Multiparametric Model for Penumbral Flow Prediction in Acute Stroke

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Background and Purpose—Identification of salvageable penumbra tissue by dynamic susceptibility contrast magnetic resonance imaging is a valuable tool for acute stroke patient stratification for treatment. However, prior studies have not attempted to combine the different perfusion maps into a predictive model. In this study, we established a multiparametric perfusion imaging model and cross-validated it using positron emission tomography perfusion for detection of penumbral flow.

Methods—In a retrospective analysis of 17 subacute stroke patients with consecutive magnetic resonance imaging and H215O positron emission tomography scans, perfusion maps of cerebral blood flow, cerebral blood volume, mean transit time, time-to-maximum, and time-to-peak were constructed and combined using a generalized linear model (GLM). Both the GLM maps and the single perfusion maps alone were cross-validated with positron emission tomography–cerebral blood flow scans to predict penumbral flow on a voxel-wise level. Performance was tested by receiver-operating characteristics curve analysis, that is, the area under the curve, and the models’ fits were compared using the likelihood ratio test.

Results—The GLM demonstrated significantly improved model fit compared with each of the single perfusion maps ($P<1\times10^{-5}$) and demonstrated higher performance, with an area under the curve of 0.91. However, the absolute difference between the performance of GLM and the best-performing single perfusion parameter (time-to-maximum) was relatively low (area under the curve difference =0.04).

Conclusions—Our results support a dynamic susceptibility contrast magnetic resonance imaging–based GLM as an improved model for penumbral flow prediction in stroke patients. With given perfusion maps, this model is a straightforward and observer-independent alternative for therapy stratification. (Stroke. 2017;48:1849-1854. DOI: 10.1161/STROKEAHA.117.016631.)

Key Words: acute stroke ◼ cerebrovascular circulation ◼ magnetic resonance imaging ◼ perfusion imaging ◼ positron emission tomography

Recently, the therapeutic efficacy of mechanical intrarterial recanalization in acute stroke has been proven. Consequently, reliable methods to detect the salvageable penumbra for stratification of patients to novel treatments in stroke are needed now more than ever.1 To detect the salvageable penumbra in the clinical setting, perfusion imaging using dynamic susceptibility contrast (DSC) magnetic resonance imaging (MRI) is a widely used method.2–5 In DSC imaging, the surrogate of the salvageable penumbra is termed mismatch and is traditionally depicted using one of the following perfusion parameters: time-to-peak, cerebral blood flow (CBF), cerebral blood volume, mean transit time, or time-to-maximum (Tmax). Studies have attempted to validate these perfusion parameters using final infarct size and gold standard imaging (eg, using positron emission tomography [PET]).6–8 However, to date, validations for penumbral flow detection are only available for individual perfusion parameters. The complex interaction of perfusion and tissue damage in acute stroke suggests that a combination of different perfusion parameters in an integrative predictive model is likely to lead to improved prediction of penumbral flow over prediction based on a single parameter. In this respect, a promising approach is a generalized linear model (GLM) that has been successfully applied to predict the final infarct size both by magnetic resonance imaging9 and computed tomography imaging.10 A GLM has the big advantage that it provides an observer-independent model that can be readily included in clinical postprocessing routines. A GLM has not yet been applied for penumbral-flow prediction validated using gold standard imaging.
In this study, we combined the DSC perfusion parameters in a GLM to predict penumbral flow. We then assessed the performance of the multiparametric model by comparison to the standard prediction with single perfusion parameters. We validated our results using comparative perfusion PET, the gold standard for in vivo perfusion imaging, as a reliable cross-validation method for penumbral flow detection.

### 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 score >2 points during the imaging procedure were excluded (National Institute of Health Stroke Scale score >0 points during the imaging procedure was included). 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 were acquired in an axial orientation (multishot 3-dimensional T2*−weighted gradient echo planar imaging sequences [PRESTO; Principles of Echo Shifting Using a Train of Observations]). 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: 64x64, and voxel size: 3.6x3.6x6 mm3 were used. The DSC protocol included 60 measurements at intervals of 1.3 s after standardized intravenous injection of 20 mL of gadolinium-diethylenetriaminepentaacetate (Magnevist, Schering AG; 10 mL/s followed by rapid infusion of 20 mL of saline). T1-weighted images were acquired using the following parameters: T1-fast field echo (20 slices, TE: 1.8 ms, repetition time: 145 ms, flip angle: 80°, matrix: 256x256, voxel size: 0.9x0.9x0.6 mm3, and interslice gap: 0.6 mm).

PET was performed in the 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 2-dimensional 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 mCi (=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 using Perfusion Mismatch Analyzer (version 5.0).13 DSC-MRI raw images were processed on a voxel-by-voxel basis to generate maps of CBF; cerebral blood volume, mean transit time, and Tmax using box-circular singular value decomposition (bSVD) deconvolution because bSVD deconvolution has shown advantages over standard singular value decomposition (sSVD) deconvolution methods in acute stroke.14 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.15,16 PET images were resliced and coregistered to the DSC-MRI maps dimensions using VINCI. The penumbra masks were automatically generated applying a threshold of PET-CBF<20 mL/100 g per minute on PET perfusion maps and then manually corrected for voxels outside of the brain (see illustration in Figure 1). 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].

#### Statistical Analysis

##### The Generalized Linear Model

The objective of the study was to combine the different single perfusion parameters in a linear model to predict penumbral flow in (sub) acute stroke patients. A GLM is a linearization of general regression that allows for a response to be dichotomous instead of continuous in linear regression. Hence, our model predicts the probability of penumbral flow (versus nonpenumbral flow) based on a set of explanatory variables according to the following relation:

\[
P(P|X) = \frac{1}{1+e^{-\beta_0-\beta_1X}}
\]

where \( P(P|X) \) is the probability for penumbral flow (PF) given the vector \( X \). PF can only take the values 1 for penumbral flow or 0 for nonpenumbral flow; \( \beta \) stands for the model parameterization.

Therefore, GLM permits relating a linear combination of the perfusion parameters to the probability of the voxel to show penumbral flow. According to the model, the probability is given by

\[
P(P|\bar{X}) = \frac{1}{1+e^{-(\beta_0+\beta_1X+C_BF+\beta_2CBV+\beta_3MTT+\beta_4Tmax+\beta_5TTP)}}
\]

where \( P(P|\bar{X}) \) is the probability of the voxel \( i \) to show penumbral flow given the perfusion parameters values for this voxel; \( \bar{X} = (C_BF, CBV, MTT, Tmax, TTP) \) denotes the perfusion parameters values for the voxel \( i \); and \( \beta \) set the model parametrization to be estimated based on the training data.

##### Addressing Potential Covariate Dependencies

Because the perfusion parameters are derived from the same signal, we can expect covariates dependencies in the model. Because a GLM relies on the assumption of little or no multicollinearity, that is, the covariates should be independent from each other, these potential covariates dependencies must be rejected. To do that, we applied least absolute shrinkage and selection operator. Least absolute shrinkage and selection operator allows to select a subset of the covariates that yields the best prediction and, therefore, presents a reduced model. A subset selection containing all covariates implies there is no redundancy of covariates.

##### Cross Validation

Cross validation offers an effective way for validating a model and for assessing how the results will generalize to an independent data set. The cross validation was applied using a leave-one-out approach on N patients: the model parameters \( \beta \) were identified based on N−1 patients and were then assessed for performance based on the excluded patient. The performance was estimated using receiver-operating characteristic curve analysis as the area under the curve (AUC) to predict penumbral flow as referenced by the gold standard PET imaging (see Data Analysis paragraph for further details). The process was repeated N times, and the final performance was taken as the median of N runs. Targeting only the upper limit of penumbral

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flow as applied in the described receiver-operating characteristic curve analysis is a standard approach because the lower limit (ie, the infarct core) is defined by diffusion-weighted imaging within the mismatch concept.4,19–21

**Comparison to Single Parameters Maps**

Prediction of penumbral flow by a single perfusion parameter can be seen as a simple case of GLM where there is only a single predictor

\[
P_i(\text{PF} \mid \text{Param}_i) = \frac{1}{1 + e^{-\beta_0 - \beta_1 \text{Param}_i}}
\]

where \(P_i\) is the probability of the voxel \(i\) to indicate penumbral flow given the value of the perfusion parameter \(\text{Param}_i\).

According to this bijective relation, \(P_i\) and the values from the single parameter perfusion map contain the same information, but with the \(P_i's\) on the same scale as the multimodal GLM above, allowing a direct comparison in terms of AUC in a receiver-operating characteristic curve analysis as above.

In addition, the accuracy of the GLM and the single parameter maps was estimated and compared as follows: an optimal threshold was identified for each map for each patient according to the Youden index. This threshold was applied to assign each voxel to penumbra/nonpenumbra, and the accuracy was calculated according to the percent of voxels which were correctly assigned.

While the derived AUC values provide valuable information of performance estimates, they cannot be directly compared because of the statistical properties of nested binary regression models. In these cases, the likelihood ratio (LR) test is a recommended approach to compare nested models.22 The LR statistics evaluates the significance of model restrictions, namely how significant are the additional covariates for prediction, using the log-likelihood objective function. Here we tested an integrated GLM, that is, the unrestricted model, compared with single-parameter models, that is, the restricted, models. A standard significance level of \(P<0.05\) was applied.

**Results**

**Clinical Data**

Seventeen patients (median age, 56 years; interquartile range, 46–63; median National Institute of Health Stroke Scale score, 13 [6–17]) matched the inclusion criteria. The median time delay between stroke and MRI was 18 hours (6.5–26), and the median time delay between MRI and PET was 79 minutes (60–161). Internal carotid artery steno-occlusion was present ipsilaterally in 6 patients and contralaterally in 2 patients.

**Rejection of Covariates Dependencies**

The least absolute shrinkage and selection operator analysis resulted in a reduced model with the exact same covariates as in the GLM and yielded virtually identical performance measures (AUC=0.91), indicating that there were no substantial dependencies between the covariate perfusion parameters.

**Performance in Penumbral Flow Prediction and Relation to the Clinical Perspective**

The extended GLM fit was found to be statistically significantly better \((P<10^{-5})\) compared with each of the single parameter models, as shown by the LR test. The GLM demonstrated improved performance (AUC, 0.91) over each of the single parameter–based models (see Figure 2). The single parameter perfusion maps showed AUC values between 0.74 and 0.87, where Tmax and time-to-peak showed best performance of the single parameters and mean transit time and cerebral blood volume demonstrated lower performance. The absolute difference in AUC between the GLM and the best-performing parameter Tmax was relatively small \((\text{difference}=0.04)\). This translates to an improvement in accuracy of at least 3% compared with Tmax and ≤12% compared with the other parameters in terms of correctly classified tissue. To exemplify the clinical implications, using a standard approach of a Tmax threshold of >6 s would yield a misclassified penumbra volume of 22 mL on average \((\text{maximum} \ 41 \text{ mL})\), whereas application of a threshold approach with the presented GLM would yield a misclassified penumbra volume of ≤16 mL on average \((\text{maximum} \ 33 \text{ mL})\).

Further illustrations of GLM prediction map versus single parameters are depicted in Figure 3.

**Discussion**

The present PET-based DSC-MRI validation study was designed to compare a multiparametric model in the form of a GLM to single perfusion maps models for the prediction of penumbral flow in (sub)acute stroke. The results of our study indicate that a combination of perfusion parameters in a GLM provides improved prediction of penumbral flow in comparison with so far used single parameters–based models.

It is important to emphasize that the use of a GLM is clinically applicable. It can be implemented in clinical post-processing routines, providing the treating physician with a penumbral flow map that can be used to calculate the mismatch. For this purpose, DSC-MRI perfusion map values need to be calculated using appropriate standard software, and then the values must be assigned voxel-by-voxel to the GLM formula to produce the final penumbral flow map. The formula is provided in Appendix 1 for further use.

The performance of DSC-MRI perfusion maps in our study is consistent with previous reports. The observation that Tmax and time-to-peak maps are most predictive of penumbral flow among the single perfusion parameters has been reported in earlier studies.6,11 Our results confirm the idea that
a multiparametric approach is beneficial over single parameter-based prediction.\textsuperscript{9,10,23} We show that a combination of DSC-MRI single parameters within a GLM framework can provide improved prediction of penumbral flow. Notably, however, the observed difference in performance between the GLM and the best-performing single parameter map Tmax was small. A possible explanation for this might be that all DSC-MRI parameter maps are derived from the same concentration–time curve. This implies that the perfusion maps share mutual information, limiting the prediction gain through combination of the individual maps. It is well known that some perfusion parameters are theoretically related, for example CBF, cerebral blood volume, and mean transit time; however, the combined interrelations between parameters are complex and in practice affected by measurement and estimation limitations. Consistent with these considerations, the least absolute shrinkage and selection operator analysis and the LR test results suggest that there is an important information gain when applying a combined model. Here, the GLM seems to maximally extract physiological information from the signal. Translating the effect size into clinically relevant terms, the means of misclassified voxels between the GLM and the best-performing map Tmax differed by 6 mL. This rather small difference does not preclude potential clinical value, however. In a large perfusion deficit, 6 mL might not be clinically relevant, but in boundary cases with a small penumbra, the accuracy gain could assure correct classification to treatment. Here, this small relative difference could amount to a clinically relevant absolute difference if many patients were measured. Thus, if a visual inspection of maps for penumbral flow detection is deemed sufficient, Tmax maps seem to be the map of choice. If, however, a (semi)automated voxel-based approach is chosen, constituting a less biased approach, a GLM might be especially suited to provide the maximum predictive value.

The present results are also promising in another major respect. Penumbral flow identification is a key issue in establishing therapies beyond the current time-based paradigm. Recent randomized clinical trials have shown the importance of selecting patients on the basis of the presence of penumbral tissue. They emphasized the necessity of valid and rapid imaging-based techniques for defining the penumbra to optimize efficiency of intervention.\textsuperscript{24,25} Furthermore, in recent years, various studies have suggested new therapeutic strategies to improve outcome over and above current treatment. These studies include nonpharmacological approaches such as normobaric oxygen therapy, enhancing collateral flow, hypothermia, and transcranial direct current stimulation as well as thrombectomy, and administration of neuroprotective agents in combination with tissue-type plasminogen activator.\textsuperscript{1,26–30} Accurate identification of penumbral flow based on imaging can be crucial for stratification to these new potential treatments, as well as their monitoring and evaluation. Particularly, penumbral imaging has the potential to improve identification of patients eligible for mechanical recanalization beyond the current time window.\textsuperscript{24,31} This is especially important because the percentage of ischemic stroke patients eligible for this new therapy under the current guidelines is extremely low.\textsuperscript{32} Notably, penumbral imaging can identify patients with a large infarct core who are prone to serious side effects, such as symptomatic hemorrhage and malignant edema.\textsuperscript{24} Thus, perfusion imaging may inform the treating physician whether intra-arterial treatment is warranted or not, as has been shown in the EXTEND-IA study (Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial).\textsuperscript{24} It should be noted that the median time delay between stroke and MRI in this study was 18.5 hours, including stroke patients outside the current time window. This is in line with previous studies indicating the clinical relevance of penumbral flow imaging ≤48 hours after stroke.\textsuperscript{33} Our study, therefore, corroborates that the above presented treatment strategies might be viable beyond the current time window.

Comparing the GLM to single parameters maps, as nested binary regression models, has been recently shown to be more complex than previously perceived because of the statistical characteristics of AUC-based performance comparisons.\textsuperscript{22} A striking point here is that while AUC values provide valuable

![Figure 2](https://stroke.ahajournals.org/)

The models performance in penumbral-flow prediction. The median area under the curve (AUC) for each of the models is displayed in A. Error bars represent the interquartile range (IQR). The performance curves for each of the models are shown in B. CBF indicates cerebral blood flow; CBV, cerebral blood volume; GLM, generalized linear model; MTT, mean transit time; Tmax, time-to-maximum; and TTP, time-to-peak.
information, they cannot be directly compared in a statistical test. LR tests can serve in this case to show whether adding covariates significantly improve the fit of the model as indicated by the log-likelihood objective function. Thus, we chose this test for the comparison of the full and the nested models.

Our study has several limitations. First, as the data were acquired with 1.5 T scanners, it is unclear to which extent our results can be translated to 3 T imaging. Additionally, the small cohort raises the random error, and therefore, the estimated model coefficients have limited precision. Thus, future studies are required to fine-tune the model. Here, the increasing availability of MR-PET scanners provide a promising opportunity. Nonetheless, this is the largest study combining DSC-MRI and PET for the multiparametric prediction of penumbral flow in (sub)acute stroke.

Conclusions
Our findings indicate that combining single parameter perfusion maps in a GLM may provide an improved model for penumbral flow prediction in acute stroke patients. These findings suggest a straightforward model that can be easily integrated in the clinical routine for improved stratification for (intra-arterial) therapy.

Appendix 1: GLM Parametrization
The following formula shows the parametrization of the GLM based on the given data set:

$$P = \frac{1}{1 + e^{-\left(1.345 + 0.162\text{CBF} - 0.2016\text{CBV} + 0.1437\text{MTT} - 0.1078\text{Tmax} - 0.2202\text{TTP}\right)}}$$

The optimal threshold for the GLM probability maps was identified as 0.517.

Disclosures
Dr Sobesky reports the following board memberships, consultancies, and payments for lectures including service on speaker’s bureaus: Boehringer-Ingelheim, Sanofi, Bayer, Pfizer, and Maquet. The other authors report no conflicts.
References


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