Shape and Volume of Lacunar Infarcts
A 3D MRI Study in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

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Background and Purpose—The shape and exact size of lacunar infarcts have been investigated only postmortem. Recent imaging techniques based on triangulation and connectivity can now be used for 3D segmentation of cerebral lesions. The shape and size of lacunar infarcts was investigated using these techniques in 10 cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) patients.

Methods—We segmented 102 lacunar infarcts on T1-weighted images. The surface of the corresponding set of voxels was computed as a mesh of triangles. Thereafter, the shape of each lesion in 3D was visually analyzed by 2 investigators.

Results—The volume of lesions ranged from 10.5 to 1146 mm, with 93% of them having a volume <500 mm; 83% lacunar infarcts had a spheroid or ovoid shape, but 17% presented as sticks, slabs, or with a complex shape. Lesions with multiple components appeared larger than the others, and a tail extension was noticed in 13 of 102 lesions.

Conclusions—These results suggest the following: (1) most lacunar infarcts in CADASIL have a volume far below one third of that of a sphere of 15 mm in diameter, the upper limit currently used for their identification on 2D imaging; (2) a significant proportion of lacunar infarcts have a shape distinct from the spheroid-ovoid morphology; and (3) lesions with a complex shape may result from the involvement of the largest small arteries, confluence of ischemic lesions, or secondary tissue degeneration. The segmentation of lacunar infarcts appears promising to better understand the pathophysiology of tissue lesions secondary to small vessel diseases. (Stroke. 2005;36:2384-2388.)

Key Words: CADASIL syndrome ■ diagnostic methods ■ lacunar infarcts ■ MRI

Descambre1 and Durand–Fardel2 were the first to use the term “lacune” for small subcortical ischemic lesions caused by the occlusion of cerebral arteries with a diameter <300 μm. Although isolated lacunar infarcts may have an embolic origin,3 most of these lesions are associated with important structural changes (lipohyalinosis and sclerosis) in the wall of small perforating cerebral arteries.4 The diagnostic value of the so-called 4 “lacunar syndromes” first reported by Fisher5–8 in association with these ischemic lesions was debated after the emergence of computed tomography-scan and MRI techniques.9,10 Nowadays, lacunar ischemic lesions can be easily detected with in vivo imaging, even in the absence of neurological manifestations (so-called silent infarcts).

The usual definition of a lacunar infarct as detected on computed tomography scan and/or MRI is based on both the location of the lesion and on the size of visible tissue damage. The maximal lesion diameter of 15 mm from autopsy studies is usually considered a key criterion for imaging diagnosis.11 However, this definition has important limitations. First, in vivo and postmortem data are not entirely comparable. In particular, tissue modifications resulting from the fixation process and removal of cerebrospinal fluid can change the size of the cavity on pathological examination.12 Second, the use of the largest diameter calculated on axial planes on 2D imaging is appropriate only if these cavities are actually ball-shaped. If this is not true, such a definition may lead to diagnostic errors.13 Fisher11 already reported that lacunar infarcts were frequently round or ovoid in the white matter but linear with irregularities in the gray matter. Recently, lacunar infarcts were distinguished from Virchow–Robin spaces also based on the diameter and shape using 2D MRI analysis.12,14–16

Recent imaging techniques based on triangulation and connectivity of imaging data have been developed for 3D segmentation of circumscribed cerebral regions. We thought that such methods are now ready for in vivo analysis of the shape and size of cerebral ischemic lesions, particularly to reassess the characteristic features of lacunar infarcts. For this purpose, we chose to analyze the shape and size of these lesions.
lesions using digital imaging techniques in 10 patients with cerebral autosomal dominant arteriolopathy with subcortical infarcts and leucoencephalopathy (CADASIL), a genetic disease responsible for ultrastructural changes in the wall of arteries of diameter <300 μm and leading to white matter demyelination and typical lacunar infarcts.17–19

**Methods**

**Subjects**
Ten symptomatic patients (mean age 46±7.3 years) with characteristic mutations in the Notch 3 gene responsible for CADASIL were included in the present study. All had previous transient ischemic attacks and/or completed strokes. Six had a history of attacks of migraine with aura. Three were demented (Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria).

**MRI**
T1-WI were obtained on a 1.5-T MRI system (Signa General Electric Medical Systems) equipped with gradient hardware allowing ≤22 mT/m. A standard quadrature head coil was used for radio frequency transmission and reception of the magnetic resonance signal. Reduction of head motion was achieved with pillows placed on either side of the participant’s head and a fixed strap positioned around the forehead. High-resolution T1-WIs (inversion recovery) were acquired in the axial plane with a spoiled gradient echo sequence (124 slices, 1.2 mm thick, repetition time = 10.3 ms, echo time = 2.1 ms, and inversion time = 600 ms) and 24×18 cm field of view (resolution of 0.937×0.937×1.2 mm).

**Segmentation and 3D Analysis of Lacunar Cavities**
Image postprocessing was performed using the Anatomist software dedicated to MRI segmentation of the brain (developed by CEA).

**Regions of Interest**
A single examiner (D.H.), who was blinded to the subject’s clinical status, performed the selection and delineation of all of the visible lesions using a dedicated tool. The delineation of the lesion was based on the local threshold of the T1 signal. All of the hypointense lesions with both a signal identical to that of cerebrospinal fluid (CSF) and a diameter >2 mm (this diameter criterion was used to exclude most of Virchow–Robin spaces) were selected manually on axial planes and thereafter delineated and filled using different colors (automatic processing using the local threshold of the signal). Only voxels with signal intensities as seen in the ventricles (CSF) were included when the lesion was not uniform. The limits of each lesion were then verified on all of the sagittal and coronal slices and corrected manually if necessary. The κ coefficient of interobserver (D.H. and H.C.) and intraobserver (D.H.) agreement on a subset of 30 lesions was 0.76 and 0.91, respectively.

**3D Reconstruction**
Each object was defined as a set of connected voxels and reconstructed in 3D using the Anatomist software. To visualize the shape of the object in 3D, the surface of this set of voxels was computed as a mesh of triangles in 2 steps. First, the centers of the voxel facets were linked together in order to get a high-resolution mesh. Then, to overcome stair artifacts, an optimal decimation algorithm reducing the number of triangles and smoothing the mesh was applied. The goal was to get the best trade-off between accuracy of the surface representation and the number of triangles (Figure 1).

**Volume, Shape, and Cerebral Location of the Lesions**
The volume of each lesion was automatically calculated after 3D reconstruction. The shape of each lesion was then analyzed by visual inspection using a dedicated tool allowing the rotation of 3D objects in all of the spatial plans (from the Anatomist software). Two examiners (D.H. and H.C.) classified the lesions in 4 categories according to their global aspect on visual analysis: slab, stick, multiple components, or ovoid/spheroid (Figure 2). The category was defined for each lesion after agreement between the 2 observers. In addition, the presence or absence of a tail extension was assessed for each lesion (evidence of a main component among the 4 previous categories associated with a filiform extension).

The exact lesion location was also defined as being either in the white matter (internal capsule, external capsule, periventricular white matter, pons, or centrum semiovale) or in the subcortical gray matter (thalamus, caudate nucleus, putamen, or pallidum).

**Statistical Analysis**
A descriptive analysis of parameters derived from all of the 3D reconstructed objects was first obtained (volume, shape, and location). Then, relationships between the shape of lacunar infarcts and their volume and/or location were analyzed using ANOVA or \( \chi^2 \) tests. Statistical analysis was performed with the SAS package (Abacus Concepts Inc.) using a level of significance <0.05.

**Results**

**Descriptive Analysis of MRI Segmented Lesions**

**Volume**
We segmented 102 lacunar infarcts. The number of lesions ranged from 1 to 16 for each patient. The volume of segmented lesions ranged from 10 to 1146 mm (median, 104; mean, 188±22). Figure 3 illustrates the number of lesions according to their size in the whole sample of patients. A total of 93%...
of lacunar infarcts had a volume <500 mm, and more than half of them were <100 mm.

**Shape and Tail Extension**
Among the segmented lesions, most of lacunar infarcts (83.3%) were ovoid or spheroid. Three lesions were shaped as sticks (2.9%), 9 were shaped as slabs (8.8%), and the last 5 had multiple components (4.9%).

Figure 4 illustrates the discrepancy between the shape of lesions as detected on 2D imaging and that observed on 3D imaging; it also shows the different shapes of lacunar infarcts, which can be detected in a single subject. Among the 102 segmented lesions, 13 presented with a tail extension. In an illustrative case (Figure 5), the tail extension of a segmented cavity followed the direction of axonal tracts within the white matter.

**Volume and Number of Lesions: Relationships With Location and Shape**
In the present series, 62 lesions were detected in the white matter and 40 in the gray matter. The volume of lacunar infarcts was larger in the white matter than in the gray matter (227 ± 260 versus 110 ± 91 mm³, respectively; \( P = 0.008 \)). ANOVA showed a significant interaction between the shape and the volume of ischemic lesions. Lacunes with complex shape (multiple components; 528 ± 239 mm³) appeared much larger than ovoid/spheroid lesions (167 ± 20 mm³), slab lesions (239 ± 60 mm³), or stick lesions (50 ± 14 mm³; \( P < 0.01 \)). However, the frequency of the different shapes did not significantly differ between the white matter and gray matter (\( P = 0.47 \)). In addition, the number of cavities with a tail extension did not significantly differ in the white matter and the gray matter (17% versus 6%, probability not significant). Patients with multiple components lesions had more ischemic lesions (mean, 12 ± 6) than patients without such complex lesions (mean, 8 ± 6), although this difference did not reach statistical significance (\( P = 0.2 \)).
Discussion

This is the first study showing that 3D segmentation of small infarctions is possible and that it allows a detailed in vivo analysis of the shape and volume of lacunar cavities in the brain. Using this technique, in 10 CADASIL patients, we found the following: (1) most lacunar infarctions in this disorder had a volume far <500 mm³; (2) nearly 1 of 5 of these lesions did not have an ovoid or spheroid shape; and (3) wallerian degeneration was probably involved in the cavitation of some of these ischemic lesions in the white matter.

The volume of 500 mm³ corresponds with less than one third of the volume of a sphere of 15-mm diameter, the upper limit usually chosen for the definition of a lacunar infarct on 2D imaging (4/3 πR³=1767 mm³). In the present study, the largest cavity corresponded to only two thirds of this reference volume. This is in line with postmortem results obtained by Fisher who reported that most infarctions secondary to diseases of perforating arteries had a diameter <4 mm (and, therefore, a maximal volume of 267 mm³) and with a recent microanatomic study of lenticulostriate arteries showing that the maximal volume irrigated by perforator arteries with a diameter <350 μm was 508 mm³. Such data suggest that the classical limit of 15 mm in diameter for the definition of lacunar cavity on 2D imaging is overestimated and that ischemic cavities >500 to 1000 mm may have a different origin or involve arteries with larger trunks.

In the present study, we found that the shape of lacunar cavities was most often ovoid or spheroid. However, 17% of lesions presented with a different morphology. The visual analysis of different lesions performed in 1 typical case demonstrated that the 2D analysis can lead to misinterpretation of the actual shape and size of these lesions. Elsewhere, we found a significant relationship between the shape and volume of the segmented lacunes. Cavities with complex shapes (multiple components) appeared much larger than ovoid/spheroid, slab, or stick lesions. The trend toward more ischemic lesions associated with complex cavities suggests that the latter may result from the confluence of multiple...
ischemic cavities. Alternatively, the involvement of perforating arteries with larger trunks and more branches may also be responsible for larger and irregular tissue necrosis.

We detected the presence of a tail extension in 13% of the segmented lacunar cavities, whatever their basic shape. The observation of a typical ischemic lacunar lesion with a long tail extension crossing the corpus callosum in an illustrative case suggests that secondary degeneration of axonal bundles originating from the lesion may be sometimes involved in the morphogenesis of lacunes. This may also explain the larger volume of cavities detected in the white matter compared with those located in gray matter. Secondary wallerian degeneration has been repeatedly observed on T2-weighted MRI in the corticospinal pathway remote from ischemic lesions,21–23 and recent diffusion tensor imaging studies revealed that this phenomenon can result in more or less severe microstructural tissue loss.24,25 These tissue changes might be involved in the cavitation of ischemic lesions particularly in the white matter, as already observed in the development of cavities in syringomyelia.26

There are several limitations in the present study: (1) the imaging analysis was performed only in a small number of CADASIL patients; (2) we chose to analyze only areas with an magnetic resonance signal identical to that of CSF on T1-weighted images, which may cause an underestimation of the exact size of ischemic lesions: lacunar infarctions are most often observed as focal areas of complete tissue necrosis with secondary cavitation (type 1a of lacune)27 but can also correspond with lesions with incomplete tissue loss and limited or absent cavitation (type 1b or incomplete small infarct)28,29; and (3) because the resolution was 1 mm, we cannot exclude partial volume effects altering the estimation of the shape and exact volume of the ischemic lesions.

However, despite of these limitations, we think that the present results are promising. In vivo 3D imaging of lacunar infarcts may be helpful in future for the following uses: (1) additional categorization of small artery diseases; (2) to evaluate the importance of secondary degenerative processes associated with small deep infarcts; and (3) to refine the classical 2D criteria used in clinical practice for the definition of lacunar infarctions.

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