Optimization and Clinical Feasibility of Free-breathing Diffusion-weighted Imaging of the Liver: Comparison with Respiratory-Triggered Diffusion-weighted Imaging

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(Received March 10, 2014; Accepted September 19, 2014; published online February 12, 2015)

Purpose: We compared the image quality of free-breathing diffusion-weighted imaging (FB-DWI) to that of respiratory-triggered DWI (RT-DWI) after proper optimization.

Materials and Methods: Three healthy subjects were scanned to optimize magnetic resonance (MR) parameters of FB-DWI to improve image quality, including spatial resolution, image noise, and chemical shift artifacts. After this optimization, we scanned 32 patients with liver disease to assess the clinical feasibility of the optimized FB-DWI. Of the 32 patients, 14 had a total of 28 hepatocellular carcinomas (HCCs), four had a total of 15 metastatic liver tumors, and the other 14 had no tumor. Qualitatively, we compared the image quality scores of FB-DWI with those of RT-DWI with the Wilcoxon signed-rank test. Quantitatively, we compared the signal-to-noise ratios (SNRs) of the liver parenchyma, lesion-to-nonlesion contrast-to-noise ratios (CNRs) and apparent diffusion coefficient (ADC) values of the liver parenchyma and liver tumor by the paired t-test.

Results: The average scores of image quality for sharpness of liver contour, image noise, and chemical shift artifacts were significantly higher for FB-DWI than RT-DWI (P < 0.05). SNRs, CNRs, and ADC values of the liver parenchyma and tumors did not differ significantly between the 2 DWI methods.

Conclusion: Compared with RT-DWI, the optimized FB-DWI provided better spatial resolution, fewer artifacts, and comparable SNRs, lesion-to-nonlesion CNRs, and ADC values.

Keywords: diffusion-weighted imaging, free-breathing, liver, magnetic resonance imaging, respiratory-triggered

Introduction

Diffusion-weighted imaging (DWI) has been widely adopted as a magnetic resonance (MR) imaging technique in clinical practice. DWI provides functional information, such as that of the motion or diffusion of water molecules, and can be used to detect and characterize malignant and nonmalignant lesions.1–7 However, DWI suffers from low spatial resolution because it must maintain a usable signal-to-noise ratio (SNR) compared to conventional T2-weighted imaging.8 In addition, DWI is generally scanned using an echo planar imaging (EPI) technique, which occasionally yields artifacts, such as ghosting, distortion, and chemical shift artifacts.7,9 Overcoming these limitations would benefit clinical practice.
Takahara and associates developed the concept of diffusion-weighted whole-body imaging with background body signal suppression (DWIBS).\(^5\) DWIBS is a powerful adjunct to anatomical whole-body MR imaging in that it detects subtle lesions and pathologic changes in structures and reduces image interpretation times without requiring administration of a contrast agent.\(^1,9\) The free-breathing technique is used for DWIBS because it can increase the SNR and contrast-to-noise ratio (CNR) without hampering the detection or characterization of focal liver lesions.\(^10\) Free-breathing DWI (FB-DWI) is not generally used for liver MR imaging because of the risk of image blurring and misregistration caused by motion artifacts, so its image quality can improve.\(^1,9,11\)

We aimed to maximize the image quality of FB-DWI for the liver, focusing on improving spatial resolution and reducing artifacts by optimizing MR parameters, and to elucidate the clinical feasibility of FB-DWI for the liver compared with respiratory-triggered DWI (RT-DWI).

### Materials and Methods

Our institutional review board approved this study, and written informed consent was obtained from each subject before MR examination. All examinations were performed on a clinical 3.0-tesla MR system (Achieva 3.0T TX; Philips Healthcare, Best, The Netherlands) using a 32-channel torso-cardiac phased-array coil and dual-source parallel radiofrequency excitation and transmission technology.

#### Optimization of MR parameter settings

Three healthy male subjects aged 37 to 38 years underwent scanning of the liver by FB-DWI using the single-shot spin-echo EPI technique. MR parameters were optimized to improve spatial resolution and reduce chemical shift artifacts. To improve spatial resolution, we tested the following parameters: parallel imaging factor (sensitivity encoding [SENSE] factor), one to 5; frequency-encoding steps (readout matrix), 96 to 128; phrase-encoding steps (scan%), 50 to 200; and number of excitations (NEX), one to 3. When an MR parameter was changed to optimize FB-DWI, other MR parameters settings were fixed to those of RT-DWI: SENSE factor of 2, readout matrix (frequency-encoding step) of 112, scan% of 68 (phase-encoding step of 112), and NEX of 2.

*TR was changed from 4,750 ms to 7,750 ms when SPAIR TR was changed, otherwise TR of 6,250 ms and TE of 56 ms were fixed during the optimization.

SENSE: sensitivity encoding, Scan%: the proportion of the number of phase-encoding steps to the number of frequency-encoding steps, TR: repetition time, TE: echo time, SPAIR: spectral selection attenuated inversion recovery, SPAIR delay: inversion time from exposure of SPAIR pulse, SPAIR TR: TR between SPAIR pulses during the scan, Frequency offset: bandwidth from the frequency of fat tissue.

| For the optimization of spatial resolution | | |
|-------------------------------------------|-------------------|
| SENSE factor (phase reduction factor)     | 1, 2, 3, 4, 5     |
| Readout matrix (frequency-encoding step)  | 96, 112, 128      |
| Scan% (phase-encoding step)               | 50, 100, 150, 200 |
| Number of excitations (number of acquisition) | 1, 2, 3 |

| For the reduction of chemical shift artifacts | | |
|----------------------------------------------|-----------------|
| SPAIR delay                                  | [ms] 20, 40, 60, 80, 100, 120 |
| SPAIR TR*                                    | [ms] 190, 210, 230, 250, 270, 290, 310 |
| Frequency offset                             | [Hz] 100, 150, 200, 250, 300 |

Note- When one MR parameter for the optimization of FB-DWI was changed, other MR parameters settings were fixed to those of RT-DWI: SENSE factor of 2, readout matrix (frequency-encoding step) of 112, scan% of 68 (phase-encoding step of 112), and NEX of 2.

*TR was changed from 4,750 ms to 7,750 ms when SPAIR TR was changed, otherwise TR of 6,250 ms and TE of 56 ms were fixed during the optimization.

SENSE: sensitivity encoding, Scan%: the proportion of the number of phase-encoding steps to the number of frequency-encoding steps, TR: repetition time, TE: echo time, SPAIR: spectral selection attenuated inversion recovery, SPAIR delay: inversion time from exposure of SPAIR pulse, SPAIR TR: TR between SPAIR pulses during the scan, Frequency offset: bandwidth from the frequency of fat tissue.
parameter settings. FOV, flip angle, slice thickness, slice gap, and b-value were fixed to the MR parameter settings of RT-DWI.

Optimization of spatial resolution
To optimize spatial resolution, 3 radiologists blinded to imaging information individually evaluated sharpness of the liver contour and image noise (i.e., visual assessment of the roughness on DWI) of each DWI with b-values of 1,000 s/mm² using a 4-point scoring system: one point, liver contour unclear or severe noise; 2 points, liver contour partially unclear or moderate noise; 3 points, liver contour mostly clear or mild noise; and 4 points, entire liver contour clear or no noise. The most appropriate MR parameter settings were selected for FB-DWI with reference to the scores of image quality.

Reduction of chemical shift artifacts
The same 3 radiologists independently evaluated chemical shift artifacts of each DWI with b-values of 1,000 s/mm² using 4-point scoring: one point, severe artifacts; 2 points, moderate artifacts; 3 points, mild artifacts; and 4 points, no artifacts. The most appropriate MR parameter settings were selected for FB-DWI with reference to the image quality scores.

Clinical study
Patients
From November 2010 to January 2011, 32 consecutive patients (23 men, 9 women; aged 36 to 83 years; mean age, 64.2 years) underwent MR imaging of the liver for chronic liver disease and/or suspicion of malignant liver tumor, such as hepatocellular carcinoma (HCC) and metastatic liver tumor. Two types of DWI were scanned for each patient for comparison. SPAIR was adopted as the fat suppression technique to optimize FB-DWI. SPAIR is minimally affected by B1 inhomogeneity for acquisition of homogeneous fat suppression without degradation of image quality and, so, is effective for liver MR imaging at 3.0T.12–14 However, preliminary data suggested that SPAIR was better for FB-DWI, but spectral presaturation with inversion recovery (SPIR) was better than SPAIR for RT-DWI. Therefore, we adopted 2 different fat suppression techniques for FB-DWI and RT-DWI. Twenty-two patients had chronic liver disease, including chronic hepatitis and cirrhosis, related to chronic viral hepatitis B or C, 14 of whom had a total of 28 HCCs. The other 10 patients had normal background liver, but four of the 10 patients had a total of 15 metastatic liver tumors originating from a gastrointestinal stromal tumor (n = 9), rectal cancer (n = 5), or renal cell carcinoma (n = one). The HCCs and metastatic liver tumors were diagnosed using validated imaging criteria.14,15–18 Elevated tumor markers (e.g., α-fetoprotein and des-γ-carboxy prothrombin for HCC, carcinoembryonic antigen, or carbohydrate antigen 19–9 for metastatic liver tumor) and follow-up imaging studies performed at least 6 months after the DWI, which showed tumor shrinkage with treatment or tumor progression without treatment.

Image assessment
For qualitative assessment, 3 radiologists blinded to imaging information and clinical data independently evaluated sharpness of the liver contour, image noise, and chemical shift artifacts on FB-DWI and RT-DWI with b-values of 1,000 s/mm² using the aforementioned 4-point scoring system. Quantitatively, a single radiologist calculated SNRs of the liver parenchyma, lesion-to-nonlesion CNRs, and apparent diffusion coefficient (ADC) values of the liver parenchyma and tumor after drawing polygonal regions of interest (ROIs) on each DWI with a b-factor of 1,000 s/mm². The SNRs and CNRs were calculated using the following equations, as described elsewhere.19,20

SNR of the liver parenchyma = \( \frac{S_I_{\text{liver}}}{S_D_{\text{liver}}} \), and

lesion to nonlesion CNR = \( \frac{|S_I_{\text{liver}} - S_I_{\text{tumor}}|}{S_D_{\text{liver}}} \),

in which \( S_I_{\text{liver}} \) is the signal intensity of the liver parenchyma and \( S_I_{\text{tumor}} \) that of the tumor, and \( S_D_{\text{liver}} \) is the standard deviation of the SI of the liver parenchyma. The SD of the liver parenchyma was used as an estimation of local noise for the calculation. In parallel imaging, noise is not distributed homogeneously throughout the image, so it is good to estimate noise in close proximity to the site of SI measurement.20 SNR cannot be calculated as a characteristic of the entire image but rather is calculated as a local property that characterizes the signal quality with respect to local noise levels.20

The averaged areas (range) of ROIs of the liver parenchyma were 400.9 (146.3 to 678.6) mm² and of tumors, 237.3 (83.73 to 475.93) mm². To calculate the SI and SD of the liver parenchyma, 3 ROIs were made as large as possible on the right and left lobes of the liver parenchyma to avoid major vessels, lesions, and artifacts. ROIs placed on one DWI were duplicated and placed at the same area on another DWI.
Statistical analysis
In optimizing MR parameter setting, 3 radiologists separately recorded their scores of image quality among imaging techniques, but their scores were aggregated for analysis to minimize reader bias. We performed 2-way analysis of variance and Tukey’s honestly significant difference post-hoc test in each MR parameter setting group. The setting with the highest image quality score was selected as an appropriate parameter in each group.

In clinical study, we used Wilcoxon signed-rank test to compare image quality scores of sharpness of liver contour, image noise, and chemical shift artifacts between FB-DWI and RT-DWI. We used weighted kappa statistic to analyze inter-reader agreement. Kappa values were interpreted as: 0.00 to 0.20, slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; and 0.81 to 1.00, almost perfect agreement.
We also compared the SNRs of liver parenchyma, lesion to nonlesion CNRs, and ADC values of liver parenchyma and tumor between FB-DWI and RT-DWI by the paired t-test. The intraclass correlation coefficient (ICC) is also used to describe the correlations of the SNRs of liver parenchyma, lesion to nonlesion CNRs, and ADC values of liver parenchyma and tumor between the 2 types of DWI. 

P < 0.05 was considered to indicate significant difference. Statistical analyses were performed using IBM SPSS statistics 18.0 (IBM Japan, Tokyo, Japan).

Results

Optimization of MR parameter settings of FB-DWI

Figures 1 and 3 show the image quality scores of each subject and example images of each MR parameter setting with regard to sharpness of the liver contour. The SENSE factor, readout matrix, and NEX were not related to the sharpness of the liver contour because the scores of each comparison did not differ significantly. On the other hand, images were significantly sharper with scan% of 150 (average score of 3 readers, 4.00) and 200 (average score, 4.00) than 50 (average score, 1.00) and 100 (average score, 2.67) (P < 0.05).

Figures 2 and 3 show the image quality scores of each subject and example images of each MR parameter setting with regard to image noise. Image noise increased significantly with SENSE factors of 4 (average score, 1.56) and 5 (average score, 1.00) compared with SENSE factors of one (average score, 4.00), 2 (average score, 3.89), and 3 (average score, 3.56) (P < 0.05). Image noise increased slightly with a SENSE factor of 3 compared with SENSE factors of one and 2, but the level was not significant. Image noise increased slightly with a readout matrix of 128 (average score, 2.56) compared with 96 (average score, 3.11) and 112 (average score, 3.00), but the level was not significant. Image noise was significantly reduced with NEX settings of 2 (average score, 2.89) and 3 (average score, 2.89) compared with one (average score; 1.33) (P < 0.05). Image noise was not related to scan%. Eventually, we selected a SENSE factor of 2, readout matrix of 112, and scan% of 200 for the optimization of FB-DWI.
Figures 4 and 5 show image quality scores and example images of each MR parameter setting with regard to chemical shift artifacts. Moreover, SPAIR delay of 100 ms (average score; 1.89) and SPAIR TRs of 230 ms (average score, 3.67), 250 ms (average score, 3.67), and 270 ms (average score, 3.67) showed significantly fewer chemical shift artifacts compared with other values in each MR parameter setting. Chemical shift artifacts were lowest with the frequency offset of 250 Hz (average score, 4.00), but scores did not differ significantly between 200 Hz (average score, 3.67) and 250 Hz and between 250 Hz and 300 Hz (average score, 3.67). Eventually, we selected SPAIR delay of 100 ms, SPAIR TR of 250 ms, and frequency offset of 250 Hz for the optimization of FB-DWI.

We referred to the results to decide the appropriate MR parameter settings of FB-DWI; Table 2 shows the details of the MR parameters.

Clinical study

Table 3 shows the results of the qualitative assessments by the 3 readers. The average image quality scores of sharpness of liver contour, image noise, and chemical shift artifacts were significantly higher for FB-DWI than RT-DWI \( (P < 0.05) \), with the exception of the grade of image noise of Reader 2. Agreements among the 3 readers were fair to substantial. Table 3 shows the kappa values. There were no significant differences between FB-DWI and RT-DWI in SNRs of liver parenchyma, lesion to nonlesion CNRs, or ADC values of liver paren-
Discussion

The breath-holding technique or respiratory-triggering technique is generally preferred for liver DWI.\(^1\)\(^,\)\(^9\) However, our results indicated no deterioration of the image quality using FB-DWI. We have several speculations regarding this result. First, the EPI technique is relatively insensitive to the effects of macroscopic patient motion, including respiration, because of the very fast readout of the complete image data.\(^1\)\(^,\)\(^2\)\(^1\) The large number of EPI factors, of k-space profiles collected per excitation, may deteriorate image quality relating to T\(_2^*\) decay. However, a large bandwidth expedites image acquisition and minimizes the influence of T\(_2^*\) decay. In addition to use of a large bandwidth, advances in MR systems may minimize the susceptibility and chemical shift artifacts of the EPI technique and blurring from T\(_2^*\) signal intensity decay during the gradient-echo train to improve the quality of images acquired with FB-DWI regardless of the many EPI factors.\(^1\)\(^,\)\(^2\)\(^1\)\(^,\)\(^2\)\(^2\) Although enlarging the bandwidth decreases the SNR, a combination of high magnetic fields of the MR system, a 32-channel receiver coil, and the free-breathing technique can compensate for this shortcoming because these devices and technique can increase the SNR. Therefore, FB-DWI can produce good SNRs and CNRs, which is consistent with the previous result.\(^1\)\(^0\)

We found that improved sharpness of the liver contour (i.e., spatial resolution) was related to a large number of phase-encoding steps rather than the SENSE factor or number of frequency-encoding steps, a finding consistent with the previous result.\(^1\)\(^3\)\(^2\)\(^3\) A large SENSE factor can reduce acquisition time but increases image noise. The large number of frequency-encoding steps increased the image noise, perhaps related to the elongation of the acquisition of k-space in the frequency direction. In

| Imaging technique | FB-DWI | RT-DWI |
|-------------------|--------|--------|
| SENSE factor      | 2      | 2      |
| TR/TE [ms]        | 6250/56| 1877/55|
| Flip angle [degree]| 90°    | 90°    |
| Field of view [mm\(^2\)]| 380 × 299 | 380 × 299 |
| Matrix (frequency × phase) | 112 × 176* | 112 × 68 |
| Slice thickness [mm] | 7      | 7      |
| Slice gap [mm]    | 1      | 1      |
| Number of slice   | 25     | 25     |
| Number of excitations | 2      | 2      |
| b-value [s/mm\(^2\)] | 0, 500 and 1,000 | 0, 500 and 1,000 |
| Respiratory compensation | Free-breathing with navigator echo | Respiratory-triggered without navigator echo |
| Fat-suppression   | SPAIR  | SPIR   |
| SPAIR delay [ms]  | 100    |        |
| SPAIR TR [ms]     | 250    |        |
| Frequency offset [Hz]| 250    | 180    |
| EPI factor        | 75     | 25     |
| Band width [Hz/pixel]| 4050.4 | 4438.5 |
| Scan time [min:sec]| 3:32   | 3:20†  |

Note. *The phase-encoding step of FB-DWI is calculated as follows: 112 (readout matrix) × 2 (scan% of 200) × 299/380 (field of view) ≈ 176.
†The mean scan time of RT-DWI because it is variable depending on the subjects’ respiration condition.

FB-DWI: free-breathing diffusion-weighted imaging, RT-DWI: respiratory-triggered diffusion-weighted imaging, EPI: echo planar imaging, TR: repetition time, TE: echo time, SENSE: sensitivity encoding, SPAIR: spectral attenuation with inversion recovery, SPIR: spectral presaturation with inversion recovery. SPAIR delay: inversion time from exposure of SPAIR pulse, SPAIR TR: TR between SPAIR pulses during the scan, Frequency offset: bandwidth from the frequency of fat tissue. EPI factor: the number of k-space profiles collected per excitation.
other words, the large number of frequency-encoding steps prolongs scanning time and thereby degrades images. However, the large number of phase-encoding steps improved the spatial resolution without deteriorating the image quality by the image noise. We speculate that a blip, which is a gap in the phase-encoding steps, is not changed regardless of the number of phase-encoding steps. Therefore, elongation of scanning time did not deteriorate image quality despite the higher spatial resolution.

Regarding the reduction of chemical shift artifacts, we used SPAIR for the FB-DWI because it is known to allow homogeneous fat suppression and reduce chemical shift artifacts. Homogeneous fat suppression is essential for DWI to avoid the image degradation caused by chemical shift artifacts during image acquisition using the EPI technique. Short inversion-time inversion recovery (STIR) is insensitive to magnetic field inhomogeneity and is thus used for robust fat suppression over an extended FOV at the abdominopelvic region. Fat suppression is superior with STIR compared to frequency-selective prepulse (e.g., chemical shift-selective imaging or SPIR). Instead, STIR decreases the SNR because of a partial loss of proton signal during the inversion time. SPAIR is effective for obtaining homogeneous fat suppression because it is minimally affected by B1 inhomogeneity so that image quality is not degraded. DWIBS originally used STIR, but our present findings show that SPAIR is also beneficial to obtain adequate fat suppression on FB-DWI.

There were no significant differences but there were moderate or good correlations between FB-DWI and RT-DWI in ADC values of liver parenchyma and tumor. Nasu and associates compared the respiratory-triggered and free-breathing techniques and found slightly lower ADC values with the respiratory-triggered technique, without significant difference. They related their results to the higher lesion-to-nonlesion CNR and fewer respiratory misregistration artifacts with the respiratory-triggered sequence compared to the free-breathing sequence. Eatesam’s group suggested that the principle of pseudo-anisotropy artifact may have contributed to the higher ADC observed with free-
breathing DWI. In the present study, the ADC values of liver tumor tended to be higher with FB-DWI than RT-DWI, without significant difference. It is possible that the good SNR and CNR obtained with FB-DWI enable the use of larger b-values that may reduce errors in the ADC calculation. In addition, optimized MR parameters of FB-DWI may minimize the misregistration of tumor or pseudo-anisotropy artifacts.

Our study has several limitations. First, several cases showed severe motion artifacts at the lateral segment of the liver on both FB-DWI and RT-DWI because of cardiac and respiratory motion. In these cases, artifacts hampered the visualization of lesions and ADC calculation. The reduction of motion artifact at the lateral segment of the liver remains a problem to be solved. Second, the scanning time of FB-DWI exceeded 3 min. However, we should keep in mind that the scanning time of RT-DWI without navigator echo is also elongated depending on the patient’s respiratory condition. In patients with unstable respiration or severe respiratory condition, RT-DWI without navigator echo occasionally needs longer scanning times than FB-DWI, which is the same finding as previously reported. Third, we did not analyze the detectability or characterization (e.g., benign versus malignant) of detectable lesions that show hyperintensity on DWI because our focus in the present study was the improvement of image quality on liver DWI using the free-breathing technique. The diagnostic performance of the 2 types of DWI should be compared in the future.

In conclusion, the image quality was better of optimized FB-DWI than RT-DWI without significant change in the SNR of the liver parenchyma, lesion-to-nonlesion CNR, or ADC values of the liver parenchyma and tumor. We propose the feasibility of optimized FB-DWI for clinical practice.

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Table 3. Results of the qualitative and quantitative assessments between FB-DWI and RT-DWI

|                        | FB-DWI     | RT-DWI     | Wilcoxon signed-rank test | Kappa statistic      |
|------------------------|------------|------------|---------------------------|----------------------|
| Sharpness of the liver |            |            |                           |                      |
| contour                |            |            |                           |                      |
| Reader 1               | 3.22 ± 0.71| 2.47 ± 0.62| p < 0.01                  | Readers 1 and 2 0.65 (0.29–1.00) p < 0.01 |
| Reader 2               | 3.34 ± 0.55| 2.63 ± 0.55| p < 0.01                  | Readers 2 and 3 0.65 (0.27–1.00) p < 0.01 |
| Reader 3               | 3.34 ± 0.65| 2.72 ± 0.63| p < 0.01                  | Readers 1 and 3 0.41 (0.13–0.67) p < 0.01 |
| Image noise            |            |            |                           |                      |
| Reader 1               | 3.06 ± 0.56| 2.69 ± 0.47| p < 0.01                  | Readers 1 and 2 0.57 (0.03–1.00) p < 0.01 |
| Reader 2               | 3.00 ± 0.55| 2.84 ± 0.57| p = 0.059                 | Readers 2 and 3 0.48 (0.11–0.85) p < 0.01 |
| Reader 3               | 3.25 ± 0.62| 2.78 ± 0.75| p < 0.01                  | Readers 1 and 3 0.42 (0.12–0.72) p < 0.01 |
| Chemical shift artifacts|           |            |                           |                      |
| Reader 1               | 3.47 ± 0.76| 2.56 ± 0.67| p < 0.01                  | Readers 1 and 2 0.61 (0.27–0.95) p < 0.01 |
| Reader 2               | 3.34 ± 0.55| 2.91 ± 0.73| p < 0.01                  | Readers 2 and 3 0.60 (0.24–0.97) p < 0.01 |
| Reader 3               | 3.16 ± 0.68| 2.81 ± 0.74| p < 0.01                  | Readers 1 and 3 0.62 (0.25–0.99) p < 0.01 |

The unit of ADC value is \(10^{-3}\) mm\(^2\)/s. FB-DWI: free-breathing diffusion-weighted imaging, RT-DWI: respiratory-triggered diffusion-weighted imaging, ICC: intraclass correlation coefficient, CI: confidence interval, SNR: signal-to-noise ratio, CNR: contrast-to-noise ratio, ADC: apparent diffusion coefficient.
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