Features and Determinants of Lacune Shape
Relationship With Fiber Tracts and Perforating Arteries

Benno Gesierich, PhD; Edouard Duchesnay, PhD; Eric Jouvent, MD, PhD; Hugues Chabrier, MD, PhD; Reinhold Schmidt, MD; Jean-Francois Mangin, PhD; Marco Duering, MD*; Martin Dichgans, MD*

Background and Purpose—Lacunes are a major manifestation of cerebral small vessel disease. Although still debated, the morphological features of lacunes may offer mechanistic insights. We systematically analyzed the shape of incident lacunes in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, a genetically defined small vessel disease.

Methods—A total of 88 incident lacunes from 57 patients were segmented from 3-dimensional T1 magnetic resonance images and 3 dimensionally reconstructed. Anatomic location, diameter, volume, surface area, and compactness of lacunes were assessed. The shape was analyzed using a size, orientation, and position invariant spectral shape descriptor. We further investigated the relationship with perforating arteries and fiber tracts.

Results—Lacunes were most abundant in the centrum semiovale and the basal ganglia. Diameter, volume, and surface area of lacunes in the basal ganglia and centrum semiovale were larger than in other brain regions. The spectral shape descriptor revealed a continuum of shapes with no evidence for distinct classes of lacunes. Shapes varied mostly in elongation and planarity. The main axis and plane of lacunes were found to align with the orientation of perforating arteries but not with fiber tracts.

Conclusions—Elongation and planarity are the primary shape principles of lacunes. Their main axis and plane align with perforating arteries. Our findings add to current concepts on the mechanisms of lacunes.

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Key Words: CADASIL ▪ cerebral small vessel diseases ▪ magnetic resonance imaging ▪ neuroimaging

Lacunes are a key manifestation of cerebral small vessel disease (SVD). They can be visualized on magnetic resonance imaging (MRI) as cerebrospinal fluid (CSF)-isointense cavities and are commonly described as round or ovoid with a maximum diameter of 15 mm.1,2 However, their exact characteristics in terms of size, shape, and anatomic distribution are still debated.3–5 Previous studies proposed specific shape categories by classifying lacunes or lacunar infarcts as spheroid, ovoid, slab, stick, and even more complex shapes.3,6,7 However, these studies were based on visual ratings and the existence of distinct classes of lacunes has never been firmly established.

The determinants of lacune shape are largely unknown. A small case series on acute lacunar infarcts suggested underlying vessel anatomy as a determining factor.8 However, this has not been explored for chronic, cavitated lesions. Also, it has been suggested that Wallerian degeneration of white-matter fibers is involved in cavitation of lacunes, causing shapes to extend along fiber tracts.7 Another unresolved issue is the upper size limit of lacunes. The most widely used criterion to differentiate lacunes from other, typically larger CSF-isointense cavities, such as those resulting from striatocapsular infarcts,3 is a maximum diameter of 15 mm. However, there is little information on whether this is applicable to all imaging planes in 3-dimensions (3D).4

In the current longitudinal study, we systematically investigated incident lacunes using in vivo MRI. The shape was analyzed with an unbiased approach using a spectral shape descriptor (Laplace–Beltrami spectrum).9,10 We further assessed the effect of anatomic location, the orientation of perforating vessels, and the orientation of fiber tracts on the lacune shape.

A major challenge in studying lacunes is the distinction from enlarged perivascular spaces and CSF-filled cavities not caused

Original Contribution

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by SVD, but eg, by cardioembolism, artery-to-artery embolism, or local atheroma of the parent artery.1,9,12 To account for these aspects, we focused on incident lacunes and on subjects with genetically defined SVD.

Methods

Study Cohort
Subjects were drawn from an ongoing prospective 2-center study (Klinikum der Universität München, Germany and Hopital Lariboisière, Paris, France) encompassing 365 cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy patients.13–16 Follow-up visits were scheduled at 18, 36, and 54 months. Details of the study design have been described elsewhere.13 Two hundred seventy-six patients had at least 1 follow-up and thus were included in the study. The ethics committees of both participating centers approved the protocol. Written and informed consent was obtained from all subjects.

MRI and Preprocessing
All patients were scanned on 1.5-T scanners (Siemens Vision [Munich, n=56] or General Electric Medical Systems Signa [Paris, n=588; Munich, n=243]). The sequence parameters have previously been described13 (Table 1 in the online-only Data Supplement). All 3D T1 follow-up images were registered to the baseline scan and normalized nonlinearly to Montreal Neurological Institute (MNI) 152 space using tools from the Functional MRI of the Brain Software Library (FSL).17,18 as described previously.13

Identification of Incident Lacunes
Newly appearing CSF-isointense cavities were identified on follow-up scans using difference imaging and Jacobian maps calculated in comparison with the preceding scan. This procedure has been described in detail and revealed a total of 99 incident cavities in the cerebral hemispheres in 63 patients. Infarctotral cavities (n=4, all of them in the cerebellum) were not included in the analysis because of the lack of available atlas data. Five cavities were excluded because they had a tubular structure with a diameter <3 mm, strongly indicative of perivascular spaces. Six additional lesions had to be excluded from the analysis because of the lack of available atlas data. To reduce dimensionality of the Laplace–Beltrami spectrum, we used principal component (PC) analysis. Lacunes were then represented in a space defined by the first 3 PCs to search for subtypes (clusters) of lacunes with different shapes.

Segmentation of Lacunes
Lacunes were segmented from 3DT1 images using a seed-growth algorithm, implemented in a custom software tool, developed using MATLAB (R2013b, The MathWorks, Natick, MA; details are given in online-only Data Supplement).

Creation of Surface Meshes
The surfaces of lacunes were represented by triangular boundary meshes created from the segmented lacunes using BrainVISA with standard settings.10,19 The vertex density of the meshes was adapted to the image resolution such that edges in the meshes were shorter than voxel edges. Only for visualization, lacunes were smoothed using the iso2mesh toolbox1 in Matlab with a low-pass filter. For visualization in MNI space, lacune meshes were transformed by nonlinear transformations of vertex coordinates using FSL. The normalization parameters were those obtained from all subjects.

Anatomic Location
The anatomic location of lacunes was rated on T1-weighted scans by 2 experienced raters (B.G., M. Duering) using the following 4 categories: basal ganglia, centrum semiovale, corpus callosum, and other. Corpus callosum was defined as a separate category to account for the spatial constraints of this anatomic structure. The agreement between raters was good (Cohen \( \kappa \) of 0.806). In the case of disagreement, a consensus was reached between the 2 raters.

Basic Characteristics
We determined the following metrics calculated in native space: lacune volume, surface area, maximum diameter, axial diameter, and compactness. Volume, surface area, and compactness were calculated from the lacune mesh using BrainVISA. The maximum diameter of each lacune was calculated as the maximum distance of all possible pairs of vertices in the respective surface mesh. The axial diameter (ie, maximum diameter in the axial imaging plane) was calculated as the maximum distance between intersection points of the surface mesh with any axial plane. Details on calculation of basic characteristics are described in the online-only Data Supplement.

Spectral Shape Descriptors
To obtain an observer-independent measure of shape, we calculated the Laplace–Beltrami spectrum from the lacune mesh in native space using the ShapeDNA tool.20 This tool defines the Laplace–Beltrami spectrum as the family of eigenvalues found by solving the Laplace eigenvalue problem (Helmholtz equation). The eigenvalues in the Laplace–Beltrami spectrum build an ordered series. Eigenvalues with a lower ordinal position represent shape changes on a larger scale (low frequency), and eigenvalues with a higher ordinal position represent changes on a smaller scale (high frequency). We restricted the analysis to the first 10 eigenvalues because we considered the most relevant shape information to be related to large-scale (low frequency) shape changes. For similar considerations, eigenvalues were divided by their ordinal position in the spectrum.21,22

We were interested in pure shape changes, independent of lacune size. Thus, eigenvalues were normalized by multiplying with the surface area of the respective lacune, in order to correct for size differences between subject. To reduce dimensionality of the Laplace–Beltrami spectrum, we used principal component (PC) analysis. Lacunes were then represented in a space defined by the first 3 PCs to search for subtypes (clusters) of lacunes with different shapes.

Principal Axes and Simplified Geometric Measures
To provide a more intuitive representation of lacune shape, we used the measures suggested by Westin et al24 for the geometric analysis of diffusion tensors. A tensor can be used to mathematically describe an ellipsoid, and the measures suggested by Westin et al24 indicate how close the corresponding ellipsoid is to the generic cases of a line (linear anisotropy), a plane (planar anisotropy), or a sphere (sphericity), respectively. We calculated these measures from the principal axes of the incident lacunes (online-only Data Supplement). Although more complex shape features (eg, bends and cone-like shapes) of lacunes would not be captured by the measures suggested by Westin et al24, they still can give a good approximation of their linear, planar, and spherical shape component. We used this approximation to get a more intuitive representation of the major shape principles represented by the spectral shape descriptor. In particular, we looked for correlations between the geometric measures suggested by Westin et al24 and the first 3 PCs, resulting from the PC analysis on the eigenvalues of the spectral shape descriptor.

Perforating Artery and Fiber Tract Orientation
The orientation of perforating arteries and white-matter tracts at the centroid of each lacune was defined using an atlas of arterial vascularization25 and a probabilistic atlas of the 20 major white-matter tracts in MNI space (Johns Hopkins University-International Consortium for Brain Mapping [JHU-ICBM] tracts).26 We developed a graphical user interface in Matlab to align slices from the vessel atlas with slices from the MNI template and to manually determine orientation vector for the perforating artery and white-matter tract at the centroid (the geometric center) of each lacune (details are given in the

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online-only Data Supplement). The resulting orientation vectors were then reverse transformed into native space. The agreement between raters was good for both perforating arteries (intraclass correlation coefficient, 0.741) and white-matter tracts (intraclass correlation coefficient, 0.919). The orientation of perforators and white-matter tracts could be determined for 74 and 53 lacunes, respectively. Lacunes in subcortical grey matter were not rated for tract orientation.

### Relationship Between Lacune Shape and Perforating Artery/Fiber Tract Orientation

To assess the relationship between lacune shapes and vascular anatomy, we calculated 2 types of angles: the angles between the main axis of the lacunes (defined as their longest principal axis) and the orientation vector of perforating arteries at the centroid of the lacunes and the angles between the main plane of the lacunes (the plane defined by their longest and second longest principal axes) and the orientation vector of perforating arteries. We then tested whether the distributions for these 2 types of angles were different from a random distribution using the χ² goodness-of-fit test. Similarly, the relationship between lacune shapes and fiber tract orientation was assessed by calculating the corresponding angles with the orientation vectors of the fiber tracts.

### Statistical Analysis

Statistical analyses were conducted with the R software package (version 3.1.0). The basic characteristics of lacunes and lacune loadings on the first 3 PCs of the ShapeDNA were compared across anatomic locations using the Kruskal–Wallis test. P values were corrected for multiple comparisons (8 tests) using the Bonferroni method. Significant results were followed by post hoc tests using pairwise Wilcoxon signed-rank tests with the Bonferroni method for adjusting P values. Linear regression was used to assess the relationship between the PCs of the spectral shape analysis and the simplified geometric measures.

### Results

The demographic features, vascular risk factors, and clinical and imaging characteristics of the 57 cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy patients with incident lacunes are reported in the Table. Symptoms were reported for 18 lacunes (20.5%; Table). Hence, the majority of lesions were clinically silent. Figure 1 depicts the anatomic distribution and shape characteristics of all incident lacunes (n=88) projected on a single glass brain in standard space (Movie I in the online-only Data Supplement).

### Characteristics of Incident Lacunes

Lacunes were most abundant in the centrum semiovale (n=30) and the basal ganglia region (n=27). They were also present in other brain regions (corpus callosum, frontal/occipital pole; n=30), whereas the temporal lobe was relatively spared (n=1).

A comparison of basic lacune features across all anatomic locations showed significant differences in maximum diameter ($H=15.76; \ P=0.01$), volume ($H=17.25; \ P=0.005$), and surface area ($H=18.76; \ P=0.002$; Table II in the online-only Data Supplement). Post hoc pairwise comparisons (Figure 2) showed that lacunes in the basal ganglia and centrum semiovale were significantly larger compared with lacunes in the corpus callosum or other regions.

### Spectral Shape Analysis

Global shape variations of lacunes were analyzed on the basis of a spectral shape descriptor, the Laplace–Beltrami spectrum. In PC analysis, the first 3 components explained 79.7% of the variance in the spectral shape descriptor, with 60.8% explained by the first component and 10.7% by the second. There was no difference in the first 3 PCs across anatomic locations (Table II in the online-only Data Supplement). As illustrated in Figure 3A, lacune shape varied continuously along the PCs without indication for clustering or subgroups.

To obtain a more intuitive representation of the shape principles captured by the first 3 PCs, we compared each PC with the following simplified geometric measures: linear anisotropy (elongation), planar anisotropy (planarity), and sphericity. PC1 is well represented by linear anisotropy (Figure 3B; adjusted $R^2=86.11; \ P=7.58\times10^{-19}$). PC2 is best represented by planar anisotropy (Figure 3C; adjusted $R^2=32.93%; \ P=3.06\times10^{-6}$). Other correlations were less
Figure 3D gives representative examples of lacunes plotted along PC1 and PC2. As can be seen from this analysis, elongation and planarity were the primary determinants of lacune shape.

Relationship With Perforating Arteries and White-Matter Tracts

To identify potential determinants of lacune shape, we next explored the spatial relationship between lacune geometry and both perforating arteries and white-matter tracts. Specifically, we examined the distribution of angles between the main lacune axis (for elongation) or main lacune plane (for planarity) and orientation vectors for perforating arteries and white-matter tracts. Small angles between perforating arteries and the main lacune axis were more common than large angles (Figure 4A). The results were significantly different from a random distribution ($\chi^2=36.68; df=8; P=1.32 \times 10^{-5}$). Similarly, small angles between perforating arteries and the main lacune plane were more common than large angles ($\chi^2=53.06; df=8; P=1.05 \times 10^{-8}$).

Figure 1. Top, Three-dimensional glass brain representation of lacunes in the Montreal Neurological Institute (MNI) space. Bottom, For a better appraisal of their spatial distribution, lacunes are represented as spheres drawn around the lesion center. Lines indicate the orientation of perforating arteries at this location. Colors depict the anatomic location (red: basal ganglia, blue: centrum semiovale, green: corpus callosum, and yellow: other areas).

Figure 2. Basic characteristics of lacunes in different anatomic brain regions. BG indicates basal ganglia; CC, corpus callosum; and CS, centrum semiovale. *$P<0.05$ **$P<0.01$ (Bonferroni-corrected pairwise Wilcoxon signed-rank test).
Figure 4B). For fiber tracts, the calculated angles did not differ from a random distribution (main axis: $\chi^2=12.38; df=8; P=0.135$; main plane: $\chi^2=11.26; df=8; P=0.187$). Hence, lacunes tend to align along perforating arteries.

Maximum Diameters of Lacunes in 3D and 2D
Routine clinical evaluation of lacunes is usually performed in 2D on axial slices, and an axial diameter of <15 mm is commonly used to distinguish lacunes from other CSF-isointense cavities. Figure 5 illustrates that 9 (10.2%) of the 88 lacunes had maximum diameters >15 mm. However, when analyzed in an axial imaging plane, only 1 lacune (1.1%) exceeded the 15-mm threshold.

Discussion
This study in a well-characterized cohort of patients with genetically defined SVD shows that incident lacunes are distributed along a continuum of shapes, primarily defined by 2 geometric measures: elongation and planarity. Our study further demonstrates that lacunes tend to align with the orientation of perforating arteries. Lacunes in the basal ganglia and centrum semiovale were larger compared with other brain regions. These findings add to current concepts on the characteristics and mechanisms of lacunes.

We found elongation to be the predominant shape principle of lacunes regardless of anatomic location, and we found lacunes to be aligned with perforating arteries. This fits with a previous small case series of patients with acute lacunar infarcts that described linear structures on MRI or computed tomography consistent with alterations in or around perforating arteries.8 Our findings extend this observation from single cases to a systematic analysis in a large sample and to chronic cavitated lesions. We further addressed tract degeneration as a potential determinant of lacune shape. Recent studies have demonstrated secondary degeneration of white-matter tracts and remote grey matter after subcortical infarcts.28–31 It was...
Our study also has limitations. The orientation of perforating arteries was derived from a single–subject atlas.$^25$ Although being the best source for determining vessel anatomy in humans to date, this atlas does not account for individual differences, thereby adding noise and possibly reducing effect size. One might speculate that the relationship between perforating arteries and lacune shape is even stronger than observed in our study. Similarly, using an atlas for white-matter tract anatomy instead of individual tractography might have reduced our power to detect the relationship between tract orientation and lacune shape. Also, although the tract atlas is still state-of-the-art, it is prone to artifacts related to crossing fibers as an inherent limitation of diffusion tensor–based tractography. For this reason, we limited the tract analysis to areas where a clear and consistent tract orientation can be assigned.

It remains open whether the features and determinants of lacune shape observed here are generalizable to nongenetic SVDs. Previous studies on shape characteristics have focused on acute infarcts rather than lacunes,$^3,6$ and we are not aware of any studies that have looked at the determinants of shape features. Of note, however, conducting similar analyses in sporadic patients will be difficult because of the known challenges in excluding competing vascular etiologies, such as atheroma of the parent artery or embolisms from proximal sources.

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Disclosures

None.

References

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Figure 5. Maximum diameters of lacunes in 3-dimensions (3D) and 2D. For each incident lacune, the maximum diameter and the axial diameter (ie, maximum diameter in the axial plane) were determined. Dashed lines at 15 mm indicate the upper size limit for lacunes commonly used in clinical practice. Note that several lacunes (n=9) exceed a maximum diameter of 15 mm, whereas only 1 lacune showed an axial diameter >15 mm.

Further suggested that these secondary changes influence lacune shape.$^7$ We found no relationship between lacune shape and fiber tract orientation. Hence, our observations suggest that the development of lacunes is primarily determined by mechanisms in or around perforating vessels, rather than by secondary effects, such as Wallerian degeneration.

Our finding of a continuum of shapes suggests that the development of lacunes is modulated by factors varying gradually and without relationship to a certain brain region. Again, one of these factors may be found in vascular anatomy. A postmortem study on lenticulostriate arteries demonstrated considerable interindividual and interhemispheric variability in branching patterns,$^32$ and a similar degree of variability can be expected for centrum semiovale perforators. Thus, the continuum of lacune shapes may, in part, reflect variations in vascular branching patterns. Detailed studies assessing individual vascularization patterns in vivo before a lacune develops are needed to verify our hypothesis but are still methodologically challenging.$^{33,34}$

The current study also has implications for diagnostic imaging. We show that the usual size criterion for lacunes (<15 mm) is valid when applied to images obtained in the axial plane. However, in a considerable proportion of lacunes, the maximum diameter in 3D exceeded 15 mm. This should be taken into account when inspecting imaging planes other than axial.

Our study has several strengths. First, we studied a well-defined cohort with genetically defined SVD. Thus, we are confident that our results are not contaminated by other causes of small cystic infarcts, such as cardiac or artery-to-artery embolism. Second, we used advanced protocols for lacune detection and focused on incident lacunes, thus excluding enlarged perivascular spaces. Another strength is the application of a spectral shape descriptor that is invariant to scale, rotation, and translation.$^10$ This enabled an unbiased and observer-independent approach without a priori assumptions on shape.

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SUPPLEMENTAL MATERIAL

Features and Determinants of Lacune Shape: Relationship with Fiber Tracts and Perforating Arteries

Supplemental Methods
Supplemental Table I: MRI sequence parameter
Supplemental Table II: Features of lacunes by brain region
Supplemental Figure I: Lacunes projected on first 3 PCs of the spectral shape descriptor
Supplemental Figure II: Correlations between PCs and geometrical measures
Supplemental Figure III: Calculation of the angles between perforator and the main axis and main plane of lacunes
Supplemental Video I: Lacunes in MNI space
Supplemental Video II: Lacunes projected on first 3 PCs of the spectral shape descriptor
SUPPLEMENTAL METHODS

Seed growing criterion for lacune segmentation
Lacunes were segmented from 3D T1 images using a seed-growing algorithm, implemented in a custom software tool, developed using MATLAB. Starting from a manually placed seed voxel we first included all neighboring voxels meeting the inclusion criterion for absolute intensity and intensity difference compared to the seed voxel. This process was then repeated starting from the newly included voxels in an iterative way resulting in binary representations of the lacunes in 3D.

The inclusion criterion for the seed-growing algorithm was based on a combined test of the absolute intensity of the tested voxel ($I_{\text{abs}}$) and its intensity difference to the neighboring seed voxel ($\Delta I$). The combination of these two parameters allowed us to account for the observation that the border of lacunes seemed not always to have a constant intensity but depended on the intensity of the surrounding tissue (e.g. WMH, normal appearing WM, basal ganglia tissue).

The inclusion criterion was defined mathematically as

$$\Delta I > \frac{I_{\text{tol}}}{e^{(I_{\text{ref}}-I_{\text{abs}}) \times k}}$$

Hereby a tested voxel was included, if $\Delta I$ was bigger than a tolerated intensity drop ($I_{\text{tol}}$, being a negative value) divided by a term taking $I_{\text{abs}}$ into account. The more $I_{\text{abs}}$ deviated (negatively) from a given reference intensity ($I_{\text{ref}}$, independently chosen from the seed and the tested voxel), the less tolerant the algorithm became to intensity differences between the seed and the tested voxel ($\Delta I$). The parameter $k$ was set to $k=0.13$ and the parameters $I_{\text{ref}}$ and $I_{\text{tol}}$ were chosen depending on the mean (mean) and standard deviation (sd) of the intensity in the cerebrospinal fluid (ICSF) segment of the T1 image.

These parameters were selected after exploratory segmentation of a representative set of lacunes with different sets of parameters. The parameters, which worked most consistent across this representative set of lacunes was then taken for the segmentation of all lacunes.

Calculation of the axial diameter
The axial diameter (i.e. the maximum diameter in the axial plane) of lacunes was calculated as the maximum distance between intersection points of the surface mesh with the axial plane. Specifically, the surface mesh of each lacune was sliced along axial planes with a slice distance of 1mm. Intersection points between the surface mesh and the axial planes were calculated using the iso2mesh toolbox. Finally, the maximum distance of all possible pairs of intersection points was calculated, considering only pairs lying within the same axial plane. The orientation of axial planes in the native space was determined by transforming the vectors representing the x- and y-axis in the MNI space back into the native space of each lacune using FSL.

Calculation of compactness
Compactness relates the volume ($V$) of a 3D object with its surface area ($A$) and is calculated as $V^2/A$. It is insensitive to rotation, spatial translation and size. A sphere represents the 3D object with the largest possible volume for a given surface area and thus has the largest possible value of compactness (0.21). Compactness decreases as a shape deviates from a regular sphere and is also affected by surface characteristics, such as regularity.
Calculation of principal lacune axes

The principal axes of lacunes were calculated by principal component analysis on the Cartesian coordinates of voxels in the binary representations of lacunes in native space. The resulting three principal components were considered the principal axes of the lacunes. The eigenvalues of these principal components represent the variance of voxel locations along these axes and represent extension or spread of the lacunes along these axes. Therefore, these eigenvalues were further used to calculate indices for how linear (prolate, cigar-shaped), planar (disk-shaped), or spherical the lacunes were.

Relationship between lacune and perforating artery

We calculated the angle between the orientation of perforating arteries at the centroid of the lacune and the longest principal axis or main plane of the lacune. The longest principal axis was derived as explained in the previous section and represented the axis of the linear shape component of the lacunes. The main plane of the lacunes was defined as the plane of the longest and second longest principal axis of the lacunes and represented their planar shape component. The orientation of the perforating arteries at the centroid of the lacunes was determined using a vessel atlas as described in the main text. After calculating the angles, we calculated their distribution, by dividing the range of possible angles from 0º (perforator oriented parallel to the longest principal axis or lying in the main plane of the lacune) to 90º (perforator oriented perpendicular) into 9 bins (each 10º wide) and counting lacunes per bin. For the angles between perforating arteries and longest principal axis of the lacunes, all possible angles would be equally likely, if they were randomly distributed. Note, however, that for the main plane of the lacunes the random distribution looks different with small angles being a priori more likely than big angles.

Perforating artery and white matter tract orientation – Description of the GUI

A graphical user interface (GUI) written in Matlab was used to determine the orientation of the perforating arteries and of white matter tracts at the centroids of the lacunes. Orthogonal slices of the MNI template centered at the centroid of each lacune were visualized. On top of these slices we overlaid the orthogonal slices from the vessel atlas (see main text) with the best anatomical fit or the corresponding slice from the white matter tract atlas. On user control the slices from the vessel atlas could be spatially translated, scaled, and rotated until they were in good alignment with the MNI template. An orientation vector could be visualized in the same Matlab GUI at the centroid of the lacune. A human rater could manipulate its orientation, until it corresponded to the orientation of the perforating artery or of the white matter tracts as indicated by the two atlases.

Glass-brain visualization

The spatial distribution of lacunes in the brain was inspected visually, by rendering all lacune meshes in MNI space (see main text, figure 1). For reference, meshes representing the lateral ventricles and the grey matter surface of the brain (glass-brain) were rendered together with the lacune meshes. To create the surface meshes for the ventricle, voxels in the MNI space, which were classified as ventricle in at least 50% of all patients with incident lacunes were included in a binary mask, which was then used to create a surface mesh with iso2mesh. The initial classification of voxels as ventricle in individual patients was done by seed-growing. For details see supplemental material, section seed growing criterion. The glass-brain mesh was created from the MNI 152 template (mni152_2009bet.nii.gz) provided with MRICroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). The template was thresholded, binarized and deep sulci were filled using dilation with subsequent erosion of the binary mask. The mask was cleaned and the cerebellum was removed manually. Finally, a surface mesh was created from the binary mask using the iso2mesh toolbox. All meshes were smoothed using iso2mesh toolbox with a low-pass filter.
SUPPLEMENTAL TABLES

**Supplemental table I.** MRI sequence parameters

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<td>0.8</td>
<td>1.02x1.02</td>
</tr>
</tbody>
</table>

TR: Repetition time, TE: Echo time, TI: Inversion time
All sequences were done without interslice gap
### Supplemental Table II. Features of lacunes by brain region

<table>
<thead>
<tr>
<th></th>
<th>Basal ganglia (BG)</th>
<th>Centrum semiovale (CS)</th>
<th>Corpus callosum (CC)</th>
<th>other</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max. diameter [mm]</td>
<td>13.12 (5.03)</td>
<td>10.23 (4.22)</td>
<td>8.23 (1.8)</td>
<td>9.05 (4.77)</td>
<td>0.010</td>
</tr>
<tr>
<td>Axial diameter [mm]</td>
<td>9.54 (5.09)</td>
<td>7.86 (3.53)</td>
<td>6.65 (1.14)</td>
<td>7.66 (3.57)</td>
<td>0.300</td>
</tr>
<tr>
<td>Volume [mm$^3$]</td>
<td>211.26 (208.1)</td>
<td>115.9 (120.06)</td>
<td>67.67 (39.17)</td>
<td>63.95 (72.62)</td>
<td>0.005</td>
</tr>
<tr>
<td>Surface area [mm$^2$]</td>
<td>257.7 (198.05)</td>
<td>147.03 (111.8)</td>
<td>103.83 (45.2)</td>
<td>101.87 (73.15)</td>
<td>0.002</td>
</tr>
<tr>
<td>Compactness</td>
<td>0.14 (0.03)</td>
<td>0.15 (0.02)</td>
<td>0.16 (0.01)</td>
<td>0.15 (0.02)</td>
<td>0.053</td>
</tr>
<tr>
<td><strong>Spectral shape descriptor (Principal Components)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC1</td>
<td>-0.91 (3.97)</td>
<td>0.06 (3.96)</td>
<td>1.93 (4.6)</td>
<td>-0.04 (4.12)</td>
<td>1</td>
</tr>
<tr>
<td>PC2</td>
<td>0 (1.28)</td>
<td>0.34 (1)</td>
<td>-0.09 (1.23)</td>
<td>0.37 (1.33)</td>
<td>1</td>
</tr>
<tr>
<td>PC3</td>
<td>-0.2 (1.13)</td>
<td>-0.09 (1.25)</td>
<td>0.56 (0.51)</td>
<td>0.19 (1.35)</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range). PC1-3: first three principal components of the spectral shape descriptor. P-values: Kruskal-Wallis tests after Bonferroni correction.
**Supplemental Figure I:** Lacunes projected onto the first three principal components of the spectral shape descriptor stratified by location (BG: basal ganglia; CS: centrum semiovale; CC: corpus callosum)
Supplemental Figure II: Correlations between the first three principal components of the spectral shape descriptor and the three geometrical measures (linear anisotropy, planar anisotropy and sphericity)
Supplemental Figure III: An example lacune is shown in different orientations to visualize the calculation of angles. In both panels (A and B), the lacune is shown on the left side oriented with it’s main plane (rectangular surface) perpendicular to the observers viewing direction and on the right side respectively with a rotation around the vertical axis maximizing the 2D projection of the angle between perforator (red line) and the main lacune axis (black line) (panel A) and of the angle between the perforator and the main plane (panel B).
SUPPLEMENTAL VIDEO LEGENDS

Supplemental Video I: Lacunes in MNI space
3D representation of lacunes in the MNI space. The viewpoint is rotating around the glass brain.

Supplemental Video II: Lacunes projected on first three PCs of shape descriptor
Lacunes projected onto the first three principal components of the spectral shape descriptor. Lacunes are stratified by location (BG: basal ganglia; CS: centrum semiovale; CC: corpus callosum). The viewpoint is moving to show different 2D projections, starting with a view on the PC1/PC2 plane, moving to the PC1/PC3 plane and finally reaching the PC3/PC2 plane.
ラクナ形状の特徴と決定因子
神経路および穿通動脈との関係

Features and Determinants of Lacune Shape
Relationship With Fiber Tracts and Perforating Arteries

Benno Gesierich, PhD 1; Edouard Duchesnay, PhD 2; Eric Jouvent, MD, PhD 3; Hugues Chabriat, MD, PhD 3; Reinhold Schmidt, MD 4; Jean-François Mangin, PhD 3; Marco Duerer, MD 4; Martin Dichgans, MD 1,2,5

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背景および目的：ラクナは脳小血管病の主病態である。まだ議論は続いているものの、ラクナの形態学的特徴はメニスムの理解を深めるきっかけになる。遺伝的血管障害、境界下脳梗塞および白質病変を伴う常染色体優性遺伝性脳動脈瘤（CANDASIL）では、発端的に発見されたラクナ（発症ラクナ）の形状を系統的に解析した。

方法：患者47例の発症ラクナ計88個を3次元T1 MRIから得た3次元CTMに再構成した。ラクナの解剖学的定位、径、面積、形状、確率を計測した。形状は、比較的、方向、位置によって変わるスペクトル形状記述子によって解析した。さらに、神経路および神経路との関係を調査した。

結果：ラクナは半卵円中心と大脳基底核に豊富に認められた。大脳基底核および半卵円中心のラクナの径、面積、形状、位置は他の脳領域のラクナより大きかった。スペクトル形状記述子により、明確なラクナ分類に基づかない連続した形状が明らかになった。長さおよび面積の形状変化が最も大きかった。ラクナの主軸および主面は穿通動脈の方向と一致したが、神経路との一致は認められなかった。

結論：ラクナの形状を神経路の重要な形成要素である。ラクナの主軸および主面は穿通動脈と一致する。本研究結果は、ラクナの発生機序に関する現在の概念を補強するものである。

ラクナ形状の特徴と決定因子

表示のため、ローバスフィルターのMatlabのiso2mesh
toolboxでラクナを平滑化した。MNI空間で表示する
ため、FSLによる頂点座標の非線形変換によりラクナ
メッシュを変換した。正規化パラメータは、対応する
T1画像をMNI 152空間に対して正規化することにより
得たパラメータであった。

解剖学的部位

ラクナの解剖学的部位は、2名の検査で豊富な評価者
（B.G., M. Duering）が大脳基底核、側頭前内、額葉、
その他の4つのカテゴリーに基づいてT1強調画像で評
価した。解剖学的構造の空間的制約を考慮に入れ、脳葉
は別カテゴリーにした。評価者の一致度は良好にあっ
た（Cohen κ 0.806）。一致しない場合は2名の評価者同
士で合意を形成した。

基本的特徴

自然空間で計画したラクナの体積、表面積、最大径、
軸位径、緊密性について評価を行った。体積、表面積、
緊密性はBrainVISAによりラクナメッシュから計画し
た。各ラクナの最大径は、各々の表面メッシュで考えな
る頂点ベアの最大距離として計算した。軸位径（軸位断
面の最大径）は軸位断面と表面メッシュの交点の最大距
離として計算した。基本的特徴の計算に関する詳細はオ
ンラインデータ補遺に述べた。

スペクトル形状記述子

評価者に依存しない形状の評価指標を得るため、
ShapeDNA法で自然空間のラクナメッシュからラブラス
-ペルトラミスペクトルを計算した。この方法は、ラ
ブラス固定値問題（ベルホルツ方程式）を解くことで
得た固定値の族としてラブラス-ペルトラミスペクトル
を定義する。ラブラス-ペルトラミスペクトルの固定値
は順序序列を構成する。順序位置が下位の固定値は大規
模（低頻度）な形状変化を表し、順序位置が上位の固定
値は小規模（高頻度）な変化を表す。最も適切な形状情
報は大規模（低頻度）な形状変化と考え、解析は最初の
10個の固定値までとした。同様の配慮により、固定値
をスペクトルの順序位置で割った。

本研究の関心事は、ラクナの大きさに関係ない純粋な
形状の変化である。そのため、各ラクナの表面積乗じ
ることにより固定値を正規化した。

ラブラス-ペルトラミスペクトルの次元を減らすため、
主成分（PC）分析を使用した。次に第1〜第3主成分で
定義した空間でラクナを表し、異なる形状のラクナのサ
プタイプ（クラスター）を探った。
主軸と簡易形状評価指標

ラクナ形状をより直感的に表現するため、Westinらが拡散テンソルの形状解析に提案した評価指標を用いた。構円体はテンソルで数学的に説明することができ、Westinらが提案した評価指標は、該当する構円体の一般的なケースの線（線形異方性）面（面内異方性）、球（球形度）のどの程度近いかを示す。これらの評価指標は偶発ラクナの主軸から計算した（オンラインデータ補遺）。Westinらの提案した指標では、さらに複雑なラクナ形状の特徴（カーブや円錐形など）を捉えられないが、線形、平面、球形成分の近似値を算出するには十分である。スペクトル形状記述子で表現した主な形状の形成原理をより直感的に表現するためにこの計算方法を使用した。特に、Westinらが提案した形状評価指標と、スペクトル形状記述子の固有値で主成分分析によって得た第1〜第3主成分の相関性を探った。

穿通動脈および神経路の方向

動脈分布アトラスとMNI空間の20の主要白質神経路の確率的アトラス[Johns Hopkins University-International Consortium for Brain Mapping (JHU-ICBM) tracts]により、各ラクナの重心における穿通動脈および白質神経路の方向を決定した31。血管アトラスのスライスをMNIテンプレートのスライスと合わせて、各ラクナの重心（幾何学的中心）で穿通動脈および白質神経路の方向ベクトルを手動で決定するため、Matlabでクォッティカルユーザーやインタフェースを開発した（詳細はオンラインデータ補遺に記載）。その結果得られた方向ベクトルを自然空間に逆変換した。評価者間の一致性は、穿通動脈（経内相関係数0.741）および白質神経路（線内相関係数0.919）ともに良好であった。穿通動脈および白質神経路の方向を特定できたラクナの数は、それぞれ74および53であった。皮質下灰白質のラクナについては神経路方向の評価を行わなかった。

ラクナ形状と穿通動脈/神経路方向の関係

ラクナ形状と血管構造の関係を評価するため、2種類の角度を計測した。1つはラクナの主軸（最も長い主軸と定義）とラクナ重心における穿通動脈の方向ベクトルの角度、もう1つはラクナの主面（最も長い主軸と次長い主軸で決定される平面）と穿通動脈の方向ベクトルの角度である。次に、これら2種類の角度の分布がランダム分布と異なるか否かについてχ²適合度検定を実施した。同様に、神経路の方向ベクトルの角度を計算することによりラクナ形状と神経路方向の関係を評価した。

統計解析

統計解析法はRソフトウェアパッケージ（バージョン3.1.0）で実施した22。Kruskal-Wallis検定により、ラクナの基本的特徴およびShapeDNA（第1〜第3主成分におけるラクナ説明力の度合いを客観的に評価する）補遺のP値を多重比較（検定）のためBonferroni法により補正した。有意な結果に対しては、Bonferroni法でP値を調整した一対の標本にWilcoxon符号付き順位検定により事後検定を施行した。スペクトル形状計画の主成分と簡易形状評価指標の関係を線形回帰により評価した。

結果

偶発ラクナが認められたCADASIL患者57例の人口統計学的特徴、脳血管障害の危険因子、臨床および画像検査所見の特徴を表に報告する。症状は18個のラクナで報告された(20.5%, 表). したがって疾患の大半は臨床的に無症状であった。図1は標準空間のガラス脳に投影した各偶発ラクナ(n = 88)の解剖学的分布と形状の特徴を示す(オンラインデータ補遺動画1).

偶発ラクナの特徴

ラクナは半卵円中心(n = 30)と大脳基底核領域(n = 27)に最も多かった。ラクナは他の脳領域にも存在したが(脳梁、前頭/後頭葉、n = 30), 側頭葉は比較的少なくなかった(n = 1)。

すべての解剖学的部位でラクナの基本的特徴を比較したところ、最大径(H = 15.76, P = 0.01), 体積(H = 17.25, P = 0.005), 表面積(H = 18.76, P = 0.002, オンラインデータ補遺表II)に有意差が認められた。事後比較(図2)で、大脳基底核および半卵円中心のラクナは脳梁などの領域のラクナに比べ有意に大きいことが示された。

スペクトル形状計画

スペクトル形状記述子であるラプラス - ベルトラミスペクトルに基づいてラクナの全体的形状変化を解析した。主成分分析で、スペクトル形状計画の変動の79.7％は第1〜第3主成分により説明され、60.8％は第1主成分で、10.7％は第2主成分で説明された。解剖学的部位では第1〜第3主成分に差はなかった(オンラインデータ補遺表II)。図3Aに示すように、ラクナの形状は主成分とともに連続的に変化し、クラスターまたはサブグループ形成の兆候は見られなかった。

第1〜第3主成分により捉えた形状の形成原理をより
表 偶発ラクナが認められた患者の特徴

<table>
<thead>
<tr>
<th>項目</th>
<th>スコア</th>
</tr>
</thead>
<tbody>
<tr>
<td>人口統計学的特徴</td>
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<tr>
<td>年齢中央値（範囲）、歳</td>
<td>51.0（34.6-73.9）</td>
</tr>
<tr>
<td>男性n（％）</td>
<td>32（56.1）</td>
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<td>脳血管障害の危険因子、n（％）</td>
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<tr>
<td>高血圧</td>
<td>10（17.5）</td>
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<td>高コレステロール症</td>
<td>27（47.4）</td>
</tr>
<tr>
<td>糖尿病</td>
<td>2（3.5）</td>
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<td>喉咽、気短覚者または現発者</td>
<td>35（61.4）</td>
</tr>
<tr>
<td>臨床的特徴、n（％）</td>
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<td>症候性ラクナ</td>
<td>18（20.5）</td>
</tr>
<tr>
<td>典型的ラクナ症候群</td>
<td>11（12.5）</td>
</tr>
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<td>純粋運動性発作</td>
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</tr>
<tr>
<td>純粋反射性発作</td>
<td>3</td>
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<td>運動失調不全片麻痺</td>
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<td>構音障害・手不器用症候群</td>
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<td>MMSE、中央値（IQR）</td>
<td>28（3）</td>
</tr>
<tr>
<td>MDRS、合計スコア、中央値（IQR）</td>
<td>139（10）</td>
</tr>
<tr>
<td>MDRS、注意サブスケール、中央値（IQR）</td>
<td>37（1）</td>
</tr>
<tr>
<td>MDRS、発動性・保存サブスケール、中央値（IQR）</td>
<td>34.5（6）</td>
</tr>
</tbody>
</table>

画像の特徴

ラクナ体積、中央値（IQR）、μL | 453.2（705.8）|
ベーシラインのラクナ数、中央値（範囲） | 6（0-29）|
追跡調査時の偶発ラクナ数、中央値（範囲） | 1（1-5）|
WMHV、中央値（IQR）、μL | 100.5（87.1）|
微小出血数、中央値（IQR） | 0.5（2）|
正常化脳体積、中央値（IQR）* | 0.81（0.06）|

IQR：四分位範囲，MDRS：Mattis Dementia Rating Scale [最大スコア144（合算）、37（注意）、27（発動性）]，MMSE：ミニメンタルステート検査，WMHV：白質高信号体積
* 脳室内腔容積で割ることにより正規化

画像資料は、Rasband W. ImageJソフトウェアを使用して取得された。解析は、Statistical Package for the Social Sciences（SPSS）11.0を使用して行った。

研究結果は、この知見を単独症例から大規模症例の系統的解析および慢性空洞化病変まで広げた。また、ラクナ形状の決定因子として、神経変の変性にも取り組んだ。皮質下梗塞の発症後、白質神経病および周辺部の灰白質に二次変性が認められることの最近の研究で明らかにされている20-31。このような二次変性はラクナ形状に影響するともいわれている32。ラクナ形状と神経変の方向に関連性はなかった。したがって、ラクナの形成はワーラー変性などの二次的影響によってはなく、主に神経変の内部または周辺部の発生機序が左右すると示唆される。

本研究で認めた亜急性変形は、ラクナの形成が徐々に変化する因子の調節を受け、特定の脳領域と関係しない。
図1 上：Montreal Neurological Institute（MNI）空間にラクナを表示した3次元ガラス脳。下：ラクナの空間分布をより正確に評価するため、病変の中心を囲む球体でラクナを表した。線はその場所の穿通動脈の方向を示す。色は解剖学的位置を表す（赤：大脳基底核、青：半卵円中心、緑：脳梁、黄：その他領域）。

ことを見記者。やや、これらの因子の1つが血管構造で見つかる可能性がある。レンズ核線条体動脈の解剖学研究で、分岐パターンにかなりの個人差および左右半球間差が認められており32、半卵円中心の穿通動脈でも同程度の変動が予想される。さらに、ラクナ形状の連続性は血管分岐パターンの変動を部分的に反映していると思われる。本研究の仮説を検証するには、個別にラクナ形成前の血管構造パターンをin vivoで評価する詳細研究が必要であるが、方法論的にまだ困難である33,34。

本研究は画像診断にも影響する。従来のラクナの大きさ基準（<15mm）を軸位断画像に適用した場合、この基準は適切である。しかし、かなりの割合を占めるラクナの3D最大径が15mmを超えていた。軸位以外の画像断面を調べる場合は、これを考慮に入れる必要がある。

図2 異なる解剖学的脳領域におけるラクナの基本的特徴。BG：大脳基底核、CC：脳梁、CS：半卵円中心。*P<0.05 **P<0.01（Bonferroniの補正を加えた一対の標本によるWilcoxon符号付き順位検定）
A. スペクトル形状記述子の第1および第2主成分（PC）に投影したラクナ（第1, 第2, 第3主成分への投影はオンラインデータ補遺の図1および個別に示す）。B. スペクトル形状記述子の第1主成分にプロットした線形異方性。C. 第2主成分にプロットした球面異方性。D. 第1主成分（ラクナ1～6）および第2主成分（ラクナ7～12）に沿って3次元（3D）表示したラクナ。主成分スコアは左から右に高くなる。x, y, z軸は各ラクナ主軸に応じ、z軸が最も大きい。ラクナは形状の特徴を示すために3軸を用いる。全体として、第1主成分については、x, y, z軸の方向と球面異方性が最も強く表現される。第2主成分については、球面異方性が最も強く表現される。

本研究にはいくつかの長所がある。第1に、SVDの遺伝的要因を持つコホートを組み立てた。そのため、心臓検査や動脈硬化検査などの要因とし小囊性検査が本研究結果に示すことはなかったと確信している。第2に、ラクナ検出における進歩の方法を用いて偶発ラクナに集中し、血管周囲の拡張を除外した。もう1つの長所は、尺度、回転、並進移動によって変わらないスペクトル形状記述子を応用することである。これにより形状に対して先駆的な設定を立てることなく、偏りのない、評価者が依存しない手法が可能となった。

本研究には限界もある。穿通動脈の方向が被験者1例のアトラスに由来することである。このアトラスはこれまでヒトの血管構造を確認するには最適な地図であったが、個人差を考慮していなかったため、ノイズの増加と効果量の低下が予想される。穿通動脈とラクナ形状の関係が本研究の結果よりかなり強い可能性もありうる。同じように各症例のトラックグラフィーではなく白質神経路の解剖学構造アトラスを使用することで、神経路の方向とラクナ形状の関係における検出能力が低下した可能性もある。また、神経路アトラスはまだ最前線ではないが、拡散テンソルに基づくトラックグラフィーに固有の限界として、交差する線維のアーチファクトを受けやすい。このような理由から、明確に一貫した神経路方向を割り当てられる領域に神経路解析を限定した。

本研究で認められたラクナ形状の特徴と決定因子が遺伝的要因に由来しないSVDでも一般化することができるか


