Optimization of the Flip Angle and Scan Timing in Hepatobiliary Phase Imaging Using T1-Weighted, CAIPIRINHA GRE Imaging

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Purpose: This study was designed to optimize the flip angle (FA) and scan timing of the hepatobiliary phase (HBP) using the 3D T1-weighted, gradient-echo (GRE) imaging with controlled aliasing in parallel imaging results in higher acceleration (CAIPIRINHA) technique on gadoxetic acid-enhanced 3T liver MR imaging.

Materials and Methods: Sixty-two patients who underwent gadoxetic acid-enhanced 3T liver MR imaging were included in this study. Four 3D T1-weighted GRE imaging studies using the CAIPIRINHA technique and FAs of 9° and 13° were acquired during HBP at 15 and 20 min after intravenous injection of gadoxetic acid. Two abdominal radiologists, who were blinded to the FA and the timing of image acquisition, assessed the sharpness of liver edge, hepatic vessel clarity, lesion conspicuity, artifact severity, and overall image quality using a five-point scale. Quantitative analysis was performed by another radiologist to estimate the relative liver enhancement (RLE) and the signal-to-noise ratio (SNR). Statistical analyses were performed using the Wilcoxon signed rank test and one-way analysis of variance.

Results: The scores of the HBP with an FA of 13° during the same delayed time were significantly higher than those of the HBP with an FA of 9° in all the assessment items (P < 0.01). In terms of the delay time, images at the same FA obtained with a 20-min-HBP showed better quality than those obtained with a 15-min-HBP. There was no significant difference in qualitative scores between the 20-min-HBP and the 15-min-HBP images in the non-liver cirrhosis (LC) group except for the hepatic vessel clarity score with 9° FA. In the quantitative analysis, a statistically significant difference was found in the degree of RLE in the four HBP images (P = 0.012). However, in the subgroup analysis, no significant difference in RLE was found in the four HBP images in either the LC or the non-LC groups. The SNR did not differ significantly in the four HBP images. In the subgroup analysis, 20-min-HBP imaging with a 13° FA showed the highest SNR value in the LC group, whereas 15-min-HBP imaging with a 13° FA showed the best value of SNR in the non-LC group.

Conclusion: The use of a moderately high FA improves the image quality and lesion conspicuity on 3D, T1-weighted GRE imaging using the CAIPIRINHA technique on gadoxetic acid, 3T liver MR imaging. In patients with normal liver function, the 15-min-HBP with a 13° FA represents a feasible option without a significant decrease in image quality.

Keywords: Magnetic resonance imaging/methods; Contrast media; Gadolinium DTPA; Breath holding; Imaging; Three-dimensional/method
INTRODUCTION

Magnetic resonance (MR) imaging of liver is widely used and is an excellent technique for detecting and characterizing focal liver lesions (1-3). The breath-hold, three-dimensional (3D), T1-weighted, gradient-echo (GRE) sequence is widely accepted as an essential sequence to evaluate focal liver disease (4). These 3D T1-weighted GRE sequences are generally used in combination with the parallel acquisition technique (PAT) in order to decrease the acquisition time or improve the spatial resolution. Among several recently developed PATs, controlled aliasing in parallel imaging results in higher acceleration (CAIPIRINHA) is used with a promising new PAT algorithm to facilitate successful acquisition of high-quality imaging and very thin sections with adequate volume coverage as well as reducing the geometry factor (g-factor)-related noise enhancement even without a higher acceleration factor (5-8).

MR imaging of liver with gadolinium-based, hepatocyte-specific contrast agents, which allows both dynamic and delayed hepatobiliary phase (HBP) imaging, has definitely improved the diagnostic performance for detection of focal liver disease compared with contrast-enhanced computed tomography (CT) and liver MRI using purely extracellular contrast agents (9-11). HBP imaging typically allows image acquisition at approximately 20 min after contrast agent injection. Recent studies suggest that decreasing the delay time of the hepatocyte-phase to 10 min may be sufficient for the detection of focal liver lesions, although this approach has yet to be thoroughly investigated (12, 13). A flip angle (FA) of approximately 9° is widely used in HBP imaging to match the FA used for early dynamic sequences, depending on the vendor-specific default setting of the MR system. Studies suggest that HBP imaging using a higher FA allow better sensitivity for the detection of focal liver lesions, although it is a controversial approach (14). These studies were performed based on HBP using 3D T1-weighted GRE imaging. The purpose of this study was to optimize the FA and the scan time for HBP imaging using 3D T1-weighted GRE imaging with CAIPIRINHA on gadoxetic acid-enhanced, 3T liver MR imaging.

MATERIALS AND METHODS

Patient Population

Our Institutional Review Board approved this retrospective study (JNUH IRB Number: 2016-03-002), and patients’ informed consent was not required. From January 2014 to May 2014, 64 consecutive patients underwent gadoxetic acid-enhanced liver MR imaging. Two patients were excluded due to the following reasons: (a) presence of multiple cirrhotic nodules to evaluate the degree of liver parenchymal enhancement; and (b) an unduly small volume of remnant liver due to previous liver surgery. The final study group consisted of 62 patients (46 men, 16 women; mean age, 58.6 years; range, 34-78 years). Thirty-seven patients had underlying liver cirrhosis (LC) (chronic hepatitis B, chronic hepatitis C or alcohol-related cirrhosis). The severity of the liver cirrhosis was based on Child-Pugh classification: 34 patients were classified as Child-Pugh class A; three as Child-Pugh class B; and none as Child-Pugh class C. The non-LC group comprised a total of 25 patients who underwent liver MR imaging for: (a) metastasis work-up (n = 18); and (b) other reasons (n = 7, i.e., four hemangiomas, two abscesses, and one intrahepatic mass-forming cholangiocarcinoma).

Preliminary Phantom Study

The phantom consisted of multiple bottles containing different gadoxetic acid concentrations and two controls including fat and water (saline). The phantom examination was performed using a 3T MR imaging unit (Skyra; Siemens Medical Systems, Erlangen, Germany) and 3D T1-weighted GRE images using the CAIPIRINHA technique with 34 different FAs. The water signal represented an increase less than a 6-degree FA and a decrease above a 6-degree FA, which suggested that a 6-degree FA (Ernst angle) resulted in the highest signal intensity for water. Otherwise, the fat signal is gradually increased to a 30-degree FA. The signals of water and fat are inverted at a 14-degree FA (Fig. 1). An inverted signal is unfamiliar and is associated with the possibility of a false reading due to the large fat content in the human body and liver. The signal intensity of gadoxetic acid is increased with increasing FA (Fig. 1). The contrast-to-noise ratio (CNR) between gadoxetic acid and saline is increased by increasing the FA, and by approximately 12.4% per degree. In consultation with a radiologist and an MR physicist, the FA of 3D T1-weighted GRE images using the CAIPIRINHA technique was set to 9° FA as recommended by the vendor and an FA of 13° was predicted to reach the maximum CNR between liver parenchyma and a vessel in the hepatobiliary phase in this preliminary test.

MR Imaging Technique

MR imaging was performed with a 3T system (Skyra;
Siemens Medical Systems, Erlangen, Germany) using a 32-channel, body coil. All of the images were acquired in the transverse plane covering the upper abdomen. The dynamic and HBP images were obtained using 3D, T1-weighted GRE images (volumetric interpolated breath-hold examination [VIBE]) with the CAIPIRINHA technique. The 3D VIBE sequence parameters were as follows: repetition time/echo time (TR/TE) of 5/2 ms; section thickness of 2.5 mm; field of view of 303 × 305 mm; and a matrix 320 × 320. Dynamic imaging including the pre-contrast image, arterial phase, portal-venous phase, delayed phase, and hepatobiliary phase, was performed. The standard dose of contrast agent (Gd-EOB-DTPA; Primovist; Bayer Schering Pharma AG, Berlin, Germany, 0.25 mmol/mL) intravenously administered was 0.1 mL/kg at a rate of 1.2 mL/s and was immediately followed by a 20-mL saline flush through a venous catheter using a power injector. HBP images were obtained at 15 and 20 min following the injection of contrast medium. Two HBP images with a 9° FA were acquired at each time point as recommended by the vendor (acquisition time, 11.33 s) and a 13° FA (acquisition time, 11.79 s).

Qualitative Analysis
Two abdominal radiologists with 17 and 13 years of clinical experience, respectively, who were blinded to the FA, image acquisition time, clinical information, and original radiology report, individually reviewed the HBP images using our institutional picture archiving and communication systems (PACS). The readers recorded subjective scores for the following items: liver edge sharpness; hepatic vessel clarity (5 = sharp, 4 = minor blurring, 3 = moderate blurring, 2 = substantial blurring, 1 = uninterpretable because of severe blurring); lesion conspicuity; artifact severity; and overall image quality (5 = very good, diagnostic, 4 = good, diagnostic, 3 = fair, diagnostic, 2 = poor, non-diagnostic, 1 = uninterpretable, non-diagnostic). The images were adjusted to an optimal window setting in each case, and the readers evaluated them under the same conditions. Focal liver lesions were designated the largest, i.e., greater than 1 cm, by a study coordinator before the image analysis. Based on statistical analyses, the average scores recorded by the two radiologists were used.

Quantitative Analysis
Quantitative relative liver enhancement and the signal-to-noise ratio (SNR) were determined by another radiologist. The signal intensities of the liver and the spleen were measured by standard region-of-interest (ROI) measurements using the copy-and-paste method. In each of the four HBP images, ROIs for liver parenchyma were drawn over the normal liver parenchyma, avoiding major

Fig. 1. Graphs (signal intensity and contrast-to-noise ratio [CNR] to flip angle) of water, fat, and gadoxetic acid obtained from an in-vitro phantom. Changing the flip angle affects the signal intensity of water, fat, and gadoxetic acid (a, b). The shape of a water curve shows a specific flip angle at 6 degrees, which produces maximum signal intensity (a). The signal intensity of water converges with fat at 14 degrees (a, b). The CNR between gadoxetic acid and water is increased by raising the flip angle 12.4% per degree (b).
vessels as well as areas of necrosis, hemorrhage, and focal lesions to the extent possible. The ROI shape was almost round and measured 100 mm$^2$ in size. The signal intensity of liver parenchyma on precontrast, T1-weighted images was measured using the same methods. The mean standard deviation (SD) of background noise was measured in the phase-encoding direction outside the body in the four HBP images.

The relative liver enhancement (RLE) and the SNR were calculated as follows:

$$RLE = \frac{SI_{\text{HBP}} - SI_{\text{pre}}}{SI_{\text{pre}}}$$

$SI_{\text{HBP}}$: average values of the mean signal intensity of three ROIs in each hepatobiliary image;

$SI_{\text{pre}}$: the mean hepatic signal intensity obtained in the precontrast images;

$$SNR = \frac{SI_{\text{HBP}}}{SD_{\text{background}}}$$

$SD_{\text{background}}$: the mean standard deviation of the background in each of the four, hepatobiliary images.

### Statistical Analysis

Statistical analyses were performed using the SPSS software (SPSS 18.0 for Windows, Chicago, IL, USA). Qualitative analyses were tested using the Wilcoxon signed rank test with subgroup analysis. For quantitative analyses, the one-way analysis of variance test was used to compare the relative liver enhancement and the signal-to-noise ratio in the four HBP images. P values < 0.05 were considered to

<table>
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<tr>
<th>Quality parameter</th>
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<th>P value</th>
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<th></th>
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<tbody>
<tr>
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<td>20 min 9°</td>
<td>15 min 9°</td>
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<td>Liver edge sharpness</td>
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<td>4.28</td>
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<td>Lesion conspicuity</td>
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<td>4.38</td>
<td>0.51</td>
<td>0.236</td>
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</table>

* P < 0.05

LC = liver cirrhosis

Table 1. Results of the Qualitative Analysis: Comparison of the Hepatobiliary Phases at Different Flip Angles and Delayed Times
indicate a statistically significant difference.

RESULTS

Qualitative Analysis

Table 1 provides an overview of each qualitative analysis in the four HBP images. The mean scores in most qualitative assessments were greater than four (good for diagnosis) in all HBP images. The 20-min-HBP with a 13° FA represented the best sequence in terms of liver-edge sharpness, hepatic vessel clarity, lesion conspicuity, artifact severity, and overall image quality, followed by 15-min-HBP images with a 13° FA, 20-min-HBP images with a 9° FA, and 15-min-HBP images with a 9° FA. The scores of HBP with a 13° FA during the same delayed time were significantly higher than

Fig. 2. MR images of a 44-year-old woman with a history of breast cancer and normal liver function. Four hepatobiliary phase (HBP), gadoxetic acid-enhanced 3D-gradient echo (GRE) images using the CAIPIRINHA technique obtained at 20 min (a) and 15 min (b) after contrast injection with a 13° flip angle (FA) and at 20 min (c) and 15 min (d) after contrast injection with 9° FA. Moderately high flip angle HBP images (a, b) showed the best delineation of intrahepatic vessels, compared with standard flip angle HBP images (c, d). At moderately high flip angle HBP images (a, b), intrahepatic vessels (arrow) were well defined with low signal intensity. The background liver showed high signal intensity due to enhanced, normal parenchyma, resulting in excellent conspicuity. The relative liver enhancement was highest with transverse, T1-weighted 3D-GRE images obtained 15 min after contrast injection with a 13° FA (b), followed by T1-weighted, 3D-GRE images obtained 20 min after contrast injection with a 13° FA (a), T1-weighted, 3D-GRE images obtained 20 min after contrast injection with a 9° FA (c), and T1-weighted, 3D-GRE images obtained 15 min after contrast injection with a 9° FA (d).
those of HBP with a 9° FA for all assessment items (P < 0.01). In the subgroup analysis of the LC and the non-LC groups, the HBP with a 13° FA was superior to the HBP with a 9° FA in all qualitative analysis (Figs. 2, 3).

With regard to the delay time, images in the same FA obtained with the 20-min-HBP images were of better quality than those obtained with the 15-min-HBP. The 20-min-HBP images with a 13° FA had significantly better scores for hepatic vessel clarity (P = 0.001), lesion conspicuity (P = 0.003), and overall image quality (P = 0.041) compared with the 15-min-HBP with a 13° FA. In the subgroup analysis of the LC group, hepatic vessel clarity and lesion conspicuity were better in the 20-min-HBP than in the 15-min-HBP with the same level of statistical significance as FA. However, in subgroup analysis of the non-LC group, no significant difference was noted between the 15-min-HBP and the 20-min-HBP images with a 13° FA (Figs. 2, 3).

Quantitative Analysis

The quantitative results of the RLE of hepatobiliary phases using different FAs and times are shown in Table 2. The 20-min-HBP images with a 13° FA had the highest scores, followed by 15-min-HBP with a 13° FA, 20-min-HBP images with a 9° FA, and 15-min-HBP images with a 9° FA. The RLE of the HBP image with a high FA was higher than that of the HBP image with a low FA. The HBP imaging with a delay time of 20 min showed a better RLE value than the HBP imaging with a delay time of 15 min. A statistically significant difference was found in the degree of RLE of the

Fig. 3. MR images of a 70-year-old man with liver cirrhosis (Child-Pugh class: A) show hepatocellular carcinoma (arrow). Four hepatobiliary phase (HBP), gadoxetic acid-enhanced, 3D-gradient echo (GRE) images using the CAIPIRINHA technique obtained at 20 min (a) and 15 min (b) after contrast injection with 13° flip angle (FA) and at 20 min (c) and 15 min (d) after contrast injection with 9° FA. Moderately high flip angle HBP images (a, b) demonstrate clearly defined hepatocellular carcinoma. The fine intrahepatic vasculatures (short arrow) are well defined in moderately high flip angle HBP images (a, b).
four HBP images (P = 0.012). In the subgroup analysis of the LC and the non-LC groups, no statistically significant difference was found in the RLE.

In the analysis of SNR (Table 2), the 20-min-HBP imaging with a 13° FA showed the highest scores, followed by 15-min-HBP with a 13° FA, 20-min-HBP images with a 9° FA, and 15-min-HBP images with a 9° FA. The SNR did not differ significantly in the four HBP images. In the subgroup analysis, the 20-min-HBP imaging with a 13° FA had the highest SNR value in the LC-group, whereas the 15-min-HBP imaging with a 13° FA showed the best SNR value in the non-LC group.

DISCUSSION

The results demonstrate that 3D T1-weighted GRE imaging using the CAIPIRINHA technique with a 13° FA in the same delayed time resulted in a significantly higher value in all the qualitative evaluations compared with those of 3D T1-weighted GRE imaging using CAIPIRINHA with a 13° FA. This finding indicates that HBP imaging using CAIPIRINHA with a 13° FA may be adequate for the evaluation of focal hepatic lesions using a 3T MR system. Clinical investigators have reported that HBP MR imaging with an increasing FA (30-40°) on a 1.5T MR system significantly increased the lesion-to-liver contrast and improved the detection of focal liver lesions, particularly of small lesions (14-17). T1-weighted, 3D GRE imaging with a very short TR is currently used for HBP imaging generally. The GRE signal intensity depends on the selection of the FA. Because the longitudinal magnetization will not fully recover in a short TR, the choice of the estimated optimal FA, also known as the Ernst angle, is critical to obtain high signal intensity. In T1-weighted, 3D GRE, imaging from one tissue is not the major concern. Instead, optimizing the contrast between the two tissues with different T1 relaxation times is a priority. Using a higher FA not only increases the signal of the enhanced liver, but also decreases that of unenhanced lesions. Therefore, the choice of a relatively high FA than the Ernst angle provides a good contrast-to-noise ratio (CNR) for improved lesion detection (14).

In our study, the specific absorption rate (SAR) is an important consideration for adopting a moderately high FA (13°). The SAR is proportionate to the square of the strength of the static magnetic field and the square of the FA. The doubling of the field from 1.5T to 3T leads to a quadrupling of the baseline SAR (18). One possible solution for this is the use of an appropriate FA, which lowers the RF energy absorption while maintaining an acceptable SNR and CNR (19). In a recently produced 3T MR systems, SAR consideration limits scanner performance with FA modulation. A previous study showed that examinations performed at 3T frequently were excluded for the study population because the FA in the high FA pulse sequence was automatically lowered below the manually set value by the SAR-monitoring algorithm incorporated into the MR system due to the excessive, estimated energy deposition (15). In a study performed by Kim et al. (20), for unknown reasons, ghost artifacts at high FAs (25° and 40°) were observed in the underlying higher contrast signal associated with the biliary system, compared with hepatobiliary imaging at low FA (12°). Therefore, a moderately high FA

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### Table 2. Results of Quantitative Analysis: Comparison of the Hepatobiliary Phase at Different Flip Angles and Times

<table>
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<tr>
<th>Parameter</th>
<th>Flip angle and delayed time</th>
<th>P value</th>
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<tr>
<td></td>
<td>20 min 13°</td>
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</tr>
<tr>
<td>Relative liver enhancement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.9141 ± 0.3751</td>
<td>0.8819 ± 0.3454</td>
</tr>
<tr>
<td>LC</td>
<td>0.9123 ± 0.3577</td>
<td>0.8760 ± 0.3307</td>
</tr>
<tr>
<td>Non-LC</td>
<td>0.9168 ± 0.4070</td>
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</tr>
<tr>
<td>SNR of the liver parenchyma</td>
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</tr>
<tr>
<td>Total</td>
<td>251.06 ± 78.62</td>
<td>245.51 ± 72.69</td>
</tr>
<tr>
<td>LC</td>
<td>245.84 ± 86.75</td>
<td>232.49 ± 73.48</td>
</tr>
<tr>
<td>Non-LC</td>
<td>258.79 ± 65.71</td>
<td>264.78 ± 68.42</td>
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</tbody>
</table>

* P < 0.05

LC = liver cirrhosis; SNR = signal-to-noise ratio
is more appropriate for increasing the SNR in the HBP, T1-weighted pulse sequence on a 3T MR system. An additional consideration is that our preliminary phantom study on a 3T MR system showed that the signal intensity of saline meets the fat signal intensity at a moderate FA (14°) as the signal intensity of saline was maximal at 6° FA, after which it gradually decreased above this level and the signal of fat gradually increased until a 30° FA. Based on this theoretical background, a moderately high FA on a 3T MR system is recommended under clinical setting to increase the CNR between liver parenchyma and a vessel in HBP for hepatic imaging because an inverted signal is unfamiliar during the interpretation of images resulting possible misinterpretation due to the large fat content in the human liver.

Our study showed that HBP imaging with a 13° FA obtained 15 min following injection of Gd-EOB-DTPA provided similar diagnostic performance compared with images obtained after 20 min, especially in patients with normal hepatic function. The duration of time delay for the HBP is a matter of discussion (13, 17, 21, 22). The hepatocyte uptake starts at 1.5 min after injection of Gd-EOB-DTPA and the maximal parenchymal enhancement was observed at 20 min after the contrast injection (10, 11). Therefore, the product brochure usually advises a 20-min delay for the evaluation of lesion detection and characterization, and most studies published to date obtained their data 20 min after contrast agent injection (23). However, due to the optimal time delay of 20 min after administration of contrast medium, the total MR examination is relatively time-consuming.

Several studies assessed the optimal timing of HBP imaging for lesion detection and characterization. One study suggested that the relative increase in the parenchymal signal intensity between five and 10 min was statistically significant (75.1% at 5 min vs. 86.3% at 10 min, respectively), while an additional 20-min series failed to further increase the signal intensity (23). It has been shown that in patients with normal functioning liver parenchyma, a delay of 10 min after Gd-EOB-DTPA injection is sufficient for adequate enhancement of the liver parenchyma (23). In our study, there was no significant difference in the qualitative scores and quantitative analysis (RLE and SNR of the liver parenchyma) between 20-min HBP and 15-min HBP in the non-LC group with the same FA indicating that the 15-min-HBP imaging was potentially comparable to the standard 20-min-HBP imaging, especially in patients with normal liver function without a clear-cut decrease in overall image quality and diagnostic performance.

Our study revealed that the degree of RLE was higher in the 20-min-HBP images than in the 15-min-HBP. It is well known that the enhancement of the liver is suppressed and delayed in patients with chronic liver disease during the HBP of gadoxetic acid-enhanced MR imaging (9, 24, 25). In our study, the value of the RLE in the LC group was lower in the 15-min-HBP imaging without statistical significance. Further, in the LC group, hepatic vessel clarity and lesion conspicuity were better in the 20-min-HBP than in the 15-min-HBP and with statistical significance at the same FA indicating that the 20-min-HBP may be equally useful for patients with liver cirrhosis.

Our study had several limitations. First, a selection bias resulting from the retrospective design of our study should be considered. Second, the quantitative analysis may be limited by inherent selection bias toward inclusion of inhomogeneous distribution of liver-to-background contrast. Nevertheless, we addressed this issue because the same area was analyzed, when comparing four HBPs. Third, most patients in the LC group showed relatively good hepatic function (Child-Pugh class A), which might be limited by a lack of diversity. A diverse range in the intensity of chronic liver disease might influence RLE and SNR of the liver parenchyma. Fourth, the CNR of focal liver lesion was not analyzed. Therefore, further studies are needed.

In conclusion, the use of a moderately high FA improves the image quality and lesion conspicuity on 3D, T1-weighted GRE imaging using CAIPIRINHA on gadoxetic acid, 3T liver MR imaging. In patients with normal liver function, the 15-min-HBP with a 13° FA represents a feasible option without a significant decrease in image quality.

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