Monitoring of Rat Liver Regeneration following Portal Vein Ligation using MR Volumetry and Hepatic Arterial Spin Labelling

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Target Audience: This abstract will be of interest to researchers interested in pre-clinical models, liver regeneration and liver perfusion.

Aim: Associated Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS)[1] is a recently developed surgical technique that encourages liver growth following selective vessel ligation. This procedure is used clinically prior to partial hepatectomy for patients with primary or metastatic hepatic malignancies where resection is the optimal curative procedure, but small remnant liver volumes result in poor clinical outcomes. This study used MRI to monitor the liver re-growth in a rat model of selective portal venous ligation (PVL) and additionally investigated the use of hepatic arterial spin labelling (hASL)[2] to determine functional liver changes.

Methods: ***PVL Surgical Procedure****:* Sprague-Dawley livers were grouped into 4 lobe groups: the Left Lateral Lobe (LLL), Right Upper and Right Lower (RU & RL), Right Median lobe (RM), and the Caudates (fig. 1A). The LLL and RU & RL portal vein branches (fig. 1A) were selectively ligated using suture in two rats; the neighbouring RM and caudate lobes will then be expected to hypertrophy as a result of the induced atrophy in the ligated lobes[3]. ***In vivo measurements***: Scans were performed on a 9.4T Agilent VNMRS (Agilent Technologies, *Santa Clara, US*) 20 cm horizontal-bore system, using a 72 mm birdcage coil. Animals were imaged on day 2, 5, and 7 after surgical procedure. Animals were anaesthetised using 1.5% isoflurane per litre of oxygen and positioned in the magnet iso-centre. Core body temperature was monitored and maintained using heated water pipes (SA Instruments*, NY, US*). ***Anatomical MRI****:* A high resolution, respiration gated, multi-slice Fast Spin Echo (FSE) sequence was used to image the whole liver. Sequence parameters: slice thickness 0.75mm, FOV 65 x 65 mm^2, matrix size 256 x 256, effective TE = 19 ms, $k_0 = 3$, ETL 4, TR=200. ***ASL acquisition***: Hepatic perfusion measurements were obtained using a respiratory-triggered inversion, segmented FAIR Look-Locker ASL sequence[2]. ***Post-processing***: Livers were segmented using Amira (FEI, Oregon, USA). Perfusion was estimated using the Belle model[3]: with a blood-tissue partition coefficient of 0.95 ml/g[4] and capillary blood T_1 of 1900 ms[5]. Perfusion estimates represent the sum of arterial and venous blood supplies.

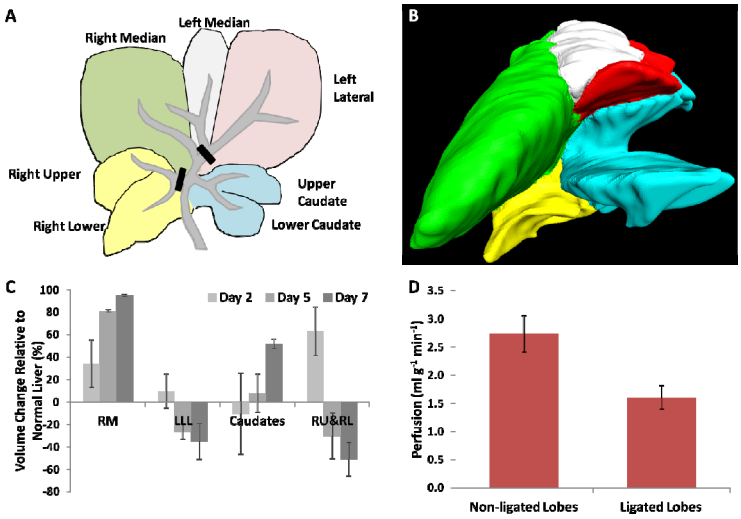

Figure 1: Schematic of rat liver lobes (A) and ligation loci (black); colour-code has been maintained for an example of caudo-cranial 3D visualisation segmented from high resolution MRI at day 7 post surgery (B). RM and caudate lobes hypertrophied while LLL and RU & RL atrophied over the course of a week (C), and a significant perfusion difference was measured between ligated and non-ligated lobes (D).

Results: The portal vein ligation induced atrophy in the LLL and RU & RL as expected, while promoting hypertrophy in the RM and caudate (fig 1B & C). Percentage volume changes relative to a weight-matched liver at day 7 were 95 ± 1 % (RM), -35% ± 16 % (LLL), 52 ± 4 % (Caudates), -51 ± 15 % (RU & RL), No trend was shown in lobe perfusion over the week, however a significant ($p < 0.01$, Mann Whitney-U) mean perfusion deficit was observed in ligated lobes (1.6 ± 0.6 $mlg^{-1}min^{-1}$) relative to hypertrophic, non-ligated lobes (2.8 ± 0.4 $mlg^{-1}min^{-1}$) averaged over the three time points (fig. 1D).

Discussion & Conclusion: This pilot study aimed to non-invasively monitor a novel model of liver regeneration. We show in this model that the right median lobe almost doubled in volume 1 week post-surgery. This rapid regeneration will be greatly beneficial to resection patients by ensuring these patients have an adequate post-resection liver volume, in addition to reducing waiting time prior to hepatectomy. We have previously shown the feasibility of localised liver perfusion measurements using a Look-Locker FAIR-ASL technique, and have here demonstrated an application to a model of selective portal ligation as means of determining viable liver tissue; in order to non-invasively improve on volumetric assessment of future liver remnant. Typically, the portal vein supplies ~75% [6] of the blood to the liver; however an approximate 40% decrease in perfusion was measured in lobes with a ligated portal supply – this may be due to the hepatic arterial buffer response, which can accommodate reduction in portal venous flow[7]. Previous clearance [4] measurements of rat livers have measured lobe perfusion at 2.41 $mlg^{-1}min^{-1}$: the hypertropic lobes display a slight raised perfusion from this value and the atrophic lobes show an expected reduction of blood delivery. Post-surgical perfusion measurements may inform surgical success and highlight candidates likely to need liver support. Additionally these measurements may offer insight to the mechanism of lobe growth. We hope to further validate the ASL in comparison to measures of hepatocyte function in this regeneration model. Finally, as brain and kidney FAIR ASL is commonplace in clinical scanners, we anticipate that translating hepatic ASL into a clinical setting would be straightforward and that non-invasive liver perfusion measurements would find application in monitoring liver regeneration as well as a number of hepatic diseases [8, 9].

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