Phase Velocity Imaging of Portal Pressure Gradients for Assessing Liver Fibrosis/Cirrhosis

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INTRODUCTION

Liver cirrhosis, a major cause of death worldwide, is the end stage of many liver diseases. Liver cirrhosis/fibrosis often leads to abnormal hemodynamics in portal vein. The current gold-standard to diagnose liver cirrhosis is needle biopsy. For non-invasive assessment of liver fibrosis we previously investigated portal pressure gradient (PPG) model in combination with phase-contrast (PC) MRI, and have demonstrated its feasibility by differentiating between control and severely fibrotic rats with cirrhosis [1]. In this report we further test the sensitivity of the PPG model to a broad range of severity of the disease in rats with carbon tetrachloride (CCl4)-induced liver fibrosis. Results from a preliminary patient study are also presented.

METHODS

Animal Preparation: The animal research protocol was approved by the Institutional Animal Care and Use Committee. Thirty-five male Wistar rats (Charles River Laboratories, Inc., Wilmington, USA): 8 control and 27 treated (IP injection) with CCl4 mixed with vegetable oil (25 microl CCl4 in a 150 microl volume (1:6)) at a frequency of three times per week for 2-16 weeks [2] (2~3 weeks (6); 6~8 weeks (12); 11~16 weeks (9)). Rats were anesthetized by subcutaneous injection of ketamine plus xylazine for imaging.

Human Subjects: Five healthy subjects and three patients with biopsy-proven liver fibrosis (stage IV, i.e., severe fibrosis and early cirrhosis) were examined. A written consent form was received from all volunteers and the study was approved by WIRB.

Theory: In the upper part of the portal vein (PV), PPG is proportional to the ratio of the mean velocity of portal blood flow to the vessel area (i.e. dp/dx ~ V/A) [1].

PC-MRI: All images were collected on a 1.5 T Siemens scanner with a phased-array wrist coil for the animal and a body coil for the human (USA Instruments, Inc., Aurora, USA) studies. The slice was selected to be perpendicular to the portal vein by referring to the coronal, sagittal and transverse scout images acquired using trueFISP. For all velocity measurements a FLASH sequence (fl_pc, Siemens) was used. In order to minimize partial volume effects, image resolution was adjusted such that the number of pixels across the vessel diameter was larger than six [3]. For the animal study, the sequence parameters were: TR/TE=45/9.7ms, flip angle=15°, FOV~120mm (512*512 matrix), 16 averages, 1 slice at upper portal vein (2.6mm thick), total scan time~5 min, low/high encoding velocity (Venc_low/Venc_high) =10/50 cm/s. Human data was collected in a single breath-hold using the following sequence parameters: TR/TE=40/9.3 ms, flip angle=15°, FOV~400mm (256*256 matrix), 2-3 averages, 1 slice (5mm thick), Venc_low/Venc_high=10/60 cm/s.

Data Processing: The vessel area was measured from the magnitude images rather than the phase image to minimize the error of vessel definition. The velocity image was reconstructed using a 3-point method [5] to increase the velocity-to-noise ratio (VNR) using the reconstruction program written in MATLAB. Portal flow volume (PFV=V*A) was also calculated and the results were compared to PPG results.

Histopathology: The animal livers were harvested after MRI and stained with Masson's trichrome. The numerical values of 0 (within normal limits, absent), 1 (minimal, < 10%), 2 (mild, 10-20%), 3 (moderate, 23-30%), 4 (marked, 30-40%) and 5 (severe, > 40%) were assigned for severity of fibrosis.

RESULTS

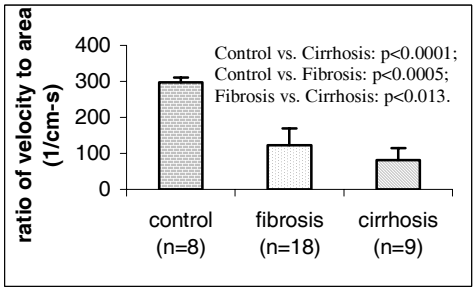

Fig 1 PPG (proportional to V/A) were reduced substantially from control to fibrosis to cirrhosis rats (mean±standard error).*: rats from 2~3weeks and 6~8weeks.**:11~16weeks treated rats.

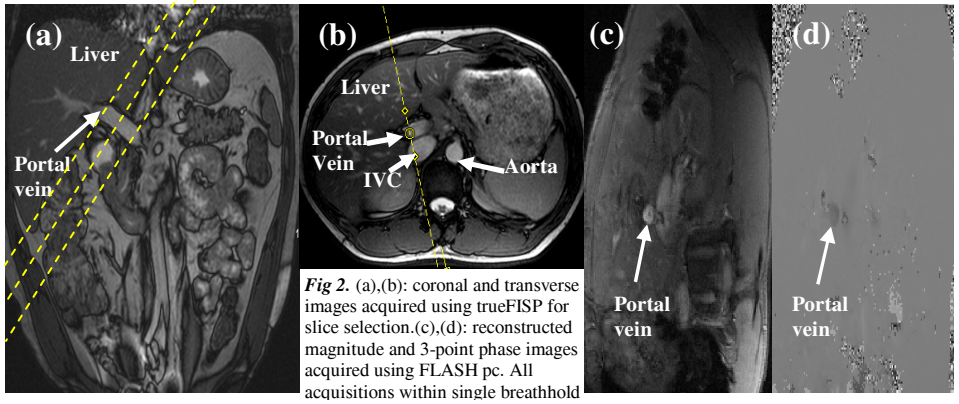

Fig 2. (a),(b): coronal and transverse images acquired using trueFISP for slice selection.(c),(d): reconstructed magnitude and 3-point phase images acquired using FLASH pc. All acquisitions within single breathhold

Histopathology: The degree of fibrosis in treated rats increased over time. The mean fibrosis scores for each animal group were: control=0, 2~3weeks=1.0(minimal), 6~8weeks=2.7(mild to moderate), 11~16weeks=4.1(marked and severe). The nine rats in the 11-16 week group had histological changes indicating cirrhosis.

MRI: Figure 1 displays the PPG values of the control, fibrotic (without cirrhosis) and cirrhotic rats. The control rats had significantly higher PPG than the fibrotic ($p<0.0005$) and cirrhotic rats ($p<0.0001$). The difference in PPG between fibrotic and cirrhotic rats were $p<0.013$. However, there was no significant difference in PFV between the control and cirrhotic rats ($p<0.28$). PPG was highly correlated with the duration of CCl4 treatment over 0-16 weeks ($r=-0.73$, $p<0.00001$). Figure 2 illustrates representative slice landmark and the reconstructed magnitude and phase images in human study. The PPG values between normal and fibrosis IV patients were significantly different ($p<0.007$), but PFV of the patients did not differ from that of the control subjects ($p<0.13$).

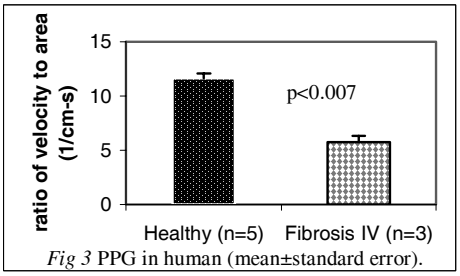

Fig 3 PPG in human (mean±standard error).

DISCUSSION

The high correlation between PPG and the duration of CCl4 treatment in the animal study supports the feasibility of MRI based PPG as a potential surrogate of portal pressure. The differentiation between control and patients with severe fibrosis is also encouraging. The fully-developed flow condition in the PPG model was verified by estimating velocities at different locations along the portal vein within a landmark range (examples shown in Fig 2(a)). The flow was laminar ($Re<2000$) and non-pulsatile. The perpendicularity of the slice was also verified by calculating 3D velocity profiles with a three-directional velocity encoding. In humans the primary challenge for a given scan time was to increase VNR while maintaining image resolution to minimize partial volume effects. Due to the complicated vessel orientation of human PV, the utility of the 3D velocity encoding will become more important for accurate slice definition. Both animal and human studies demonstrate that PPG is a more sensitive measure to the disease severity than portal flow volume measurement because both the vessel dilation and the decrease of portal flow velocity occur in cirrhosis. In conclusion PPG approach is potentially useful in diagnosis of liver cirrhosis clinically.

REFERENCES: [1] Wang et al, ISMRM Proceeding14:#2211,2006.[2] Hernandez-Munoz,Hepatology26:1100,1997.[3] Wolf et al,MRM30:82,1993.[4] Pelc et al,MRM33:122,1995.

ACKNOWLEDGEMENT: This work was supported by Pfizer Inc.