Quantification of Cerebral Volumes on MRI 6 Months After Aneurysmal Subarachnoid Hemorrhage

Jeroen de Bresser, MD, PhD; Koen L. Vincken, PhD; Anne J. Kaspers, MSc; Gabriel J.E. Rinkel, MD; Max A. Viergever, PhD; Geert Jan Biessels, MD, PhD

**Background and Purpose**—MRI can be used to assess structural damage to the brain after aneurysmal subarachnoid hemorrhage. We tuned, validated, and applied k-Nearest Neighbor-based segmentation to quantify cerebral volumes on MRI 6 months after aneurysmal subarachnoid hemorrhage.

**Methods**—After tuning, the accuracy of k-Nearest Neighbor-based segmentation was assessed with manual segmentations. Next, supratentorial cerebral parenchymal, peripheral cerebrospinal fluid, and lateral ventricular volumes of 55 patients who were compared with those of 25 age- and sex-matched control subjects and related to clinical outcome (modified Rankin Scale).

**Results**—k-Nearest Neighbor-based segmentation showed good agreement with manual segmentations. Compared with control subjects, patients had a larger lateral ventricular volume (difference: log-transformed values 0.54; 95% CI, 0.33–0.75), smaller peripheral cerebrospinal fluid volume (−26 mL; 95% CI, −40 to −11), and similar cerebral parenchymal volume (2 mL; 95% CI, −10 to 15). In patients, parenchymal (median split; OR, 38.8; 95% CI, 4.6–329.0) and ventricular volumes (7.4; 95% CI, 1.6–33.5) correlated with functional outcome.

**Conclusions**—k-Nearest Neighbor-based segmentation provides accurate cerebral volume measurements after aneurysmal subarachnoid hemorrhage. In this proof-of-principle study of this volumetric technique, we demonstrated volume changes relative to controls, which correlated with functional outcome. (**Stroke. 2012;43:2782-2784.**)

**Key Words:** brain MRI ■ brain segmentation ■ infarcts ■ image processing ■ subarachnoid hemorrhage

The long-term functional consequences of aneurysmal subarachnoid hemorrhage (aSAH) are probably due to both focal lesions (ie, infarcts) and global change (ie, reductions in brain volume and ventricular enlargement) in the brain. Quantification of the volumes of these abnormalities on MRI may be of value for etiologic and intervention studies. However, due to the heterogeneity of the MRI abnormalities after aSAH, quantification with (semi-)automated methods is challenging and has only been described in a few published studies.1,2

We tuned and validated k-Nearest Neighbor-based segmentation (kNN)3 to quantify brain volumes on MRI after aSAH, compared volumes between patients and control subjects, and related volumes to functional outcome.

**Materials and Methods**

Patients (n=55) were derived from a prospective study that compared MR angiography with intra-arterial digital subtraction angiography to assess aneurysm occlusion with coils 6 months (±2 months) after aSAH4 (for details, see the online-only Data Supplement Methods). The study only included patients with a relatively favorable clinical outcome, reflected in a modified Rankin Scale of ≥3 at the time of the MRI.5 Patients with a history of stroke (aSAH or other) were excluded.

An age- and sex-matched control group consisted of 18 persons who had endovascular treatment for unruptured intracranial aneurysms and 7 persons who were screened for aneurysms (for details, see the online-only Data Supplement Methods). The study was approved by the medical ethics committee of the UMC Utrecht. All participants provided written informed consent.

The World Federation of Neurosurgical Societies SAH grading scale was recorded at admission.6 Treatment with a ventricular drain for hydrocephalus and occurrence of delayed cerebral ischemia (defined as new focal deficits or decreasing level of consciousness with new infarcts on CT) were also recorded. Clinical outcome was assessed with the modified Rankin Scale6 at the time of the MRI scan.

Scans were acquired on a 3-T Philips MR system with a standardized protocol (24 contiguous slices, voxel size: 0.45×0.45×4.00 mm) consisting of an axial T1 (TR/TE=500/10 ms) and T2 (TR/TE=3000/80 ms). kNN was tuned and the accuracy was assessed with manual segmentations on scans of patients after aSAH with heterogeneous cerebral damage (see the online-only Data Supplement Methods). Agreement between kNN and the manual segmentations was expressed as a fuzzy similarity index.7
Supratentorial cerebral parenchymal, peripheral cerebrospinal fluid (pCSF), and lateral ventricular volumes were measured (Figure) and compared between patients and control subjects (and additionally between patients with or without infarcts) by linear regression analyses adjusted for age, sex, and intracranial volume and in additional analyses also for cerebral infarct volume. Within the patient group, the relationship between cerebral volumes (relative to intracranial volume, dichotomized by a median split) and clinical outcome after aSAH (dichotomized at a modified Rankin Scale ≤2 or modified Rankin Scale ≥2) was assessed by logistic regression analyses adjusted for age and sex and in additional analyses also for cerebral infarct volume.

Results
kNN segmentations of intracranial (fuzzy similarity index: 0.98), cerebral parenchymal (fuzzy similarity index: 0.93), and lateral ventricular volumes (fuzzy similarity index: 0.92) showed good agreement with the manually segmented validation data (see online-only Data Supplement Table). kNN segmentations of pCSF volume (fuzzy similarity index: 0.71) showed moderate agreement with the validation data.

The characteristics of the patients and controls are shown in Table 1. At 6 months after aSAH, patients had a larger lateral ventricular volume and smaller pCSF volume than control subjects; cerebral parenchymal volume was not affected (Table 2).

An episode of delayed cerebral ischemia was recorded in 10 patients (19%). Infarcts were observed in 26 patients (10 of 10 with clinically manifest delayed cerebral ischemia, 16 of 45 without delayed cerebral ischemia; see also Table 1).

Median infract volumes were 8.7 mL (10th–90th percentile, 0.4–61.3) among these 26 patients. Infarcts were also observed in 2 control subjects (0.2 and 2.0 mL). Patients with cerebral infarcts had a larger lateral ventricular volume (log-transformed values: 0.32; 95% CI, 0.07–0.57) compared with patients without infarcts. Cerebral parenchymal (−5.6 mL; 95% CI, −19.0 to 7.9) and pCSF volume (−12.0 mL; 95% CI, −28.4 to 4.3) were not significantly different. The differences in pCSF and lateral ventricular volumes between patients and control subjects remained statistically significant after adjustment for infarct volume.

In the patient group, both a higher lateral ventricular volume and lower cerebral parenchymal volume (median split) were associated with worse outcome on the modified Rankin Scale (OR, 7.4; 95% CI, 1.6–33.5) and 38.8 (95% CI, 4.6–329.0), respectively; after additional adjustment for in-
farct volume: 3.8 (95% CI, 0.7–20.5) and 36.8 (95% CI, 3.9–346.1). A higher pCSF volume was not related to outcome (OR, 2.3; 95% CI, 0.6–8.0).

Discussion
At 6 months after aSAH, patients had abnormal brain MRI volumes relative to control subjects, and these volumetric abnormalities appeared to be functionally relevant.

kNN segmentation provided accurate probabilistic measurements of cerebral volume after aSAH. We specifically tuned kNN for segmentation of cerebral volumes in patients after aSAH. The automated segmentation was supplemented by manual segmentations of focal lesions (ie, infarcts, drain trajectories), coil artifacts, and incidental findings.

The focus of our study was to demonstrate feasibility and accuracy of cerebral volume measurements after aSAH as a proof of concept for application of this technique in this patient population. The volumetric results concern a group of patients with a relatively favorable outcome and a control group that mainly consisted of people treated for unruptured aneurysms. This selection might have underestimated the impact of an aSAH on the brain. Future studies can use this technique to unravel the exact contribution of the aSAH, secondary complications, treatment, and vascular risk factor profile on change in cerebral volume.

Despite the fact that all patients in our sample regained functional independence and the modest sample size of our study, the subtle volumetric abnormalities that could be identified with kNN did correlate with functional outcome independent of infarct volume. Although this observation will have to be confirmed in larger studies, it is of importance for future studies that may wish to apply this volumetric technique in etiologic or intervention studies on functional and cognitive deficits after aSAH.

Acknowledgments
The help of C. Jongen with the manual segmentations is gratefully acknowledged.

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Disclosures
None.

References

Table 2. Cerebral Volumes of Patients After aSAH and Control Participants

<table>
<thead>
<tr>
<th></th>
<th>Patients 6 Months After aSAH</th>
<th>Control Participants</th>
<th>Differences Between Patients and Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial volume, mL</td>
<td>1197±125</td>
<td>1232±122</td>
<td>. . .</td>
</tr>
<tr>
<td>Cerebral parenchyma, mL</td>
<td>948±105</td>
<td>973±80</td>
<td>2 (−10 to 15)</td>
</tr>
<tr>
<td>Peripheral CSF, mL</td>
<td>199±40</td>
<td>232±53</td>
<td>−26 (−40 to −11)*</td>
</tr>
<tr>
<td>Lateral ventricles, mL</td>
<td>38 (23–86)</td>
<td>24 (15–43)</td>
<td>0.54 (0.33–0.75)**†</td>
</tr>
</tbody>
</table>

Supratentorial intracranial, cerebral parenchymal, and peripheral CSF volumes of patients and control subjects are means±SD. Lateral ventricular volumes are medians (10th–90th percentile). Differences between patients and control subjects are adjusted for age, sex, and intracranial volume (regression B coefficients [95% CI]).

aSAH indicates aneurysmal subarachnoid hemorrhage; CSF, cerebrospinal fluid.

*P<0.001.
†For differences between patients and control subjects, lateral ventricular volumes were natural-log-transformed.
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Supplemental Material

Quantification of cerebral volumes on MRI 6 months after aneurysmal subarachnoid hemorrhage

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\end{itemize}
Supplemental methods

Participant selection
In the University Medical Center Utrecht a patient cohort that underwent endovascular treatment for a ruptured intracranial aneurysm was followed prospectively. This cohort had MRI scans 6 months after aneurysmal subarachnoid hemorrhage (aSAH) to compare MR angiography with intra-arterial digital subtraction angiography in the assessment of the occlusion of aneurysms treated with coil placement. Participants over 18 years of age who had aSAH and a proven aneurysm treated with endovascular coils were included. The study only included patients with a relatively favorable clinical outcome after 6 months, reflected in a modified Rankin Scale (mRS) of 3 or better. Exclusion criteria were MRI contraindications or claustrophobia (n=12) and treatment of additional aneurysms with neurosurgical clips that contained ferromagnetic material (n=10).

None of the participants had a past medical history of another aSAH or ischemic or hemorrhagic stroke. Participants who proved to have silent infarcts were not excluded. Thus 55 consecutive patients who had an MRI scan 6 months (± 2 months) after aSAH were included in the current study.

A group of 25 persons, matched for the average age and sex-distribution of the patient group served as controls. This group consisted of 18 persons who had endovascular treatment for unruptured intracranial aneurysms (of whom 4 had an aneurysm detected at screening because of positive family history, 7 had symptomatic but unruptured aneurysms and in 7 persons the aneurysm was an incidental finding on a scan for another indication) and 7 persons who were screened for aneurysms, without a history of other neurological disease. The study was approved by the medical ethics committee of the University Medical Center Utrecht, and all participants signed an informed consent form.

Pre-processing
Pre-processing is required to prepare the scans for segmentation by k-Nearest Neighbor based segmentation (kNN); it involved the tuned registration, shading correction and mask creation. The first step was rigid registration of the T1 image to the T2 image with Elastix. Scan inhomogeneities were corrected by a shading correction algorithm. The next step was to create a mask. Cortical infarcts, which are commonly observed after aSAH, proved to hinder mask creation with the widely used Brain Extraction Tool. In test runs, mask creation by k-means clustering was less sensitive to disturbances by cerebral infarcts than the Brain Extraction Tool. With k-means clustering the infarcts were either clustered with other cerebral compartments or formed their own cluster. These clusters could easily be used to create an adequate brain mask. Therefore, brain masks were created by a k-means clustering algorithm with 10 clusters. The clusters that contained brain or cerebrospinal fluid (CSF) were selected automatically and holes were filled by a standardized protocol of morphological operators. A 9-voxel 2D dilation of the mask was performed to include all CSF. Imperfections and incorrectly included structures (e.g. eyes) that were included in a few mask images, were removed manually. Infratentorial structures were also removed from the mask manually.

In the final step of the pre-processing, the uncorrected T1 and T2 images were multiplied voxelwise with the mask image, followed by a shading correction. On the scans of two participants incorrect segmentations occurred, because of large infarcts that affected the shading correction. In these scans the infarcts were segmented manually and excluded from the images before the shading correction.
Training data

Training data are required to train kNN for segmentation of specific brain structures in a certain group of subjects. Training data consisted of scans of 7 patients after aSAH and 3 controls; all from this cohort. The patients were selected to reflect the range of MRI abnormalities typical for the whole study population. Segmentations generated by kNN using previously established 1.5T training data were used as a starting point for manual segmentation of the new training data. Manual segmentations were performed on T2 images by a medical doctor experienced in neuroimaging (JB). The segmentations distinguished between cerebral parenchyma, peripheral CSF (pCSF), lateral ventricles and background (e.g. bone). Partial volume voxels (voxels in which different tissue compartments are present) were not included in the actual training data. Importantly, despite the absence of partial volume voxels in the training data, the feature space of kNN (which uses spatial and voxel intensity information; for details see 8) does allow voxels of new scans that are segmented to be classified with partial volume contents. This is because tissue probabilities in voxels are calculated based on the relations to many (k) neighbors from the training data, which may contain various tissue compartments.

Segmentation by kNN and post-processing

The cerebral volume measurements were performed on the T1 and T2 images by kNN classification with the constructed training data and a ‘k’ of 100. Cerebral parenchymal, pCSF, and lateral ventricular volumes were all classified in this way. Focal lesions, in particular cerebral infarcts (subdivided into small subcortical (<1.5 cm), large subcortical and cortical infarcts), ventricular drain trajectories, coil artefacts, and other, less frequent brain abnormalities (e.g. small meningioma’s) cannot be segmented by kNN and were therefore segmented manually and removed from the kNN segmentations. Moreover, the pCSF near the lateral ventricles could initially end up in the lateral ventricular segment. To improve lateral ventricular and pCSF segmentation, a 3D blob approach was performed on the segmentation of the lateral ventricles, whereby the largest blob was retained. Voxels that should also have been retained (often the posterior or inferior horns) were added to the lateral ventricles manually; the remaining voxels were added to the pCSF. To exclude some incorrectly classified voxels outside the pCSF, cerebral parenchymal volume was calculated within a 6-voxel eroded brain mask image. All segmentations were checked visually and were considered to be accurate (see figure 1 for an example).

Calculation of cerebral volumes

To calculate the volumes of the cerebral tissue compartments, voxel probabilities for all voxels were added separately per compartment and the results were multiplied by the volume of one voxel. The following segmentation compartments were considered: the cerebral parenchymal (without infarct volume), pCSF and lateral ventricular volumes that were segmented by kNN, and the cerebral infarct and ventricular drain trajectory volumes that were segmented manually. The supratentorial intracranial volume was calculated by adding the volumes of all these compartments.

Validation data

Scans of 12 participants (8 patients after aSAH, 4 controls) with representative abnormalities were selected for validation of the kNN segmentation. From these scans, 12 slices from different parts of the brain were selected for manual segmentation of either the left or the right hemisphere, to limit the amount of work. These slices were segmented manually by two observers experienced in neuroimaging, who did not classify the training data. Every tissue compartment was segmented manually in such a way that all voxels that contained the tissue...
were included. This approach resulted in an oversegmentation of all tissue compartments. The validation dataset was constructed for each observer separately by combining all segmented tissue compartments. For each voxel the probability to be part of a certain tissue compartment was calculated by: ‘1/n’, were n is the number of tissue compartments segmented in that voxel. This resulted in fractional validation data, in which voxels with partial volume effects by different tissue compartments had a lower probability for a tissue. The fractional manual segmentations of both observers were averaged to yield one fractional reference.

Validation
Fuzzy overlap measures were used for the validation to compare the probabilistic kNN segmentations with the fractional validation data of each tissue compartment separately \(^9\), based on the similarity index \(^{10}\). The fuzzy similarity index (fSI) was defined as:

\[
    fSI = \frac{2 \times (\text{FractVal} \cap \text{ProbSeg})}{\text{FractVal} + \text{ProbSeg}} = \frac{2 \times \Sigma_i \min(F^i, P^i)}{\Sigma_i (F^i + P^i)}
\]

In this definition ‘FractVal’ denotes the voxel values of the fractional validation data, ‘ProbSeg’ denotes the voxel probabilities of the kNN segmentation, \(F^i\) is the fractional value of the \(i^{th}\) voxel from the manually segmented validation data, \(P^i\) is the probability of the \(i^{th}\) voxel segmented by kNN, and \(\Sigma_i\) is a summation over all voxels. Fuzzy overlap measures were also used to calculate the sensitivity and specificity \(^9\). The sensitivity and specificity were defined as:

\[
    \text{Sensitivity} = \frac{\Sigma_i \min(F^i, P^i)}{\Sigma_i (F^i)}
\]
\[
    \text{Specificity} = \frac{\Sigma_i (1 - \max(F^i, P^i))}{\Sigma_i (1 - F^i)}
\]

The inter-observer agreement for the manual segmentations in the validation data was good with an fSI of 0.98 for intracranial, 0.95 for cerebral parenchymal and 0.95 for lateral ventricular volume, and moderate with an fSI of 0.77 for pCSF volume.
References

**Supplemental table: Validation of the kNN segmentations with the combined manual segmentations of the validation data**

<table>
<thead>
<tr>
<th></th>
<th>fSI</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<td>Intracranial volume</td>
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<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>Cerebral parenchyma</td>
<td>0.93</td>
<td>0.92</td>
<td>0.99</td>
</tr>
<tr>
<td>Peripheral CSF</td>
<td>0.71</td>
<td>0.74</td>
<td>0.99</td>
</tr>
<tr>
<td>Lateral ventricles</td>
<td>0.92</td>
<td>0.92</td>
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</table>

Agreement of the kNN segmentations and the combined manual segmentations of the validation data for all cerebral volumes, expressed by means of the fuzzy similarity index (fSI), sensitivity and specificity.