The MR perfusion diffusion (PI/DWI) mismatch concept for the selection of patients for intravenous thrombolysis (IVT) was introduced with several smaller case series in the late 1990s and early 2000s, followed by larger series by many international groups over the last 8 years. A potentially salvageable penumbra was operationally defined as a PI/DWI-(volume) mismatch where PI indicates the hypoperfused tissue and DWI shows the more or less severe ischemic core. A mismatch volume of 20% (PI>DWI) has been widely accepted as indicator of a penumbral MRI setting. In an ideal world perfusion postprocessing would provide absolute values for cerebral blood flow (CBF). Perfusion maps could then indicate penumbra based on different thresholds for gray and white matter and thus also take sufficient collateral flow into account. However, absolute CBF values cannot be generated from dynamic susceptibility contrast enhanced PI, and no consensus has been established regarding the optimal perfusion algorithm and mismatch volume threshold.

Three large observational studies using stroke MRI in an extended time window in clinical practice as well as 2 randomized phase II trials—the DIAS and the DEDAS trial—have been published, all showing a better safety and efficacy profile of MRI based treatment despite of later time windows. Only in the small phase 2 trials DIAS and DEDAS, a randomized placebo controlled design was used; the other series were larger but open and used contemporary or historical controls. Other points in favor of stroke MRI are that normal findings in stroke mimics and additional findings, such as early blood brain barrier disruption, microbleeds, leucoaraiosis, and lack of collateral flow may guide treatment decisions leading to further improved patient selection.

Further efforts were undertaken to assess the validity of the PI/DWI mismatch concept with 2 multicenter studies, DEFUSE and EPITHET. DEFUSE, simply stated, shows that mismatch patients benefit from IVT whereas those without mismatch or large DWI lesions do not. Although EPITHET missed the primary outcome (infarct volume reduction in rt-PA–treated patients), trends and significant results were seen for secondary outcomes such as late reperfusion, which again was associated with reduced infarct growth and improved neurological as well as functional outcomes. A pooled analysis of DEFUSE and EPITHET is underway. It must be noted that neither DEFUSE nor EPITHET used PI/DWI-mismatch for patient selection. Patients were selected by noncontrast CT and then received MRI after treatment was initiated.

The first MR mismatch based IVT phase 3 trial—DIAS-2—has not reached the primary end point. From presentations at the European and International Stroke Conferences 2007 and 2008 there are hints that patients with proven vessel occlusion on MR angiography or with MR mismatch volume of >75 cc had a 19% absolute difference in clinical response between placebo and investigational product.

Another facet of MR mismatch lies in improving imaging technique: high-resolution DWI, rapid and harmonized sequence parameters, and postprocessing using the same (imperfect) PI algorithms in all centers. Infarct size measurement should be conducted at adequate window settings (narrow window and low center value) to avoid lesion overestimation. The Japanese Stroke research network for standardization of stroke imaging (http://plaza.umin.ac.jp/~asist/) provided a software platform to calculate MR mismatch in a semiautomated way. The PMA 2.0.9.0 software gives fully automated arterial input function selection and different parameter maps. Whether this approach will pave a way for characterization of the “perfect” penumbra is under investigation.

Until finally a randomized controlled trial is performed, we do continue to recommend MR PI/DWI-mismatch based...
patient selection for thrombolysis as an individual therapeutic approach for patients otherwise not eligible for treatment. Again, we call for an adequately powered study or controlled prospective registry with a sufficient sample size to finally settle this issue once and for all.

Fortes fortuna adiuvat (Fortune favors the brave)
—Latin proverb

Disclosures
P.D.S. is a member of the Boehringer Ingelheim speakers board and received honoraria. J.B.F. is a consultant to Paion, Forest, Lundbeck, and Perceptive and has received honoraria.

References

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MR Mismatch Is Useful for Patient Selection for Thrombolysis: Yes
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