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FULL PAPER

Development of a diffusion-weighted MRI protocol for multicentre abdominal imaging and evaluation of the effects of fasting on measurement of apparent diffusion coefficients (ADCs) in healthy liver

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Objective: To assess the effect of fasting and eating on estimates of apparent diffusion coefficient (ADC) in the livers of healthy volunteers using a diffusion-weighted MRI protocol with b -values of 100, 500 and 900 s mm⁻² in a multicentre study at 1.5 T.

Methods: 20 volunteers were scanned using 4 clinical 1.5-T MR scanners. Volunteers were scanned after fasting for at least 4 h and after eating a meal; the scans were repeated on a subsequent day. Median ADC estimates were calculated from all pixels in three slices near the centre of the liver. Analysis of variance (ANOVA) was used to assess the difference between ADC estimates in fasted and non-fasted states and between ADC estimates on different days.

Results: ANOVA showed no difference between ADC estimates in fasted and non-fasted states ($p = 0.8$) nor

between ADC estimates on different days ($p = 0.8$). The repeatability of the measurements was good, with coefficients of variation of 5.1% and 4.6% in fasted and non-fasted states, respectively.

Conclusion: There was no significant difference in ADC estimates between fasted and non-fasted measurements, indicating that the perfusion sensitivity of ADC estimates obtained from b -values of 100, 500 and 900 s mm⁻² is sufficiently low that changes in blood flow in the liver after eating are undetectable beyond the variability in the measurements.

Advances in knowledge: Assessment of the effect of prandial state on ADC estimates is critical, in order to determine the appropriate patient preparation for biological validation in clinical trials.

Diffusion-weighted MRI (DW-MRI) has wide application in oncology with several studies indicating its utility for characterizing liver lesions.^{1–6} DW-MRI is a relatively

simple technique, which does not require administration of exogenous contrast agents, and provides qualitative and quantitative information. It measures the thermal mobility

of water molecules in biological tissues, which is affected by their interactions with cell membranes and by the presence of macromolecules. The biexponential behaviour of the DW-MRI signal, which is characterized by a steep attenuation at low b -values ($0\text{--}100\text{ s mm}^{-2}$) and a slower attenuation at higher b -values ($>100\text{ s mm}^{-2}$), is believed to represent the perfusion of the blood in the microcirculatory vessels (so-called pseudo-diffusion), and the diffusion of the extracellular water molecules, respectively.⁷ Until recently, most clinical studies have used a monoexponential curve fitted to b -values, $0\text{--}1000\text{ s mm}^{-2}$ to estimate the apparent diffusion coefficient (ADC), where the reliability of this ADC estimation is affected by the lower b -values, thus including the influence from the pseudodiffusion component of the signal.^{1,3,5} However, there is increasing recognition of the need to exclude the lower b -values in order to eliminate the effects of perfusion, particularly in tissues such as the liver where blood flow is high.^{8–10}

Over the past decade, several investigators have proposed and documented the importance of the addition of DW-MRI sequences to the standard MR sequences for the identification of liver lesions as well as for assessing treatment response.^{1,4,5} However, in clinical trials, variability of the measurement owing to technical (multivendor platforms) and biological (physiological variations) factors remains a challenge.¹¹ It is crucial, therefore, to standardize imaging protocols for data acquisition to minimize variability and achieve as reproducible a measurement as possible. To implement diffusion-weighted (DW) imaging in a clinical trial, standardized acquisition parameters within the capability of a range of scanner types should be addressed. Furthermore, in order to ensure reduction of physiological variation, the effects of patient preparation and biological status on the measurement need to be understood. Several individual studies in the literature have attempted to investigate the effect of calorie intake on the ADC estimates of the liver.^{12–14} However, no study addresses the effect of fasting or feeding on the ADC measurement in the context of a standardized multivendor acquisition protocol in a multicentre study.

We therefore designed a protocol with acquisition parameters that were implemented across 1.5-T scanners from a variety of manufacturers and prospectively studied the effects of fasting on the ADC estimates in healthy livers, recording the variability in the measurement at two time points. A minimum b -value of 100 s mm^{-2} was employed in estimation of ADCs in order to minimize the influence of perfusion on our measurements.

METHODS AND MATERIALS

Patients and schedule

Over a period of 14 months (May 2012 to June 2013), 20 healthy volunteers aged 30–66 years (mean, 46.7 years; standard deviation, 15.0 years) were scanned, with their informed consent, using 4 clinical 1.5-T MR scanners [Signa® HDxt (GE Healthcare, Waukesha, WI); Achieva® (Philips Healthcare, Best, Netherlands); 2 MAGNETOM® Avanto (Siemens AG, Erlangen, Germany)] at 4 tertiary referral sites (5 volunteers per scanner). The volunteers were recruited through advertising within the respective institutions after local ethical committee approval. The study was not formally registered as a clinical trial owing to

its exploratory nature. Each volunteer was scanned four times according to the following schedule: Scan 1, after fasting for at least 4 h; Scan 2, 30–60 min after having a meal, on the same day as Scan 1; Scan 3, after fasting for at least 4 h, between 1 and 7 days after Scans 1 and 2; Scan 4, 30–60 min after having a meal, on the same day as Scan 3. The volunteers were asked to eat a sandwich and drink a glass of juice or have a larger meal. The interval between fasted and non-fasted scans was 1–9 h. Data were transferred to one site for analysis.

Imaging methods

A common protocol was used for the DW-MRI sequences on the four scanners (Table 1). DW-MR images were acquired covering the liver.

Quality assurance

An ice-water phantom was scanned on the four scanners in order to assess accuracy and repeatability of ADC estimates.¹⁵

Data analysis

Volumes of interest (VOIs) were constructed by a single observer on high b -value-computed DW images using in-house software (Adept; Institute of Cancer Research, London, UK).¹⁶ Regions of interest (ROIs) were drawn around the whole area of the liver on three contiguous slices and were combined to give a VOI per examination that included a large number of pixels (8440–15,718 pixels per examination). Large VOIs were used as fasting or eating was expected to have a global effect on the liver. Furthermore, the use of large ROIs reduces variability owing to positioning of ROIs, thus improving the repeatability of the ADC estimates and hence the ability of the measurement to detect an effect. Monoexponential curves were fitted to all pixels in the VOIs using a least-squares fit of all b -values (trust-region-reflective algorithm, MATLAB® 2014; MathWorks® Inc., Natick, MA).

Statistical analysis

The median ADC estimate from all pixels in the VOIs was determined for each volunteer for each examination. The repeatability of the ADC estimates was assessed using the coefficients of variation (CV) of the fasted (Scans 1 and 3) and non-fasted (Scans 2 and 4) measurements.

The difference between ADC estimates in fasted and non-fasted states was investigated using two-way analysis of variance (ANOVA) with factors representing prandial status (fasted and non-fasted) and measurement (Days 1 and 2) (MATLAB 2014).

Bland–Altman plots were used for a visual assessment of the repeatability of the ADC estimates, as well as the differences between the ADC estimates in fasted and non-fasted states on the first (Scans 1 and 2) and the second days (Scans 3 and 4).¹⁷

RESULTS

17 volunteers were included in the analysis (1 was excluded owing to very low signal in the liver, resulting from iron overload; 1 owing to very low signal in the images overall, owing to an unexplained problem with the acquisition; and 1 owing to gallstones, which had unknown implications for the measurements

Table 1. Protocol for diffusion-weighted MRI sequences

Parameter	Value
Receive coil	Body matrix/torso coil
Breathing	Free breathing
Sequence	Single-shot echoplanar imaging
Slice orientation	Axial
Phase-encode direction	Anteroposterior
Field of view [mm (read) $\times$ mm (phase)]	380 $\times$ 332
Acquired matrix (read)	128
Reconstructed matrix (read)	256
Acquired pixel resolution [mm (read) $\times$ mm (phase)]	3 $\times$ 3
NSA	4
Slice thickness (mm)	5
Number of slices	40
Parallel imaging reduction factor	2
TE (ms)	75–88 (minimum TE on each scanner)
Repetition time (ms)	8000–8500
Fat suppression	Spectral fat suppression (3) Water excitation (1)
Diffusion gradient scheme	Double spin echo (2) or single spin echo (2)
Diffusion-encoding scheme	Three-scan trace (2) or equivalent (2)
Diffusion weightings (s mm^{-2})	100, 500, 900

NSA, number of signal averages; TE, echo time.

Numbers in parenthesis indicate number of sites using method.

and impeded drawing ROIs of similar sizes and locations to the other volunteers). Figure 1 shows example images from one volunteer. The full stomach was visible in the volunteers scanned after eating. The CV was 5.1% for the fasted measurements and 4.6% for the non-fasted measurements. ADC estimates using an ice-water phantom showed a between-site CV of 3%.

ANOVA showed no difference between ADC estimates in fasted and non-fasted states ($p = 0.8$) and no difference between measurements on different days ($p = 0.8$).

The Bland–Altman plots illustrate the good repeatability of the ADC estimates, which is comparable in fasted (Scans 1 and 3, Figure 2a) and non-fasted measurements (Scans 2 and 4, Figure 2b). The Bland–Altman plots also illustrate that there was no significant difference between the ADC estimates in fasted and non-fasted states on the first day (Scans 1 and 2, Figure 2c) nor on the second day (Scans 3 and 4, Figure 2d). Figure 2 also demonstrates that the differences between the ADC estimates in fasted and non-fasted states were similar in size to the variation between the repeated measurements in the same prandial state.

DISCUSSION

The good repeatability of the ADC estimates ($\text{CV}_{\text{fasted}} = 5.1\%$ and $\text{CV}_{\text{non-fasted}} = 4.6\%$) in a multicentre setting confirmed the robustness of the proposed protocol across the different imaging centres. In this context, we have shown that there was no significant difference in the median ADC estimates between pre- and post-prandial states (Figure 2c,d). ADC estimates using an ice-water phantom also showed good agreement between sites (between-site $\text{CV} = 3\%$), as reported in previous studies.¹⁵ Assessment of differences between scanners did not form part of this study owing to small numbers of volunteers from each site. No clear differences, however, were observed in ADC estimates from the four scanners, in concordance with previous studies that reported small intervendor differences between ADC estimates in abdominal organs at 1.5 T.¹⁸ Additionally, we note that taking the difference between ADC estimates in fasted and non-fasted states reduces the effects of intervendor variability by scanning the same patient on the same platform.

Similar findings have been reported by Jajamovich et al.¹³ and Pazahr et al.,¹⁴ who both demonstrated that the ADC, obtained at high b -values, did not change significantly with a calorie intake. In the study by Pazahr et al.,¹⁴ a tri-exponential analysis was used for the ADC estimation and resulted in three ADC estimates, each one corresponding to the three different ranges of the b -values. In an anatomical sectional analysis, Hollingsworth and Lomas¹² showed that there was no significant difference between pre- and post-prandial ADC estimates derived from the posterior right lobe of the liver using b -values of 0 and 500 s mm^{-2} or 0 and 750 s mm^{-2} , whereas the anterior right lobe showed a significant increase in ADC estimates post-prandially. Their

Figure 1. (a–c) Diffusion-weighted images ($b = 100, 500, 900 \text{ s mm}^{-2}$) from one volunteer scanned after eating.

Figure 2. Bland-Altman plots showing apparent diffusion coefficient (ADC) estimates for 17 volunteers. Solid lines show mean differences between two measurements. Dashed lines show 95% limits of agreement. (a) Repeatability of ADC estimates in fasted state (Scans 1–3); (b) repeatability of non-fasted measurements (Scans 2–4); (c) differences between ADC estimates in fasted and non-fasted states on the first day (Scans 1 and 2); (d) differences between ADC estimates in fasted and non-fasted states on the second day (Scans 3 and 4). The same scales have been used on the axes to aid comparison.

data also demonstrated a significant increase in ADC estimates in both posterior and anterior right lobes in ADCs derived from low b -values (0 and 200 s mm^{-2}), but they were unable to correlate these ADC changes with portal flow.

It is well known that the calculated ADC is not a pure measure of diffusion of tissue water, but also is affected by the contribution of blood perfusion, which is in turn determined by the choice of b -values.^{6–10,19,20} Therefore, it has been recommended that the perfusion component of the ADC estimate can be eliminated by only including b -values $>100 \text{ s mm}^{-2}$. The increase in portal blood flow in response to the consumption of calories, and consequent increase in hepatic perfusion, has been demonstrated.^{12,14} Our multicentre study, however, did not show an effect of prandial status using a low b -value of 100 s mm^{-2} .

Portal flow can be measured directly in pre-clinical models using invasive electromagnetic flowmeters and was shown to be $1.5 \text{ ml min}^{-1} \text{ g}^{-1}$ in healthy livers of anaesthetized rats.²¹ Subsequently, the use of non-invasive techniques such as Doppler ultrasound to measure velocity in the early 1990s indicated portal flow velocities to be of the order of 15 cm s^{-1} .²² As it is likely that the steep attenuation at low b -values ($b < 100\text{--}150 \text{ mm}^{-2}$) corresponds to tissue perfusion (or pseudodiffusion), which after feeding is largely owing to an increase in portal flow, we excluded low b -values in our assessment of ADC.

The major limitation of this study was the uncontrolled calorie context of each volunteer meal. This control was deemed

unnecessary, as we merely wished to establish whether or not fasting was a requirement for patient preparation in ADC measurements in multicentre clinical trials. Also, differences in scan schedules across centres and eating habits in different countries would have made this control difficult; volunteers therefore were allowed to choose their meals according to their requirements and tastes. Secondly, there was no strict control of the interval between the meal and the subsequent scans, except for being carried out between 30 min and 1 h after eating. This was deliberately flexible to facilitate scheduling of these volunteers' scans in busy radiology departments with an excess of patient pressures. Furthermore, no restrictions were placed on consumption of other food prior to the "study meal" before the non-fasted scans. Another limitation was the absence of an independent measurement of portal vein flow to confirm the expected increase in perfusion. However, our objective was only to demonstrate the lack of effect of feeding on the ADC estimate using b -values $\geq 100 \text{ s mm}^{-2}$. Additionally, we note that the timing of the non-fasted scans was chosen to correspond to the maximum changes in portal flow after eating, as described in previous studies.¹² Finally, we did not do a formal assessment of artefacts; however, with the exception of two cases with very low signal, no gross artefacts were visualized on either the T_2 weighted or on the DW images of all four scanners, which emphasizes the robustness of the proposed protocol.

CONCLUSION

The DW-MRI protocol described in this study can be used on clinical 1.5-T MR scanners from three manufacturers. The ADC estimates showed good repeatability ($\text{CV}_{\text{fasted}} = 5.1\%$ and $\text{CV}_{\text{non-fasted}} = 4.6\%$), in agreement with results from body DW-MRI measurements in other studies. There was no significant difference in ADC estimates between fasted and non-fasted measurements, indicating that the perfusion sensitivity of ADC estimates obtained from b -values of 100, 500 and 900 s mm^{-2} is sufficiently low that changes in blood flow in the liver after eating are undetectable beyond the variability in the measurements.

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