The detection of penumbral flow is of high importance in acute stroke diagnosis. It refers to hypoperfused but viable tissue that can be salvaged by early recanalization and reperfusion. It thus represents a treatment-relevant acute imaging target (TRAIT) according to the latest acute stroke imaging guidelines.1 Penumbral flow has been defined by a reduction of cerebral blood flow (CBF) between 12 and 20 mL/100 g per minute (penumbral flow) as identified by 15O-water positron emission tomography (PET). 2,3 In clinical magnetic resonance imaging (MRI) studies, however, the penumbral flow is assessed by dynamic susceptibility–weighted contrast–enhanced MRI (DSC-MRI) in comparison with the infarct core defined by diffusion-weighted imaging, approximating the penumbra as the so called mismatch. 3 The choice of the best suited DSC maps is a matter of ongoing debate and they need to be validated for clinical use.1,4 In this respect, comparative MRI-PET studies have identified better suited DSC parameters.5–9 Important methodological questions, however, are still unanswered and need to be validated by comparison with gold-standard imaging. The most commonly used deconvolution methods are standard and block-circulant singular value decomposition (sSVD and bSVD). bSVD has been introduced to overcome some limitations of the sSVD method, most importantly to reduce its sensitivity to blood delay, which is a critical part of the pathophysiology of acute stroke.10 Thus, the choice of the deconvolution

**Background and Purpose**—Dynamic susceptibility–weighted contrast–enhanced (DSC) magnetic resonance imaging (MRI) is used to identify the tissue-at-risk in acute stroke, but the choice of optimal DSC postprocessing in the clinical setting remains a matter of debate. Using 15O-water positron emission tomography (PET), we validated the performance of 2 common deconvolution methods for DSC-MRI.

**Methods**—In (sub)acute stroke patients with consecutive MRI and PET imaging, DSC maps were calculated applying 2 deconvolution methods, standard and block-circulant single value decomposition. We used 2 standardized analysis methods, a region of interest–based and a voxel-based analysis, where PET cerebral blood flow masks of <20 mL/100 g per minute (penumbral flow) and gray matter masks were overlaid on DSC parameter maps. For both methods, receiver operating characteristic curve analysis was performed to identify the accuracy of each DSC-MR map for the detection of PET penumbral flow.

**Results**—In 18 data sets (median time after stroke onset: 18 hours; median time PET to MRI: 101 minutes), block-circulant single value decomposition showed significantly better performance to detect PET penumbral flow only for mean transit time maps. Time-to-maximum (Tmax) had the highest performance independent of the deconvolution method.

**Conclusions**—Block-circulant single value decomposition seems only significantly beneficial for mean transit time maps in (sub)acute stroke. Tmax is likely the most stable deconvolved parameter for the detection of tissue-at-risk using DSC-MRI. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.010246.)

Key Words: magnetic resonance imaging ● perfusion imaging ● positron-emission tomography ● neuroimaging ● stroke
method might have major impact on the resulting perfusion maps in acute stroke. This question is especially important, as current clinical studies use DSC imaging, for example, ECASS-4:ExTEND, and the type of deconvolution could influence results across studies and study sites because of differing postprocessing routines. In this study, we therefore evaluated the performance of DSC perfusion parameter maps applying sSVD deconvolution in comparison with bSVD deconvolution in a cohort of patients with multimodal MRI and PET perfusion imaging in (sub)acute stroke.

Materials and Methods

Patients

In a retrospective analysis, patients with acute and subacute ischemic hemispheric stroke admitted to the Neurological University Hospital in Cologne between 2003 and 2006 were included. Small vessel strokes and pure subcortical strokes were excluded. Patients with thrombolysis or patients with a change of the National Institute of Health Stroke Scale (NIHSS) score >2 points during the imaging procedure were excluded (NIHSS evaluated at: in the study, before MRI, and before PET imaging). An experienced stroke neurologist supervised the patients during imaging according to stroke unit standards. All patients gave written informed consent. The study was approved by the local ethics committee. Some patients have been described in previous publications of our group.

Imaging

MRI was performed on a 1.5 Tesla (T) whole-body scanner (Philips Intera Master). DSC images acquired in an axial orientation (multishot 3-dimensional [3D] T2*−weighted gradient echoplanar imaging sequences [PRESTO], 20 slices, slice thickness: 6 mm, interslice gap: 0.6 mm, effective echo time [TE]: 25 ms, flip angle: 9°, echoplanar imaging factor: 17, matrix: 64×51, and voxel size: 3.6×3.6×6 mm3) were used. The DSC protocol included 60 measurements at intervals of 1.3 s after standardized intravenous injection of 20 mL of gadolinium-diethylenetriaminepentacetate (gadolinium-DTPA, Magnevist, Schering AG; 10 mLs followed by rapid infusion of 20 mL of saline). T1-weighted images were acquired using the following parameters: T1-fast field echo (T1-FFE 20 slices, TE: 1.8 ms, repetition time [TR]: 145 ms, flip angle: 80°, matrix: 256×256, voxel size: 0.9×0.9×6.0 mm3, and interslice gap: 0.6 mm).

PET was performed in a resting state on an ECAT EXACT HR scanner (Siemens/CTI, Knoxville, TN). CBF was acquired with 15O-water according to the intravenous bolus method in a 2D data acquisition mode providing 47 contiguous 3-mm slices of 5 mm full width at half-maximum in plane reconstructed resolution. Scan duration was 90 s with 60 mL (≈2.2 GBq). Continuous arterial blood sampling (radial artery) was used to calculate absolute CBF values.

Data Postprocessing

The postprocessing of the DSC raw images was performed by Perfusion Mismatch Analyzer (PMA, version 5.0). DSC-MRI raw images were processed on a voxel-by-voxel basis to generate maps of CBF, cerebral blood volume (CBV), mean transit time (MTT), and time-to-maximum (Tmax) using (1) the model-independent nonparametric sSVD and (2) the bSVD. Four arterial input functions for deconvolution were chosen manually from the contralateral proximal M1 segment and visually checked for optimal relative shape of the bolus curve.

Image analysis was performed using Vinci (Max Planck Institute for Neurological Research, Cologne, Germany) as described previously. PET images were rezised to the MR images. PET and DSC maps were then coregistered to T1 images.

Region of Interest–Based Image Analysis

Individual T1 images were used to create a 3D brain mask. By manual segmentation on each slice, we excluded the ventricles, most of the periventricular white matter, large vessels, and the sinuses. Within this individual atlas, a region of interest (ROI) analysis of the MRI and PET images was performed. On the axial cuts of the 3D brain mask, we placed 10-mm diameter circular ROIs along the cortex using Vinci. All ROIs were then copied onto the coregistered PET-CBF maps and on the DSC-MR maps obtained with sSVD and bSVD. The mean ROI values were used for further analysis. In addition, every ROI was labeled according to the threshold of PET-CBF<20 mL/100 g per minute. Voxels within the infarcted tissue without contrast agent arrival were excluded from further analysis (Figure 1B for a schematic overview).

Voxel-Based Image Analysis

PET-CBF maps were used to form penumbra masks, which were used as the gold-standard reference for penumbral tissue. The penumbra masks were automatically generated applying a threshold of PET-CBF<20 mL/100 g per minute on PET perfusion maps and manually corrected for voxels outside of the brain (Figure 1A1).

Gray matter masks were automatically generated from T1 maps using Medical Image Processing, Analysis and Visualization (MIPAV version 7.0.1, Center for Information Technology [CIT], National Institutes of Health [NIH]) and using brain extraction (BSE module) followed by automated segmentation (single channel fuzzy.

Figure 1. Schematic overview of the applied methodologies. Voxel-based: (A1) positron emission tomography (PET) penumbra mask representing the penumbral flow of cerebral blood flow (CBF)<20 mL/100 g per min was created. A2, From T1−weighted images, a gray matter (GM) mask and ipsilateral hemispheric mask (blue) were created. The penumbra mask and ipsilateral GM mask were overlayed to create the final analysis mask. A3, The analysis mask was overlaid with dynamic susceptibility−weighted contrast−enhanced (DSC) parameter maps of time−to−peak, cerebral blood volume (CBV), mean transit time (MTT), and time−to−maximum (Tmax). Receiver operating characteristics curve analysis was then performed to assess the performance of each DSC parameter map to predict GM penumbral flow. B, Region of interest (ROI)−based analysis of positron emission tomography (PET) CBF and DSC perfusion parameter maps (eg, Tmax). Circular ROIs (diameter, 10 mm) were manually drawn along the cortical rim and copied on the PET and DSC maps. Ventrices and periventricular white matter, large arteries, sinuses, and areas of severely delayed contrast agent were excluded.
C-means). The gray matter masks were resliced to the DSC-MRI maps dimensions and manually corrected for misclassified voxels using MeVisLab (version 2.5, MEVIS medical solutions, Bremen, Germany). Finally, hemispheric masks ipsilateral to the lesion were created using MeVisLab.

The following data analysis was performed using an in-house developed MATLAB code (version 7.10.0.499 R2010a, MathWorks, Natick, MA). First, DSC-MRI parameter maps were smoothed by a Gaussian filter with a convolution kernel size of (5 5 1) followed by box smoothing filter with a convolution kernel size of (7 7 3). In the next step, the PET penumbra mask, the gray matter mask, and the ipsilateral hemispheric mask were overlaid on each DSC-MRI parameter mask to create one final analysis mask, where voxels matching PET status 1 (PET-CBF <20 mL/100 g per minute) were compared with voxels matching PET status 2 (PET-CBF >20 mL/100 g per minute). Patients with a final penumbral flow volume <2 mL were excluded (for a schematic method overview, Figure 1A1–A3).

**Statistical Analysis**

For both the ROI-based and the voxel-based values, we performed receiver operating characteristics curve analysis. Receiver operating characteristics curve analysis is a highly suitable method to evaluate the performance of a parameter (DSC-MRI parameter values) to predict a binary status (PET status 1 versus PET status 2) and allows for the calculation of a threshold independent accuracy measure of penumbral flow detection by the area under the curve (AUC) which is a measure for the overall performance of a DSC-MRI parameter to predict PET penumbral flow.

The receiver operating characteristics curve analysis was performed separately for each patient, for each method (ROI/VOI), and each DSC-MRI parameter. Finally, AUCs were compared between sSVD and bSVD using the paired Wilcoxon signed-rank test implemented in Sigmapiot 11 (San Jose, CA). A significance level of \( P<0.05 \) was applied.

**Results**

**Patient Characteristics**

Seventeen patients (median age, 58 years; interquartile range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]) matched the inclusion criteria, 1 patient contributed with 2 data sets (range, [49–64]; median NIHSS score, 12 [6–14]).

**ROI-Based Analysis**

Based on the AUCs, the best performing map was Tmax (sSVD, 0.93; bSVD, 0.92) for both deconvolution methods. CBF and MTT performed similarly well (sSVD, 0.91/0.86; bSVD, 0.90/0.92). CBV performed worse (sSVD, 0.74; bSVD, 0.78). Only MTT showed a significant difference between the 2 deconvolution methods (\( P=0.001 \); Table for detailed values and Figure 2 for a graphical overview).

**Voxel-Based Analysis**

Based on the AUCs, the best performing maps were Tmax (sSVD, 0.86; bSVD, 0.82) and CBF (0.81 for both deconvolutions). CBV and MTT performed worse (sSVD, 0.70/0.60; bSVD, 0.73/0.77). The only parameter which showed significant differences between sSVD and bSVD deconvolution was MTT (\( P=0.002 \)) confirming the ROI-based analysis (Table for detailed values and Figure 2 for a graphical overview).

**Discussion**

In the present article, we applied 2 different analysis strategies to investigate the difference between the 2 most popular deconvolution methods (sSVD and bSVD) for the assessment of penumbral flow in acute stroke. Both analysis strategies showed that only MTT benefitted from bSVD deconvolution and that Tmax was the most stable parameter for the detection of penumbral flow. This supports the use of Tmax in multicenter studies, where postprocessing might differ across study sites.

The standardized ROI analysis revealed high AUC values for both deconvolution methods especially for Tmax, which is in line with previous publications.\(^{3,6,20}\) In the comparison of sSVD and bSVD, only MTT benefitted significantly from

| Table. Overview of the AUCs of the DSC Parameter Maps for the Prediction of Positron Emission Tomography Penumbral Flow and the Deconvolution Comparison Using the Wilcoxon Signed-Rank Test |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | ROI-Based       |                |                | Voxel-Based     |                |                |
|                | Analysis AUC    | IQR            | \( P \) Value  | Analysis AUC    | IQR            | \( P \) Value  |
| CBF sSVD       | 0.91            | 0.83–0.94      | 0.828          | 0.81            | 0.74–0.87      | 0.799          |
| CBF bSVD       | 0.90            | 0.83–0.91      | 0.81           | 0.76–0.89       |                |                |
| Tmax sSVD      | 0.93            | 0.90–0.95      | 0.768          | 0.86            | 0.78–0.89      | 0.766          |
| Tmax bSVD      | 0.92            | 0.89–0.95      | 0.82           | 0.77–0.87       |                |                |
| MTT sSVD*      | 0.86            | 0.83–0.89      | 0.001          | 0.60            | 0.46–0.76      | 0.002          |
| MTT bSVD*      | 0.92            | 0.90–0.94      | 0.77           | 0.69–0.85       |                |                |
| CBV sSVD       | 0.74            | 0.62–0.85      | 0.098          | 0.70            | 0.66–0.91      | 0.609          |
| CBV bSVD       | 0.78            | 0.66–0.87      | 0.73           | 0.65–0.83       |                |                |

Only MTT showed a significant improvement applying bSVD (marked by an asterisk). AUC indicates area under the curve; bSVD, block-circulant single value decomposition; CBF, cerebral blood flow; CBV, cerebral blood volume; DSC, dynamic susceptibility-weighted contrast-enhanced; IQR, interquartile range; MTT, mean transit time; sSVD, standard single value decomposition; and Tmax, time-to-maximum.

\( * \)Significantly \( (P<0.05) \) lower AUC value for sSVD.
the more sophisticated bSVD deconvolution method. MTT and CBV map calculation rely on an accurate estimation of the whole area under the deconvolved tissue curve.\textsuperscript{10,21} This estimation seems to be improved by the bSVD deconvolution method which accounts for tracer recirculation and might explain the benefit of using bSVD for MTT-based penumbral flow detection.

Generally, the AUCs were lower with our volumetric voxel-wise method in comparison with the standardized manual ROI placement, but were comparable with a (non-PET based) study of Christensen et al., which used a similar voxel-wise method. Because the manual placement of the ROIs allows to exclude artifacts and areas of artificial values within DSC maps, AUCs are generally higher with this method. The voxel-wise method, however, avoids user bias in this respect. The voxel-wise approach confirms the high performance of Tmax and CBF seen with the ROI-based method. In most previous validation studies and in the ROI methodology, MTT outperformed CBV, which was confirmed only for bSVD deconvolution applying the voxel-wise methodology. The gap between MTT sSVD and bSVD values is bigger in the voxel-wise method than in the ROI approach. An explanation for this is that MTT using sSVD deconvolution is prone to artificially low values within the areas with highest delay. This can be avoided using a manual approach but will inevitably influence an observer-independent voxel-wise method. Notably, distinct DSC postprocessing solutions deal differently with these artifacts and other software implementations than PMA might give better results for MTT sSVD. In addition, it should be mentioned that for the voxel-wise method we applied segmentation of gray matter. Our results thus reflect pure gray matter values which have not been described before. Most importantly, we could confirm the main finding of the ROI-based analysis that only MTT showed significant improvement when bSVD deconvolution was applied. From a technical point of view, bSVD deconvolution was introduced to overcome the intrinsic delay-sensitivity of the sSVD deconvolution method.\textsuperscript{10} Yet, a validation with a gold-standard in acute stroke has only been performed in a study with the limited number of 5 patients in the past.\textsuperscript{8} Given that acute stroke can be seen as a model disease for tracer delay in perfusion measurements, it was surprising that in our study only MTT parameter maps benefitted significantly from bSVD deconvolution. This is, however, in line with the findings of the aforementioned study. Although the use of bSVD is highly recommended for use in acute stroke imaging from a theoretical point of view, our study could not confirm this conclusion. Our data suggest that the fast sSVD deconvolution is an appropriate approach in acute stroke patients, at least as long as other parameters than MTT are used.

It should be emphasized that Tmax was insensitive to the type of deconvolution and showed the highest AUC. Therefore, our data clearly indicate that Tmax is the best suited deconvolved parameter for multicenter studies, where MRI postprocessing might differ across sites (eg, in the ongoing ECASS-4:ExTEND study\textsuperscript{11}). If available, Tmax should be preferred over other parameters for penumbral flow detection.

Our study has several limitations. First, although we present the largest PET-MR patient sample in acute stroke, it is still limited because of the logistic difficulties to perform \textsuperscript{15}O-water PET in acute stroke patients. Only clinically stable patients with a hemispheric stroke, without thrombolysis, and who were able to give informed consent could be included. This has to be kept in mind if our results are applied to the general population of acute stroke patients. Second, because of the logistic constraints using PET in hyperacute stroke, we included acute as well as subacute stroke patients in our study. Even though all patients showed significant penumbral tissue on PET imaging, this might influence the extrapolation of our results if applied to hyperacute stroke patients. Third, only data at 1.5T were available for our study. To what extent the results can be transferred to the use at 3T cannot be estimated. A validation using 3T data should be performed in future studies. Fourth, it should be kept in mind that only 1 academic software implementation of sSVD and bSVD was analyzed in our study and that other

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**Figure 2.** Graphic overview of the dynamic susceptibility–weighted contrast–enhanced parameter maps analyzed in our study arranged according to perfusion parameters and analyzed deconvolutions. The performance is measured by the area under the curve (AUC). Interquartile ranges are given as error bars. bSVD indicates block-circulant single value decomposition; CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; ROI, region of interest; sSVD, standard single value decomposition; and Tmax, time-to-maximum.
software alternatives may give different results. Efforts should be made to validate more and most importantly commercial software solutions. Fifth, the delay between MRI and PET imaging may lead to perfusion changes between the scans. However, there was no change in neurological presentation during the imaging studies. Perfusion changes which cannot be controlled by these measures are a general limitation of consecutive comparative imaging studies and might influence the results.

In conclusion, bSVD deconvolution only provides a significant benefit for MTT in MRI-based penumbral flow detection, and MTT maps should be interpreted with caution when sSVD deconvolution is used. Tmax is especially suited for clinical stroke trials owing to its high performance and insensitivity to the applied deconvolution method.

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Disclosures

None.

References


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