Does Diffusion-Weighted Imaging Represent the Ischemic Core? An Evidence-Based Systematic Review

BACKGROUND AND PURPOSE: Diffusion-weighted imaging (DWI) hyperintensity is hypothesized to represent irreversibly infarcted tissue (ischemic core) in the setting of acute stroke. Measurement of the ischemic core has implications for both prognosis and therapy. We wished to assess the level of evidence in the literature supporting this hypothesis.

MATERIALS AND METHODS: We performed a systematic review of the literature relating to tissue outcomes of DWI hyperintense stroke lesions in humans. The methodologic rigor of studies was evaluated by using criteria set out by the Oxford Centre for Evidence-Based Medicine. Data from individual studies were also analyzed to determine the prevalence of patients demonstrating lesion progression, no change, or lesion regression compared with follow-up imaging.

RESULTS: Limited numbers of highly methodologically rigorous studies (Oxford levels 1 and 2) were available. There was great variability in observed rates of DWI lesion reversal (0%–83%), with a surprisingly high mean rate of DWI lesion reversal (24% of pooled patients). Many studies did not include sufficient data to determine the precise prevalence of DWI lesion growth or reversal.

CONCLUSIONS: The available tissue-outcome evidence supporting the hypothesis that DWI is a surrogate marker for ischemic core in humans is troublingly inconsistent and merits an overall grade D based on the criteria set out by the Oxford Centre for Evidence-Based Medicine.

Identifying threatened but still-viable brain tissue in patients with stroke remains an important goal of acute stroke imaging. Most stroke imaging work to date has focused on characterizing ischemic tissue as nonviable (ie, will not survive with immediate therapy) or as viable (ie, tissue that is salvageable with appropriate therapy). Nonviable ischemic tissue is termed “core,” whereas viable ischemic tissue is termed “penumbra.” There are 2 reasons to measure the extent of core. First, the risk of cerebral hemorrhage from acute revascularization therapy appears to be related to the size of the ischemic core. For this reason, patients with large regions of ischemic tissue suspected of being nonviable core are usually excluded from receiving revascularization therapy. Second, most, but not all, definitions of penumbra (the tissue targeted for therapy) require subtraction of the extent of core from the total ischemic lesion extent. Thus, accurate knowledge of both the total ischemic lesion extent and the core extent is needed to measure penumbra extent accurately. If decisions about providing or withholding therapy are to be based on imaging, the imaging test must accurately discriminate core from penumbra and from nonischemic tissue.

If either in the clinical setting or during clinical research, one attempts to use core–penumbra imaging for patient selection for therapy, there are potentially serious consequences if the measurement of core extent is inaccurate. For example, if an imaging method overestimates core extent, there are potentially 2 negative effects on patient selection. First, patients who could benefit from therapy might be incorrectly excluded from receiving therapy for safety reasons if their lesion size falsely appears to exceed the accepted limit. Second, the extent of penumbra could be underestimated when the overestimated core is subtracted from total ischemic lesion size (eg, the size of the perfusion abnormality). Thus patients who could benefit might also be excluded because of lack of sufficient apparent penumbra, the target tissue. Similarly, if an imaging method underestimates core extent, patients who are unlikely to benefit from therapy, due either to large actual core or small actual penumbra, could be incorrectly selected to receive therapy with its associated risks.

Currently, many investigators consider the MR imaging diffusion-perfusion mismatch (DPM) model to be the most accurate representation of both core and penumbra. According to this model, hyperintense signal intensity on diffusion-weighted imaging (DWI) is hypothesized to represent the extent of ischemic core and the surrounding perfusion abnormality represents the penumbra. Current use of and regard for the DPM model goes beyond merely theoretic considerations, however. Many of the recent ongoing and completed major stroke therapy and imaging trials have DWI in central roles. For example, the presence of mismatch is used as an inclusion criterion in the Desmoteplase in Acute Ischemic Stroke Trial (DIAS), DIAS-2, and Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) trials; large DWI lesions are a reason for exclusion in the ReoPro Retavase Reperfusion of Stroke Safety Study—Imaging Evaluation (ROSIE) trial; and validation of the DPM model is central to the Echo-Planar Imaging Thrombolysis Evaluation Trial (EPITHET), Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution, and MR and Recanalization of Stroke Clots Using Embolectomy (MR-RESCUE) trials. Given the wide use and acceptance of the DPM model, it seems important to assess formally the evidence on which a key component of this hypothesis is based (ie, DWI core). We studied the level of evidence supporting the hypothesis that in human
patients, DWI hyperintensity identifies areas of solely irreversible infarction and thus is a surrogate for the ischemic core in acute stroke. If valid, one would expect most infarct sizes depicted on DWI to be either stable or increased on follow-up imaging. On the basis of this hypothesis and current prevailing views expressed in the literature, we expected DWI reversible lesions to represent a very small minority of observed cases.

Materials and Methods

Studies to Be Evaluated

We performed an evidence-based systematic review of the published human literature concerning tissue outcomes of stroke lesions that were initially hyperintense on DWI and made an assessment of the evidence by using the methods established by the Oxford Centre for Evidence-Based Medicine.13

The search strategy was designed to capture as many studies as possible containing information on the relationship between DWI in the acute stroke setting and final infarct volumes on follow-up imaging. To make the scope of the search as broad as possible, we reviewed studies for possible inclusion regardless of whether determining the relationship between initial DWI lesion volume and final infarct volume was a stated primary goal of the study. Our inclusion criteria were the following: 1) acute stroke presentation in adult humans, 2) DWI performed within 24 hours, 3) follow-up imaging including CT or MR imaging performed at or >24 hours from onset of symptoms, and 4) English language publications. Both prospective and retrospective studies were included. Exclusion criteria included the following: 1) case reports or review articles, 2) evaluation of primarily subcortical stroke or transient ischemic attack, and 3) evaluation of infratentorial stroke.

Search Methodology

The Ovid MEDLINE database was searched on February 28, 2008, with the following strategy:

1. “Cerebrovascular accident” OR “exp cerebral infarction” OR “brain ischemia.”
2. “Diffusion magnetic resonance imaging” OR “diffusion.mp.”
3. Time factors OR exp cohort studies.
4. Numbers 1 AND 2 AND 3.
5. Limited to humans and English language.

All studies in the data base were included in the evaluation regardless of publication date.

Study Quality and Data Analysis

Studies were evaluated for methodologic rigor by using the criteria set forth for diagnostic studies in the Oxford Centre for Evidence-Based Medicine levels of evidence.13 These criteria grade the methodologic rigor of studies from level 1 (systematic reviews, validating cohort studies) to level 5 (expert opinion). The level of evidence for each study was recorded, along with the specific details of the study that led to the assignment of that level.

In addition to the assessment of methodologic rigor, we also collected data tailored to assessment of stroke MR imaging studies, including the number of patients, time to initial MR imaging, time to follow-up imaging, collection of clinical performance data (eg, National Institutes of Health Stroke Scale [NIHSS], modified Rankin Scale [mRS]), and use of thrombolytic therapy, according to a standardized assessment form as detailed in Table 1. Where possible, the exact percentage of patients within a study demonstrating lesion growth or reversal was calculated. Approximately one third of the studies were initially assessed by both reviewers to develop the approach and to establish satisfactory concordance between reviewers. After satisfactory concordance was reached, the remaining studies (two thirds) were assessed by 1 reviewer.

In studies in which there were quantitative data regarding the change in lesion volumes between initial and follow-up studies, patients were stratified into the following 3 categories: progression (patients showing >10% increase in lesion volumes), no change (patients showing <10% increase to <10% decrease in lesion volumes), and reversal (patients showing >10% decrease in lesion volumes). For studies that did not supply individual data points but described lesions qualitatively showing progression, no change, or reversal, patients were stratified according to the definitions included in the study.

Results

The initial MEDLINE search identified 389 studies. On review of the abstracts, 215 were rejected for not satisfying our outlined criteria. The remaining 174 studies, including studies in which satisfaction of inclusion or exclusion criteria was unclear on the basis of abstract review, were submitted to full text review. Of these studies, 61 met all of our criteria and were analyzed.

Studies were grouped according to the degree to which the data allowed determination of exact levels of DWI growth or reversal (Fig 1). These groups do not reflect any particular stratification of methodologic quality or outcomes but rather reflect the degree to which data were available in the individual studies that could be used to evaluate our hypothesis. Because studies were included in the analysis provided they met the inclusion/exclusion criteria and without regard to the original purpose of the study, a sizeable number of studies provided some information on growth but did not present sufficient data to determine exact rates of reversal.

In 18 of the 61 studies (assigned to group A), it was possible to determine the exact prevalence of DWI growth or reversal on the basis of the data provided.14-31 In 8 of 61 studies (assigned to group B), there were limited data indicating that at least 1 patient demonstrated DWI reversal, but it was impossible to calculate the exact number of patients with lesion re-
versal. Of the 8 group B studies, 4 showed evidence of DWI reversal in a subgroup of patients; however, the number of patients in that subgroup was not explicitly stated. Three studies demonstrated evidence of some DWI reversal in figures; however, the absence of numeric data points associated with these graphs precluded precise analysis. One study provided a data range for change in the size of lesions that indicated at least 1 reversal; however it was not possible to determine if >1 reversal occurred. Finally, in 35 of 61 studies (group C), data concerning growth of some lesions was presented, but there was insufficient information provided to determine whether any instances of DWI reversal occurred. Many of these group C studies reported average lesion volumes for initial DWI and final infarct volumes for the study population as a whole but did not include individual data points or make specific comments on the presence or absence of cases of DWI reversal. Because averaging all lesion volumes together could mask instances of reversible lesions, such group C studies could not be used to measure the precise rates of DWI growth and reversal.

The results of the study methodology evaluation by using the Oxford Centre Criteria are presented in Fig 2. No level 1 studies were found in either group A or B. Of the 3 level 1 studies in group C, 2 were designed as therapeutic trials rather than diagnostic trials and the third study was designed to compare CT and MR imaging in the acute setting by using a quantitative scoring system and did not include quantitative lesion volumes at follow-up.

The methodologic details of the group A studies are presented in Table 2. Data concerning DWI lesion growth, stability, or reversal found in group A studies are presented in Table 3. The median rate of DWI reversal (>10% lesion reduction)
was 22%, with a range of 0%–83%. Pooled individual patient data from the 18 studies, comprising a total of 572 patients, revealed a 24% rate of DWI reversal. Approximately half (51%) of pooled patients received either intravenous or intraarterial thrombolytic agents (range, 0%–100%).

Seven of 18 studies (39%) in group A reported rates of tissue reperfusion either from assessment of vessel patency or by using perfusion imaging. Seventeen of 18 studies (94%) collected clinical performance data in the form of the NIHSS, mRS, Barthel Index (BI), or other clinical scales. Thirteen of 18 (72%) studies attempted to correlate the results of clinical performance data with lesion volumes. Only 1 study (6%) attempted to assess the degree of collateral blood flow to the affected area.

### Discussion

DWI has been reported to be a highly sensitive method for imaging cerebral ischemia. Clinical observations and many published reports showing a high correlation between the extent of abnormality on DWI and final stroke volume have encouraged the view that DWI depicts regions of nonviable ischemic tissue. Contrary to this view, however, are published reports showing examples of salvageable ischemic lesions that were seen to be hyperintense on initial DWI. We undertook this study first to assess the level of available evidence in support of the currently prevailing hypothesis that DWI high-signal intensity depicts the extent of nonviable ischemic core and second to measure the reported incidence of DWI lesion reversal, which we expected to be small.

The guidelines of the Oxford Centre for Evidence-Based Medicine on assessing levels of evidence is a widely used system, which grades the methodologic rigor of studies. The inclusion criteria used in our literature search were designed to be broad enough to capture studies with data regarding DWI growth or reversal without regard to the primary purpose of the study itself. This was done to help ensure a comprehensive scope to the review. Our limitation to studies pertaining to acute presentation of supratentorial stroke in adults was designed to target the population of greatest clinical relevance. Because the accepted in vivo standard for the extent of final infarction is lesion size on follow-up T2 volume, true-negative and false-negative results were not part of this evaluation. Thus, sensitivity and specificity calculations are not strictly applicable to this research.

The results of our search revealed a predominance of Oxford Centre level 3 and 4 studies, with few level 2 studies and
no level 1 studies among those from which it was possible to
determine precise tissue outcomes (our group A). The large
number of studies in the level 3 or 4 category reflects the stud-
ies in which consecutive patients were not used, or at least not
specified, and the use of retrospective studies, respectively.
Assigning lower levels of evidence to some studies does not
cast doubt, per se, on the validity of the results for the popu-
lation studied in those particular investigations but rather
raises concern for the degree to which bias might affect the
generalizability of the findings. As such, conclusions drawn
from level 3 and 4 studies must be validated by using methods
less susceptible to bias before being accepted as universally
applicable. The paucity of level 1 and 2 studies of DWI for
prediction of tissue outcome highlights the need for more pro-
spective validating studies using consecutive patients and con-
sistent reference standards.

Despite concerns about the level of available evidence men-
tioned above, the existing evidence shows a substantial inci-
dence (24% of pooled patients) of partial or complete DWI
reversal. Especially notable were a few reported instances of
complete reversal of individual DWI lesions. The cases of par-
tial or complete reversal represent patients for whom the as-
sumption would be invalid that initial diffusion hyperinten-
sity depicts solely regions of irreversible infarction. They also
represent patients who could, in theory, be inappropriately tri-
aged for stroke therapy on the basis of prevailing assumptions.
Given the wide range of reported rates of DWI reversal (0%–
83%) and the high overall prevalence of partial or complete
DWI reversal reported, we question use of DWI as an accurate
surrogate marker for ischemic core for patients with acute
stroke.

Our review of the evidence related to tissue outcomes in
patients with stroke is concordant with the findings from basic
and other types of human investigations of the biochemical
and physiologic environments within DWI hyperintense le-
sions. In animal models of ischemia, it has been shown that
reductions in brain apparent diffusion coefficient (ADC), the
quantitative measure of diffusion abnormality, are reversible
following reperfusion in a temporally dependent manner and
that specific ADC thresholds do not predict tissue fate.77 In-
vestigations of human patients have similarly demonstrated
that absolute ADC thresholds do not predict response to
thrombolysis or tissue fate.78 Investigation of oxygen metabo-
lism in DWI lesions by using 15O-Positron-emission tomog-
raphy by Guadagno et al revealed spatial variability in the
cerebral metabolic rate of oxygen with individual DWI lesions
and considerable variability of oxygen extraction fractions and
cerebral blood flow relationships within single DWI lesions,
ranging from areas with decreased flow relative to oxygen de-
mand (“misery perfusion”) to areas with increased flow rela-
tive to demand (“absolute luxury perfusion”). These findings
contribute to the idea of hyperintense DWI lesions as hetero-
genous regions comprising varying biochemical and meta-
bolic environments, which may be variably amenable to sal-
vage rather than as homogeneous regions of ischemic core
tissue.

Understanding the physical properties that result in DWI
hyperintensity in stroke would be expected to contribute to our
understanding of the meaning and prognostic significance of
these lesions. Decreased ADC values have been observed in
animals following the intracerebral administration of ouabain,
a selective inhibitor of Na+, K+-adenosine triphosphatase,
implicating the failure of energy-dependent ion channels in
the development of DWI hyperintensity.80 Many investigators
have suggested that DWI hyperintensity reflects areas of trap-
ing of intracellular fluid due to failure of these ion channels,
resulting in restricted-motion water in the intracellular com-
partment.80-83 Others have implicated decreased movement of
water molecules in the extracellular compartment.84-86 More-
ever, although clearly ischemia does result in eventual bioen-
ergic failure, the contribution of processes other than energy
failure alone to DWI hyperintensity is supported by the obser-
vation in animals that in early ischemia, the DWI lesion is
initially larger than areas of adenosine triphosphate (ATP) de-
pletion, more closely corresponding to areas of pH alteration
due to anaerobic metabolism in which ATP levels remain rel-
atively preserved.87 At present, the precise etiology of DWI
lesions remains an area of investigation.

A significant limitation of many of the studies we reviewed
was the inability to determine precise rates of DWI growth or
reversal. Many studies reported only a single average change in
lesion volume between initial and follow-up imaging for their
study population as a whole. This limitation was typical of a
significant portion of the studies classified by us as group C.
The reporting of only average lesion sizes has the potential to
hide the results from patients in the numeric minority (eg,
patients with DWI reversal). Moreover, reliance on studies
that report individual data points has the potential to bias the
analysis in favor of studies with smaller study populations, for
which this approach is more feasible. We recommend that
future studies of acute stroke imaging report explicitly their
rates of lesion growth and regression, even if the large size of
their population precludes inclusion of individual patient
data.

We found high variability in the reporting of study infor-
mation specifically related to stroke, such as time to initial
imaging from symptom onset, time to thrombolysis, time to
follow-up imaging, rates of thrombolysis, efficacy of throm-
bolysis, and rates of tissue reperfusion or vessel recanaliza-
tion. Correlation of these variables with rates of DWI growth
and reversal is beyond the scope of the present study; this analysis
is currently underway and will be reported separately. In our
opinion, the most reliable data with regard to imaging of core
and penumbra would be derived from studies of patients with
stroke with documented arterial occlusion who received effec-
tive revascularization in a clinically relevant timeframe (eg,
<6 hours from symptom onset) and in whom the precise time
and degree of reperfusion are known.

In summary, review of the available literature regarding
evolution of DWI lesions in humans revealed limited numbers
of generalizable studies. The available data revealed high vari-
ation in the observed rates of DWI lesion reversibility, the
mean of which was substantial and higher than we expected
(24%). This substantial rate of DWI lesion reversal seems es-
specially notable considering the fact that only approximately
half of the pooled patients received thrombolytic therapy. Fur-
thermore, substantial rates of DWI lesion reversal were seen
in studies with low or no use of thrombolytic therapy.28,29,31 To
make a final assessment, the Oxford Centre for Evidence-
Based Medicine provides grades of recommendations for rat-
ing the overall level of evidence supporting a hypothesis, ranging from a grade A for a well-supported hypothesis to grade D for low levels of evidence or inconsistent results in the literature.13 These grades for final assessment are intended to summarize the evidence for a topic as a whole, and are distinct from the Oxford Centre levels of evidence discussed above, which are used to evaluate the individual papers. Overall, the level of evidence supporting the hypothesis that DWI measures solely ischemic core tissue in human stroke merits a grade D (the lowest grade of evidence) based largely on the highly inconsistent rates of DWI reversal reported in the literature. Because of the substantial incidence of partial or complete DWI reversal seen in our review, we support the modified hypothesis that in the first 24 hours after stroke onset, DWI hyperintensity in human stroke represents a combination of both reversible and irreversible ischemic tissue. Further investigations of high methodologic rigor are needed in this area to determine whether this modified hypothesis can be accepted and when and under what conditions it is appropriate to do so.

Conclusions

The available tissue-outcome evidence supporting the hypothesis that DWI hyperintensity is a surrogate marker for ischemic core is troublingly inconsistent and merits an overall grade D (the lowest grade) based on the criteria set out by the Oxford Centre for Evidence-Based Medicine. Further prospective studies specifically designed to determine whether DWI can discriminate reversible from irreversible ischemia are needed.

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