MR Imaging of Oxygen Extraction and Neurovascular Coupling

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Since the approval of tissue-type plasminogen activator (tPA) for the treatment of acute ischemic stroke by the Food and Drug Administration, the search for means to identify patients who may benefit from this treatment beyond the approved therapeutic window has been actively pursued. One of the most successful examples is the European Cooperative Acute Stroke Study III (ECASS III) trial, which demonstrated that efficacy of tPA treatment could be extended from the original 3 hours to 4.5 hours from onset. In addition, with an accumulating arsenal of mechanical clot retrieval devices, promising to achieve more effective reperfusion than intravenous-tPA, it is likely that the therapeutic windows for these retrieval devices will differ from that of intravenous-tPA. Different collateral flow patterns, comorbidities, and intrinsic tissue vulnerabilities among individual patients further complicate the use of a fixed therapeutic time-window for all patients and different treatments. Therefore, insights into brain tissue viability at the time of presentation may aid in the management of acute stroke.

Toward this end, imaging approaches have been actively sought to provide a potential signature for tissue viability. Specifically, the diffusion/perfusion mismatch (DPM) concept has been widely advocated as a potential approach to depict the presence or absence of ischemic penumbra. The underlying hypothesis is that lesions defined by abnormal diffusion most likely reflect irreversible injury, whereas regions defined by abnormal perfusion represent critically hypoperfused tissue. The region of DPM with normal diffusion but abnormal perfusion is, in theory, the region at risk of evolving to infarction if reperfusion-promoting therapies are not administered. Although the overall hypothesis of DPM is straightforward and diffusion weighted images (DWI) and perfusion-weighted images (PWI) are readily available, the means by which DWI and PWI lesions are defined vary widely, leading to potentially inconsistent results among groups with the use of DPM to predict outcomes.

For example, the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 (DEFUSE-2) investigators proposed a set of criteria for defining DPM, termed target DPM, based on observations of DWI lesion growth and clinical outcome in patients undergoing intra-arterial therapy for acute hemispheric stroke. However, the observations of the acute reversal of DWI lesions and the failure of all diffusion lesions to evolve to infarction suggest that the presumption that all DWI-defined lesions truly reflect the irreversibly damaged ischemic core may be invalid. Similarly, it has been difficult to define specific thresholds for PWI that differentiate tissue that is mildly hypoperfused but not in danger of infarction from tissue that is critically hypoperfused and will go on to die quickly if not reperfused. Therefore, a more direct means to assess tissue viability using imaging may improve our ability to stratify patients for individualized treatment.

Positron emission tomography (PET)–measured cerebral metabolic rate of oxygen use is capable of discerning brain tissue viability in both transient and permanent middle cerebral artery occlusion primate models. However, the need for an onsite cyclotron as well as access to an arterial line for quantitative measures have largely limited the clinical usability of PET, particularly for imaging patients with acute stroke. Alternatively, using blood oxygen level-dependent contrast and a signal model proposed by Yablonskiy and Haacke, our group has developed an MR-based approach for obtaining quantitative measures of cerebral blood oxygen extraction fraction (MR_OEF). Extensive validation studies have been performed in animal models and in human volunteers. With animals exposed to different levels of gas challenges to induce a physiologically relevant range of cerebral oxygen extraction, MR_OEF shows highly accurate results when directly compared with blood samples taken from the jugular vein. In addition, normal volunteer studies have confirmed that MR measured OEF values in humans under normal physiological conditions are consistent with that reported using PET; OEF is decreased in response to hypercapnic challenge in humans, which agrees with the expected physiological response.

With the ability to noninvasively measure OEF using MRI, an index of cerebral metabolic rate of oxygen use (MR_OMI) is derived as MR_OEF × cerebral blood flow, where cerebral blood flow can be readily obtained using either the dynamic susceptibility contrast or arterial spin labeling approaches. Although the intrinsic differences between PET cerebral metabolic rate of oxygen and MR_OMI...
prevent a direct comparison of absolute values, evidence suggests that the MR_OMI is a physiological parameter closely related to PET-measured cerebral metabolic rate of oxygen, with all of the inherent advantages of using MRI rather than PET. Specifically, MR_OMI reveals that the oxygen use in gray matter is 2× higher than that in the white matter, consistent with that reported in the PET literature. Furthermore, with a rat middle cerebral artery occlusion model, MR_OMI reveals spatiotemporal changes of oxygen metabolism during acute ischemia consistent with PET studies in nonhuman primates and, more importantly, severe reductions of MR_OMI are highly predictive of final infarction. Here, we report our results on the use of MR_OMI in delineating the ischemic penumbra in patients with acute ischemic stroke. A total of 41 patients with acute ischemic stroke were imaged at 3.0 hours (tp1), 6.2 hours (tp2), and 1 month (tp3) after symptom onset. Dynamic susceptibility contrast and asymmetry spin echo measured cerebral blood flow and OEF, respectively. Some patients received intravenous tPA, which was started before and continued during tp1 imaging without delaying treatment. Images from the same subjects, but acquired at different time points, were coregistered.

Figure provides examples of MR_OMI illustrating its ability to provide information on spatiotemporal dynamics of lesion progression in 4 representative clinical cases. Here, we compare MR_OMI with the widely used DWI/PWI approaches. Specifically, Figure A and B show 2 patients, both with DWI/PWI-matched lesions throughout tp1 and tp2. Based on the notion of DPM, the presence of DWI/PWI-matched lesions implies little salvagable tissue at the time of imaging. Indeed, all 3 imaging approaches (DWI/PWI/MR_OMI) exhibit similar information showing a stable lesion in Figure A, which is highly consistent with the final infarction. However, although DWI and PWI again provide a similar representation of an ischemic lesion at both tp1 and tp2 in Figure B, MR_OMI reveals a continuous worsening of the ischemic lesion from tp1 to tp2 (circles), suggesting that viable tissue may exist at tp1, but it evolves to final infarction because reperfusion was not accomplished. In contrast to the first 2 examples, Figure C and D show 2 other patients, both with DPM lesions. As suggested by the concept of DPM, early reperfusion of the mismatched region may salvage reversibly injured tissue, whereas no reperfusion would result in infarction of the mismatched region. Consistent with this premise, the reperfused region (Figure C, arrow) did not evolve into infarction, and again DWI/PWI/MR_OMI provide similar information characterizing the ischemic lesion and are consistent with the final lesion. However, although early reperfusion is not observed in Figure D, MR_OMI shows a rather stable lesion during both tp1 and tp2, which is more consistent with the final lesion than that provided by DWI/PWI. Together, although qualitatively, the above examples suggest that the MR_OMI may provide more underlying...
metabolic insights and more faithfully depict tissue viability than that of DPM.

To further determine the effectiveness of MR_OMI in delineating the ischemic penumbra, a quantitative study was performed. Our analysis approach postulates an ideal case in which 2 MR_OMI threshold values could be obtained to bracket the ischemic penumbra: one threshold would distinguish ischemic core from penumbra (Thr1); the other threshold would distinguish penumbra from oligemia (Thr2) such that core, penumbra, and oligemia are defined as MR_OMIcore>Thr1, Thr1<MR_OMIpenumbra<Thr2, and MR_OMIoligemia>Thr2. With this assumption, voxels classified as core should all die (100% infarct probability [IP]), whereas voxels defined as oligemia should all survive (IP=0%), both independent of whether or not reperfusion occurs. In contrast, the final fate of voxels in the ischemic penumbra should vary depending on the presence or absence of reperfusion; if reperfusion is achieved (similar to Figure C), all reperfused penumbra should survive (IP=0%), whereas all nonreperfused penumbra should die (IP=100%). To this end, normalized MR_OMI (nMR_OMI) within gray and white matter was obtained by separately normalizing their MR_OMI to the median MR_OMI of the contralateral hemisphere gray and white matter, respectively. In addition, prolonged mean transit time (MTT), defined as the difference of MTT in the ipsilateral hemisphere from the median MTT of the contralateral hemisphere, was used to determine the presence or absence of reperfusion. Specifically, a voxel with prolonged MTT at tp1>4 seconds and prolonged MTT at tp2>4 seconds was considered to have been hypoperfused then reperfused. Subsequently, a search method was used to determine an optimal pair of Thr1 and Thr2 for each patient by minimizing the average prediction error, defined as the average differences for each tissue group’s actual IP from the ideal IP (Table). The predictive abilities of the thresholds were tested in the same cohort using leave-one-out cross-validation, and the average prediction error averaged across the population. The core/penumbra OMI threshold and the penumbra/oligemia OMI threshold ranged from 0.24 to 0.28 and 0.42 to 0.44 in individual patients, respectively. The median IPs (interquartile range) for the 4 tissue groups are shown (Table). The population-averaged average prediction error was 11.4% (2.69%, 21%). Our results show the robustness of the MR_OMI in predicting the final fate of ischemic tissue. Although 90.6% of the core evolved to infarction, only 6.28% of oligemic tissue was infarcted. More importantly, MR_OMI also demonstrated its ability to delineate penumbra, by predicting reperfusion-dependent tissue fate: IP=9.95% with reperfusion and IP=89.7% without reperfusion. These findings support the predictive value of MR_OMI. Nevertheless, definitive conclusions regarding the true clinical utility of MR_OMI will need to be evaluated with a prospective study using clinical outcomes.

In summary, we have provided evidence for the ability of MR_OMI to delineate the ischemic penumbra. The validity of this tissue categorization is revealed by its ability to predict final tissue fate in the presence or absence of reperfusion with a low error rate. Although these findings are promising, a larger multisite prospective study to evaluate the clinical usability of MR_OMI systematically in patients with acute ischemic stroke is needed. If these results are validated in a larger study, MR_OMI may provide a physiological alternative to our current time–based therapeutic window for identifying patients for acute therapeutic interventions.

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Disclosures
None.

References

Table. Averaged Infarct Probability with optimal MR_OMI thresholds

<table>
<thead>
<tr>
<th>Reperfusion Status</th>
<th>Core</th>
<th>Penumbra</th>
<th>Oligemia</th>
<th>APE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonreperfused</td>
<td>IP=90.6% (61.5%, 97.7%)</td>
<td>IP=89.7% (78%, 95.2%)</td>
<td>IP=6.28% (1.72%, 14.0%)</td>
<td>11.4% (2.69%, 21.0%)</td>
</tr>
<tr>
<td>Reperefused</td>
<td>IP=9.95% (0.33%, 28.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APE indicates average prediction error; and IP, infarct probability.

*APE=[((100%−IPcore)+(100%−IPpenumbra_nonreperfused)+(IPpenumbra_reperfused−0%)+(IPoligemia−0%))/4]

Key Words: acute stroke ■ cerebral oxygen ■ ischemic penumbra metabolism ■ MRI ■ neuroimaging
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