Non-invasive myocardial and hepatic R2* assessment in a juvenile hematochromatosis mouse model at high magnetic field

P. R. Allegrini[1], C. Weidensteiner[1], H. Nick[1]
[1]Novartis Inst. for BioMedical Research, Basel, BS, Switzerland

Introduction

Chronic blood transfusions due to anemias such as β-thalassemia or sickle cell disease and hemochromatosis, inborn errors of iron metabolism, produce progressive tissue iron loading and toxicity. The majority of the excess iron is stored in the liver. Although iron chelation in thalassemia patients reduces early mortality, cardiac complications remain and cardiac failure is the most common cause of death. The standard method for the assessment of liver iron concentration (LIC) involves the performing of a liver biopsy which cannot be applied routinely to the heart. Recently MRI techniques based on organ R_2 or R_2* measurement were introduced for hepatic and myocardial iron assessment in vivo.

In hemojuvelin knock out ($HJV^{-/-}$) mice, a model for juvenile hemochromatosis, iron is accumulating in liver and heart (1). Non-invasive iron determination in these organs, especially in the heart, is essential for monitoring time course of iron accumulation and its alteration with chelation therapy (2).

The aim of this study was to develop noninvasive myocardial and hepatic R_2* determination in mice using a small animal MRI scanner at 4.7 T.

Material and Methods

MRI: All experiments were performed on a 4.7 T Biospec DBX MR imager.

Myocardial R_2* assessment: Single slice ECG gated double oblique short axis view gradient echo images were acquired at end diastole (3). Parameters: TR ≥ 300 ms, TE = 2.8, 5.6, 6.5, 7.5, 9, 12, and 15 ms (single echo each acquisitions), FOV = 35^2 mm^2, matrix 256x128, slice 1.2 mm

Hepatic R_2* assessment: Single slice transversal gradient echo images were acquired at the center of the liver. Parameters: TR = 200 ms, TE = 2.8, 3.5, 4, 5.6, 9, and 15 ms (single echo each acquisitions), FOV = 35^2 mm^2, matrix 256x128, slice 1.2 mm

Post-processing: R_2* was computed by mono-exponential decay fitting of signal to noise offset. R_2* was calculated of the heart septum in order to minimize susceptibility effects of the nearby lung. Large blood vessels in the liver were excluded from evaluation.

Results

Gradient echo images of a $HJV^{-/-}$ mouse heart and liver are displayed in figures 1 and 2. Some animals were measured twice to assess reproducibility of the method which resulted in a decent correlation with 13% and 20% variation, resp. (Fig. 3a). The time course of R_2* alteration in heart and liver of 6 animals (3 per group, Fig. 3b, c) was assessed for 3 to 4 months. It revealed an increasing difference of myocardial R_2* between the groups and a considerable, constant one in the liver.

Discussion

Multi-echo approaches are known to be inappropriate due to imperfections of the pulse program. Therefore multiple single-echo technique was applied with reasonable acquisition time due to very short TR. Good image quality permitted to measure reproducibly R_2* in heart and liver of mice (Fig. 3a) despite the short TR of ≥ 300 ms or 200 ms, resp.

Hepatic and myocardial iron was previously determined chemically in the $HJV^{-/-}$ mouse strain. While hepatic iron increased rapidly and reached a plateau at 4 months of age (~150 µmol/g dw) cardiac iron steadily accumulated up to 300 days of age (~40 µmol/g dw). Our data are in line with these findings. Myocardial R_2* of $HJV^{-/-}$ at 186 days of age (last assessment) was 136 ± 25 s^{-1} (control 56 ± 0.2 s^{-1}) whereas that of the liver amounted to 641 ± 26 s^{-1} (control 82 ± 1 s^{-1}). Assuming linear relationship to iron concentration, the liver accumulated approx. 7x more iron than the heart, which compares to the corresponding of approx. 6 between the two organs as chemically determined at 2.5 months of age. Furthermore, myocardial R_2* tended to steadily increase during the observation period, whereas hepatic R_2* apparently had reached a plateau before the first assessment at 80 days of age.

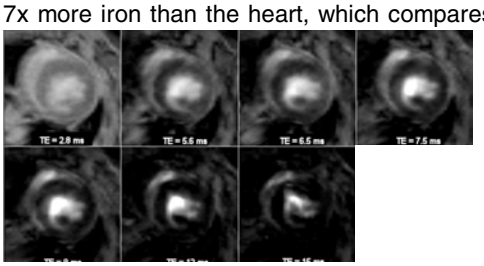

Figure 1. Multiple gradient echo images of a $HJV^{-/-}$ mouse heart.

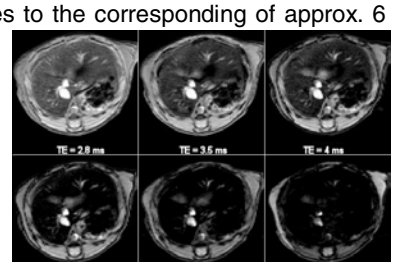

Figure 2. Multiple gradient echo imag of a $HJV^{-/-}$ mouse liver.

Conclusion

The feasibility of hepatic and myocardial R_2* assessment in mice was demonstrated with a adequate quality for pharmacological studies. Time course study with healthy control and $HJV^{-/-}$ mice demonstrated the feasibility to detect differences of R_2* between control mice and $HJV^{-/-}$ mice hemochromatosis model.

References

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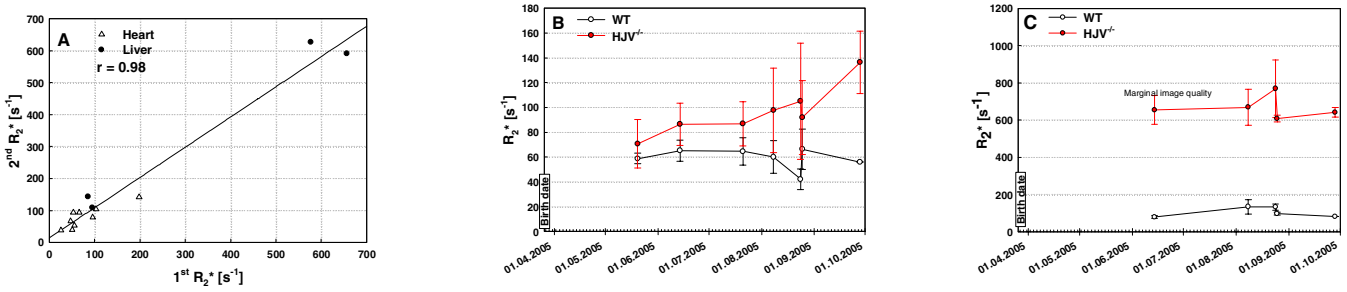

Figure 3. (A) Reproducibility of ***R2**** assessment. (B) ***R2**** time course in the heart of wildtype and $HJV^{-/-}$ mice. (C) Time course of hepatic ***R2**** of wildtype and $HJV^{-/-}$ mice.