Title:
Multi-organ quantitative MRI for the assessment of liver disease – a whole much more than the sum of its parts

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Non-invasive assessment of liver disease remains a major challenge. Ultrasound derived biomechanical measurements (FibroScan and shear wave elastography) are widely used because of their relatively low cost and proximity to the patient bedside but sample only small areas of the liver, and thus suffer the same sampling limitations of liver biopsy. MR based methods are inherently more comprehensive, sampling the whole organ, with the potential to assess tissue composition using T1 mapping[1], alongside accurate quantification of liver fat (proton-density fat fraction mapping)[2] and liver iron (T2* mapping)[3].

While our ability to non-invasively assess liver disease continues to grow, the evolution of chronic liver disease remains unpredictable. Against a backdrop of progressive hepatic fibrosis and eventual cirrhosis, vascular derangements underpinning decompensation arise in concert with dysfunction in other organs such as the spleen, kidneys and heart. The implications of this are two-fold: firstly that effective non-invasive assessment and prognostication of liver disease calls for methods that evaluate both haemodynamic and tissue characterisation; secondly, that methods focussing purely on assessing the liver are missing out on major pieces of the puzzle[4].

In this issue of the journal, Bradley et al.[5] take on this challenge by proposing a quantitative MRI protocol that measures organ volume, afferent vessel flow, tissue T1 and arterial spin labelling (ASL) perfusion in the liver, spleen and kidneys, with imaging of the heart for measurements of cardiac output and ventricular muscle mass. The MR methods proposed do not require any intravenous contrast, and to improve patient acceptability, comfort and clinical practicality, can be completed within a single scan lasting less than one hour.

Liver T1 measurements for patients with advanced fibrosis are validated with biopsy, ELF scores and transient elastography – correlative data is reassuring and matches previously published validation data for liver T1[6]. Liver ASL perfusion validation using ICG PDR and R15 rates is less impressive but this may reflect limitations in the validation standard rather than ASL, as formal ICG clearance was not used[7]. Four-week reproducibility in a small cohort of healthy volunteers is poorest for measurements of hepatic arterial flow (coefficient of variation of 22.7%), reflecting challenges that arise from bulk flow measurements of this vessel[8], but for T1 measurements, is less than 2.0%, and an acceptable 12.0% for liver ASL perfusion. Reproducibility was, however, not tested in the patient cohort.

The authors present data from compensated cirrhotics, and compare this with healthy volunteers and a small cohort of decompensated cirrhotics. Increasing liver T1 and significant reductions in liver ASL perfusion are seen with increasing disease severity, alongside increases in bulk total liver blood flow. Associations between disease severity and liver T1 are consistent with previous reports[9] but reductions in liver ASL perfusion are novel and highlight the potential clinical/research applications for this method. The disparity between changes in bulk total liver blood flow and liver ASL perfusion are intriguing. Normalising bulk liver blood flow to liver volume still does not mirror the systematic decline in liver ASL perfusion and normalised bulk total liver blood flow only exceeds ASL perfusion in the decompensated cohort. The authors postulate that this may be related to intrahepatic shunting, but this would be difficult to prove. Intrinsic methodological differences between Flow-sensitive Alternating Inversion Recovery (FAIR) ASL and bulk flow phase-contrast MRI data could account for this, in addition to the many technical challenges that arise when assimilating multimetric MR data[10].

Increasing disease severity was associated with increases in splenic T1, reduced splenic ASL perfusion alongside increased arterial inflow and bulk SMA flow. Increasing splenic T1 likely reflects evolving tissue compositional changes but the reduction in splenic perfusion is a novel observation, highlighting the presence (and importance) of multiorgan vascular dysfunction. Interestingly, splenic arterial velocity has previously been identified as a predictive variable for hepatic venous pressure gradient (HVPG)[11] and in this study, volume normalised bulk splenic arterial blood flow reduces with disease severity (unlike in the liver).

Reductions in renal cortical T1 with progressive disease severity underscore the importance of multiorgan assessment and potential utility of the protocol to probe liver disease pathophysiology and complications such as hepatorenal syndrome. Reductions in T1 signal may be due to hypoperfusion[12], although reductions in renal ASL perfusion were not significant.

Systemic vascular dysfunction, demonstrated through rises in cardiac index, heart rate and reduced body surface area normalised left ventricular wall mass are also seen with increasing disease severity. Cardiac dysfunction in liver disease is well documented[13,14] but the ability to assess the degree of dysfunction alongside changes in the hepatic, splanchnic and renal vascular beds, offers great potential for comprehensive evaluation of new and established vasoactive treatments such as beta-blockers, that may have deleterious systemic effects in patients with decompensation.[15].

Longitudinal data for a small number of adverse liver-related outcomes (LROs) over a period of 6 years are also used to assess the predictive potential of MRI measures. Despite the small sample size, associations between LROs and higher liver T1, lower renal T1, lower liver and splenic ASL perfusion, lower bulk total liver blood flow and higher SMA flow were seen, which is encouraging. These data underscore the need for larger-scale multicentre MRI studies with the potential to develop new composite biomarkers for patient prognostication and treatment stratification and for trial endpoints, particularly in the context of more advanced disease.

Ultimately, the authors use the MR data to postulate that the combination of hyperdynamic systemic circulation, structural changes in the liver, reduced hepatic perfusion and splanchnic pooling may simultaneously drive increases in HVPG. MR data is used to model HVPG and highlight differences between the cohorts. This data is again encouraging but it is worth noting that work used to develop the HVPG model, reported only weak correlations between hepatic and splenic ASL perfusion and HVPG[11]. The authors go on to propose that failure to compensate for reduced effective circulatory volume may represent the tipping point underlying poor clinical outcomes in the presence of sepsis and increased inflammation. The prospect of using MR protocols to non-invasively test these hypotheses in the clinical setting is tantalising and promises to yield much needed data in this vulnerable cohort.

The authors acknowledge important limitations of this study, the most significant being the small sample size of the decompensated cohort and number of LROs. The study also includes a small number of patients already on beta-blockers (n=6) – the impact of these on the overall conclusions is unclear. Methodological considerations must also be highlighted: T1 relaxometry using inversion recovery with fat suppression is an important strength given the prevalence of steatosis in liver disease, particularly as liver fat is a potential confounder when using other published methods such as modified Look-Locker inversion recovery[16]. This also raises important wider questions about the compositional implications of T1 itself – although a clear link with increasing disease severity has been reported here and elsewhere, studies exploring the compositional changes in fat, protein-content (i.e. collagen deposition) and iron, and their effect on T1 are needed[1]. Looking ahead, the authors have amassed broad experience of using FAIR ASL but other more complex ASL approaches may yet be able to provide even more detailed hepatic haemodynamic characterisation. We look forward for example, to the implementation of pseudo-continuous ASL, which may yield greater insight through separate quantification of hepatic arterial and portal venous perfusion[17]. Non-invasive MR methods for quantification of important haemodynamic parameters such as intrahepatic shunting are also still lacking.

Multiorgan phase-contrast MRI protocols have been applied previously, with increases in hepatic arterial flow and splanchnic pooling reported in smaller cohorts of patients[18,19]. MR protocols have also been applied to evaluate the effects of vasoactive drugs including serelaxin and beta-blockers[20,21]. The multiorgan evaluation of tissue composition (using T1 relaxometry) and perfusion (using ASL) are however novel and in this study demonstrate how application of these methods alongside measures of bulk flow, can yield new insights into liver disease.

In conclusion, the data presented by Bradley et al[5] in this issue of the journal heralds the arrival of multi-organ quantitative MRI as an exciting and useful tool for the assessment of liver disease. Applications go beyond assessment and prognostication and include new insights into pathophysiology and a much-needed tool to better guide therapeutic intervention in portal hypertension and haemodynamically driven LROs. The immediate challenge for the wider hepatological and imaging community will be in adopting and driving forward large scale multicentre studies collecting data from decompensated and compensated cirrhotics. More streamlined, faster multi-organ quantitative MRI protocols will then enable each part to genuinely sum to an even greater whole.

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