, the stroke subtype symptomatic of carotid disease, we infer that retinal venular widening is associated with symptomatic carotid disease. Why are retinal arterioles not similarly associated with carotid disease? Previous studies have shown that the impact of systemic processes varies not similarly associated with carotid disease? Previous studies have shown that the impact of systemic processes varies between retinal arterioles and venules.13 Hypoxia,23 hyperglycemia,23 and inflammation24 do not appear to affect retinal arteriolar caliber.23 Furthermore, there may be concomitant opposing effects of arteriolar luminal narrowing, intimal thickening, and medial hyperplasia due to other risk factors.25

Strengths of our study include the objective measurement of carotid disease by the degree of stenosis on which guidelines for carotid intervention are based, masked assessment of retinal vessel caliber changes using a validated, automatic quantitative assessment method, and a large sample size of patients with acute stroke recruited within 7 days of stroke onset. We were able to demonstrate that severe carotid stenosis was significantly and independently associated with wider retinal venular caliber despite a relatively low prevalence of severe carotid disease in this sample. Our study also had some limitations. First, carotid assessment was conducted in different centers, resulting in some minor methodological differences. We adjusted for study site in our analyses in an attempt to minimize these differences. Carotid disease was determined by the degree of stenosis alone without using criteria for velocities, because this was not available in one center. Although velocities are recommended for carotid stenosis assessment,26 the sensitivity and specificity of duplex alone are fair compared with angiography (72% and 92% for stenosis 80% to 99%, 92% and 99% for complete occlusion).27 Second, there was some selection bias in the stroke cohort, because severely ill patients were excluded because they could not undergo retinal photography. Our findings may therefore not apply to patients with more severe acute stroke. Finally, our cross-sectional analyses do not permit us to determine the temporal sequence of events. Longitudinal studies are warranted to determine whether carotid disease precedes changes in the retinal microvasculature.

### Summary

In this study, patients with ischemic stroke with wider retinal venular caliber were more likely to have severe ipsilateral carotid disease independent of age and conventional vascular risk factors. Our findings may explain, in part, why retinal venular widening is a risk factor for stroke in the general population and suggest that concomitant cerebral microvascular disease may be present in patients with carotid large vessel disease.

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### Disclosures

None.

### References


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