Repeatability and Variability of Pre-Clinical Hepatic Arterial Spin Labelling

Rajiv Ramasawmy[1,2], Adrienne E. Campbell-Washburn[3], Sean Peter Johnson[1], Jack Anthony Wells[1], Rosamund Barbara Pedley[2], Mark Francis Lythgoe†[1], and Simon Walker-Samuel†[1]

[1]*Centre for Advanced Biomedical Imaging, University College London, London, Greater London, United Kingdom,* [2]*Cancer Institute, University College London, London, Greater London, United Kingdom,* [3]*National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD, United States*

Target audience: This abstract will be of interest to those who research arterial spin labelling, liver perfusion and liver disease.

Purpose: Arterial spin labelling (ASL) has been developed in various organs to measure perfusion[1,2,3] but has not yet found extensive utility in the liver, in part due to challenges associated with robustly accommodating its dual vascular supply and susceptibility to respiratory motion. Non-invasive liver perfusion measurements could allow the monitoring of hepatic disease progression and drug efficacy in pre-clinical models of cirrhosis [4] and tumour metastasis [5]. Our previous work has demonstrated the feasibility of single-slice Look-Locker Flow-Sensitive Alternating Inversion Recovery (FAIR) hepatic ASL (hASL) measurements [6]. The aim of this study was to characterise the reproducibility of hASL measurements in mice both within the same imaging session and from imaging sessions separated by one week.

Methods: *ASL acquisition*: Scans were performed on a 9.4T Agilent VNMRS (Agilent Technologies, *Santa Clara, US*) MRI system, using a 39 mm birdcage coil (Rapid Biomedical, Rimpar, Germany). Single-slice perfusion measurements were obtained using a respiratory-triggered inversion, segmented FAIR Look-Locker ASL sequence with a spoiled gradient-echo readout [6]. *In vivo measurements*: Ten age- and weight-matched mice were anaesthetised using 1.5% isoflurane in O_2. Body temperature was monitored and maintained using heated water-pipes. *Repeatability Protocol:* Respiratory-gated fast spin echo images were used to identify an axial imaging slice at the porta hepatis. Four consecutive ASL scans were performed in each mouse, and the protocol repeated one week later.

Post-processing: Perfusion maps were calculated using the Belle model [2], with a blood-tissue partition coefficient of 0.95 ml/g [7] and liver capillary blood T1 of 1900 ms [8]. Perfusion was assumed to be from both the arterial and venous systems. Coefficient of variation (CV) and repeatability coefficients (RC) were calculated for within-session (WS), between-session (BS) and between-animal (A) perfusion[8] for two ROIs: 1) over the whole liver parenchyma visible within the slices, and 2) over a smaller area, typical of a metastastatic lesion approximately 3.5mm^2.

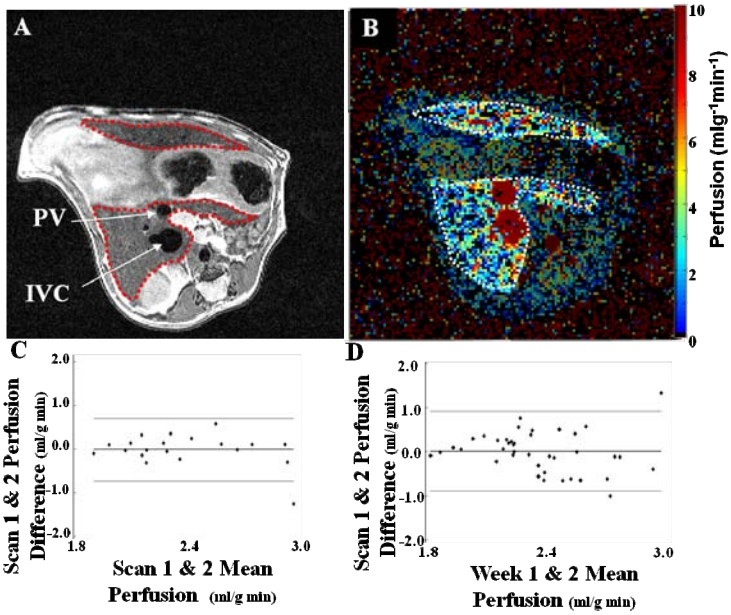

Figure 1: (A) T2w axial abdominal slice with liver region (outlined red) and portal vein (PV) and inferior vena cava (IVC) labelled. (B) Corresponding hASL perfusion map. Bland-Altman plot of mean liver perfusion from measurments acquired within a single imaging session (C) and measurements from acquisitions separated by a week.

Results: Fig. 1 shows an example anatomical T2-weighted image (A) and corresponding perfusion map of the liver (B). On the anatomical images, blood vessels (labelled) appear hypo-intense and intestines appear hyper-intense compared to liver tissue (outlined). The major vessels can be visualised in Fig. 1B due to a high, non-physiological perfusion signal. Across all scans and subjects, mean liver perfusion was measured at 2.2 ± 0.8 mlg^{-1}min^{-1} and agrees well with invasive clearance measurements [7,9]. Within-session (Fig. 1C) and between-session (Fig. 1D) Bland-Altman analysis over the liver parenchyma or metastases-sized ROI (data not shown) shows no magnitude dependence or trend. The smaller ROI produced a larger variability and RCs (Table 1). The largest variability for both ROIs was observed between each animal, suggestive that inter-animal variations are larger than the ASL variability, although robustly isolating each source of variability is not straightforward.

	Whole Liver	Met-sized ROI
CV_{WS}	7 ± 1%	20 ± 2%
CV_{BS}	9 ± 1%	30 ± 4%
CV_A	15 ± 1%	33 ± 1%
RC_{WS}	18%	43%
RC_{BS}	29%	80%

Table 1: Coefficients of Variation (CVs) and Bland Altman Repeatability Coefficients (RCs) calculated over the whole liver and a metastasis-sized ROI. Values are calculated for within-session (WS), between-session (BS) and between animal (A).

Discussion & Conclusions: We have previously shown the feasibility of mouse hepatic ASL (hASL), using a Look-Locker FAIR approach [6]. hASL is still relatively novel and has not yet been extensively reported in the literature, and here we have quantified its repeatability, which will enable study design in the application of the technique to pre-clinical disease models. The calculated CVs and RCs for the whole-liver ROIs (approx. 85mm^2) will find utility monitoring gross hepatic diseases such as cirrhosis and fibrosis. However, the smaller, metastasis-sized ROI RCs indicate that a much larger change in perfusion is required to be for statistical significance; the technique may be limited to longitudinally monitor perfusion variations between different sessions, but may be sensitive enough to detect acute induced fluctuations within an imaging session. Also, given that hASL does not require the injection of a contrast agent, repeated scans can be used to probe acute changes in liver or lesion blood flow, such as we recently showed following treatment of liver metastases with a vascular disrupting agent [10].

Acknowledgements: This work was supported by an MRC Capacity Building Studentship, the British Heart Foundation, King's College London and UCL Comprehensive Cancer Imaging Centre CR-UK & EPSRC, in association with the DoH (England).

References: [**1**] Golay X, *et al*. *Top Magn Reson Imaging*. 2004; 15:10-27. [**2**] Belle V, *et al*. *J Magn Reson Imaging* 1998;8;1249-1245. [**3**] Karger N, *et al. Magnetic Resonance Imaging*. 2000; 18:641-647. [**4**] Van Beers B, *et al. AJR.* 2001;176:667-673. [**5**] de Bazelaire C, *et al*. *Clin Cancer Res.* 2008; 14:5548-5554. [**6**] Ramasawmy R. *et al. Proc Intl Soc Magn Reson Med* 2012 20:2900. [**7**] Rice G *et al*, J Pharmacol Methods. 1989 Jul;21(4):287-97. [**8**] Campbell-Washburn AE, *et al Magn Reson Med* 2012 2013 Jan;69(1):238-47. doi: 10.1002/mrm.24243. Epub 2012 Mar 12. [**9**] Pollack,G.M., *et al*. *Drug Metab Dispos.* 1990, **18**, 197-202. [**10**] Johnson SP, *et al. Proc Intl Soc Magn Reson Med.* 2013 21:0506.