Diffusion Analysis with Triexponential Function in Liver Cirrhosis

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Purpose: To acquire more detailed information noninvasively through on diffusion and perfusion in normal and cirrhotic livers, we analyzed three diffusion components using triexponential function.

Materials and Methods: Thirty-nine subjects (10 with noncirrhotic liver, 29 with cirrhosis) were assessed using diffusion-weighted magnetic resonance imaging (DWI) with multiple b-values. We derived perfusion-related diffusion, fast free diffusion, and slow restricted diffusion coefficients (Dp, Df, Ds) and fractions (Fp, Ff, Fs) calculated from triexponential function using DWI data. Moreover, the triexponential analysis was compared with biexponential and monoexponential analyses. All derived diffusion coefficients were correlated with relative enhancement ratio (RER) using dynamic contrast-enhanced MRI.

Results: In triexponential analysis, Fp, Dp, and Ds were significantly reduced in cirrhosis, whereas Ff was significantly increased in cirrhosis. There was no correlation between each diffusion coefficient obtained with the triexponential analysis in both groups, i.e., Dp, Df, and Ds did not necessarily provide the same kind of information, but there was a positive correlation between each diffusion coefficient with the biexponential analysis in cirrhosis. A positive correlation was found between Dp and RER in the portal phase.

Conclusion: Triexponential analysis makes it possible to noninvasively obtain more detailed tissue diffusion and perfusion information and to assist in the diagnosis of liver cirrhosis.

Key Words: apparent diffusion coefficient (ADC); diffusion weighted imaging (DWI); intravoxel incoherent motion (IVIM); liver; cirrhosis

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MATERIALS AND METHODS

All MR images were acquired by using the 1.5 Tesla (T) system (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) with a phased array matrix coil (anterior) and a spine matrix coil (posterior) for signal reception.

Subjects

Subjects consisted of the healthy liver volunteer group ($n = 10$; M/F 6/4; mean age, 29.7 years; range, 24–43 years), and the cirrhotic liver group ($n = 29$; M/F 23/6; mean age, 65.7 years; range, 36–87 years), that underwent dynamic contrast enhanced (DCE) liver MRI, because of liver disease. DWI was a part of a routine liver MRI study and was performed in all subjects. The healthy liver group consisted of healthy volunteers without a history of chronic liver disease or significant alcohol intake. Cirrhosis was attributed to chronic hepatitis B ($n = 9$), chronic hepatitis C ($n = 19$), or alcohol intake ($n = 1$). Of the 29 patients with cirrhosis, 22 were graded as Child-Pugh Stage A and seven as Stage B; they underwent MRI between January 2010 and June 2010. The clinical diagnosis of cirrhosis was assigned based on a combination of physical findings, such as jaundice; routine biochemical and hematologic blood tests revealing abnormalities such as a decreased platelet count or an increased ratio of aspartate to alanine aminotransferase (AST/ALT); and MRI or CT imaging revealing an enlarged spleen, small nodular liver, ascites, or the presence of a portosystemic shunt.

The study was approved by the institutional review board of our institution and was performed there between January 2010 and May 2012.

DWI

DWI was acquired from all subjects, using navigator-echo triggered (PACE: prospective acquisition correction, Siemens Healthcare) (15) single shot-echo planar imaging (SS EPI) acquisition, with tri-directional gradients. The scan parameters of SS EPI sequence were set at: field of view (FOV) = 420 × 315 mm, matrix size = 128 × 72, repetition time (TR) = 1 respiratory cycle, echo time (TE) = 77 ms, slice thickness = 7 mm, number of signal averaged (NSA) = 2, bandwidth = 1502 Hz/pixel, b-values = 0, 50, 100, 200, 350, 500, 650, 800, 1000, 1200, and 1500 s/mm$^2$, parallel imaging factor = 2, and Generalized autocalibrating partially parallel acquisitions (GRAPPA) (16) was used as parallel imaging.

DCE-MRI

DCE-MRI was performed in the cirrhotic liver group using gadolinium ethoxybenzyl diethylenetriamine pentaaetic acid (Gd-EOB-DTPA, Primovist, Bayer-Schering, Osaka, Japan). Primovist (dosage 0.1 mL/kg) was injected at 1 mL/s followed by 40 mL of physiological saline. The dynamic study included the arterial phase and portal phase. Arterial phase images were acquired after the visual detection of contrast material at the celiac artery by using a real-time bolus display method (CARE-bolus: Siemens). Portal phase images were acquired with a fixed image delay of 70 s after contrast agent injection. A fat-suppressed three-dimensional volumetric interpolated breathhold examination (3D-VIBE) was performed along with the dynamic study. The 3D-VIBE parameters were as follows: FOV = 350 × 262.5 mm, matrix size = 320 × 144, TR = 3.98 ms, TE = 1.51 ms, slice thickness = 2.5 mm, NSA = 1, bandwidth = 420 Hz/pixel parallel imaging factor = 2, and GRAPPA was used as parallel imaging. The acquisition time was 19 s.

DWI Analysis

Regions of interest (ROIs) were manually positioned on DWIs on a commercial workstation (Syngo, Siemens Healthcare) for all b-values, and signal intensity (SI) was measured referring to the b-value of 0 and 50 s/mm$^2$ images (Fig. 1). Three ROIs of the same size were positioned in the right hepatic lobe away from large vessels. The size of the ROI was unified by 12 pixels, and the averaged SI of three ROIs was used for analysis. The left hepatic lobe was excluded from this study due to cardiac motion artifacts (11).

So as to extract diffusion coefficients and fractions of three diffusion components, the relation between SI and b-value was fitted using the Levenberg Marquardt algorithm (17) by a triexponential function:

$$S_b = S_0 \cdot \left[ F_P \cdot \exp(-bD_P) + F_Y \cdot \exp(-bD_Y) + F_S \cdot \exp(-bD_S) \right] ,$$

where $S_b$ is the signal intensity at b-value $b$, $S_0$ is the signal intensity at $b=0$, $F_P$, $F_Y$, and $F_S$ are the fractions of the three diffusion components, and $D_P$, $D_Y$, and $D_S$ are the diffusion coefficients for water, protein, and lipid diffusion, respectively.

Figure 1. ROIs setting using liver diffusion weighted image with b-value of (a) 0 s/mm$^2$ and (b) 50 s/mm$^2$. 3 ROIs were placed away from large vessels.
where $S_0$ and $S_B$ are the SI at a given b-value and no diffusion weighting, $F_p$ and $D_p$ are the perfusion-related diffusion component (representing incoherent microcirculation within the voxel) fraction and coefficient, $F_f$ and $D_f$ are the fast diffusion component (mainly related free diffusion) fraction and coefficient, and $F_s$ and $D_s$ are the slow diffusion component (mainly related restricted diffusion) fraction and coefficient, respectively.

To avoid the fitting error that would be caused by calculating many unknowns at a time, fitting was carried out in two steps. The perfusion-related diffusion coefficient is significantly greater than the pure molecular diffusion coefficient (6), so that when the b-value is greater than 200 s/mm$^2$, the influence of perfusion to the signal decay is quite small (10,11). Therefore, fitting was performed in b-values higher than 200 s/mm$^2$, and then $D_f$ and $D_s$ were extracted using biexponential function:

$$S_B = S_{int} \cdot [F_f \cdot \exp(-bD_f) + F_s \cdot \exp(-bD_s)],$$

where $S_{int}$ is the b = 0 intercept of the high b-value fit, and $F_f$ and $F_s$ are the temporary fast and slow diffusion component fractions, respectively. Furthermore, the ratio of $F_f$ to $F_s$ (r = $F_f$ / $F_s$) is calculated for the purpose of reducing one unknown in the next procedure. Next, $D_f$ and $D_s$, which were calculated by Eq. [2], were applied to Eq. [1], and $F_f$ was replaced with $r \cdot F_s$. Then, fitting was performed by Eq. [1] using all b-values. Thus, $D_p$, $F_p$, $F_f$, and $F_s$ were calculated.

In addition, we analyzed IVIM with conventional mono and biexponential analyses by Eq. [3], Eq. [4], and Eq. [5]:

$$S_B = S_0 \cdot \exp(-bADC_m),$$

$$S_B = S_{int} \cdot \exp(-bD),$$

$$S_B = S_0 \cdot [F \cdot \exp(-bD^*) + (1 - F) \cdot \exp(-bD)],$$

where $ADC_m$ is an apparent diffusion coefficient with monoexponential analysis, $D$ is a perfusion-free diffusion coefficient, and $D^*$ and $F$ are a perfusion-related diffusion coefficient and a fraction with biexponential analysis, respectively. In a monoexponential analysis, $ADC_m$ was obtained using Eq. [3] with all b-values. In the case of biexponential analysis, segmented fitting was also used. First, monoexponential fitting was performed with high b-values (≥200 s/mm$^2$) by Eq. [4], and $D$ was obtained. Next, $D$ was applied to Eq. [5], and $D^*$ and $F$ were derived from biexponential function by Eq. [5] with all b-values.

### Assessment of Reproducibility of DWI Parameters

DWI was repeated 5 times in one healthy male volunteer (24 years) to assess the reproducibility of obtained parameters with mono, bi, and triexponential analyses.

### Relative Enhancement Ratio of DCE-MRI

ROI was manually positioned at the liver’s right lobe, away from large vessels on 3D-VIBE images. SI was measured on a commercial workstation in plain, arterial, and portal phases. The size of the ROI was unified by 125 pixels. Relative enhancement ratio (RER) in the arterial and the portal phases was calculated by Eq. [6]:

$$RER = 100 \cdot \frac{SI_{post} - SI_{pre}}{SI_{pre}},$$

where $SI_{post}$ is the SI in the arterial or portal phase, and $SI_{pre}$ is the SI in the plain phase.

### Statistical Analysis

All statistical analyses were performed by using software (Excel Tokei, SSRI, Tokyo, Japan). Each parameter derived for the normal liver group and the cirrhotic liver group was compared by the Mann-Whitney U test. The relationship between each diffusion coefficient of tri and biexponential analyses was assessed using the Pearson correlation. Similarly, each diffusion coefficient was correlated with RER. Statistical significance was defined as $P < 0.05$. Reproducibility of derived diffusion parameters from mono-, bi-, and triexponential analyses was evaluated using coefficient of variation (CV = SD / mean of five measures) analysis.

### RESULTS

Each parameter obtained with our analysis is shown in Table 1. In triexponential analysis, perfusion-
related diffusion fraction $F_p$, coefficient $D_p$, and slow diffusion coefficient $D_s$ were significantly reduced in the cirrhotic liver group compared with in the healthy liver group ($P < 0.05$, $P < 0.001$, and $P < 0.01$), whereas the fast diffusion $F_f$ was significantly increased in cirrhosis ($P < 0.05$). There were no significant differences in the fast diffusion coefficient $D_f$ and slow diffusion fraction $F_s$ between both groups. In conventional mono and biexponential analysis, $\text{ADC}_m$, $D^*$, and $D$ were significantly reduced in the cirrhotic liver group compared with the healthy liver group ($P < 0.001$, $P < 0.05$, and $P < 0.001$). On the other hand, there was no significant difference found in perfusion fraction $F$ with biexponential analysis between both groups.

Signal decay curves of the liver in control and cirrhotic groups fitted by triexponential function were shown in Figure 2. The attenuation of signal intensity was more moderate in the cirrhotic group than in the control group, especially in the low b-values.

Table 2 shows the correlation coefficient and $P$-value between each diffusion coefficient in biexponential and triexponential analyses, respectively. No correlation was found between each diffusion coefficient with the triexponential analysis in both groups, but there was a moderately positive correlation between $D^*$ and $D$ with the biexponential analysis in the cirrhotic liver group ($R = 0.450; P < 0.05$).

Table 3 shows the correlation between each diffusion coefficient and RER at arterial and portal phases obtained with DCE MRI in the cirrhotic liver group. A weakly-positive correlation was found between the perfusion-related diffusion component $D_p$ obtained with triexponential analysis and RER at portal phase ($R = 0.372; P < 0.05$). However, there was no significant correlation between the other diffusion coefficients and RER at each phase.

Table 4 shows the CV of each parameter obtained in all exponential analyses. CVs of $F_f$, $F_s$, $D$, $F$, and $\text{ADC}_m$ were less than 10%, and CVs of other parameters were in the range of 10% to 20%.

**DISCUSSION**

ADC obtained with monoexponential analysis contains information from the perfusion and diffusion of water molecules. On the other hand, because the two types of diffusion information can be analyzed separately with biexponential analysis, it is known that the order of diffusion coefficients is $D^* > \text{ADC} > D$. In our research, triexponential analysis techniques revealed the order of diffusion coefficients was $D^* > D$. The attenuation of signal intensity was more moderate in the cirrhotic group than in the control group, especially in the low b-values.

**Table 2**

|                  | Control group |   | Cirrhotic group |   |
|------------------|---------------|---|-----------------|---|
|                  | $D_p$         | $D_f$ | $D_s$         | $D_f$ |
| Triexponential analysis | 0.200 | n.s. | 0.198 | n.s. |
| Biexponential analysis | 0.023 | n.s. | 0.167 | n.s. |
|                  | $D_f$         | $D_s$ | $D_f$         | $D_s$ |
|                  | -0.533 | n.s. | -0.353 | n.s. |

*n.s.: not significant, †: $P < 0.05$.

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**Table 3**

|                  | Arterial phase | Portal phase |   |   |
|------------------|---------------|--------------|---|---|
|                  | $D_p$         | $D_f$        | $D_s$ | $D_f$ |
| Triexponential analysis | 0.310 | n.s. | 0.372 | † |
| Biexponential analysis | 0.069 | n.s. | 0.272 | n.s. |
|                  | $D_p$         | $D_s$ | $D_f$ | $D_s$ |
|                  | < 0.001 | n.s. | 0.173 | n.s. |
|                  | $D^*$         | $D_f$        | $D_s$ | $D_f$ |
|                  | 0.096 | n.s. | 0.233 | n.s. |
|                  | $D^*$         | $D_s$        | $D_f$ | $D_s$ |
|                  | 0.016 | n.s. | 0.013 | n.s. |
|                  | $ADC_m$       | $D_f$        | $D_s$ | $D_f$ |
|                  | 0.185 | n.s. | 0.130 | n.s. |

*n.s.: not significant, †: $P < 0.05$. 

**Table 2**

|                  | Control group |   | Cirrhotic group |   |
|------------------|---------------|---|-----------------|---|
|                  | $D_p$         | $D_f$ | $D_s$         | $D_f$ |
| Triexponential analysis | 0.200 | n.s. | 0.198 | n.s. |
| Biexponential analysis | 0.023 | n.s. | 0.167 | n.s. |
|                  | $D_f$         | $D_s$ | $D_f$         | $D_s$ |
|                  | -0.533 | n.s. | -0.353 | n.s. |

*n.s.: not significant, †: $P < 0.05$.
between parameters, there was a significant correlation. The fact indicated that triexponential parameters, i.e., $D_{p}$, $D$, and $D_{s}$ do not necessarily provide the same kind of information. Therefore, triexponential analysis could well separate diffusion information such as perfusion-related diffusion component, fast diffusion component-related free diffusion, and slow diffusion component-related restricted diffusion more than biexponential analysis.

It is well accepted that the portal flow decreases in the cirrhotic liver by intrahepatic portal hypertension, and the arterial flow increases to compensate for the reduced portal flow. Nevertheless, the increased arterial flow is insufficient to compensate for the reduced portal flow (18). In this study, the reduction of $D_{p}$, $D$, and $F_{p}$ reflected this hepatic flow change. Additionally, in triexponential analysis, it is likely that destruction of the vascular system in liver cirrhosis led to the reduction in the perfusion fraction $F_{p}$ and the relative increase in the fast diffusion fraction $F_{f}$. Furthermore, liver parenchyma is destroyed and the proportion of collagen fibers is increased in the cirrhotic liver. The increased proportion of collagen fibers is believed to impair Brownian water motion. In the present study, it was suggested that this change in cell structure influenced the reduction of $D$ and $D_{s}$. Patel et al (11) reported that $D$ was reduced in the cirrhotic liver group compared with the healthy liver group. In triexponential analysis, although the change of $D_{f}$ was not significant, $D_{s}$ was significantly reduced in the cirrhotic liver group; therefore, reduced $D$ in biexponential analysis strongly reflected a change in the slow diffusion component.

Patel et al (11) reported that there was no significant correlation between $D^{*}$ found with biexponential analysis and DCE MRI parameters (arterial blood flow, portal blood flow, total liver blood flow, etc.). Although we could not obtain these DCE MRI parameters, there was a significant correlation between $D_{p}$ with triexponential analysis and RER in the portal phase. Eighty percent of normal liver parenchyma is supplied by the portal vein, and only 20% by the hepatic artery. In the case of cirrhosis graded as Child-Pugh Stage A and B, portal vein blood flow volume exceeds arterial blood flow (19). Thus, in the liver, $D_{p}$ was mainly reflected portal blood flow, and triexponential analysis could acquire more detailed perfusion information than biexponential analysis.

As a result of the evaluation of reproducibility using CV, it was at the same level as the past report (11). Furthermore, our technique does not need breath hold, and because DWI is obtained in approximately 5 min, the burden of patients is quiet small. In addition, because mono and biexponential analyses are also possible with the same DWI data, and diffusion information clearly increases, triexponential analysis is satisfactory in clinical use.

Our study has several limitations. First, we were unable to use a histological method because of its invasiveness and analysis of each stage of cirrhosis was not performed. In the research on the quantification of liver cirrhosis with ADC, it has been reported that ADC decreases as the cirrhotic liver stage progresses (2,3). Thus, if the stage of the cirrhosis group inclines toward one of the cirrhotic liver stage in biexponential or triexponential analysis, the result of each parameter also may be affected. In this study, because the question of whether liver diffusion could be analyzed by using triexponential analysis was the first focus, analysis of each stage of cirrhosis was not performed. That point needs further consideration and a histological method will be needed for further studies. Second, the average age of the cirrhotic liver group was significantly higher than that of the normal liver group. However, Pasquinelli et al (20) have reported that there are no significant differences in each derived parameter from DWI ($ADC$, $PF$, $D^{*}$, and $D$) between younger and older subjects on healthy parenchyma. Therefore, it is believed that the results derived from our analyses did not depend on age in this research. Third, we could not use higher b-values than 1500 s/mm$^2$. In general, a fast component and a slow component are evaluated at higher b-value. However, in liver, the signal intensities with b-values of more than 1500 s/mm$^2$ reached the noise level under the clinically practicable scan settings. Therefore, we used b-values up to 1500 s/mm$^2$.

In conclusion, triexponential analysis makes it possible to noninvasively obtain more detailed tissue diffusion and perfusion information and to assist in the diagnosis of liver cirrhosis.

**REFERENCES**

1. Koimura M, Ohashi I, Hanafusa K, Shibuya H. Apparent diffusion coefficient measurements with diffusion-weighted magnetic resonance imaging for evaluation of hepatic fibrosis. J Magn Reson Imaging 2005;22:80–85.

2. Taouli B, Tolia AJ, Losada M, et al. Diffusion-weighted MRI for quantification of liver fibrosis: preliminary experience. AJR Am J Roentgenol 2007;189:799–806.
3. Lewin M, Poujol-Robert A, Boelle PY, et al. Diffusion-weighted magnetic resonance imaging for the assessment of fibrosis in chronic hepatitis C. Hepatology 2007;46:658–665.
4. Padhani AR, Liu G, Koh DM, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia 2009;11:102–125.
5. Miller FH, Hammond N, Siddiqi AJ, et al. Utility of diffusion-weighted MRI in distinguishing benign and malignant hepatic lesions. J Magn Reson Imaging 2010;32:138–147.
6. Le Bihan D, Breton E, Lallemant D, Aubin ML, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology 1988;168:497–505.
7. Morvan D. In vivo measurement of diffusion and pseudo-diffusion in skeletal muscle at rest and after exercise. Magn Reson Imaging 1995;13:193–199.
8. Yamada I, Aung W, Himeno Y, et al. Diffusion coefficients in abdominal organs and hepatic lesions: evaluation with intravoxel incoherent motion echo-planar MR imaging. Radiology 1999;210:617–623.
9. Moore RJ, Issa B, Tokarczuk P, et al. In vivo intravoxel incoherent motion measurements in the human placenta using echo-planar imaging at 0.5 T. Magn Reson Med 2000;43:295–302.
10. Luciani A, Vignaud A, Cavet M, et al. Liver cirrhosis: intravoxel incoherent motion MR imaging–pilot study. Radiology 2008;249:891–899.
11. Patel J, Sigmund EE, Rusinek H, Oei M, Babb JS, Taouli B. Diagnosis of cirrhosis with intravoxel incoherent motion diffusion MRI and dynamic contrast-enhanced MRI alone and in combination: preliminary experience. J Magn Reson Imaging 2010;31:589–600.
12. Sigmund EE, Cho GY, Kim S, et al. Intravoxel incoherent motion imaging of tumor microenvironment in locally advanced breast cancer. Magn Reson Med 2011;65:1437–1447.
13. Maier SE, Mulkern RV. Biexponential analysis of diffusion-related signal decay in normal human cortical and deep gray matter. Magn Reson Imaging 2008;26:897–904.
14. Lait J, Nilsson M, Wirestam R, et al. In vivo visualization of displacement-distribution-derived parameters in q-space imaging. Magn Reson Imaging 2008;26:77–87.
15. Taouli B, Sandberg A, Stemmer A, et al. Diffusion-weighted imaging of the liver: comparison of navigator triggered and breathhold acquisitions. J Magn Reson Imaging 2009;30:561–568.
16. Griswold MA, Jakob PM, Heidemann RM, et al. Generalized auto-calibrating partially parallel acquisitions (GRAPPA). Magn Reson Med 2002;47:1202–1210.
17. Marquardt DW. An algorithm for least-squares estimation of nonlinear parameters. J Soc Indust Appl Math 1963;11:431–441.
18. Moreno AH, Burchell AR, Rousselet LM, Panke WF, Slaifsky F, Burke JH. Portal blood flow in cirrhosis of the liver. J Clin Invest 1967;46:436–445.
19. Van Beers BE, Leconte I, Materne R, Smith AM, Jamart J, Horsmans Y. Hepatic perfusion parameters in chronic liver disease: dynamic CT measurements correlated with disease severity. AJR Am J Roentgenol 2001;176:667–673.
20. Pasquinelli F, Belli G, Mazzoni LN, Grazioli L, Colagrande S. Magnetic resonance diffusion-weighted imaging: quantitative evaluation of age-related changes in healthy liver parenchyma. Magn Reson Imaging 2011;29:805–812.