Identifying the ischaemic penumbra by probing tissue metabolism and imaging changes in tissue lactate.

W. M. Holmes[1], M. R. Lopez Gonzalez[2], L. Gallagher[1], G. A. Deuchar[1], I. M. Macrae[1], and C. Santosh[3]
[1]GEMRIC, Wellcome Surgical Institute, Univeristy of Glasgow, Glasgow, United Kingdom, [2]SINAPSE, Clinical Physics, University of Glasgow, Glasgow, United Kingdom, [3]Institute of Neurological Sciences, Southern General Hospital, Glasgow, United Kingdom

Introduction Reliable identification of potentially salvageable (penumbral) tissue within the ischaemic brain would assist in appropriate treatment decisions and improved patient care. Currently MRI based perfusion-diffusion mismatch is used, which is an indirect measure lacking precision. Here we propose a new MRI method for imaging the ischaemic penumbra based on the brain's capacity to use lactate as a metabolic substrate. The Astrocyte-Neuron Lactate Shuttle Hypothesis (ANLSH)[1] suggests that lactate, far from being the harmful end product of anaerobic gycolysis, is actually an important (even preferred) oxidative energy substrate for neurons, but not astrocytes which use glucose.

Hypothesis In ischaemic tissue lactate is already present at elevated levels due to anaerobic gycolysis. It is only the reduced rate of oxygen delivery that limits aerobic metabolism. We therefore hypothesise that increasing the rate of oxygen delivery to tissue (via a 100% O_2 challenge) would increase aerobic metabolism, using lactate as the oxidative substrate, leading to a reduction in lactate in metabolically viable tissue. Whereas, in ischaemic tissue that is metabolically inactive, tissue lactate would remain unaffected.

Method Sprague Dawley rats were anesthetized with 1-2% isoflurane in a mixture of 70:30 N_2O:O_2, artificially ventilated and the middle cerebral artery permanently occluded (MCAO) by the intraluminal filament technique. Animals were then ventilated under air and blood gas analyses performed regularly. Changes in the rate of O_2 delivery were achieved by changing the ventilation from air to 100% O_2 for 20minutes, between 1 and 2 hours post stroke. This increases the rate of oxygen delivery by 3-4% [2], by slightly increasing haemoglobin saturation (to approx 99%) and increasing the amount of free unbound oxygen dissolved in the blood plasma. Imaging was performed on a Bruker Biospec 7T/30 cm system. Two series of experiments were performed, in the first series (n=6) localised spectroscopy (PRESS) was used to observe the effect of a 100% oxygen challenge on the lactate resonance, Fig 1. In the second series (n=6) spectroscopic Imaging was performed using a pulse sequence design specifically for imaging changes in lactate. This sequence comprised of water suppression, fat saturation slices, a 6ms frequency selective Gaussian RF pulse (excitation bandwith 452Hz, centred at 1.06ppm) and a RARE imaging module. The spectroscopic images combine signal from macromolecule, lipid and lactate. As lipid concentrations only increase slowly over many hours following MCAO [2], they can be assumed constant over the time course of the experiment. Thus, subtraction of spectroscopic images, on air and on 100% oxygen, results in lactate change maps.

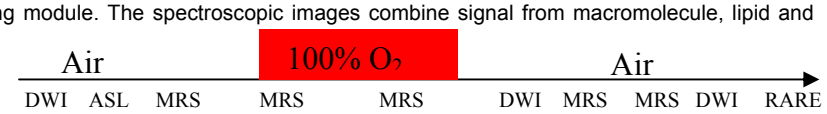

Fig 1. Protocol for series 1. Same protocol for series 2 except with spectroscopic imaging

Results The localised spectroscopy experiments confirmed our hypothesis. In the presumed penumbral region (defined by PWI/DWI mismatch, Fig 2a), tissue lactate decreased during 100% oxygen, Fig 2b-c, as aerobic metabolism increased. On returning from 100% oxygen to air, lactate levels in this region increased, Fig 1d. In the ischaemic core, changing from air to 100% oxygen, no change in lactate was seen Fig 2e, indicating this tissue is metabolically inactive. In the normal contralateral hemisphere no change in lactate levels were seen, Fig 2f, as this tissue has no requirement for the extra oxygen delivered.

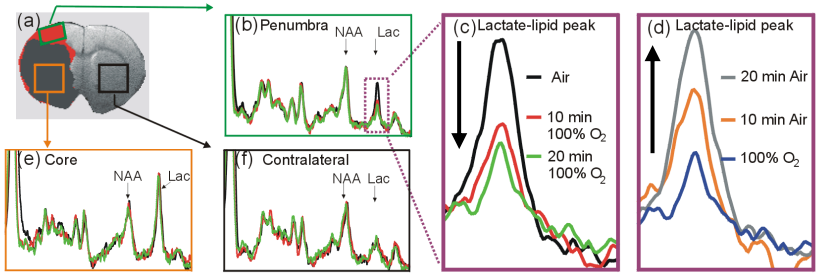

Fig 2. Localised ^{1}H spectroscopy in ischaemic core, contralateral striatum and cortical penumbra

Spectroscopic imaging was used to confirm the spatial location of the changes in tissue lactate. Fig 3a shows elevated lactate levels in the ipsilateral hemisphere. Fig 3a-c shows that on changing from air to 100% oxygen there was a decrease in lactate level in the PWI/DWI mismatch region, Fig 3d. Figure 3e-g shows that returning from 100% oxygen back to air, resulted in an increase in lactate in the PWI/DWI mismatch region.

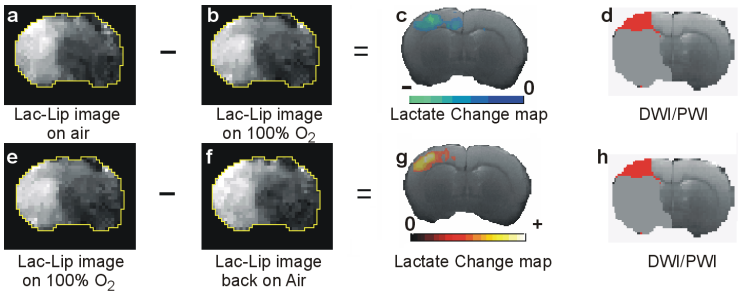

Fig 3. Spectroscopic Imaging used to map changes in tissue lactate.

Conclusion The present study has successfully demonstrated a novel approach to imaging the ischaemic penumbra based on lactate metabolism. As this method is directly based on tissue metabolism, it may prove more accurate than the indirect perfusion-diffusion mismatch method in defining the ischaemic penumbra.

References

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