# Evaluation of Hepatic Fibrosis with Portal Fraction and Portal Pressure Gradient using MRI

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## INTRODUCTION

Regardless of etiology, hepatic fibrosis is characterized by excessive accumulation of extracellular matrix (ECM), which induces the increased resistance to blood flow at the sinusoidal level and leads to portal hypertension [1]. Portal pressure (PP) is shown to be a quantitative means of assessing liver pathology. MRI permits non-invasive measurement, and a previous perfusion study using dynamic contrast-enhanced MRI (*DCE-MRI*) has reported that portal fraction (PF) is highly correlated to PP in cirrhotic patients and therefore may be used as a surrogate of the highly invasive PP measurement [2]. In addition, the recently proposed model of portal pressure gradient (PPG) in conjunction with phase contrast MRI (*PC-MRI*) has demonstrated its potential application in evaluating the disease in rats [3]. This work aims to evaluate the performance of these two MRI methods in rats with various degrees of hepatic fibrosis induced by CCl4. The actual sensitivity and specificity in diagnosing liver fibrosis are compared in terms of the receiver operating characteristics (ROC) plot.

## METHODS

***Animal Preparation:*** The animal research protocol was approved by University Institutional Animal Care and Use Committee. Thirty-one male Wistar rats (Charles River Laboratories, Inc., Wilmington, USA) were studied: 7 control rats and 24 treated rats with IP injection of CCl4 + vegetable oil (25 ul CCl4 + 150 ul oil) at a frequency of three times per week for 2-16 weeks to induce progression of hepatic fibrosis [4]. Rats were anesthetized (ketamine+xylazine) prior to MRI. For *DCE-MRI*, an IV catheter was interested into the tail vein for administration of Gd-DTPA (OMNISCAN$^{TM}$-Amersham Health Inc., Oslo, Norway).

***MRI:*** All images were collected on a 1.5 T Siemens scanner with a phased-array wrist coil (USA Instruments, Inc., Aurora, USA). For *PC-MRI*, the slice was selected to be perpendicular to the rats' portal vein (PV) by referring to the coronal, sagittal and transverse scout images acquired using trueFISP. A FLASH sequence (fl_pc, Siemens) was utilized for velocity measurement with optimized parameters: TR/TE=45/9.7ms, flip angle=15$^o$, FOV~120mm (512x512 matrix), 16 averages, 1 slice (2.6mm thick), total scan time~5 min, two velocity encodings (Venc_low/Venc_high)=10/50 cm/s to increase velocity-to-noise ratio (VNR). For *DCE-MRI*, a gradient echo sequence was utilized with TR/TE=15/2.1ms, flip angle=40$^o$, FOV=180x120 (119x192 matrix), 1 average, 1 slice (3mm thick), total scan time ~ 4 min 30 sec. Following a 15-sec baseline scan, Gd-DTPA (0.05mM/Kg) was administered and the time-dependent signal intensity changes in the aorta, PV, and liver tissue were continuously recorded (1.3 ms/image) [2].

***Data Analysis:*** For *PC-MRI*, the complex raw data were acquired and velocity image was reconstructed using a three-point phase unwrapping algorithm [5] written in MATLAB. The cross-sectional area of PV was measured from the magnitude image and PPG was obtained (PPG=mean velocity across the pixels in PV/area of PV) [4]. For *DCE-MRI*, the time-dependent signal intensity changes in the ROI were converted into time-dependent concentrations of Gd-DTPA. Using the single-compartment two-input kinetic model, PF (=portal inflow/portal + arterial inflow) was calculated via a non-linear least-square fitting algorithm [6] in MATLAB.

***ROC curve:*** We chose the cutpoints for PF and PPG below which we consider the subject as fibrosis and above which we consider the subject as normal. These cutpoints were set as [mean + k*STD], where mean and STD were mean value and standard deviation of the control group and k was an integer varied from -4 to 1. The cut points were 80, 75, 70, 65, 60, 55 for PF and were 420, 320, 220, 120, 20 for PPG. Sensitivity was defined as true positive (i.e., how good the test at identifying fibrosis correctly) and specificity was defined as (1-false positive) (i.e., how good at correctly identifying normal) [7].

***Histopathology:*** The livers were harvested after MRI scan and stained with hematoxalin and eosin. The semi-quantitative scores ranging 0-5 were assigned according to the amount of collagen deposition in the liver samples: 0 (normal), 1 (minimal), 2 (mild), 3 (moderate), 4 (marked) and 5 (severe).

## RESULTS

Fig1 (a) shows the histology result where the severity of hepatic fibrosis was highly correlated with the duration of CCl4 treatment. Both PPG and PF decreased as hepatic fibrosis progressed, as shown in Fig 1(b) and (c). Both PPG and PF demonstrated high correlation with fibrosis scores (r = -0.88, p<0.01 for PF; r = -0.89, p<0.01 for PPG) (Fig1 (d)). There were significant differences in PPG and PF between control and 11-16 wks group (p<0.003 for both). However, the difference between control and 2-3 wks group was statistically significant only for PPG (for PF, p=0.3; for PPG, p<0.01). The ROC plot for PF and PPG illustrated in Fig 2 showed the PPG measurements appeared to yield more accurate diagnosis results (further away from worthless diagonal) than PF measurements.

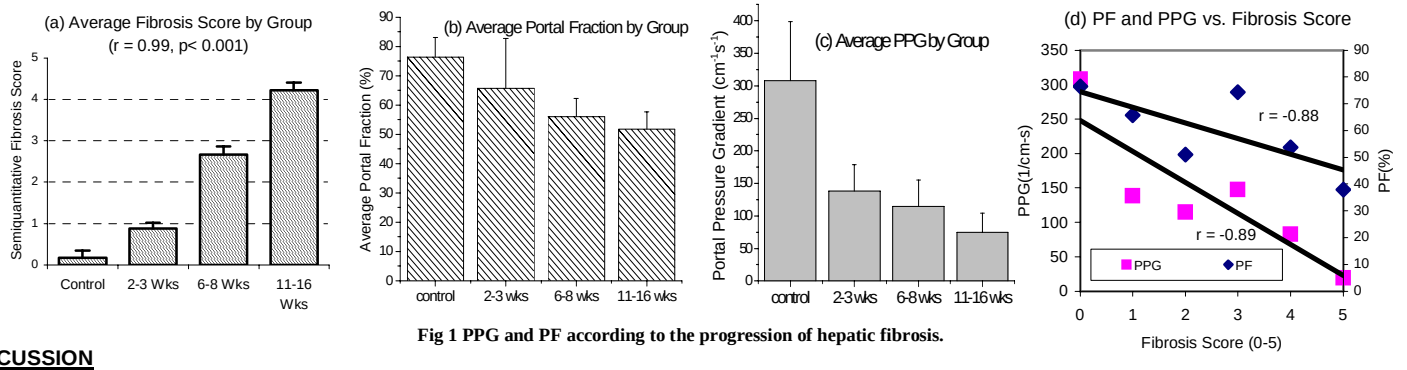


**Fig 1 PPG and PF according to the progression of hepatic fibrosis.**

## DISCUSSION

Previously, PF measurement using *DCE-MRI* has demonstrated its feasibility as a surrogate of the highly invasive PP measurement in assessing liver fibrosis/cirrhosis [2, 6], which is further supported herein according to the high correlation between the MRI measure and the severity of the disease. In our study, PPG is also highly correlated with the progression of liver fibrosis. Considering its encouraging differentiation between control and the 2-3 wks group and its better performance in diagnosing hepatic fibrosis according to ROC curve, PPG modeling in conjunction with PC-MRI may potentially have a place in clinical MRI. Furthermore, PPG approach has the advantage of not requiring any administration of a contrast agent. In conclusion, while its efficacy needs to be further tested in humans where the signal-to-noise ratio is challenging because the data are collected in a single breathhold, the PPG approach may be potentially useful as a non-invasive means of assessing liver fibrosis.

**REFERENCES:** [1] Benyon, JPGN 1998;27(1):75; [2] Annet, Radiology 2003;229:409; [3] Wang, ISMRM 2006,#2211; [4] Hernandez-Munoz, Hepatology 1997;26:1100; [5] Lee et al, MRM 1995;33:122; [6] Marterne MRM 2003;47:135; [7] Obuchowski, Radiology 2003;229:3.

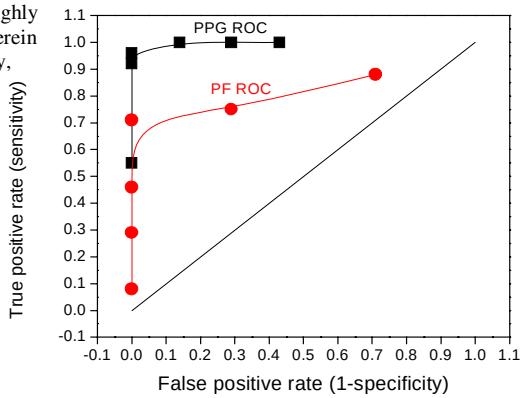


**Fig 2 ROC curves of PPG and PF.**