Cavitation of Deep Lacunar Infarcts in Patients With First-Ever Lacunar Stroke
A 2-Year Follow-Up Study With MR
Caroline M.J. Loos, MD; Julie Staals, MD, PhD; Joanna M. Wardlaw, MD, FRCR, FRCP, FMedSci; Robert J. van Oostenbrugge, MD, PhD

Background and Purpose—Studies in patients with lacunar stroke often assess the number of lacunes. However, data on how many symptomatic lacunar infarcts cavitate into a lacune are limited. We assessed the evolution of symptomatic lacunar infarcts over 2-year follow-up.

Methods—In 82 patients with first-ever lacunar stroke with a lacunar infarct in the deep brain regions (excluding the centrum semiovale), we performed a brain MR at presentation and 2 years later. We classified cavitation of lacunar infarcts at baseline and on follow-up MR as absent, incomplete, or complete. We recorded time to imaging, infarct size, and vascular risk factors.

Results—On baseline MR, 38 (46%) index infarcts showed complete or incomplete cavitation. Median time to imaging was 8 (0–73) days in noncavitated and 63 (1–184) days in cavitated lesions (P<0.05). On follow-up imaging, 94% of the lacunar infarcts were completely or incompletely cavitated, most had reduced in diameter, and 5 (6%) had disappeared. Vascular risk factors were not associated with cavitation.

Conclusion—Cavitation and lesion shrinkage were seen in almost all symptomatic lacunar infarcts in the deep brain regions over 2-year follow-up. Counting lacunes in these specific regions at a random moment might slightly, however not substantially, underestimate the burden of deep lacunar infarction. (Stroke. 2012;43:2245-2247.)

Key Words: cerebral small vessel disease ■ lacunar infarcts ■ lacunes ■ MRI

Lacunar stroke is characterized by one of the clinical lacunar syndromes with a compatible lacunar infarct on brain imaging.1 Lacunar infarcts are small infarcts located deep within the brain caused by occlusion of a single perforating artery due to cerebral small vessel disease.2 Radiologically, old lacunar infarcts are considered to be represented by lacunes, which are focal cavities.2

Lacunes on brain imaging are often used as markers of cerebral small vessel disease. However, precise data on the proportion of lacunar infarcts that cavitate and become a lacune are limited. Former MRI studies found that only 28% to 60% of the symptomatic lacunar infarcts progress to definite cavitation, leading to the conclusion that many lacunar infarcts stay noncavitated white matter lesions. However, these studies included patients over a wide range of times to follow-up imaging and symptomatic lacunar infarcts in all subcortical brain regions. There is some evidence that although lacunar infarcts in the deep brain regions are caused by cerebral small vessel disease, lacunar infarcts in the centrum semiovale have different causes.5–7

We studied cavitation of symptomatic lacunar infarcts in the basal ganglia, pons, and internal capsule, for which there was no other cause than intrinsic cerebral small vessel disease, in patients with first-ever lacunar stroke, all of whom had a 2-year follow-up MRI.

Subjects and Methods
For a detailed description, see the online-only Data Supplemental Methods. In short, we included 82 patients with first-ever lacunar stroke who had a MRI at baseline and after 2 years (fluid-attenuated inversion recovery and T2 sequences); 59% also had diffusion-weighted imaging at baseline. An acute lacunar infarct was defined as a round T2-weighted hyperintense lesion (<20 mm) with, if diffusion-weighted imaging was performed, restricted diffusion, located in the basal ganglia, internal capsule, or pons, and compatible with clinical findings. We excluded all patients with symptomatic centrum semiovale infarcts at baseline. Cavitation on imaging (fluid-attenuated inversion recovery), at baseline and follow-up, was classified into: absent, incompletely, or completely cavitated infarcts (Figure). The total diameter of each lacunar infarct was measured. We also assessed the presence of asymptomatic lacunes and graded white matter lesions according to the Fazekas scale.

Results
Cavitation at Baseline MR
Table 1 shows baseline measurements. Median time between stroke onset and baseline MRI was 22 days (0–184 days). At
baseline, 44 of the 82 lacunar infarcts (53%) showed no cavitation, 27 (33%) were incompletely cavitated, and 11 (13%) were completely cavitated. Longer time interval between stroke onset and baseline imaging was significantly associated with cavitation. No other patient-related or imaging-related variables (white matter lesions or asymptomatic lacunes) were associated with cavitation.

Cavitation on Follow-Up MR

Results are shown in Table 2. The follow-up brain MRI was performed at mean 759±58 days after the baseline MRI. In the group without cavitation at baseline (n=44), 16 (36%) showed incomplete cavitation, 24 (55%) were completely cavitated, and in 4 cases (9%), no lesion was seen on follow-up imaging. In the group with incomplete cavitation at baseline (n=27), 5 (19%) were still incompletely cavitated, 21 (78%) showed complete cavitation, and in one case, no lesion was seen on follow-up. There was no association between vascular risk factors and cavitation on follow-up.

Infarct Size

The total diameter of the noncavitated lesions at baseline (11.5±3.7 mm) reduced to 6.5±3.4 mm on follow-up imaging (P<0.05). Infarct size in the group of 11 completely cavitated lesions at baseline was 8.8±4.0 mm and showed a significant reduction (6.6±3.7 mm; P<0.05) on follow-up.

Discussion

We assessed the evolution of symptomatic lacunar infarcts in the basal ganglia and internal capsule due to presumed cerebral small vessel disease over a period of 2 years. We found that all symptomatic lacunar infarcts, except those no longer visible, cavitate over time and that longer time interval between stroke onset and imaging is the sole predictor of cavitation. Furthermore, we found a significant reduction of infarct size on follow-up.

Potter3 found definitive cavitation in one fifth of patients with symptomatic lacunar stroke and concluded that many lacunar infarcts long term may resemble white matter lesion. However, they included symptomatic lacunar infarcts both in the centrum semiovale and the basal ganglia, their time interval to follow-up imaging was generally shorter, they partly used CT for imaging, and their MR scoring methods might not completely correspond with ours. Koch4 found that cavitation occurred in 61% of patients with lacunar stroke, but their follow-up time interval

<table>
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<tr>
<th></th>
<th>Cavitation</th>
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<th>Cavitation</th>
<th>Cavitation</th>
<th>P Value</th>
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<tr>
<td></td>
<td>(N=82)</td>
<td>No (N=44)</td>
<td>Incomplete (N=27)</td>
<td>Complete (N=11)</td>
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<td>Age, y, mean±SD</td>
<td>63±11</td>
<td>61±12</td>
<td>66±9</td>
<td>62±12</td>
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<td>Imaging parameters</td>
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<tr>
<td>Onset to baseline MR, d (range)</td>
<td>22 (0–184)</td>
<td>8 (0–73)</td>
<td>54 (1–62)</td>
<td>78 (15–184)</td>
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<td>Diameter infarct, mm, mean±SD</td>
<td>11.0±4.0</td>
<td>11.5±3.7</td>
<td>11.2±4.3</td>
<td>8.8±4.0</td>
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<td>Asymptomatic lacunes (%)</td>
<td>53 (65)</td>
<td>29 (66)</td>
<td>16 (59)</td>
<td>8 (73)</td>
<td>0.71</td>
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<tr>
<td>Extensive periventricular WML (%)</td>
<td>31 (38)</td>
<td>16 (36)</td>
<td>11 (41)</td>
<td>4 (37)</td>
<td>0.93</td>
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<td>Extensive deep WML (%)</td>
<td>28 (34)</td>
<td>14 (32)</td>
<td>11 (41)</td>
<td>3 (27)</td>
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<td>Vascular risk factors</td>
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<tr>
<td>Hypertension (%)</td>
<td>60 (73)</td>
<td>31 (71)</td>
<td>20 (74)</td>
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<td>Diabetes (%)</td>
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<td>Hypercholesterolemia (%)</td>
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<td>35 (76)</td>
<td>22 (82)</td>
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<td>Smoking (%)</td>
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<td>20 (46)</td>
<td>8 (30)</td>
<td>5 (46)</td>
<td>0.63</td>
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</table>

WML indicates white matter lesion.

Figure. Fluid-attenuated inversion recovery sequences. A, Lacunar infarct in the right thalamus without cavitation. Time to baseline imaging was 10 days. B, At follow-up, the lesion has completely cavitated. C, Incompletely cavitated lacunar infarct, with a spongiform appearance, in the right internal capsule.
was widespread and their patient sample with MRI follow-up was relatively small. Because there is a shortage of data on long-term appearances of symptomatic lacunar infarcts, our data almost double the number of the total published MRI cases so far, even if there are limitations such as the restricted definition of location of lacunar infarcts in our study.

We did not include lacunar infarcts in the centrum semiovale in contrast to these 2 studies, because the centrum semiovale is generally supplied by medullary branches of the cortical arteries and these infarcts may have different causes than those arising in the territory of the deep perforators.5–7 It may also be that the deep gray and white matter respond differently to lacunar damage, gray matter being more likely to cavitate than white matter. It would be interesting to directly compare cavitation rates between small deep and centrum semiovale infarcts.

Even when cavitation has been reached, it seems that the lacune is still in a dynamic process because we showed reduction in size over time. In 5 cases the lesion even disappeared on follow-up MR. Although it is possible that the brain tissue healed without the formation of a lacune, it seems more likely that these infarcts have progressed into small, collapsed lacunes that can be missed by brain imaging, possibly corresponding to microinfarcts.

The main strengths of our study are a relatively fixed long follow-up time and MRI in all patients, which is superior to CT for the detection of lacunar infarcts.9 A limitation is that we did not use the same MR field strength in all patients due to the clinical setting of this study; however, other MRI settings were standardized. Furthermore, not all patients had diffusion-weighted imaging, which could have caused that the wrong lesion was counted for the symptomatic lacunar infarct. However, we only included patients with a definitive clinical diagnosis of first-ever lacunar stroke and the lesion had to be compatible with clinical signs.

In conclusion, cavitation of symptomatic lacunar infarcts was present in all, except for those that disappeared over time. Cavitation seems to be a dynamic process with a reduction in size over time and with a definitive lacune as a final result. Because it takes time to cavitate, counting lacunes at a random moment might slightly, however not substantially, underestimate the burden of deep lacunar infarcts, but these results cannot be applied to lacunar infarcts in the centrum semiovale.

**Source of Funding**

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**Disclosures**

None.

**References**


| Table 2. Clinical and Imaging Parameters on Follow-Up MR |

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<th>Diameter infarct, mm, mean±SD</th>
<th>Vascular risk factors</th>
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<td>778 (638–858)</td>
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<td>16 (76)</td>
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<td>4 (19)</td>
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<td>*n=77; lost lesions were excluded.</td>
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P Value | 0.43 | 0.95 | 1.00 | 0.74 | 1.00 | 0.67 |

*P Value
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Cavitation of deep lacunar infarcts in first-ever lacunar stroke patients: a two year follow-up study with MR.

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**Brain Research Imaging Centre, Division of Clinical Neurosciences, SINAPSE Collaboration, University of Edinburgh, Western General Hospital, Edinburgh, UK.
Supplemental methods

Study Population

From a lacunar stroke project with first-ever lacunar stroke patients presenting at Maastricht University Medical Centre or Orbis Medical Centre Sittard, the Netherlands, we selected all first-ever lacunar stroke patients who had a baseline brain MR between 2004 and 2007 and a two year follow-up brain MR. All patients participated with informed consent, in this ongoing research project, which has been approved by the local Medical Ethical Committee. Lacunar stroke was defined as one of the recognised lacunar stroke syndromes with a lacunar lesion in the deep grey matter, pons or internal capsule, compatible with occlusion of a single deep perforating artery. Patients with symptomatic centrum semioval infarcts were not included, as the cause of these may differ from deep grey matter, pons and internal capsule lesions in the territory of the deep perforators arising from the proximal arteries of the circle of Willis. Patients with potential cardioembolic sources or > 50% carotid stenosis in at least one carotid artery were not included.

Of the original cohort of 138 included first-ever lacunar stroke patients, we excluded 35 patients (25%) that had a clinical diagnosis of lacunar stroke but did not show a symptomatic lesion at baseline. Twenty-one patients did not participate in follow-up imaging, leaving 82 patients, who had a two-year follow-up brain MR. Thirty-four patients (41.5%) presented with a pure motor lacunar syndrome, 22 patients (26.8%) with a sensorimotor stroke, 13 patients (15.9%) with a pure sensory stroke, 8 patients (9.8%) with a dysarthria-clumsy hand syndrome and 5 cases (6.2%) with other lacunar syndromes. Age at stroke onset, gender and vascular risk factors were recorded as defined earlier. The baseline characteristics of our follow-up study population did not differ from those that did not participate on follow-up.
MR scoring

MR images (1.5 or 3T MRI scanner, Philips) were obtained as soon as possible and within 6 months after stroke onset. The MR protocol consisted of standard axial T2-weighted fast spin echo [TR shortest; TE 100 ms; flip angle 90°; field of view (FOV) 230 mm; matrix 512x512] and fluid attenuated inversion recovery (FLAIR) sequences [TR 8000 ms; TE 120 ms; inversion time 2000 ms; FOV 230 mm; matrix 256x256 reconstructed to 512x512], with slice thickness of 5 mm and gaps 0.5 mm. Forty-eight of 82 patients (59%) also had diffusion-weighted imaging (DWI) at baseline. Two vascular neurologists independently assessed the location of the acute lacunar infarct at baseline. An acute lacunar infarct was defined as round lesion (3 to 20 mm in diameter) of hyperintense signal on T2-weighted imaging with, if DWI was present, a compatible diffusion restriction lesion on DWI, located in the basal ganglia, internal capsule, thalamus or pons, and compatible with clinical findings. The interobserver agreement for presence of a symptomatic infarct, determined before this study, was 0.89 (Cohen’s kappa). Cavitation at baseline imaging was classified by consensus into three groups: absent cavitation, incompletely or completely cavitated. In case of uncertainty or no consensus, images were reviewed by an experienced third party. Absent cavitation was defined as a lesion without any evidence of cavitation. Incomplete cavitation was defined as a lesion with hypointense core on FLAIR and the presence of one or more of the following characteristics: an irregular gliotic border, a spongiform appearance with areas of marked hypointensity in the core of the lesion or a hypointense core with a different signal intensity compared to CSF. Complete cavitation (lacune) was defined as a small cavity with hypointense signal intensity comparable to CSF, with a thin surrounding hyperintense halo (gliosis) on FLAIR. The total diameter (hypointense core and gliotic rim) of each index lacunar infarct was measured, in three directions, and we report maximum diameter. Patients had a follow-up brain MR (1.5T or 3T MRI scanner), with T2-weighted imaging and FLAIR.
sequences, two years after the first MR. The MR protocol was similar to the baseline protocol. The appearance of the lacunar infarct on T2-weighted and FLAIR was classified into four groups: absent cavitation, incompletely and completely cavitated lesions, or disappearance of the lesion, using the same imaging criteria as baseline imaging. The total diameter of the lacunar infarct was again assessed on follow-up imaging. The presence of extensive deep and periventricular white matter lesions (WML) according to Fazekas’ scale and the number of asymptomatic lacunes elsewhere in the brain were assessed, as defined earlier.

Statistical analysis

Categorical variables are presented as N with frequencies (%). Data are presented as mean ± standard deviation (SD) for normally distributed data and as medians with range for non-parametric data. Differences between groups were tested using independent-sample t-test or ANOVA for normally distributed variables and Mann-Whitney U test and Kruskal-Wallis test for variables with skewed distributions. Categorical variables were explored by Pearson χ² and Fisher test. Diameter at baseline and after 2 years were compared with paired t-test. Statistical significance was set at p < 0.05 (2-tailed). Analyses were performed using SPSS statistical software package (version SPSS 18.0; SPSS Inc).
Supplemental references


