Shear Wave Speed and Attenuation as Surrogate Imaging Biomarkers for the Quantification of Liver Fibrosis and Inflammation

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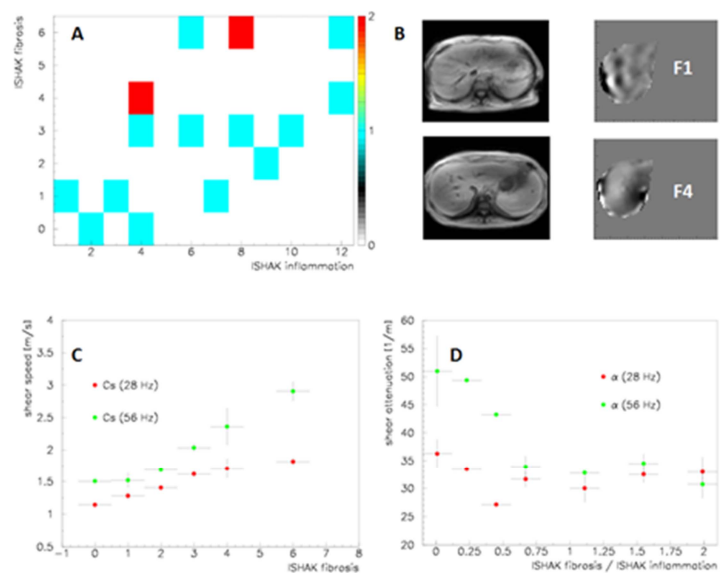
PURPOSE: The staging and management of liver fibrosis is multifactorial and complex. For instance, staging of liver fibrosis is complicated when inflammatory components are present, which is often the case. Among the available imaging biomarkers for assessing the degree of fibrosis, shear stiffness measurements have shown great promise. However, inflammation changes liver stiffness equally, rendering the stiffness parameter sensitive to the presence of fibrosis/inflammation, but not specific. This clinical study included 17 patients with biopsy proven chronic liver disease. The biomechanical parameters used for the analysis were shear wave speed c_s $[m/s]$ and shear wave attenuation α $[1/m]$. The advantage of this formulation is that those parameters are describing physical phenomena which are completely disentangled from each other, different to the formulation in terms of complex-valued shear modulus G^*. The aim is to provide a set of two physical shear wave parameters (c_s, α) that represent surrogate imaging biomarkers for fibrosis and inflammation simultaneously.

METHODS: 17 patients with biopsy proven chronic liver disease, including steatohepatitis and chronic hepatitis C, underwent a 3T liver MR-elastography (MRE). The protocol consists of a modified FFE sequence[1], with motion sensitized gradients at 165Hz (fractional motion encoding), an in-phase echo time of TE=6.9ms (no fat suppression), 8 snap-shots of the mechanical wave, and an isotropic resolution of 4x4x4mm³. Mechanical waves are generated via a surface transducer attached to the right side of the rib cage vibrating either at 28Hz or at 56Hz. Mechanical waves are imaged in all 3 directions within a volume of 9 slices centered transversally in the middle of the liver. The MRE protocol consists of 4 scans (the 3 spatial motion directions and one reference scan) performed in breath-hold, each taking ~14sec. Detailed histological analysis was performed on the biopsy samples for all patients providing the modified histologic activity index (ISHAK) fibrosis and inflammation score[2]. Reconstruction of the MRE data was done as described in[3] with the difference that we solve for the k-vector of wave propagation, i.e. $k = \beta + i\alpha$, which yields directly the shear wave attenuation α and via $c_s = \frac{\omega}{\beta}$ the shear wave speed. Analysis of the data was performed by blinded operator.

RESULTS: Fig.A shows the distribution of our patient collective in the ISHAK score space, ISHAK fibrosis versus ISHAK inflammation score. There is an overall trend that increased fibrosis is accompanied by increased inflammation, however the spread is rather large and does not allow one parameter to be deduced from the other. As presented in **Fig.B**, shear wave penetration is very good and increased fibrosis leads clearly to increased shear wavelengths (indicating increased shear wave speed and hence increased liver stiffness). **Fig.C** shows the calculated shear wave speeds c_s at the two vibration frequencies 28Hz and 56Hz as a function of ISHAK fibrosis score. As expected from previous studies[4], shear wave speed increases with increasing fibrosis score which allows determining the first histological parameter. The higher excitation

A: patient cohort in the ISHAK plane of fibrosis score vs inflammation score. **B:** selected patient examples for F1 and F4 showing good wave penetration and increased shear wave length for F4 compared to F1. **C:** shear wave speed c_s as a function of ISHAK fibrosis score at 2 different frequencies. **D:** shear wave attenuation α as a function of ISHAK score ratio. While α @ 28Hz does not yield any valuable information, α @ 56Hz is for score ratio values below 1 significantly increasing.

frequency at 56Hz provides a larger dynamical range (due to the underlying power law for the viscoelastic parameters) which is beneficial for the classification. **Fig.D** shows the wave attenuation as a function of *(SR)*, i.e. the normalized ISHAK fibrosis score divided by normalized ISHAK inflammation score. For $SR > 1$, the fibrotic component is stronger than the inflammatory component. On the contrary, for $SR < 1$, the inflammatory component is dominant over the fibrotic component. Apparently, the shear attenuation α at 28Hz does not provide valuable information. This is most likely due to SNR limitations preventing us to properly measure α at frequencies as low as 28Hz (mind that $\alpha \propto \omega^y, y \in [0,1]$, hence resulting in low attenuation for low frequencies). On the contrary, α at 56Hz is getting sufficiently large and we observe a significant increase for score ratios SR below 1, while for score ratios above 1 a flat behavior is found. This allows estimating for attenuation values $\alpha > 35$ $\left[\frac{1}{m}\right]$ the score ratio SR. That score ratio in combination with the absolute ISHAK fibrosis score measured via the shear wave speed c_s enables us to evaluate the missing inflammation score. Hence, both absolute ISHAK score can be recuperated from (c_s, α).

CONCLUSION & CLINICAL IMPACT: Assessment of liver fibrosis and inflammation is critical to the clinical management of liver disease patients. Here, we propose to utilize shear wave speed c_s and attenuation α measured at 56Hz to non-invasively estimate the ISHAK scores for fibrosis and inflammation. This method is capable of detecting various stages of fibrosis in addition to inflammation when the latter is more dominant than fibrosis (score ratio SR<1 in **Fig.D**). On the contrary, in case of a dominant fibrotic component ($SR > 1$), α does not allow an adequate estimation of inflammation. These observations are probably a reflection of the increased density of infiltrating white blood cells measured by the ISHAK inflammation score. Such necroinflammatory activity may also be associated with increased fluid accumulation as a consequence of denser and leakier microvasculature that usually results from the released cytokines and chemokines related to inflammation. The attenuation measurements are thus increased when these changes overwhelm the hepatic microenvironment as indicated by lower fibrosis/inflammation ratio. A higher frequency is probably more susceptible to these small attenuation changes synonymous to the effect of obesity on higher frequency ultrasound probes. Overall, these findings might be of substantial clinical implication, as inflammation frequently accompanies and accentuates liver damage and the development of fibrosis. Additionally, inflammation is usually easier to reverse and reverses prior to fibrosis when using therapy to treat the underlying liver disease. Thereby this technique allows for a non-invasive method of simultaneously assessing both hepatic fibrosis and inflammation and potentially monitoring the effects of therapies.

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