Computed Tomography–Based Imaging of Voxel-Wise Lesion Water Uptake in Ischemic Brain

Relationship Between Density and Direct Volumetry

Gabriel Broocks, MD,* Fabian Flottmann, MD,* Marielle Ernst, MD,* Tobias Djamshed Faizy, MD,* Jens Minnerup, MD,† Susanne Siemonsen, MD,* Jens Fiehler, MD,* and Andre Kemmling, MD*‡§

Objectives: Net water uptake per volume of brain tissue may be calculated by computed tomography (CT) density, and this imaging biomarker has recently been investigated as a predictor of lesion age in acute stroke. However, the hypothesis that measurements of CT density may be used to quantify net water uptake per volume of infarct lesion has not been validated by direct volumetric measurements so far. The purpose of this study was to (1) develop a theoretical relationship between CT density reduction and net water uptake per volume of ischemic lesions and (2) confirm this relationship by quantitative in vitro and in vivo CT image analysis using direct volumetric measurements.

Materials and Methods: We developed a theoretical rationale for a linear relationship between net water uptake per volume of ischemic lesions and CT attenuation. The derived relationship between water uptake and CT density was tested in vitro in a set of increasingly diluted iodine solutions with successive CT measurements. Furthermore, the consistency of this relationship was evaluated using human in vivo CT images in a retrospective multicentric cohort. In 50 edematous infarct lesions, net water uptake was determined by direct measurement of the volumetric difference between the ischemic and normal hemisphere and was correlated with net water uptake calculated by ischemic density measurements.

Results: With regard to in vitro data, water uptake by density measurement was equivalent to direct volumetric measurement (r = 0.99, P < 0.0001; mean ± SD difference, −0.29% ± 0.39%, not different from 0, P > 0.0001). In the study cohort, the mean ± SD uptake of water within infarct measured by volumetry was 44.7 ± 26.8 mL and the mean percent water uptake per lesion volume was 22.7% ± 7.4%. This was equivalent to percent water uptake obtained from density measurements: 21.4% ± 6.4%. The mean difference between percent water uptake by direct volumetry and percent water uptake by CT density was −1.79% ± 3.40%, which was not significantly different from 0 (P > 0.0001).

Conclusions: Volume of water uptake in infarct lesions can be calculated quantitatively by relative CT density measurements. Voxel-wise imaging of water uptake depicts lesion pathophysiology and could serve as a quantitative imaging biomarker of acute infarct lesions.

Key Words: cerebrovascular disease, stroke, computed tomography, edema, volumetry

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From the *Department of Diagnostic and Interventional Neuroradiology, University Medical Center Hamburg-Eppendorf; †Department of Neurology, University Hospital Münster; ‡Department of Neuroradiology, University Hospital Schleswig-Holstein, Luebeck; and §Department of Radiology, University Hospital Münster, Münster, Germany. E-mail: g.broocks@uke.de.

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MATERIALS AND METHODS

Derivation of Net Water Uptake as a Function of CT Density: In Vitro Measurements and Validation

The CT value of a tissue T correlates unambiguously with the tissue density and atomic number as defined by the linear attenuation coefficient $\mu_T$ that is calibrated to the attenuation of water. Thus, water-equivalent tissue exhibits a CT density value of 0 HU by definition in every CT image. This calibration has a direct implication on how CT density changes with volume and water content.\(^b\) Considering a body of volume unit $V$ with uniform CT density $D$ that is expanded to a volume $V_{\text{new}}$ by adding pure water (with $D_{\text{water}} = 0$ HU) with resulting new density $D_{\text{new}}$, the following relationship remains true regardless of the volume of added water (see Supplemental Digital Content, http://links.lww.com/RLI/A360).

$$V_{\text{initial}} : D_{\text{initial}} = V_{\text{new}} : D_{\text{new}} = (V_{\text{initial}} + \Delta V_{\text{water}}) : D_{\text{new}}$$

(1)

The proportion of added water $w$ within the final volume is $\Delta V_{\text{water}} / V_{\text{new}}$, and can be expressed by the initial and new density:

$$w = \frac{\Delta V_{\text{water}}}{V_{\text{new}}} = 1 - \frac{D_{\text{new}}}{D_{\text{initial}}}$$

(2)

We tested the validity of the principle in Equations 1 and 2 by in vitro CT density measurements in a dilution series of a sucrose solution with known baseline volume and water content and known added volumes of pure water. A baseline solution of 1000 mL was prepared by dissolving 300 g of sucrose in pure water to obtain a %w/v concentration of 30% (equivalent to 70% water content) with added iodinated contrast medium so that the baseline density was measured at approximately 100 HU. We performed our measurements on a 256 dual-slice scanner (Philips Brilliance iCT 256, 120 kV, 4 mm slice reconstruction, 0 mm increment, H30s soft core, 223 mA). The dilution series was performed as follows: A 70 mL volume of the baseline solution with approximately 100 HU and 70% water content was increased by adding successively 10 mL pure water up to a total of 370 mL. After each successive step of adding water, the CT density and total volume of the diluted solution were measured in a standard cylinder and the total amount of added water and resulting water content were documented (Fig. 1).

Quantitative Lesion Water Uptake by CT Density in Acute Stroke: In Vivo Measurements and Validation

Patient Selection

For this study, anonymized data from prospectively collected stroke registries (September 2008 to December 2012) from 4 academic primary stroke centers were pooled as previously described with accordance to the ethical guidelines (Ethik-Kommission der Ärztekammer Hamburg).\(^7\) The study included first-ever thromboembolic major stroke patients due to proximal large vessel occlusion in the anterior circulation with significant size of a core lesion. Patients were screened consecutively based on a priori defined inclusion criteria: (1) acute ischemic middle cerebral artery (MCA) stroke with non-enhanced CT (NECT), CT angiography (CTA), and CT perfusion (CTP) performed on admission; (2) visually evident circumscribable hypoattenuation due to ischemia suitable for volumetric measurement in CT imaging within 24 hours from onset; (3) documented time of onset to imaging; (4) National Institutes of Health Stroke Scale score higher than 3; and (5) absence of intracranial hemorrhage or preexisting thromboembolic or hemodynamic infarctions or preexisting significant carotid stenosis.

The CT images were screened with the intention to reduce patient heterogeneity and limiting lesion measurement error of CT density and infarct volume, excluding very small embolic lesions with no effect on total hemispheric volume, very large embolic lesions with brain shift affecting the contralateral normal side, or lesions that were not clearly visible. Patients with very small (<30 mL) or very large (>400 mL) lesion volumes were therefore excluded. Baseline clinical characteristics and demographic information were extracted from the medical records, including utilization of intravenous lysis or mechanical recanalization.

**FIGURE 1.** In vitro dilution series with increasing volume and corresponding decrease of density. A 70 mL volume of the baseline sucrose solution with approximately 100 HU and 70% water content was increased by adding successively 10 mL pure water up to a total of 370 mL. After each successive step of adding water, the CT density and total volume of the diluted solution were measured.
In brief, within the maximum extent CT-Based Lesion Water Uptake in Ischemic Brain Volume 00, Number 00, Month 2017

Image Acquisitions
All patients received a comprehensive stroke imaging protocol at admission with NECT, CTA, and dynamic time-resolved perfusion CT performed in equal order on 64 or 128 dual-slice scanners (Siemens Definition AS+/; Siemens Definition Flash; Philips iCT 256)—CT: 120 kV, 280 to 320 mA, 5.0 mm slice reconstruction; CTA: 100 to 120 kV, 260 to 300 mA, 1.0 mm slice reconstruction, 5 mm MIP reconstruction with 1 mm increment; CTP: 80 kV, 200 to 250 mA, 5.5 mm slice reconstruction (maximum, 10 mm), slice sampling rate 1.50 seconds (minimum, 1.33 seconds), scan time 45 seconds (maximum, 60 seconds), biphasic injection with 30 mL (maximum, 40 mL) of highly iodinated contrast medium with 350 mg iodine/mL (maximum, 400 mg/mL) injected with at least 4 mL/s (maximum, 6 mL/s) followed by 30 mL sodium chloride chaser bolus. All perfusion datasets were inspected for quality and excluded in case of severe motion artifacts.

Image Analysis
Edematous stroke lesions were quantified by 2 image analysis methods to determine the net water uptake per volume of infarct lesion (Fig. 2). In analogy to the in vitro validation experiment, net water uptake was measured by direct volumetry as the first method (ie, hemispheric volume difference per volume of infarct lesion) to validate consistency of the second method (net water uptake measured by the proposed densitometric relationship in Equation 2). For all measurements, anonymized CT images were processed at an external core laboratory and segmented manually using commercially available software (Analyze 11.0, Biomedical Imaging Resource, Mayo Clinic, Rochester, MN).

First method: for measurement of water uptake by direct volumetry, supratentorial brain hemispheres were segmented with the help of semiautomatic image analysis tools to increase precision. Hemispheres were segmented manually slice by slice with automated edge detection to obtain the supratentorial hemispheric volumes excluding cerebrospinal fluid (CSF), calcified structures, cerebellum, and mesencephalon. The CSF was removed using a histogram threshold of 20 HU with visual adjustment of ±1 HU. We tested this operational method of hemispheric volumetry by measuring 40 normal brain CT images (with 2 repetitive measurements per CT) to estimate the expected mean hemispheric volume difference attributed to normal anatomic variation and intrinsic variability and reproducibility of measurement. Accordingly, in stroke patients, the volume of the infarcted hemisphere ($V_{\text{ischemic hemisphere}}$) and contralateral hemisphere ($V_{\text{normal hemisphere}}$) was measured. For volumetry of infarct ($V_{\text{infarct}}$), we used CTP images to confirm our judgment of native CT when identifying edematous infarct lesions. In brief, within the maximum extent of ischemia (time to drain map), we identified the cerebral blood volume core lesion as probable early infarct and used this visual cue to further identify and specify the ischemic infarct lesion in native CT for volumetric segmentation and region of interest (ROI) placement for density measurement. Subsequently, the volumetric difference of both segmented hemispheres was divided by the infarct volume ($V_{\text{infarct}}$) according to Equation 3 to calculate the volumetric percentage of net water uptake per infarct volume.

$$w = \frac{\Delta V_{\text{water}}}{V_{\text{infarct}}} = \frac{V_{\text{ischemic hemisphere}} - V_{\text{normal hemisphere}}}{V_{\text{infarct}}}$$

Second method: Net water uptake was calculated from densitometric CT measurements. A visually evident circumscribable hypoattenuation was identified as described above for analysis. $D_{\text{infarct}}$ was measured in a ROI defining the ischemic lesion. The corresponding normal density at the time of onset ($D_{\text{normal}}$) was determined in a ROI mirrored symmetrically to the normal nonschismic hemisphere and adjusted anatomically to exclude sulci. The ROI histogram was sampled between 20 and 80 HU to exclude voxels that likely belong to CSF or calcification. On

![CT segmentations for quantitative image analysis](image_url)

FIGURE 2. CT segmentations for quantitative image analysis. The baseline CT was segmented to obtain supratentorial hemispheric brain volumes ($V_{\text{ischemic hemisphere}}$ in red, $V_{\text{normal hemisphere}}$ in green). The infarct lesion was segmented and mirrored to obtain infarct volume ($V_{\text{infarct}}$) and measurements of infarct density ($D_{\text{infarct}}$ in red) and contralateral normal tissue ($D_{\text{normal}}$ in green). Figure 2 can be viewed online in color at www.investigativeradiology.com.
Based on $D_{\text{infarct}}$ and $D_{\text{normal}}$, we calculated the net water uptake per volume of infarct (Equation 4):

\[ w = \frac{\Delta V_{\text{water}}}{V_{\text{infarct}}} = 1 - \frac{D_{\text{infarct}}}{D_{\text{normal}}} \tag{4} \]

**Statistical Analyses**

The results of both methods to quantify water uptake were compared to evaluate the degree of correlation, each in the in vitro and in vivo image assessments. Continuous variables are shown as means ± standard deviations. A statistically significant test was accepted at a $P$ value of less than 0.05. Analyses were performed using MedCalc (version 11.5.1.0; Mariakerke, Belgium). The Pearson correlation coefficient was used because water uptake by density and volumetric measurements was expected to be linearly equivalent on a line of equality. Both methods were tested by 1-sample $t$ test for significant difference from 0. To describe the quality of agreement between the 2 methods across all data points, we conducted Bland-Altman plots and calculated the intraclass correlation coefficients.

**RESULTS**

**In Vitro Analysis**

There was a nonlinear inverse relationship between absolute CT density and the total volume after each dilution step. With each dilution step, absolute CT density decreased asymptotically toward 0 HU, and total water content increased asymptotically toward 100% (Fig. 3A). The volume and CT density of the prepared baseline solution were 70 mL and 102.70 ± 3.07 HU, respectively. The product between the total volume and measured density (Equation 1) was 7189 HU mL, which remained constant for each following solution with increased volume and decreased density after adding water. Error bars indicate 95% CI (1.96 × SD) with error propagation at each dilution step. Figure 3 can be viewed online in color at www.investigativeradiology.com.

**In Vivo Analysis**

In vivo measurements: the net water uptake per total volume of infarct measured by direct volumetry was plotted against the net water uptake calculated by the method of CT density measurements (line of equality in red). Both methods correlated significantly ($r = 0.91$, 95% CI, 0.84-0.94, $P < 0.0001$). Figure 4 can be viewed online in color at www.investigativeradiology.com.
and remained constant for each following dilution step with increased volume and decreased density after adding water (Fig. 3B). The proportion of net water uptake to the final volume was calculated afterward from the acquired volumetric measurements (Equation 2) and plotted against the water uptake based on CT density measurements (Fig. 4A). Both methods of water uptake calculation were equivalent ($r = 0.99$, $P < 0.0001$). The mean difference between percent water uptake by direct volumetric measurement and percent water uptake by CT density was $-0.29\% \pm 0.39\%$, which was not significantly different from 0 ($P < 0.0001$). The differences between the 2 methods were plotted against their mean, showing that more than 95% of data points were within $\pm 2$ SD of the mean difference, confirming good agreement without bias from 0 (line of equality shown in red) without bias across all data points. Figure 5 can be viewed online in color at www.investigativeradiology.com.

In Vivo Analysis

The operational method of hemispheric volumetry was tested in 40 normal brain CT images. The mean volumetric percentage difference between healthy left and right supratentorial hemispheres (ie, absolute volume difference per mean of both normal hemispheres) was 1.9% and not significantly different from 0%. In 95% of all normal test measurements, the left and right hemispheric difference attributed to normal anatomic variation and intrinsic variability of the method of measurement was less than 5%. With regard to reproducibility, the mean absolute difference between repeat hemispheric measurements was $5.3 \pm 3.4$ mL ($1.2\% \pm 0.7\%$ volume difference). The data of 50 screened patients were analyzed. The patient characteristics are listed in Table 1. In this cohort, the mean hypodense lesion size was $189.7 \pm 97.0$ mL, with a mean density of $27.2 \pm 3.5$ HU. The CT density of the contralateral normal tissue was $34.7 \pm 3.6$ HU. In-}

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**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>n = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>65.7 (15.3)</td>
</tr>
<tr>
<td>Sex male, %</td>
<td>57.9</td>
</tr>
<tr>
<td>Baseline NIHSS, mean (SD)</td>
<td>14.1 (5.3)</td>
</tr>
<tr>
<td>Time onset to imaging, mean, h</td>
<td>12.6</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Smoker</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Stroke etiology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>26 (52)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>17 (34)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale.
The aim of this study was to prove a quantitative relationship between infarct edema and CT density expressed as volume of water uptake per volume of infarct. This CT-based imaging biomarker has recently been investigated as a predictor of lesion age and time of onset in acute stroke. Minnerup et al. showed that in theory, the proportion of water uptake per volume of ischemic infarct is related to ischemic and preischemic density measurements based on changing attenuation coefficients and proofed this relationship in an in vitro volumetric experiment. However, the method of using CT density to quantify net water uptake in brain infarct has not been validated by direct volumetric measurements so far, and this study was designed to validate this method on multiple levels (theoretical derivation of a volume-density relationship, validation by in vitro measurements, and validation by measurements in brain CT of patients with acute stroke).

For any mixed body consisting of pure water and dry matter (as brain tissue), the mean CT value is a linear function of each contributing part. Because the CT attenuation value is calibrated to water (0 HU), we derived a volume-density relationship based on the principle that the product between a volume of a body and its mean density remains constant regardless of added water. We furthermore performed an in vitro experiment in analogy to Minnerup et al. to prove Equation 1 (the product of volume and density remains constant regardless of added water) and to verify our hypothesis, that volumetric water uptake can be quantified by density measurements. Finally, we validated the consistency of the 2 methods in vivo by showing that net water uptake in infarct lesions calculated by CT density is equivalent to direct volumetric measurement.

The presented method of quantifying water uptake in acute stroke is methodologically straightforward in a clinical context using a representative ROI sampling the center of an early infarct region (and mirrored contralateral normal) without having to define the exact boundaries of the core lesion, which are often difficult to discern visually. In contrast, a direct volumetric approach to calculate water uptake within infarct (performed in this study as validation method with time consuming segmentation of lesions and hemispheres) is not feasible in a clinical context. Considering that CT hypodensity in acute stroke imaging is often difficult to circumscribe in an early stage, using a CTP mask might help to define the region of interest in those cases in a hyperacute setting.

A neuroimaging biomarker that characterizes the dynamics of brain edema over time has important clinical applications. Imaging of brain lesion water uptake per brain voxel may be used to investigate heterogeneous lesion pathophysiology. As example, Figure 6 shows a quantitative map of voxel-wise water uptake within an infarct lesion. The need for advanced imaging biomarkers in acute ischemic stroke trials has previously been reported. Quantification of net water uptake over time may serve as a surrogate marker of infarct severity in acute stroke trials and contribute to measure drug activity in neuroprotective trials. Furthermore, net water uptake could contribute to the improvement of triaging wake-up stroke patients and guide the decision to use thrombolysis in patients with unknown time of stroke onset.

In addition, water uptake as quantitative imaging marker may have important implications for predicting malignant edema. Up to 10% of all stroke patients and up to 30% of proximal MCA occlusive stroke patients develop a malignant media infarction with affection of...
Within minutes of acute artery occlusion, cytotoxic and, ischemic brain edema develops, which is a marker for lesion pathophysiology. Potential applications may include identifying biomarker of lesion pathophysiology. Potential applications may offer a better comparability and reproducibility with regard to water uptake.\(^1\)\(^1\)\(^5\)\(^6\) Within minutes of acute artery occlusion, cytotoxic and, subsequently, ionic edema eventually leads to the breakdown of endothelial junctions with blood-brain barrier disruption.\(^7\)\(^12\)\(^13\)\(^14\) The result is space-occupying vasogenic edema with net uptake of water into the tissue. A direct CT imaging approach that stratifies early infarct not only by size but also by edema dynamics (net water uptake per time) has not been investigated so far and might bring forth new insights with regard to the development of malignant edema.

Our work has direct technical implications for already available algorithms that quantify acute infarct lesions.\(^1\)\(^9\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\) The potential benefit of an automatic method to localize ischemic infarct lesions may be improved by calculating volume of water uptake as a biomarker for symptom onset or stratification of malignant infarctions.\(^8\)\(^9\) Furthermore, net water uptake as a possible predictor for outcome could be implemented in existing multivariable models of infarct prediction.\(^9\)

The limitations of our study include the relatively small number of patients, owing to strict inclusion/exclusion criteria. The accuracy of attenuation measurements is affected by limited dimensional resolution and possible volume averaging, depending on the definition of ROI. Moreover, manual volumetric lesion segmentation in CT is prone to error and the excluded minority of very small or very large lesion volumes could introduce a method bias.

In conclusion, the volume of net water uptake in ischemic brain lesions can be quantified by relative CT density measurement. Voxel-wise imaging of brain lesion water uptake may be used as an imaging biomarker of lesion pathophysiology. Potential applications may arise from characterizing dynamics of water uptake over time to identify patients at risk for developing malignant infarction.

REFERENCES

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