Cortical Microinfarcts Detected In Vivo on 3 Tesla MRI
Clinical and Radiological Correlates

Jan Willem van Dalen, MSc; Eva E.M. Scuric, MSc; Susanne J. van Veluw, MSc; Matthew W.A. Caan, PhD; Aart J. Nederveen, PhD; Geert Jan Biessels, PhD; Willem A. van Gool, PhD; Edo Richard, PhD

Background and Purpose—Cortical microinfarcts (CMIs) are a common postmortem finding associated with vascular risk factors, cognitive decline, and dementia. Recently, CMIs identified in vivo on 7 Tesla MRI also proved retraceable on 3 Tesla MRI.

Methods—We evaluated CMIs on 3 Tesla MRI in a population-based cohort of 194 nondemented older people (72–80 years) with systolic hypertension. Using a case–control design, participants with and without CMIs were compared on age, sex, cardiovascular risk factors, and white matter hyperintensity volume.

Results—We identified 23 CMIs in 12 participants (6%). CMIs were associated with older age, higher diastolic blood pressure, and a history of recent stroke. There was a trend for a higher white matter hyperintensity volume in participants with CMIs.

Conclusions—We found an association of CMIs with clinical parameters, including age and cardiovascular risk factors. Although the prevalence of CMIs is relatively low, our results suggest that the study of CMIs in larger clinical studies is possible using 3 Tesla MRI. This opens the possibility of large-scale prospective investigation of the clinical relevance of CMIs in older people. (Stroke. 2015;46:255-257. DOI: 10.1161/STROKEAHA.114.007568.)

Key Words: infarction ■ magnetic resonance imaging ■ stroke

Cortical microinfarcts (CMIs) are a common postmortem finding in the older general population at autopsy. They range in size from 50 μm to ≈5 mm and are associated with cardiovascular risk factors, cognitive decline, and dementia.1,2 In vivo detection of CMIs is possible using 7 Tesla (7T) field strength MRI.3 Moreover, CMIs detected using 7T MRI have been proven retraceable on 3 Tesla (3T) MRI.4 Because 7T MRI technology is not widely available, in vivo detection of CMIs on 3T MRI would facilitate large-scale, prospective investigation of their clinical relevance. The aim of this study was to examine the prevalence of CMIs detected on high-resolution 3T MRI in a population-based cohort of older people with hypertension and their association with markers and risk factors for cerebrovascular disease.

Methods

Participants

We studied a population-based cohort of 195 nondemented older people (72–80 years) with systolic hypertension (>140 mm Hg), recruited from the Prevention of Dementia by Intensive Vascular care (PreDIVA) trial.4 Medical history and cardiovascular risk factors were obtained from clinical assessment and general practitioners’ medical records. All participants provided written informed consent.

MRI

Imaging included 3-dimensional T1-weighted (1.1×1.1×1.2 mm^3), 3D fluid-attenuated inversion recovery (1.1×1.1×1.2 mm^3), and 3D susceptibility weighted imaging (1.0×1.0×1.2 mm^3) sequences, performed on 3T with a SENSE-8-channel head coil (Intera; Philips Healthcare, Eindhoven, The Netherlands).

CMIs were defined as small, hypointense lesions on the T1-weighted sequence, hyperintense or isointense on fluid-attenuated inversion recovery, and not appearing as an artery or vein on the susceptibility weighted imaging.1 The lesion had to be detectable on sagittal, coronal, and axial views, <5 mm in diameter, and restricted to the cortex (Figure). One rater (E.E.M.S.) sensitively screened all scans for any lesions possibly qualifying as CMIs. These potential CMIs were subsequently evaluated by 2 additional raters (S.J.v.V. and J.W.v.D.) in a consensus meeting. If consensus could not be reached, lesions were labeled uncertain.

White matter hyperintensities (WMHs) were segmented automatically.5 Total brain and intracranial volumes were obtained using SPM 8 (Wellcome Trust Center for Neuroimaging, University College London, United Kingdom) in Matlab 7.12.0 (MathWorks; Boston, MA). To correct for brain volume, the WMH load was calculated as the ratio of WMH volume/total brain.

We compared participants with and without CMIs on age, sex, history of stroke or transient ischemic attack, history of other cardiovascular diseases (angina pectoris, myocardial infarction, and peripheral arterial disease), diabetes mellitus, body mass index, smoking status, systolic and diastolic blood pressures, and WMH volume.1

Received September 23, 2014; final revision received October 28, 2014; accepted October 29, 2014.

From the Department of Neurology (J.W.v.D., E.E.M.S., W.A.v.G., E.R.) and Department of Radiology (M.W.A.C., A.J.N.), Academic Medical Center, Amsterdam, The Netherlands; Department of Neurology, Brain Center Rudolf Magnus, University Medical Center, Utrecht, The Netherlands (S.J.v.V., G.J.B.); and Department of Neurology, Radboud University Medical Center, Nijmegen, The Netherlands (E.R.).

Correspondence to Jan Willem van Dalen, MSc, Department of Neurology, Academic Medical Center, H2-235 Meibergdreef 9, Amsterdam 1105AZ, The Netherlands. E-mail j.vandalen@amc.nl

© 2014 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.114.007568
Statistical Analysis
We dichotomized into participants with any CMI versus no CMI. The small CMI sample size precluded parametric testing. We used 2-tailed Mann–Whitney U tests to compare continuous variables and $\chi^2$ tests to compare proportions of binary variables. Analyses were performed with SPSS version 20 (IBM, Armonk, NY).

Results
One scan was excluded because of insufficient quality, leaving 194 participants for evaluation. Screening identified 92 potential CMIs. In the consensus meeting, 26 lesions in 14 participants (7%) were rated as definite (23) or uncertain (3) CMIs. The 23 definite CMIs in 12 participants (6%) were used for analyses. One participant had 6 CMIs, 3 participants had 3 CMIs, and 8 participants had 1 CMI.

Comparisons between participants with and without CMIs are presented in the Table. Participants with CMIs were older (79 versus 77 years; $P=0.02$) and had a higher diastolic (86 versus 80 mm Hg; $P=0.04$) but not systolic blood pressure (166 versus 148 mm Hg; $P=0.38$). Stroke within 2 years before MRI was more common in participants with CMIs than in participants without CMIs (17% versus 3%; $P=0.02$). There was a trend for a more higher WMH load (9.9 versus 5.2 mm$^3$; $P=0.06$) in patients with CMIs.

Discussion
We identified CMIs on 3T MRI in 6% of our population of community-dwelling older people with hypertension. People with CMIs are older, have higher blood pressure, more often had a recent stroke, and have a higher WMH load.

The detected prevalence is relatively low compared with the 30% to 40% reported in vivo in general older populations at 7T MRI, and the 25% reported for cerebral microinfarcts in postmortem studies. This could be explained by previous findings, which suggest that only 25% of CMIs identified on 7T are detectable on 3T MRI. The association between CMIs and recent stroke fits in with previous reports. The association of CMIs with older age has been reported inconsistently and not been established in vivo before. CMIs and high blood pressure have not been associated in vivo before. Postmortem studies have reported associations with a history of high systolic blood pressure. Possibly, the absence of an association with systolic blood pressure in our study is related to systolic hypertension being an inclusion criterion. CMIs and higher WMH volume have been associated previously, although recent studies, both at autopsy and on 7T MRI, could not consistently reproduce this association.

This study has some limitations. The sensitivity of 1 mm$^3$ 3T MRI is limited, and small CMIs may be left undetected. Nevertheless, the subset of individuals in whom CMIs were identified differed on several clinical features from those without CMIs, suggesting that this tip of the iceberg has a clinically meaningful signal. Moreover, developments in 3T MRI have the potential to improve sensitivity.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No CMI, $n=182$</th>
<th>≥1 CMI, $n=12$</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>77 (75–79)</td>
<td>79 (78–80)</td>
<td>0.02</td>
</tr>
<tr>
<td>Women, n, %</td>
<td>100 (55)</td>
<td>4 (33)</td>
<td>0.15</td>
</tr>
<tr>
<td>Stroke, n, %</td>
<td>18 (10)</td>
<td>3 (25)</td>
<td>0.11</td>
</tr>
<tr>
<td>Recent, &lt;2 y, n, %</td>
<td>6 (3)</td>
<td>2 (17)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiovascular disease, n, %</td>
<td>42 (23)</td>
<td>2 (16)</td>
<td>0.56</td>
</tr>
<tr>
<td>Diabetes mellitus, n, %</td>
<td>19 (10)</td>
<td>1 (8)</td>
<td>0.82</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>26 (24–28)</td>
<td>25 (24–27)</td>
<td>0.76</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never, n, %</td>
<td>85 (47)</td>
<td>4 (33)</td>
<td>0.37</td>
</tr>
<tr>
<td>Former, n, %</td>
<td>86 (47)</td>
<td>7 (58)</td>
<td>0.46</td>
</tr>
<tr>
<td>Current, n, %</td>
<td>11 (6)</td>
<td>1 (8)</td>
<td>0.75</td>
</tr>
<tr>
<td>RR systolic, mm Hg</td>
<td>148 (138–162)</td>
<td>166 (140–176)</td>
<td>0.38</td>
</tr>
<tr>
<td>RR diastolic, mm Hg</td>
<td>80 (74–89)</td>
<td>86 (80–96)</td>
<td>0.04</td>
</tr>
<tr>
<td>WMH volume, mm$^3$/cm$^3$</td>
<td>5.2 (2.8–9.2)</td>
<td>9.9 (4.1–14.6)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Reported are medians and interquartile ranges unless stated otherwise. CMIs indicate cortical microinfarcts; n (%), number and percentage; RR, blood pressure; and WMH volume, white matter hyperintensity volume in mm$^3$/cm$^3$ of total brain volume.
technology now allow scanning at even higher, submillimeter resolutions, probably improving the relatively low sensitivity compared with 7T MRI. The stepped rating procedure with a consensus panel judgment is likely to have produced specific CMI ratings (ie, few false-positives), but the sensitivity of the initial single rater may have affected the detection rate. The low prevalence of CMIs reduced the statistical power of our study. This precluded multivariate analysis of the interrelation between variables. Also, the multiple comparisons between the small subset of individuals with CMIs and those without CMIs may have led to type I and II errors.

To our knowledge, this study is the first to report that CMIs can be detected on 3T MRI in a population-based cohort of older people. Reproduction in larger cohorts could provide more conclusive data about their clinical and radiological correlates. The laborious visual detection of CMIs would benefit from the development of (semi)automatic segmentation techniques. In vivo detection of CMIs using 3T opens the possibility to study CMIs on a substantially larger scale and in clinical settings, allowing for prospective research into the clinical relevance of CMIs in older people, including their role in the development of cognitive impairment.

Acknowledgments
We thank I. Stijnman and C.E. Miedema for logistics and planning.

Sources of Funding
This work was supported by grant number 50-50110-98-020 from the Dutch Ministry of Health, grant number 05-234 from Innovatiefonds Zorgverzekeraars, grant number 62000015 from ZonMW, and grant number 10157 from Internationale Stichting Alzheimer Onderzoek.

Disclosures
None.

References
Cortical Microinfarcts Detected In Vivo on 3 Tesla MRI: Clinical and Radiological Correlates

Stroke. 2015;46:255-257; originally published online December 2, 2014;
doi: 10.1161/STROKEAHA.114.007568
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 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/46/1/255

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/