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

Michael H. Lev, MD

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 intravenously thrombolytic therapy 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 was associated with MRI mismatch in multivariate analysis (OR, 0.96/hr; P=0.04). These results are important because the major completed clinical trials supporting intravenous thrombolysis up to 9 hours postictus had low sensitivity (53%) 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...
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. 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), attempts to increase specificity by such stratification introduce the possibility of spectral bias. 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 applicable 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 time 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 detection 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 perfusion imaging as a reliable method for detecting infarct core, and established thresholds for delineating salvageable penumbra, almost all of the major clinical trials aimed at extending the time window for thrombolysis have used advanced MR perfusion and angiography and MRI in selecting stroke patients treated with intraarterial therapy. 


Chalela JA, Donnante GA, Butcher KS, Parsons M. Selection of thrombolytic therapy beyond 3 hours using magnetic resonance imaging. 


CT/NIHSS Mismatch for Detection of Salvageable Brain in Acute Stroke Triage Beyond the 3-Hour Time Window: Overrated or Undervalued?
Michael H. Lev

*Stroke*. 2007;38:2028-2029; originally published online May 31, 2007; doi: 10.1161/STROKEAHA.107.488379

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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/38/7/2028