Rates of change of 1H and 31P MRS cerebral metabolites vs Lactate/NAA in the 48h following global transient hypoxia-ischaemia in the newborn piglet

N. J. Robertson, S. Faulkner, A. Bainbridge, M. Chandrasekaran, D. Kelen, S. Thayyil, E. Cady, X. Golay, and G. Raivich
1 Institute for Women's Health, University College London, London, United Kingdom, 2 Medical Physics and Bioengineering, University College Hospitals, London, United Kingdom, 3 UCL Institute of Neurology, London, United Kingdom

Background: Perinatal asphyxia affects 2-3 per 1000 term births in the developed world and is associated with high morbidity and mortality rates. Therapeutic hypothermia is now established as a safe and effective therapy for perinatal asphyxia. Other adjunct therapies are needed, however, as 50% of treated infants still have an adverse outcome and surrogate endpoints are required to speed up clinical trials. A recent meta-analysis demonstrated that the cerebral 1H-MRS lactate/N-acetyl aspartate (Lac/NAA) peak area ratio acquired between 5-14 days after birth is the most sensitive and specific MRI biomarker of long term neurodevelopmental outcome in infants following perinatal asphyxia; lactate/NAA is already used as a translational biomarker in pre-clinical studies and surrogate endpoint in phase II neuroprotection trials. The reciprocal changes in lactate and NAA (increase and decrease respectively) following hypoxia-ischaemia improve the sensitivity to detect neural injury in the sub-acute phase after hypoxia-ischaemia. Further validation of other biomarkers is important for monitoring neuroprotective therapies and refining surrogate endpoints.

Aim: To compare the rates of change of different metabolite peak area ratios vs Lac/NAA following transient global hypoxia-ischaemia in a validated piglet model.

Methods: Twenty-eight Large White male piglets (aged<24 h) underwent transient global hypoxia-ischaemia and serial 1H (white matter (WM) and deep grey matter (DGM)) and 31P MRS (whole brain) data acquisitions. The rate of change (slope) of 1H and 31P metabolite ratios (logarithmic scale) was assessed for each individual animal. Comparative sensitivity to injury was assessed by fitting of WM and DGM metabolite ratios vs WM Lac/NAA.

Results: During the 48h after transient hypoxia-ischaemia WM and DGM Lac/Cr was more sensitive to lower degrees of injury than Lac/NAA, as demonstrated by a steeper slope in the 1st portion of the graph (Fig. 1a). Cho/Cr showed no correlation with Lac/NAA. NAA/Cr demonstrated a reduced sensitivity to mild injury as compared with more severe injuries (with a steeper slope in the 2nd portion of the graph) (Fig 1c). Responding 31P MRS biomarkers exhibited a similar reduced sensitivity to mild injury vs more severe brain damage, ranging from comparatively moderate (Pi/EPP) to very pronounced (NTP/EPP and pH_i) (Fig 2). In other words, when Lac/Cr and Lac/NAA already indicated definite abnormalities, NTP/EPP and pH_i still remained unaffected.

Conclusion: 1H and 31P MRS based biomarkers change at different rates in the 48 h following a transient global hypoxic-ischaemic insult. Compared to Lac/NAA, Lac/Cr changed most rapidly and was most sensitive to lower degrees of injury while NAA/Cr, NTP/EPP and pH_i were least sensitive to injury and responded last. Lac/NAA appears to provide sufficient sensitivity detect moderate to severe brain damage following global hypoxia-ischaemia.

References:
1. Edwards AD et al., BMJ 2010; 340:c363
2. Thayyil et al., Pediatrics 2010;125:E 382-95