

Validation Of A Novel Fine Structure MRI Technique Using A Porcine Liver As Phantom For Liver Fibrosis

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Background Recent progress towards understanding the pathogenesis of liver fibrosis and the growing list of potential drug targets highlights the need for safe and accurate diagnostic tools for quantifying the fine fibrotic structures present in chronic liver disease (CLD), [1]. Conventional MRI is excellent for directly visualising fibrotic change in advanced disease but it is resolution-limited at detecting fibrosis during the early, preclinical stages of liver disease. *Fine structure MR analysis* may be ideally suited for this purpose as it provides a quantitative measure of macro- and microstructures. High resolution is achieved through the selective excitation of an internal volume and the subsequent analysis of one-dimensional finely sampled, spatially encoded complex echoes [2]. In characterizing early stage fibrotic disease the fine structure “signature” would be expected to change significantly with the development and progression of bridging fibrous septa in CLD. Establishing and quantifying the fine structure signatures in CLD progression is problematic due to the difficulty of getting accurate histological references. In addition, clinical imaging limitations prevent MR from providing sufficient resolution to quantify these fine structures in human liver tissue, particularly in early disease.

Aims The aim of this study is to demonstrate the utility of ex-vivo livers as phantoms for establishing fine structure signatures in order to inform the development of suitable MR imaging protocols for the clinical assessment of CLD.

Methods Fresh livers from recently slaughtered oxen and pigs were used as phantoms to simulate healthy and fibrotic CLD in humans. A healthy pig’s liver exhibits a distinct “chicken wire” fibrotic structure with sizes ranging between ~1.5-4mm, very similar to the fibrotic pattern in human CLD. Healthy ox liver does not exhibit fibrosis and has a similar vascular structure to healthy human liver, where the vascular spacing is in the range of ~0.6 to ~1.5mm. Figure 1a shows the fibrotic structure of porcine liver lobules, which is not visible in ox livers at the same magnification. Samples from the individual livers were placed side by side in suitable containers to allow simultaneous scanning. A human Siemens 3T Trio TIM MRI scanner running an in-house developed pulse sequence provided one-dimensional complex data from a finely-sampled, selectively-excited internal volume of 15x15x70mm that encompassed both samples. We used TRs of 500 and 2000ms, with a spin echo TE of 12.5ms to match the acquisition parameters in an on-going clinical study. For this phantom study we were able to use 200 repetitions to ensure a high SNR rather than the eight repetitions possible in a single breath hold in clinical use. Analysis with in-house-developed signal processing software produced the structural wavelength spectra such as shown in fig. 1c.

Results and discussion Figure 1c shows representative examples from the fine structure spectra of the pig and ox liver specimens generated by analysis of the leading edge of the 12.5ms spin echo with a TR of 500ms. These spectra exhibit distinctly different spectral “signatures” characteristic of the fine structures observed in histology. Two major categories of repetitive structures (textures) – vessel to vessel spacing (0.5 to 1.5mm) and lobule to lobule spacing (1.5 to 4mm) are apparent in histology and the fine structure spectra as seen in fig. 1b and c. Pig liver clearly shows a predominance of the larger wavelength structures corresponding to the size of the lobules. This is because the lobules are “decorated” by fibrotic tissue, which not only enhances the repeating lobule wavelength, but also makes vessel to vessel spacing less apparent by bridging between the vessels and attenuating the peaks indicative of this smaller spacing. The observed spectral differences clearly differentiate pig from ox livers. These results support the use of fine structure analysis to distinguish between normal and fibrotic liver tissue in diagnosing, staging, and monitoring CLD. Optimisation of sequences for human use is ongoing.

References [1] RG Wells, *Gastroenterology*, 2009; 136:387–388. [2] GS Almeida et al., “Structural spectroscopic analysis of tumor vasculature before and after contrast agent administration to mice”, presented at Joint Annual Meeting ISMRM-ESMRMB, Stockholm, Sweden 2010.

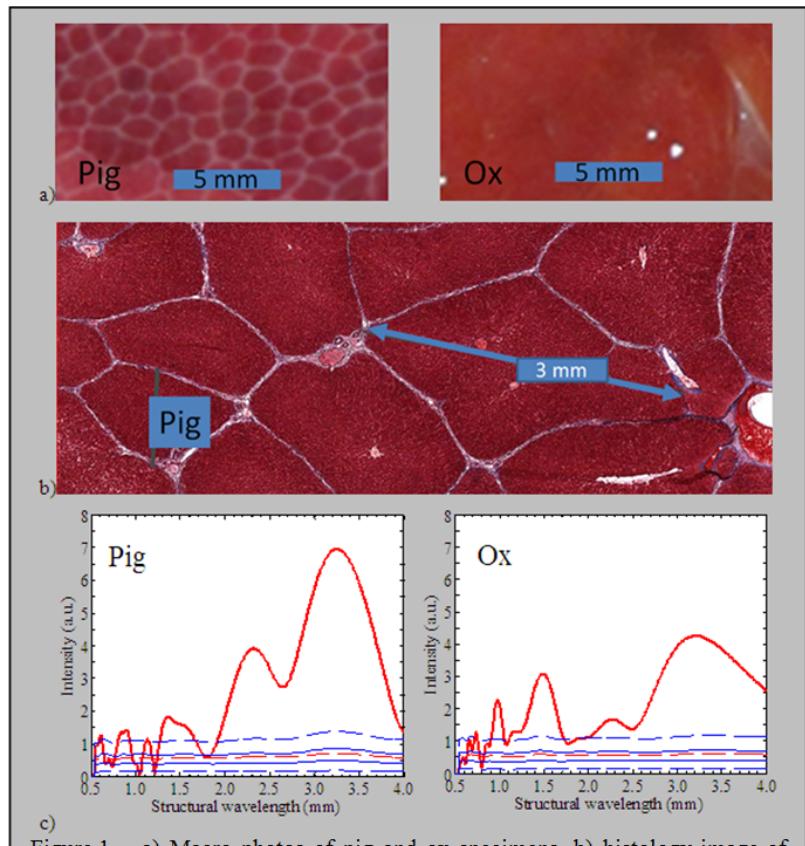


Figure 1 a) Macro photos of pig and ox specimens, b) histology image of pig liver – note the vascular spacing and lobule sizes, c) structural spectra from pig and ox liver specimens. The dashed red line indicates mean noise level and the blue lines ± 1 and $\pm 2\sigma$ confidence intervals. The magnitude of the structural features with wavelengths below ~1.5mm are clearly attenuated relative to those >~1.5mm for the pig relative to the ox.