Separation of arterial and portal blood supply to mouse liver and tumour tissue using pseudo-Continuous Arterial Spin Labelling (pCASL)

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Target Audience: This work will be of interest to researchers studying liver perfusion, and mouse models of cancer.

Purpose: Non-invasive measures of liver blood flow (LBF) could be used to monitor hepatic disease progression and drug efficacy in pre-clinical models of cirrhosis[1] and tumour metastasis[2]. We have previously demonstrated Look-Locker Flow-Sensitive Alternating Inversion Recovery (FAIR) ASL measurements for measuring total (arterial and venous) liver perfusion[3], however pseudo-continuous ASL[4] offers increased perfusion signal and vessel selective tagging to individually estimate the portal vein (PV) and the descending aorta (DA) perfusion[5]. In healthy livers, the PV delivers approximately 75% of the blood to the liver, and the ability to assess the relative blood supply could be a powerful tool in the study of liver diseases[6]. Here we examine the feasibility of using a vessel selective pCASL method to measure mouse hepatic perfusion and compare it to FAIR.

Methods: Mice were scanned in a 9.4T Agilent VNMRS 20 cm system (Santa Clara, USA), using a 39 mm birdcage coil (Rapid Biomedical, Rimpar, Germany). PV (n = 8) and DA (n = 5) tagging was performed separately by positioning the mouse so that the tagging vessel and imaging slice were local to the isocentre in order to reduce B_0 inhomogeneties and optimise the EPI readout. In order to only invert portal venous blood, the tag location was centred inferior to the celiac trunk, to eliminate hepatic artery tagging. A single-shot gradient-echo EPI readout (TE = 7s) followed a balanced pCASL preparation (20 control-tag pairs, tag duration 3s, post-labelling delay 0.3s, Hanning duration/spacing 0.6 ms/ 1.2 ms, minimum tag gap 2mm). PV tag: G_{max}/G_{ave} = 6.3/0.3 Gcm^{-1}, DA tag: G_{max}/G_{ave} = 4.2/0.2 Gcm^{-1}. These were both optimised for the vessel velocities as measured with phase-contrast MRI. The pulse train was respiratory-triggered, and the readout was timed to be in a phase of respiratory quiescence[7]. Perfusion was calculated using the general kinetic model, using a reported tagging efficiency estimated from mice kidney pCASL[7]. For comparison, total liver perfusion measurements were also obtained using a Look-Locker FAIR ASL sequence[6]. Finally, an experiment tagging both the PV and DA was performed in a mouse with liver tumours[8]. Hepatic perfusion index (HPI) was calculated as the using LBF_{DA} / $(LBF_{DA} + LBF_{PV})$ [9].

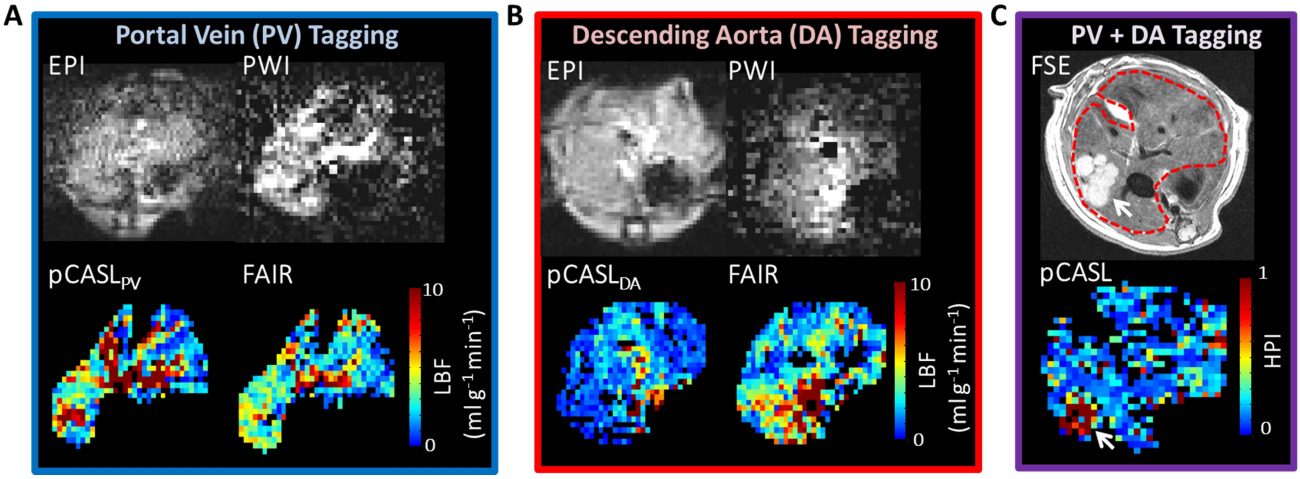

Fig 1: Estimating hepatic perfusion from PV (A) and DA (B) pCASL tagging in two separate example mice: Anatomical single shot GE-EPI image within the liver, resultant perfusion weighted image (PWI), calculated pCASL perfusion map and corresponding FAIR perfusion map. (C) Application of a PV and DA pCASL tag to a model of liver metastasis – the tumour region appears hyper-intense (arrow) relative to the liver (red outline) on fast spin echo (FSE) images. In the corresponding HPI map, the tumour region exhibits a distinctly arterial supply as shown by a markedly increased HPI (arrow).

Results: Figure 1 shows example data sets with selective PV (A) and DA (B) tagging in separate mice. Single-shot EPI was found to be suitable within a mouse liver at high-field; the resultant perfusion weighted image (PWI) exhibit a good SNR. Calculated pCASL perfusion maps are shown adjacent to resolution matched FAIR images. A good visual correspondence can be seen in the PV and FAIR images (A), LBF_{FAIR} = 3.4 ± 0.7 $mlg^{-1}min^{-1}$, LBF_{PV} = 3.0 ± 0.3 $mlg^{-1}min^{-1}$ (n = 8, mean ± std), and a lower DA perfusion value was measured (B), LBF_{DA} = 1.0 ± 0.5 $mlg^{-1}min^{-1}$, LBF_{FAIR} = 2.2 ± 0.5 $mlg^{-1}min^{-1}$ (n = 5). Combined pCASL perfusion (mean ± std) was greater than the FAIR estimates: $(LBF_{PV} + LBF_{DA})/ LBF_{FAIR}$ = 137 ± 27%, though the mean ratio of the LBF_{DA} to the $(LBF_{DA}+LBF_{PV})$ was 25 ± 14%. The median HPI measured in the tumour region (arrow, C) was 108%, and the median HPI measured in the liver parenchyma was 16%, indicative of the metastases being arterially perfused.

Discussion: This is the first demonstration of pseudo-continuous ASL in a mouse liver. The PV-tagged perfusion images show encouraging visual correspondence to previously established Look-Locker FAIR perfusion estimates of total liver blood flow, and the DA perfusion exhibited expectedly lower perfusion. The portal vein delivers approx. 75% of the total blood supply to the liver, and the ratio of pCASL perfusion estimates agrees well with this. However, the combined pCASL perfusion was greater than the FAIR measurements, which could be due to the different quantification approaches applied[3,7]. The HPI was seen to be markedly increased in the tumour region, as has been previously described[9]. However, the normal liver HPI is underestimated which may be due to different tagging efficiencies of the PV and DA.

References: [1] Van Beers B, *et al. AJR.* 2001;176:667-673. [2] de Bazelaire C, *et al. Clin Cancer Res.* 2008; 14:5548-5554. [3] Ramasawmy R. et al. Proc Intl Soc Magn Reson Med 2014 22:2725. [4] Dai WY, Garcia D, de Bazelaire C, Alsop DC. Magn Reson Med 2008;60:1488–1497. [5] Schalkx H, et al. *Proc Intl Soc Magn Reson Med* 2014 22:372. [6] Ballatyne KC, *et al.* Nucl Med Commun. 1990 Jan;11(1):23-8. [7] Duhamel G, *et al.* Magn Reson Med 2013;71:1186-1196. [8] Dearling,J.L. *et al. Nucl. Med. Biol.* 2009; 36, 883-894. [9] Miles KA, *et al. Radiology.*1993; 188:405–411.

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