

## The influence of inflammation and fibrosis on multifrequency and monofrequency MR elastography parameters: a study in 47 patients with chronic viral hepatitis

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**Purpose** The quantification of liver inflammation is important for therapeutical decisions and follow-up in several chronic liver diseases such as nonalcoholic steatohepatitis and chronic viral hepatitis. Yet, there is currently a lack of accurate and noninvasive methods for assessing liver inflammation, and histopathological analysis of percutaneous liver biopsy samples remains the gold standard despite its invasiveness and lack of spatial coverage. Inflammation is characterized by contraction of hepatic stellate cells, differential expression of matrix metalloproteases, and an altered hemodynamic state(1), and can induce matrix synthesis through profibrotic processes. All these factors are susceptible to have an influence on the frequency response of the mechanical properties of tissues(2). Hence, the purpose of this study was to evaluate multifrequency MR elastography as a method for assessing liver inflammation in patients with viral hepatitis.

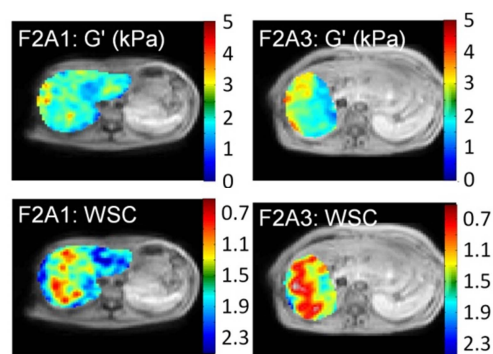
**Methods** Forty-seven patients with viral hepatitis B (n=16) or C (n=31) were examined with multifrequency MRE using a gradient-echo acquisition sequence and simultaneous excitation frequencies of 28Hz, 56Hz and 84Hz(3). Mechanical properties (absolute value of the shear modulus:  $|G^*|$ , real part:  $G'$  (storage modulus), imaginary part:  $G''$  (loss modulus)) were reconstructed using a complex local viscoelastic reconstruction. For all parameters, the frequency response was assessed using a power law. The frequency response of  $|G^*|$ , which we named "wave scattering coefficient" (WSC), was analyzed in more details. ROC curves of pooled inflammation and fibrosis scores were calculated, as well as calculation of Obuchowski metrics. Uni and multivariate analyses were carried out.

**Results** WSC decreased with increasing inflammation grades (Metavir activity score A0:  $1.47 \pm 0.19$ , n=7; A1:  $1.24 \pm 0.22$ , n=27; A2:  $1.04 \pm 0.13$ , n=10; A3:  $0.96 \pm 0.06$ , n=3), while, in agreement with previous reports(4), fibrosis resulted in increased storage modulus  $G'$  (Metavir fibrosis score F0:  $2.09 \pm 0.22$ kPa, n=5; F1:  $1.93 \pm 0.16$ kPa, n=19; F2:  $2.58 \pm 0.41$ kPa, n=9; F3:  $2.80 \pm 1.03$ kPa, n=9; F4:  $4.49 \pm 1.33$ kPa, n=5). Typical parametric maps are represented in Fig. 1. For inflammation grades  $<2$  vs.  $\geq 2$ , the ROC area for WSC was 84% at a threshold of 1.22 (Se=100%, Sp=68%) and a 86% Obuchowski score. For fibrosis stages  $<2$  vs.  $\geq 2$ , the ROC area was 91% at a threshold of 2.25kPa (Se=83%, Sp=96%) and a 88% Obuchowski score. At univariate analysis, WSC was mildly but significantly correlated to inflammation grade (Spearman  $r = -0.63$ ,  $p < 0.0001$ ) and to fibrosis (Spearman  $r = -0.50$ ,  $p < 0.001$ ). The only other parameter with significant correlation to inflammation was  $G'$  at 56Hz, with a lower correlation (Spearman  $r = 0.34$ ,  $p < 0.05$ ). The highest correlation for fibrosis was obtained with the monofrequency parameter  $G'$  at 56Hz (Spearman  $r = 0.65$ ,  $p < 0.0001$ ). At stepwise multivariate analysis, fibrosis was found to significantly influence the 56Hz parameters  $G'$  ( $R^2 = 0.3$ ,  $p < 0.001$ ),  $G''$  ( $R^2 = 0.48$ ,  $p < 0.0001$ ), and  $|G^*|$  ( $R^2 = 0.45$ ,  $p < 0.0001$ ), while inflammation was found to be the sole independent variable for WSC ( $R^2 = 0.36$ ,  $p < 0.0001$ ). Patients with F2 fibrosis and A1 inflammation had significantly higher WSC than F2 patients with inflammation grades A2 or A3. The same observation and statistical significance were obtained in patients with F3 fibrosis.

**Discussion** Our results indicate that in patients with viral hepatitis, WSC, the slope of  $|G^*|$ , is mainly determined by inflammation, while monofrequency parameters are mainly determined by fibrosis. Hence, measurements of WSC with multifrequency MR elastography have the potential to grade liver inflammation independently from the underlying fibrosis.

### References

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**Fig.1:** Illustrative parametric maps of two F2 patients with mild or significant inflammation. Top row: parametric maps of  $G'$  at 56Hz (kPa). Bottom row: parametric maps of WSC (dimensionless). Parametric maps are overlaid on top of the magnitude image of the MRE dataset. Patients with different inflammation have similar  $G'$  (A1: 2.33kPa, A3: 2.36kPa), while a significant decrease of WSC is seen in the patient with A3 inflammation (A1: 1.46; A3: 0.99).