The Effect of Therapeutic Hypothermia on Cerebral Metabolism in Neonates with Hypoxic-Ischemic Encephalopathy

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Target audience: Those interested in brain injury and neuroprotection; MR spectroscopists and radiologists interested in the clinical applications of MRS.

Introduction: Therapeutic hypothermia (TH) nearly doubles the chance of normal survival in neonatal hypoxic-ischemic encephalopathy[1, 2]. Although the mechanism of neuroprotection is incompletely understood, laboratory research has suggested that hypothermia decreases the cerebral metabolic rate[3] as well as the availability of excitatory amino acids[4]. Our aim was to investigate the effects of TH on cerebral metabolism *in vivo* in neonates with HIE.

Methods: 26 neonates (10 M, 16 F; mean GA = 39.2 ± 1.4 weeks) with moderate (23) and severe (3) Sarnat stage HIE, underwent MR scans during TH and after re-warming. 1H-MRS spectra were acquired on a Philips 3.0T Achieva using a PRESS sequence (TE = 35ms, TR = 2000ms) with regions of interest localized to the basal ganglia (BG), thalamus (THAL), parietal white matter (WM; n=16) and cortical grey matter (GM). During TH, hypothermia was maintained with a Blanketrol system (CSZ Medical; modified with extension tubing) and continuously monitored with a rectal temperature probe. Absolute concentrations (mmol/kg) of metabolites related to energy metabolism, neurotransmission and excitotoxicity/free radical injury were quantitated using LCModel (V6.13-1C, Stephen Provencher). Paired *t*-tests (SPSS, version 22) were used to compare concentrations during and after TH. To ensure valid quantitation of phosphocreatine (PCr) and glutamate, key metabolites of interest, we excluded spectra of poor quality (i.e., FWHM > 0.05; SNR < 10).

Results: During TH, PCr concentrations were elevated by 20-40% in the THAL, BG, WM and GM, relative to re-warming while free creatine was reduced by a similar degree (all *p*'s < 0.01) (**Fig. 1**). Additionally, glutamate was reduced by approximately 20% in all regions (*p*'s < 0.01) while GABA was reduced by 27% in the THAL and 20% in the BG (*p*'s < 0.05). Glutathione was increased by 7% in the THAL and 17% WM (*p*'s < 0.05). No effect of TH was observed on lactate concentrations, ketones or glutamine. Also noted was that across all studies (during and post TH) higher PCr correlated with lower lactate concentrations (r=-0.440, p<0.001, n=204).

Disussion: In neonates with moderate to severe HIE, TH appears to increase energy reserve (i.e, PCr) and decrease excitatory and inhibitory neurotransmission relative to after re-warming, consistent with decreased cerebral metabolic demand. Additionally, TH appears to reduce free radical toxicity in the THAL and WM. Overall, these findings are consistent with prior observations in animal models and support the hypothesis TH exerts neuroprotective effects via multiple mechanisms.

Conclusion/Clinical Relevance: MR Spectroscopy is not only a key instrument for the diagnosis and management of pediatric brain disorders, but also is poised to aid in the development and evaluation of neuroprotective therapies.

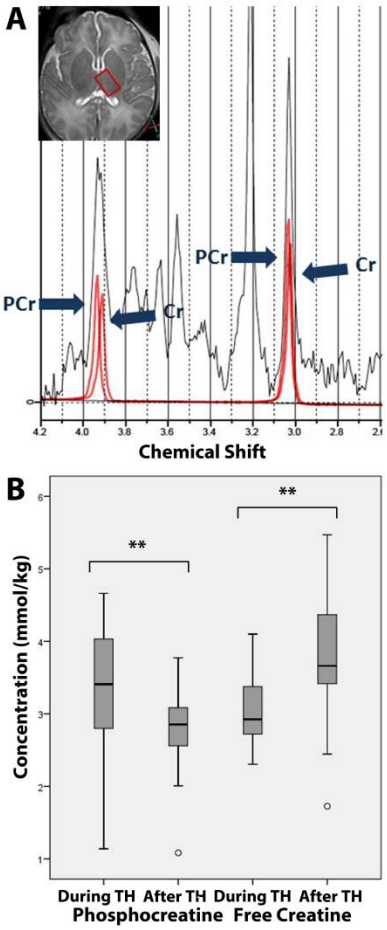

Fig. 1: (A) Albeit the separation of PCr and Cr is challenging, 3T spectra of the newborn brain are generally of sufficient quality to detect the small chemical shift difference of the PCr and Cr resonances at ≈ 3.95 ppm. (B) PCr was higher during TH, relative to after TH, while Cr was lower. ** $p < 0.01$.

Acknowledgement: Support provided by the Gerber Foundation and the Rudi Schulte Research Institute.

References: 1. Edwards AD, Brocklehurst P, Gunn AJ, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *Bmj.* 2010;340:c363. 2. Tusor N, Edwards AD. Birth Asphyxia: 100 Years of Progress. In press, 2014. 3. Laptook AR, Corbett RJ, Sterett R, et al. Quantitative relationship between brain temperature and energy utilization rate measured in vivo using 31P and 1H magnetic resonance spectroscopy. *Pediatr Res.* 1995;38:919-925. 4. Nakashima K, Todd MM. Effects of hypothermia on the rate of excitatory amino acid release after ischemic depolarization. *Stroke* 1996;27:913-918