CT Perfusion Imaging of Acute Stroke: The Need for Arrival Time, Delay Insensitive, and Standardized Postprocessing Algorithms?[1]

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Computed tomographic (CT) perfusion imaging has been increasingly advocated as a means of patient selection for advanced treatment of acute stroke and vasospasm but the optimal postprocessing algorithms for defining infarct core (irreversibly dead brain) and ischemic penumbra (at-risk potentially salvageable brain tissue) have yet to be determined. In this issue of *Radiology*, Kudo and colleagues (1) take an important step in the right direction.

The authors postprocessed CT perfusion data from 10 acute stroke patients with major arterial occlusions by using five commercial software packages, each with a different reconstruction algorithm. They compared ischemic lesions on the resulting perfusion maps, not only with the final infarct, but also with maps postprocessed by using in-house software created on the basis of two common deconvolution algorithms. The major difference between these latter two algorithms was in their sensitivity to the hemodynamic effects of delayed contrast tracer arrival time, with one delay-sensitive and one relatively delay-insensitive algorithm. They found that the ischemic lesions defined by the cerebral blood flow (CBF) and mean transit time (MTT) maps varied significantly with the software, whereas those defined by the cerebral blood volume (CBV) maps were relatively invariant. Moreover, the CBF and MTT lesions processed with delay-sensitive algorithms overestimated final infarct size, whereas those derived from delay-insensitive algorithms better matched final infarct size.

This differing performance of the software packages highlights the continued need for validation and standardization of CT perfusion methods in patient selection for novel stroke therapies. The results of the 2008 European Cooperative Acute Stroke Study, for example, which expanded the 3-hour time window for intravenous thrombolysis, revealed that although safe and effective up to 4.5 hours after stroke onset, treatment benefits roughly one-half as many patients as those treated within 3 hours (2,3). Hence, the ratio between the hemorrhagic risk of treatment versus the potential clinical benefit of treatment becomes a more critical consideration as the time window for therapy is expanded with newer intravenous and intra-arterial techniques. It is the mismatch between the size of the infarct core (proportional to hemorrhagic risk) and the size of the ischemic penumbra (proportional to potentially salvageable tissue), as determined by using CT perfusion, that provides an imaging measure of this risk-to-benefit ratio. Evidence suggests that core/penumbra mismatch may persist up to 24 hours in some patients (4,5).

Despite this evidence, some large clinical trials that used mismatch as patient selection criteria, such as the Desmoteplase in Acute Ischemic Stroke (DIAS)-2 study, which used both CT perfusion and magnetic resonance (MR) perfusion up to 9 hours after stroke onset, have failed to show a benefit of treatment (6). In DIAS-2, technical differences between CT perfusion and MR perfusion, including differences between the volume of the brain imaged at different centers as well as the lack of standardization and validation in acquisition and postprocessing protocols, might have contributed, in part, to less-than-optimal patient selection (7). Several other recent studies, however, have indeed underscored the potential of advanced CT perfusion and MR perfusion imaging in extending the therapeutic window for thrombolysis in acute stroke patients. Copen et al (8) reported that persistence of at least 160% mismatch after 9 hours from stroke onset is common and a recent retrospective review of delayed

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endovascular recanalization (>8 hours) in 30 carefully selected patients with mismatch reported a mean improvement of 3.5 points in the National Institutes of Health (NIH) Stroke Scale (9).

Validation and standardization of perfusion methods also requires a stricter definition of penumbra than is currently popular. By using typically accepted cutoffs for MTT and CBF, salvageable ischemic penumbra is currently overestimated by including hypoperfused but otherwise functional brain tissue (benign oligemia) reflecting regions with delay in contrast material arrival time but without significant ischemia, and hence, at low risk for infarction. Olivot et al (10) in a post hoc analysis of data from the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution study (11), helped clarify the time-to-peak (TTP) of residue function threshold level (calculated with delay-sensitive deconvolution software) that most accurately identifies true salvageable penumbra in MR perfusion lesions. They found that the correlation between infarct growth and penumbra salvage volume was significantly better for MR perfusion lesions, defined as having a TTP of more than 6 seconds versus TTP of more than 2 seconds, as was the difference in median penumbra salvage volume in patients with favorable versus an unfavorable clinical response. Data from the Echoplanar Imaging Thrombolytic Evaluation Trial also suggests that a TTP of 4–6 seconds might provide a more realistic estimate of salvageable penumbra (12). These results are in keeping with a study (13) that compared quantitative positron emission tomographic CBF with MR TTP maps in acute ischemic stroke, which suggested that the TTP threshold level is crucial in reliably identifying salvageable penumbra. Low TTP threshold levels included not only regions of salvageable penumbra, but also large portions of normoperfused, benign oligemic tissue. A TTP threshold level of more than 4 seconds best identified true ischemic penumbra. This is relevant because the TTP threshold level of more than 2 seconds has been selected to define MR perfusion lesions in several important studies of mismatch (11,14). Inclusion of benign oligemia in the estimation of salvageable penumbra has the potential to select for treatment without true tissue-at-risk, and hence, not likely to benefit from recanalization therapy beyond 3 hours of stroke onset. Moreover, standardized threshold levels have the advantage of avoiding the use of eyeball technique in penumbral assessment, a particular issue arising from the DIAS-2 trial (15).

The study by Kudo et al (1) therefore represents an important clinical advance in the performance evaluation of commercially available CT perfusion postprocessing software. The authors have demonstrated that software with delay-sensitive deconvolution algorithms overestimate penumbra (ie, MTT or CBF lesion volume), and consequently final infarct volume, whereas penumbra estimated with delay-insensitive software, and/or with software that uses the maximum slope technique, correlates well with final infarct volume. These results highlight the important implications of different deconvolution-based methods. Deconvolution is a mathematic process that removes the effects of the arterial input function (AIF) on the brain tissue time-density concentration curve used to calculate the various perfusion parameters. In practice, AIF is obtained from a major artery (ie, middle cerebral or intracranial internal carotid artery), assuming that *(a)* it represents the only input to the tissue of interest, *(b)* there is no circulatory delay of contrast material, and *(c)* there is no circulatory dispersion of contrast material. AIF delay can be a result of extracranial (including poor left ventricular ejection fraction, atrial fibrillation with poor cardiac output, or critical extracranial internal carotid artery stenosis) or intracranial (intracranial obstructive thrombus/embolism) pathologic features. In cases of intracranial obstructive thrombus, the contrast bolus can spread over multiple collateral pathways, resulting in dispersion. Delay and dispersion can grossly underestimate CBF and overestimate MTT in standard, delay-sensitive deconvolution methods (16–18). The block-circulant decomposition matrix approach removes the causality assumption, part of standard treatment approaches, that the tissue-of-interest signal intensity cannot arrive before the AIF is measured (as can happen if the AIF is obtained from an obstructed vessel). This approach has been shown to be insensitive to circulatory delay with numeric stimulations and clinically acquired MR and/or CT data in patients with cerebrovascular steno-occlusive disease (18–20).

Delay-sensitive methods may also overestimate CBV lesion size (until recently considered as an MR diffusion weighted imaging–like CT measure of infarct core) in patients with concomitant intra- or extracranial severe hemodynamic delay (21). Overestimation of infarct core by using delay-sensitive software could result in underestimation of core/penumbra mismatch, unnecessarily excluding otherwise eligible patients from receiving thrombolytic therapy.

The results of the study by Kudo et al (1) also support the use of the maximum slope method for CT perfusion postprocessing. Indeed, a recent MR imaging study (22) of acute stroke patients reported higher positive predictive values for infarction by using maximum slope–derived parameters (first moment, TTP), versus both delay-sensitive and delay-insensitive deconvolution-derived parameters. These results highlight the delay-insensitive nature of perfusion maps derived from maximum-slope algorithms. At present, however, there remains insufficient evidence to suggest whether maximum-slope methods outperform delay-insensitive deconvolution algorithms.

CT perfusion acquisition optimization is critical for appropriate postprocessing. Optimal acquisition requires scanning for at least 60–75 seconds to allow sufficient time for the first-pass wash-in and washout of contrast material, especially in cases of potential circulatory delay such as carotid occlusion or atrial fibrillation (23). A complete tissue time-density concentration curve is necessary to meet the mathematic assumptions of the deconvolution postprocessing models as closely as possible.

CT perfusion coverage along the z-axis (vertical coverage) is another clinically important acquisition parameter requiring optimization and standardization. A minimum tissue slab coverage of 4–8 cm (to include the entire anterior circulation territory) has been recommended by a large international consensus panel of stroke imaging experts (24,25). This could be accomplished by the administration of at least two contrast boluses for CT scanners with detector widths of less than 4 cm. Alternatively, vertical coverage could be doubled for each bolus by using a shuttle-mode technique in which the scanner table moves back and forth, switching between two cine views, albeit at a reduced temporal resolution (26). With the newest generation of 320 detector–row scanners, 16 cm of z-axis coverage that assesses both the anterior and posterior circulations can be accomplished per cine bolus (27). Results of one study (28) underscored the equivalence of MR and CT perfusion methods in determining mismatch (and hence, in determining patient selection for clinical trial inclusion) only when CT perfusion coverage was sufficient.

Both the recent expert consensus on acute stroke imaging research roadmap (24,25), and the Acute Stroke Imaging Standardization group in Japan (*http://plaza.umin.ac.jp/index-e.htm*), have emphasized the need for standardization of CT perfusion acquisition and optimization and validation of commercially available CT perfusion postprocessing software, especially with regard to the evidence-based assessment of deconvolution and delay-correction techniques. Ultimately, technical development is driven by clinical need, and for perfusion imaging to become a robust clinical application, not only in large tertiary centers but also in smaller community hospitals, organized radiology must demonstrate to hardware/software vendors, as well as to the wider community, added value in the selection of stroke patients for treatment beyond currently accepted time windows. To this end, multidisciplinary collaborative industry/academic efforts are already underway, most notably by the Stroke Imaging Repository group (*http://stir.ninds.nih.gov/html/index.html*), an international consortium of radiologists, stroke neurologists, emergency physicians, NIH and regulatory agency representatives, and major imaging vendors. Organizations such as the American College of Radiology Imaging Network (*http://www.acrin.org*) also have the potential to make important contributions to such efforts. The current study by Kudo et al (1) indeed represents an important early step along the road to defining the role of advanced CT and MR imaging in patient selection for novel stroke therapies.

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