Liver magnetic resonance diffusion weighted imaging: 2011 update

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Available online 22 June 2011

Summary Diffusion-Weighted-Imaging (DWI) assesses proton motion on a cellular scale. Owing to recent instrumentation developments, diffusion sequences are now routinely used for liver imaging. This review will go through the physical principles that underlie this technique, and then highlight up-to-date liver applications including quantification of liver fibrosis, focal lesions detection and characterization, and therapy response monitoring.

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Introduction Magnetic Resonance (MR) Diffusion weighted imaging (DWI) allows the assessment of so-called Brownian motion. These short-distance and disorganized displacements are in direct relation with the temperature and viscosity of the studied environment. As a result, monitoring Brownian motion can highlight specific features of a given environment. Stejskal and Tanner first reported that MR sequences could be sensitive to these protonic motions, which can differ significantly in situations as opposite as necrotic foci or highly cellular tumors [1]. Liver MR-DWI is now fully integrated to routine liver MR imaging protocols. However, the switch of liver MR-DWI to clinical practice has only been allowed by the concomitant developments of ultra-fast imaging sequences, high-MR gradient amplitudes, multichannel coils and parallel imaging [2,3]. Hence, the development and use of liver MR-DWI are first conditioned by a proper understanding of these instrumental MR advances. The objectives of this short review will be first to highlight instrumental prerequisites of liver MR-DWI, before reviewing present and future clinical applications.

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doi:10.1016/j.clinre.2011.05.001
Magnetic Resonance Diffusion weighted imaging (MR-DWI): is it that simple?

Diffusion principles

MR-DWI uses a modified T2-weighted MR sequence, applying an additional and symmetrical pair of diffusion-sensitizing gradients to a conventional spin-echo scheme. When exposed to the first diffusion-sensitizing gradient, protons acquire a phase shift. Only the nonmoving protons are perfectly rephased by the second diffusion-sensitizing gradient: as a result, dephased moving protons lose their MR signal (unrestricted diffusion motion), while nonmoving protons retain their MR signal (diffusion restriction). This signal decrease of moving protons can further be quantified following Stejskal-Tanner equation [4].

\[ S(b)/S(0) = e^{-bD} \]

where \( D \) is the diffusion coefficient, \( S \) and \( S(0) \) the respective mean signal intensity with and without diffusion gradient and \( b \) the diffusion gradient.

Quantification of diffusion-related motion: what is the apparent diffusion coefficient (ADC)?

The Apparent Diffusion Coefficient (ADC) is an estimation of the protonic diffusion motions, calculated with at least two \( b \) values, as in the following equation:

\[ S(b)/S(0) = \exp(-b \times ADC) \]

ADC is considered low in highly cellular tissue —where the protons are less mobile accounting for diffusion restriction— and high in free fluid—fully mobile protons accounting for unrestricted diffusion — and less organized parenchyma [5,6]. ADC value can be computed for every organ or tumor lesion including the liver. But is quantification on MR-DWI that simple?

Le Bihan et al. demonstrated that the signal decrease in a diffusion-weighted sequence within a voxel not only reflects pure molecular diffusion but also microcirculation. Thus, the signal attenuation of the liver with increasing \( b \) values is nonlinear [7,8] and follows a multieponential decrease. Signal attenuation seen on MR-DWI performed with \( b \)-values below \(< 200 \text{s/mm}^2 \) is influenced by microcirculation, while signal attenuation seen on MR-DWI performed with higher \( b \)-values is related to pure molecular diffusion [9,10]. Molecular diffusion and microcirculation can hence be distinguished using Intravoxel Incoherent Motion Imaging Theory (IVIM) with the following equation [11,12]:

\[ S(b)/S(0) = (1-f) \exp(-bD) + f \exp(-b(D+D^*)) \]

where \( D \) is the pure molecular diffusion, \( D^* \) is the perfusion related diffusion factor and \( f \) is the fraction of the diffusion linked to microcirculation (Fig. 1).

Depending on the \( b \)-values used, ADC estimation provided by most MR systems combines this double component. This partly explains the liver ADC variations reported in the literature: liver ADC values computed with low \( b \) values are higher than when computed with only high-\( b \) values [13–15]. To date, no consensus has yet been reached on which values should be used for liver MR-DWI, although some authors have recommended to compute ADC values using only \( b \) values \( > 200 \text{s/mm}^2 \) [16]. Not only ADC depends on instrumental developments and \( b \)-values selection, but also the reproducibility of ADC is still questioned. Reported intra-individual variations of ADC in healthy subjects reach up to 14% [17] and should be taken into account when dealing with tumor ADC quantification [18]. In addition, there is still limited experience of liver DWI at high field imaging, which could also impact ADC measurements [19,20]. Again, standardization of MRI-DWI instrumentation appears as a prerequisite before reaching functional parametric assessment of liver with DWI.

How is liver Magnetic Resonance Diffusion weighted imaging (MR-DWI) performed?

The most commonly used imaging sequence is a single shot spin echo (SE) echo planar technique [21] combined with fat suppression. TE depends on the chosen phase matrix. When TE is short, Signal-to-Noise-Ratio (SNR) increases. To reduce
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Key-points
- MR-DWI reflects Brownian motion.
- In free fluid, there is loss of signal due to non-restricted diffusion motions. ADC is high.
- In highly cellular tissue, the MR-DWI signal remains high even with increasing $b$ values, accounting for restricted diffusion: the resulting ADC is low.
- Depending on the $b$-values used, both true molecular diffusion and microcirculation can be analyzed with DWI.
- Standardization of MR-DWI is necessary when using quantification on MR-DWI.

TE, parallel imaging and short diffusion gradients should be selected [22]. Although the normal liver parenchyma is isotropic [14]—i.e. with identical diffusion parameters in all directions—most MR DWI sequences use three orthogonally applied diffusion sensitizing gradients.

MR-DWI and ADC computation are sensitive to respiratory motion, inherent to liver imaging. Several strategies have been developed to overcome this limitation: breath-hold acquisitions are easy to perform, at the expense of increased distortion and limited SNR within the acquisition time. Furthermore, the number of $b$ values is limited [23].

Figure 2  Liver Signal decrease on Diffusion Weighted imaging of cirrhotic (blue curve) and healthy liver (red curve) with increasing $b$-values: signal drop-out on low-$b$ values is significantly lower in cirrhotic liver, accounting for decreased perfusion. On high-$b$ values, cirrhotic livers hence display higher signal intensity, reflecting liver diffusion restriction associated with liver fibrosis.

as well as phase matrix size [24]. Free breathing images can ideally be combined to respiratory gating—whether using a pneumatic belt or using respiratory triggering—thereafter improving image quality, SNR and ADC quantification at the expense of increased acquisition time [23].

Figure 3  Diffusion Weighted MRI and liver lesion detection: 54-year-old patient with right lobe liver metastasis: the lesion was overlooked on both T1 WI (A), T2-WI (B) and portal phase T1 WI following Gadolinium-chelates injection (C) owing to its location close to vessels, but is easily detectable on DWI using a diffusion factor of $b=800$ s/mm$^2$ (arrow in D).
Figure 4  Liver Diffusion and HCC detection: 61-year-old patient with Segment 4 hepatocellular carcinoma showing isosignal intensity on T1 WI (arrow in A), faint hypersignal intensity on T2 WI (arrow in B), with early enhancement following Gadolinium chelates injection (arrow in C) followed by washout on portal phase (arrow in D). This lesion shows hyperintensity on DWI using both $b = 100\,\text{s/mm}^2$ (E) and $b = 800\,\text{s/mm}^2$ (arrow in F) with restricted diffusion on ADC map ($\text{ADC} = 1.09\,\text{mm}^2/\text{s}$) (arrow in G).
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Figure 5 Liver Diffusion Weighted Imaging and focal liver lesion characterization: 45-year-old patient with biliary cyst (arrow) in segment 7 and neuroendocrine cystic metastasis (arrowhead) in segment 8. Both lesions show high signal intensity on T2 WI (arrow and arrowhead in A) and on DWI using a diffusion factor of \( b = 100 \text{s/mm}^2 \) (arrow and arrowhead in B) whereas only the metastasis retains its high signal intensity on DWI using a diffusion factor of \( b = 800 \text{s/mm}^2 \) (arrow and arrowhead in C). ADC is lower in metastasis (arrowhead D) than in biliary cyst (arrow in D) reflecting diffusion restriction within the malignant tumor as opposed to that of biliary cyst.

Key-points
- Liver MR DWI is based on Single Shot spin echo planar technique sequence with fat suppression.
- Respiratory trigger or breath hold technique are mandatory in order to overcome movement artifacts.

Clinical applications of liver Magnetic Resonance Diffusion weighted imaging (MR-DWI): liver tissue characterization and liver tumor detection

Liver fibrosis and cirrhosis

Liver MR DWI is known to provide noninvasive assessment of hepatic fibrosis: all reported studies suggest that the ADC of cirrhotic liver is significantly lower than that of healthy liver. Lewin et al. used MR-DWI with respiratory gating and parallel reconstructions, to discriminate F0–F2 fibrosis stages from F3–F4 (METAVIR [25]) in chronic HCV patients with respective sensitivity and specificity of 87% and 87% using a cut-off ADC value of \( 1.21 \times 10^{-3} \text{mm}^2/\text{s} \) [26]. Patients with moderate to severe fibrosis (F2–F3–F4) had lower liver ADC values than those without or with mild fibrosis (F0–F1) and healthy volunteers. The performance of MR-DWI was comparable to that of elastography or of serum markers of fibrosis in identifying F3–F4 patients. Similar results were reported by Taouli et al. [6,27]. The diagnostic accuracy of liver MR-DWI could be further optimized using the spleen as an internal reference [28].

However, the mechanisms leading to diffusion restriction in fibrotic liver are probably incompletely understood. Annet et al., studying an animal model of liver fibrosis, issued that diffusion restriction was only present in living animals, suggesting that alterations in liver perfusion could partly explain decreased ADC of cirrhotic livers [8]. Luciani et al., using a 10-b factor MR-DWI sequence, showed that restricted diffusion observed in patients with cirrhosis were mainly related to decreased diffusion-related perfusion [7] (Fig. 2). These results were confirmed more recently by Patel et al., who additionally demonstrated that the diffusion parameters derived from MR-DWI sequences were not correlated to perfusion parameters obtained after dynamic injection.
Malignant liver lesion detection

Detecting metastases within the liver is of crucial importance, especially prior to liver surgery. Liver MR-DWI improves focal liver detection compared to conventional T2 sequences [30–34]. The detection rate of liver MR-DWI is also known to reach that of liver-specific contrast-agent-enhanced liver MR: Nasu et al. reported that DWI performed better than Small Particle of Iron Oxide (SPIO) — enhanced liver MRI in detecting liver metastases [35]. Similar results were reported by Soyer et al. who compared conventional Gadolinium-chelates enhanced MRI to MR-DWI [36]. The performances of MR-DWI are nevertheless lower when dealing with small less than 2 cm large liver lesions [37]. As a result, combined use of contrast agents and MR-DWI is reported as an optimal tool for liver metastases detection [38,39] (Fig. 3).

For long, the role of liver MR-DWI in Hepatocellular Carcinoma (HCC) detection has been questioned: both HCC lesions and fibrotic livers display restricted diffusion. Thus, few studies have suggested that MR-DWI could improve HCC nodule detection [40–42]. Recently Piana et al. demonstrated that combining hypersignal intensity on MR-DWI to the vascular enhancement pattern of cirrhotic liver nodules could improve the efficiency of noninvasive HCC diagnosis [43] (Fig. 4).

Liver lesion characterization: can liver Magnetic Resonance Diffusion weighted imaging (MR-DWI) help in distinguishing benign from malignant liver lesions?

Typical benign liver lesions and Magnetic Resonance Diffusion weighted imaging (MR-DWI)

Signal intensity of benign cystic liver lesions decreases with increasing $b$ values on liver MR-DWI-unrestricted...
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**Figure 7** Apparent Diffusion Coefficient (ADC) overlaps between benign and malignant tumors: typical aspect of liver metastasis on DWI using a diffusion factor of $b = 800 \text{s/mm}^2$ (arrowhead in A) and on ADC mapping (arrowhead in B). The liver metastasis ADC value is $1.5 \times 10^{-3} \text{mm}^2/\text{s}$. Typical aspect of a Focal nodular hyperplasia in a distinct patient on DWI using a diffusion factor of $b = 800 \text{s/mm}^2$ (arrow in C) and on ADC mapping (arrow in D). The liver FNH ADC value is $1.063 \times 10^{-3} \text{mm}^2/\text{s}$, i.e. lower than that of liver metastasis.

diffusion – whereas highly cellular tumors remain hyperintense—restricted diffusion (Fig. 5). However, focal lesions with high signal-intensity on T2 sequences such as hemangiomas may retain their high signal-intensity on high $b$-values images. This phenomenon called "T2-shine-through" effect can be a confounding factor although ADC computation in this setting can demonstrate the absence of restricted diffusion (Fig. 6). On the opposite, ADC values of focal nodular hyperplasia (FNH) and adenoma, although frequently reported to remain below $1.5 \text{mm}^2/\text{s}$, show too much overlapping with malignant lesions to be used as a strong diagnostic tool (Fig. 7).

Distinguishing malignant from benign liver lesions: can apparent diffusion coefficient (ADC) computation be useful?

On the opposite to liver cysts and hemangiomas, malignant liver lesions are known to induce restricted diffusion on liver MR-DWI, leading to reduced ADC values. Authors hence proposed to use an ADC threshold to distinguish benign from malignant liver lesions: ADC threshold values of either $1.5 \times 10^{-3} \text{mm}^2/\text{s}$ [14] or $1.6 \times 10^{-3} \text{mm}^2/\text{s}$ [30] have been reported to reach respective sensitivity, specificity and positive predictive values for malignant lesions characterization as high as 84, 89 and 87% for the first author and 74.2, 77.3 and 85.5% for the second one. However ADC values of both solid benign (adenoma, FNH) and malignant lesions (HCC, metastasis) overlap, limiting the impact of ADC quantitative assessment for focal liver tumor characterization [33,44,45] (Table 1) (Fig. 7). In the absence of standardized acquisition protocols, using absolute ADC values for tumor characterization still appears challenging.

Tumor differentiation and liver Magnetic Resonance Diffusion weighted imaging (MR-DWI)

Reported studies correlating liver MR-DWI to tumor differentiation are scarce: very recent reports have suggested that MR-DWI features could help in differentiating HCC from dysplastic nodules [40]. However, results are preliminary, and some have reported that no correlation could be established between histopathologic grade and ADC values [46].

Functional tumor imaging: can liver Magnetic Resonance Diffusion weighted imaging (MR-DWI) provide adequate tumor response monitoring?

Several studies have demonstrated that early tumor response to chemotherapy is characterized by ADC increase prior to size change. Chemotherapy combined to targeted biotherapy indeed leads to progressive ischemia, necrosis and fibrosis which all impact diffusion measurements [47]. On MR-DWI, tumor response can be documented by an early decrease in perfusion-related diffusion [47], followed
Table 1  Mean Apparent Diffusion Coefficient (ADC) of focal liver lesion.

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patient/lesion</td>
<td>53/211</td>
<td>66/52</td>
<td>102/204</td>
</tr>
<tr>
<td>b values (s/mm²)</td>
<td>0/50/500</td>
<td>0/500</td>
<td>50/300/600</td>
</tr>
<tr>
<td>ADC (× 10⁻³ mm²/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>2.19</td>
<td>2.45</td>
<td>NA</td>
</tr>
<tr>
<td>Cyst</td>
<td>2.54</td>
<td>3.63</td>
<td>3.02</td>
</tr>
<tr>
<td>FNH - adenoma</td>
<td>1.49</td>
<td>NA</td>
<td>1.40</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>2.04</td>
<td>2.95</td>
<td>1.92</td>
</tr>
<tr>
<td>Malignant</td>
<td>1.39</td>
<td>1.08</td>
<td>NA</td>
</tr>
<tr>
<td>HCC</td>
<td>1.31</td>
<td>1.33</td>
<td>1.05</td>
</tr>
<tr>
<td>Metastasis</td>
<td>1.50</td>
<td>0.94</td>
<td>1.22</td>
</tr>
</tbody>
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NA: not applicable.

by an increase in true molecular diffusion accompanying tumor necrosis and ADC increase [48–51] (Fig. 8). Similarly, HCC chemoembolization leads to increased ADC, paralleling tumor necrosis [48,52–54].

In addition, a high pretreatment ADC seems to predict poor response to chemotherapy of liver metastases [51]. Liver MR-DWI could here enable the identification of highly necrotic and poorly vascularized liver tumors, prompt to reduce chemotherapy efficiency.

Figure 8  Liver DWI and treatment response assessment: 61-year-old patient with neuroendocrine liver metastases: liver DWI shows a significant increase in tumor ADC values between pretherapeutic MRI (ADC = 0.51 × 10⁻³ mm²/s) (arrow in A) and after 4 cycles of chemotherapy (ADC = 2.12 × 10⁻³ mm²/s) (arrow in B).

Key-points

- Liver fibrosis leads to reduced ADC-restricted diffusion.
- Both perfusion-related and true-molecular diffusion play a role in reduced ADC observed in fibrotic liver.
- Liver MR-DWI is now systematically included in liver MR protocols, especially to improve liver metastases detection.
- Liver MR-DWI is a helpful tool for lesion characterization but remains limited owing to important ADC overlap between malignant and benign lesions.
- Liver MR-DWI is sensitive to tumor necrosis and could in the future be used as a functional tool for tumor response assessment.

Conclusion

MR-DWI is a promising functional imaging technique. MR instrumental developments have enabled liver applications when adequate modern MR systems are available in terms of field homogeneity, gradient quality, parallel imaging and respiratory triggering; liver fibrosis can be quantified; metastatic liver lesions detection is improved. Research studies linking cell differentiation to MR-DWI parameters are under way. Optimization and standardization of liver MR-DWI protocols must however be pursued in order to provide reproducible parametric quantification.

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