Editorial Commentary

Is MRI relaxometry parameter $T_{1\rho}$ specific to fibrosis or confounded by concomitant pathological features?

Stefanie J. Hectors

Department of Radiology, Weill Cornell Medicine, New York, NY 10021, USA

Correspondence to: Dr. Stefanie J. Hectors. Department of Radiology, Weill Cornell Medicine, 515 E 71st St, Office S-117. New York, NY 10021, USA. Email: sjh4002@med.cornell.edu.

Submitted Aug 27, 2020. Accepted for publication Sep 22, 2020.
doi: 10.21037/qims-20-1089
View this article at: http://dx.doi.org/10.21037/qims-20-1089

Fibrosis, defined as the excessive accumulation of extracellular matrix proteins, is a key feature in most chronic inflammatory diseases (1). Fibrosis can affect nearly all tissues and organs in the body. While fibrosis is typically reversible, for example as part of normal wound healing, it can become irreversible when the tissue injury is chronic, severe or repetitive. Permanent scarring can lead to organ failure and ultimately even to death. It is therefore of key importance that patients are routinely monitored to evaluate the severity of fibrosis for effective management of their disease. The reference standard for detection and staging of fibrosis is pathological sampling. However, next to being invasive, needle biopsy procedures only sample a small part of the tissue, while fibrogenesis has shown to be a highly heterogenous process (2). Therefore, there is increasing interest in the development of noninvasive imaging methods for assessment of fibrosis.

From the evaluated imaging techniques, elastography methods measuring tissue stiffness have proved particularly promising to evaluate fibrosis, especially in the liver (3). However, an increase in stiffness is not specific to fibrosis, as other pathological changes including inflammation may also increase tissue stiffness (4). In addition, elastography methods require propagation of external mechanical waves into the tissue of interest. Wave propagation may be limited in obese patients or when applying the elastography method for imaging of organs located deeper in the body. Thus, there remains a need for an alternative imaging method that is more specific to fibrosis and is more widely applicable in all patients and all organs.

The paper by Zhao *et al.* (5) evaluates the sensitivity of MRI relaxation parameter $T_{1\rho}$ to liver fibrosis in a rat model of non-alcoholic fatty liver disease (NAFLD). $T_{1\rho}$, defined as the longitudinal relaxation time in the rotating frame, is a measure of the decay of magnetization in the transverse plane in the presence of a spin-lock pulse that is applied parallel to the magnetization vector. As $T_{1\rho}$ is sensitive to low-frequency interactions between macromolecules and bulk water, there has been significant interest in application of $T_{1\rho}$ for measurement of collagen deposition in fibrotic tissues, including in the liver (6,7), kidney (8), myocardium (9) and spleen (10). A significant positive correlation of collagen content with $T_{1\rho}$ has been observed in both kidney (8) and liver tissues (11). While $T_{1\rho}$ has consistently shown an increase in the presence of fibrosis (6-8,11), the exact mechanism of this $T_{1\rho}$ elevation has not been determined. Intuitively, one would expect a decrease in $T_{1\rho}$ in fibrotic tissues, due to increased interactions between extracellular matrix proteins and water protons. The observed increase in $T_{1\rho}$ may therefore be related to other concomitant pathological processes, including inflammation and steatosis in the context of liver fibrosis.

The elegant design of the study by Zhao *et al.* allowed for more detailed elucidation of the pathological changes that drive $T_{1\rho}$ elevation in NAFLD. MRI and histopathological evaluation of the liver were performed at several time points during methionine and choline-deficient (MCD) diet in the NAFLD group. A separate control group was also included. This study design allowed for separate analysis of the influence of fibrosis, inflammation and steatosis on liver $T_{1\rho}$. A highly significant positive correlation was found between collagen content and liver $T_{1\rho}$ ($r=0.82$, $P<0.0001$),

while the correlation of liver $T_{1\rho}$ with inflammation was nonsignificant (P=0.1). In a subgroup of rats, with similar collagen content, trends toward negative correlation of liver $T_{1\rho}$ with fat content were observed. Interestingly, another subset analysis was performed in rats without positive inflammation score. There continued to be a high significantly positive correlation of collagen content with liver $T_{1\rho}$ in this subset of rats, suggesting that the $T_{1\rho}$ elevation in liver fibrosis is indeed directly related to collagen deposition.

While this study provides convincing data on the direct association of $T_{1\rho}$ with collagen content, the underlying biophysical mechanism of collagen causing an increase in $T_{1\rho}$ was not evaluated. In several studies, it has been suggested that changes in chemical exchange rates due to collagen deposition could explain the observed $T_{1\rho}$ contrast in fibrotic tissues (12,13). However, the previous studies in which $T_{1\rho}$ was evaluated at a single spin-lock strength do not allow for quantitative analysis of exchange rates. For such analysis, a so-called $T_{1\rho}$ dispersion analysis is needed, which includes $T_{1\rho}$ measurements at a multitude of spin-lock strengths. Recently, a first report on $T_{1\rho}$ dispersion analysis in the context of kidney fibrosis was published (14). A drop in R_2 ($1/T_2$) and $R_{1\rho}$ ($1/T_{1\rho}$) at different spin-lock strengths was observed in fibrosis. In addition, it was found that parameters related to chemical exchange significantly changed during the progression of fibrosis. A highly significant reduction in the exchange parameter was observed, which is thought to be related to the slow exchange rate of hydroxyl protons in collagen (14). This dispersion analysis thus provides strong evidence on the sensitivity of $T_{1\rho}$ to collagen deposition. Nevertheless, other pathological changes such as inflammation could also have contributed to the overall reduction of R_2 and $R_{1\rho}$. The evaluated exchange parameters may therefore be more specific to collagen deposition, as this dispersion analysis is highly sensitive to the chemical components present in the tissue of interest.

In summary, these recent studies provide further evidence on the sensitivity of $T_{1\rho}$ to collagen deposition in fibrosis. Nevertheless, confounding factors including inflammation and other pathological features dependent on the disease and tissue of interest may not be ignored. Analysis of chemical exchange rates from $T_{1\rho}$ dispersion analysis seems to be an elegant solution to improve the specificity of $T_{1\rho}$ metrics to fibrosis. Further research in this field is clearly warranted, including additional optimization of the performance of $T_{1\rho}$ for fibrosis imaging as well as reduction in acquisition times in particular when a multitude of spin lock strengths needs to be acquired.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Quantitative Imaging in Medicine and Surgery*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-20-1089). The author has no conflicts of interest to declare.

References

1. Wynn TA, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. Nat Med 2012;18:1028-40.
2. Distler JHW, Gyorfi AH, Ramanujam M, Whitfield ML, Konigshoff M, Lafyatis R. Shared and distinct mechanisms of fibrosis. Nat Rev Rheumatol 2019;15:705-30.
3. Kennedy P, Wagner M, Castera L, Hong CW, Johnson CL, Sirlin CB, Taouli B. Quantitative Elastography Methods in Liver Disease: Current Evidence and Future Directions. Radiology 2018;286:738-63.
4. Shi Y, Guo Q, Xia F, Dzyubak B, Glaser KJ, Li Q, Li J, Ehman RL. MR elastography for the assessment of hepatic fibrosis in patients with chronic hepatitis B infection: does histologic necroinflammation influence the measurement of hepatic stiffness? Radiology 2014;273:88-98.
5. Zhao F, Zhou N, Wang JL, Zhou H, Zhou LQ, Zhong WX, He J, Zheng CJ, Yan SX, Wáng Y. Collagen deposition in the liver is strongly and positively associated

T1rho elongation while fat deposition is associated with T1rho shortening: an experimental study of methionine and choline-deficient (MCD) diet rat model. Quang Imaging Med Surg 2020;10:2307-2321.
6. Allkemper T, Sagmeister F, Cicinnati V, Beckebaum S, Kooijman H, Kanthak C, Stehling C, Heindel W. Evaluation of fibrotic liver disease with whole-liver T1rho MR imaging: a feasibility study at 1.5 T. Radiology 2014;271:408-15.
7. Rauscher I, Eiber M, Ganter C, Martirosian P, Safi W, Umgelter A, Rummeny EJ, Holzapfel K. Evaluation of T1rho as a potential MR biomarker for liver cirrhosis: comparison of healthy control subjects and patients with liver cirrhosis. Eur J Radiol 2014;83:900-4.
8. Hectors SJ, Bane O, Kennedy P, El Salem F, Menon M, Segall M, Khaim R, Delaney V, Lewis S, Taouli B. T1rho mapping for assessment of renal allograft fibrosis. J Magn Reson Imaging 2019;50:1085-91.
9. van Oorschot JW, Guclu F, de Jong S, Chamuleau SA, Luijten PR, Leiner T, Zwanenburg JJ. Endogenous assessment of diffuse myocardial fibrosis in patients with T1rho -mapping. J Magn Reson Imaging 2017;45:132-8.
10. Hectors SJ, Bane O, Stocker D, Carbonell G, Lewis S, Kennedy P, Schiano TD, Thung S, Fischman A, Taouli B. Splenic T1rho as a noninvasive biomarker for portal hypertension. J Magn Reson Imaging 2020;52:787-94.
11. Wang YX, Yuan J, Chu ES, Go MY, Huang H, Ahuja AT, Sung JJ, Yu J. T1rho MR imaging is sensitive to evaluate liver fibrosis: an experimental study in a rat biliary duct ligation model. Radiology 2011;259:712-9.
12. Sharafi A, Baboli R, Zibetti M, Shanbhogue K, Olsen S, Block T, Chandarana H, Regatte R. Volumetric multicomponent T1rho relaxation mapping of the human liver under free breathing at 3T. Magn Reson Med 2020;83:2042-50.
13. Zhang Y, Zeng W, Chen W, Chen Y, Zhu T, Sun J, Liang Z, Cheng W, Wang L, Wu B, Gong L, Ferrari VA, Zheng J, Gao F. MR extracellular volume mapping and non-contrast T1rho mapping allow early detection of myocardial fibrosis in diabetic monkeys. Eur Radiol 2019;29:3006-16.
14. Wang F, Colvin DC, Wang S, Li H, Zu Z, Harris RC, Zhang MZ, Gore JC. Spin-lock relaxation rate dispersion reveals spatiotemporal changes associated with tubulointerstitial fibrosis in murine kidney. Magn Reson Med 2020;84:2074-87.

Cite this article as: Hectors SJ. Is MRI relaxometry parameter $T_{1\rho}$ specific to fibrosis or confounded by concomitant pathological features? Quant Imaging Med Surg 2020;10(12):2408-2410. doi: 10.21037/qims-20-1089

