Commentary

Imaging the ischaemic penumbra with T_2^* weighted MRI

Christopher McCabe

Correspondence:

Dr Christopher McCabe

Institute of Neuroscience & Psychology,

College of Medical, Veterinary & Life Sciences,

Wellcome Surgical Institute,

University of Glasgow,

Glasgow, G61 1QH, UK

Fax: +44 141 943 0215

Telephone: +44 141 330 5822

Email: Chris.McCabe@glasgow.ac.uk

The positive results from the recent multicentre randomised clinical trials of mechanical thrombectomy have at long last reinvigorated the stroke community and open up new possibilities for protective strategies dealing with reperfusion-based injury. With efficacy demonstrated up to 6 hours after stroke onset and with some patients in the ESCAPE trial[1] being treated beyond 6 hours, it raises the possibility of an extended time window in a select group of patients. In order for this to be the case, there is a need for advanced imaging techniques to identify patients with viable ischaemic penumbra if treatment (i.e alteplase, thrombectomy and/or new protective strategies) is to be given, particularly outside the current time window.

The recent study by Shen et al.,[2] in the current issue of *JCBFM,* provides further validation of a promising MRI technique for identifying the ischaemic penumbra based on tissue metabolism. This technique utilises inhalation of oxygen (oxygen challenge, OC) during T_2^* weighted MRI to exploit differences in deoxy/oxyhaemoglobin ratio within ischaemic core, penumbra and normal tissue. Within the ischaemic penumbra, where oxygen extraction fraction and therefore deoxy/oxyhaemoglobin ratio are elevated, the OC results in a greater T_2^* signal change. Originally developed by Santosh and colleagues[3] this technique has been evaluated in a number of pre-clinical stroke studies to confirm that tissue displaying an increased T_2^* signal change to OC displays morphologically normal neurones, glucose metabolism, reduction in lactate during OC and recovery following reperfusion[3-7]. Deuchar and colleagues further developed the technique using intravenous oxygen carriers to amplify the T_2^* signal change and remove potential confounds of 100% oxygen in the clinic[8].

One of the limitations of the OC technique is that large veins and venules will display an increased T_2^* signal change, similar to that observed in the 'ischaemic penumbra' thereby making it difficult to distinguish these non-specific changes. Shen et al.,[2] attempt to overcome this by investigating the time to peak (TTP) of the OC signal in addition to the amplitude of signal change. They

demonstrated that tissue at risk (i.e. penumbra) can be better stratified with a delayed TTP in addition to an amplified T_2^* signal during OC and that this tissue showed good correspondence with tissue at risk identified with perfusion-diffusion mismatch MRI. In contrast, large veins and venules did not show a delayed TTP. Initiation of reperfusion returned the TTP to normal and attenuated the OC T_2^* signal change (within tissue at risk). Importantly, this tissue was not incorporated into the infarct when followed up at 24 hours post-stroke.

This development represents a further refinement in the OC technique for identifying tissue at risk following stroke. In view of positive animal data from two independent groups, plus preliminary data in acute stroke patients[9], the potential for successful translation looks promising. Further validation of the technique, such as establishing appropriate thresholds, is required before it would likely be implemented as a diagnostic technique for acute ischaemic stroke management.

References

(1) Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015 Mar 12;**372**(11):1019-1030.

(2) Shen Q, Huang S, Duong TQ. T2* weighted fMRI Time to Peak of Oxygen Challenge in ischemic stroke. 2015. *J Cereb Blood Flow Metab* 2015, in print.

(3) Santosh C, Brennan D, McCabe C, Macrae IM, Holmes WM, Graham DI, et al. Potential use of oxygen as a metabolic biosensor in combination with T2*-weighted MRI to define the ischemic penumbra. *J Cereb Blood Flow Metab* 2008 Oct;**28**(10):1742-1753.

(4) Robertson CA, McCabe C, Gallagher L, Lopez-Gonzalez MR, Holmes WM, Condon B, et al. Stroke penumbra defined by an MRI-based oxygen challenge technique: 1. Validation using [14C]2-deoxyglucose autoradiography. *J Cereb Blood Flow Metab* 2011 Aug;**31**(8):1778-1787.

(5) Robertson CA, McCabe C, Gallagher L, Lopez-Gonzalez MR, Holmes WM, Condon B, et al. Stroke penumbra defined by an MRI-based oxygen challenge technique: 2. Validation based on the consequences of reperfusion. *J Cereb Blood Flow Metab* 2011 Aug;**31**(8):1788-1798.

(6) Shen Q, Du F, Huang S, Duong TQ. Effects of cerebral ischemic and reperfusion on T2*-weighted MRI responses to brief oxygen challenge. *J Cereb Blood Flow Metab* 2014 Jan;**34**(1):169-175.

(7) Holmes WM, Lopez-Gonzalez MR, Gallagher L, Deuchar GA, Macrae IM, Santosh C. Novel MRI detection of the ischemic penumbra: direct assessment of metabolic integrity. *NMR Biomed* 2012 Feb;**25**(2):295-304.

(8) Deuchar GA, Brennan D, Griffiths H, Macrae IM, Santosh C. Perfluorocarbons enhance a T2*-based MRI technique for identifying the penumbra in a rat model of acute ischemic stroke. *J Cereb Blood Flow Metab* 2013 Sep;**33**(9):1422-1428.

(9) Dani KA, Santosh C, Brennan D, McCabe C, Holmes WM, Condon B, et al. T2*-weighted magnetic resonance imaging with hyperoxia in acute ischemic stroke. *Ann Neurol* 2010 Jul;**68**(1):37-47.