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

Deidre A. De Silva, MRCP; Gerald Liew, MMed; Meng-Cheong Wong, FRCP; Hui-Meng Chang, MRCP; Christopher Chen, FRCP; Jie Jin Wang, PhD; Michelle L. Baker, MBBS; Peter J. Hand, MRCP; Elena Rochtchina, MSc; Erica Yang Liu, BSc; Paul Mitchell, MD, PhD; Richard I. Lindley, FRACP; Tien Yin Wong, FRCSE, PhD

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. 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, also predicts clinical and subclinical stroke plus other cerebrovascular diseases. In the Rotterdam Study, wider retinal venular caliber was associated with a higher risk of lacunar infarct and progression of white matter disease. In the Cardiovascular Health Study, wider retinal venular caliber tripled the risk of stroke, comparing the widest with the narrowest quartiles. 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. In the Rotterdam Study, retinal arteriolar narrowing was associated with increased carotid intima media thickness and retinal venular widening with higher carotid plaque score, and similar results were reported from the Hoorn study. Other studies have reported no association of retinal vascular caliber with carotid intima media thickness. 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
tissue caliber. We therefore studied the association of retinal vascular caliber with extracranial carotid stenosis in a pro-
spectively 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 recur-
rent acute stroke within 7 days of onset from 3 major centers (Singapore General Hospital, Singapore; Royal Melbourne Hospital, Melbourne, Australia; Westmead Hospital, Sydney, Australia) be-
tween 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 ultrasonography. Stroke was subtype 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, cardioem-
bolic 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
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 rela-
tionship of retinal vascular caliber and carotid disease with age- and
gender-adjusted as well as multivariable-adjusted (age, gender,
etnicity, 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.

Table 1. Associations of Severe Carotid Disease With Vascular Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Severe Carotid Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent (n=954)</td>
</tr>
<tr>
<td>Mean age, years (95% CI)</td>
<td>65 (41–89)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>586 (61)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>479 (50)</td>
</tr>
<tr>
<td>White</td>
<td>316 (33)</td>
</tr>
<tr>
<td>Malay</td>
<td>66 (7)</td>
</tr>
<tr>
<td>Indian</td>
<td>51 (5)</td>
</tr>
<tr>
<td>Other ethnicity</td>
<td>39 (4)</td>
</tr>
<tr>
<td>TOAST stroke subtype, n (%)</td>
<td></td>
</tr>
<tr>
<td>Large artery</td>
<td>349 (37)</td>
</tr>
<tr>
<td>Small artery</td>
<td>359 (38)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>154 (16)</td>
</tr>
<tr>
<td>Other etiology</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>76 (8)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>648 (68)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>327 (34)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>414 (43)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>246 (26)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>103 (11)</td>
</tr>
<tr>
<td>Study site, n (%)</td>
<td>586 (61)</td>
</tr>
<tr>
<td>Singapore</td>
<td>233 (24)</td>
</tr>
<tr>
<td>Melbourne</td>
<td>135 (14)</td>
</tr>
</tbody>
</table>
| Sydney                       | 3696 Stroke December 2009

Severe 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 rela-
tionship of retinal vascular caliber and carotid disease with age- and
gender-adjusted as well as multivariable-adjusted (age, gender,
etnicity, 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

Downloaded from http://stroke.ahajournals.org/ by guest on November 11, 2017
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 versus 211±24 μm, P < 0.001). Similarly, mean CRVE of the left eye was wider among patients with severe left carotid disease (221±31 versus 213±24 μm, 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 versus 133±16 μm, P = 0.219) nor between mean central retinal artery equivalent of the left eye and severe left carotid disease (138±15 versus 135±15 μm, 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 μm, 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 μm, 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.5,8,21

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 2. Associations of Retinal Vascular Caliber and Severe Carotid Disease Using Generalized Estimating Equations

<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>1.00</td>
<td></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>1.18 (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 3. Association of Retinal Venular and Arterial Caliber With Severe Carotid Disease (excluding patients with bilateral carotid disease)

<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.
Table 4. Subgroup Analysis for Patients With Large Artery Stroke Using the Generalized Estimating Equations

<table>
<thead>
<tr>
<th>No. at Risk (n=364)</th>
<th>n (%)</th>
<th>Multivariate* OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>First quartile</td>
<td>182</td>
<td>10 (5.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Second quartile</td>
<td>186</td>
<td>5 (2.7)</td>
<td>0.55 (0.16–1.83)</td>
</tr>
<tr>
<td>Third quartile</td>
<td>182</td>
<td>19 (10.4)</td>
<td>2.22 (0.93–5.32)</td>
</tr>
<tr>
<td>Fourth quartile</td>
<td>186</td>
<td>28 (15.1)</td>
<td>4.11 (1.74–9.75)</td>
</tr>
<tr>
<td>Per SD increase</td>
<td>736</td>
<td>62 (8.4)</td>
<td>1.82 (1.31–2.52)</td>
</tr>
</tbody>
</table>

*Multivariate adjustment for age, gender, ethnicity, 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 mural hypoxia or ischemia in retinal veins, thereby causing retinal venular widening. This possibility is supported by work showing retinal venular widening is associated with cerebral hypoxia, particularly in the presence of reduced cerebral blood flow. 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 with symptomatic carotid disease. Why are retinal venular widening 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.

Sources of Funding

This study was supported by grants from the Australian National Health and Medical Research Council (National Health and Medical Research Council grant number 352337) and Singapore National Medical Research Council (National Medical Research Council grant number 2004073). R.I.L. is supported by an infrastructure grant from NSW Health.

Disclosures

None.

References


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

Deidre A. De Silva, Gerald Liew, Meng-Cheong Wong, Hui-Meng Chang, Christopher Chen, Jie Jin Wang, Michelle L. Baker, Peter J. Hand, Elena Rochtchina, Erica Yang Liu, Paul Mitchell, Richard I. Lindley and Tien Yin Wong

Stroke. 2009;40:3695-3699; originally published online October 8, 2009;
doi: 10.1161/STROKEAHA.109.559435

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 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/40/12/3695

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/