Influence of diffusion and perfusion components of the signal in determining parenchymal apparent diffusion coefficient (ADC) in patients with liver cirrhosis: preliminary results of a study of diffusion-weighted MRI

Poster No.: C-1430
Congress: ECR 2011
Type: Scientific Paper
Authors: R. Girometti, D. Bagatto, G. Esposito, L. Cereser, M. Bazzocchi, C. Zuiani; Udine/IT
Keywords: Abdomen, MR-Diffusion/Perfusion, MR, Diagnostic procedure, Imaging sequences, Cirrhosis, Liver
DOI: 10.1594/ecr2011/C-1430

Any information contained in this pdf file is automatically generated from digital material submitted to EPOS by third parties in the form of scientific presentations. References to any names, marks, products, or services of third parties or hypertext links to third-party sites or information are provided solely as a convenience to you and do not in any way constitute or imply ECR's endorsement, sponsorship or recommendation of the third party, information, product or service. ECR is not responsible for the content of these pages and does not make any representations regarding the content or accuracy of material in this file.

As per copyright regulations, any unauthorised use of the material or parts thereof as well as commercial reproduction or multiple distribution by any traditional or electronically based reproduction/publication method is strictly prohibited.

You agree to defend, indemnify, and hold ECR harmless from and against any and all claims, damages, costs, and expenses, including attorneys' fees, arising from or related to your use of these pages.

Please note: Links to movies, ppt slideshows and any other multimedia files are not available in the pdf version of presentations.

www.myESR.org
Purpose

Background

Over the last years, Diffusion-weighted Imaging (DWI) has been largely investigated as a tool to provide noninvasive detection [1] and quantification of liver fibrosis [2-3]. Fibrosis results from the accumulation of extracellular matrix components, which causes distortion of the parenchymal architecture [4], and theoretical restriction of water diffusion in the affected liver [5]. As expected, hepatic apparent diffusion coefficient (ADC), measured by means of DWI, has been shown to decrease proportionally to the degree of fibrosis and/or inflammation [6-9]. Nonetheless, the mechanism underlying ADC decrease is not completely understood, and probably depends more on alterations in liver perfusion rather than in properly said true diffusion [5, 10-11]. Thus, real radio-pathologic correlation of what DWI measures in liver fibrosis must be further elucidated.

Purpose

On this basis, the purpose of this study was to investigate the impact of perfusion component of the signal in determining liver ADC. Cirrhotic patients were enrolled to form a homogeneous population of patients with end-stage liver fibrosis.
Methods and Materials

Patients

Over the period June-December 2010 we prospectively enrolled twenty-four subjects. Of these, twelve were patients with clinically and histologically proven hepatic cirrhosis (7 male, 5 female; age range 45-71, mean 54.1 y-o), addressed to Magnetic Resonance Imaging (MRI) surveillance of regenerative nodules (n=11) and hepatocellular carcinoma treated with radiofrequency ablation (n=1). All patients showed a Child-Pugh grade A. Median time between hepatic biopsy and MRI examination was of 7.2 months. Remaining twelve subjects (8 male, 4 female; age range 26-53, mean 31.4 years-old) were enrolled to form a control group without history of chronic liver disease. The group included nine healthy volunteers and 3 patients addressed to upper abdomen MRI for the following indications: suspected intrapancreatic accessory spleen, suspected liver haemangiomas, assessment of multiple renal cysts. Excluded were cirrhotic patients with known or suspected newly diagnosed hepatocellular carcinoma, ascitic patients, oncologic patients, and subjects showing history of chronic liver disease without clinical and/or histological confirmation of cirrhosis.

Institutional review board approval was obtained for this study.

DWI protocol

Examinations were performed on a 3.0T magnet (Achieva; Philips Medical Systems, Best, The Netherlands), equipped with a 16-elements phased-array surface coil. All patients underwent a routine upper-abdomen MRI protocol, including dynamic imaging after gadolinium injection in fifteen of them (no post-contrast study was performed in healthy volunteers).

Before contrast administration, DWI was performed by using a respiratory-triggered, single shot spin-echo echoplanar imaging sequence characterized by sequential, independent motion probing gradients that were applied - within the same acquisition - along the frequency-encoding (x), phase-encoding (y), and section-select (z) directions. B-values of 0, 400 and 800 sec/mm² were used. Remaining acquisition parameters are reported in Tab. 1 on page 6. Parallel imaging technique was not used, to avoid any additional signal loss in ADC determination [12]. Spectral fat-saturation with Spectral Presaturation by Inversion Recovery (SPIR) was employed systematically, in order to avoid chemical-shift artefacts.

A preliminary phantom study was performed to validate our system (not shown).

Image analysis and ADC determination
DWI acquisition determined 3 sets of images, corresponding to the x, y and z gradient directions. Each set included images obtained at different b-values (0, 400 and 800 sec/mm\(^2\)). For each set, two abdominal radiologists in consensus (R.G., D.B.) positioned 3 regions of interest (ROI) on a slice obtained with b=0 sec/mm\(^2\), at two different hepatic sites: a) 1 cm above the portal plane (plane 1) (ROIs on the hepatic segments IVa, VII and VIII, respectively); b) 1 cm below the portal plane (ROIs on the hepatic segments IVb, V and VI, respectively) (Fig. 1 on page 6). ROIs measured 2 cm\(^2\) each in diameter. Positioning carefully avoided inclusion of vascular structures, bile ducts or focal liver lesions. No measurements were performed on the left lateral lobe, to avoid artifacts from standing-wave effect [13] or respiratory motion. After this preliminary operation, ROIs were copied and pasted on same slices obtained at b=400 and 800 sec/mm\(^2\). Signal intensity of each slice was calculated as the average of the three measurements. On this basis, liver ADC was calculated according to the following equation [14]:

\[
ADC = \frac{1}{b_i} \times \ln \left( \frac{S_0}{S_i} \right) \quad (1)
\]

where \(S_0\) is the averaged signal sampled without diffusion probing gradients \((b_i = 0 \text{ s/mm}^2)\), and \(S_i\) the averaged signal sampled with \(b_i = 400\) and 800 sec/mm\(^2\), respectively. In summary, in each patient we obtained two sets of liver ADC (0-400 and 0-800 sec/mm\(^2\)), at two different anatomic sites (planes 1 and 2), along x, y and z gradients direction.

To provide additional information regarding the influence of microcirculation changes in our model, we estimated also the perfusion fraction \(f\) [14], corresponding to the fraction of water within the voxel flowing in the capillary system [11,14]. According to the theory of intravoxel incoherent motion (IVIM), b-values greater than 200 sec/mm\(^2\) make the influence of perfusion (D*) negligible in determining the ADC. Thus, liver ADC value becomes approximated to the pure diffusion coefficient (D) [11]. Accordingly, \(f\) was calculated based on the equation [14]:

\[
f = 1 - \exp \left[ -b \left( ADC - D \right) \right] \quad (2)
\]

where ADC corresponds to the ADC calculated at the set of b 0-400 sec/mm\(^2\), D was assumed to correspond to the ADC calculated at the set of b 0-800 sec/mm\(^2\), and b is 400 sec/mm\(^2\). Perfusion fraction \(f\) values were obtained in each patient at both planes 1 and 2, along x, y and z gradients directions.

**Data analysis**

Isotropy (or not) of the liver was assessed by comparing the differences of ADC values obtained along x, y and z gradient directions within controls and cirrhotic patients, at both planes 1 and 2. After checking for data normality with the Levene's test, we achieved this
goal by using the analysis of variance (ANOVA) for repeated measures. Same analysis was performed to compare $f$ values within subjects.

Furthermore, we estimated the significance of the difference in ADC values as follows: a) within controls and cirrhotic, by comparing ADC values between planes 1 and 2; b) between cirrhotic patients and controls; c) within cirrhotic patients and controls between the 0-400 and 0-800 sec/mm$^2$ b-values set. Analysis a) and b) was performed also for the $f$ value. Paired- or unpaired t-test were used accordingly.

Statistical significance was assumed for a $p$ less than 0.01.
**Fig. 0:** Tab. 1 - Acquisition parameters of the single-shot spin-echo echo-planar diffusion-weighted sequence used in the study.

© Institute of Diagnostic Radiology, University of Udine - Udine/IT
**Fig. 0:** In each study subject, liver ADC was calculated at two different anamotic sites, i.e. planes 1 and 2 as illustrated. At each plane, signal was averaged. ADC was finally obtained by proper calculation (see text). Example images in the figure refer to b=400 sec/mm², and were obtained along phase-direction of the diffusion gradient.

© Institute of Diagnostic Radiology, University of Udine - Udine/IT
Results

Consistency of measurements

Despite the presence of outliers, no significant difference was observed by comparing liver ADC (Tab. 2 on page 9) and perfusion fraction \( f \) (Tab. 3 on page 9) of the plane 1 vs. that of the plane 2, both in controls and cirrhotics (\( p > 0.01; \) unpaired t-test). These results were obtained regardless of the motion-probing gradient direction that has been applied. It is arguable that the methodology of ADC measurement and the use of ultra-high field strength provided consistent results throughout the liver in our model.

ADC and within controls and cirrhotic patients

Along each gradient direction, liver ADC significantly decreased by increasing the maximum b-value from 400 to 800 sec/mm\(^2\) (\( p < 0.01; \) paired t-test), both in controls and cirrhotic patients (Tab. 4 on page 10-5 on page 11). (Note that the set with \( b = 800 \) sec/mm\(^2\) was assumed to represent the true Diffusion D.) Exceptions occurred in cirrhotic patients, along the y direction, both at planes 1 and 2, with a nearly statistical significant difference (\( p = 0.0288 \) and 0.0111, respectively). However, ADC decrease was larger in controls than in cirrhotics, showing a mean of 0.57 (at the plane 1) and 0.54 (at the plane 2) \( \times 10^{-3} \) mm\(^2\)/sec vs. 0.17 (at the plane 1) and 0.26 (at the plane 2) \( \times 10^{-3} \) mm\(^2\)/sec (Tab. 4 on page 10-5 on page 11).

Diagnosis of cirrhosis and volume fraction \( f \)

As expected, liver ADC was found lower in cirrhotic patients as compared to controls, regardless of the maximum b-value, gradient direction and plane of measurement (Tab. 6 on page 12). The difference in ADC was significant in all cases (\( p < 0.01; \) unpaired t-test), except along the x (\( p = 0.0139 \)) and y (\( p = 0.0174 \)) directions at the plane 1, by using the maximum \( b = 800 \) sec/mm\(^2\).

Also the perfusion fraction \( f \) was found lower in cirrhotic patients as compared to controls, regardless of the gradient direction and plane of measurement (Tab. 7 on page 13). The difference was statistically significant (\( p < 0.01; \) unpaired t-test), except along the x direction (\( p = 0.0106 \)) at the plane 1 x and z directions at the plane 2 (\( p = 0.0553 \) and 0.0235, respectively).
Fig. 0: Along each gradient direction, reported are p values of the ADC differences within controls and cirrhotics at two different anatomic planes (1 vs. 2). It is arguable that ADC measurements are consistent in our model. ADC values are reported in Tab. 4-5. X=frequency-encoding direction of the diffusion gradient; y=phase-encoding direction; z=select-section direction.

© Institute of Diagnostic Radiology, University of Udine - Udine/IT
Fig. 0: Tab. 3 - Along each gradient direction, reported are p values of differences in the fraction volume f within controls and cirrhotics at two different anatomic planes (1 vs. 2). It is arguable that measurements of f are consistent in our model. Fraction volume f values are reported in Tab. 5. X=frequency-encoding direction of the diffusion gradient; y=phase-encoding direction; z=select-section direction.

© Institute of Diagnostic Radiology, University of Udine - Udine/IT
**Tab. 4** - Liver ADC values in study subjects as measured at the plane 1, along three different directions of the diffusion gradient (x=frequency-encoding direction; y=phase-encoding direction; z=select-section direction). No significant differences between ADCs were found within controls and cirrhotics, regardless of the b-values set employed. Along each gradient direction, liver ADC decreased by increasing the maximum b-value from 400 to 800 sec/mm², both in controls and cirrhotic patients, but at a lesser degree in the latter subgroup. Note that the set with b=800 sec/mm² was assumed to represent the true Diffusion D.

<table>
<thead>
<tr>
<th></th>
<th>Gradient direction</th>
<th>Controls</th>
<th>ADCs are expressed in $\times 10^{-3}$ mm²/sec</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLANE 1</td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td>1.95±0.41</td>
<td>1.96±0.34</td>
</tr>
<tr>
<td>ADC</td>
<td>0-400 sec/mm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC (D)</td>
<td>0-800 sec/mm²</td>
<td>1.42±0.25</td>
<td>1.33±0.24</td>
</tr>
<tr>
<td>p*</td>
<td></td>
<td>0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Cirrhotics</strong></td>
<td></td>
<td>1.35±0.25</td>
<td>1.25±0.24</td>
</tr>
<tr>
<td>ADC</td>
<td>0-400 sec/mm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC (D)</td>
<td>0-800 sec/mm²</td>
<td>1.13±0.28</td>
<td>1.08±0.23</td>
</tr>
<tr>
<td>p*</td>
<td></td>
<td>0.0012</td>
<td>0.0288</td>
</tr>
</tbody>
</table>

*p*paired t-test

© Institute of Diagnostic Radiology, University of Udine - Udine/IT
**Tab. 5 - Liver ADC values in study subjects as measured at the plane 2, along three different directions of the diffusion gradient (x=frequency-encoding direction; y=phase-encoding direction; z=select-section direction). No significant differences between ADCs were found within controls and cirrhotics, regardless of the b-values set employed. Along each gradient direction, liver ADC decreased by increasing the maximum b-value from 400 to 800 sec/mm², both in controls and cirrhotic patients, but at a lesser degree in the latter subgroup. Note that the set with b=800 sec/mm² was assumed to represent the true Diffusion D.**

<table>
<thead>
<tr>
<th>Gradient direction</th>
<th>x (Controls)</th>
<th>y (Controls)</th>
<th>z (Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC 0-400 sec/mm²</td>
<td>2.00±0.40</td>
<td>2.03±0.40</td>
<td>1.94±0.42</td>
</tr>
<tr>
<td>ADC (D) 0-800 sec/mm²</td>
<td>1.48±0.19</td>
<td>1.41±0.17</td>
<td>1.44±0.20</td>
</tr>
<tr>
<td>p*</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>x (Cirrhotics)</th>
<th>y (Cirrhotics)</th>
<th>z (Cirrhotics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC 0-400 sec/mm²</td>
<td>1.49±0.40</td>
<td>1.40±0.38</td>
<td>1.33±0.238</td>
</tr>
<tr>
<td>ADC (D) 0-800 sec/mm²</td>
<td>1.187±0.29</td>
<td>1.17±0.20</td>
<td>1.07±0.17</td>
</tr>
<tr>
<td>p*</td>
<td>0.0058</td>
<td>0.0111</td>
<td>0.0024</td>
</tr>
</tbody>
</table>

*p=paired t-test

© Institute of Diagnostic Radiology, University of Udine - Udine/IT
**Fig. 0:** Tab. 6 - Differences between ADC values of controls and cirrhotics are reported, together with statistical significance.

© Institute of Diagnostic Radiology, University of Udine - Udine/IT
**Fig. 0**: Tab. 7 - Volume fraction $f$ values in study subjects as measured along three different directions of the diffusion gradient (x=frequency-encoding direction; y=phase-encoding direction; z=select-section direction). Differences between $f$ were either significant or not significant, probably reflecting liver inhomogeneity due to cirrhosis.

© Institute of Diagnostic Radiology, University of Udine - Udine/IT
Conclusion

1. Liver ADC at 3.0T

Liver ADC values in healthy subjects have been reported either significantly increased [15] or decreased (but not significantly) [16] at 3.0 T as compared to those obtained at 1.5T. "Noise floor" from lower signal-to-noise ratio (SNR) at 1.5T and decrease in liver T2 relaxation time at 3.0T have been proposed as potential explanations for these opposite findings, respectively. By considering both planes of measurement, the ADCs we showed in controls (Tab. 4-5) are consistent with those reported by Dale et al. (2.26 and 1.56 x 10^-3 mm^2/sec at 0-400 and 0-800 sec/mm^2, respectively) [15] rather than by Rosenkrantz et al. [16] (1.49 ± 0.47 and 1.12 ± 0.36 x 10^-3 mm^2/sec at comparable b-values set). Considering that we used a TE of 66 msec instead of 76 msec [15-16], which partially compensate for decreased T2 at 3.0T, our data may support the hypothesis formulated by the former Authors, suggesting that increasing SNR at higher field strength impacts on the ADC value of the liver. It is questionable whether the use of ultra-high field strength may have affected measurements on cirrhotic patients. Like explained in our EPOS 2011 exhibit #3051, isotropy was shown in cirrhotic patients, regardless of the anatomic plane of measurement and the b-values set. Accordingly, ADC values (Tab. 4 on page -5 on page ), are consistent throughout the liver. However, it remains questionable whether 1.5 or 3.0T provide more precise estimation of liver ADC, considering that many other confounding equipment-related, patients-related and DWI protocol-related factors currently limit its reproducibility [4].

2. Diagnosis of hepatic cirrhosis

The accumulation of extracellular matrix component characterizing fibrosis theoretically reduces water diffusion within the liver, i.e. parenchymal ADC [5]. This assumption has been verified by a number of studies [6-9] and in our series, since ADC in cirrhotic patients was shown lower than in controls (Tab. 6 on page ). Nonetheless, by using higher b value set (b=0-800 sec/mm^2) we showed that DWI is unreliable in differentiating between healthy and cirrhotic livers, because the ADC lowering in cirrhotics resulted not statistically significant at one of two planes of measurements, and along two of three gradient directions (y and z). Note that ADC at this b-value set was assumed to be approximated to the true diffusion coefficient D. Our data match with previous observations on animal model and humans, suggesting that the so called perfusion-related diffusion, or fast component of diffusion (D*) is larger in controls than in patients with liver fibrosis [10-11]. By virtually eliminating the effects of D*, i.e. by calculating the ADC with b-values higher than 400-500 sec/mm^2, the difference between cirrhotic and healthy livers is lost after proper correction for image noise [5]. Thus, perfusion rather than properly said diffusion is advocated to represent the differential factor. Furthermore, ADC
decreased as the maximum b-value increased from 400 to 800 sec/mm$^2$ (in most cases with a p<0.01), but at a lesser degree in cirrhotic patients than in controls (Tab. 4 on page -5 on page ). Although the assessment of D* was not possible in our model, we performed indirect estimation by calculating the volume fraction f (corresponding to the volume of water flowing into capillaries within the voxel) [11]. Differently from Luciani et al. [11], and more coherently with the decrease of D* these Authors showed, we observed that f is reduced in cirrhotic patients as compared to controls, regardless of the gradient direction and site of measurement (Tab. 7 on page ). Inhomogeneity in liver fibrosis distribution may explain why differences were not always statistically significant. Our findings are in accordance with well documented reduction of blood volume in cirrhosis [17].

3. Final consideration

In our opinion, our findings further emphasize the need for a still lacking, reliable radiopathological correlation between fibrotic or cirrhotic changes and parenchymal ADC. Targeted studies are needed to this purpose, possibly by using diffusion tensor imaging (DTI) [18]. At the state-of-the-art situation, DWI is probably technically immature to provide reliable information on liver fibrosis and cirrhosis.

Limitations

First, we estimated liver ADC by using two b-values sets, with two b-values each (0-400 and 0-800 sec/mm$^2$). Acquisition with multiple b-values might have improved the accuracy of ADC measurements [18], especially because - as discussed above - the influence of ultra-high field strength on ADC is still undetermined, and led to perfusion D* estimation [11]. We did not use multiple b-values to avoid: a) excessive increase in acquisition time, that was already longer than usual (nominally about seven minutes) because of the application of sequential gradients along three different directions; b) additional image degradation at longer acquisition time (see discussion above).

Second, similarly to previous Authors [15-16], we used a maximum b of 800 sec/mm$^2$, i.e. lower than feasible at 3.0T. This choice was based on the assumption that, irrespective of the field strength, influence of perfusion D* should be minimal in determining the ADC at the b-value set of 0-800 sec/mm$^2$ [11]. Even if the approximation to the true diffusion coefficient D would have been inaccurate, the general trend of our results is not affected. Besides, we tried to avoid image degradation inherent to larger b-values.
References


15. Dale BD, Braithwaite AC, Boll DT, Merkle EM. Field strength and diffusion encoding technique affect the apparent diffusion coefficient measurements in diffusion-weighted imaging of the abdomen. Invest Radiol 2010;45:104-108


Personal Information

Dr. Rossano Girometti

Istituto di Radiologia Diagnostica

Università di Udine

via Colugna, 50

33100- Udine

Italy

rgirometti@sirm.org

Do not hesitate to contact me for any question or comment.