

Fast & localized ^{31}P saturation transfer at 7T reveals slower hepatic metabolic rates in NASH patients

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Introduction:

Invasive liver biopsy is the only method currently used for distinction between non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH). Hepatic energy metabolism is of high interest as its alterations are indicative for inflammatory and neoplastic liver diseases as demonstrated in type 2 diabetes patients at 3T [1, 2]. ^{31}P -MRS provides information about concentration of high energy metabolites (i.e. PCr, ATP, Pi) and combined with magnetization transfer (MT) technique enables measurement of metabolic activity at rest *in vivo*. Recently, ultra high field systems such as 7 T have been shown to provide sufficient SNR for localized MT measurement of human liver in clinically applicable measurement time [3]. Therefore the goal of this study was to test the feasibility of MT measured at 7T for non-invasive distinction of NAFLD and NASH.

Materials and Methods:

^{31}P -MRS 1D-ISIS MT measurements of ten suspected NAFLD/NASH patients (6m/4f, $a = 49.5 \pm 13.2\text{y}$) were performed one day prior the liver biopsy. Additionally four young healthy male volunteers ($a = 25.3 \pm 2.9\text{y}$) were measured as controls. Examinations were performed on a 7 T MR system (Siemens Healthcare, Erlangen, Germany) using double-tuned surface coil ($^1\text{H}/^{31}\text{P}$) (Rapid Biomedical, Wimpar, Germany), with a diameter of 10 cm. Patients were lying in the lateral position with the right lobe of the liver placed over the coil. The chemical exchange between Pi and ATP was calculated from the liver spectra acquired w/o frequency selective saturation of γ -ATP and the apparent longitudinal relaxation (T_1^{app}) was measured with inversion-recovery sequence with eight inversion times (0.08-3 s) and continuous saturation of γ -ATP. The sequence parameters were set as follows: rectangular 400 μs excitation, $TE^* = 0.4\text{ ms}$, $TR = 5\text{ s}$, slab thickness 30 mm and total acquisition time $\sim 23\text{ min}$. Unsaturated 1D-ISIS spectra were obtained to assess the Pi concentration, using the γ -ATP as internal concentration reference. The calculated forward rate constant (k) and unidirectional metabolic flux (F) were correlated with the histology, regarding disease status and steatosis degree.

Results and Discussion:

The representative spectra from the liver MT experiment of one patient are depicted in Fig. 1. Minimal contamination by phosphocreatine from the muscles and full saturation of the γ -ATP signal was achieved in all data sets. The data from the MT experiment are given in Tab. 1, where the patient group is resolved by the histological diagnosis into steatosis (NAFLD; $n=4$) and steatohepatitis (NASH; $n=6$) subgroups. The NASH patients had significantly lower k values when compared to NAFLD (*, $p=0.001$) and also to healthy volunteers ($\#$, $p=0.002$), with no

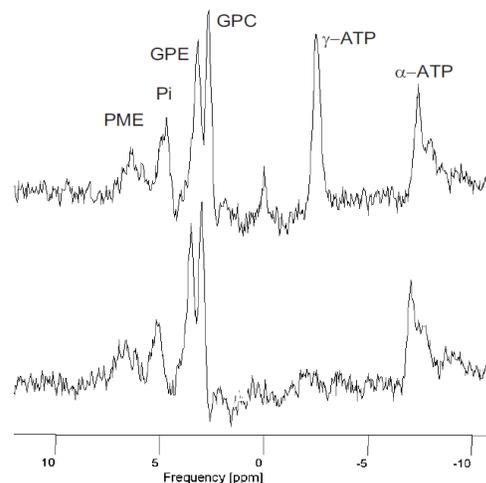


Fig. 1 Sample ^{31}P liver spectra of the MT experiment. In the equilibrium spectra (top) are the peaks of phospho-monoesters (PME), inorganic phosphate (Pi), glycerol-phosphorylethanolamin (GPE), glycerol-phosphorylcholine (GPC) and the ATP visible. In the steady state spectra (bottom) is the γ -ATP signal saturated and therefore absent.

Tab.1	NAFL (n = 4)	NASH (n = 6)	controls (n = 4)
[Pi]' (mM)	1.19 ± 0.15	1.04 ± 0.22	1.25 ± 0.04
T_1^{app} (s)	0.80 ± 0.09	0.72 ± 0.19	0.79 ± 0.18
k (s^{-1})	0.34 ± 0.04	$0.18 \pm 0.05^{*\#}$	0.31 ± 0.03
F (mM/s)	0.39 ± 0.03	$0.19 \pm 0.08^{*\#}$	0.38 ± 0.05

Conclusion:

Liver Pi-ATP exchange, measured *in vivo* by the magnetization transfer technique at 7T, is decreased in NASH in comparison to NAFLD patients and controls. This difference is connected to the lower exchange rate constant and might provide a clinical tool for future distinction between NASH and NAFLD.

References:

1. Szendroedi, J., Chmelik, M., et al., *Hepatology*, **50**: 1079-1086, 2009.
2. Schmid, A.I., Szendroedi, J., et al., *Diabetes Care*, **34**: 448-453, 2011.
3. Valkovič, L., et al. in *ESMRMB 2012*. Lisbon, Portugal.

overlap between the NAFLD and NASH subgroups. The same was true for the metabolic flux, as the assessed Pi concentrations were similar in all three groups. As no absolute quantification was performed, the assessed concentration of Pi might differ from the real value, given that concentration of ATP might be different in liver pathology [1]. Furthermore, the forward rate constant of the chemical exchange between Pi and ATP as determined by the MT experiment correlated well with the histologically assessed steatosis degree (Fig. 2).

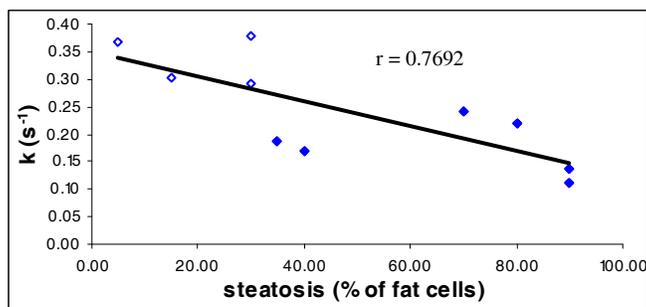


Fig. 2 Correlation between rate constant (MT) and fat content (biopsy). Empty diamonds depict NAFLD and full NASH patients. Note no overlap in k values between NAFLD and NASH subgroups.