Validity of Shape as a Predictive Biomarker of Final Infarct Volume in Acute Ischemic Stroke

Carole Frindel, PhD; Anaïs Rouanet, MSc; Mathilde Giacalone, MSc; Tae-Hee Cho, MD, PhD; Leif Østergaard, MD, PhD; Jens Fiehler, MD, PhD; Salvador Pedraza, MD, PhD; Jean-Claude Baron, MD, PhD; Marlène Wiart, PhD; Yves Berthezène, MD, PhD; Norbert Nighoghossian, MD, PhD; David Rousseau, PhD

Background and Purpose—This study examines whether lesion shape documented on magnetic resonance diffusion-weighted imaging during acute stroke improves the prediction of the final infarct volume compared with lesion volume only.

Methods—Diffusion-weighted imaging data and clinical information were retrospectively reviewed in 110 consecutive patients who underwent (n=67) or not (n=43) thrombolytic therapy for acute ischemic stroke. Three-dimensional shape analysis was performed on admission diffusion-weighted imaging data and 5 shape descriptors were developed. Final infarct volume was measured on T2-fluid-attenuated inversion recovery imaging data performed 30 days after stroke.

Results—Shape analysis of acute ischemic lesion and more specifically the ratio of the bounding box volume to the lesion volume before thrombolytic treatment improved the prediction of the final infarct for patients undergoing thrombolysis ($R^2=0.86$ in model with volume; $R^2=0.98$ in model with volume and shape).

Conclusions—Our findings suggest that lesion shape contains important predictive information and reflects important environmental factors that might determine the progression of ischemia from the core. (Stroke. 2015;46:976-981. DOI: 10.1161/STROKEAHA.114.008046.)

Key Words: MRI ▪ stroke

Stroke is the fourth leading cause of death in industrialized countries. Hemodynamic status and size of the ischemic lesions combined to early reperfusion and collateral flow are the main predictive factors of tissue outcome. In this context, magnetic resonance imaging (MRI) is a technique of choice to assess patients with acute ischemic stroke. Different approaches of MRI-based models of prediction of the final infarct volume have been proposed. From an image analysis point of view, 2 main approaches have been reported to date to assess the evolution of acute ischemic lesions using objective measurements from MRI: volumetric region of interest or pixel-by-pixel analyses.

Recent studies have demonstrated that another type of analysis based on shape of the acute ischemic lesion may also contain important predictive information. Shape reflects the global exchange surface between lesion and well-irrigated tissues. This is a mechanistic point of view not embedded by global volumetric analysis and nor by a local independent pixel-by-pixel approach. To date, the shape of ischemic lesion has essentially been investigated in lacunar stroke and has been assessed in 2-dimensional (2D) or qualitatively from 3D visual observations in acute ischemic stroke. In this article, we propose an original method based on computer vision to perform a 3D quantitative analysis of the acute ischemic lesion shape and combine this analysis with acute lesion volume measures in linear regression models to predict the final infarct volume for patients managed conservatively (group 1; n=43) or with intravenous thrombolysis (group 2; n=67).

Our hypotheses were therefore 3-fold. First, we sought to determine whether linear regression models that combine volumetric and shape information provide more reliable prediction of the final infarct volume than models using volumetric information only. Second, we examined whether the effect of shape information in the models differs between the 2 treatment groups. Third, we hypothesized that the acute lesion shape correlates with early reperfusion: a holey structure of the lesion may indicate the presence of collateral arteries that may facilitate early reperfusion. We tested the 3 hypotheses by retrospectively analyzing MR diffusion-weighted images (DWI) acquired from patients with acute stroke and comparing the performances of the models in predicting the final

Revised November 6, 2014; final revision received January 19, 2015; accepted February 4, 2015.

From Université de Lyon, CREATIS, CNRS UMR5220, INSERM 1044, Université Lyon 1, INSERM Lyon, Villeurbanne, France (C.F., A.R., M.G., T.-H.C., M.W., Y.B., N.N., D.R.); Department of Clinical Medicine, Center of Functionally Integrative Neuroscience, Århus University, Århus, Denmark (L.O.); Departments of Diagnostic and Interventional Neuroradiology, University Hospital Hamburg-Eppendorf, Hamburg, Germany (J.F.); Department of Radiology, Girona Biomedical Research Institute, Hospital Universitari de Girona Doctor Josep Trueta, Girona, Spain (S.P.); and INSERM U894, Université Paris Descartes, Sorbonne Paris Cité, Paris, France (J.-C.B.).

Correspondence to David Rousseau, PhD, CREATIS–INSA de Lyon, 7 Ave Jean Capelle, 69621 Villeurbanne Cedex, France. E-mail david.rousseau@univ-lyon1.fr

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

© 2015 American Heart Association, Inc.

DOI: 10.1161/STROKEAHA.114.008046
Infarct volume as determined by follow-up 30-day T2 fluid-attenuated inversion recovery (FLAIR) MRI.

Material and Methods
All procedures followed were in accordance with the ethical standards of the regional responsible committee on human experimentation and with the Helsinki Declaration as revised in 2008. Informed consent was obtained from all patients for being included in the study.

Patients
We retrospectively studied consecutive patients with acute stroke (n=168) from October 2004 to October 2009 from the I-KNOW multicenter study, whose aim was to include patients with anterior circulation stroke who underwent admission and follow-up MRI. Inclusion criteria were (1) admission National Institutes of Health Stroke Scale score ≥24; (2) DWI and perfusion-weighted imaging consistent with an acute anterior circulation ischemic stroke; (3) admission MRI completed within 6 hours or ≤12 hours if, respectively, intravenous tissue-type plasminogen activator (tPA) or conservative treatment was proposed. Patients with lacunar or posterior circulation stroke, unknown time of onset, or intracerebral hemorrhage observed on MRI were excluded (n=58).

Thus, 110 patients were analyzed. Among them, n=43 (group 1) were managed without any reperfusion therapy (ie, no thrombolysis) and n=67 (group 2) with intravenous tPA.

MRI Protocol
Details of the admission DWI and follow-up T2-FLAIR MRI imaging protocol have been reported previously.20

Ischemic Lesion Segmentation
Four examiners performed the selection and segmentation of all visible lesions in the admission DWI and follow-up T2 FLAIR data using a dedicated in-house tool. For each slice of the MRI data, one or several regions of interest were drawn by the examiner around the lesions to determine what he considered to be the lesion parts. Then, in these regions of interest, the segmentation of the lesion was based on thresholding with a value set manually by the examiner. Finally, we combined the segmentation results from the 4 examiners by a voting procedure: a pixel is classified as part of the lesion if it is selected by ≥2 of the 4 examiners.

Acute and Final Infarct Volumes
The acute (Vf) and final (Vf) lesion infarct volumes were calculated from the segmentation results of admission DWI and 30-day T2-FLAIR, respectively.

Ischemic Lesion Shape Description
The morphology of the acute DWI lesions was highly variable. To apprehend the diversity of lesion shapes among patients, the lesions were observed in 3D (Figure 1) and 5 descriptors were developed to quantify the variety of observed shapes.

Ratio Between Lesion Surface and Lesion Volume: SV
The first descriptor computes the ratio of the area of the surface of the lesion to its volume. This descriptor, $SV \text{ (mm}^{-2}\text{)}$, gauges the roughness of the surface of the lesion: for 2 lesions with identical volumes, the roughest one will have a higher $SV$. $SV$ also takes into account the volume of the lesion, characterizing the exposure to the environment: when computed with the 3 lesions of Figure 2, $SV$ is higher when the components have smaller sizes and it decreases as the volume of the lesion increases much more than does the roughness of the surface.

Ratio Between the Volume of the Bounding Box and the Volume of the Lesion: BE
The second descriptor is based on the bounding box of the lesion (Figure 3). $BE$ is the ratio of the volume of this bounding box to the volume of the lesion. This ratio is >1 because the lesion is included in the bounding box and it quantifies the holey structure of the lesion. In Figure 2, $BE$ decreases as the lesion gets less holey and more compact.

Number of Connected Components: CC
Two binary sublesions are counted as not connected if the 2 sublesions do not share any faces, edges, or corners. Thus, the number of distinct components $CC$ indicates the fragmentation of the lesion. As visible in Figure 2, more compact lesions have a $CC$ closer to 1.

Ratio of the Size of the Largest Component to the Size of the Smallest One: SS
The ratio of the volume of the largest component to the volume of the smallest one, $SS$, evaluates the level of fragmentation of the lesion. $SS$ equals 1 if the lesion is single (see Figure 2C) and increases as the main component of the fragmented lesion gets larger compared with other components (Figure 2B).

Fractal Dimension: FD
This descriptor is built on the definition of the fractal dimension by the box-counting method. This method consists in counting how many size-fixed cubes are necessary to cover the whole volume of an object. This number $N$ is then considered as a function of the characteristic size $x$ of the cubes in a logarithmic graph and is computed for

Figure 1. Three-dimensional representation of different types of initial lesions in the I-KNOW database.
all the possible sizes \( x \). If the slope of the function \( N(x) \) is constant, the fractal object can be characterized by its fractal dimension, defined by \( \lim_{x \to 0} f(x) = \lim_{x \to 0} \log N(x)/\log 1/x \). The dimension is 1 if the object is arranged along a line, 2 if it is arranged in a bounded plane, and 3 if it occupies the whole space. By analogy with the definition, we consider the slope of \( N(x) \) at small scales of \( x \). This descriptor thus tells us about the 3D configuration of the lesion at small levels of detail. In Figure 2A, FD is <2 because the lesion components are organized along a thick line. In Figure 2B, the lesion has a higher FD because it contains 3 components, which are arranged in a plane.

**Early Reperfusion**

Early reperfusion was assessed between admission and 3-hour follow-up perfusion-weighted imaging data. The perfusion lesion was defined by a \( T_{\text{min}} \geq 26 \) s. Reperfusion was a voxel-based, coregistered measurement and required \( \geq 50\% \) reduction of the perfusion lesion volume between the 2 perfusion-weighted imaging scans. For more details on the processing method, please refer to this previous study.20 This measurement, demanding more imaging data, was achieved on 60 patients (n=20 in group 1; n=38 in group 2).

**Statistical Analysis**

Linear regression analyses were performed separately in groups 1 and 2 using the final infarct volume \( V_f \) as the outcome variable and the initial infarct volume \( V_i \) and the 5 shape descriptors: \( SV \), \( BE \), \( CC \), \( SS \), and \( FD \), as input variables.

Variables were transformed to achieve optimal linearity between input and outcome data for multivariate linear regression. \( V_f \) was logarithmically transformed because the distribution of \( \log(V_f) \) was more symmetrical (skewness=0.19) than the distribution of \( V_f \) (skewness=2.07). To account for possible power laws between the logarithm of \( V_f \) and the shape descriptors, we also considered the logarithm of a specific shape descriptor if the logarithmic transformation increased (according to \( R^2 \) and \( P \) value) the univariate linear regression between \( V_f \) and the specific shape descriptor. \( SV \) and \( Vi \) met this test.

Forward and backward stepwise regressions were then performed to carry out automatically the choice of the significant input variables. For the forward selection, we started with no variable in the model, and then tested the addition of each variable using the Bayesian Information Criterion and added variables (if any) that improved the model the most, and repeated the process until none further improved the model. For the backward elimination, we started with all input variables, and then tested the deletion of each variable using Bayesian Information Criterion and deleted the variables (if any) that improved the model the most by being deleted, and repeated this process until no further improvement was possible. If the models, resulting from both stepwise regressions, were nested, they were compared using an \( F \) test. The simplest model was retained if the null hypothesis was accepted (with \( \alpha=5\% \)).

The relationships of shape descriptors to reperfusion were evaluated by splitting the data set into 2 subsamples according to the reperfusion status (0=no reperfusion; 1=reperfusion) and applying Welch \( t \) test. \( P \) values \( \leq 0.05 \) were accepted as indicating a significant difference between the 2 subsamples.

**Results**

There was no significant recruitment bias between the 2 groups of patients. Both patient groups were composed of a majority of men (group 1: 59%; group 2: 65%). Median age in years for groups 1 and 2 was 68 and 71 (group 1: interquartile range [IQR], 58–76; group 2: IQR, 64–78), respectively. Median acute National Institutes of Health Stroke Scale score for groups 1 and 2 was 8 and 11 (IQR, 5–11 for group 1 and 7–15 for group 2), respectively. There was a significant difference between both groups in the time from symptom onset to MRI, with earlier admission MRI (Welch \( t \) test; \( P=5.039e^{-08} \)) in the tPA treatment group (median, 128 minutes; IQR, 94–168) than in group 1 (median, 280 minutes; IQR, 186–400). However, 75% of the patients of group 1 had an admission MRI within 6 hours of stroke onset. No significant difference was found in acute DWI lesion volumes (group 1, 8944 cm\(^3\); group 2, 10860 cm\(^3\)), or in the final lesion volumes measured on follow-up (group 1, 12340 cm\(^3\); group 2, 13970 cm\(^3\)). Finally, no significant differences were found in the 5 shape descriptors between patients of groups 1 and 2.

Shape descriptor \( BE \) was selected in the statistical model and improved the prediction of final infarct volume in tPA-treated patients. Based on the stepwise regressions, the models that performed best are shown in the Table for the 2 patient groups. The initial volume of the lesion \( V_i \) was chosen as a
In other words, an initial lesion with a holey structure better predicts the final volume of the lesion is expected to be in group 2. The smaller the initial lesion, the smaller the final infarct volume. As shown in the Table, one shape descriptor was selected in the modeling process: the ratio between the volume of the bounding box and the volume of the lesion (BE). The sign of the weighting coefficient is negative for BE, indicating that the holeier an ischemic lesion is initially (higher BE), the smaller the final volume of the lesion is expected to be in group 2. In other words, an initial lesion with a holey structure better responds to thrombolytic therapy.

<table>
<thead>
<tr>
<th>Predictive Variables</th>
<th>$V_i=V_i$</th>
<th>Estimate</th>
<th>SE</th>
<th>$V_i=V_i+BE$</th>
<th>Estimate</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_i$</td>
<td>0.99</td>
<td>0.021</td>
<td></td>
<td>0.99</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>$BE$</td>
<td>…</td>
<td>…</td>
<td></td>
<td>−0.002</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.983</td>
<td>…</td>
<td></td>
<td>0.989</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_i$</td>
<td>1.01</td>
<td>0.0131</td>
<td></td>
<td>1.15</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>$BE$</td>
<td>…</td>
<td>…</td>
<td></td>
<td>−0.17</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.8615</td>
<td>…</td>
<td></td>
<td>0.9764</td>
<td>…</td>
<td></td>
</tr>
</tbody>
</table>

The first model $V_i=V_i$ uses only volumetric information, whereas the second model $V_i=V_i+BE$ combines volumetric and shape information. The columns labeled estimate and SE represent the mean and SD, respectively, of the weighting coefficient for the selected predictive variables.

**Discussion**

We have proposed a 3D analysis of the shape of the DWI lesions in acute cerebral ischemia and of its impact on the final infarct volume. A large variety of lesion shapes were observed, as reported in a previous study. Our results demonstrate for the first time that an assessment of the acute DWI lesion shape improves the prediction of the final infarct size in tPA-treated patients. This prognostic benefit was not observed in patients without thrombolysis, indicating that lesion structure may influence the response to treatment. Indeed, we found that acute DWI lesion holeyness was associated with early reperfusion and reduced final infarct size. This is in agreement with the study of Olivot et al., where reperfusion was more frequently observed in patients with multiple lesions.

Several factors may explain this relationship. Lesion with a holey structure may be a marker of an effective collateral circulation. A lesion with a holey structure might be the result of a network of collateral arteries maintaining perfusion to segments of the ischemic tissue. The presence of a collateral circulation increases the likelihood of reperfusion, limits infarct growth, and is independently associated with a favorable clinical outcome. Holey lesions could also be the result of spontaneous clot fragmentation and distal migration, which may be more responsive to thrombolysis. To confirm this hypothesis, it would be interesting to design longitudinal studies including diagnostic cerebral angiography, with assessment of collateral flow using validated scales.

This demonstrates the importance to consider the shape of the acute ischemic lesion for the prediction of the final infarct volume after thrombolysis, where usually the performance of the regression models is reduced for the tPA-treated group compared with the group receiving standard treatment. This lack of performance may be related to an alteration in the natural progression of the ischemic cascade. In this study, we have demonstrated...
that incorporating lesion shape at baseline enhanced the $R^2$ value of the model in tPA-treated patients to a level similar to that of patients managed without thrombolysis. This suggests that lesion shape reflects important environmental factors which will determine the progression of ischemia from the core.

A limitation of this study is the potential impact of the segmentation step on the volumetric and shape analysis of the ischemic lesion. The interexaminer variability imposed by the segmentation step in lesion volume measurements was quantified in an earlier study and found to be $\approx 10\%$. Based on the segmentation results presented in this study, we have quantified the interexaminer variability to be 13.9% in lesion volume which is consistent with the results reported before and 9.5% in lesion shape descriptor $BE$. It should be emphasized that the interexaminer variability represents in the case of our work an upper bound since the segmentation step was followed by a voting strategy to harmonize the choices made by the examiners. Another point for discussion in this study is its retrospective design. Further prospective studies should be undertaken to determine the predictive value of acute lesion shape, specifically for validation of new imaging biomarkers to improve stroke treatment. In this context, it would be interesting to investigate whether the statistical model proposed in this paper can provide new criteria (in similar ways as in $^{26}$) to predict the success of thrombolytic therapy as judged by reduction of final infarct volume.

This pilot study opens various interesting perspectives. Recently, some groups have introduced in silico simulation of cerebral ischemic lesions. It would therefore be possible to test the realism of such numeric simulations in terms of correlations of the 3D shape and volume of the initial lesion with the final volume of the lesion, as described in our study. Also, the shape descriptors chosen in this study have been proposed to quantify the fragmentation and holey structure of the initial DWI lesion. If multiple acquisitions are taken after stroke onset, it would be possible to estimate the local evolution of the lesion with other descriptors quantifying these changes. One could, for instance, transpose to cerebral ischemia the spherical harmonics decomposition which has been used for the detection of local lesion change in multiple sclerosis.

**Sources of Funding**

This work was performed within the framework of the LABEX PRIMES (ANR-11-LABX-0063) of Université de Lyon, within the program “Investissements d’Avenir” (ANR-11-IDEX- 0007) operated by the French National Research Agency (ANR). I-KNOW project was funded by the European Commission’s Sixth Framework Program/FP6.

**Disclosures**

None.

**References**


Validity of Shape as a Predictive Biomarker of Final Infarct Volume in Acute Ischemic Stroke

Carole Frindel, Anaïs Rouanet, Mathilde Giacalone, Tae-Hee Cho, Leif Østergaard, Jens Fiehler, Salvador Pedraza, Jean-Claude Baron, Marlène Wiart, Yves Berthezène, Norbert Nighoghossian and David Rousseau

Stroke. 2015;46:976-981; originally published online March 5, 2015;
doi: 10.1161/STROKEAHA.114.008046
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/4/976

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/