Oxygen Imaging by MRI
Can Blood Oxygen Level-Dependent Imaging Depict the Ischemic Penumbra?

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Mapping the ischemic penumbra (ie, the neurophysiologically silent but still viable ischemic tissue) is increasingly part of routine assessment in suspected acute stroke, although whether this approach is cost-effective is still unclear.1,2 The penumbra is characterized by both low cerebral blood flow (CBF; <20 mL · 100 g⁻¹ · min⁻¹) and elevated oxygen extraction fraction (OEF).3 The latter is considered a critical marker of tissue viability and is therefore a key imaging target. The penumbra was originally documented in humans using positron emission tomography (PET),2,3 a validated method to map CBF, and clinical metabolic rate of oxygen (CMRO₂),4 but clinical access to PET is scarce. Consequently, MR-based diffusion and perfusion imaging (PWI) and CT-based perfusion imaging are widely used as substitutes.1 However, both methods have limitations for penumbra imaging2 and do not directly assess oxygen metabolism.

A method combining the advantages of MR and the ability to map OEF would therefore be highly desirable. Blood oxygen level-dependent (BOLD) imaging has recently emerged as a possible candidate for this purpose. However, several BOLD techniques with different levels of validation, accuracy, and clinical applicability are in concurrent development, making the situation somewhat confusing. This review aims to clarify whether BOLD imaging might be of use to map oxygen in the clinical setting. We systematically review and critically discuss all studies published to date in the English language, both experimental and clinical, that have applied BOLD in acute stroke. Because our focus is tissue oxygen metabolism, we do not address the T₂*-weighted method to visualize leptomeningeal vessels,5 the mapping of ΔCMRO₂ during physiological challenges,6 or the emerging ¹⁷Ο imaging method.7

Principles of BOLD MRI
Oxyhemoglobin is diamagnetic, whereas deoxyhemoglobin (DHb) is paramagnetic. Transverse relaxation is sensitive to paramagnetic substances such as DHb,8 hence the acronym BOLD. Because high OEF results in increased DHb concentration in the end-capillaries and venules,9 it should be detectable using BOLD. Equation 1 describes the fraction of DHb (χDHb) in the microvasculature:¹⁰

\[ \chi_{DHb} = 1 - s_{O_2} \cdot m \cdot OEF \cdot s_{O_2} \]

where \( s_{O_2} \) represents the oxygen saturation in arterial blood and \( m \) the fraction of oxygen extracted at a given point of the vascular bed. Assuming a linear oxygen extraction along the latter, theoretical maximum average \( m \) is 0.5, that is, under extreme ischemic conditions, \( m=0 \) at the arteriole and \( m=1 \) at the venule level (ie, \( s_{O_2}=0 \)). The OEF is closely related to CMRO₂, CBF, and the oxygen content of blood by Equation 2. The oxygen content of blood is typically approximately 18 mL O₂/100 mL and is the product of the hemoglobin level, \( s_{O_2} \), and oxygen-binding capacity (approximately 1.36 mL O₂/g hemoglobin).

\[ \text{OEF} = \frac{\text{CMRO}_2}{\text{CBF} \cdot s_{\text{O}_2}} \]

Thus, in situations of maximum OEF and optimal SaO₂, \( \chi_{DHb} \) tends to its maximum of 50%. It follows that penumbra tissue should be detectable by DHb-sensitive imaging. A rise in \( \chi_{DHb} \) will lead to a drop in signal intensity on images sensitive to transverse relaxation and affected tissues will appear hypointense.

Experimental and Clinical Acute Stroke Studies Using BOLD MRI Techniques
A detailed account of each study appears in the online-only Data Supplement, and only summaries are presented here. Experimental studies are only reviewed in the present review if focal ischemia or controlled cerebral hypoperfusion was induced.
T2 Blood Oxygen Level-Dependent Imaging

T2 sequences are sensitive to a rise in \( \Delta \text{DHb} \). Although the signal drop is distinct, it is very small (a few percent). Hahn-echo sequences yield greater signal reduction than Carr Purcell Meibloom Gill multiple echoes, and spin-echo sequences show a smaller signal reduction than gradient echo sequences.

Six experimental and 1 clinical study have been published using T2, none relevant since 2001 (online-only Data Supplement Table I). The former consistently showed a variable drop of T2 value immediately after vessel occlusion, up to 10% depending on field strength. This was followed 30 to 60 minutes later by a steady T2 increase due to vasogenic edema within the ischemic core or if CBF fell <30 mL \( \cdot \text{g}^{-1} \cdot \text{min}^{-1} \) (determined with the \( \text{H}_2 \) clearance method), whereas T2 remained low within the noninfarcted penumbral or mildly hyperperfused areas. In the clinical study, \( \text{T2}^* \) hypointense lesions adjacent to the subcortical core were observed, possibly representing cortical penumbra.

\( \text{T2}^* \)

\( \text{T2}^* \) is 3- to 5-fold more sensitive to BOLD-related changes than T2, even at lower field strengths. Apart from scanning under baseline conditions, breathing challenges have been used to enhance the sensitivity of \( \text{T2}^* \) imaging to depict the penumbra.

\( \text{T2}^* \) in Baseline Conditions

Two experimental and 4 clinical reports using \( \text{T2}^* \) (including prebolus arrival scans from PWI) have been published (online-only Data Supplement Table II). In the former, a \( \text{T2}^* \) drop of up to 8% was consistently seen, even at low fields. This was followed 1 to 2 hours later by a gradual increase in \( \text{T2}^* \), similar to the increase in T2 described previously and also due to vasogenic edema. The clinical studies reported inconsistent results, and low \( \text{T2}^* \) in the appropriate area has been observed in only a handful of patients despite the widespread use of PWI. This may partly reflect the particular sensitivity of \( \text{T2}^* \) to vasogenic edema. Systemic hypoxia during scanning may facilitate identification of \( \text{T2}^* \). The reported lack of agreement with PET-derived OEF further suggests prebolus arrival \( \text{T2}^* \) may not have adequate sensitivity.

\( \text{T2}^* \) With Breathing Challenge

Five percent \( \text{CO}_2 \), a vasodilatory stimulus widely used to test cerebrovascular reactivity, increases oxygen supply relative to demand and hence induces decreases in \( \text{DHb} \) concentration. It is speculated that under this challenge only viable tissue, but not damaged tissue, will exhibit \( \text{T2}^* \) increase, because cerebrovascular reactivity is abolished in the latter only. In some experimental studies, an anoxic challenge was used instead, the hypothesis being that oxygenated tissue will display a \( \text{T2}^* \) drop in comparison to preanoxic images, whereas already damaged tissue will not. Another sort of challenge is to deliver normobaric 100% oxygen (oxygen challenge \( \text{OFC} \)), the hypothesis here being that viable (penumbral) tissue will avidly take up the extra oxygen supplied, in turn increasing the pre-OC reduced \( \text{T2}^* \) signal as compared with core and oligemia.

Eleven experimental studies have used \( \text{T2}^* \) with breathing challenge (online-only Data Supplement Table III). During anoxic challenge, image intensity in \( \text{T2}^* \)-weighted images significantly dropped in the core, penumbra, and healthy tissue, but these changes could not clearly differentiate these tissue types without the information from diffusion-weighted imaging. \( \text{CO}_2 \) challenge induced no signal change in the ischemic core, whereas both the penumbra and healthy tissue displayed a signal increase, which again could not be well differentiated with \( \text{T2}^* \) weighting alone. In contrast, OC induced a larger \( \text{T2}^* \)-weighted image intensity increase within the penumbra than in the other tissue compartments and seemingly allowed it to be differentiated from both the core and healthy tissue. A 40% OC provided sufficient signal change at the same time as avoiding some unwanted effects of 100%, particularly on blood pressure. The findings using OC have been validated against autoradiographic \( \text{C-2-deoxyglucose mapping} \). Two clinical studies, both using OC, which has greater clinical applicability, have been published so far. The results supported some potential for penumbra mapping suggesting this method could be widely applied in the clinical setting, although with some caveats (see “Discussion”).

\( \text{T2}^* \) Blood Oxygen Level-Dependent Imaging

\( \text{T2}^* \) is equivalent to \( \text{T2}^* \) with the major difference that it is corrected for the spin–spin T2 effects that develop within hours due to vasogenic edema. \( \text{T2}^* \) and \( \text{T2}^* \) are linked through Equation 3. Note that this method requires generating \( \text{T2}^* \) and \( \text{T2}^* \) maps followed by their voxel-based inversion and subtraction.

\[
\frac{1}{\text{T2}^*} = \frac{1}{\text{T2}} - \frac{\text{T2}}{\text{T2}^*} \quad \text{(with } \frac{1}{\text{T2}} = \text{R2'})
\]

\( \text{T2}^* \) imaging has been used in 3 experimental studies and 3 clinical studies thus far (online-only Data Supplement Table IV). Normative values for \( \text{T2}^* \) in humans and rats have also been reported. Experimentally, \( \text{T2}^* \) was generally found to be decreased in the penumbra and, as expected, provided clearer findings than \( \text{T2}^* \). In the clinical studies, \( \text{T2}^* \) maps showed low signal in affected hemisphere areas expected to have high OEF (Figure). Furthermore, the \( \text{T2}^* \) lesion appeared to predict diffusion-weighted imaging lesion growth better than PWI. However, quantitative analyses did not show the expected significant differences among tissue compartments, whereas the \( \text{T2}^* \) maps obtained in the clinical setting were noisy and artifacted and their visual assessment moderately reproducible.

Magnetic Resonance CMRO2

In this approach, a 2-dimensional multiecho gradient-echo/spin-echo sequence is used to derive \( s_2 \text{O2} \) from \( \text{R2}^* \) and the venous blood volume fraction and in turn OEF. Relative \( \text{CMRO}_2 \) is then estimated by multiplying OEF by CBF (derived from standard PWI). Estimates of \( s_2 \text{O2} \) with this method have been experimentally validated against blood
oximetry obtained in the cerebral venous sinuses. One experimental and 1 clinical stroke studies have been published so far (online-only Data Supplement Table V). In both studies, MR-CMRO₂ provided meaningful images and relative CMRO₂ estimates that agreed well with the PET literature.

Discussion
The experimental and clinical literature reviewed infers that as predicted, all technical variants of BOLD MRI are able to detect elevated OEF as reduced intensity on T2 and T2* images. However, several factors common to essentially all BOLD techniques dim this apparent success. First, as discussed, vasogenic edema may develop as early as 2 hours after occlusion and obliterate the OEF-related changes, although it can theoretically be corrected using T2/H₁ imaging. Second, local hematocrit may drop in low-flow areas and lead to an overestimation of OEF. Third, as further discussed subsequently, changes in cerebral blood volume that occur in stroke also influence the BOLD signal. Finally, decreased perfusion pressure slightly increases precapillary oxygen loss, altering the constant m in Equation 1. Although some of these issues may be partly circumvented by carrying out side-to-side comparisons, doing so gives up absolute quantification.

Although T2 BOLD can in principle pick up T2 changes of a few percent, parenchymal T2 hypointensities have so far been reported in 1 clinical article of 9 patients only. There are 2 main reasons for this: (1) T2 relaxation is field strength-dependent and most experimental reports have used very high fields that are not clinically available yet; and (2) the absolute T2 changes are very small, and clinically available sequences might not be sensitive enough. It is thus questionable if this technique will ever translate to the clinical setting.

In contrast, the T2* effect is in principle detectable at clinically available field strengths, yet the convincing T2* changes reported in animal studies are rarely reported in humans, and the 1 study testing T2* against PET found no correlation with OEF. Apart from T2* susceptibility artifacts, for example, on the brain surface, and artifacts from by magnetic field inhomogeneity, obliteration of T2* by early vasogenic edema probably largely explains this discrepancy, because clinical MR is rarely started within the first hour after symptom onset. A more promising alternative may therefore be T2’, which corrects for such spin–spin effects.

T2* imaging with anoxic challenge appears to enable differentiation of core, penumbra, and healthy tissue better than CO₂ breathing does, but neither is likely to ever have clinical application in stroke because both endanger the highly oxygen-dependent penumbra. In comparison, OC ap-
pears promising because it seems to differentiate penumbra from core, although perhaps less efficiently from oligemia as well, and is clinically applicable. However, several aspects of the method still need to be addressed and might confound its reliability. Particularly, the induced T2* changes are small in humans (approximately 2%), and the changes in OEF induced by hyperoxia can be difficult to disentangle from other effects that also cause T2* changes, namely (1) CBF increases in ischemic tissue; (2) hypercapnia; (3) local changes in hematoctrit; and (4) local changes in cerebral blood volume, especially because cerebral blood volume may be elevated in penumbra, locally increasing the apparent response to OC due to a higher concentration of DHb. In addition, in this method, OC is delivered to the subject for diagnostic purposes, yet normobaric hyperoxia may influence the fate of the penumbra. Nevertheless, the T2* OC method clearly deserves further investigations.

The T2* method has shown potential in delineating hypoxic tissue although its ability to differentiate core, penumbra, and oligemia has not been clearly demonstrated. Preliminary clinical results show the expected signal changes and a reasonably good match with hypoperfusion and final infarct and T2* may actually depict the penumbra better than PWI.

However, T2* is characterized by substantial image noise (Figure) because even small changes in T2* and T2 can lead to large changes in computed T2* (Equation 3). Furthermore, T2*-weighted images are prone to substantial distortions, introducing additional errors. Although acquisition time for T2* is not particularly long, head motion can lead to misalignment of the T2* images and hence additional T2* noise. These drawbacks probably explain the reported modest interobserver agreement, which in turn calls into question the method’s robustness for clinical applications, although deeper training in image reading might improve detection of artifacts and distortions. Regardless, this technique is clearly worth further investment.

To date, 1 group only has published on the use of MR CMRO2, and <20 patients have been reported since it first appeared in 2003. Calculated relative CMRO2 for tissue at risk has been in agreement with historical PET data in both rodents and humans, lending support to the validity of the method. However, absolute quantification of OEF and CMRO2 still appears elusive, and the MR sequence used to estimate OEF suffers from poor signal-to-noise ratio. In addition, quantification of CBF with PWI is notoriously difficult, which together with the risk for misalignment of OEF with CBF images may introduce additional errors in CMRO2 estimates. Finally, based on the images published so far, the spatial resolution of the method appears limited.

So far, indirect validation has been reported against the H2 clearance CBF method,14,16 14C-2-deoxyglucose autoradiography,23 and sinus vein oxymetry47 for T2 BOLD, T2* with OC and MR CMRO2, respectively, and only the prebolus T2* technique has been directly compared with PET.23 However, back-to-back PET and MR in hyperacute stroke is extremely challenging, and accordingly scans in the latter study were acquired relatively late after stroke. Novel “hybrid” PET/MR systems, which allow simultaneous acquisition of both modalities, may prove useful in this respect. In any scenario, however, validation of hyperacute BOLD against PET will remain challenging, even in animal models. Thus, although using nonhuman primates would be optimal with 15O-PET,6 these models are extremely cumbersome and expensive and raise ethical issues. 15O-PET is feasible in rodents57 but is hampered by poor spatial resolution due to the highly energetic 15O positron. Alternatively, a PET hypoxia tracer such as 18F-fluoromisonidazole could be considered, but it has specific drawbacks.58

Conclusions

Although T2 mapping was successfully used in animal studies and indirectly validated, its clinical translation is unlikely due to small signal at clinically available fields. T2*-weighted imaging has proven unreliable in acute stroke, including poor correlation with PET, probably from contamination by early vasogenic edema. T2' mapping corrects for this effect and seems promising but appears limited by image noise and processing artifacts. T2*-weighted imaging with anoxic challenge or CO2 breathing is of experimental interest but clinical applications are unlikely. MR CMRO2 is in principle attractive but has methodological issues and has not been formally validated. T2*-weighted imaging with OC has yielded particularly interesting and promising results, but its signal may be affected by cerebral blood volume changes and formal validation is still missing, whereas its clinical value and applicability remain uncertain. Overall, therefore, BOLD MRI is promising to depict the penumbra but still requires formal validation and, although still difficult to predict, is unlikely to replace diffusion-weighted/PWI for clinical applications, at least in the near future.

Acknowledgments

We thank T.A. Carpenter, PhD, for editing the article.

Sources of Funding

U.J.-K. is supported by the Deutsche Forschungsgemeinschaft (DFG Je 598/1-1).

Disclosures

None.

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**KEY WORDS:** oxygen extraction fraction, T2* stroke
Oxygen Imaging by MRI: Can Blood Oxygen Level-Dependent Imaging Depict the Ischemic Penumbra?
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Stroke. 2012;43:2264-2269; originally published online May 15, 2012;
doi: 10.1161/STROKEAHA.111.632455

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/43/8/2264

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Results

1. T2 BOLD (Supplemental Table 1)

Experimental studies

Van der Toorn and coworkers\(^1\) produced the first evidence for T2 BOLD in acute experimental ischemia. They permanently occluded the MCA (pMCAo)\(^2\) in cats and performed sequential MRI. They a priori defined three voxels in which they measured T2; one within the presumed ischemic core and two within the penumbra. They found a slight T2 drop during the first hour followed by a steady increase until 9hrs. Both changes were similar in the core and the penumbra. The authors concluded that T2 drops within the first hours but increases when vasogenic edema develops.

In a subsequent study\(^3\), rats were examined. Six received distal pMCAo, and 12 transient MCAo (tMCAo). Six of the latter animals were breathing spontaneously, and the rest were ventilated to control pCO\(_2\). In the distal pMCAo model a permanent reduction of T2 in an area significantly exceeding the small infarct was found. In the spontaneously breathing tMCAO animals an initial T2 drop within the ischemic core was found, which later normalized and exceeded the baseline values when vasogenic edema developed. Outside the core, T2 values stayed low throughout the experiment and matched areas with impaired perfusion. In the ventilated animals there was a reduction of T2 during the first 35 min, which increased afterwards in all areas finally progressing towards infarction (as determined by late structural T2). In a subsequent experiment, the same group\(^4\) induced tMCAo or distal pMCAo in rats; hypoperfusion was determined by PWI, vasogenic edema by late structural T2, and infarction by histology. In line with the previous study, T2 decreased by \(~7\%\) within the hypoperfused but not infarcted areas. In the tMCAo group no shortening but a steady
increase of T2 was found and matched the areas of vasogenic edema. From these two studies the authors concluded that hypoperfusion induces a reduction of T2 of ~7-10% which is followed by steady increase when vasogenic edema develops in the infarct core. It remains low in tissue that does not progress towards infarction but remains hypoperfused.

Calamante and coworkers\textsuperscript{5} could demonstrate T2 changes in rats subjected to pMCAo; ASL perfusion and DWI were used to characterize tissue types. Multiple echo sequences were used to measure T2. There was a marked T2 drop in areas both defined as “severely affected” and “moderately affected” ~1 min after the occlusion. In the ischemic core, T2 rose steadily after the initial drop. Within the moderately affected tissue there was a normalisation after 30-60 min, followed by a steady signal increase. Thus, this study replicated at 8.5 T the results of Gröhn et al.\textsuperscript{3}.

Gröhn and coworkers\textsuperscript{6} could demonstrate a U-shaped dependency of T2 values on CBF. They used a model of misery perfusion which allowed a graded reduction of CBF in rats. They found the lowest T2 values between 15 and 60 \% CBF reduction were the curve reaches a depression. When it fell below the threshold of 30 ml/100g/min, T2 increased again. They concluded that beyond these CBF values CMRO\textsubscript{2} is so severely compromised that tissue does not extract oxygen anymore, consistent with PET\textsuperscript{7,8}

Finally, Kavec and coworkers\textsuperscript{9} demonstrated shortened T2 in a rat model of misery perfusion. They found a 6 \% drop of T2, thereby reproducing the above-described findings at 9.4 T and 4.7 T. Importantly, no infarct as defined by DWI was found. The authors concluded that the BOLD effect is discernible at 1.5 T.

Clinical study

As of today, only one report on human stroke has been published. Ida and coworkers\textsuperscript{10} reported on nine patients with acute cortical stroke who presented with adjacent subcortical hypointense lesions on T2. They concluded that this might represent cortical penumbra.
2.2. T2* BOLD

2.2.1. T2* BOLD in baseline conditions (Supplemental Table 2)

Experimental studies

The first data from T2* BOLD in cerebral ischemia were reported by de Crespigny and coworkers\textsuperscript{11}. They performed tMCAo in cats. Immediately after occlusion T2* dropped by up to 8 % and remained low until the occlusion was released. Upon reperfusion the signal displayed an overshoot. This was explained by tissue hyperoxygenation due to reactive hyperemia\textsuperscript{12}. No DWI lesion was detected so the authors concluded that the signal drop was indeed caused by increased DHb concentration.

Roussel and coworkers\textsuperscript{13} performed pMCAo in rats and acquired T2* and DWI sequences. Similar to de Crespigny et al.\textsuperscript{11}, T2* dropped by 5-7 % upon occlusion. When DWI changes became visible at 30 min, the T2* hypointense lesion was significantly larger than the DWI lesion. After the first 1-2hrs, T2* began to increase beyond the baseline value within the DWI lesion whereas outside it T2* remained low. After terminal anoxia was induced, a 15% T2* drop in the whole brain with the exception of the ischemic core was observed. After that the signal returned to baseline. They explained the T2* drop with the inflow of fully deoxygenated blood, and the return to baseline with progressive heart failure and subsequent decreased CBV. The authors conclude that T2* is able to distinguish between hypoperfused and normal tissue, and with the help of DWI even between core and penumbra.

Clinical studies

Tamura and coworkers\textsuperscript{14} retrospectively evaluated the prebolus arrival images of PWI for hypointensities. They included six patients with large vessel occlusion (MCA or ICA) within 4hrs of symptom onset. In five of them, two independent neuroradiologists found hypointense regions highly consistent with the side of the vascular occlusion. The stroke volumes assessed by follow up imaging were
statistically not different from the hypointense T2* lesions volume. They concluded that T2* might detect increased OEF.

Wardlaw and von Heijne\textsuperscript{15} reported on a single patient who displayed a hypointensity exceeding the DWI lesion on the T2* prebolus arrival images. A CT scan performed 10 min later showed early ischemic signs in that area. Interestingly, the patient inadvertently experienced a drop in oxygen saturation which lasted throughout the scan. This case resembles the experimental and clinical studies described below where tissue at risk of infarction was demonstrated by introducing an anoxic challenge. The authors concluded that T2*-weighted images may have a role in identifying tissue at risk.

Morita and coworkers\textsuperscript{16} examined the presence of parenchymal T2* hypointensity in 24 patients with MCA or ICA occlusion within 12 hrs of symptom onset. Inter-observer agreement was good. This sign was present in 14 patients, which was consistent with asymmetry on perfusion imaging in a subset of 17 patients. The authors concluded that this sign might be a marker of severe ischemia.

Donswijk and coworkers\textsuperscript{17} tested the validity of prebolus arrival T2* imaging against quantitative $^{15}$O$_2$ PET using back-to-back MR and PET in five patients with carotid artery stroke within 21 hrs of onset. ROIs of high OEF on PET and low T2* on MR were drawn by two independent observers. No correlation between OEF and T2* ratios was found and the interobserver agreement was very poor. It was concluded that T2* is not sensitive to increased OEF.

2.2.2. T2* BOLD with breathing challenge (Supplemental Table 3)

Experimental studies

De Crespigny et al.\textsuperscript{18} used the same experimental protocol as before\textsuperscript{11}, but additionally introducing apnea. Upon vessel occlusion, hypointensity in T2*-weighted imaging developed as expected, but when apnoea was initiated there was no change in the ischemic core whereas a drop off in normal white grey matter took place. The partially ischemic tissue, defined as hypoperfused tissue without DWI change,
behaved like healthy tissue, with the difference that a delayed and extended signal recovery and overshoot occurred upon reperfusion. The authors concluded that introducing an anoxic challenge might offer information about the metabolic state of tissue.

Jones et al.\textsuperscript{19} compared T2* with PWI in rats subjected to tMCAO. Animals were scanned at several time points throughout 2hrs of ischemia and 90mins of reperfusion. During the gradient echo sequences an anoxic challenge was introduced. The signal intensity change was assessed as $\Delta R2*$ between anoxic and postanoxic values. To account for preanoxic signal offset which is lost in this calculation, this was additionally compared with the contralateral side. Marked differences were found between ischemic and non-ischemic tissue. The latter displayed pronounced $\Delta R2*$ rises during anoxia, and marked and delayed postanoxic $\Delta R2*$ drops. No difference was found between severely and moderately ischemic tissues. Concerning the preanoxic phase, the ischemic core showed decreased signal intensity compared to moderately ischemic tissue 15min after vessel occlusion. Ten minutes after reperfusion the signal in severely ischemic tissue normalised whereas there was a transient increase in moderately ischemic tissue. This was explained by increased OEF in the core before vasogenic edema had developed, and increased CBF in the surrounding penumbra. The authors concluded that BOLD imaging did not add additional information to PWI.

Dijkhuizen and coworkers\textsuperscript{20} conducted a similar experiment. They performed T2*-weighted imaging 25 min after pMCAo during which they introduced a 60s anoxic challenge. In the DWI lesion the signal decrease was significantly lower as compared with still viable but not infarcted and contralateral regions. They concluded that the anoxic challenge can reveal residual flow, i. e. penumbra.

Ono et al\textsuperscript{21} subjected rats to pMCAo or tMCAo. They introduced CO\textsubscript{2} breathing during which signal intensity was assessed. In areas finally infarcted based on DWI and histology, no significant change in T2* was found. In healthy areas and areas which temporarily became hypoxic, the signal increase was 4-6 %. The authors concluded that CO\textsubscript{2} reactivity can indicate tissue viability.
Harris et al.\textsuperscript{22} performed complete and partial\textsuperscript{23} pMCAo in rats. At 2.35 T they performed continuous T2* during vessel occlusion and CO\textsubscript{2} reactivity testing. They defined four distinct areas with a combination of ADC changes and CO\textsubscript{2} reactivity. In the complete occlusion group they found 1) reduced ADC and no reactivity in the ischemic core; and 2) reduced ADC and retained CO\textsubscript{2} reactivity in a so-called border zone. Interestingly, the core region was smaller than the region with reduced ADC. In the partial occlusion group they found 1) normal ADC and retained reactivity; and 2) normal ADC and no reactivity.

Santosh et al.\textsuperscript{24} introduced an oxygen challenge (OC) by breathing 100\% oxygen during the acquisition of T2*-weighted images. In rats subjected to pMCAo they demonstrate a significant increase in T2* within the mismatch zone, as opposed to no significant change in the core and a two-fold smaller increase in the contralateral hemisphere.

This finding was further validated\textsuperscript{25} using concomitant \textsuperscript{14}C-2-deoxyglucose autoradiography. Glucose utilization was below detection levels in the core, as opposed to unchanged values in the penumbra compared to unaffected tissue. This was matched by a signal decrease and a substantial T2* increase, respectively.

To avoid the detrimental effects of OC, Baskerville and coworkers compared 100 \% OC with 40 \% OC\textsuperscript{26}. In rats they separately examined pO\textsubscript{2} and CBF and signal change during OC. They found a significant increase in pO\textsubscript{2} and CBF in penumbral tissue with 100 \% OC. They also found a significant increase in blood pressure with 100 \% OC. The signal changes were significantly smaller with 40 \% OC but the three tissue compartments (penumbra, core, unaffected) could still be reliably separated. In conclusion, 40 \% OC provided sufficient signal change while avoiding unwanted effects of 100 \%.

Robertson and coworkers also tried to validate OC based on the consequences after reperfusion\textsuperscript{27}. They induced tMCAo in rats and performed OC during occlusion, directly after and seven days after reperfusion. They found a significant drop in signal change in the penumbra right after reperfusion while signal behaviour of core and normal tissue did not change. After seven days the previously penumbral tissue did
not behave differently than unaffected tissue and appeared normal on T2-weighted scans. In ischemic core there was a significant signal drop compared to normal tissue.

Recently, these results have been replicated by another group who could demonstrate a significant difference between core, penumbra and oligemia during OC.

Clinical studies

Dani et al. acquired T2*-weighted images during OC in 25 patients with acute ischemic stroke at median 18hrs of onset. There was a significantly reduced response within the DWI lesion as compared to healthy tissue, whereas a trend towards larger responses was seen within the penumbra.

Dani and coworkers examined the influence of other factors on the signal behaviours of T2* during OC. CBV, T_max and ADC were analyzed in 12 patients within voxels of unaffected tissue, DWI-lesion, reperfused DWI-lesion and DWI-PWI-mismatch using multivariate analysis. They found that CBV and ADC were independently predictive of signal behavior. The authors concluded that OEF accounts for much of the unexplained variance.

In conclusion, T2* imaging with an oxygen challenge could distinguish between metabolically active and inactive tissue and could provide a more precise assessment of the penumbra.

3.5. T2’ BOLD (Supplemental Table 4)

Experimental studies

In rats with tMCAo studied, Grüne et al. produced ΔR2’ maps, i.e. subtracted pre and post occlusion R2’ maps where hypoxygenated areas appear hyperintense. They reported an additional value of R2’ in comparison to T2*, PWI, and DWI maps. The ΔR2’ maps could demonstrate areas of putatively increased OEF more clearly than the R2* maps which were blurred by vasogenic edema. Different
patterns of altered oxygenation were observed which could not be appreciated on the other MR maps. They concluded that ΔR2'-maps delivered information on oxygenation that were not available from other parametric maps.

Jensen and coworkers\textsuperscript{32} investigated the behavior of T2' after reperfusion. Low T2' was present within hypoperfused DWI lesions, whereas high T2' values were found within hyperperfused DWI lesions. These observations are consistent with the assumption of the presence of deoxyhemoglobin in the nonperfused ischemic core and excessive but futile oxygen supply in severely damaged but reperfused tissue.

Zhang et al.\textsuperscript{33} induced 1hr tMCAo in monkeys. DWI, PWI and R2' were acquired during vessel occlusion, and repeatedly after reperfusion for 48hrs. Three regions were defined: core (irreversible DWI lesion), penumbra (reversible DWI lesion) and oligemia (MTT lesion). The MRI-defined core was consistent with histology. R2' showed a sharp initial drop within the core and stayed low even after reperfusion. Within the penumbra and oligemia they observed an initial increase followed by a plateau after 6-24hrs and a secondary increase after 24hrs. The paradoxical signal decrease within the ischemic core as opposed to the findings by Geisler and coworkers\textsuperscript{34} was explained by the different definition of core used, and possible inclusion of penumbra into the core, in that study\textsuperscript{34}.

Clinical studies

Geisler and coworkers published the first study employing this technique in stroke patients within 6hrs of onset\textsuperscript{34}. They obtained DWI, TTP maps and T2' maps. Follow-up imaging was performed to depict final infarct. In several patients they observed the presence of reduced T2' on the side and vascular territory appropriate to the clinical symptoms and overlapping with the perfusion abnormalities, the pattern of which was suggestive of OEF increase. Three regions were defined: the initial DWI lesion, lesion growth and surviving tissue. However, the ROIs were manually outlined and not objectively defined. T2' values were significantly lower in all three regions when compared to corresponding contralateral tissue, with no significant differences between the three. A signal increase was expected within the infarct core which is supposed to show low OEF. They explained the observed signal drop within the core.
by two phenomena 1) severely compromised CBF hampers effective DHb removal; and 2) the presence of some penumbra within DWI lesions. Despite these inconsistencies, the authors concluded that T2’ may offer information on oxygen utilization and provide a better estimation of the penumbra.

In a subsequent study, Fiehler and coworkers\(^3\) evaluated the visual assessment of the T2’ lesion in 20 patients using the same inclusion criteria and imaging protocol. Two independent observers, blinded to clinical details, identified the side of the T2’ lesion. This was rated correct in 80 and 50%, incorrect in 5 and 40% and not visible in 15 and 10% by readers 1 and 2, respectively. Interobserver agreement was only fair. The T2’ lesion was smaller than the DWI lesion in 20 %, equal in 30 % and larger in 50 %. The OR for infarct growth was 3.5. It was concluded that T2’ may be sensitive to infarct growth, but that the T2’ lesion can be difficult to assess visually.

In a larger study from the same group, Siemonsen and coworkers\(^3\) examined 100 patients, again using the same inclusion criteria and imaging protocol. Two independent observers blinded to clinical details assessed whether the T2’ lesion or the TTP lesion exceeded the initial DWI lesion. The OR for lesion growth was consistently better for T2’. The authors concluded that T2’ is a more specific predictor for lesion growth than TTP maps, but again with moderate inter-observer agreement.

2.3. MR-CMRO\(_2\) (Supplemental Table 6)

All studies on MR defined CMRO\(_2\) in acute stroke so far, either experimental or clinical, have been reported by a single group. They termed it OMI, MR_OMI, MR_COMI, or MR-CMRO\(_2\); for convenience, we will use the latter term in the following.

Experimental studies

An and coworkers\(^3\) simultaneously performed blood oximetry in the superior sagittal sinus and jugular vein in rats and estimated \(s_vO_2\) by MRI in the whole brain over a wide range of blood oxygenations. They found a very good correlation between
the two. Additionally, in another set of rats, 90min tMCAo was performed. They acquired serial MR-CMRO₂ every 15mins until reperfusion and structural T2-weighted images 24hrs later. MRI perfusion was performed immediately before reperfusion. MR-CMRO₂ was found to be significantly lower within the final infarct, and decreased over time in agreement with impaired oxygen metabolism and previous PET studies. The degree of reduction of relative CMRO₂ in the ischemic core was similar to historical PET values.

Clinical studies

Lee and coworkers³⁸ examined six patients within 4.5 ± 0.9hrs of symptom onset. The imaging protocol included DWI, PWI and a multi-echo gradient echo/spin echo sequence encompassing the center of the DWI lesion to obtain an estimation of the OEF. The DWI and MTT lesions were delineated by comparison with the contralateral hemisphere. Acute-stage MR-CMRO₂ was determined within the final infarct depicted at 3-month follow-up imaging. Compared to the contralateral hemisphere, a ratio of 0.4 ± 0.24 was found within the final infarct, as compared to 0.55 ± 0.11 within the DWI-PWI mismatch (statistical significance not reported), consistent with values derived from PET³⁹-⁴¹.

An et al³⁷ employed MR-CMRO₂ in six acute stroke patients (five received rtPA) in sequential MRI at 3 h and 6 h additionally to MTT and DWI and a FLAIR at one month. While the PWI-lesion was consistently larger, the DWI lesion was either smaller or larger than the final infarct. Only MR-CMRO₂ exactly displayed the final infarct, regardless of reperfusion status. Dead tissue at one month consistently had a low MR-CMRO₂.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Species</th>
<th>Field strength</th>
<th>Vessel occlusion</th>
<th>Reference method</th>
<th>Results (absolute T2)</th>
<th>Conclusion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Toorn et al., 1994$^1$</td>
<td>Cats (n=8)</td>
<td>4.7 T</td>
<td>MCA ligature</td>
<td>DWI</td>
<td>60.0 ± 0.7 ms (control) 2.2 ± 0.5 ms (initial drop) 5.2 ± 1 ms (secondary increase)</td>
<td>T2 drops within the first hour and then increases.</td>
<td>No significant difference between core and penumbra.</td>
</tr>
<tr>
<td>Gröhn et al., 1998$^3$</td>
<td>Rats (n=6/12)</td>
<td>9.4 T</td>
<td>pMCAo tMCAo</td>
<td>FI (T2) PWI</td>
<td>35.9 ± 0.8/0.4 ms (control) ~3.5 ms drop (hypoperfused areas) 36.2 ± 0.5/35.9 ± 0.7 ms (controls) 1.5-3.5 ms drop, then increase</td>
<td>Hypoperfusion induces T2 reduction; within core T2 increase when edema develops.</td>
<td>Core and penumbra can be differentiated.</td>
</tr>
<tr>
<td>Gröhn et al., 1999$^4$</td>
<td>Rats (n=7/5)</td>
<td>4.7 T</td>
<td>tMCAo pMCAo</td>
<td>FI (T2) Histology PWI</td>
<td>50.2 ± 0.3 ms (control) 3.5 ± 0.9 ms (drop) Steady increase in core</td>
<td>Hypoperfusion induces T2 reduction.</td>
<td>Replication of Gröhn et al., 1998 at 4.7 T.</td>
</tr>
<tr>
<td>Calamante et al., 1999$^5$</td>
<td>Rats (n=10)</td>
<td>8.5 T</td>
<td>pMCAo</td>
<td>DWI ASL</td>
<td>40.7 ± 0.5/42.5 ± 0.9 ms (control) Rapid initial drop, then increase</td>
<td>T2 drops immediately after occlusion, then increases when edema develops.</td>
<td>• Signal drop not quantified  • Core and penumbra could be differentiated</td>
</tr>
<tr>
<td>Gröhn et al., 2000$^6$</td>
<td>Rats (n=26)</td>
<td>4.7 T</td>
<td>Bilateral VA occlusion, graded CCA occlusion</td>
<td>H$_2$-clearance DWI</td>
<td>T2 50.5 ± 1.5 ms (in normal CBF) Drop of 2.5-2.8 ms with CBF reduction of 15-60%; rises with further CBF decrease</td>
<td>U-shaped dependence of T2 on CBF</td>
<td>Results in agreement with PET.</td>
</tr>
<tr>
<td>Kavec et al., 2001$^9$</td>
<td>Rats (n=18)</td>
<td>1.5 T</td>
<td>Modified 3-vessel occlusion</td>
<td>H$_2$-clearance DWI</td>
<td>Maximum drop from 66.9 ± 0.4 to 64.7 ± 7.1 ms</td>
<td>Hypoperfusion causes decreases in T2</td>
<td>1.5 T is clinically available.</td>
</tr>
<tr>
<td>Ida et al., 1994$^{10}$</td>
<td>Human (n=9)</td>
<td>1.5 T</td>
<td>Acute stroke</td>
<td>Nil</td>
<td>subcortical T2 hypointensity</td>
<td>Penumbral (?) tissue can appear hypointense in acute cortical stroke.</td>
<td>Only study describing this phenomenon in humans.</td>
</tr>
</tbody>
</table>

**Table 1**: Studies (experimental and clinical) using T2 BOLD MRI.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Species</th>
<th>Field strength</th>
<th>Vessel occlusion</th>
<th>Reference method</th>
<th>Results</th>
<th>Conclusion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Crespigny et al., 1992&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Cats (n=4)</td>
<td>4.7 T</td>
<td>tMCAo occlusion</td>
<td>DWI</td>
<td>T2* drop seconds after occlusion; overshoot after reperfusion</td>
<td>T2* drop detectable.</td>
<td>Duration of overshoot dependent on occlusion duration</td>
</tr>
<tr>
<td>Roussel et al., 1995&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Rats (n=6)</td>
<td>2.35 T</td>
<td>pMCAo</td>
<td>DWI</td>
<td>T2* drop, exceeding the infarct core, then signal increase in core</td>
<td>T2* drop in core and penumbra, increase in core after 1-2 hours.</td>
<td>Core and penumbra can be differentiated.</td>
</tr>
<tr>
<td>Tamura et al., 2002&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Human (n=6)</td>
<td>3 T</td>
<td>Acute stroke</td>
<td>DWI PWI FI (MRI/CT)</td>
<td>Hypointense area in occluded vessel’s territory</td>
<td>Hypointense area on prebolus T2* consistent with side of occlusion</td>
<td>Prebolus T2* are always available from PWI but rarely reviewed.</td>
</tr>
<tr>
<td>Wardlaw and von Heijne, 2006&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Human (n=1)</td>
<td>N/A</td>
<td>Acute stroke</td>
<td>DWI FI (CT)</td>
<td>Hypointense area exceeding DWI lesion</td>
<td>Hypointense area presumably penumbra</td>
<td>Patient experienced SaO₂ drop during scan.</td>
</tr>
<tr>
<td>Morita et al., 2008&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Human (n=24)</td>
<td>3 T</td>
<td>Acute stroke</td>
<td>DWI FAIR-ASL</td>
<td>Area of hypointense parenchyma coincides with lower perfusion.</td>
<td>Hypointense parenchyma coincides with lower perfusion.</td>
<td>Combination of vessel and parenchymal signs, vessel signs more consistently seen.</td>
</tr>
<tr>
<td>Donswijk et al., 2009&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Human (n=5)</td>
<td>3 T</td>
<td>Acute stroke</td>
<td>¹⁵O PET</td>
<td>T2* vs OEF correlation: R² = 0.02 Poor interobserver agreement.</td>
<td>No correlation between OEF determined by ¹⁵O PET and T2*</td>
<td>Only correlation study with true OEF</td>
</tr>
</tbody>
</table>

**Table 2:** Studies (experimental and clinical) using T2* BOLD MRI without a breathing challenge.

MCA: middle cerebral artery, FAIR-ASL: Flow-sensitive alternating inversion recovery arterial spin labeling, OEF: oxygen extraction fraction
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Species</th>
<th>Field strength</th>
<th>Vessel occlusion</th>
<th>Reference method</th>
<th>Results</th>
<th>Conclusion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Crespigny et al., 1993&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Cats (n=9)</td>
<td>2 T</td>
<td>tMCAo</td>
<td>DWI PWI</td>
<td>T2* drop in normal and partially ischemic brain, no change in core. Partially ischemic brain shows delayed and extended overshoot.</td>
<td>The three regions behave differently on T2* images with anoxic challenge</td>
<td>• Core, penumbra and normal tissue can be differentiated. • Anoxic challenge</td>
</tr>
<tr>
<td>Jones et al., 1996&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Rats (n=7)</td>
<td>2.35 T</td>
<td>tMCAo</td>
<td>PWI</td>
<td>Only ischemic and non ischemic tissue could be differentiated.</td>
<td>No additional value compared to PWI.</td>
<td>• Possible differentiation of core and penumbra at 15 min ischemia. • Anoxic challenge.</td>
</tr>
<tr>
<td>Dijhuizen et al., 1997&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Rats (n=6)</td>
<td>4.7 T</td>
<td>pMCAo</td>
<td>DWI PWI</td>
<td>T2* drop in core, penumbra and healthy tissue: 6.1 ± 3 % to 7.8 ± 2.5, 12.7 ± 5.2 % to 17.1 ± 10.1 % and 21.5 ± 4 % to 28.5 ± 4.5 %, respectively</td>
<td>Enhanced T2* drop within viable tissue.</td>
<td>Anoxic challenge</td>
</tr>
<tr>
<td>Ono et al., 1997&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Rats (n=5/9)</td>
<td>2 T</td>
<td>pMCAo tMCAo</td>
<td>DWI Histology</td>
<td>T2* increase on CO₂ breathing, no change in infarct.</td>
<td>Viable tissue shows CO₂ reactivity.</td>
<td>• Penumbra and healthy tissue could not be differentiated. • CO₂ challenge</td>
</tr>
<tr>
<td>Harris et al., 2001&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Rats (n=7/8)</td>
<td>2.35 T</td>
<td>Complete and incomplete pMCAo</td>
<td>DWI</td>
<td>Four regions: DWI lesion with/without CO₂ reactivity, normal DWI with/without CO₂ reactivity</td>
<td>Partly CO₂ reactivity in ischemic core, partly absent in penumbra</td>
<td>• Heterogeneity of tissue is demonstrated. • CO₂ challenge</td>
</tr>
<tr>
<td>Santosh et al., 2008&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Rats (n=10)</td>
<td>7 T</td>
<td>pMCAo</td>
<td>DWI ASL Histology</td>
<td>3.7 ± 1.4 % T2* increase in penumbra, no significant changes in core (0.24 ± 0.42 %); and 1.8 ± 0.68 % in contralateral hemisphere</td>
<td>T2* increase in penumbra during oxygen challenge as opposed to other regions.</td>
<td>Oxygen challenge</td>
</tr>
</tbody>
</table>

**Table 3**: Studies (experimental and clinical) using T2* BOLD MRI with a breathing challenge.
<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>T</th>
<th>T2* Method</th>
<th>Imaging</th>
<th>Findings</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robertson et al., 2011&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Rats (n=6)</td>
<td>7</td>
<td>pMCAo</td>
<td>14C-2-DG auto-radiography DWI PWI</td>
<td>Glucose utilization below detection in the core but unchanged in penumbra, correlating with increases in T2* of -0.49 % and 9.2 %, respectively.</td>
<td>See above</td>
</tr>
<tr>
<td>Shen et al., 2011&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Rats (n=8)</td>
<td>7</td>
<td>pMCAo</td>
<td>DWI ASL</td>
<td>Significant difference in signal increase between core, penumbra and oligemia</td>
<td>Replication of data by the Glasgow group</td>
</tr>
<tr>
<td>Baskerville et al., 2011&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Rats (n=25)</td>
<td>7</td>
<td>pMCAo</td>
<td>DWI ASL Histology</td>
<td>10 % CBF increase, 64 % pO2 and 60 % MABP increase with 100 % OC T2* in penumbra (%) 4.56 ± 1.61 vs. 8.65 ± 3.66</td>
<td>40 % OC is sufficient for diagnostic use</td>
</tr>
<tr>
<td>Robertson et al, 2011&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Rats (n=8)</td>
<td>7</td>
<td>tMCAo</td>
<td>DWI ASL</td>
<td>T2* increase in penumbra: 8.4 ± 4.1 vs. 3.25 ± 0.81 % No difference after reperfusion.</td>
<td>OC can reliably detect penumbra</td>
</tr>
<tr>
<td>Dani et al., 2010&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Human (n=25)</td>
<td>3</td>
<td>Acute stroke</td>
<td>DWI PWI</td>
<td>T2* increase: 1.1 ± 1.1 % (core) 2.4 ± 2.2 % (penumbra) 1.7 ± 0.6 to 2.3 ± 0.8 % (healthy tissue)</td>
<td>See above</td>
</tr>
<tr>
<td>Dani et al., 2011&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Human (n=12)</td>
<td>N/A</td>
<td>Acute Stroke</td>
<td>DWI PWI</td>
<td>Multivariate analysis: ( r ) (CBV) = 0.2, ( p &lt; 0.0001 ) ( r ) (ADC) = 0.1, ( p &lt; 0.0001 ) ( R^2 = 7.2 % )</td>
<td>OEF is responsible for much of the remaining variance.</td>
</tr>
</tbody>
</table>

Table 3 (continued): Studies (experimental and clinical) using T2* BOLD MRI with a breathing challenge. N/A: not applicable.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Species</th>
<th>Field strength</th>
<th>Vessel occlusion</th>
<th>Reference method</th>
<th>Results</th>
<th>Conclusion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grüne et al., 1999</td>
<td>Rats (n=20)</td>
<td>4.7 T</td>
<td>tMCAo</td>
<td>DWI ASL</td>
<td>R2’ changes visible even after edema develops.</td>
<td>R2’ delivers additional information on oxygenation.</td>
<td>Focused on methodological aspects.</td>
</tr>
<tr>
<td>Jensen et al., 2009</td>
<td>Rats (n=7)</td>
<td>3 T</td>
<td>tMCAo</td>
<td>DWI/PWI Histology</td>
<td>Low T2’ values in hypoperfused DWI lesions, high values in hyperperfused DWI lesions</td>
<td>T2’ provides informations on oxygen metabolism (OEF)</td>
<td>No information on the penumbra but the effects of reperfusion</td>
</tr>
<tr>
<td>Zhang et al., 2011</td>
<td>Monkeys (n=4)</td>
<td>1.5 T</td>
<td>tMCAo</td>
<td>DWI/PWI Histology</td>
<td>T2’ increased in core and decreased in penumbra and oligemia.</td>
<td>T2’ can provide additional information on oxygen metabolism.</td>
<td>Questionable concept of penumbra and oligemia.</td>
</tr>
<tr>
<td>Geisler et al., 2006</td>
<td>Human (n=32)</td>
<td>1.5 T</td>
<td>Acute stroke</td>
<td>DWI/PWI F1 (FLAIR/CT)</td>
<td>15.7 % T2’ drop in core, 10.5 % (penumbra) 8 % (oligemia) (not significant between the regions)</td>
<td>T2’ decreased in core and penumbra.</td>
<td>No differentiation between core and penumbra.</td>
</tr>
<tr>
<td>Fiehler et al., 2007</td>
<td>Human (n=20)</td>
<td>1.5 T</td>
<td>Acute stroke</td>
<td>DWI/PWI F1 (MRI/CT)</td>
<td>OR 3.5 for DWI lesion growth Fair interobserver agreement (κ = 0.239)</td>
<td>T2’ promising to predict infarct growth.</td>
<td>Detectability of T2’ lesion unreliable</td>
</tr>
<tr>
<td>Siemonsen et al., 2008</td>
<td>Human (n=100)</td>
<td>1.5 T</td>
<td>Acute stroke</td>
<td>DWI/PWI F1 (MRI/CT)</td>
<td>OR 4.59/3.1 (T2’) OR 2.22/1.73 (TTP) for DWI lesion growth (reader 1/2)</td>
<td>T2’ lesion better to predict infarct growth than TTP.</td>
<td>Moderate interobserver agreement (κ = 0.53)</td>
</tr>
</tbody>
</table>

**Table 4**: Studies (experimental and clinical) using T2’ BOLD MRI.  
FLAIR: fluid attenuated inversion recovery
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Species</th>
<th>Field strength</th>
<th>Vessel occlusion</th>
<th>Reference method</th>
<th>Results</th>
<th>Conclusion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al., 2003(^{38})</td>
<td>Human (n=5)</td>
<td>1.5 T</td>
<td>Acute stroke</td>
<td>DWI/PWI FI (T2)</td>
<td>0.4 ± 0.24 threshold for infarction 0.55 ± 0.11 for “tissue at risk” (compared to contralateral tissue)</td>
<td>MR-CMRO(_2) may provide estimates of CMRO(_2)</td>
<td>In agreement with PET but no formal validation</td>
</tr>
<tr>
<td>An et al., 2009(^{46})</td>
<td>Human (n=6)</td>
<td>N/A</td>
<td>Acute stroke</td>
<td>DWI/PWI FI (FLAIR)</td>
<td>Low MR-CMRO(_2) corresponds well with infarcted voxels at one month.</td>
<td>MR-CMRO(_2) predicts final infarct better than ADC and MTT.</td>
<td>Published as conference abstract</td>
</tr>
<tr>
<td>An et al., 2009(^{37})</td>
<td>Rats (n=22)</td>
<td>3 T</td>
<td>tMCAo</td>
<td>FI (T2) Literature</td>
<td>MR- CMRO(_2) lower in core and continuously decreased.</td>
<td>MR-CMRO(_2) may estimate CMRO(_2)</td>
<td>See above</td>
</tr>
</tbody>
</table>

**Table 5**: Studies (experimental and clinical) using MR-CMRO\(_2\).
References


