Mapping changes in lactate-to-pyruvate signal ratio using hyperpolarized ^{13}C-pyruvate in early Radiation Induced Lung Injury post conformal radiotherapy of the lung

Kundan Thind[1,2], Elaine Hegarty[1], Albert P Chen[3], Heeseung Lim[1,2], Francisco Martinez[1], Michael Jensen[2], Eugene Wong[1,4], Timothy J Scholl[1], and Giles E Santyr[1,5]
[1]Robarts Research Institute, Western University, London, ON, Canada, [2]Dept. of Medical Biophysics, Western University, London, ON, Canada, [3]GE, Toronto, ON, Canada, [4]Dept. of Physics and Astronomy, Western University, London, ON, Canada, [5]Dept. of Medical Imaging, Western University, London, ON, Canada

TARGET AUDIENCE: Hyperpolarized ^{13}C-MRI/S community

PURPOSE: Radiation-Induced Lung Injury (RILI) limits radiotherapy of thoracic cancers. Detection of Radiation Pneumonitis (RP) associated with early RILI may provide an opportunity to adjust treatment before the onset of irreversible fibrosis. Previously we have demonstrated the use of hyperpolarized [1-^{13}C]-pyruvate to measure an increase in lactate-to-pyruvate signal ratio during early RILI in whole rat lungs and heart two weeks post whole-thoracic irradiation (14 Gy) [1]. In this work, lactate-to-pyruvate signal ratio was quantified regionally and longitudinally in rat lungs and heart, day 10 and 15 post conformal radiotherapy of the lower-medial right lung. These results were also compared to histology and blood analysis.

METHODS: *All procedures followed animal care protocols approved by the University of Western Ontario (ACVS) and were consistent with procedures used by the Canadian Council on Animal Care (CCAC).* The lower-medial right lungs of 6 Sprague Dawley rats were irradiated with a total dose of 18.5 Gy using a modified micro-Computed Tomography system [2] (in two equal fractions, 24 hours apart). ^{13}C data were acquired from 3 irradiated and 4 age-matched healthy rats at day 10 post radiotherapy and 3 irradiated and 3 age-matched healthy at day 15 post radiotherapy. ^{13}C-labelled pyruvate was hyperpolarized using a commercial DNP system (Hypersense, Oxford Instruments). A similar protocol was followed for polarization, injection and data acquisition as described in previous work [1]. Arterial blood was collected from each animal prior to the pyruvate injection and was analyzed for blood lactate concentration and arterial oxygen concentration (p_aO_2). SAGE software (GEHC, Waukesha, WI) was used for processing and visualization of the 2D-CSI ^{13}C data. 4 voxels were selected from the left lung, right lung and the heart region from each animal and were analyzed for lactate-to-pyruvate signal ratio. Fig. 1 shows the selected voxels in the ^{13}C-spectra grid overlaid on a standard proton T_1-weighted image.

RESULTS: A statistically significant increase in lactate-to-pyruvate signal ratio from 0.25±0.05 (n=4) to 0.39±0.02 (n=3) in the right lung ($p < 0.01$) and from 0.22±0.04 (n=4) to 0.38±0.07 (n=3) in the left lung ($p < 0.01$) was observed for healthy and irradiated animals respectively at day 10. A statistically significant increase in lactate-to-pyruvate signal ratio from 0.24±0.0.03 (n=3) to 0.37±0.02 (n=3) in the right lung ($p < 0.01$) and from 0.21±0.07 (n=3) to 0.41±0.08 (n=3) in the left lung ($p < 0.05$) was observed for healthy and irradiated animals respectively at day 15. No statistically significant change in lactate-to-pyruvate signal ratio in the heart, blood lactate concentration and p_aO_2 were observed between healthy and irradiated animals for either day 10 and 15 post radiotherapy. Fig. 2 shows a summary of lactate-to-pyruvate signal ratio for left and right lung at day 10 and 15. Accompanying histology from another cohort of identically irradiated rats confirmed onset and spread of inflammation at day 10 and 15 post radiotherapy. Furthermore, no histological evidence of inflammation was observed in the heart at day 10 and 15 post radiotherapy.

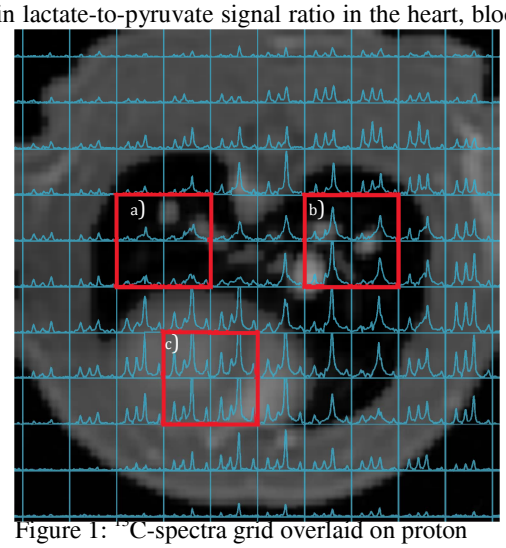

Figure 1: ^{13}C-spectra grid overlaid on proton image. Highlighted regions a), b) and c) show chosen voxels in the left lung, the right lung and the heart respectively.

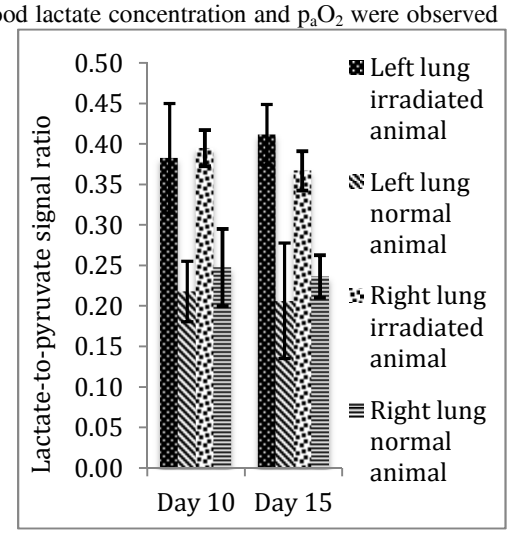

Figure 2: Regional change in lactate-to-pyruvate signal ratio in lungs post conformal radiotherapy

DISCUSSION: The increase in lactate-to-pyruvate signal ratio in the right lung at day 10 and day 15 is consistent with increases in hypoxia/hypoxemia associated with RP in early RILI. Furthermore, increases in lactate-to-pyruvate signal ratio at day 10 and day 15 seen in the left lung confirm the spread of the hypoxia/hypoxemia to the entire organ. This was also verified by proliferation of macrophages and inflammation across the lung based on histology. Lack of increase in lactate-to-pyruvate signal ratio in the heart and in blood lactate concentration at day 10 and day 15 indicate the lack of a systemic effect. Lastly, absence of a significant difference in elevated lactate-to-pyruvate signal ratio at day 15 compared to day 10 in irradiated animals indicate that the inflammatory cycle in early RILI has not yet subsided. Early and regional detection of RILI may be useful in modifying the course of on going radiotherapy to pervert radiation fibrosis.

ACKNOWLEDGEMENTS: Funding from CIHR and NSERC is gracefully acknowledged. KT was supported by OGS and CaRTT.

REFERENCES: [1] Thind et al. (2012), "Detection of radiation-induced lung injury using hyperpolarized ^{13}C magnetic resonance spectroscopy and imaging", MRM. doi: 10.1002/mrm.24525

[2] M. Jensen et al (2012), "Commissioning motorized jaws for a micro-CT/RT", AAPM 54th Annual Meeting, Charlotte NC. Poster Presentation doi:10.1118/1.4735341