Rapid interleaved proton and phosphorous MRS at 4T: metabolic effects of hyperventilation

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Background: Persistent hypocapnia, or reduced partial pressure of expired CO2 (pCO2) is a common symptom of certain conditions such as panic disorder, chronic obstructive pulmonary disease (COPD), and asthma (Laffey 2002). Experimental manipulation of CO2 occurs in several types of studies: 1) core physiological research investigating general acid-base changes to pCO2 manipulation (Kogure 1975), 2) hypocapnia/hyperventilation (HV) as a model of birth complications (Fritz 2004) or major physiological stressor (Clausen 2004), 3) HV in situations of clinical patient management (e.g. traumatic brain injury, Marion 2002), and 4) HV as a physiological stressor to induce anxiety within susceptible populations (Dager 1995; Friedman (in press)). Recent literature has stressed that HV should always be avoided because it can result in severe metabolic compromise (Clausen 2004; Fritz 2004). This statement has been supported by anesthetized animal studies that demonstrated marked blood flow decreases (~80%), large pH increases (.2-.3 units) and high-energy phosphate decreases (20-30%) during HV (Clausen 2004; Nioka 1987; Fritz 2004). However, other animal literature does not support these findings (none-.05 unit pH increases and none-10% high energy phosphate decreases)(Cady 1987; Sieber 1992). These latter results concur with two human MRS studies performed to date; both measured small pH changes (.05 units) and no measurable high-energy phosphate changes during HV (van Rijen 1989; Friedman (in press)). Since HV impacts glial and neuron coupling, it is possible that anesthesia creates a confounding metabolic factor. With this in mind, a reappraisal of these findings is warranted.

Aim: To measure pH, high-energy phosphates, and lactate changes concurrently with high sensitivity in awake humans during HV. To accomplish this aim, an interleaved proton(1H)-phosphorous(31P) spectroscopy sequence was developed and implemented at 4T.

Methods: Using a dual-tuned volume coil and Varian 4T scanner, six healthy control subjects (3 Males, 3 Females) were studied during HV challenge (10 minute baseline, 20 minute HV period (paced breathing of 18 breaths-per-minute to reach pCO2=20mm Hg) and 20 minute recovery period). Large voxel volumes were selected to maximize signal-to-noise of the individual free-induction-decays (FIDs). MRS parameters were as follows: (1H) TE=30, TR=4s, PRESS sequence, (31P) pre-acquisition delay 1.75ms/TR=4s, pulse-acquire acquisition. Spectra were combined in 128s blocks to optimize signal-to-noise prior to analyses (See example spectra in the Figure below). Using LCModel for spectral fitting,1H metabolites were referenced to internal brain water and expressed as millimolar concentrations (mM). 31P data was processed using FITMAN and each metabolite expressed as a ratio to the total 31P signal. Ph was calculated from the inorganic phosphate-phosphocreatine shift and displayed in usual metrics. Across the paradigm, resultant metabolite time-courses are shown in the Figure below. The red diamond corresponds to the start of HV, the green diamond the start of the recovery period.

Results: Brain pH consistently demonstrates very small increases to HV (.05 units). Glutamine and glutamate increases likely result from this induced alkalosis, following a cascade of events starting with the disinhibition of glutamine synthetase in astrocytes (Nissim, 1999). As excess glutamate had been found to stimulate astrocytic glycolysis in a dose dependent manner, it is possible that the small phosphocreatine decreases (~5%), inorganic phosphate increases, and 1H lactate changes, reflect this increased metabolic rate preferentially within astrocytes. Since lactate increases have been shown to be partially neuroprotective in conditions of excess glutamate (Pellerin 2005), the integrity of this described energetic system may have implications for understanding both normal energy coupling and system resiliency to physiological stress.

Conclusions: HV changes in the awake human are much less severe than suggested by animal investigations employing certain anesthesia protocols. Though the excess free radical production (oxygen) and distributed blood flow decreases (~20%, Posse 1997) that occur during HV may not be harmless if sustained, the metabolic compromise associated with this procedure for an intact energetic system appears small.

References:

Laffey JG, N Engl J Med 2002; 347(1):43-53
Kogure K et al.: Am J Physiol 1975; 228(6);1862-1867.
Fritz et al.: Neurochem Res 2004 29(4); 791-796.
Clausen et al.: Brain Res 2004 1019(1-2);113-123.
Marion et al.: Crit Care Med 2002 30;2619-2625
Dager SR et al.: Am J Psych 1995; 152(5):666-72
Cady et al.: J Physio 1987 382;1-14
Nioka et al.: J Appl Physiol 1987 62(5);2094-2102
Sieber et al.: Am J Physio 1992; 263;H1864-H1871
Van Rijen et al.: MRM 198910(2); 182-193.
Friedman S et al.: Am J Psych (in press)
Nissim I: Am J Physiol 1999 277(4 Pt 2):F493-7
Pellerin L: Mol Neurobiol 2005 32(1);59-72.
Posse S et al.: MRM 2001 46(2);264-271

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