Carotid Intima-Media Thickness Is Different in Large- and Small-Vessel Ischemic Stroke

The SMART Study

D. Martijn O. Pruissen, MD; Susan A.M. Gerritsen; Talitha J. Prinsen, MSc; Joke M. Dijk, MD, PhD; L. Jaap Kappelle, MD, PhD; Ale Algra, MD, PhD, FAHA; on behalf of the SMART Study Group

Background and Purpose—The role of atherosclerosis in the difference between the pathogenesis of large-vessel disease (LVD) and small-vessel disease (SVD) is a matter of debate. Common carotid artery intima-media thickness (CCA IMT) is a marker of atherosclerosis. Our aim was to compare CCA IMT between SVD and LVD patients.

Methods—Two independent observers classified ischemic stroke or transient ischemic attack as caused by SVD or LVD, primarily based on imaging and in addition on clinical features. Mean CCA IMT was calculated based on 6 measurements for each patient.

Results—Four hundred and seventeen patients were classified LVD and 115 SVD. Mean CCA IMT was higher in patients with LVD (1.08 mm) than in patients with SVD (0.92 mm). The crude mean difference was 0.16 mm (95% CI, 0.09 to 0.23). After adjustment for age, sex and hypertension, the mean difference was 0.11 mm (95% CI, 0.05 to 0.18).

Conclusions—CCA IMT is higher in LVD patients than in SVD patients supporting the hypothesis that LVD and SVD have a different pathogenesis. 

Key Words: atherosclerosis ■ brain ischemia ■ intima-media thickness ■ lacunar infarcts ■ pathogenesis ■ risk factors ■ stroke subtype ■ symptomatic carotid stenosis ■ transient ischemic attack

The differences in the pathogenesis of large-vessel disease (LVD) and small-vessel disease (SVD) are still a matter of debate.1 SVD may be less often caused by atherosclerosis. Common carotid artery intima-media thickness (IMT) is a marker of atherosclerosis.2 It is higher in nonlacunar strokes compared with lacunar strokes in one study.3 Two other studies did not find such a difference.4,5 In this study we investigated CCA IMT in a large series of patients with SVD or LVD.

Subjects and Methods

The Second Manifestations of Arterial disease (SMART) study is an ongoing prospective single-center cohort study in patients aged 18 to 80 years with cardiovascular disease or risk factors.7 The study was approved by the medical ethics committee of our hospital. Written informed consent was obtained from all participants. We selected SMART patients with ischemic stroke, transient ischemic attack, transient monocular blindness or retinal infarction at baseline, that was presumably caused by atherosclerosis. Patients with cardiac embolism or another identified cause of stroke were excluded.

Stroke subtype classification was primarily based on imaging. Stroke subtype classification based on clinical features were used if imaging was uninformative or unavailable. Cortical function disorder or motor or sensory deficit of one area of the face, arm or leg was classified LVD. Motor or sensory deficit of 2 or 3 areas of face, arm and leg without cortical function disorder were classified SVD as were patients with an ataxic hemiparesis or a dysarthria-clumsy hand syndrome. If imaging was uninformative or unavailable, cerebellar syndromes were classified LVD and brain stem syndromes as SVD. Retinal ischemia was classified LVD.4 If imaging and clinical features were insufficient to classify subtype, patients with symptomatic ipsilateral carotid stenosis >70% were classified LVD, whereas the others were classified SVD.

Two independent observers performed subtype classification (κ for agreement 0.72 for 30 testcases). A mean IMT was calculated for each patient based on 6 far-wall measurements of the left and right common carotid arteries as described previously.2

We used linear regression analysis to calculate the mean difference of CCA IMT between the LVD and SVD group with corresponding 95% CIs and to adjust for potential confounding.

Results

The study population consisted of 417 LVD patients and 115 SVD patients aged between 23 to 82 years. Imaging was available in 369 patients with a relevant infarction in 183 patients and irrelevant infarctions in 114 patients. In 50 patients subtype classification was based only on symptomatic carotid stenosis because of insufficient clinical and radiological information. Cerebellar or brain stem ischemia
We used an unvalidated subtype classification system. Nevertheless, there was a satisfactory agreement between observers. Moreover, classification based on imaging and clinical features is considered superior to classification based on risk factors. Classifying lacunar syndromes (without infarct on imaging) as SVD can cause LVD misclassification. However, in our study this would only lead to an underestimated IMT difference between LVD and SVD patients. SVD misclassification based on symptomatic carotid stenosis was probably uncommon. Carotid stenosis is unlikely to cause lacunar infarctions because the relative risks for ipsilateral and contralateral carotid stenosis in lacunar versus nonlacunar infarction are similar and because of a lower benefit of carotid endarterectomy for lacunar stroke patients. The generalizability of our results may be limited because symptomatic carotid stenosis was more common than in most previous studies.

In conclusion, we found that CCA IMT in LVD is higher than in SVD. This supports the hypothesis that LVD and SVD have a different pathogenesis.

**Appendix**

Members of the SMART study group are as follows: A. Algra, MD, PhD, Y. van der Graaf, MD, PhD, D. E. Grobbee, MD, PhD, and G. E. H. M. Rutten, MD, PhD, Julius Center for Health Sciences and Primary Care; J. D. Banga, MD, PhD, and F. L. J. Visseren, MD, PhD, Department of Vascular Medicine; H. A. Koomans, MD, PhD, Department of Nephrology; B. C. Eikelboom, MD, PhD, and F. L. Moll, MD, PhD, Department of Vascular Surgery; L. J. Kappelle, MD, PhD, Department of Neurology; W. P. T. M. Mali, MD, PhD, Department of Radiology; and P.A. Doevendans, MD, PhD, Department of Cardiology, University Medical Center, Utrecht, The Netherlands.

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**Disclosures**

None.

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**TABLE 1. Baseline Characteristics of Patients With LVD and SVD**

<table>
<thead>
<tr>
<th></th>
<th>LVD (%)</th>
<th>SVD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years, SD)</td>
<td>63.0 (9.5)</td>
<td>58.2 (11.8)</td>
</tr>
<tr>
<td>Male sex</td>
<td>312 (74.8)</td>
<td>89 (77.4)</td>
</tr>
<tr>
<td>Index event type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>151 (36.2)</td>
<td>77 (67.0)</td>
</tr>
<tr>
<td>TIA</td>
<td>172 (41.2)</td>
<td>38 (33.0)</td>
</tr>
<tr>
<td>Retinal infarct</td>
<td>12 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Transient monocular blindness</td>
<td>82 (19.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Symptomatic carotid stenosis</td>
<td>295 (70.7)</td>
<td>12 (10.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>238 (58.2)</td>
<td>69 (61.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>80 (19.6)</td>
<td>24 (21.4)</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.

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**Discussion**

CCA IMT was higher in LVD patients than in patients with SVD. We did not adjust for symptomatic carotid stenosis because we hypothesized the higher prevalence in LVD patients is a reflection of the pathogenesis of LVD and adjustment could lead to the loss of a true effect on mean IMT. All other baseline characteristics in our study are similar to previous studies. Three other studies provide data on CCA IMT and stroke subtype (Table 2). One study showed similar results as ours although in this study lacunar stroke was compared with all types of nonlacunar stroke. Two studies did not show differences in CCA IMT between LVD patients or with SVD. This may be caused by the use of automatic IMT measurement or by exclusion of patients with carotid stenosis of >60%.

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**TABLE 2. Review of Studies on CCA IMT in LVD and SVD**

<table>
<thead>
<tr>
<th></th>
<th>Touboul et al</th>
<th>Cupini et al</th>
<th>Nagai et al</th>
<th>Current Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (LVD/SVD)</td>
<td>104/103</td>
<td>196/96</td>
<td>72/113</td>
<td>417/115</td>
</tr>
<tr>
<td>Mean age, y (LVD/SVD)</td>
<td>65/71†</td>
<td>70.3/68.4</td>
<td>64/64</td>
<td>63.0/58.2</td>
</tr>
<tr>
<td>Male sex, % (LVD/SVD)</td>
<td>81/65.1</td>
<td>66.3/57.3</td>
<td>82/66</td>
<td>74.8/77.4</td>
</tr>
<tr>
<td>Mean CCA IMT in SVD, mm (SD)</td>
<td>0.80 (0.13)</td>
<td>0.91 (0.16)</td>
<td>0.91 (0.21)</td>
<td>0.92 (0.31)</td>
</tr>
<tr>
<td>Mean CCA IMT in LVD, mm (SD)</td>
<td>0.83 (0.14)</td>
<td>1.04 (0.25)</td>
<td>0.92 (0.18)</td>
<td>1.08 (0.34)</td>
</tr>
<tr>
<td>Crude mean CCA IMT difference of LVD vs SVD, mm (95% CI)</td>
<td>0.025 (−0.012−0.062)‡</td>
<td>0.13 (0.08−0.18)‡</td>
<td>0.01 (−0.05−0.07)‡</td>
<td>0.16 (0.09−0.23)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjustment variables</th>
<th>None</th>
<th>None</th>
<th>None</th>
<th>Age, sex, hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtype classification system</td>
<td>Own criteria based on clinical features and imaging</td>
<td>TOAST</td>
<td>Own criteria based on clinical features and imaging</td>
<td>Own criteria based on clinical features and imaging</td>
</tr>
<tr>
<td>Stroke population recruited</td>
<td>Admissions (multicenter)</td>
<td>Consecutive admissions</td>
<td>Admissions who had carotid ultrasonography</td>
<td>Admissions and vascular clinic outpatients</td>
</tr>
</tbody>
</table>

†Median; ‡95% CI calculated on basis of original publications.
References


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