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Quantitative perfusion MRI of tumor model in mouse

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Introduction: Perfusion in the body provides valuable information about physiological status and disease progression. Measuring perfusion in tumors is considered important with the recognition of angiogenesis, the process of developing new blood vessels, as a key element in the pathophysiology of tumor growth and metastasis[1]. Many studies have used Gd contrast agents to evaluate tumor blood flow and vasculature but quantification has been complicated and model/agent dependent. Arterial spin labeling (ASL) is a noninvasive and quantitative technique that measures perfusion by magnetically labeling water as a freely diffusible endogenous tracer. Application of ASL to measure perfusion in tumor is a challenge due to the low perfusion values and artifacts caused by movement, susceptibility difference and fat in the abdomen, where tumors in experimental models are typically transplanted. Previously, we successfully demonstrated and quantified mouse renal perfusion using ASL[2]. To optimize the sensitivity of ASL and determine the quantification error of low flow region, lumbar muscle was studied as a reference region for low blood flow. Subsequently, we applied the optimized protocol for perfusion measurements in an oncology model.

Methods:

All animal studies were approved by the local Institutional Animal Care and Use Committee (BMSI, A*STAR, Singapore).

Sequence Optimization in muscle: Experimental optimization of scan parameters in muscle was carried out in C57BL/6 mice (n=5). To determine the sensitivity, flow values under various data averaging up to 100 ASL pairs were calculated in muscle. Although typically single TI is used to quantify flow with minimal scan time, the quantification accuracy has not been verified. We compared the quantification error using single TI versus multiple TI, with matched total scan time. The mean flow of 80, 90 and 100 averaging was regarded as the actual flow value for calculating the quantification error in each animal. The relationship between the quantification error and the SNR of the control image was determined from 2 regions of interest (ROIs) from 5 animals.

Measurement of flow in tumor: For tumor studies, female BALB/cOlaHsd-Foxn1*nu* mice were intradermally inoculated with 1.25 million renal carcinoma cells (of A498 cell line) in 50% matrigel. MRI was carried out using the optimized sequence on 70 to 74 days after inoculation while anaesthetized with 1-2% isoflurane.

Imaging and Analysis: Flow-sensitive Alternating Inversion Recovery (FAIR) ASL was implemented on a Bruker ClinScan 7T using single-shot spin-echo EPI. To improve sensitivity of ASL, a 10 mm receive surface coil was placed close to the region of interest. The FAIR method was carried out without global pre-saturation and using an optimized short TR of 6s and a minimal TE of 18 ms. Dummy scans were used to ensure that the signal was at steady state. Water excitation and 3D shim were used to minimize artifacts. An axial slice of 2 mm thickness crossing the lumbar muscle or the center of the tumor were acquired with in-plane resolution of 0.44 x 0.44 mm. TIs were varied from 0.2 s to 4 s to allow more accurate quantification. T1 measurement was performed with inversion recovery SE-EPI with TI changing from 0.2 s to 8 s. Using Matlab, the perfusion was calculated based on the pair-wise subtracted FAIR images and the T1 map.

Results

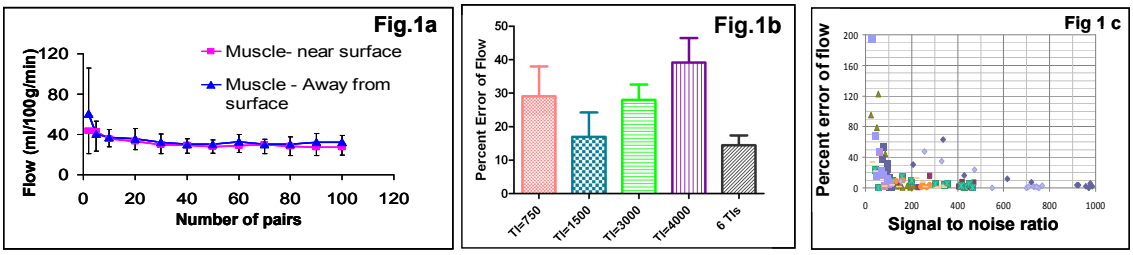

Fig 1: Blood flow measured in muscle under various number of data averaging (n=5) (a), quantification error of single TI vs. multiple TI (b) and Quantification error vs. SNR (c)

Discussion: We demonstrated and optimized quantitative perfusion to measure low perfusion in mouse. Flow as low as 34±7 ml/100g/min was measured in muscle. When the SNR was greater than 100, flow quantification error less than 15% can be obtained in 90% of the ROI analyzed in muscle. The quantification error was 18±5% when using 20 averages with 6 TIs, acquired in 25 minutes. Compared with just using single TI for quantification, results based on multiple TIs have lower variation (Fig.1). Using the optimized sequence, we were able to quantitatively map tumor perfusion in mice. In the tumor, regions of high perfusion can be seen near the periphery and inside the tumor with an average flow of 170±20 ml/100 g/min (n=10). These high flow regions may indicate active angiogenesis in the tumor, compared to the low flow regions in the tumor which had an average flow of 31± 5 ml/100g/min. The non-invasive nature of the technique makes it possible to monitor changes in perfusion rates longitudinally in the tumor which may have the potential to differentiate early drug candidates in preclinical efficacy studies or for early determination of drug efficacy and optimization of treatment strategy in the clinic. The continued development and application of such translational methods may help to elucidate the role of perfusion in tumor development and mechanisms related to treatment in experimental animal models and the clinic.

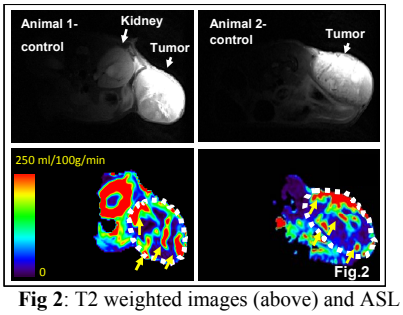

Fig 2: T2 weighted images (above) and ASL flow maps (below) showing heterogeneous perfusion in tumors. Region of high perfusion (yellow arrows) suggest angiogenesis.

References

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