



Physiological variation of liver iron concentration may not be dominantly responsible for the liver T1rho variations associated with age and gender

Yì Xiáng J. Wáng[^]

Department of Imaging and Interventional Radiology, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China

Correspondence to: Dr. Yì Xiáng J. Wáng. Department of Imaging and Interventional Radiology, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China. Email: yixiang_wang@cuhk.edu.hk.

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Liver fibrosis, a common feature of almost all chronic liver diseases, involves the accumulation of collagen, proteoglycans, and other macromolecules in the extracellular matrix (ECM). T1rho (T1ρ) relaxation time describes spin-lattice relaxation in the rotation frame at the presence of an external radiofrequency pulse in the transverse plane. It has been demonstrated that T1rho elongation is a sensitive biomarker for collagen deposition, both in the liver and in the kidneys (1-3). Allkemper *et al.* (4) reported that T1rho value was significantly associated with the Child-Pugh staging of the patients. In patients with chronic liver diseases, Takayama *et al.* (5) demonstrated liver T1rho values showed significant positive correlations with the serum levels of total bilirubin, direct bilirubin, and indocyanine green (ICG-R15), and significant negative correlations with the serum levels of albumin and γ -glutamyl transpeptidase.

To translate liver T1rho MRI into clinical practise, it is important to understand physiological liver T1rho measure in healthy subjects. We have performed a healthy volunteer study in 62 women (mean age: 38.9 years; range, 18–75 years) and 34 men (mean age: 44.7 years; range, 24–80 years) (6). We reported that the female liver T1rho value ranged between 35.07 and 51.97 ms and showed an age-dependent decrease, with younger women having a higher measurement. The male liver T1rho value ranged between 34.94 and 43.39 ms, with no evidential age

dependence (*Figure 1*). Note the T1rho data acquisition had very high scan-rescan reproducibility (6-9). We have hypothesized that the observed age- and gender- related liver T1rho differences among healthy subjects might be largely due to the differences of liver iron deposition between men *vs.* women and between young subjects *vs.* older subjects (9). However, with re-consideration of the existing and also newly available data, we suggest that the observed age- and gender- related liver T1rho physiological differences are unlikely being primarily caused by liver iron concentration variation.

In healthy subjects there are iron storage depots containing ferritin and hemosiderin, which are located for the most part in the liver, spleen, and bone marrow. One-third of the body storage iron is found in the liver and its contents reflects the level of total body storage. If a subject is in iron balance, there is usually relatively little exchange between the stores and the rest of iron in the body. States of negative iron balance occur when the body requirements for iron exceed the amounts being absorbed from the gastrointestinal tract. This may be the result of physiological events such as growth spurts, menstruation and pregnancy, or of any pathological state that causes blood loss. There are numerous reports on the association between age and liver iron deposit. While variable results have been reported (the results partially affected by the study subjects' dietary style), there are sufficient evidences

[^] ORCID: 0000-0001-5697-0717.

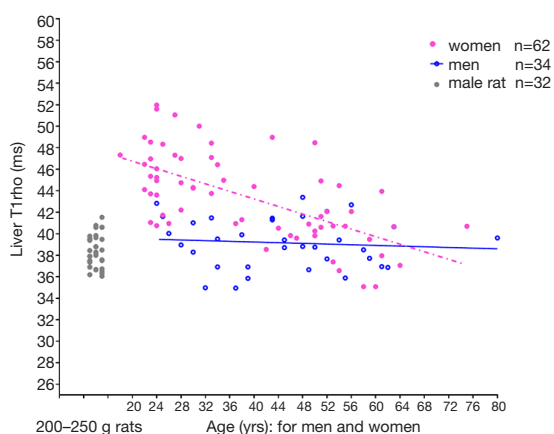


Figure 1 The relationship between age and liver T1rho. Women's liver T1rho shows an age-related decrease, with younger women showing a higher measurement. The men's liver T1rho has no evidential age dependence. After the age of 50 years, men and women have similar liver T1rho values. 32 young male rats have liver T1rho measures similar to those of men of various ages. Reproduced with permission from reference (6) and reference (7).

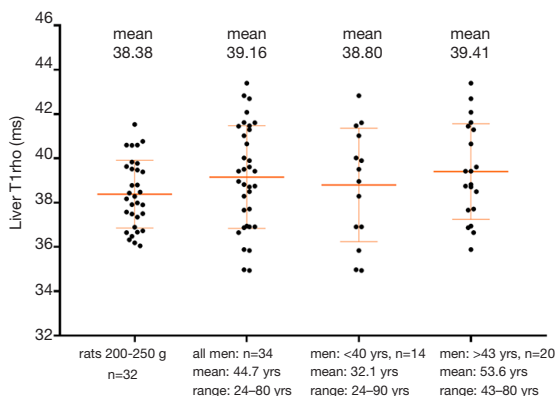


Figure 2 The relationship between age and liver T1rho in young male rats, total men participants, men <40 years old, and men >43 years old. Reproduced with permission from reference (6) and reference (7).

that, in healthy subjects without diet iron deficiency, liver iron concentration rises sharply in men toward the end of the adolescent growth spurt in the late teens and reached maximum before 40 years old. After 40 years old, liver iron level remains constant or slightly increases until approximately age 70 years, after which it may declines (10-13). This liver iron level physiological change pattern differs from the liver T1rho change over age in healthy men. *Figure 1* and *Figure 2* show there is no apparent

aged related change observed for men of 24–80 years. If higher liver iron in older subjects (>40 years) caused T1rho shortening (as compared with younger subjects), then we would expect to see the >43 years group had shorter mean T1rho value than the <40 years group, which was not the case in *Figure 2*. Moreover, for all the male study subjects (mean: 44.7 years), the mean liver T1rho was similar to the young male rats of 200–250 gram.

On the other hand, age related liver iron increase has been observed with a number of MRI methods. Schwenzer *et al.* (14) reported that a statistically significant correlation of T2* decrease over age in men (for men, Pearson correlation coefficients $r=-0.30$, $P<0.05$, $n=44$; for women, $r=-0.46$, $P<0.0001$, $n=85$). In 34 men and 52 women, Metens *et al.* (15) investigated how normal liver parenchyma visibility on diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) quantification are influenced by age and iron content. Liver visibility (lower visibility denotes higher liver iron concentration) was better in young women but degrades with age in both genders. For $b=1,000$ s/mm² images (other b -value images showed the same trend), inverse correlation between liver visibility score and age was significant with a Spearman coefficient $R=-0.58$ in women ($P<0.0001$) and $R=-0.44$ in men ($P<0.01$). The liver average ADC was negatively and weakly correlated with age (Spearman coefficient $R=-0.23$; $P=0.05$), and the values were higher in women ($785\pm 147 \times 10^{-6}$ mm²/s) than in men ($742\pm 103 \times 10^{-6}$ mm²/s; $P=0.027$). Higher liver iron content is known to be associated with lower liver ADC measure (16).

In women, it is well known that liver iron concentration remains relatively low until after the fourth decade of life, after which they exhibit a steep rise. Maximum levels observed in women after menopause are approximately two thirds of those for men of comparable age (10-13,17-19). The relative low mean value among women in the 21- to 40-year-old group is associated with a high iron demand of menstruation during the childbearing age.

Recently, we performed a study with 30 men and 36 women on the correlation between intravoxel incoherent motion (IVIM) parameters and age. We demonstrated a trend of D_{slow} decreasing related to healthy aging (20). *Figure 3* shows a comparison of the relationship between D_{slow} vs. age, and relationship between liver T1rho vs. age in men. A trend is noted for healthy aging associated with lower D_{slow} , however, this trend does not exist for T1rho vs. aging, suggesting T1rho measure is at least less sensitive to liver iron concentration compared with D_{slow} measure.

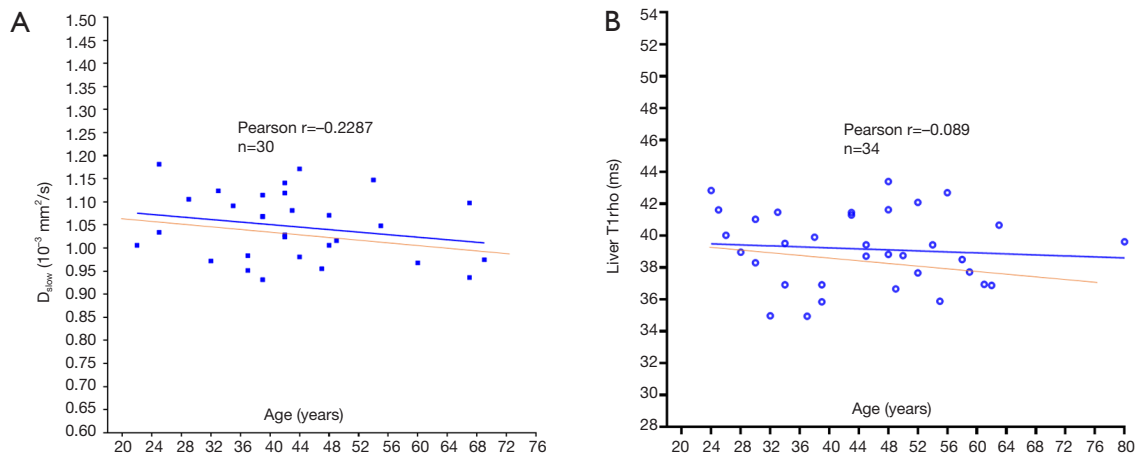


Figure 3 The relationship between D_{slow} of intravoxel incoherent motion analysis *vs.* age (study subjects: residents in Shenzhen, China) and liver T1rho *vs.* age in men (study subjects: residents in Hong Kong SAR, China). All study subjects were from South China thus with comparable dietary styles (the same for *Figure 4*). The men's liver T1rho has no evidential age dependence. The men's liver D_{slow} has a weak correlation with age (expected to be statistically significant if the sample size is increased to $n=60$). Orange line presents the slope of D_{slow} decreasing over aging. Reproduced with permission from reference (6) and reference (20).

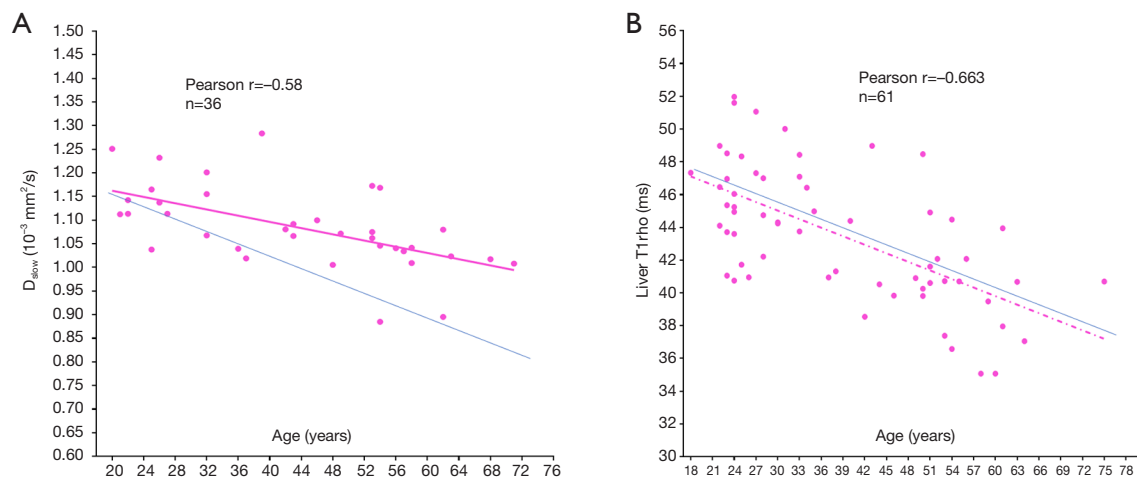


Figure 4 The relationship between liver D_{slow} of intravoxel incoherent motion analysis *vs.* age (A, study subjects: residents in Shenzhen, China) and liver T1rho *vs.* age in women (B, study subjects: residents in Hong Kong SAR, China). Age has a correlation of moderate strength both for D_{slow} ($P<0.001$) and T1rho ($P<0.0001$). Blue line presents the slope of liver T1rho decreasing over aging, which is much steeper than that of D_{slow} . Reproduced with permission from reference (6) and reference (20).

Figure 4 shows a comparison of the correlation between D_{slow} *vs.* age and correlation between liver T1rho *vs.* age in women. Apparent and statistically significant inverse trends of healthy aging associated with both lower D_{slow} and shorter T1rho are noted. However, the opposite to men's results, the decreasing slope for liver T1rho over aging is steeper than that of D_{slow} suggesting the decreasing slope for liver T1rho over aging is not primarily caused by

increased liver iron concentration over aging. If liver T1rho is not as sensitive to iron as D_{slow} to iron (as shown in men's results) but liver T1rho change still reflect liver iron change in women, then we would expect the women's liver T1rho slope over aging would be less steep than the slope of D_{slow} over aging. Secondly, between the age of 50–60 years liver iron concentration is expected to still substantially higher in men than in women; while for liver T1rho, men's and

women's liver T1rho measures converged. Thus, we argue that the physiological T1rho change over aging is not dominantly caused by liver iron concentration variation. Compared with other MRI techniques such as T2* and diffusion imaging, T1rho is relatively insensitive to liver iron deposition at least when the iron concentration is within or close to physiological ranges. In a limited analysis of 16 liver cirrhosis patients with 4 of them had iron overload, Allkemper *et al.* (4) also did not find a correlation between liver T1rho and semi-quantitative liver iron overload.

Moreover, the opposite to our previous discussion (2), since young male rats had very similar liver T1rho to healthy men of various age (6,7), it is more likely the liver fat content difference had not substantially contributed to the gender- and age- difference of T1rho demonstrated in our last health volunteer study. For subjects without apparent liver steatosis (i.e., <5% fat content) and when fat suppression technique is applied for T1rho acquisition, the contributed from liver fat to T1rho shortening would be limited relative to the physiological variation of liver T1rho. Our previous analysis suggests that 10% additional liver fat contribute to 1.55 ms liver T1rho shortening (21). Also, in our previous report we noted that, for both women and men, no association was seen between body mass index and liver T1rho (6).

Our rat study demonstrated that the liver T1rho individual variation is unlikely due to measurement imprecision (7,9). Instead, the variation more likely reflect genuine biochemical difference among individual rats. Based on our recent study on collagen's contribution to T1rho elongation (2,22), we tentatively suggest that among healthy human subjects there are sufficient age and gender related macromolecular biochemical differences which contribute to the liver T1rho variations observed in healthy human beings (6). The effects of growth, aging and gender on liver tissue composition has long been a topic of research (23–26). The exact mechanism for the age and gender associated liver T1rho difference remains to be further clarified.

Furthermore, the high sensitivity of T1rho to collagen shall allow the possibility to image tumor ECM. Many solid tumors express high levels of various ECM molecules like fibrillar collagens, fibronectin, elastin, and laminins. In some tumors, the ECM compromises up to 60% of the tumor mass. Like the other components of the tumor microenvironment, the ECM in solid tumors differs significantly from that in normal organs. Source of these ECM molecules can be the tumor cells themselves, but to

an even larger degree cancer-associated fibroblasts. The ECM does not only influence malignancy and growth of the tumor but also its response toward therapy. The infiltration of fibroblasts/myofibroblasts and the subsequent accumulation of significant amounts of collagenous ECM is observed in many solid tumors. This process, called desmoplasia, is strongly linked to poor prognosis and resistance to systemic therapy (27). Our recent work (2) shall justify further research into the role of T1rho for tumor characterisation as well as therapeutic monitoring (28–32).

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Footnote

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