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MR IMAGING OF OXYGEN EXTRACTION AND NEUROVASCULAR COUPLING

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Since the FDA's approval of tPA for the treatment of acute ischemic stroke [1], 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 ECASS III (European Cooperative Acute Stroke Study III) trial [2, 3], which demonstrated efficacy of tPA treatment could be extended from the original 3hrs to 4.5hrs from onset. In addition, with an accumulating arsenal of mechanical clot retrieval devices promising to achieve more effective reperfusion than IV-tPA[4–6], it is likely that the therapeutic windows for these retrieval devices will differ from that of IV-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 potentially provide a signature for tissue viability [7]. Specifically, the diffusion/perfusion mismatch (DPM) concept has been widely advocated as a potential approach to depict the presence or absence of ischemic "penumbra" [8–10]. The underlying hypothesis is that lesions defined by abnormal diffusion most likely reflect irreversible injury while 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. While 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 DEFUSE-2 investigators[11] propose 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 (IA) 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 [12, 13]. 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

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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 utilization ($CMRO_2$) is capable of discerning brain tissue viability in both transient and permanent middle cerebral artery occlusion (MCAO) primate models [14]. However, the need for an onsite cyclotron as well as access to an arterial line for quantitative measures have largely limited the clinical utility of PET, particularly for imaging acute stroke patients. Alternatively, using blood oxygen level dependent (BOLD) contrast and a signal model proposed by Yablonskiy and Haacke [15], our group has developed an MR-based approach for obtaining quantitative measures of cerebral blood oxygen extraction fraction (MR_OEF) [16–20]. Extensive validation studies have been conducted, in animal models [19] and in human volunteers [16, 18]. 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 to blood samples taken from the internal jugular vein[19]. 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[18, 20].

With the ability to non-invasively measure OEF using MRI, an index of cerebral metabolic rate of oxygen utilization (MR_OMI) is derived as MR_OEF x cerebral blood flow (CBF) [21–23] where CBF can be readily obtained using either the dynamic susceptibility contrast and/or arterial spin labeling approaches. Although the intrinsic differences between PET $CMRO_2$ 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 CMRO2, with all of the inherent advantages of using MRI rather than PET. Specifically, MR_OMI reveals that the oxygen utilization in gray matter is two times higher than that in the white matter, consistent with that reported in the PET literature[21]. Furthermore, with a rat MCAO model, MR_OMI reveals spatiotemporal changes of oxygen metabolism during acute ischemia consistent with PET studies in non-human primates and more importantly, severe reductions of MR_OMI are highly predictive of final infarction[19]. Here, we report our results on the utilization of MR_OMI in delineating the ischemic penumbra in acute ischemic stroke patients. A total of 38 acute ischemic stroke patients were imaged at 3.0 hr (tp1), 6.2 hr (tp2), and 1 month (tp3) after symptom onset. Dynamic susceptibility contrast and asymmetry spin echo measured CBF and OEF, respectively. Some patients received intravenous tPA, which was started prior to and continued during tp1 imaging without delaying treatment. Images from the same subjects but acquired at different time points were co-registered.

Fig 1 provides examples of MR_OMI illustrating its ability to provide information on spatiotemporal dynamics of lesion progression in four representative clinical cases. Here we compare MR_OMI with the widely used DWI/PWI approaches. Specifically, Fig 1a and Fig 1b show two 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 salvageable tissue at the time of imaging. Indeed, all three imaging approaches (DWI/PWI/MR_OMI) exhibit similar information showing a stable lesion in Fig. 1a, 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 Fig. 1b, 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 since reperfusion was not accomplished. In contrast to the first two examples, Fig. 1c and Fig. 1d show two 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 (Fig. 1c, 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 Fig. 1d, 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 conducted. Our analysis approach postulates an ideal case in which two MR_OMI threshold values could be obtained to bracket the ischemic penumbra: One threshold would distinguish ischemic core from penumbra (Thr1); a second threshold would distinguish penumbra from oligemia (Thr2) such that core, penumbra, and oligemia are defined as $MR\_OMI_{core} < Thr1$, $Thr1 < MR\_OMI_{penumbra} < Thr2$, and $MR\_OMI_{oligemia} > Thr2$. With this assumption, voxels classified as core should all die (100% infarct probability (IP)) while 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 area should vary depending on the presence or absence of reperfusion; if reperfusion is achieved (similar to Fig. 1c), all reperfused penumbra should survive (IP=0%) whereas all non-reperfused penumbra should die (IP=100%)[24]. 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 MTT (pMTT), 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 pMTT at tp1 >4 sec and pMTT at tp2 < 4sec 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 (APE)”, 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 APE averaged across the population. The core/penumbra OMI threshold and the penumbra/oligemia OMI threshold ranged from 0.21–0.22 and 0.41–0.43 in individual patients, respectively. The median IP’s [IQR] for the 4 tissue groups are shown (Table). The population averaged APE was 15% [5%, 24%]. Our results show the robustness of the MR_OMI in predicting the final fate of ischemic tissue. 91.6% of the core evolved to infarction while only 4.5% of oligemic tissue was infarcted. More importantly, MR_OMI also demonstrated its ability to delineate penumbra, by predicting reperfusion-dependent tissue fate: IP=6.8% with reperfusion and IP=73.6% 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. While these findings are promising, a larger multi-site prospective study to systematically evaluate the clinical utility of MR_OMI in acute ischemic stroke patients is needed. If these results are validated in a larger study, MR-OMI may provide a physiological alternative to our current time-based therapeutic time-window for identifying patients for acute therapeutic interventions.

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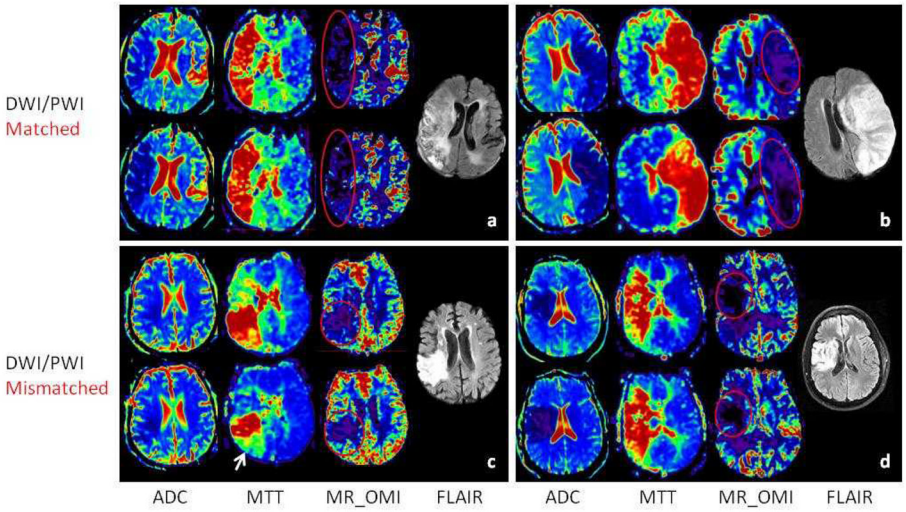

Fig. 1.

Four examples of acute lesion evolution characterized by DWI, PWI and MR_OMI are provided. Specifically, **a** and **b** show two patients with DWI/PWI matched lesions throughout both tp1 and tp2 whereas **c** and **d** provide two examples of DPM lesions, respectively. Patient shown in **a** received tPA at 2:09hrs and tp1 and 2 imaging at 2:40hrs and 6:20hrs from onset, respectively. Patient in **b** did not receive tPA due to secondary increase of BP and seizure. The time of imaging for tp1 and tp2 was 4:30hrs and 6:45hrs from onset, respectively. Please note that the FLAIR of this patient was acquired 72hrs after onset, showing edema and the resulted midline shift and thus may not represent the true extend of final infarction. Patient in **c** received tPA at 1:37hrs and time of imaging at 1:58hrs and 6:05hrs for tp1 and tp2 from onset, respectively. Finally, **d** shows a patient who received tPA at 1:19hrs and imaged at 2:10hrs and 6:28hrs after onset, respectively.

TABLE

Reperfusion Status	Core	Penumbra	Oligemia	APE†
Non-reperfused	IP = 91.6% [76%, 97%]	IP = 73.6% [55%, 96%]	IP = 4.5% [2.9%, 13%]	15% [5%, 24%]
Reperfused		IP = 6.8% [3.1%, 42%]		

† **Average Prediction Error (APE) =** $[(100\% - IP_{core}) + (100\% - IP_{penumbra\_non\text{-}reperfused}) + (IP_{penumbra\_reperfused} - 0\%) + (IP_{oligemia} - 0\%)] / 4$