Combined IVIM and DTI for simultaneous assessment of diffusion and flow anisotropy of the kidney
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Purpose: Diffusion weighted imaging characterizes water motion on a molecular level and provides information about renal microstructure and function. One variant, intravoxel incoherent motion (IVIM), distinguishes tubular/vascular flow from passive diffusion through collecting data over a range of diffusion weightings (b-values) (1, 2). Another, diffusion tensor Imaging (DTI), is sensitive to direction of restriction (anisotropy) to diffusion through analysis of multiple diffusion-sensitizing directions, and demonstrates clear anisotropy in the renal medulla (2, 3). However, the biophysical underpinning of this anisotropy remains unproven, particularly regarding the roles of (a) structural restrictions of tubules and collecting ducts and (b) active flow in oriented tubular or vascular structures (5). Resolving this ambiguity requires a more comprehensive acquisition and analysis approach. In the present study, we examined a combined IVIM-DTI methodology to distinguish structural from flow effects on renal tissue anisotropy, which may be useful in the evaluation of diabetic nephropathy or allograft rejection.

Material and Methods: Eight healthy volunteers were examined using a clinical 3T-scanner (VERIO, Siemens Healthcare). IVIM-DTI was acquired during free-breathing using a twice-refocused spin echo Echo-Planar-Imaging sequence with extra fat suppression and nonlinear phase correction and with following parameters: TR 2600ms; TE 79ms; 2 averages; 20 diffusion directions; b-values 0, 10, 30, 50, 80, 120, 200, 400, 600, 800 s/mm2; slice thickness 6mm. Retrospective 2D affine coregistration of all images to mitigate respiratory motion artifact was performed with FireVoxel software (6). IVIM-DTI analysis of the renal cortex and medulla was performed using custom code (IgorPro 6, Wavemetrics, Inc.). Several variants of analysis were performed to investigate the interplay of flow and anisotropy. First, mean diffusivity (MD) and fractional anisotropy (FA) from conventional DTI analysis was measured for the low (b= 0-200), high (b=400-800) and full (b=0-800) b-value range. Second, for each acquired direction, IVIM-parameters perfusion fraction $f_p$, pseudo-diffusivity $D_p$ and tissue diffusivity $D_t$ were calculated with a segmented voxelwise analysis: (1) $D_t$ was determined from a monoexponential fit using values for b > 200 s/mm2; (2) The zero intercept from step (1) is used along with the b=0 signal to determine $f_p$. (3) $D_p$ was calculated from a biexponential fit with constrained $D_t$ and $f_p$. Maps of mean and standard deviation (i.e. directional variance) of $D_t$, $f_p$, and $D_p$ over all directions were generated. The global anisotropies of $D_t$ and $f_p$ were visualized as: Regions of interest (ROIs) were manually drawn segmenting cortex and medulla on all slices. The primary diffusion eigenvector $\xi_1$ in each voxel was measured from a diffusion tensor analysis of the measured $D_t$ values. Then, the $D_t$ or $f_p$ values from all ROI voxels in 20 directions (total >1000 points/subject) were plotted as a function of the relative angle between the diffusion direction $\xi_1$ and median medullary values of the parameters described above (*p<0.05).

Results: FA of the medulla was significantly higher than of the cortex for all 3 b-value-regimes, however the corticomedullary difference is smaller for the high b-value range (Table 1 and Figure 1). Table 2 summarizes data from the combined IVIM-DTI analysis for all 8 volunteers in this study. A significantly higher $f_p$ and higher $D_t$ was determined for the cortex than for the medulla (Figure 2) Both $f_p$ and $D_t$ showed a significantly higher directional variance in the medulla than cortex (Table 2). The polar plot analysis depicts nearly isotropic $f_p$ and $D_t$ in the cortex and anisotropy for both $D_p$ and $f_p$ parameters in the medulla (Figure 3).

Conclusions: Our data suggest that a combined IVIM-DTI protocol is feasible during free-breathing, when combined with coregistration. The combined IVIM-DTI approach also provides several compelling findings. First, we observe significantly higher $f_p$ of the cortex than medulla, in distinction from previous studies finding comparable $f_p$ in both tissues. Second, higher medullary FA at the low b-value range and high directional variance of medullary $f_p$ suggest anisotropy of the perfusion fraction. Similarly, both flow and diffusion appear to contribute to the diffusion anisotropy of the renal medulla. Future application of this novel method may be useful in separating decreased tubular flow from irreversible structural tubular damage, e.g. in diabetic nephropathy.