Quantification of TAE-induced Alterations in Tumor Metabolism using Hyperpolarized ^{13}C-MRSI

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Introduction:

Transarterial embolization (TAE) is the procedure in which arterial blood flow to an organ is stopped by injecting small particles or beads directly into the artery via a catheter. TAE is applied clinically in patients with hepatocellular carcinoma (HCC) via the haptic artery to deprive tumors of nutrients oxygen and also to localize chemotherapy [1]. Alterations in metabolism of tumor cells under such conditions can provide insight into tumor response to therapy. The goal of this study was to quantitatively measure alterations in tumor metabolism using hyperpolarized carbon-13 technology. Results show significant reduction in pyruvate to lactate conversion 15 minutes post embolization, lasting over two hours.

Methods and Materials:

A 6-week old Male Wistar rat was induced with hepatocellular carcinoma using *ab libitum* oral administration of 0.01% Diethylnitrosine (DEN) for 12 weeks. A catheter was inserted through the carotid artery and guided using fluoroscopy into the lobar hepatic artery [2]. MRI experiments were performed using a 4.7T 50cm horizontal bore Varian system with the animal in the supine position. Carbon-13 data was acquired using a 30mm surface coil (m2m Imaging) positioned over the liver. The coil and bedding were placed inside a 70mm quadrature 1H volume resonator (m2m imaging). Isofluorine was delivered nasally at 2ml/min during the entire study. Mutli-slice T_2-weighted spin-echo respiratory-gated proton images (55 x 55 x 1 mm) were acquired to localize the tumor. 28.5 mg [1-^{13}C] pyruvic acid (Cambridge Isotope Laboratories) was polarized to ~18% at 1.4 K and 94 GHz with a HyperSense DNP system (Oxford Instruments). 4 mL Tris-buffered saline were heated to 190°C at 10 bar, and were used to rapidly dissolve the frozen sample, yielding a neutral, isotonic solution of 80 mM [1-^{13}C] pyruvate. A rapid delivery system consisting of an HPLC pump and PEEK tubing was used to administer 3ml of hyperpolarized agent via the tail vein at a rate 10 ml/min within 20 seconds of dissolution. The total dead volume of the delivery system was ~0.5 ml. Thirty carbon-13 images at a resolution of 16 x 16 were acquired starting 25 seconds after sample delivery using an Echo Planar Spectroscopic Imaging (EPSI) sequence (TR/TE = 300/17 ms) with a of 20^{o} flip angle RF pulse over an 8-mm slice and an 55 x 55mm field of view. Spectral bandwidth was set to 1.1 KHz (128 points), centered on [1-^{13}C] pyruvate (171 ppm). An 8M urea phantom (163.5 ppm) was used as a reference. Embolization was performed 1 hour after the first injection and was followed by two additional hyperpolarized injections 15 minutes and 2 hours after. Data was processed using custom-made MATLAB (MathWorks) routines.

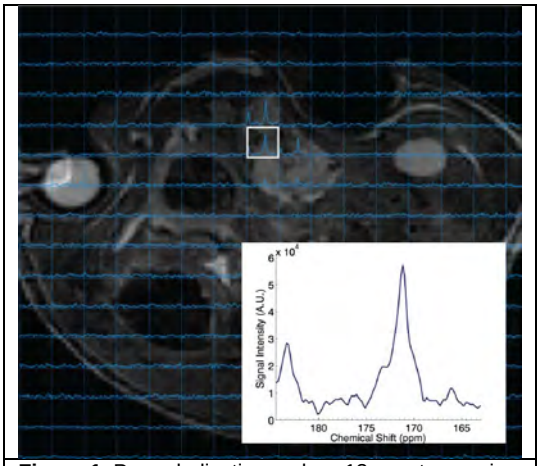

Figure 1. Preembolization carbon-13 spectroscopic image.

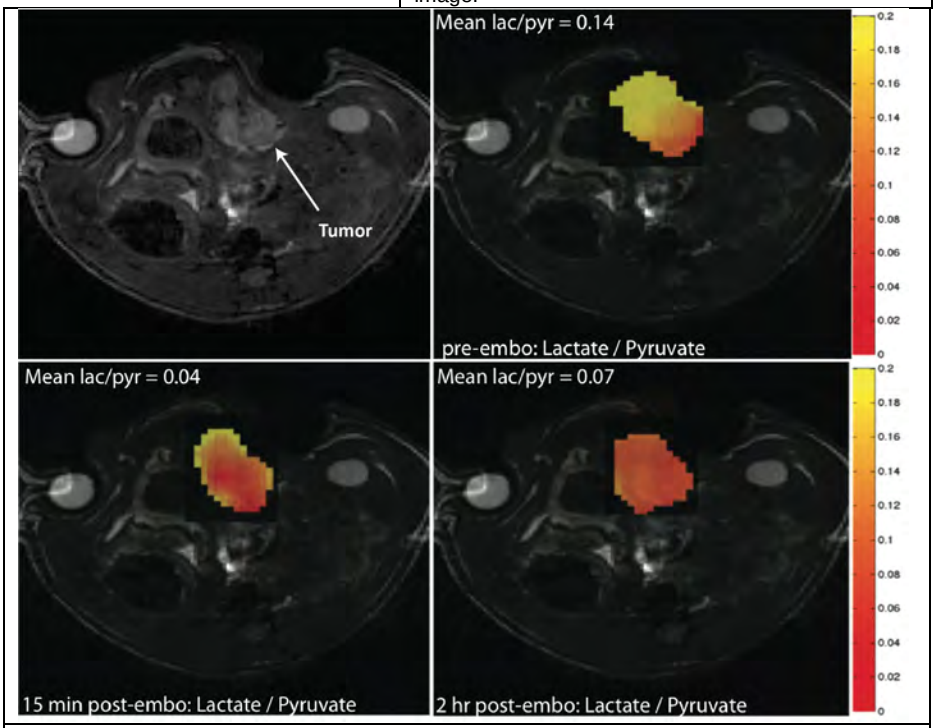

Figure. 2. Lactate to Pyruvate ratio images overlaid on T2-weghted proton image.

Results and Discussion: Carbon-13 spectroscopic imaging shows decreased conversion of pyruvate to lactate by 70%, 15 minutes following embolization. This effect, as earlier studies suggest [3], may be explained by an increase in glycolytic flux as well as reduction in oxygen consumption in surviving cancerous tissue. Carbon imaging two hours post-embolization shows a 50% increase in net lactate production when compared to the pre-embolization image.

Conclusion: In vivo carbon-13 spectroscopic allows for real-time quantitative characterization of pyruvate metabolism upon TAE. Characterization of metabolic changes in cells surviving TAE- like ischemia may provide a functional measure of tumor response in humans.

References: [1] Chatziooannou AN. et al. J Vasc Interv Radiol. 2013, [2] Gade T, et al., In press 2014. [3] Gade et. al, submitted to SIR, 2015