Comparison of PGSE and STEAM DTI acquisitions with varying diffusion times for probing anisotropic structures in human kidneys

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Purpose: To evaluate the sensitivity of stimulated-echo acquisition mode (STEAM) and pulsed-gradient spin-echo (PGSE) diffusion tensor imaging (DTI) acquisitions with different diffusion times for measuring renal tissue anisotropy.

Methods: Twelve healthy volunteers underwent an MRI examination at a 3T scanner including STEAM and PGSE DTI with variable diffusion times Δ (20.3, 37 and 125 ms). Three volunteers were scanned twice to test the reproducibility for repeated examinations. Diffusion parameters fractional anisotropy (FA) and apparent diffusion coefficient (ADC) in the automatically segmented cortical and medullary regions of interests in both kidneys were calculated and averaged over all subjects for further analysis. Moreover, 5-grade qualitative evaluation of the FA and ADC maps from each sequence was conducted by two experienced radiologists in a consensus.

Results: The cortex-medulla difference in the STEAM sequence was significantly higher than that in PGSE with short Δ = 20.3 ms (P < 0.001) and in PGSE with intermediate Δ = 37 ms (P < 0.05) diffusion times. Reproducibility of the FA/ADC measurements was very good and comparable for all acquisition modes investigated. For the FA maps, the PGSE sequence with intermediate diffusion time scored highest in the subjective visual assessment of radiologists.

Conclusion: The delineation of anisotropy in renal tissue is depending on the used diffusion time of the DTI sequence. A PGSE acquisition at a diffusion time of about 37 ms provides reproducible results with optimal corticomedullary contrast in FA and ADC maps and good image quality.

KEYWORDS
DWI, FA map, kidney, PGSE, renal DTI, STEAM
1 | INTRODUCTION

In recent years, diffusion-weighted imaging (DWI) has emerged as a valuable tool for the diagnosis and clinical management of patients with kidney diseases as well as renal transplant recipients. Standard isotropic diffusion can be described quantitatively by the apparent diffusion coefficient (ADC). However, because tubules, collecting ducts, and blood vessels in the kidney medulla account for spatially restricted water diffusion, renal diffusion tensor imaging (DTI) provides additional information over DWI regarding diffusion directionality and anisotropy. The sensitivity of the DTI protocols to different microstructural length scales increases with diffusion time $\Delta$. Thus, the selection of the optimal diffusion time can maximize the contrast in tissue exhibiting restricted diffusion.

Up to now, the DWI acquisition protocols have mostly been optimized for applications in the human brain. Only recently, a consensus on recommended acquisition protocol for renal DWI was formed. Nevertheless, the role of the diffusion time in renal tissue has not been conclusively clarified.

Whereas most human axons have a diameter between 0.2 and 20 $\mu$m, the renal tubule is differentiated into several segments of different diameters ranging from 20 to 50 $\mu$m, as estimated from renal biopsy in healthy individuals in early studies. For investigating diffusion anisotropy of such large-scale structures, diffusion time must be long enough to ensure that significant quantities of water molecules are able to encounter hindering obstacles such as the luminal surface of the tubule. Previously, it has been shown that the stimulated-echo acquisition mode (STEAM) may offer advantages over the pulsed-gradient spin-echo (PGSE) diffusion MRI when long diffusion times beyond the T2 value of the tissue are required.

To the best of our knowledge, there is no study optimizing the diffusion time for DTI of the human kidney. Here, we aimed to evaluate the sensitivity of STEAM and PGSE DTI acquisitions with different diffusion times for measuring tissue anisotropy in the human kidney on a clinical MRI system. For this purpose, we (a) estimated the differences in FA/ADC values among the used sequences, (b) assessed the corticomedullary differentiation in FA maps, and (c) investigated the reproducibility of FA and ADC measurements in the same and repeated examinations.

2 | METHODS

2.1 | Study population

The study protocol was approved by the local ethics committee, and written informed consent was obtained from all participants. The study population comprised 12 healthy volunteers (5 females and 7 males; age range: 23-31 years; mean age 25.8 $\pm$ 2.7 years) with no history of kidney diseases and no abnormal renal MRI findings (except for small cysts). Three volunteers were initially scanned as a part of the protocol optimization. Furthermore, three subjects were examined twice to test the intrasession reproducibility. All images were obtained without any restriction of fluid or food intake prior to MRI examination.

2.2 | In vivo MRI experiments

MR data were acquired with a 3T whole-body system (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany) using a 18-channel torso array coil and a 32-channel spine coil. A half-Fourier single-shot turbo spin echo (HASTE) sequence in all three image axes (axial, coronal and sagittal) was used to acquire anatomical images. DW images at $b=0$ and 500 $s/mm^2$ were obtained using a prototype single-shot echo-planar imaging (EPI) sequence with monopolar PGSE as well as STEAM diffusion preparation. The following parameters were common to all DWI sequences: FOV, 370 $\times$ 370 mm²; matrix, 176 $\times$ 176; number of slices, 3; slice thickness, 5 mm; averages, 4; bandwidth, 1895 Hz/px; diffusion directions, 12. SPAIR (SPectral Attenuated Inversion Recovery) technique was incorporated for effective fat saturation. For the initial protocol optimization, this acquisition was carried out in 3 volunteers with identical parameters but the following different diffusion times: $\Delta=(17.2, 21.2, 37.2, 42.4, 48.2)$ ms for PGSE and $\Delta=(21.2, 37.2, 42.2, 48.2, 82.2, 125.2, 281.2, 500)$ ms for STEAM. Based on the subjective image quality assessment performed by 2 radiologists, 3 optimal diffusion times were selected for further study, namely $\Delta=20.3$ ms (at minimal TE = 46 ms) and $\Delta=37.0$ ms (at minimal TE = 62 ms) for a monopolar PGSE sequence as well as $\Delta=125.0$ ms (at minimal TE = 39 ms) for a STEAM acquisition. The echo time was set to its minimum in each sequence in order to maximize SNR, while allowing a $b$-value of 500 $s/mm^2$ to be obtained. DWI data were acquired using respiratory triggering in the expiratory phase. A trigger delay of 100 ms with a threshold of 20% was used. The acquisition time of each sequence was about 3:30 minutes, depending on the respiratory frequency of each individual subject.

2.3 | Data analysis

DTI datasets were processed using in-house-developed routines written in MATLAB (Matlab 2018b, Mathworks, Natick, Massachusetts). One of three acquired slices with maximal renal area and no visible renal vessels was selected for further analysis. Retrospective motion correction
was not performed, as it did not significantly improve the image quality. The fractional anisotropy (FA) and the apparent diffusion coefficient (ADC) maps were generated by built-in vendor’s software that utilizes the complete b-matrix information and takes into account all gradients’ contributions. This was particularly important for the STEAM sequence, in which imaging gradients generate much stronger contributions to diffusion weighting compared with the conventional PGSE. The right kidney was selected for further analysis because of lower potential for artefacts from heart motion. The entire right kidney parenchyma was manually extracted from the surrounding tissues in the \( b = 0 \) image. To eliminate operator bias, the cortical-medullary regions of interest (ROIs) were automatically segmented based on the FA map. The segmentation algorithm used here fits 2 Gaussian distributions to the histogram of the parenchymal FA values in order to find an optimal threshold to separate cortex from medulla. Mean FA values and standard deviations (SD) of the segmented cortical and medullary ROIs were calculated and stored for further analysis. Moreover, the ROIs obtained from the FA maps were applied to the ADC maps to measure the mean ADC values. Eventually, mean values, SDs, and standard errors of mean (SE) of the mean FA and ADC values among the 12 volunteers were calculated. The cortex-medulla contrast was evaluated as a difference in the FA values between cortex and medulla. The same analysis was performed in the left kidney in order to study reproducibility within the same examination. Additionally, the reproducibility of the repeated examinations was tested based on the data obtained in 3 subjects scanned twice. The mean SNR value (relative to the noise standard deviation) from the DW image with \( b = 0 \) was also calculated. A noise ROI was placed outside the body, whereas the renal ROI encompassed the renal parenchyma. Furthermore, 5-grade qualitative evaluation of the FA and ADC maps from each sequence was conducted by 2 radiologists in a consensus. The evaluation was made in 5-grade scoring, as follows: 1, not evaluable; 2, poor (cortex-medulla difference is not visible); 3, moderate (visible cortex-medulla difference, but not clear); 4, good (reasonable cortex-medulla difference); 5, excellent (clear cortex-medulla difference).

### 2.4 | Statistical analysis

The differences between the ADC and FA values of the cortex and medulla were compared using Wilcoxon’s rank-sum test. To investigate the effect of variable sequences on the cortex-medulla differences in FA values, repeated measures analysis of variance (ANOVA) was used. Reproducibility of FA and ADC measurements within the examination was assessed with the box-plot method. To examine the reproducibility of the examination, the within-individual standard deviation (Sw) was calculated, as follows:

\[
V = \text{variance of the two values (FA or ADC) measured in cortex or medulla at two separate sessions.}
\]

\[
Sw = \sqrt{\text{average of } V \text{ in all volunteers}}
\]

### 3 | RESULTS

All datasets were acquired with sufficient quality and could therefore be used for further analysis.

Table 1 shows the FA and ADC values in the cortex and medulla averaged across the 12 volunteers who were scanned with 3 different acquisition modes. For the PGSE sequence with short \( \Delta \), PGSE with intermediate \( \Delta \) and STEAM with long \( \Delta \), the mean cortical FA values were 0.13 ± 0.04, 0.18 ± 0.06, and 0.26 ± 0.07, and the mean medulla FA values were 0.28 ± 0.06, 0.37 ± 0.06, and 0.48 ± 0.08, respectively. The cortical ADC values ranged from \((2.23 \pm 0.15) \times 10^{-3} \text{ mm}^2/\text{s}\) to \((2.53 \pm 0.05) \times 10^{-3} \text{ mm}^2/\text{s}\), whereas the medulla ADC values were between \((2.10 \pm 0.15) \times 10^{-3} \text{ mm}^2/\text{s}\) and \((2.49 \pm 0.22) \times 10^{-3} \text{ mm}^2/\text{s}\). The FA values of the renal cortex were significantly lower than the medulla FA in all sequences \((P < 0.001)\), which is consistent with the literature. Moreover, the ADC values

| Table 1 | FA and ADC values in renal cortex and medulla |
|---------|------------------------------------------------|
| | Cortex | Medulla | ADC \((×10^{-3} \text{ mm}^2/\text{s})\) |
| | mean | SD | Mean | SD | Mean | SD |
| PGSE \((\Delta = 20.3 \text{ ms})\) | 0.134 | 0.042 | 0.280 | 0.060 | 2.231 | 0.145 |
| PGSE \((\Delta = 37.0 \text{ ms})\) | 0.185 | 0.062 | 0.366 | 0.057 | 2.382 | 0.294 |
| STEAM \((\Delta = 125.0 \text{ ms})\) | 0.262 | 0.072 | 0.477 | 0.076 | 2.528 | 0.048 |

Abbreviations: ADC, apparent diffusion coefficient; FA, fractional anisotropy; PGSE, pulsed-gradient spin-echo; STEAM, sensitivity of stimulated-echo acquisition mode.
obtained in the cortical ROIs were significantly higher compared to those calculated in the medullary ROIs only in the PGSE sequence with the short diffusion time ($P < 0.05$). Only the difference between the ADC values measured with the PGSE at short $\Delta$ and the STEAM at long $\Delta$ was statistically significant in the renal cortex and medulla ($P < 0.001$).

Both the cortical and medullary FA values were significantly different in all sequences ($P < 0.05$).

Figure 1 shows the differences in FA values between the medulla and cortex. The cortex-medulla difference in the STEAM sequence was significantly higher than that in the PGSE with short $\Delta$ ($P < 0.001$) and in the PGSE with intermediate $\Delta$ ($P < 0.05$). For the PGSE acquisition, significantly higher difference in FA values between the medulla and cortex was obtained at higher diffusion time ($P < 0.05$). The results obtained with the shortest diffusion time showed the smallest variability among the considered sequences. Moreover, a test of within-subject effects (repeated-measures ANOVA) revealed that the cortex-medulla differences were affected by the different sequences ($F$-value, 23.39; $P < 0.001$).

Figure 2 shows intraindividual differences of the FA and ADC in the cortex and medulla measured in the right and left kidney within the same examination. No significant differences in FA and ADC values between the right and the left kidney at the 5% significance level could be observed regardless of the protocol used.

Table 2 displays $Sw$ in cortex and medulla calculated from repeated examinations in 3 volunteers. For the FA values, $Sw$...
ranged from 1.4% to 12.4% of the mean with the smallest Sw values obtained with PGSE sequence at ∆ = 37.0 ms. Sw for the ADC values in the cortex and medulla were between 2.0% and 8.8%. The highest repeatability of the ADC measurement was achieved with the PGSE sequence using short diffusion time.

The subjective quality of the FA maps obtained using the PGSE acquisition with intermediate diffusion time (ranked 4.8 ± 0.4 on the 5-point scale) was superior to those calculated from data collected at short (4.3 ± 0.5) and long diffusion times by STEAM (4.3 ± 0.5). For the ADC maps, the PGSE sequence with short ∆ scored highest (3.7 ± 0.5) compared with the PGSE acquisition at intermediate ∆ (3.1 ± 0.5) and the STEAM sequence with long ∆ (2.3 ± 0.5). Figure 3 shows exemplary FA and ADC maps obtained with 3 different protocols.

The mean SNRs of the kidney in b = 0 images were 152 ± 84, 138 ± 81, and 77 ± 34, measured in PGSE with short ∆, PGSE with intermediate ∆, and STEAM with long ∆, respectively. There were significant differences in SNR values between the different acquisitions (P < 0.05), except from the 2 PGSE protocols (P = 0.674).

4 | DISCUSSION

Our study aimed to compare three different DTI acquisition protocols with varying diffusion times for measuring anisotropy in human kidneys. Diffusion parameters were obtained by averaging data from 12 volunteers. Good SNR was achieved, among others, through minimizing TE in each sequence. A recent study demonstrated the lack of relationship between the FA/ADC estimates and TE, meaning that T2 weighting did not affect the measured diffusion parameters in our study.9 Combining the results of the FA and ADC values, corticomedullary contrast, reproducibility, and visual radiologists’ assessment, the acquisition using a PGSE sequence with ∆ = 37 ms provided the best protocol.

Assuming D = 1.8 × 10⁻³ mm²/s²⁰ and ∆ = 37 ms, we obtain a two-dimensional diffusion length L₀d ≈ √4D∆ of about 16 µm, which enables sensitivity to the radial length scale of the thin segment of loop of Henle occurring within the inner medulla.¹²,¹⁵ Similarly, L₀d ≈ 30 µm at a diffusion time of 125 ms amplifies sensitivity to the distal and

| TABLE 2 | Intraindividual standard deviations (Sw) of FA and ADC values measured in the right kidney in repeated examinations. Sws are given as an absolute variance and as a percentage of the repeated examination mean |
|---------|---------------------------------|---------------------------------|-----------------|---------------------------------|---------------------------------|-----------------|
|         | FA                              | ADC                            |                 | FA                              | ADC                            |                 |
|         | Cortex                          | Medulla                        | Cortex          | Medulla                        | Cortex                          | Medulla          |
|         | Sw %                            | Sw %                           | Sw %            | Sw %                           | Sw %                           | Sw %            |
| PGSE (∆ = 20.3 ms) | 0.006 4.7 | 0.035 12.4 | 0.057 2.5 | 0.043 2.0 |
| PGSE (∆ = 37.0 ms) | 0.003 1.4 | 0.017 5.9 | 0.209 8.8 | 0.13 5.7 |
| STEAM (∆ = 125.0 ms) | 0.11 4.4 | 0.033 6.9 | 0.11 4.4 | 0.109 4.4 |

Abbreviations: ADC, apparent diffusion coefficient; FA, fractional anisotropy; PGSE, pulsed-gradient spin-echo; STEAM, sensitivity of stimulated-echo acquisition mode; Sw, within-individual standard deviation.
proximal tubules that are found in the outer medulla and cortex.13,15

Consistent with findings from previous studies, the medulla FA values measured in all sequences were significantly higher than those obtained in the renal cortex, whereas the ADC values of the medulla were significantly lower than of the cortex only in PGSE with short Δ.4,20 The high diffusion anisotropy of the medulla is related to centripedically oriented anatomic structures of the kidney.4 The higher cortical ADC compared with medulla ADC could be due to the faster water molecule transporting in the cortical glomerulus, higher blood volume, and larger tubular diameters.21,22 The results of the FA measurements demonstrated higher intra-individual variability of the medulla FA compared with the cortical FA values. The opposite trend was observed for the ADC values. One reason for this might be the increased noise in the cortex that led to the overestimated ADC values and higher variability among the volunteers.4,23 Although our overall results are in line with previous studies, direct comparison of the estimated FA and ADC values is difficult because of the differences in the acquisition protocols used at different sites.1,9

Reproducibility of the FA/ADC measurements in the same examination was very good and comparable for all acquisition modes investigated. Similarly, reproducibility obtained in repeated examinations did not differ considerably regardless of the protocol used. Higher variability of the medulla FA may be related to the functional changes in FA between 2 measurements.4

Our results showed a significant increase of FA values with increasing diffusion time, which is consistent with a higher sensitivity to the microstructure at higher diffusion times.14 Moreover, previous study reported an upward bias of FA as SNR decreased, which could also at least to some extent explain the increase in FA at higher Δ.24 Further, a surprising increase in ADC as a function of diffusion time was observed in our study. An opposite trend was reported in the brain and skeletal muscle.7,25 We believe that the time-dependent increase of ADC in the kidney might be attributable to perfusion that strongly affects the ADC values, especially at lower b-values.21 Renal perfusion was reported to be higher than perfusion in the brain, heart, or skeletal muscle.26 In order to better understand the influence of the renal perfusion on diffusion biomarkers at different diffusion times, an intravoxel incoherent motion (IVIM) model could be employed in a future study.27 IVIM technique was shown to better fit the diffusion signal in the kidney than the one-compartment model used here.28

Although the STEAM sequence with long Δ provided the highest difference in FA values between cortex and medulla, the corresponding ADC maps showed relatively poor cortex-medulla differentiation. This might be due to the inherently low SNR of STEAM sequences.29 If not compensated, low SNR can lead to inaccurate diffusion parameter estimates and degrade image quality.23 Thus, a reasonable trade-off between SNR and anisotropy should be made to achieve optimal results in practical applications. SNR can usually be enhanced by increasing the number of averages. However, this comes at the expense of a longer acquisition time. Further technical developments such as radial encoding strategies with data undersampling combined with iterative image reconstruction should be considered for accelerating the STEAM acquisition while maintaining or improving the SNR level.30,31

Apart from low SNR, one major drawback of the STEAM sequence is that the diffusion weighting and diffusion directions are strongly affected by the imaging gradients, especially at longer diffusion times. To reduce this effect, we analyzed the FA and ADC maps that were computed using the full b-matrix. Nevertheless, a previous study found that the effective gradient direction may still differ depending on the diffusion time.8 To correct the directional bias introduced by the butterfly gradients, the use of the "compensated acquisition" method as proposed by Lundell et al16 should be considered in further studies.

Despite the previously discussed issues, our study showed promising results concerning the use of the STEAM sequence for renal DTI. The possibility of using longer diffusion times, while maintaining a reasonably short acquisition time, gives an opportunity to better understand the relationship between the diffusion-weighted MRI signal and underlying tissue microstructure.25 In particular, previous studies have shown that the time-dependent STEAM-DTI might be an useful tool for characterizing normal breast tissues and breast pathologies,8 as well as estimating muscle fiber diameters in healthy volunteers and patients with chronic exertional compartment syndrome.7,32

This study has several limitations worth mentioning. First, this was a preliminary study with a small number of healthy young volunteers. The results should be assessed in a larger cohort of healthy subjects and/or patients with renal pathologies. Second, it might be necessary to further optimize the DWI sequence parameters including b-values, number of gradient directions and averages in order to achieve better contrast enhancement within a reasonable scan time. Third, even during respiratory-triggered acquisition, misregistration artifacts due to respiration can occur. One solution to this problem could be the use of navigator-triggered sequences.

5 | CONCLUSIONS

We conclude that adjusting the diffusion time might be an important factor to consider in renal DTI. Our study suggests that a conventional PGSE sequence at a diffusion
time of about 37 ms provides reproducible results with optimal corticomedullary contrast in FA and ADC maps and good image quality. Furthermore, we demonstrated that the STEAM-DTI has promising potential for probing renal tissue anisotropy despite its inherently low SNR characteristics.

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