Features and Determinants of Lacune Shape

Relationship With Fiber Tracts and Perforating Arteries

Benno Gesierich, PhD; Edouard Duchesnay, PhD; Eric Jouvent, MD, PhD; Hugues Chabriat, 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.

(Stroke. 2016;47:1258-1264. DOI: 10.1161/STROKEAHA.116.012779.)

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 However, their exact characteristics in terms of size, shape, and anatomic distribution are still debated.2–5 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 form other, typically larger CSF-isointense cavities, such as those resulting from striatocapsular infarcts,9 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).10,11 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...
by SVD, but eg, by cardioembolism, artery-to-artery embolism, or local atheroma of the parent artery. 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. Follow-up visits were scheduled at 18, 36, and 54 months. Details of the study design have been described elsewhere. 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 described (Table I in the online-only Data Supplement). All 3DT1 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) as described previously.

**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 and revealed a total of 99 incident cavities in the cerebral hemispheres in 63 patients. Infratentorial 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 because of incomplete cavitation (n=3), concomitant large vessel stroke (n=2), or insufficient image contrast (n=1). The final sample consisted of 88 incident lacunes detected in 57 cerebral autosomal dominant arteriopathy patients and provided the basis for all subsequent analyses.

**Segmentation of Lacunes**

Lacunes were segmented from 3DT1 images using a seed-growing algorithm, implemented in a custom software tool, developed using MATLAB (R2013b, The MathWorks, Natick, MA; details are given in the 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. 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 toolbox 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 presented in a space defined by the first 3 PCs to search for subtypes (clusters) of lacunes with different shapes.

**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. 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.

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.

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 al for the geometric analysis of diffusion tensors. A tensor can be used to mathematically describe an ellipsoid, and the measures suggested by Westin et al 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 al, 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 al 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 vascularization 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). 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 vectors for the perforating artery and white-matter tract at the centroid (the geometric center) of each lacune (details are given in the online-only Data Supplement).
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 \( \chi^2 \) 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 (elongation), PC2 is best represented by planar anisotropy (Figure 3C; adjusted \( R^2=32.93%; P=3.06\times10^{-9} \)), and PC3 is well represented by linear anisotropy (Figure 3B; adjusted \( R^2=86.11%; P=3.06\times10^{-9} \)). Other correlations were less
strong (Figure II in the online-only Data Supplement). 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 ($\chi^2=36.68; df=8; P=1.32\times10^{-5}$). Similarly, small angles between perforating arteries and the main lacune plane were more common than large angles ($\chi^2=53.06; df=8; P=1.05\times10^{-8}$).
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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.

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. 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. It was...
Our study also has limitations. The orientation of perforating arteries was derived from a single–subject atlas. 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, 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.

Acknowledgments

We thank Denis Rivière for assistance with the implementation of processing steps done in BrainVISA.

Sources of Funding

This work was supported by an FP6 European Research Area Network NEURON grant (01 EW1207) and the Vascular Dementia Research Foundation.

Disclosures

None.

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Stroke. 2016;47:1258-1264; originally published online April 5, 2016;
doi: 10.1161/STROKEAHA.116.012779
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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http://stroke.ahajournals.org/content/47/5/1258

Data Supplement (unedited) at:
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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 3DT1 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_{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

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

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_{abs} into account. The more I_{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

<table>
<thead>
<tr>
<th>Scanner</th>
<th>TR [ms]</th>
<th>TE [ms]</th>
<th>TI [ms]</th>
<th>Slice [mm]</th>
<th>In-plane [mm]</th>
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<tr>
<td>Munich Vision</td>
<td>11.4</td>
<td>4.4</td>
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<td>Munich Signa</td>
<td>22</td>
<td>6</td>
<td>-</td>
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<tr>
<td>Paris Signa</td>
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<td>1.9</td>
<td>-</td>
<td>0.8</td>
<td>1.02x1.02</td>
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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>
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</thead>
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<tr>
<td><strong>Basic features</strong></td>
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<td></td>
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<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>
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<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>
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<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>
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<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>
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<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>
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<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>
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<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 its 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.
脳血管病（SVD）の重要な病態である。ラクナは脳MRIで脳脊髄液（CSF）と等信号の空洞として表現され、一般的には最大径15 mmの円形または卵形病変と表現される。しかし大きさ、形、解剖的分布の点で正確な特徴はまだ定まっていない。先行研究は、ラクナまたはラクナ梗塞を回転楕円形、卵形、板状、棒状、あるいはさらに複雑な形状と分類することにより、特定の形状分類を提示した。しかししながらすべての3次元（3D）画像面にこれが当てはまるか否かに関しては、情報がほとんどない。

本研究では、in vivo MRIにより偶発的に発見されたラクナ（偶発ラクナ）を統合的に調査した。形状や、スペクトル形状記述子（ラプラスベクトルトマトラディスペクトル）によるバイアスのない方法で解析した。解剖学的位置、穿通枝の方向、神経路の方向がラクナ形状に及ぼす影響も評価した。

ラクナの研究で大きな課題となるのは、SVDではなく、心原性塞栓、動脈原性塞栓、無脈脈の局所アテロームなどにより拡張した血管周囲腔やCSFが充満した空洞とは対照的である。こうした側面を考慮し、遺伝的要因によるSVDの発症者の偶発ラクナに焦点を当てた。

研究対象
対象は、皮質下梗塞および白質脳症を伴う常染色体優性遺伝性脳動脈瘤（CADASIL）患者365例を登録して現在進行中の前向き2施設共同研究（Klinikum
ラクナ形状の特徴と決定因子

ラクナ形状の特徴と決定因子

解剖学的定位

ラクナの解剖学的定位は、2名の経験豊富な評価者（B.G., M. Duering）が大脳基底核、頭蓋骨、その他の計4つのカテーテリーに基づいて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、ラクナは別カテーテリーに分類した。評価者の一致率は良好である（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

自然空間で計算したラクナの体積、表面積、最大径、軸径、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算した。各ラクナの最大径は、各々の表面メッシュで考えられる頂点ベアの最大距離として計算した。軸径（軸断面の最大径）は軸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プラシス-ペルトランスペクトルを計算した10。この方法は、ラプラシス固有値問題（ペルトランス方程式）を解くことで得た固有値の族としてラプラシス-ペルトランススペクトルを定義する。ラプラシス-ペルトランススペクトルの固有値は順序列に構成する。順位位置が下位の固有値は大規模（低頻度）な形状変化を表し、順位位置が上位の固有値は小規模（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）な形状変化を考慮に入れ、解析は最初の10個の固有値までとした11。同様の適応により、固有値をスペクトルの順位位置で割った12。

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、各ラクナの表面積を乗じることにより固有値を正規化した13.

ラプラシス-ペルトランススペクトルの変元を減らすため、主成分（PC）解析を用いた。主成分（PC）分析を用いた。第1次元を第1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ブタイプ（クラス）を探った。

ラクナ形状の特徴と決定因子
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24が拡散テンソルの形状分析に提案した評価指標を用いた。橋円体はテンソルで数学的に説明することができ、Westin ら 24 が提案した指標は、該当する橋円体が一般的なケースの線(線形異方性)、面(面内異方性)、球(真球度)のどれの程度近いかを示す。これらの指標は偶発ラクナの主軸から計算する(オンラインデータ補載)。Westin ら 24 の提案した指標では、さらに複雑なラクナ形状の特徴(カープや円錐形など)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概念方法を使用した。特に、Westin ら 24 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的方向

動脈分布アトラス25とと 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、各ラクナの中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26。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、各ラクナの中心(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でクラティックユーザーエンタフェースを開発した(詳細はオンラインデータ補載に記載)。その結果決定された方向ベクトルを自然空間にて逆変換した。評価者間の一致度は、穿通動脈(縦横相関数 0.741)および白質神経路(縦横相関数 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

ラクナ形状と穿通動脈/神経路方向の関係を評価するため、2 種類の角度を計算した。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 つはラクナの主平面(最も長い主軸と次に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 x^2 適合度検定を実施した。同様に、神経路の方向ベクトルと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 27。Kruskal-Wallis 検定により、ラクナの基本的特徴および ShapeDNA 法の第 1～第 3 主成分へのラクナ読み込み値を解剖学的位置から比較した。P 値は多重比較(8 検定)のため Bonferonni 法により補正した。有意な結果に対しては、Bonferoni 法で P 値を調整した一対の標本の Wilcoxon 短順位検定により事後検定を続行した。スペクトル形状解析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)。したがって病変の主因は臨床的に無症状であった。図 1 は標準空間のガラススライスに投影した全偶発ラクナ (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載動画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) に最も多くった。ラクナはその他の脳領域に存在したが(脳梁、前頭/前頭極、n=30)、側頭葉は比較的少なかった (n=1)。

すべての解剖学的位置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載表2) 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。

スペクトル形状解析

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、スペクトル形状記述子の変動の 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。解剖学的位置では第 1～第 3 主成分に差はなかった (オンラインデータ補載表2)。図 3A の示すように、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的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>入口検診学的特徴</td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>脳血管障害の危険因子、n（%）</td>
<td></td>
</tr>
<tr>
<td>高血圧</td>
<td>10（17.5）</td>
</tr>
<tr>
<td>高コレステロール血症</td>
<td>27（47.4）</td>
</tr>
<tr>
<td>糖尿病</td>
<td>2（3.5）</td>
</tr>
<tr>
<td>咳嗽、気道障害または気道障害</td>
<td>35（61.4）</td>
</tr>
<tr>
<td>臨床的特徴、n（%）</td>
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<tr>
<td>症候型ラクナ</td>
<td>18（20.5）</td>
</tr>
<tr>
<td>風疹のラクナ症候群</td>
<td>11（12.5）</td>
</tr>
<tr>
<td>純粋運動性発作</td>
<td>1</td>
</tr>
<tr>
<td>純粋発作性発作</td>
<td>3</td>
</tr>
<tr>
<td>運動発作不全症発作</td>
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</tr>
<tr>
<td>構音障害・手不器用症候群</td>
<td>4</td>
</tr>
<tr>
<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、発達性・保続サブスケール、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）、mL | 453.2（705.8） |
| ベースラインのラクナ数、中央値（範囲） | 6（0-29） |
| 退院調査時の偶発ラクナ数、中央値（範囲） | 1（1-5） |
| WMHV、中央値（IQR）、mL | 100.5（87.1） |
| 微小出血数、中央値（IQR） | 0.5（2） |
| 正規化脳腫瘍、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 (合計)、37（注意）、37（発達性）]、MMSE：ミニメンタルステート検査、WMHV：白質損傷体積

* 腦室内腔容積に割ることにより正規化

直感的に表すため、線形異方性（伸長性）、面内異方性（平面性）、真球面からの線形異方性評価指標で各主成分を比較した。第1主成分は線形異方性で十分に表現できた（図3B：調整$R^2 = 86.11, P = 7.58 \times 10^{-3}$）。第2主成分は面内異方性に最もよく表現された（図3C：調整$R^2 = 32.93\%$, $P = 3.06 \times 10^{-3}$）。その他の相関は強くなかった（オンラインデータ補遺図II）。図3Dは第1主成分と第2主成分に沿ってプロットしたラクナの代表図である。この解析から分かるように、伸長性と平面性がラクナ形状の主要な決定因子であった。

穿通動脈および白質神経路との関係

ラクナ形状の決定因子を特定するため、次にラクナの形状と穿通動脈および白質神経路の空間的関係を探った。具体的には、ラクナの主軸（伸長性）、またはラクナの主平面（平面性）を、穿通動脈および白質神経路の方向ベクトルの角度分布を検討した。

穿通動脈のラクナの主軸の間は大角度より小角度が多かった（図4A）。結果はランダム分布と有意に異なっていた（$x^2 = 36.68, df = 8, P = 1.32 \times 10^{-5}$）。同様に、穿通動脈のラクナの主平面の間は、大角度より小角度が多かった（$x^2 = 53.06, df = 8, P = 1.05 \times 10^{-4}$、図4B）。神経路の場合、計算した角度はランダム分布と差がなかった（主軸：$x^2 = 12.38, df = 8, P = 0.135$。主平面：$x^2 = 11.26, df = 8, P = 0.187$）。よって、ラクナは穿通動脈と一致する傾向にある。

3Dおよび2Dのラクナの最大径

ラクナに対するルーチンの臨床評価は、通常2Dの転位スライスで行われ、CSF等の空洞からラクナを区別する基準として転位径15mm未満が最もよく使用される。図5が示すように88例のラクナのうち9個（10.2%）が最大径15mmを超えていた。しかし、転位断面で解析すると、15mmの閾値を超えるラクナは1個（1.1%）だけだった。

考察

遺伝性SVDの特徴的患者群を対象とした本研究は、主に伸長性と平面性の2つの形状指標が決定する線形的な形を偶発ラクナが分布することを示した。ラクナが穿通動脈の方向と一致する傾向にありうることを示された。脳基底核および半卵円中心のラクナは他の脳領域に比べ大きかった。以上の結果は、ラクナの特徴および発生機序に関する現在の概念を補強するものである。

伸長性は解剖学的位置に関知ないラクナ形状の主な形成原理であり、穿通動脈とラクナが一致することを突き止めた。これは、穿通動脈の内部または周辺部の変化とMRIまたはCTの線形構造の変化を報告した急性ラクナ梗塞患者の小規模な症例集積研究と一致する。本研究結果は、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にまで及んだ。また、ラクナ形状の決定因子として、神経路の変性にも取り組んだ。

皮質下梗塞の発症後、白質神経路および通路部の灰質と二次変性が認められることが最近の研究で明らかにされている。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。ラクナ形状と神経路の方向に関連性はなかった。したがって、ラクナの形成はウーラー変性などの二次的影響によってではなく、主に穿通動脈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。

本研究で認めた線形的形状は、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）。

ことを意味する。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。レントゲン線条体動脈の解剖研究で、分岐パターンにかかわる個人差および左右半球間差が認められており、半卵円中心の穿通動脈でも同程度の変動が予想される。それに、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。

本研究は画像診断に影響する。従来のラクナの大きさ基準（＜15 mm）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15 mm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あ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)。
ラクナ形状の特徴と決定因子

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の調査であった。そのため、心塞栓や動脈硬化性塞栓などを原因とする小脳性横梗塞が本研究結果に混在することはなかったと確信している。第2に、ラクナ検出に進歩の方法を採用して初発ラクナに集中し、血管閉塞の拡張を除外した。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記述子を応用したことである。これにより形状に対して先駆的仮定を立てることなく、偏りのない、評価者に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、個人差は考慮されていないため、ノイズの増加と効果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クトグラフィーではなく、白質神経路の解剖構造アトラスを使用したこと、神経路の方向とラクナ形状の関係に対する検出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先端ではないが、拡散テンソルに基づくトラクト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示すことができるか

A. スペクトル形記述子の第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および図2に表示）。B. スペクトル形解析の第1主成分にプロットした線形相関関数C. 第2主成分にプロットした面内相関関数。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向かう。x、y、z軸は3つのラクナ主軸に対応し、z軸が最も大きい。ラクナは形状の特徴が焦点を当てるため、体積により正規化し、x-z面（上）とy-z面（左）の2方向から全測定値に対する3D形状の変化を示した。第1主成分では、両方向とも主成分の面の增大は平面性の増大を示す。
はまだ分からない。形状の特性に関する先行研究はラクナではなく急性梗塞が中心であり、形状の特性の決定因子に着目した研究を我々は知らない。親脳のアテレオと近距離血管からの栄養など、同時に混在する血管性の病因の除去が難しいことは明らかであり、病気が散発する患者で同様の解析を実施することは特に困難である。

謝辞
BrainVISAの処理工程の実施にご協力いただいたDenis Rivière氏に感謝する。

研究費の財源
本研究はFP6 European Research Area Network NEURONの助成金（01 EW1207）およびVascular Dementia Research Foundationの支援を受けた。

情報開示
なし。

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References


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Graph 5

3Dおよび2Dでのラクナの最大径。各機器ラクナについて最大の直径および軸径（軸対面の最大径）を求めた。15 mmの点線は臨床診断で一般的に使用されるラクナの上限サイズ。いくつものラクナ（n = 9）は最大径15 mmを超えているが、軸径15 mmを超えるラクナは1個だけであることに注意。


