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Evaluation of Intrarenal Oxygenation at 3.0 T Using 3-Dimensional Multiple Gradient-Recalled Echo Sequence

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Abstract

Objective—The objective of this study was to validate quantitation of R_2^* and ΔR_2^* measurements obtained with a 3-dimensional (3-D) multiple gradient-recalled echo (mGRE) sequence for evaluating intrarenal oxygenation in humans.

Materials and Methods—Validation was accomplished (1) by comparing R_2^* values with previously established 2-D techniques ($n = 5$, mean age = 33.6 years) and (2) by measuring change in ΔR_2^* after furosemide (20 mg intravenously) administration ($n = 5$, mean age = 22 years). Additional pre- and postfurosemide scans were done at 1.5 T for comparison purposes.

Results— R_2^* measurements with the 3-D technique showed good agreement with the 2-D techniques. The baseline medullary R_2^* at 3.0 T was about twice the value found at 1.5 T. Furosemide-induced change in R_2^* was observed within 5 minutes after administration.

Conclusions— R_2^* measurements with 3-D mGRE were comparable with those reported using 2-D techniques. The 3-D implementation facilitates observation of temporal changes in the medullary oxygenation without compromising spatial coverage.

Keywords

kidney; BOLD MRI; 3-D mGRE; oxygenation; 3.0 T

The renal medulla operates at low oxygenation levels (renal medullary hypoxia) making it more susceptible to mild reductions in blood flow.^{1–3} Renal medullary hypoxia is thought to play a role in the pathogenesis and/or progression of acute renal failure,^{4–6} hypertension,^{7,8} and diabetic nephropathy.^{9,10} Blood oxygenation level-dependent (BOLD) magnetic resonance imaging (MRI) has been used to evaluate intrarenal oxygenation levels noninvasively in humans under normal conditions and during physiological and pharmacologic maneuvers at field strengths of 1.5 T^{10–14} and most recently at 3.0 T.¹⁵

To date, all BOLD MRI applied to the human kidney for functional evaluation have used single-shot echo planar (EPI)¹³ or 2-dimensional (2-D) breathhold multiple gradient-recalled echo (mGRE) techniques.¹⁴ Despite the advantage of faster acquisition times, the single-shot EPI technique suffers from limitations such as having high sensitivity to susceptibility

differences, which can lead to signal loss, image distortions, and increased blurring resulting from T_2^* decay during data acquisition.¹⁴ The 2-D mGRE technique, although efficacious in terms of R_2^* mapping, requires multiple acquisitions to achieve adequate spatial coverage, typically a breathhold for each slice acquisition. In this study, we validated the quantitation of R_2^* and ΔR_2^* using a 3-D implementation of mGRE to perform intrarenal oxygenation studies. R_2^* measurements obtained by the 3-D technique were compared with measurements acquired with the 2-D sequence used in previous studies. Changes in R_2^* (ΔR_2^*) after administration of furosemide were also compared against previous reports.

Furosemide is a loop diuretic that has been shown to improve medullary oxygenation, presumably because it selectively decreases oxygen consumption by blocking active transport in the thick ascending limbs.^{1,16} We hypothesized that the relatively fast acquisitions afforded by the 3-D implementation method would allow us to monitor the temporal response after administration of furosemide without sacrificing spatial coverage.

MATERIALS AND METHODS

Studies were performed on a short bore 1.5 T and/or a 3.0 T Twin Speed scanner with Excite technology (General Electric Medical Systems, Milwaukee, WI). Both scanners have a maximum gradient strength of 23 mT/m and a slew rate of 77 mT/m/ms. An 8-element coil array was used for signal reception. All participants gave informed consent according to a protocol approved by the Institutional Review Board.

To implement the 3-D sequence with acquisition time on the order of a single breathhold, we resorted to brute force reduction of the repetition time (TR) compared with our current 2-D mGRE sequence. This was accomplished in the following manner: the number of echoes was reduced from 16 to 8, the bandwidth (BW) was increased from 62.5 kHz to 83.3 kHz, and a shorter radiofrequency (RF) pulse was used in place of a selective water excitation pulse. To further reduce the overall acquisition time, the matrix size was reduced and partial Fourier encoding was used along both the slice (70%) and phase (80%) directions. Table 1 shows the specific acquisition parameters used with each sequence.

Comparison of the 3-D versus single-slice 2-D implementations was performed at 3.0 T in 5 male subjects with no known history of renal disease (mean age 33.6 ± 7.0 years). The 3-D mGRE sequence with 8 echoes was used to acquire data during a breathhold of 23 seconds. The sequence acquired data from 10 (coronal) slices. Two slices on either end were not reconstructed to avoid wraparound artifacts. The choice of echo times (TE) was consistent with known values of T_2^* in the renal medulla (approximately 25 ms).¹⁵ For comparison, data were acquired with a 2-D mGRE sequence with 8 echoes to obtain 4 matched slices in a single breathhold of 19 seconds. The positions of the 2-D slices were matched to those of the 3-D acquisitions with no slice gap. Data was also acquired using the current standard prescription at our laboratory, a 2-D mGRE sequence with 16 echoes, to acquire 4 matched slices with one slice per 13 second breathhold. In all sequences, partial Fourier encoding in the phase direction (80%) along with 80% phase field of view were applied.

Five healthy young volunteers (4 female and one male, mean age = 22 ± 1.2 years) with no history of renal disease took part in the furosemide study. The volunteers came to the study after abstaining from food and water for at least 12 hours overnight. Baseline BOLD MR images using the 3-D mGRE sequence were first acquired at 1.5 T. The subjects were then moved to the 3.0 T scanner. After the baseline scans at 3.0 T, 20 mg furosemide was administered intravenously over a 2-minute period. The postfurosemide scans at the 3.0 T scanner were conducted immediately after the administration of furosemide for approximately 10 minutes at the rate of one scan per minute. The volunteers were then

returned to the 1.5 T scanner for additional postfurosemide scanning. The relatively fast acquisitions and the availability of both scanners in the same suite facilitated the multiplatform scanning protocol. The 3-D mGRE sequence parameters used for BOLD MRI at 1.5 T were the same as those at 3.0 T (described in Table 1).

The BOLD parameter R_2^* ($=1/T_2^*$), which has been shown to be closely related to the content of deoxyhemoglobin in blood, was used to interpret changes in tissue oxygenation. Decreases in the R_2^* values imply increases in the tissue pO_2 levels. R_2^* maps were constructed on an Advantage Workstation (General Electric Medical Systems) using FUNCTOOL by fitting a single exponential function to the signal intensity versus TE data. For the analysis, a threshold value was defined so as to avoid fitting to data points approaching noise levels. Approximately 40 regions of interest (ROIs) covering at least 10 pixels each were carefully placed on the anatomic template and R_2^* values were read off the corresponding R_2^* maps. The ROIs were positioned in the cortex and medulla on all of the 6 slices that were acquired using the 3-D mGRE sequence. Figure 1B shows an example of the placement of a few ROIs for one of the 6 acquired slices. The data from the ROIs were combined to obtain a single representative mean value for R_2^* per subject per timepoint. A 2-tailed paired Student *t* test was used to evaluate any statistical significance of the differences between the pre- and postfurosemide R_2^* values. Owing to the temporal variations, we empirically chose the last 3 time-points obtained to represent postfurosemide values.

RESULTS

Figure 1 shows 3 different sets of images acquired at 3.0 T in the coronal orientation. Figure 1A shows images acquired from one slice at each of the 8 different echo times with the 3-D mGRE sequence. Figure 1B illustrates the placement of ROIs on one representative slice. For comparison purposes, Figure 1C includes anatomic images and their respective R_2^* maps at the same slice position obtained with each of the 3 sequences used. The coronal view allows for excellent visibility of the cortical and medullary regions in both the anatomic images and R_2^* maps.

Table 2 quantitatively compares R_2^* values obtained with the 3-D mGRE (8 echoes), 2-D mGRE (8 echoes), and 2-D mGRE (16 echoes) sequences. The R_2^* values obtained with 3-D mGRE sequence are in close agreement with those obtained using the 2-D mGRE techniques.

Figure 2 demonstrates the temporal response in R_2^* measurements after administration of furosemide in one representative subject. Within approximately 5 minutes postadministration, the medullary R_2^* values begin to approach those of the cortex, implying improved oxygenation.

Table 3 summarizes the R_2^* data for all the 5 subjects who partook in the furosemide study. Note the average baseline medullary R_2^* at 3.0 T is close to twice the value at 1.5 T (26.4 ± 2.0 1/s [mean $\pm$ standard deviation] vs 14.8 ± 0.5 1/s). This is consistent with the scaling of the BOLD effect with field strength and our previous reports using 2-D mGRE technique.¹⁵ The cortex and medulla both showed statistically significant differences when pre- to postfurosemide changes in R_2^* values were compared. The magnitude of difference in the cortex was less pronounced compared with that in the medulla. The change in medullary R_2^* after furosemide was found to be more than twice at 3.0 T compared with 1.5 T.

DISCUSSION

Our preliminary evaluation of the 3-D mGRE sequence demonstrates that the R_2^* quantitation is comparable to the 2-D mGRE technique. R_2^* values measured by the 3 different acquisitions used in this study were in good agreement. Although there was no statistical significance between the 3-D and 2-D acquisitions in the medulla, the values in the cortex showed a significant difference. However, the magnitude of difference in the mean value was relatively modest compared with the standard deviation in the measurements (Table 2). The mean difference $\pm$ standard deviation was determined to be 2.06 ± 1.3 (for 3-D vs 2-D with 8 echoes) and 3.54 ± 2.5 (for 3-D vs 2-D with 16 echoes). The 2-D version was performed with 2 sets of parameters, one reflecting the parameters used in most of our previous reports and the other to optimize the maximum TE to be close to T_2^* of the medulla and comparable to the 3-D acquisition. Table 1 outlines the parameter differences (eg, choice of RF pulse, TE, TR, flip angle, BW, the number of acquired slices per breathhold, and so on) between the 2-D and 3-D 8-echo sequences.

The 3-D mGRE sequence allowed the examination of a temporal BOLD response in the human kidneys after administration of furosemide without compromising the spatial coverage. Although it would have been possible to follow the temporal response using a multislice 2-D mGRE sequence with matched 3-D mGRE sequence parameters, the fundamental advantage of using the 3-D implementation is the improved SNR compared with the 2-D acquisitions. Previous studies typically acquired one set of postfurosemide data over 10 to 15 minutes. Because furosemide is a relatively fast-acting drug, the temporal response (as shown here) after its administration is rapid, within 5 minutes. Also, the response is similar both in terms of magnitude and rate among all subjects.

Although not the primary interest for this study, by taking advantage of the fast acquisition times and the proximity of the 1.5 T and 3.0 T scanners, we were able to collect additional BOLD MRI data at 1.5 T before and after the data acquisition at 3.0 T. Similar to the 3.0 T, all of the volunteers showed a statistically significant change at 1.5 T when comparing the baseline and postfurosemide R_2^* values for both the cortex and medulla. However, compared with our previous experience,¹⁵ the change in R_2^* in the medulla at 1.5 T was less than half of that seen at 3.0 T (Table 3). This is probably the result of the fact that the time of acquisitions for the postfurosemide data was significantly different at the 2 field strengths as a result of the interleaving of acquisitions between 1.5 T and 3.0 T. At 3.0 T, the postfurosemide scans were performed immediately after administration, whereas at 1.5 T, a time period of at least 15 minutes had elapsed before data acquisition. Cortical R_2^* did not differ significantly with field strength, probably as a result of the fact that the susceptibility weighting was relatively smaller owing to the better oxygenation. Similar to our previous report, the susceptibility artifacts at 3.0 T were not significantly different from those at 1.5 T.

When comparing the R_2^* values at 3.0 T in Tables 2 and 3 (baseline), it is interesting to note that there is a noticeable difference. This disparity is most likely attributed to the differences in the group of subjects (eg, age and hydration status). The values determined in Table 2 were more consistent with a previous report on 3.0 T in which the age group was more similar.¹⁵

We report for the first time the temporal response in R_2^* values after administration of furosemide. The 3-D mGRE sequence allows for monitoring temporal responses in intrarenal oxygenation after pharmacologic maneuvers without having to sacrifice spatial coverage. The availability of a 3-D mGRE technique may also facilitate the use of BOLD MRI in a clinical setting. However, the breathhold duration of 23 seconds may not be

feasible in patients. Fewer numbers of slices and/or use of parallel imaging techniques^{17,18} may further reduce the data acquisition times. The technique may also potentially allow for acquisition of thinner slices and hence isotropic resolution.

In conclusion, the 3-D implementation of mGRE sequence provides R_2^* quantitation that is comparable to our previously used 2-D protocol, however with better spatial coverage. The relatively fast acquisitions available with the 3-D implementation permitted the monitoring of the temporal response after the administration of furosemide. In all subjects studied, furosemide caused a temporal change in R_2^* in the medulla within approximately 5 minutes, with the medullary R_2^* values approaching those of the cortex. The baseline medullary R_2^* values were significantly higher at 3.0 T (by a factor close to 2) when compared with 1.5 T.

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FIGURE 1.

(A) Three-dimensional multiple gradient-recalled echo images from each of the 8 echo times at the same slice position. (B) An anatomic (left) and R_2^* map (right) from one slice position containing a few representative regions of interest. (C) Anatomic (top row) and corresponding R_2^* maps (bottom row) at the same slice position for each of the 3 sequences. All images in Figure 1 were acquired at 3.0 T.

FIGURE 2.

A graphical representation of the R_2^* values as a function of time obtained in one representative subject. The first 4 points represent the mean baseline R_2^* values. Zero on the time axis represents the time of furosemide administration. The errors bars represent the standard deviation of the pixel data for all of the regions of interest used to determine a single time point. Note that the cortical R_2^* remain relatively constant over the entire acquisition period, whereas medullary R_2^* approaches that of the cortex after administration of furosemide.

TABLE 1

Specific Acquisition Parameters for the 2-D and 3-D Sequences*

	3-D (8 Echoes)	2-D (8 Echoes)	2-D (16 Echoes)
TR (ms)	25.5	35	60
TE (ms)	1.86–22.9	7.59 –23.4	7.59 – <i>41.4</i>
Flip angle	10°	20 °	<i>30</i> °
Bandwidth (kHz)	83.3	62.5	62.5
Slice (mm)	5	5	5
Matrix	256 × 160	256 × 160	256 × 256
Field of view (cm)	36–42	36–42	36–42
“Water excite” radiofrequency pulse	No	Yes	Yes
Partial Fourier in phase direction (80%)	Yes	Yes	Yes
Acquired slices per breathhold	10	4	<i>1</i>
Slices used for evaluation	6	4	4
Breathhold time (seconds)	23	19	<i>13</i>

* Parameters in bold highlight differences between 2-D and 3-D sequences. Italicized parameters detail differences between the 8 and 16 echo 2-D acquisitions. All sequences had 80% phase field of view, and the 3-D sequence additionally used 70% partial Fourier encoding along slice direction.

TABLE 2Comparison of R_2^* Values Between 3-D and 2-D mGRE Sequences at 3.0 T*

	Cortex R_2^* (s^{-1})	Medulla R_2^* (s^{-1})
3-D (8 echoes)	18.5 ± 2.6	37.7 ± 3.8
2-D (8 echoes)	$20.5 \pm 2.9^\dagger$	36.6 ± 3.0
2-D (16 echoes)	$22.0 \pm 3.1^\dagger$	36.7 ± 2.2

* Shown are mean $\pm$ standard deviation for cortex and medulla over all subjects. A single mean value for each subject was obtained by placing pairs of regions of interest (cortex and medulla) in each slice acquired.

$^\dagger P < 0.05$ by paired 2-tailed t test when compared with 3-D mGRE.

TABLE 3
Comparison of R₂* Values for Cortex and Medulla (Pre- and Postfurosemide) at 1.5 T and 3.0 T*

Subject	1.5 T				3.0 T			
	Cortex		Medulla		Cortex		Medulla	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	11.4	10.7	15.3	11.7	13.4	12.4	25.5	17.0
2	11.0	10.7	14.8	13.2	13.5	13.3	24.7	17.0
3	11.3	10.6	14.9	13.0	13.3	12.9	24.6	17.2
4	11.0	10.5	15.1	13.0	15.4	13.3	28.9	17.7
5	10.8	10.3	14.1	12.8	15.6	14.0	28.2	18.6
Mean	11.1	10.6 [†]	14.8	12.7 [†]	14.2	13.2 [†]	26.4	17.5 [†]
Standard deviation	0.3	0.2	0.5	0.6	1.2	0.6	2.0	0.7

The average of the last 3 timepoints was used as the postfurosemide data at 3.0 T. All R₂ values have units of 1/s. Each R₂* number represents a single mean value obtained from regions of interest placed in both the cortex and medulla on all 6 slices for both kidneys at different timepoints.

[†] P < 0.05 using a paired 2-tailed t test when compared with prefurosemide.