In vivo biochemical imaging of HCC tumor bearing rats using hyperpolarized [1-13C]pyruvate and 18F-FDG

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Introduction

Hyperpolarised 13C Metabolic MR imaging using [1-13C]pyruvate (Pyr) allows for real-time in-vivo detection of energy metabolism, i.e. mitochondrial PDH activity and LDH activity in healthy and tumor bearing animals [1]. Recently [2, 3] proposed to use IDEAL spiral CSI in combination with single-shot spiral acquisition to simultaneously encode position, time and spectrum to study metabolic processes in-vivo. In this study we evaluated the comparison of a group of 23 male Buffalo rats with subcutaneous HCC tumor of varying grade of necrosis and size, which received both 18F-FDG PET and hyperpolarized [1-13C]pyruvate.

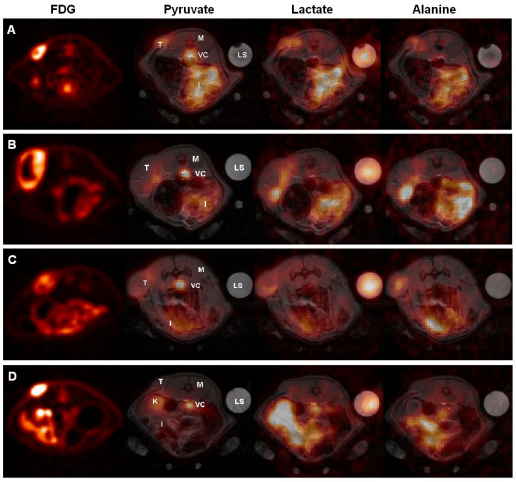

Fig 1: Comparison of 18F-FDG PET and 13C metabolite images (integrated and normalized metabolite signal). A: Tumor with strong signal and small necrotic part. B: Tumor with strong signal and large necrotic part. C: Tumor with moderate signal. D: Tumor with no visible signal T: tumor; M: muscle; VC: vena cava; I: intestines; LS : lactate syringe ; K : kidney

Methods

Subcutaneous tumours were induced by injection of 1 Mio McA-RH7777 HCC and grown until they reached 1 cm diameter. FDG PET and IDEAL spiral CSI [2] of hyperpolarized pyruvate were performed on two consecutive days under isoflurane anaesthesia. Animal experiments were approved by the local governmental agency. 3D PET data was acquired for 60 min (list mode) using Inveon small animal PET/CT scanner (Siemens, Knoxville, USA) starting with injection of [18F]-FDG (6,09 - 22,45 MBq). PET data was reconstructed using an OSEM3Dß1 algorithm (normalized and corrected for randoms, dead time, decay, but not for attenuation or scatter).

[1-13C]pyruvic acid was hyperpolarized using a HyperSense DNP (Oxford Instruments, Oxford, UK) dissolved for physiological pH and temperature (liquid state polarization 19-31 %) and 5 mL/kg was injected with 0.17 mL/s into the tail vein of the tumor bearing rats (~215 g). Anatomical ^{1}H reference images and ^{13}C-IDEAL spiral CSI data sets were acquired on a GE Signa Excite 3 T scanner (GE Healthcare, Milwaukee, WI, USA) of a 10 mm thick, transversal slice through the tumor with a 10° flip angle, using a dual-tuned (13C-1H) quadrature coil. Data reconstruction was performed according to [2] resulting in 32 consecutive ^{13}C metabolite images. Images acquired with both methods (18F-FDG PET and 13C metabolic MR) were visually assessed for signal strength in target tissue. Regions of interest (ROIs) were placed over tumor and dorsal muscle according to anatomical proton MR images. Additional ROIs were placed of the gastrointestinal tract (GIT) and the vena cava in the CS images. From the ROIs in the PET images the standardized uptake value (SUV) and tumor to muscle ratio (TMR) were calculated and from CS images the maximum peak (MP), TMR and lactate to pyruvate ratio (LPR).

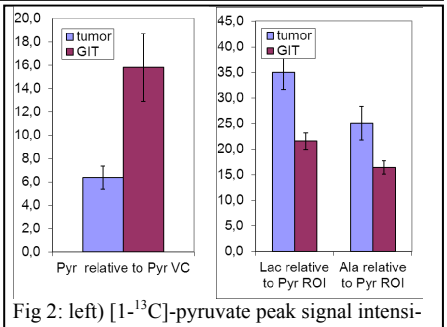

Fig 2: left) [1-^{13}C]-pyruvate peak signal intensities relative to vena cava in tumours and the GIT. A significantly smaller amount reached the tumours than the GIT. right) In relation more of the [1-^{13}C]-label in tumor tissue was transferred or turned over to [1-^{13}C]-lactate and [1-^{13}C]-alanine than in the GIT.

Results and Discussion

In this study we evaluated a group of 23 rats with subcutaneous HCC tumors regarding CS measurements of hyperpolarized [1-13C]-pyruvate and its metabolites [1-13C]-lactate and [1-13C]-alanine. [18F]-FDG-PET imaging verified that all tumors were metabolically active, had comparable uptake and were easily distinguishable from surrounding tissue by eye. Further analysis of a subgroup showed that the tracer delivery to the tumor during the first two minutes of PET imaging was comparable in all tumors analyzed (data not shown).

Visual assessment of integrated [1-13C] metabolite maps, on the other hand, presented high variability of contrast between [1-13C]-pyruvate, [1-13C]-lactate and [1-13C]-alanine signal in tumors and in other tissue in the FOV (see Fig. 1). [1-13C]-lactate provided most cases of good contrast in the tumor and [1-13C]-pyruvate the best image quality regarding SNR. The variability could not be readily explained by physiological differences in the animals (e.g. blood lactate or glucose – data not shown), nor by tumor stage regarding size and of grade of necrosis (data not shown) in the same way as reported previously [4]. Tissue analysis of a subgroup of the tumors ruled out lack of LDH level to cause lack of visual contrast by simple integration of metabolite signal intensity (data not shown). Referencing [1-13C]-pyruvate peak signal intensities in the tumors to the vena cava and the GIT, serving as a well perfused reference tissue, showed that a statistically significantly smaller amount reached the tumors than the GIT (Fig. 2a). In relation however, statistically significantly more of the [1-13C]-label in tumor tissue was metabolized to [1-13C]-lactate and [1-13C]-alanine than in the GIT (Fig. 2b). [5] had already described a much higher turnover of [1-13C]-pyruvate to [1-13C]-lactate and [1-13C]-alanine in orthotopic tumors of the same cell line, growth of these tumors in an ectopic location, with a different microenvironment and at a higher growth rate (700 mm³ in 12-14 days compared to 100-200 mm³ as reported by Dapolor and colleagues) is likely to lead to a different, presumably lower grade of vascularization, which could explain the relatively low amount of [1-13C]-pyruvate detected in the tumor region compared to other organs in the FOV. In addition, peripheral perfusion could also be compromised by anesthesia, during which blood pressure decreases and only vital organs such as the GIT might stay well perfused, or intermittent acute hypoxia in tumor.

Conclusion:

In PET images all tumors showed high signal intensities, whereas in pyruvate images less than half (40 %) and in lactate images only 2/3 (70 %) showed visible signal in tumors. No correlation could be found between TMR from PET and from CS images or between SUV and LPR. Analysis of the MPs revealed that a higher proportion of the pyruvate that could be detected in the blood vessel reached the GIT than the tumors. But in tumors turnover of pyruvate to lactate and alanine was higher than in the GIT. This effect of compartmentalization of [1-13C]pyruvate and its downstream metabolites demands a more sophisticated data analysis than simple integration of the metabolite signal curves for visual display, which captures the individual dynamic rather than the absolute signal. This may be achieved by kinetic modeling [6].

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References

[1] Brindle, K.M., et al., MRMed, 2011. **66**(2): p. 505-519. [2]Wiesinger, F., et al., MRMed, 2011(in press). [3] Mayer, D., et al., MRM, 2006. **56**(4): p. 932-7. [4] Larson, P.E.Z., et al., MRM. **63**(3): p. 582-591. [5] Darpolor, M.M., et al., NMR Biomed **24**(5): p. 506-513. [6] Gomez, P.A. et al. ESMRMB 2011.