A Simple Positron Emission Tomography-Based Calibration for Perfusion-Weighted Magnetic Resonance Maps to Optimize Penumbral Flow Detection in Acute Stroke

Olivier Zaro-Weber, MD; Walter Moeller-Hartmann, MD; Wolf-Dieter Heiss, MD; Jan Sobesky, MD

Background and Purpose—Perfusion-weighted (PW) MRI is increasingly used to identify the tissue at risk. The adequate PW-MRI map and threshold remain controversial due to a considerable individual variation of values. By comparative positron emission tomography, we evaluated a simple MR-based and positron emission tomography-validated calibration of PW maps.

Methods—PW-MRI and quantitative positron emission tomography (15O-water) of patients with acute stroke were used to calculate averaged as well as individual thresholds of penumbral flow (positron emission tomography cerebral blood flow (<20 mL/100 g/min) for maps of time to peak, mean transit time, cerebral blood flow, and cerebral blood volume. A linear regression analysis studied the variability of the individual thresholds using 3 different PW reference regions (hemispheric, white matter, gray matter). The best model was used for volumetric analysis to compare averaged and scaled individual thresholds and to calculate look-up tables for PW maps.

Results—In 26 patients, the averaged thresholds were (median/interquartile range): cerebral blood flow 21.7 mL/100 g/min (19.9 to 32); cerebral blood volume 1.5 mL/100 g (0.9 to 1.8); mean transit time seconds 5.2 (3.9 to 6.9); and relative time to peak 4.2 seconds (2.8 to 5.8). The large individual variability was best explained by the mean value of the hemispheric reference derived from a region of interest on a level with the basal ganglia of the unaffected hemisphere ($R^2$: cerebral blood flow 0.76, cerebral blood volume 0.55, mean transit time 0.83, time to peak 0.95). Hemispheric reference-corrected thresholds clearly improved the detection of penumbral flow. Look-up tables were calculated to identify the individual thresholds according to the hemispheric reference value.

Conclusion—The individual variation of PW values, even if calculated by deconvolution, remains a major obstacle in quantitative PW imaging and can be significantly improved by a simple MR-based calibration. Easily applicable look-up tables identify the individual best threshold for each PW map to optimize mismatch detection. (Stroke. 2010;41:1939-1945.)

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

Detecting and rescuing the ischemic penumbra is the main target of acute stroke therapy.1 Diffusion-weighted MRI and perfusion-weighted (PW) MRI help to estimate the tissue at risk, although several methodical issues are currently under debate.2,3 Using the MRI-based mismatch concept, it is of major importance how precise the perfusion threshold of <20 mL/100 g/min (as established by O15-water positron emission tomography [PET]) can be estimated by maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP) because this penumbral flow (PF) threshold defines the functionally compromised viable tissue.1

In our previous comparative MRI-PET study,4 individual flow thresholds were defined and the results were presented as averaged values. In line with other studies,5-7 however, we found a considerable individual variation of the flow thresholds. This finding emphasized the need for an additional individual correction procedure: the variations of MR-based flow values in the patient samples suggest that 1 common correction factor may not be sufficient because under- and overestimation of PF was described. This problem has been issued by previous studies that used PET-based8 or MR-based calibration techniques.7,9,10 These approaches, although highly desirable, are technically challenging, are time-consuming, and require a recalculation of the complete data sets on a voxel level. Thus, their application in clinical routine is as yet difficult.

In a comparative PET-MRI data set, we therefore (1) described individual PW thresholds of PF; (2) tried to explain the variation of these best thresholds by reference regions; and (3) proposed a simple MR-based and PET-validated calibration technique to determine the best PF threshold.
Materials and Methods

Patients
In a prospective imaging study, MRI and PET imaging were performed in patients presenting with acute and subacute ischemic stroke. Patients with small vessel strokes, pure subcortical strokes, and patients with alterations of their neurological status were excluded. Part of this patient population as well as the inclusion details have been described in a previous publication of our group. All patients gave informed consent and the study was approved by the local ethics committee.

Data Acquisition and Postprocessing
Data acquisition and postprocessing have been described in detail in a recent study. In brief, MRI was performed on a 1.5-T whole-body scanner (Philips Intera Master). PW images were acquired using gradient echoplanar imaging sequences (TR 1.3 seconds, effective TE 25 ms, 20 slices, slice thickness 6 mm, interslice gap of 0.6 mm, field of view 23 cm). 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 after intravenous bolus injection of 15O-water (60 mCi=2.2 GBq). Continuous arterial blood sampling (radial artery) was used to calculate absolute CBF values.

The postprocessing of the PW raw images was performed by STROKETOOL, Version 2.3 (DIS, Düsseldorf, Germany). On a pixel-by-pixel basis to generate maps of TTP from the tissue response curve as well as CBF, CBV, and MTT using the model-independent nonparametric standard singular value decomposition deconvolution method described by Ostergaard.

The arterial input function was defined under visual control (5 to 10 intravascular voxels) within the proximal segment of the middle cerebral artery and the distal segment of the internal carotid artery of the unaffected hemisphere. The resulting input function was visually inspected for peak sharpness, amplitude width, and bolus peak time to select only nondistorted bolus curves. Image analysis was performed using a multimodal imaging tool (VINCI). 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.

Figure 1. The mean PWI value of the HR of 1 slice on a level with the basal ganglia and ventricles is used to identify the corresponding individual PF threshold using the look-up Table 2 (red arrows). A range of mean PW imaging hemispheric HR is used to generate the look-up Table 2 by using the regression equations (see “Results”) to calculate the corresponding PW imaging PF thresholds (green arrow).

Calculation of the Individual Best Threshold for Penumbral Flow
As described in a previous study, the penumbral flow thresholds on PW-MR images were determined by a receiver operating characteristic curve analysis. We used PET as a gold standard to define penumbral CBF values <20 mL/100 g/min. Cortical regions of interest (ROIs) placed on the affected hemisphere were labeled as “normal” or as “penumbral flow” according to their mean values on PET-CBF. For each patient and each PW map, varying thresholds were applied to calculate the best PF thresholds in a receiver operating characteristic curve analysis. This approach yielded the best threshold for PF for each patient and each modality as defined by PET-CBF. Thus, every patient received 1 threshold value per PW map. In a pooled analysis, these individual thresholds were plotted to illustrate the interindividual variability of these PF thresholds.

Reference Regions
Three reference ROIs were used: (1) gray matter reference: multiple 10-mm circular ROIs were placed along the cortex on 2 axial cuts; (2) white matter reference: the centrum semiovale was manually outlined on 1 axial cut; and (3) hemispheric reference (HR): the unaffected hemisphere was manually outlined on 1 axial cut through the basal ganglia (including the ventricles).

The ROIs were placed on the unaffected hemisphere of the individual T1-weighted images and then copied to the realigned PW images. The mean ROI values were used for further analysis.

Dependence of the Best Threshold Values on the Reference Values
To show how individual PF thresholds depend on the reference values, we performed a linear regression analysis. For each reference region, that is, for gray matter reference, white matter reference, and HR, the dependence of the PF thresholds was calculated.

Evaluation of Individual PF Thresholds
The results of the linear regression analysis were used to estimate the possibility to identify the best threshold by the reference values. The benefit of using individual PF thresholds in terms of volumetric fit was described by a visual comparison of the PET-CBF volume <20 mL/100 g/min with the PW imaging (PWI)-based volume of PF using (1) the averaged threshold; and (2) the scaled individual threshold. A Bland-Altman analysis for CBF and TTP imaging was performed: the target volume of <20 mL/100 g/min was defined by PET-CBF. For MRI-CBF images, we calculated the volumes of PF using (1) the averaged threshold (“1 threshold for all patients”; 21.7 mL/100 g/min) on the one hand; and (2) the scaled individual PF thresholds on the other hand. For MRI-TTP images, we calculated the volumes of PF using the scaled individual PF thresholds.

Calibration of the Individual PF Threshold Using a Look-Up Table
Calibration of the individual best penumbral flow threshold using a look-up table was performed in 3 steps (Figure 1): (1) the ROI of the HR was manually outlined on 1 axial cut on a level with the basal ganglia including the whole hemisphere and ventricles (mean value of the HR); (2) this mean HR value is used to determine the corresponding individual PF threshold in the look-up table; and (3) this individual PF threshold can then be directly applied to the corresponding PW image.

Statistics
Because most of the study values were not normally distributed, the results were presented as median and interquartile range if not indicated
otherwise. A linear regression analysis was performed to describe the association of threshold values and reference values. Statistical significance was set at $P \leq 0.05$. Data were analyzed by Sigmastat 3.11 (SYSTAT Software, Inc) and Med Calc Software (Version 11).

**Results**

**Clinical Data**

Seventeen of 26 patients (median age 56.5 years) were imaged within 24 hours after stroke (median, 9.2 hours) and 9 were measured beyond 24 hours (median, 48 hours). The median time delay between MRI and PET was 68 minutes. Detailed patient data are described in Zaro-Weber et al.4

**Individual Variability of PF Thresholds**

The receiver operating characteristic analysis of our previous study found the following PWI thresholds (median) as “averaged” thresholds for the detection of PF (compared with PET): CBF $< 21.7$ mL/100 g/min, CBV $< 1.5$ mL/100 g, MTT $> 5.2$ seconds, TTP $> 33$ seconds and TTP delay threshold $> 4.2$ seconds. Figure 2 illustrates these averaged values and shows the considerable interindividual variance of the PF threshold values emphasizing that 1 (“averaged”) threshold for all patients may not be adequate.

**HR Values**

The mean values of the HR were as follows (mean; SD): PW-CBF 63 ($\pm 30$) mL/100 g/min, PW-CBV 2.4 ($\pm 1.2$) mL/100 g, PW-MTT 3.2 ($\pm 1.4$) seconds, and PW-TTP 33.3 ($\pm 14.6$) seconds.

**Dependence of the Best Threshold From the Reference Regions**

The individual PF thresholds showed a strong association to the flow values of the HR; the results of the linear regression analysis are shown in Table 1. Gray matter reference and white matter reference did not well explain the individual variance of the threshold values except for TTP maps. The HR values well explained the variability of individual PF thresholds. Accordingly, we continued the analysis for the HR. The scatterplots for HR are displayed in Figure 3 and illustrate that the hemispheric mean flow (on PWI) can be used to identify the best individual PF threshold (that should be used to yield the best estimate of PET-based PF). The regression equations were as follows:

- CBF penumbra threshold = $6.540 + (0.293 \times \text{mean CBF of HR})$
- CBV penumbra threshold = $0.316 + (0.388 \times \text{mean CBV of HR})$
- MTT penumbra threshold = $1.519 + (1.203 \times \text{mean MTT of HR})$
- TTP penumbra threshold = $2.563 + (1.069 \times \text{mean TTP of HR})$

Based on these equations, we calculated a (PET-validated) look-up table (Table 2) using a range of values of the HR for each modality (Figure 1). This look-up table was then used to calibrate the best individual PF threshold.

**Evaluation of Individual PF Thresholds**

On visual inspection, the spatial correspondence of PET- and PWI-based detection of PF was clearly improved in all

---

**Table 1. $R^2$ Values of the Linear Regression Analysis**

<table>
<thead>
<tr>
<th>PW Imaging Modality</th>
<th>$R^2$ WMR</th>
<th>$R^2$ GMR</th>
<th>$R^2$ HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF</td>
<td>0.48*</td>
<td>0.64*</td>
<td>0.76*</td>
</tr>
<tr>
<td>CBV</td>
<td>0.20‡</td>
<td>0.32‡</td>
<td>0.55*</td>
</tr>
<tr>
<td>MTT</td>
<td>0.23‡</td>
<td>0.72*</td>
<td>0.83*</td>
</tr>
<tr>
<td>TTP</td>
<td>0.92*</td>
<td>0.93*</td>
<td>0.95*</td>
</tr>
</tbody>
</table>

The best individual PF threshold was plotted against the reference value.

* $P \leq 0.001$.
† $P \leq 0.01$.
‡ $P \leq 0.05$.

WMR indicates white matter reference; GMR, gray matter reference.

---

**Figure 2.** Box plots of individual penumbral flow thresholds derived from the ROC analysis. Mean, IQR, and range of values are displayed for each PW imaging modality. ROC indicates receiver operating characteristic; IQR, interquartile range.

**Figure 3.** Individual PF thresholds are plotted against their corresponding mean value of the unaffected HR. A linear regression analysis is performed for all 4 PW imaging modalities; the results from the regression analysis are shown in the plot.
<table>
<thead>
<tr>
<th>PW-CBF, mL/100 g/min</th>
<th>PW-CBV, mL/100 g</th>
<th>PW-MTT, Seconds</th>
<th>PW-TTP, Seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Values of the HR</td>
<td>Individual PF Threshold</td>
<td>Mean Values of the HR</td>
<td>Individual PF Threshold</td>
</tr>
<tr>
<td>18 11.8 0.7 0.6 10 27.2 20 23.9</td>
<td>20 12.4 0.8 0.6 11 28.4 21 25.0</td>
<td>22 13.0 0.0 0.3 12 29.6 22 26.1</td>
<td>24 13.6 1.0 0.7 13 30.8 23 27.2</td>
</tr>
<tr>
<td>34 16.5 1.5 0.9 18 36.8 28 32.5</td>
<td>36 17.1 1.6 0.9 19 38.0 29 33.6</td>
<td>38 17.7 1.7 1.0 20 39.3 30 34.6</td>
<td>40 18.3 1.8 1.0 21 40.5 31 35.7</td>
</tr>
<tr>
<td>50 21.2 2.3 1.2 26 46.5 36 41.0</td>
<td>52 21.8 2.4 1.2 27 47.7 37 42.1</td>
<td>54 22.4 2.5 1.3 28 48.9 38 43.2</td>
<td>56 23.0 2.6 1.3 29 50.1 39 44.3</td>
</tr>
<tr>
<td>66 25.9 3.1 1.5 34 56.1 44 49.6</td>
<td>68 26.5 3.2 1.6 35 57.3 45 50.7</td>
<td>70 27.1 3.3 1.6 36 58.5 46 51.7</td>
<td>72 27.6 3.4 1.6 37 59.7 47 52.8</td>
</tr>
<tr>
<td>82 30.6 3.9 1.8 42 65.7 52 58.2</td>
<td>84 31.2 4.0 1.9 43 66.9 53 59.2</td>
<td>86 31.7 4.1 1.9 44 68.1 54 60.3</td>
<td>88 32.3 4.2 1.9 45 69.3 55 61.4</td>
</tr>
<tr>
<td>98 35.3 4.7 2.1 50 75.3 60 66.7</td>
<td>100 35.8 4.8 2.2 51 76.5 61 67.8</td>
<td>102 36.4 4.9 2.2 52 77.7 62 68.8</td>
<td>104 37.0 5.0 2.3 53 79.0 63 69.9</td>
</tr>
<tr>
<td>114 39.9 5.5 2.5 59 86.2 68 75.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*According to the flow value of the HR, these PF thresholds can be directly applied to the PW imaging maps.
patients if individual scaled thresholds were used instead of averaged thresholds. Figure 4 illustrates a representative patient.

The Bland-Altman plot showed a clear improvement of the volumetric congruence of PET-based and PWI-based detection of PF if the scaled individual thresholds were used instead of the averaged threshold (Figure 5A–B). The mean difference between PET and PW-CBF volumes was \(-17.3\) cm\(^3\) for the averaged threshold and \(-9.9\) cm\(^3\) for the individual threshold. The SD was 71.3 cm\(^3\) and 27.3 cm\(^3\). The limits of agreement were from \(+122.4\) cm\(^3\) to \(-157\) cm\(^3\) and from \(+43.6\) cm\(^3\) to \(-63.5\) cm\(^3\), thus including 95\% of the values. Both plots show a slight overestimation of PW-CBF volumes as compared with PET-CBF volumes. The increase in variability of the differences for the uncorrected volumes as the magnitude of the measurements increases (Figure 5A) was attenuated if the scaled individual PF thresholds were used (Figure 5B). The Bland-Altman analysis for TTP revealed that the mean difference between PET and PW-TTP volumes was \(-1.3\) cm\(^3\) for the scaled individual thresholds (SD 6.3 cm\(^3\); limits of agreement were from \(+11.1\) cm\(^3\) to \(-13.7\) cm\(^3\) including 95\% of the values).

**Discussion**

The current MRI-based mismatch concept requires the volumetric assessment of PF and thus the use of quantitative thresholds in perfusion imaging. Although the current literature shows that PW maps well delineate hypoperfusion, the absolute quantification of PW maps still remains difficult, which motivated the present study.

PW maps show an important individual variation of the PF threshold values despite the use of deconvolution algorithms and despite the implementation of input functions.\(^{10,16}\) This interindividual variation of PF thresholds seems mainly due to a methodological error of PW imaging, because these thresholds were derived from a direct comparison with PET. In our study, using PW maps derived from standard singular value decomposition, the mean hemispheric flow (PW-CBF) in the unaffected hemisphere was 63 mL/100 g/min ranging from 17 to 128 mL/100 g/min. This spreading of values is in line with the literature\(^{6,9,10,17,18}\) and represents the problem of quantification of PW maps.

The interindividual variation of perfusion values leads to an important error in the estimation of the hypoperfusion volume. Previous stroke studies tried to derive PF thresholds from MR data alone\(^{19,20}\) or from comparative PET/single photon emission CT data.\(^{5,21–25}\) Unfortunately, the results were mostly presented as a pooled analysis that results in 1 (averaged) threshold per data set. In our study, we identified each patient’s threshold for the detection of PF as defined by PET imaging and we showed the wide range of these “best thresholds.” This finding suggests that if using an averaged threshold, the error in individual patients might be important regarding the volumetric difference required in current mismatch definitions.\(^{2}\)

Several approaches have been proposed to correct for the individual variability of PW values after deconvolution. Data from our comparative MR-PET study,\(^4\) in line with a previous study,\(^6\) showed a strong and partly linear correlation of PET- and PW-based flow values in individual patients. However, if
different patients were pooled, this association could not be maintained. One reason is that the linear regression lines that describe the association of PW and PET perfusion values in individual patients have different offsets and different slopes. Thus, the pooled analysis is not successful. These data suggest that common linear correction factors derived from MRI or PET may be very helpful but cannot account for the whole variability of the data, which seems more complex and needs individual correction factors.

Previous studies aimed at optimizing the PW maps by the use of, for example, the venous output function, the correction by separated measurement of CBV, or by advanced mathematical, or partial volume artifact and bulk-blood corrections. These approaches are highly desired but technically challenging and need further validation. We therefore tested whether the individual variability of flow values could be explained by reference regions that are simple to obtain. We found that the best individual threshold (identified by comparative PET imaging) depends on the mean flow of the contralateral hemisphere. In other words, the estimate of the global flow on PW images well explained the variability of the individual PF threshold values. The linear regression analysis between PET-validated individual PF thresholds and mean values of the unaffected hemisphere on PW imaging maps was good for CBF and MTT and less pronounced for CBV indicating that these modalities benefit from our correction procedure. However, the regression analysis showed the best agreement for TTP. Based on these results, we calculated a (PET-validated) look-up table (Table 2) to derive the best individual PF threshold from the values of the hemispheric reference for each modality.

This finding is remarkable for CBF, CBV, and MTT because these maps have been already processed by deconvolution (see “Materials and Methods”). Our results raise the question whether the deconvolution procedure, although technically correct, eliminates relevant information that could be needed for an exact quantification of PW maps as discussed previously.

Our approach of a PET-based calibration of PW imaging maps differs from a mere MR-based normalization procedure that does not use a reference imaging method and harmonizes the patients flow values by MR data alone. Our approach describes the best available in vivo correction of absolute PW imaging values validated by PET.

In contrast to other studies, we did not propose a further voxelwise postprocessing of the volumetric data set that would result in a rescaling of the PW values. We chose a practical approach to transfer the results into a fast clinical application; the PW maps can be generated according to the current standard using commercially available postprocessing tools (such as, for example, STROKETOOL in our case). Then, the mean value of the contralateral hemispheric ROI has to be assessed. This value will be searched in the look-up table (calibrated by PET data) and the corresponding individual PF threshold for PW imaging maps can be determined.

The benefit of applying an individual threshold instead of an averaged threshold was clear in the visual analysis; the volumes of PF on PW-CBF and PET-CBF became more congruent if processed by individual thresholds. The Bland-Altman analysis confirmed a clear improvement of volumetric congruence comparing PW and PET imaging.

Several limitations of our study have to be discussed. First, our imaging and postprocessing protocol influenced the calculation of absolute values as discussed in detail previously. Second, although this is the largest patient sample of PW imaging compared with quantitative PET in acute stroke, a further validation of our proposed calibration has to be performed in an independent cohort. Third, it has to be kept in mind that the classic PET-CBF threshold of <20 mL/100 g/min only forms part of the penumbra definition, and the additional acquisition and validation of the oxygen extraction fraction and cerebral metabolic rate of oxygen would be desirable to detect the penumbra in future studies. Fourth, our clinical approach did not include a correction of the individual PW imaging values for reasons of feasibility in the clinical setting.

In conclusion, we provided an individual calibration procedure for PW images based on quantitative 15O-water PET. This easy-to-use MR-based and PET-validated calibration improved the detection of PF in the acute stroke setting. We provided individual calibrated thresholds instead of a recalculation of the whole data set. Further work is needed to implement this approach in a standardized PW imaging protocol.

Acknowledgments

We express our gratitude to the members of the neurocritical care unit (Department of Neurology), to the staff of the MRI facility (Department of Neuroradiology), and especially to the staff of the PET unit (Max-Planck-Institute for Neurological Research) for helpful cooperation in this multimodal imaging study. This work was supported by the W.-D. Heiss foundation. We express our gratitude as well to Dr. H.-J. Wittsack, University of Düsseldorf (Department of Radiology), for providing the Stroke-Tool, which was used to calculate the perfusion-weighted images.

Disclosures

None.

References


A Simple Positron Emission Tomography-Based Calibration for Perfusion-Weighted Magnetic Resonance Maps to Optimize Penumbral Flow Detection in Acute Stroke
Olivier Zaro-Weber, Walter Moeller-Hartmann, Wolf-Dieter Heiss and Jan Sobesky

Stroke. 2010;41:1939-1945; originally published online July 29, 2010;
doi: 10.1161/STROKEAHA.110.584029

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/9/1939

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/