CT/NIHSS Mismatch for Detection of Salvageable Brain in Acute Stroke Triage Beyond the 3-Hour Time Window

Overrated or Undervalued?

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See related article, pages 2079–2084.

Although the only FDA-approved medical therapy for acute stroke to date remains intravenous tissue plasminogen activator administered within 3 hours of onset, there is increasing evidence that identification of potentially salvageable brain using advanced imaging may facilitate the selection of patients for safe and effective intravascular thrombolysis up to 9 hours postictus. Specifically, the mismatch between infarct core (brain likely to be irreversibly infarcted despite treatment) and ischemic penumbra (hypoperfused brain at risk for infarction in the absence of reperfusion) may identify patients with both a low hemorrhagic risk (small core) and a high likelihood of treatment benefit (large penumbra). In clinical practice, core can be operationally defined using either MR diffusion-weighted imaging (DWI) or CT cerebral blood volume imaging, and penumbra with either MR or CT perfusion-weighted imaging (PWI); conventional unenhanced CT provides a less sensitive measure of core. Because many sites do not currently have access to advanced CT and MR modalities, however, and not all patients are candidates for such scanning even when it is available, there has been interest in using the mismatch between CT hypodensity and clinical NIHSS as a surrogate for radiographic core/penumbra mismatch.

In this issue of Stroke, Messe et al report that, for a community-based cohort of acute stroke patients, CT/NIHSS mismatch “could not be validated as a means to identify ischemic penumbra as defined by MRI diffusion-perfusion mismatch.” MRI mismatch (>25%) was present in 41% of 143 patients scanned 2.5 to 13.9 hours after stroke onset (median, 4.5 hours). Despite an association between mismatch and higher NIHSS scores in univariate analysis, only shorter time-to-scan (P=0.04). These results are important because the major completed clinical trials supporting intravenous thrombolysis beyond 3 hours—Desmoteplase in Acute Ischemic Stroke (DIAS), Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS), Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE), the German Multicenter Trial, as well as trials still underway, including Desmoteplase in Acute Ischemic Stroke 2 (DIAS 2), Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET), ReoPro Retavase Reperfusion of Stroke Safety Study Imaging Evaluation (ROSI), and MR and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE)—have all used DWI/PWI mismatch for patient selection. These results expand on those of an earlier study by Kent et al, which concluded, using a combined database of 2131 patients from 4 major clinical trials of IV thrombolytic therapy, that “clinical-CT mismatch . . . does not reliably identify patients more or less likely to benefit from IV tPA.”

Given these findings, does there remain a potential role for imaging/clinical mismatch when perfusion scanning is neither available nor advisable? For certain highly selected patients with focal clinical syndromes, and for whom DWI, which is more sensitive than CT for overall stroke detection can be obtained, the answer may be a qualified “yes.” In study of 81 consecutive patients with acute-onset aphasia, simple brief tests of oral naming or repetition were successfully used to estimate the PWI lesion and produce a clinical diffusion mismatch score that correlated with short-term language improvement (P<0.02). This suggests that a more sophisticated “location-weighted” scoring system for rating ischemic lesions, one that assigns higher values to critical regions, including language and primary motor areas, might more closely correlate with clinical NIHSS score than a simple volume-weighted system, such as the Alberta Stroke Program Early CT Score (ASPECTS). In a series of 80 patients rated using such an atlas-based approach, volume-based estimates of stroke severity were only moderately correlated with NIHSS (r=0.62), whereas combined volume/location based estimates were significantly better correlated with NIHSS (r=0.79, P<0.03). In another study that used a DWI lesion volume cutoff of 25 mL and an NIHSS cutoff of 8 to define clinical diffusion mismatch, MR diffusion/perfusion mismatch was detected with high specificity (93%) and positive predictive value (95%), but low sensitivity (53%). Subacute infarct growth was higher in those with clinical diffusion mismatch than without (P=0.01). A more recent study had similar success in predicting the risk of early neurological decline (P<0.05). Moreover, an abstract presented at this year’s International Stroke Conference has proposed that “adjusting the definition of clinical-diffusion mismatch to patient deficit severity, rather than applying a fixed threshold to all patients, improves sensitivity and overall accuracy in identifying patients harboring treatable penumbral tissue.” In this investigation, using a severity

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adjusted definition of clinical diffusion mismatch identified
>90% of all stroke patients with salvageable penumbra.

The studies cited above all measured DWI/NIHSS mismatch. Might similar results be possible for some patients using CT/
NIHSS mismatch? It has been estimated that up to 20% of acute
stroke patients are unable to undergo MRI for various reasons.18
Unfortunately, although certain subgroups in both the Messe and
Kent articles displayed a weak trend toward a correlation between
CT/NIHSS mismatch and either MRI mismatch
($P=0.11$ in the third row of Table 2) or intravenous tissue
plasminogen activator benefit ($P=0.08$ in the third row of Table
2),11 attempts to increase specificity by such stratification intro-
duce the possibility of spectral bias.19 As underscored by Messe
et al, because their cases consisted mostly of mild strokes
(median admission NIHSS 4), a larger cohort of exclusively
severe strokes may be required to reveal an association between
CT/NIHSS and DWI/PWI mismatch.

The conclusions of Messe et al are not only in agreement
with those of recent post hoc analyses of major thrombolytic
trials performed within the 3-hour window (including the
NINDS rt-PA study) but also, more importantly, are applica-
ble to patients who presented well beyond 6 hours (25% presented after 14 hours). This is noteworthy because, despite
the fact that the sensitivity of unenhanced CT for stroke
detection more closely approximates that of DWI at these later
points, still no correlation between CT/NIHSS and
DWI/PWI mismatch was observed.

In summary, CT/NIHSS mismatch, compared with MRI
mismatch, does indeed appear to be overrated for the detect-
ion of salvageable penumbra when selecting thrombolysis
candidates beyond a 3-hour window. When PWI is not available or contraindicated, but DWI can be performed, DWI/NIHSS mismatch may be of value for certain patients.

Although many investigators have both advocated CT perfu-
sion imaging as a reliable method for detecting infarct core, and
established thresholds for delineating salvageable penum-
bra,14–18 almost all of the major clinical trials aimed at extending the
time window for thrombolysis have used advanced MR rather than CT imaging for triage. Because CT scanning is
typically faster and more available than is MRI, as these major
trials continue to evolve into a new standard of care, further
validation and standardization is urgently required to determine the
degree to which CT perfusion measures of mismatch are
interchangeable with their MR DWI/PWI counterparts.20

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