Diagnosis of Cirrhosis With Intravoxel Incoherent Motion Diffusion MRI and Dynamic Contrast-Enhanced MRI Alone and in Combination: Preliminary Experience

Jignesh Patel, MD, Eric E. Sigmund, PhD, Henry Rusinek, PhD, Marcel Oei, MD, James S. Babb, PhD, and Bachir Taouli, MD*

Purpose: To report our preliminary experience with the use of intravoxel incoherent motion (IVIM) diffusion-weighted magnetic resonance imaging (DW-MRI) and dynamic contrast-enhanced (DCE)-MRI alone and in combination for the diagnosis of liver cirrhosis.

Materials and Methods: Thirty subjects (16 with noncirrhotic liver, 14 with cirrhosis) were prospectively assessed with IVIM DW-MRI (n = 27) and DCE-MRI (n = 20). IVIM parameters included perfusion fraction (PF), pseudodiffusion coefficient (D*), true diffusion coefficient (D), and apparent diffusion coefficient (ADC). Model-free DCE-MRI parameters included time to peak (TTP), upslope, and initial area under the curve at 60 seconds (IAUC60). A dual input single compartmental perfusion model yielded arterial flow (Fa), portal venous flow (Fp), arterial fraction (ART), mean transit time (MTT), and distribution volume (DV). The diagnostic performances for diagnosis of cirrhosis were evaluated for each modality alone and in combination using logistic regression and receiver operating characteristic analyses. IVIM and DCE-MR parameters were compared using a generalized estimating equations model.

Results: PF, D*, D, and ADC values were significantly lower in cirrhosis (P = 0.0056–0.0377), whereas TTP, DV, and MTT were significantly increased in cirrhosis (P = 0.0006–0.0154). There was no correlation between IVIM- and DCE-MRI parameters. The highest Az (areas under the curves) values were observed for ADC (0.808) and TTP-DV (0.952 for each). The combination of ADC with DV and TTP provided 84.6% sensitivity and 100% specificity for diagnosis of cirrhosis.

Conclusion: The combination of DW-MRI and DCE-MRI provides an accurate diagnosis of cirrhosis.

Key Words: diffusion-weighted MRI; dynamic contrast-enhanced MRI; liver; cirrhosis


Noninvasive diagnosis of liver fibrosis and cirrhosis in patients with chronic liver disease is critical, as cirrhotic patients are at higher risk of end-stage liver disease, portal hypertension, and hepatocellular carcinoma (HCC) (1). In addition, cirrhotic patients with chronic viral hepatitis are less likely to respond to antiviral therapy (2,3).

Magnetic resonance imaging (MRI) is a promising method for assessment of diffuse liver disease, given the potential for multiparametric information. In vivo metrics obtained with both diffusion-weighted (DW) MRI (4–14) and dynamic contrast-enhanced (DCE) MRI (15,16) have been shown to represent potential markers of fibrosis and cirrhosis. The mechanism of perfusion changes in liver fibrosis are better understood than changes observed with DW-MRI. Depending on the acquisition parameters, apparent diffusion coefficient (ADC; \( \times 10^{-3}\) mm²/s) is known to reflect variable combinations of diffusion and perfusion effects. The concept of IVIM (intravoxel incoherent motion)—initially described by Le Bihan et al (17–20) in brain imaging—has the potential to measure both true molecular diffusion and incoherent motion of water molecules in the capillary network, known as pseudodiffusion. Because cirrhosis involves accumulation of extracellular matrix that may affect both true diffusion and microcirculation, IVIM DW-MRI should be sensitive to cirrhotic changes. However, the IVIM model has been rarely described in the liver (21–23). Yamada et al (21) were the first to assess IVIM DW-MRI in abdominal organs, although they used only a limited number of b-values (30, 300, 900, and 1100 s/mm²), and did not calculate pseudodiffusion values.
DCE-MRI was performed in 20 patients (nine healthy volunteers and one patient with renal insufficiency did not have contrast injection). Perfusion imaging of the whole liver was performed using a 3D interpolated spoiled gradient-recalled echo sequence in the coronal plane. Patients fasted for 6 hours before the study. The arms were elevated to minimize aliasing artifacts. Three acquisitions were performed before contrast injection, and the first postcontrast acquisition started at the end of the injection of 10 mL of gadobenate dimeglumine (Multihance, Bracco Diagnostics, Princeton, NJ) followed by a 20-mL saline flush injected at 5 mL/sec using an MR-compatible power injector (Spectris, Medrad, Indiana, PA). Fifty coronal volumetric acquisitions images were acquired every 3.5–5 seconds for ≈3–4 minutes (parameters in Table 1). Patients were instructed to suspend respiration at end expiration (in order to minimize misregistration) during all acquisitions, with the first breath hold lasting ≈25–30 seconds and subsequent free shallow breathing. The rationale of coronal plane imaging was to minimize flow-related enhancement of the aorta (25). IVIM DW-MRI and DCE-MRI were incorporated into the routine MRI protocol and added ≈10 minutes to the total imaging time.

Image Analysis
MR images were assessed by three observers (observer 1, who was a body MRI fellow; observer 2, who was a medical student; and observer 3, a radiologist with 5 years experience in body MRI).

IVIM DW-MRI Analysis
ROI (region of interest) placement. All ROIs were manually positioned by observers 1 and 2 in consensus on SS EPI diffusion images on a commercial workstation (Syngo, Siemens Healthcare) for all b-values. A large ROI (2–3 cm) was positioned in the right hepatic lobe on three consecutive slices centered on the main portal vein (Fig. 1). ROIs were placed away from lesions, confluent fibrosis, and large intrahepatic vessels. The left hepatic lobe was excluded due to potential cardiac motion artifacts that may artificially increase values of IVIM parameters. Mean signal intensity (SI) was measured within each ROI, and values of three ROIs (from three slices) were averaged for biexponential fitting (see below).

In addition, for each slice position an ROI was placed over air for b = 1000 s/mm² images. This value was compared to SI of the right hepatic lobe as detailed above. All slice positions or entire datasets were excluded when the ratio of the liver signal intensity to that in the air ROI (defined here as signal-to-noise ratio, SNR) was less than 2 and thus were potentially biased by Rician noise (26).
Segmented biexponential fitting (Fig. 2). The fitting was performed by an expert observer (observer 4, with 12 years experience in DW-MRI) to derive PF, D, D*, and ADC. The values obtained on a per-patient basis were calculated by averaging the three ROI measurements.

The IVIM concept (17) is based on the assumption that water molecules in a voxel can be separated into two compartments, i.e., an intravascular component with volume fraction PF, representing the water molecules flowing in the pseudorandom oriented capillary network (pseudodiffusion coefficient, D*) and the extravascular component with volume fraction 1 - PF, showing passive, restricted diffusion (D). When the MR signal is measured with a sufficient number of different diffusion-weighting factors (b-values), the two

Table 1  
IVIM DW- and DCE-MRI Sequence Parameters for the Different 1.5 T Systems Used (Avanto and Symphony/Sonata, Siemens Healthcare)

<table>
<thead>
<tr>
<th></th>
<th>Avanto (n = 21*)</th>
<th>Symphony/Sonata (n = 10*)</th>
</tr>
</thead>
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<tr>
<td><strong>Acquisition plane</strong></td>
<td>Coronal</td>
<td>Coronal</td>
</tr>
<tr>
<td>Acquisition scheme</td>
<td>PACE SS EPI</td>
<td>Free breathing SS EPI</td>
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<tr>
<td>TR</td>
<td>1 respiratory cycle</td>
<td>2000</td>
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<tr>
<td>TE</td>
<td>76</td>
<td>86</td>
</tr>
<tr>
<td>b-values (sec/mm²)</td>
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<td>192</td>
</tr>
<tr>
<td>Field of view (mm)</td>
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</tr>
<tr>
<td>Slice thickness/interslice gap (mm)/number of slices</td>
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</tr>
<tr>
<td>Parallel imaging factor</td>
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<td></td>
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<tr>
<td>Scan time (min)</td>
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<td>1:52</td>
</tr>
<tr>
<td>Number of averages</td>
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<td>2</td>
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<tr>
<td>Acquisition matrix</td>
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</tr>
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**DCE-MRI**

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<td>TR</td>
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</tr>
<tr>
<td>TE</td>
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<tr>
<td>Flip angle</td>
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<tr>
<td>FOV Read (mm)</td>
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<tr>
<td>FOV Phase (%)</td>
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<tr>
<td>Slice thickness/mm/number of slices</td>
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<tr>
<td>Parallel imaging factor</td>
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<td>Scan time (min)</td>
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<tr>
<td>Number of averages</td>
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<tr>
<td>Acquisition matrix</td>
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<td>Temporal resolution (sec)</td>
<td>~3.6</td>
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<tr>
<td>Number of volumes acquired</td>
<td>50</td>
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</table>

*Four volunteers had both free breathing and PACE (PACE: prospective acquisition correction) acquisition.

Figure 1. ROI placement for signal intensity measurement used to quantify IVIM diffusion parameters in a 43-year-old male volunteer. Three consecutive coronal SS EPI images centered on the portal vein for b = 50 s/mm² are shown. ROIs are copied into the remaining images with different b-values.
Here \( S_{\text{int}} \) is the baseline SI (in log scale) measured in liver parenchyma. X-axis: \( b \)-values (multiple \( b \)-values, 0-50-100-150-200-300-500-700-1000 s/mm\(^2\) are used for sampling). The perfusion (or pseudodiffusion) effect is seen as an early drop in SI observed with \( b \)-values lower than 200 s/mm\(^2\). Perfusion fraction (PF) is measured as the difference between SI for \( b = 0 \) s/mm\(^2\) and the intercept of the high \( b \)-value monoexponential fit. \( D^* \) (pseudodiffusion coefficient) measures the curvature of the initial curve. \( D \) (true diffusion coefficient) is measured with \( b \)-values higher than 200 s/mm\(^2\). ADC was measured using all \( b \)-values with a monoexponential fit. PF values can be calculated by using a partially constrained nonlinear regression algorithm based on Eq. [1].

The ADC was obtained by using all \( b \)-values (0–1000 s/mm\(^2\)) and then fitted to the equation:

\[
S_b = S_0 \exp(-b \text{ADC})
\]  

All regression algorithms and parametric map generation of the parameters PF, \( D \), \( D^* \), and ADC were performed with custom-written code written in IgorPro software (Wavemetrics, Lake Oswego, OR). The above algorithm was employed primarily for the DW-MRI ROI analysis, from which all quantitative metrics were derived for correlation with other data. The same procedure was applied on a voxelwise basis to select normal and cirrhotic cases for pure qualitative illustration, since the SNR per voxel is significantly less than that of the large ROI analysis.

**Assessment of Reproducibility of IVIM Parameters**

Test/retest evaluation was performed to assess reproducibility by repeating IVIM DWI in the same subjects within a 1–2 week time period on the same MR unit without any intervention in the interval. IVIM DW-MRI was repeated in five subjects (one patient with noncirrhotic liver and four volunteers) using PACE (\( n = 5 \)) and free breathing acquisitions (\( n = 4 \)).

**DCE-MRI Analysis**

**ROI placement.** The images were transferred to a PC for analysis. Home-grown software was used for analysis (Firevoxel). To determine the vascular input functions (VIF), ROIs were manually drawn on the main portal vein (at the level of the porta hepatis) and proximal abdominal aorta (at the level of the celiac axis, used as a surrogate of the hepatic artery). ROIs for the portal vein were drawn for each timeframe to correct for spatial misregistration due to respiratory motion. In addition, six liver ROIs (measuring 2–3 cm, 3 in the right lobe and 3 in the left lobe) were placed by observers 2 and 3 in consensus. Large vascular structures or liver lesions were avoided.

**Model-free perfusion parameters.** All perfusion computations were performed by an expert observer (observer 5, with 20 years in perfusion modeling and image processing). For each liver region three parameters (TTP [time to peak], upslope, and IAUC60 [area under the curve at 60 sec]) were defined using simplified, model-free computations that did not require information about arterial or portal vein input functions. From each signal activity curve \( S(t) \) the values of rise time \( t_{\text{rise}} \) and peak time \( t_{\text{peak}} \) were identified. The value \( t_{\text{rise}} \) was defined as the earliest sample with signal exceeding the baseline threshold:

\[
M_0 + 2\sigma_0
\]  

With \( D \) and PF values determined by using Eq. [2], \( D^* \) values can be significantly greater than \( D \) (17) by a factor of \( 10 \), so that when \( b \) value is greater than 200 s/mm\(^2\), the influence of the pseudodiffusion term on the signal decay is quite small. Thus, in the higher \( b \)-value regime, Eq. [1] can then be simplified into a linear fit equation whereby \( D \) can be estimated:

\[
S_b = S_{\text{int}} \exp(-bD)
\]  

Here \( S_{\text{int}} \) is the \( b = 0 \) intercept of the high \( b \)-value exponential fit, which allows the perfusion fraction to be estimated according to:
where $M_0$ was the mean value $M_0$ and $\sigma_0$ the standard deviation of the signal measured during the first five (i.e., preinjection) acquisitions. The value $t_{\text{peak}}$ was the timepoint at which $S(t)$ reached its maximum. These timepoints $t_{\text{rise}}$ and $t_{\text{peak}}$ served to define TTP, peak concentration $c_{\text{max}}$, and average upslope $U$ according to:

\[
\text{TTP} = t_{\text{peak}} - t_{\text{rise}} \\
\text{c}_{\text{max}} = C(t_{\text{peak}}) \\
U = C(t_{\text{peak}})/\text{TTP}
\]

$C(t)$ in the above equation denotes the concentration-versus-time curve derived from $S(t)$. In addition, the area under the time activity curve of gadolinium contrast over 60 seconds from the start of contrast enhancement was quantified (IAUC60).

**Perfusion modeling.** SI measurements were normalized by subtracting the SI value of the initial unenhanced image from the SI measurements of the subsequent enhanced images, then dividing the difference by the initial SI value. SI curves were then obtained from all ROI data (Fig. 3). A linear relationship was assumed between SI and gadolinium concentration for the range of expected concentrations in the liver (0.0–0.5 mM/L) and blood (0–5 mM/L). Our conversion was therefore based on the approximation: $c = k (S - S_0)/S_0$ (31), in which $S_0$ is precontrast SI, $S$ is postcontrast SI, and $k$ the scaling constant (0.395 for liver and 0.201 for blood). These constants are based on prior phantom and human calibration study (32). The resulting time–activity curves were fitted using a dual-input single compartmental model which was validated previously (15,16,33). This model reflects the dual blood supply from the portal vein and hepatic artery received by the liver. The general equation for the dual-input kinetic model is:

\[
C_L(t) = \int_0^t \left[ k_{1a}C_a(t' - \delta) + k_{1p}C_p(t') \right] e^{-k_2(t-t')} dt' \tag{9}
\]

where $C_a(t)$, $C_p(t)$, and $C_L(t)$ represent the concentrations of the contrast in the aorta, the portal vein, and the liver, respectively; $\delta$ represents the transit times from the aorta region to the liver region of interest, $k_{1a}$ represents the aortic inflow rate constant, $k_{1p}$ the portal venous inflow rate constant, and $k_2$ the outflow rate constant. A fitting procedure was performed to determine $k_{1a}$, $k_{1p}$, $k_2$, and $\delta$ using locally developed software written in C++. The distribution volume (DV in %) of Gd-contrast through the liver compartment was calculated as $DV = 100 (k_{1a} + k_{1p})/k_2$, and mean transit time (MTT in sec) as $1/k_2$. MTT is the average time it takes a Gd molecule to traverse the liver from arterial/portal entry to venous exit. Inflow constants $k_{1a}$, $k_{1p}$, were converted to arterial and portal flow rates $F_a$ (arterial liver blood flow), $F_p$ (portal liver blood flow), both expressed in ml/100g/min, and then used to compute the total flow ($F_a + F_p$) as well as the arterial fraction (ART, in %) = 100 × $F_a/(F_a + F_p)$.

**Statistical Analysis**

SAS v. 9.0 (Cary, NC) was used for statistical computations. All statistical analyses employed result from ROI analysis. An exact Mann–Whitney test was used to compare cirrhotic and noncirrhotic subjects in terms of each imaging measure. Binary logistic regression was used to derive models to predict cirrhosis using sets of two or more imaging measures. Receiver operating characteristic (ROC) curve analysis was used to identify cutoff values for the imaging measures that maximized the average of sensitivity and specificity when the threshold was used to define patients as test positive or test negative for cirrhosis. A generalized estimating equations (GEE) model was
used to compare sensitivity and specificity of IVIM and DCE-MRI parameters. All reported P values are two-sided. Each of PF and D* were correlated with DCE-MRI parameters using the Pearson correlation test. Statistical significance was defined as \( P < 0.05 \). Reproducibility of imaging parameters was evaluated using coefficient of variation (CV = SD/mean of 2 measures) analysis.

RESULTS

**IVIM DW-MRI Parameters (Table 2)**

ROI analysis results showed that ADC values were significantly higher than D values in both the noncirrhotic and cirrhotic subjects (\( P = 0.001 \) and 0.002, respectively), confirming the perfusion effect on ADC values. All IVIM parameters (ADC, D*, D, PF) were significantly reduced in the cirrhotic group compared to the noncirrhotic group (\( P = 0.0071-0.0392 \)) (Table 2, Figs. 2, 4). The most significant difference was observed for ADC. The relationships shown in Table 2 and Figure 4, derived from robust large ROI analysis, are qualitatively consistent with example parametric maps of IVIM parameters in a normal and cirrhotic patient (Fig. 5). Although spatial textures are complex, the mean values of each IVIM parameter across the liver are lower in the cirrhotic versus normal patient.

Reproducibility of IVIM parameters (in the subset of patients in whom repeat PACE or free-breathing DWI was performed) was excellent for ADC and D, good for PF, and fair for D* (Table 3). Reproducibility was higher with the navigator triggered acquisition.

**DCE-MRI Parameters (Table 4)**

TTP, DV, and MTT were all significantly increased in the cirrhotic group when compared to the noncirrhotic group (\( P = 0.002-0.0187 \)) (Table 4, Figs. 3, 6). F_a and

<table>
<thead>
<tr>
<th>Non cirrhotic (n = 14)</th>
<th>Cirrhosis (n = 13)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF (%)</td>
<td>32.16 ± 8.13</td>
<td>25.40 ± 7.48</td>
</tr>
<tr>
<td>D* (x 10^{-3} mm^2/s)</td>
<td>39.61 ± 12.34</td>
<td>27.89 ± 10.48</td>
</tr>
<tr>
<td>D (x 10^{-3} mm^2/s)</td>
<td>1.17 ± 0.21</td>
<td>1.04 ± 0.20</td>
</tr>
<tr>
<td>ADC (x 10^{-3} mm^2/s)</td>
<td>1.73 ± 0.31</td>
<td>1.41 ± 0.25</td>
</tr>
</tbody>
</table>

Mean ± SD are shown for each parameter.


Figure 4. Boxplot distribution of IVIM parameters in cirrhotic and noncirrhotic patients (n = 27). ADC showed the best discrimination. Top and bottom of boxes: 25%-75% percentiles of data, line in box: median value, *outliers. PF: perfusion fraction (%), D*: pseudodiffusion coefficient (\( \times 10^{-3} \) mm\(^2\)/s), D: true diffusion coefficient (\( \times 10^{-3} \) mm\(^2\)/s), ADC: apparent diffusion coefficient (\( \times 10^{-3} \) mm\(^2\)/s). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
ART were increased, whereas upslope and IAUC60 were decreased in cirrhosis, with a trend toward significance ($P = 0.0791–0.0913$), likely due to sample size. Portal venous flow ($F_P$) and total liver flow ($F_L + F_P$) were decreased in cirrhosis without reaching significance.

**Correlation Between IVIM and DCE-MRI Parameters**

There was no significant correlation between each of PF and $D^*$ with DCE-MR parameters (Pearson correlation coefficients ranging from $-0.35$ to $0.40$; $P > 0.14$, Table 5).

**Diagnostic Performance of IVIM DW- and DCE-MRI Alone and in Combination (Table 6)**

Stepwise variable selection in the context of logistic regression identified ADC as the best predictor of cirrhosis from among the IVIM measures ($A_z 0.808$, sensitivity $84.6\%$, specificity $71.4\%$). The stepwise variable selection identified $D^*$ and TTP as the best predictors of cirrhosis from among the DCE measures ($A_z 0.952$, sensitivity $85.7\%$, specificity $100.0\%$ for both) followed by $MTT$ ($A_z 0.845$, sensitivity $100.0\%$, specificity $83.3\%$), and IAUC60 ($A_z 0.804$, sensitivity $85.7\%$, specificity $75.0\%$).

The $A_z$ of $D^*$ and TTP were higher than that of ADC: however, the comparison between IVIM and DCE-MR parameters using the GEE model showed no significant difference ($P = 0.9281$ for sensitivity and 1.0 for specificity).

In the 17 patients who had both IVIM DW- and DCE-MRI, the combination of ADC with TTP and $D^*$ provided $84.6\%$ sensitivity ($11/13$), $100\%$ specificity ($4/4$), $100\%$ positive predictive value ($11/11$), $66.6\%$ negative predictive value ($4/6$), and $88.2\%$ ($15/17$) accuracy for diagnosing cirrhosis (Fig. 7). All four noncirrhotic patients had decreased TTP and $D^*$, and the $11/13$ cirrhotic patients had decreased ADC and increased TTP or increased $D^*$.

**DISCUSSION**

In our study we demonstrated altered IVIM (ADC, PF, $D^*$, and $D$) and DCE-MR parameters (TTP, DV, and $MTT$) in liver cirrhosis, with excellent diagnostic accuracy for diagnosing cirrhosis using ADC and TTP-DV. In addition, we showed that the combination of ADC with TTP and DV yielded $84.6\%$ sensitivity and $100\%$ specificity for diagnosing cirrhosis. To our knowledge, this is the first study reporting the use of combined IVIM and DCE-MR acquisitions in liver imaging.

Patients with chronic hepatitis (including mostly viral, alcoholic, and nonalcoholic steatohepatitis) are at high risk of developing liver fibrosis and cirrhosis (1). Accurate diagnosis of liver cirrhosis is critical, as cirrhotic patients are at higher risk of endstage liver disease.

**Table 3**

Mean Coefficient of Variation (CV, in %) of IVIM Parameters Measured With Navigator Triggered (PACE: Prospective Acquisition Correction) and Free-Breathing SS EPI DW-MRI Acquisitions in five Subjects

<table>
<thead>
<tr>
<th></th>
<th>All ($n = 5$)*</th>
<th>PACE ($n = 5$)*</th>
<th>Free breathing ($n = 4$)*</th>
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<tr>
<td>PF</td>
<td>11.4</td>
<td>7.7</td>
<td>16.0</td>
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<tr>
<td>$D^*$</td>
<td>23.8</td>
<td>14.6</td>
<td>39.1</td>
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<tr>
<td>$D$</td>
<td>5.0</td>
<td>3.8</td>
<td>6.4</td>
</tr>
<tr>
<td>ADC</td>
<td>3.2</td>
<td>3.0</td>
<td>3.4</td>
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</table>

* $n$: number of subjects (four subjects had both PACE and free breathing IVIM repeated, and one subject had only PACE IVIM DW-MRI repeated).
disease, portal hypertension, and HCC. The degree of fibrosis is commonly determined from liver biopsy, used to assess prognosis and guide therapy (34). However, liver biopsy is relatively invasive, expensive, limited by sample size, and difficult to repeat (35–40). Thus, noninvasive tools to assess the degree of injury and fibrosis of the whole liver are urgently needed.

DW-MRI (4–14) and DCE CT or MRI (15,16,33,41) parameters have been shown to be potentially useful for detection of liver fibrosis and cirrhosis, with a reported range of areas under the curve of 0.896–0.93 (11–13) for diagnosis of advanced fibrosis or cirrhosis. Most of these diffusion studies showing decreased liver ADC in cirrhosis (4–9,13) or fibrosis (10–12,14) compared to normal liver or mild degrees of fibrosis have quantified diffusion using a monoexponential fit, and have assumed pure diffusion restriction in relation with extracellular matrix accumulation. However, our findings and those from other investigators (21,23,42) suggest that both pure molecular diffusion and capillary perfusion contribute to signal attenuation in liver diffusion imaging. This is primarily

### Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Noncirrhotic (n = 6)</th>
<th>Cirrhosis (n = 14)</th>
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<tr>
<td>TTP (sec)</td>
<td>46.40 ± 9.93</td>
<td>87.85 ± 35.51</td>
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<td>Upslope [mmol/(L.min)]</td>
<td>0.49 ± 0.20</td>
<td>0.33 ± 0.12</td>
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<td>IAUC60 (mM.s)</td>
<td>15.89 ± 3.24</td>
<td>12.14 ± 2.94</td>
<td>0.0791</td>
</tr>
<tr>
<td>DV (%)</td>
<td>23.67 ± 8.44</td>
<td>45.20 ± 13.03</td>
<td>0.0006</td>
</tr>
<tr>
<td>MTT (sec)</td>
<td>17.36 ± 15.38</td>
<td>25.11 ± 11.87</td>
<td>0.0154</td>
</tr>
<tr>
<td>ART (%)</td>
<td>16.33 ± 3.29</td>
<td>29.99 ± 14.25</td>
<td>0.0913</td>
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<tr>
<td>F_a (ml/100g/min)</td>
<td>18.89 ± 10.60</td>
<td>34.12 ± 18.05</td>
<td>0.1253</td>
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<tr>
<td>F_p (ml/100g/min)</td>
<td>114.45 ± 73.11</td>
<td>90.73 ± 44.50</td>
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<tr>
<td>F_a + F_p (ml/100g/min)</td>
<td>133.34 ± 82.35</td>
<td>124.49 ± 48.13</td>
<td>0.6457</td>
</tr>
</tbody>
</table>

Mean ± SD are shown for each parameter. IAUC60: integrated area under the time activity curve of gadolinium contrast over 60 s from the start of contrast enhancement, ART: arterial fraction, DV: distribution volume, F_a: arterial liver blood flow, F_p: portal liver blood flow, F_a + F_p: total liver blood flow, MTT: mean transit time, TTP: time to peak.

Figure 6. Boxplot distribution of DCE-MRI parameters in cirrhotic and noncirrhotic patients (n = 20). DV (distribution volume) and TTP (time to peak) showed the best discrimination between noncirrhotic and cirrhotic patients. Top and bottom of boxes: 25%–75% percentiles of data, line in box: median value, *outliers. ART: arterial fraction (%), IAUC60: integrated area under the time activity curve over 60 s (mM.s), DV: distribution volume (%), F_a: arterial liver blood flow (ml/100g/min), F_p: portal liver blood flow (ml/100g/min), F_a + F_p: total liver blood flow (ml/100g/min), MTT: mean transit time (sec), TTP: time to peak (sec) [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
Diagnosis of Cirrhosis With IVIM and DCE MRI

 attributed to the IVIM effect observed with the use of b-values \(<200\text{ s/mm}^2\). The IVIM model—initially described in the brain by Le Bihan et al (17)—can discriminate true molecular diffusion from capillary perfusion (or pseudodiffusion). There is a paucity of data to discriminate true molecular diffusion from capillary perfusion (or pseudodiffusion). There is a paucity of data to discriminate true molecular diffusion from capillary perfusion (or pseudodiffusion). There is a paucity of data to discriminate true molecular diffusion from capillary perfusion (or pseudodiffusion). There is a paucity of data to discriminate true molecular diffusion from capillary perfusion (or pseudodiffusion). There is a paucity of data to discriminate true molecular diffusion from capillary perfusion (or pseudodiffusion). There is a paucity of data to discriminate true molecular diffusion from capillary perfusion (or pseudodiffusion). 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focusing errors, as this parameter typically displays the largest fitting uncertainty in IVIM studies. Our results suggest that PF is lower in the cirrhotic group than in the noncirrhotic group, and our data support the theory that differences in total ADC between noncirrhotic and cirrhotic patients have a significant perfusional component but restriction of Brownian motion still plays a role at higher b-values. In our study, ADC was still the best IVIM parameter in terms of accuracy, with the best reproducibility, likely due to increased data points (including low and large b-values).

Previous reports have shown that advanced fibrosis and cirrhosis lead to reduced portal venous flow and increased arterial flow (known as the arterial buffer response) (44), as well as increased MTT and DV measured with DCE CT or MRI (15,16,33,41). A recent study has showed that DV was the best predictive parameter for diagnosing advanced fibrosis and cirrhosis (Az of 0.824, sensitivity of 76.9%, and specificity of 78.5% for DV ≥ 21.05%) (16). The current study showed higher Az for DV and MTT compared to the prior study by Hagiwara et al (16), which likely relates to a different patient selection (intermediate stages of fibrosis were not included in the current study). Model-free DCE-MR parameters have never been described before for the diagnosis of liver cirrhosis, and these may have a role in future studies, as these parameters are easy to quantify, without the need for vascular input function.

The relationship between perfusion parameters measured with IVIM versus those measured with DCE-MRI is unclear. In an opinion article, Le Bihan and Turner (45) suggested that the combination of PF and D* may potentially provide useful data for microcirculation physiology (PF measures the fractional volume of capillary blood flowing in each voxel, and D* is proportional to the mean capillary segment length and to average blood velocity). They also suggested that CBF (cerebral blood flow) is directly proportional to the product PF × D*. In a contradictory opinion article, Henkelman (46) suggested that IVIM does not measure tissue perfusion as does DCE-MRI, as it is more sensitive to blood volume transit through a voxel. Data corroborating or contradicting these opinions is sparse, even in neuroimaging. For example, Wirestam et al (30) correlated brain IVIM parameters with dynamic susceptibility-contrast (DSC) MRI (calculating cerebral blood volume and flow, CBV and CBF) in 28 volunteers. They demonstrated a moderate significant correlation between PF and CBV (r = 0.56, P < 0.001) using asymptotic fitting (ie, segmented analysis). A key point in the comparison of IVIM and DCE or DSC MRI techniques is the effect of compartmental exchange. The evolution time of the DW-MRI sequence (≈100 msec) is insufficient for significant water exchange and thus the signal can be interpreted as separate intra- and extravascular compartments, with the parameters PF and D* referring to the intravascular compartment. Conversely, DCE-MRI tracks contrast continuously over much longer periods (several minutes) and thus necessarily involves intravascular, extravascular, and exchange dynamics. Correspondingly, of the parameters of the DCE-MRI model, eg, those reported in this study, none exclusively reflect microvascular volume or flow, but instead some composite encompassing total tracer transit. DSC MRI, on the other hand, employs susceptibility contrast on short timescales and, particularly for vasculature with a blood–brain barrier, also provides access to purely intravascular parameters (eg, CBF and CBV), motivating the aforementioned comparison of IVIM and DSC-MRI metrics. Indeed, since “perfusion” usually connotes not only vascularity but also the extravasation of blood products to surrounding parenchyma, the terms “perfusion fraction” or “perfusion-induced pseudodiffusion” can be misleading. While the terms historically arose to differentiate vascular from parenchymal effects in DW-MRI, care must be taken in attempts to reconcile them with DCE-MRI, which has distinctly different biophysical sensitivity. Finally, other effects unique to hepatic tissue may confound the association of IVIM exclusively with perfusional vascularity, including fast flow of bile ducts and venous drainage.

Based on this perspective and the current study results, we can confidently suggest that liver perfusion measurements with IVIM are not equivalent to perfusion parameters obtained with DCE-MRI, with no correlations observed. Therefore, we do not believe that IVIM can be used as a surrogate for DCE-MRI perfusion. Since the parameters measured with each method do not relate, it is very attractive to combine the two methods for improved diagnostic accuracy, as shown in our patient population. This could be further assessed for prospective detection of intermediate stages of fibrosis.

An important issue with DW- and DCE-MRI is reproducibility. Moteki and Horikoshi (22) reported a
large variability of D and D* values with CV of 25.4% and 28.2% for D and D* values (measured on a single volunteer 11 times); however, their study was limited by the number of b-values used (3, 50, 300 s/mm²), and they did not report CV of ADC and PF. A recent study on volunteers showed mean CV of 12.8% for liver ADC measurement using free-breathing DW-MRI (47). More recently, Koh et al (48) found better reproducibility of ADC total (using all b-values: 0, 50, 100, 250, 500, and 750 s/mm²) and ADC high (using 100, 250, 500, and 750 s/mm²), compared to ADC low (using 0, 50, and 100 s/mm²). In our study we found good to excellent reproducibility of ADC, D, and PF, especially with the navigator triggered acquisition (CV <6% for ADC and D, and <12% for PF). D* had the worse reproducibility (with CV of 14.6% and 39.1% for navigator triggered and free breathing acquisitions, respectively). Regarding reproducibility of liver perfusion measurements, Miyazaki et al (49) recently reported excellent reproducibility of hepatic perfusion index (a semiquantitative perfusion parameter) measured in patients treated with an antiangiogenic compound.

We did not measure reproducibility of DCE-MR parameters in our study, and this could be assessed in a separate study. Our study had several limitations. The ability to recruit noncirrhotic patients prospectively for the DCE-MRI portion of study was limited and as a result only four patients were included in this portion of the study. In the cirrhotic group, histopathologic confirmation was only available for three patients. Furthermore, we did not assess intermediate stages of fibrosis in this evaluation. One patient included in our noncirrhotic group was found to have heterogeneous areas of periportal fibrosis on pathology and this may have negatively skewed our results. Future studies assessing different stages of fibrosis using IVIM and DCE-MR parameters may be conducted. In our initial experience, only five b-values less than or equal to 200 s/mm² were implemented. Because our aim was to evaluate perfusion-related diffusion parameters, a greater number of b-values less than 200 s/mm² would be better at showing more subtle differences in perfusion-related parameters (PF and D*) or lack thereof. A final limitation of the study protocol could arise from injecting a constant volume of 10 mL of gadolinium contrast in patients of different weight. Some of the model-free perfusion parameters (including $c_{max}$, upslope, and IAUC60) could be confounded by this dose-related variability.

In conclusion, our findings show that perfusion and diffusion are both affected in cirrhosis. IVIM perfusion parameters do not correlate with DCE-MR parameters, and that the combination of diffusion and DCE-MR parameters (ADC and DV-TTP) provides excellent diagnostic performance for the detection of liver cirrhosis.

REFERENCES