Non-invasive identification of functional brown adipose tissue in rodents using hyperpolarized 13C imaging

Angus Z. Lau[1,2], Albert P. Chen[3], Michelle Ladouceur-Wodzak[1], Krishna S. Nayak[4], and Charles H. Cunningham[1,2]

[1]*Imaging Research, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada,* [2]*Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada,* [3]*GE Healthcare, Toronto, Ontario, Canada,* [4]*Department of Electrical Engineering, University of Southern California, Los Angeles, California, United States*

Purpose. The recent identification of functional brown adipose tissue (BAT) in adult humans has potential implications for the treatment of obesity, an independent risk factor for multiple diseases, including diabetes, stroke, and heart failure [1]. The development of new agents targeting BAT activation requires a non-invasive imaging modality to assess whether the tissue is functional. Currently, activated BAT can be located *in vivo* in humans using FDG-PET, which carries an undesired radiation dose in an otherwise healthy population, especially in juveniles. In this work, we demonstrate the feasibility of using hyperpolarized ^{13}C imaging to non-invasively identify functional BAT in less than one minute in a rodent model.

Methods. Male Sprague-Dawley rats (n=4, weight 308 g, SD 22 g) were kept at a room temperature of 22°C and anesthetized with ketamine/xylazine. The animals were scanned in a supine position using a 3T GE MR750 scanner with a ^{1}H/^{13}C birdcage T/R volume coil. Two hyperpolarized scans were performed during baseline (n=4) and stimulated (n=2) conditions (15 minutes after 2.5 mg/kg i.p. norepinephrine (NE) injection), separated by ~1 hour to prepare the hyperpolarized sample. Pyruvate, bicarbonate, and lactate were imaged using a single-shot time-resolved ^{13}C spiral imaging pulse sequence [2] (FOV 48, in-plane res. 6.8 x 6.8 mm^2, 6 slices, 10 mm Thk / 1 mm Spc, TR 5 s, pyruvate FA 10°, bicarbonate and lactate FA 60°, scan time 1 min) previously developed for large animal cardiac imaging. The scan was started simultaneously with a ~10 s infusion of 2.0 mL pre-polarized [1-^{13}C] pyruvate. ROIs were drawn over the heart and in the dorsal interscapular region. The images and metabolite signals in these ROIs were normalized to the temporal maximum pyruvate signal in the heart, and corrected for nominal FA. 2D FSE IDEAL (4.7x4.7x5 mm^3 resolution) was used to obtain water and fat images.

Results and Discussion. Fig. 1 shows representative axial images through the heart (dashed arrows) and the interscapular BAT depot on the dorsal side of the rat (solid arrows), a known deposit of BAT in rodents. Significant increases in hyperpolarized ^{13}C bicarbonate (3.7-fold, $p<0.01$) and ^{13}C lactate (3.5-fold, $p<0.001$) signals were observed in the regions associated with BAT following NE infusion. Fig. 2 shows representative metabolic time courses, and Fig. 3 shows metabolite ratios in BAT-associated regions before and after NE infusion. The increase in ^{13}C bicarbonate signal associated with interscapular BAT is consistent with increases in oxygen consumption upon stimulation [3]. Increased ^{13}C lactate signal associated with BAT is consistent with complete deoxygenation of draining venous blood from activated BAT. Presumably, increased bicarbonate signal indicates increased TCA cycle flux, which contributes to non-shivering thermogenesis mediated via mitochondrial uncoupling protein (UCP1), and increased lactate signal indicates additional aerobic and anaerobic glycolytic capacity in BAT. In future studies, pre-polarized fatty acids may be an interesting alternative to probe BAT metabolism, given that fatty acids are the primary substrate in BAT for oxidative metabolism, contributing ~90% to total oxygen consumption [1].

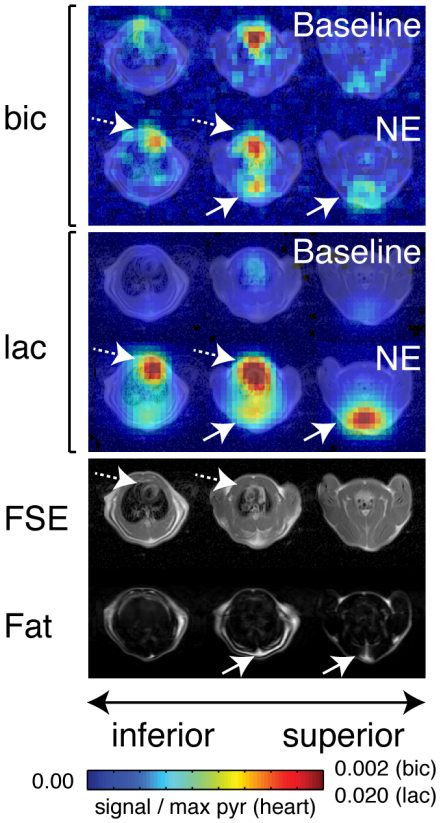

Fig 1. Representative *in vivo* ^{13}C axial images at baseline and with norepinephrine (NE) stimulation. Solid arrows indicate an interscapular BAT deposit. Dashed arrows indicate the heart. Images are cropped to 6x6 cm^2.

Conclusions. We demonstrate the novel use of hyperpolarized ^{13}C imaging to non-invasively identify activated deposits of brown adipose tissue *in vivo*. The radiation-free nature and recent translation into the clinic [4] of this imaging test may potentially facilitate trials of therapeutics targeting BAT activation in humans.

References. 1. Virtanen KA et al. *NEJM* 2009;360(15):1518–1525. 2. Lau AZ et al. *MRM* 2012 Jul 3. 3. Khanna A, Branca RT. *MRM* 2012;68(4):1285–1290. 4. Nelson SJ, et al. *Proc ISMRM* 2012; 274.

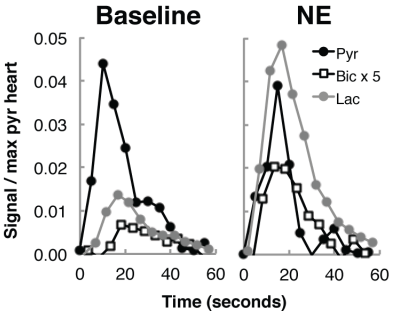

Fig. 2. Interscapular brown adipose tissue metabolite time courses at baseline and with norepinephrine (NE) stimulation.

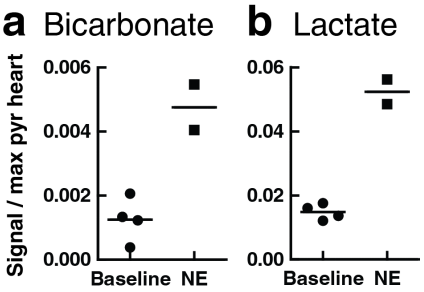

Fig. 3. Metabolite ratios for (a) bicarbonate and (b) lactate in the interscapular region, normalized to cardiac pyruvate signal. The difference between the two conditions was significant for both metabolites ($p<0.01$).