The Performance of MRI-Based Cerebral Blood Flow Measurements in Acute and Subacute Stroke Compared With 15O-Water Positron Emission Tomography
Identification of Penumbral Flow

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Background and Purpose—Perfusion-weighted MRI-based maps of cerebral blood flow (CBF_{MRI}) are considered a good MRI measure of penumbral flow in acute ischemic stroke but are seldom used in clinical routine due to methodical issues. We validated CBF_{MRI} on quantitative CBF measurement by 15O-water positron emission tomography (CBF_{PET}).

Material and Methods—Comparative CBF_{MRI} and CBF_{PET} were performed in patients with acute and subacute stroke. In a voxel-based seed-growing technique, predefined CBF_{MRI} thresholds (<40, <30, <20, <10 mL/100 g/min) were applied and the resulting volumes were compared with the hypoperfusion volume detected by the penumbral threshold (<20 mL/100 g/min) on CBF_{PET}. The volumetric comparison was expressed as the C-ratio (volume CBF_{MRI}/volume CBF_{PET}) to identify the best MRI threshold. The influence of vessel pathology, hypoperfusion size, and time point of imaging was described. The proportion of voxels correctly classified as hypoperfused and the proportion of voxel correctly classified as nonhypoperfused of the best CBF_{MRI} threshold was calculated and a Bland-Altman plot illustrated the method-specific differences.

Results—In 24 patients (median time MRI to PET: 68 minutes; 16 patients imaged within 24 hours after stroke), the median volume of hypoperfusion <20 mL/100 g/min (CBF_{PET}) was 78.5 cm³. Median hypoperfusion volume on CBF_{MRI} ranged from 245.9 cm³ (<40 mL/100 g/min) to 35.5 cm³ (<10 mL/10 g/min). On visual inspection, an excellent qualitative congruence was found. The quantitative congruence was best for the MRI-CBF threshold <20 mL/100 g/min (median C-ratio: 1.0), reaching a proportion of voxels correctly classified as hypoperfused of 76% and a proportion of voxel correctly classified as nonhypoperfused of 96%, but a wide interindividual range (C-ratio 0.3 to 3.5) was found. Ipsilateral vessel pathology, time point of imaging, and size of hypoperfusion did not significantly influence the C-ratio. The Bland-Altman analysis for the volumetric difference of CBF_{MRI} and CBF_{PET} found a good overall agreement but a large SD.

Conclusion—Hypoperfusion areas below the CBF_{PET} penumbral threshold can be well identified by the CBF_{MRI} threshold <20 mL/10 g/min at a group level, but a large individual variance (exceeding 20% of volume in nearly half of the patients) could not be explained. Our results support a prudent use of MRI-based quantitative CBF measurement in clinical routine. (Stroke. 2009;40:2413-2421.)

Key Words: acute stroke ■ cerebral blood flow ■ cerebral ischemia ■ perfusion weighted magnet resonance imaging ■ positron emission tomography

The concept of mismatch using diffusion-weighted (DW) and perfusion-weighted (PW) MRI has importantly influenced acute stroke management1 and the imaging-based patient selection for aggressive treatment has become the focus of today’s stroke research.2–4 The hypoperfused but still viable tissue is the target for early reperfusion in acute stroke. The so-called “penumbra” is characterized by specific metabolic patterns and can be detected by positron emission tomography (PET).5 Recent MRI data have simplified this concept by the introduction of the “mismatch” in which the volumetric difference between hypoperfusion (PWI) and tissue damage (DWI) defines the tissue at risk. This concept largely relies on the performance of perfusion imaging because hypoperfusion values between 20 and 12 mL/100 g/min identify the tissue at risk. In stroke MRI, the PWI abnormality is supposed to represent the penumbral flow threshold of 20 mL/100 g/min, whereas the DWI lesion is supposed to represent the threshold of 12 mL/100 g/min.5,6 The use of PWI in clinical practice, however, is restrained by yet unsolved methodical issues. Most studies used time-
to-peak (TTP) or mean transit time maps for mismatch calculation because these parameters are robust and easy to obtain.7–13 The MRI-based measurement of cerebral blood flow (CBF_{MRI}), although considered a close estimate of cerebral perfusion,14 was applied in only few clinical studies.5,15–21 CBF_{MRI} was mainly described with respect to infarct development on follow-up MRI that suffered from the uncertainty of perfusion changes between early MRI and follow-up imaging. There is no conclusive data how precise the hypoperfusion volume can be estimated by MRI-based CBF in acute human stroke. This question can only be answered by a direct comparison of CBF_{MRI} with a reference method for quantitative perfusion imaging.

In a comparative study of patients with acute and subacute stroke, we therefore validated CBF_{MRI} on quantitative CBF assessed by PET (CBF_{PET}). We tested whether CBF_{MRI} is able to detect hypoperfusion below the penumbral threshold (<20 mL/100 g/min) and aimed to identify the adequate CBF_{MRI} threshold for mismatch definition.

## Materials and Methods

### Patients

In a prospective imaging study, patients presenting with acute and subacute ischemic hemispheric stroke in our university hospital between March 2003 and 2006 were included if MRI and subsequent quantitative PET imaging was feasible (n=43 patients). Small vessel strokes and pure subcortical strokes were excluded (n=5 patients). For clinical purposes, PET always followed MRI; the time delay was kept as short as possible. We only included patients with stable clinical presentation. The imaging procedure was supervised by an experienced stroke neurologist under continuous monitoring according to stroke unit standards. The study was approved by the local ethics committee. Patients undergoing thrombolysis or any patients with a change of their National Institute of Health Stroke Scale score >2 points during the imaging procedure (measured at inclusion into the study, before MR and before PET) did not receive PET after MRI and were not included in the study. Fourteen patients had to be excluded for insufficient data quality in either PET or MRI. Six patients have been part of previous publications of our group.5,12

### Magnetic Resonance Imaging

MRI was performed on a 1.5-T whole-body scanner (Philips Intera Master). PW images were acquired in an axial direction (20 slices, 6-mm slice thickness, 0.6-mm interslice gap, field of view 23 cm) using multishot 3-dimensional T2*-weighted gradient echo echoplanar imaging sequences (PRESTO; TR 17 ms, effective TE 25 ms, flip angle 9°, echoplanar imaging factor 17, matrix 64×51, resulting voxel size 3.6×3.6×6 mm). The perfusion study consisted of 60 measurements at intervals of 1.3 seconds after a standardized intravenous injection of 20 mL gadolinium-DTPA (Magnevist; Schering AG) with a flow rate of 10 mL/s.

### Positron Emission Tomography

PET was performed in a resting state on an ECAT EXACT HR Scanner (Siemens/CTI). CBF was acquired in a 2-dimensional data acquisition mode providing 47 contiguous 3-mm slices of 5-mm full-width half-maximum in plane-reconstructed resolution.22 After intravenous bolus injection of 150-water (60 mCi=2.2 GBq), the tracer distribution was measured for 90 seconds. Continuous arterial blood sampling (radial artery) was used to calculate absolute CBF values (for details, see references 21–25).

### Data Postprocessing

Image analysis was performed by investigators blinded to clinical data and to the other imaging modality (PET: O.Z.W., MRI: J.S., W.M.H.). MRI and PET images were analyzed by an IDL-based multimodal imaging tool (VINCI).26 Due to the different spatial resolution in the z-axis, PET images were resliced to the MRI images and then realigned by an automated observer-independent algorithm.27 Because head positioning was different in MRI and PET, realignment of the volumetric data by 3-dimensional rotation allowed a volumetric fusion of the data sets.

The postprocessing of the PW images was performed by a specific software, STROKETOOL, Version 2.3.28,29 PW raw images were processed on a pixel-by-pixel basis to generate maps of CBF using the model-independent standard singular value decomposition method (nonparametric standard singular value decomposition deconvolution) described by Ostergaard.30,31 In brief, the concentration time course of each voxel is deconvolved with the arterial input function (AIF) using a standard singular value decomposition algorithm. The central equation of the calculation of the quantitative CBF is:

\[
C_{\text{VOI}}(t) = F \cdot \int_{0}^{t} C_{A}(\tau) R(t-\tau) d\tau
\]

C_{VOI}(t) is the contrast agent concentration within a given volume of interest that can be expressed as a function of time (t) where \(C_{A}(t)\) is the contrast agent concentration of the arterial input. F is tissue blood flow and R(t) is the vascular residue function.30,31

The AIF needed for the calculation based on the singular value decomposition algorithm to determine CBF was defined under visual control by 5 to 10 intravascular voxels within the proximal segment of the middle cerebral artery (MCA) and the distal segment of the internal carotid artery (ICA) of the unaffected hemisphere.32 The resulting input function was visually inspected for peak sharpness, amplitude width, and bolus peak time to select only nondistorted bolus curves.33

### Volumetric Analysis

For every patient, a 3-dimensional brain atlas was used to exclude the ventricles, most of the periventricular white matter, large vessels, and the sinuses. The atlas was created using the individual T1 images. Ventricles and periventricular white matter were excluded by manual segmentation on each slice (Figure 1A). Within this individual atlas, the volumetric analysis of the MRI and PET images was performed. The definition of the CBF_{MRI} and CBF_{PET} hypoperfusion volumes was performed by a semiautomatic voxel-based algorithm using a threshold function. Only voxels that fulfilled the predefined thresholds were included in the volumetric analysis. On PET–CBF images, the volume of CBF <20 mL/100 g/min was delineated as the reference volume. On MRI-CBF images, 4 volumes were assessed: CBF_{MRI} <40, <30, <20, and <10 mL/100 g/min.

Figure 1. Volumetric comparison of CBF_{PET} and CBF_{MRI} volumes. Within an individual brain atlas of the affected hemisphere (A), the volume of CBF <20 mL/100 g/min on PET (red) and the volumes of predefined CBF thresholds on MRI (blue) were generated (B). Then, PET and MRI volumes were compared (C). The degree of congruence was expressed as the ratio C (C_{x}/volume CBF_{PET} <20; x refers to the thresholds <40, <30, <20, <10 mL/100 g/min).

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g/min. Thus, every patient received one PET volume and 4 stepwise decreasing MRI volumes (Figure 1B).

The volumetric analysis was performed in 4 steps: Part A, the volumes of the different MRI–CBF thresholds were plotted against the target volume (PET); Part B, to express the degree of volumetric congruence, the C-ratio was calculated (Figure 1C): C = (volume CBF \(_{\text{MRI}}\) <x)/(volume CBF \(_{\text{PET}}\) <20), where x refers to the chosen CBF \(_{\text{MRI}}\) threshold (for example, C\(_{20}\) represents the ratio of the volume of CBF <20 mL/100 g/min on MR–CBF imaging divided by the target volume of CBF <20 mL/100 g/min on PET imaging). If MRI underestimated PET, then the C-ratio was below 1, and if MRI overestimated PET, then the C-ratio was above 1. Every patient received 4 C-ratios corresponding to the 4 threshold-defined CBF\(_{\text{MRI}}\) volumes. For every threshold (C40, C30, C20, and C10), the median C-ratio across all patients has been calculated to identify the best median estimate of hypoperfusion volume. For every threshold (C40, C30, C20, and C10), the median C-ratio across all patients has been calculated to identify the best median estimate of hypoperfusion volume. For every threshold (C40, C30, C20, and C10), the median C-ratio across all patients has been calculated to identify the best median estimate of hypoperfusion volume.

The C-ratios were compared in patients with and without a hemodynamically relevant ipsilateral ICA stenosis (\(< 90\%\) according to duplex criteria). For the influence of imaging time, patients were dichotomized for the time between stroke and imaging. For the influence of the hypoperfusion volume, the C-ratios were correlated for the time between stroke and imaging. For the influence of imaging time, patients were dichotomized for the time between stroke and imaging. For the influence of the hypoperfusion volume, the C-ratios were correlated for the time between stroke and imaging.

### Results

Of the 24 patients (median age, 56.5 years), 16 patients were imaged within 24 hours after stroke (median, 9.3 hours), and 8 were measured later than 24 hours (median, 6 days). The median time delay between MRI and PET was 68 minutes. The median volume of hypoperfusion below the penumbral threshold on CBF\(_{\text{PET}}\) (< 20 mL/100 g/min) was 78.5 cm\(^3\). The median volume of hypoperfusion on CBF\(_{\text{MRI}}\) ranged from 245.9 cm\(^3\) (for the threshold < 40 mL/100 g/min) to 35.5 cm\(^3\) (for the threshold < 10 mL/100 g/min). Twelve patients showed ipsilateral and 3 of them bilateral vessel pathology. One patient exclusively presented contralateral vessel pathology. Detailed patient data are shown in the Table.

On visual inspection, an excellent spatial correspondence of the hypoperfused areas on MRI and CBF was found (Figure 2). The median of the C-ratios for each threshold is shown in Figure 3. Across all patients, the median degree of congruence (C-ratio) ranged from 2.6 (C40) to 0.3 (C10). This represents an average threshold-dependent overestimation on the one hand (260% for C40) and underestimation (30% for C10) on the other hand. The best volumetric fit was found for CBF\(_{\text{MRI}}\) < 20 (median C-ratio: 1.0; Figure 3). Taken this best fit, however, a wide range of C-ratios was found (0.3 to 3.5; Table). Patients were divided according to the presence or absence of ipsilateral vessel pathology. The volume of hypoperfusion below the penumbral threshold on CBF\(_{\text{PET}}\) tended to be lower if ICA pathology was present.

### Statistics

Because most of the study values were not normally distributed, the results were presented as median and interquartile range if not indicated otherwise. For correlation analysis, Spearman rank correlation was used. Group differences were calculated by the Mann-Whitney rank sum test. A regression analysis was performed to measure the strength of the relation and a Bland-Altman analysis was performed to provide an analysis of agreement between the 2 imaging modalities. All data analysis was performed by Sigmapstat 3.1.1 (SYSTAT Software, Inc, 2004).
(55.9 versus 147.6 cm$^3$; $P=0.194$), but this difference was not significant. The C20 ratio did not differ between these groups (1.0 versus 1.1; $P=0.544$). To rule out effects of the time point of imaging, patients were dichotomized according to the stroke onset time (cutoff: 20 hours). There was no significant difference of the C20 values in early versus late imaging (0.99 versus 1.08; $P=0.624$). Accordingly, the C20 ratios did not correlate to the time delay between stroke and imaging on the one hand ($r=0.01$; $P=0.93$) nor to the time delay between MRI and PET on the other hand ($r=0.04$; $P=0.8$). The C20 ratios were not correlated to the CBF$\text{PET}$ hypoperfusion volume ($r=0.1$; $P=0.62$).

The volumetric comparison of the different MRI thresholds with the target volume (CBF$\text{MRI}=20$ mL/100 g/min) is shown in Figure 4. The best fit was found for CBF$\text{MRI}=20$ mL/100 g/min ($r^2=0.71$; slope=1.0; intercept=13.6). For this threshold, a proportion of voxels correctly classified as hypoperfused of 76% and a proportion of voxels correctly classified as nonhypoperfused of 96% was calculated.

The Bland-Altman plot$^{34,35}$ compared the hypoperfusion volumes that were obtained by the threshold of CBF$\text{MRI}=20$ mL/100 g/min and by CBF$\text{PET}=20$ mL/100 g/min. The mean difference between PET and MRI volumes was $-13.3$ cm$^3$. The SD was 69.3 cm$^3$. The limits of agreement were between $-122.5$ cm$^3$ and $-149.2$ cm$^3$, thus including 95% of the values. This analysis shows a slight overestimation of CBF$\text{MRI}$ volumes as compared with CBF$\text{PET}$ volumes as well as an increase in variability of the differences as the magnitude of the measurements increases (Figure 5).

**Discussion**

We present the first volumetric comparison of MRI-based CBF measurement (CBF$\text{MRI}$) and 15O-water-PET (CBF$\text{PET}$) in a large patient sample of acute and chronic human stroke. We found that CBF$\text{MRI}$ allowed an excellent qualitative assessment of cerebral hypoperfusion. The pooled volumetric analysis identified a CBF$\text{MRI}$ threshold of $<20$ mL/100 g/min as the best indicator of penumbral threshold with a good
proportion of voxels correctly classified as hypoperfused (76%) and a high proportion of voxels correctly classified as nonhypoperfused (96%). However, a considerable under- or overestimation was seen in individual patients. This variance was not explained by the underlying vessel pathology, by the time point of imaging, or by the hypoperfusion volume.

The clinical mismatch definition requires a volumetric difference between the hypoperfusion (PWI) and the early ischemic tissue lesion (DWI). For diffusion imaging, a visual delineation of the lesion yields acceptable results and quantitative thresholds are generally accepted. For example, a relative DWI threshold of 120% on the normal intensity on DW images predicts final infarction with a high specificity and sensitivity.36 In contrast, the definition of hypoperfusion by perfusion imaging is a matter of ongoing discussion. TTP maps without AIF have been frequently studied, because they are easy to obtain, robust, and well comparable among different imaging facilities.8,12,37 Regarding the underlying principles, however, AIF-based maps may be superior and maps of the mean transit time or the CBF should be favored.

Because MRI-based CBF was seldom used in clinical trials and because a clinically relevant volumetric approach is not yet available, our study adds important evidence to the validation of MRI-based CBF measurement.

Concerning the flow thresholds that are relevant for imaging cerebral ischemia, it has to be considered that areas with flow values <20 mL/min/100 g include not only penumbral flow, but also tissue with critical ischemia <12 mL/min leading to infarction.8 We followed the clinical concept of mismatch defined by the difference of DWI and PWI. Here, the area of critical ischemia is represented by the DWI lesion and the mismatch volume is estimated by the volumetric difference of hypoperfusion below 20 mL/100 g/min minus the DWI lesion. This volume, the mismatch, may serve as a surrogate of penumbra keeping in mind several methodical restrictions.

Our study followed a clinically relevant threshold-based approach that differs from previous region of interest (ROI)-based analysis.17,38,39 We tested the performance of 4 predefined CBFMRI thresholds (10, 20, 30, 40 mL/100 g/min) with respect to PET hypoperfusion and expressed the volumetric congruence by a ratio (C-ratio). High thresholds overestimated the hypoperfusion volume up to 260% and low thresholds underestimated the hypoperfusion volume up to 20%.

### Table. Clinical Data, Vessel Pathology, and Volumetric Data of All Patients With Comparative Imaging

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<th>MRI to PET, Minutes</th>
<th>ICA Stenosis IPSI, %</th>
<th>ICA Stenosis CONTR, %</th>
<th>Volume CBFPET &lt;20 mL/100 g/min, cm³</th>
<th>Congruence Ratio (C) for CBFMRI Thresholds C40 C30 C20 C10</th>
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*Stroke to imaging refers to the time delay between stroke onset and MRI scan. MRI to PET refers to the time between the scans. The degree of stenosis of the ICA was classified in percent by ultrasound. PET volume refers to the volume of hypoperfusion CBF <20 mL/100 g/min on 15O-water PET. The congruence ratio (C-ratio) refers to the volumetric ratio CBFMRI/CBFPET as described in the “Methods” section.

NIHSS indicates National Institutes of Health Stroke Scale; IPSI, ipsilateral to the site of ischemia; CONTR, contralateral; L, left; R, right; IQR, interquartile range.
difference was calculated and showed no relevant difference because the data were not normally distributed, the median measurement as previously indicated in animal studies,40,41 in detection of PET hypoperfusion correctly classified as nonhypoperfused of 96% for the best C-ratio and found a proportion of voxels correctly of ischemia42 and chronic carotid occlusive disease.42,44,45 However, the aforementioned clinical studies did not include patients with acute stroke and used ROI-based values instead of a volumetric analysis. More important, they did not present a direct comparison, because PET and MRI were separated by several days. In line with a recent comparative study of a small patient sample using a ROI-based approach,39 our results provide additional evidence that CBF measurement by MRI is valid in acute human ischemia as well.

The C-ratio compared the volumes but did not account for their volumetric congruence. Although the visual inspection suggested that there were no misclassifications of the hypoperfusion site, we performed a volumetric analysis for the best C-ratio and found a proportion of voxels correctly classified as hypoperfused of 76% and a proportion of voxels correctly classified as nonhypoperfused of 96% for the detection of PET hypoperfusion <20 mL/100 g/min. Thus, MRI correctly identified three fourths of the hypoperfused and nearly all of the normoperfused tissue if the CBF threshold was set to <20 mL/100 g/min. These data can be compared with a previous volumetric analysis of TTP maps that found a higher sensitivity (84%) but a lower specificity (77%) for a relative TTP prolongation of ≥4 seconds12 and are in line with previous outcome-based MRI studies of TTP maps.37,50

The C-ratio, however, only reflected the median value of our data. On an individual level, it showed a considerable variation in our sample. The interquartile range for the best C-ratio (median, 1; interquartile range, 0.8 to 1.3) indicates that in half of the patients, the volumetric fit was beyond 0.8 and 1.3. In other words, hypoperfusion was underestimated by 30% to 80% in one fourth of the sample and was overestimated by 130% to 350% in another fourth of the sample.

This finding is in line with the Bland-Altman analysis, which gives the limits of agreement between CBF–PET and CBF–MRI showing a spreading out of the data for larger measurements and the SD indicating a large individual variance of the 2 methods (Figure 5). This is a relevant finding taking into account that a volumetric difference of 20% between DWI and PWI volume is commonly postulated for mismatch definition.4,7,10,11,44 This methodological problem has already been addressed in previous ROI-based studies of a small patient sample39,42 and in healthy volunteers.38 These studies, like in our sample, found good agreement of ROI values on an individual basis. However, because the slopes and the intercepts of the regression lines vary within the patients, the pooled data showed less agreement.

Our analysis of 24 patients provides the clinically applicable volumetric counterpart of a recent comparative ROI-based PET–MRI study in a small sample of 5 patients imaged 16.3 hours (mean) after stroke by PW-MRI and quantitative CBFPET.39 Takasawa et al found a good qualitative correspondence of the distribution of the hypoperfused areas on MRI and PET–CBF maps. They found a moderate correlation between MRI and PET–CBF values within subjects but a weaker correlation when the data of all subjects were pooled because of substantial individual variations. These findings are in line with our present work as well as with other previous studies.38,42,44 The study of Takasawa et al did not use a volumetric approach with stepwise decreasing CBF MRI thresholds. Therefore, a direct comparison is not possible. To reduce the intersubject variability, Takasawa et al normalized the MRI and PET values to the mean of the whole brain to decrease the individual variations. In these conditions, a threshold based on absolute CBF values cannot be used like in our study, and instead, Takasawa et al proposed a threshold based on mean transit time delay, TTP delay, or Tmax to define the penumbra in a clinical setting.

We tested several influencing factors that could explain the variability of our data. First, the time point of imaging was not found to be relevant. This is an interesting finding because time-dependent changes of mean transit time and cerebral blood volume due to different stages of vasodilatation after ischemia can be assumed49 and may influence the performance of CBF maps. Second, the hypoperfusion size was not significantly related to the degree of congruence. The C-ratios as well as the Bland-Altman plot showed that with increasing hypoperfusion size, the volumetric difference increases in both directions (Figure 5). Third, the underlying vessel pathology had no significant effect. According to previous studies of TTP maps in patients with high-grade ICA stenosis, vessel pathology was supposed to influence the reliability of PWI maps.37,50 However, we found the performance of CBF MRI not related to the presence of extracranial vessel pathology because an ipsilateral stenosis or occlusion did not significantly change the C-ratio. This discrepancy to the previous studies can be explained by the fact that CBF maps are less sensitive to collateral flow than TTP maps.50,51 The finding that the few patients with contralateral ICA pathology (n=4) did not differ in their performance of CBF MRI is of considerable interest but should be clarified in larger patient samples. Taken into account our sample size and the resulting subgroups of vessel pathology, these results suggest that the AIF-based CBF measurement seems mainly independent of ipsilateral vessel pathology.

Several methodical issues concerning this comparative imaging study have to be addressed. First, the spatial distortion of PWI images may influence image realignment and the comparison of small volumes. We therefore optimized the coregistration procedure by using an observer-independent and previously validated algorithm.27 We cannot rule out errors due to spatial distortion. This error would mainly influence the volumetric agreement in small volumes. In our
data, however, small volumes showed a comparable or even better agreement than large volumes (Figure 5). Second, the postprocessing itself may influence the results. Our postprocessing tool performed an offline calculation of the PWI maps and was used in previous studies.3,29,30 It is based on the algorithm described by Ostergaard31 and uses the standard singular value decomposition,30,31 which seems to be more sensitive to tracer delay than the circular singular value decomposition,32 although both methods yield comparable results for CBF in the ischemic range according to a recent study.39 The AIF technique is sensitive to postprocessing errors because small variations of pixel placement may lead to relevant changes of calculated CBF values.53 The AIF is known to lead to higher hypoperfusion volumes if derived from the contralateral MCA segment,21 but a standardized respective protocol has not yet been established.54 One study of 7 patients with chronic carotid occlusive disease found that the AIF selection relative to the side of carotid occlusion did not influence MRI–CBF values.44 These findings differ from studies of acute ischemia in which AIF selection does affect quantitative parameters.37,50 A manually chosen AIF is highly observer dependent, whereas automatic algorithms could be helpful but are not fully validated yet.55 We therefore constantly derived the AIF from intravascular voxels33 of the first 2 segments of the MCA or from the distal ICA of the unaffected hemisphere.29,32 We used a fixed dose of 20 mL of Gd-DTPA. It can be assumed that a weight-adapted dose would circumvent the problem of applying either a low dose, leading to a reduced signal drop and reducing the sensitivity to subtle changes of CBF, or a high dose leading to a more pronounced signal drop and increasing the discrimination between gray and white matter but decreasing the quality of the perfusion maps.56

Third, in our study, we did not use PET-based calibration correction for the following reasons. A fixed common calibration value, like for example the CBF in white matter as described by Ostergaard30 (22 mL/100g/min), is not adequate because a wide variation of CBF values in white matter (21 to 45 mL/100g/min) has been described in patient studies.38,44 An individual PET-based calibration factor would be highly desirable but is not available in clinical routine. Because we followed a clinical approach, we performed no individual PET-based correction. MR-based individual correction factors are highly desirable and the respective studies37,42,57 yielded promising results. However, because the optimal correction factor and tissue-specific differences are still a matter of ongoing debate58 and because technically challenging methods are not yet feasible in the acute stroke setting, we did not apply a MR-based correction factor in line with previous studies.58

Fourth, the head-to-head comparison of PET and MRI is, alongside with xenon CT, the best available in vivo validation of PWI, but perfusion changes during the imaging procedure cannot be ruled out with certainty. The median interval of 68 minutes between MRI and PET in our study is the smallest delay available in the literature for a comparable sample size in patients with acute and subacute stroke but cannot completely exclude perfusion changes. We minimized this effect because we only included patients with stable clinical presentation and performed continuous monitoring that identified patients with change of the neurological symptoms during the imaging procedure. Additionally, although PET is considered the current gold standard for CBF measurement, a certain method-intrinsic error and a variability of the PET measurements cannot be excluded and may impair the validation of the MR_{CBF} maps.38,58

Fifth, our volumetric approach was guided by the routine clinical application of mismatch estimation. We therefore did not differentiate between gray and white matter because this is not feasible in the acute phase of stroke. The penumbral threshold for CBF (ie, 20 mL/100 g/min) is valid for gray matter only and the inclusion of white matter may lead to higher hypoperfusion volumes and to FP results. As mentioned before, it is not applicable to patients with subcortical stroke. This is a limitation in a clinical setting. However, we minimized this error by creating a brain mask that excluded the ventricles and most of the periventricular white matter. Additionally, MRI and PET were analyzed on the same individual brain mask so that this error would account equally for both modalities. Another approach would be the use of time-based maps of hemodynamic compromised areas (like mean transit time and TTP or T_{max}) that could be more adapted to clinical routine, because the selective thresholds are valid for both gray and white matter.

In summary, our data yield encouraging results. On the one hand, we described the potential of valid CBF measurement by MRI using a standardized and user-friendly algorithm. On the other hand, our results point at several pitfalls that still await clarification. The AIF procedure alone does not seem to identify the best threshold sufficiently. Individual correction factors have to be found to optimize quantitative CBF assessment.

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Disclosures
None.

References
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The Performance of MRI-Based Cerebral Blood Flow Measurements in Acute and Subacute Stroke Compared With 15O-Water Positron Emission Tomography: Identification of Penumbral Flow
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